The Saline Oscillation Hypothesis: Endocannabinoid-Mediated Fungal-Hominid Coevolution in the East African Rift Valley

Jim Craddock
Redacted Science Research Initiative
redactedscience.org | jimcraddock.com
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Abstract

This paper extends the *Mammalia candidus* pan-mammalian co-evolution hypothesis (Craddock, Pan-Mammalian) by proposing a specific environmental mechanism: cyclical lake salinity variation in the East African Rift Valley during the Plio-Pleistocene as the driver that activated and deepened the symbiosis between *Candida* species and hominid hosts. Drawing on paleoclimatological evidence of alternating humid and arid periods producing dramatic lake-level and salinity oscillations (Maslin *et al.*, 2014; Trauth *et al.*, 2005), paleoanthropological evidence of concurrent hominid speciation and encephalization events (Shultz and Maslin, 2013), and established literature on the endocannabinoid system (ECS) as a conserved master regulatory system across mammals (Elphick, 2012), we propose that cycling exposure to increased electrolyte concentrations in drinking water followed by freshwater periods producing electrolyte disruption analogous to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) provided the environmental conditions under which a fungal symbiont capable of managing host perfusion and electrolyte balance gained decisive selective advantage. This cycling of conditions served as a forge providing directed evolution in a localized area over a timescale allowing a focused advancement of evolution for both partners in the symbiosis.

The symbiont's capacity to fill this role is not limited to the ECS. We present a synthesis of peer-reviewed evidence demonstrating that *Candida albicans* occupies a unique position in the mammalian internal ecology: it is the only organism in the host microbiome that simultaneously signals across kingdoms (to bacteria, competing fungi, and the mammalian host), possesses physical tissue mobility through hyphal morphological transition, and accesses the host's endogenous receptor infrastructure. Confirmed molecular targets of *C. albicans* metabolites include nuclear transcription factors (FXR, PPARs), voltage-gated calcium channels, GABA-A neurotransmitter receptors, the GLP-1 incretin system, cholinergic receptors, and multiple arms of both innate and adaptive immunity. The endocannabinoid system, while the primary and most ancient interface, represents the trunk of a signaling architecture whose canopy extends across the broader GPCR superfamily and beyond. We reinterpret farnesol, the first quorum-sensing molecule identified in a eukaryote (Hornby *et al.*, 2001), not as a self-regulatory signal but as a multi-target effector molecule deployed to manage the host environment, consistent with the twenty-five-year absence of any identified farnesol receptor in *C. albicans* itself. The organism possesses confirmed receptors or binding proteins for at least six classes of host hormone, including estrogen, luteinizing hormone, corticosteroids, and androgens, while governing additional endocrine axes through upstream management of pituitary perfusion and ECS-mediated signaling — a two-tier architecture in which the organism senses hormones that

provide inbound information and modulates hormones it controls through the producing gland. This same architecture drives increased melanin production as an emergent byproduct, both systemically via elevated pituitary α-MSH output and locally via TLR4 recognition and PGE_2 stimulation of epidermal melanocytes, providing an additive driver to conventional UV-folate selection and helping explain the geographic distribution of extreme pigmentation in modern African populations (Jablonski & Chaplin, 2000; Tapia *et al.*, 2014).

The framework further demonstrates that the same biochemical computer architecture, when disrupted by high-potency exogenous THC, produces cannabinoid hyperemesis syndrome (CHS) as an interface-overload state, resolving the paradoxical tissue-specific CB1 downregulation, TRPV1 dysregulation, and compulsive hot-shower relief through Hgt4 glucose sensing and arachidonic-acid competition while unifying immune activation patterns absent ECS transcript changes (Meltzer *et al.*, 2025; GSE303922).

The framework is applied to cannabinoid hyperemesis syndrome (CHS), a condition of rising prevalence that lacks a consensus mechanism in the standard pharmacological model. The organism-mediated model resolves three longstanding gaps — tissue-specific differential downregulation of CB1 receptors (brain vs. gut), TRPV1 dysregulation, and the compulsive hot-shower phenomenon — while unifying the immune activation profile and absence of ECS transcript changes reported in a 2025 whole-blood RNA-seq study (Meltzer *et al.*, 2025; GSE303922). It positions CHS as an interface-disruption state in which high-potency THC overloads the symbiont's primary signaling channels, triggering a positive-feedback loop driven by Hgt4 glucose sensing and arachidonic-acid competition.

The model generates eight falsifiable CHS predictions, including an immediate zero-cost intervention: prodromal caloric loading to maintain blood glucose above the organism's calibrated ~5 mM threshold. A practical dietary test is also proposed — gradual incorporation of documented anti-*Candida* foods (virgin coconut oil, Ceylon cinnamon, crushed garlic, oregano oil, and iodized salt) — with explicit guidance on step-wise introduction, potential die-off responses, and the need to differentiate effects in patients with simple THC-triggered disruption versus those with deeper underlying colonization states. No prior published work has proposed *C. albicans* as a mechanistic contributor to CHS.

We further propose that the social component of the co-evolutionary architecture was initiated before the salinity oscillations through the discovery and communal use of exogenous phytocannabinoids, which promoted peaceful social bonding, group cohesion, and cooperative behavior. This pre-linguistic social flywheel, reinforced epigenetically through transgenerational cannabinoid-induced methylation changes and evolution of cannabis variants through cultivation, established cooperative social structure before the emergence of language. Language did not create the co-evolutionary trinity of symbiont, host physiology, and social structure. It fulfilled the requirements of a civilization based around the passage of knowledge, allowing it to accelerate. Additionally, we note discipline on the order of a religion was necessary to complete the final arcs of coevolution.

The framework predicts that host physiology has co-evolved adaptations to accommodate the symbiont's chronic operational demands. Three independent examples are documented: prolactin discharge mechanisms with species-specific timing architecture (anticipation-triggered in stallions, sustained in rodents, climax-locked in humans); host-side nitric oxide pathway tuning enabling erectile function under the low-volume circulatory state of the *Homo candidus* phenotype; and absence of endogenous fungal circadian machinery consistent with outsourcing of rhythm function to the host. Together these examples establish bidirectional adaptation as a

structural feature of the *Mammalia candidus* relationship rather than an incidental consequence, with implications for the reinterpretation of multiple physiological phenomena currently lacking unifying mechanistic explanation.

Single-cell transcriptomic evidence (Dumeaux *et al.*, 2023) demonstrating pre-positioned bet hedging, distributed survival strategies, and controlled genome destabilization in *C. albicans* populations is reinterpreted within this co-evolutionary framework as architectural rather than merely pathogen-adaptive, consistent with an organism refined across approximately 200 million years of mammalian co-evolution. It is the ultimate survivor: a biochemical computer continuously recalculating what moves might be required next. The *C. albicans* genome (14.3Mb, approximately 6,400 genes) encodes over 1,300 genes with no orthologs in other yeast species, the majority of which remain functionally uncharacterized.

We designate the symbiont-active hominid phenotype *Homo candidus* and argue that a subsequent genetic shift in cardiac architecture from suction-dominant to pump-dominant circulation disrupted the co-evolutionary trinity, producing the modern human condition in which the symbiont persists commensally but can no longer execute its full physiological program. Twenty testable predictions are presented, including proposed experiments in simulated gastric environments, comparative mycobiome analysis of Rift Valley populations, computational genomic analysis of uncharacterized *C. albicans* genes using biological foundation models, and molecular dating of the *C. albicans* / *C. dubliniensis* divergence.

We further specify Gate One as a two-phase event — a slow priming phase of organism-mediated paracellular barrier remodeling followed by an acute pressure-driven NaCl breach — initiating a deterministic barrier cascade in which each successive physiological failure defines the conditions the next barrier cannot withstand, providing a precision-mapping method for chronic disease progression in modern hosts whose developmental preservation windows have closed.

Keywords: fungal-hominid coevolution; East African Rift Valley; Plio-Pleistocene paleoclimate; saline oscillation; Homo candidus; language evolution; SIADH; pituitary perfusion; pituitary governance; autonomic governance; colonization density; salt sensitivity; phenotypic switching; bet hedging; cell communication; bidirectional signaling; GPCR; farnesol; candidalysin; Ece1; Kex2; peptide transporters; prohormone convertase; LILR; peptide mimicry; neuropeptides cross-kingdom signaling; GLP-1; cholinergic signaling; oxylipin; prostaglandin E_2; arachidonic acid; arachidonic acid substrate competition; Th1/Th2 polarization; molecular mimicry; eicosanoid; pH manipulation; potassium homeostasis; Na^+/K^+-ATPase reversal; candidalysin pore formation; bioelectric signaling; Tok1; ammonia excretion; extracellular vesicles; small RNA; cross-kingdom RNA interference; DHX29; codon optimality; vesicle cargo; cannabinoid hyperemesis syndrome; CHS; differential CB1 downregulation; TRPV1; hot shower phenomenon; glucose override; Hgt4 glucose threshold; morning nausea; palliative trap; cannabidiol antifungal; CBD negative allosteric modulation; capsaicin; medium-chain fatty acids; lauric acid; caprylic acid; allicin; cinnamaldehyde; dietary antifungal; iodized salt; coconut oil; haloperidol; NK1 antagonist; ondansetron resistance; gut immune activation; IgE elevation; transcriptomic signature; symbiosis; endocannabinoids/metabolism; endocannabinoids/physiology; Candida albicans; hypothalamic-pituitary-gonadal axis; pituitary gland; epigenetic memory; DNA methylation/genetics; leukocyte immunoglobulin-like receptor B1/metabolism; incretins; receptors cholinergic; oxylipins; dinoprostone; arachidonic acid; Th1 cells; Th2 cells; eicosanoids; acid-base equilibrium; potassium; potassium channels; sodium-potassium-exchanging ATPase; membrane potentials; ammonia; RNA small untranslated; RNA interference; RNA helicases; codon usage; transport vesicles; hypertension; gastrointestinal microbiome; rimonabant; luteinizing hormone; receptors estrogen; cannabinoid hyperemesis syndrome; TRPV cation channels; receptors cannabinoid; glucose; nausea; lauric acids; cannabidiol; capsaicin; acrolein; antifungal agents; ondansetron; immunoglobulin E; transcriptome; neurokinin-1 receptor antagonists; skin pigmentation; melanins; melanocytes; modern calibrated electrolyte set-point; bidirectional electrolyte

deviation; antifungal-induced endocrine cascade; multi-input context integration; carbon-source ancestral program; archidonic acid branch point confirmation

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Methodological Note on Sources and Extraordinary Circumstances

This paper cites several works by the author (Craddock, 2013; Craddock, 2022 log; Craddock, Biochemical Computer; Craddock, Pan-Mammalian; Craddock, Redacted Science; Craddock, Exposé). In standard academic practice, self-citation of this density would warrant scrutiny. The circumstances here are not standard.

The theoretical framework described in this paper derives in part from a 1995 peer-reviewed article that was subsequently redacted by removal from institutional access and citation indices under circumstances the author has documented extensively (Craddock, Exposé). The original article described a longitudinal cohort study of a physiological condition involving fungal-host interaction, endocannabinoid system modulation, and progressive organ system changes. The author encountered this article in 1995, retained key observations from it, and over the subsequent thirty years developed the condition described therein, becoming, in effect, both researcher and subject.

Because the original source was redacted, no conventional citation chain exists. The author's self-published works represent the only extant documentation of both the original findings and the thirty-year longitudinal case study that followed. These works are distributed across censorship-resistant platforms (IPFS, Nostr, GitHub) and indexed by major search engines. The author's identity as the primary source for "Redacted Science" is independently verifiable via Google and other search indices.

Additionally, the author's primary works are unconventional in format, reflecting both intentional stylistic choices and the tools available during their construction. The data co-located with the most current version includes daily logs, over a decade of laboratory results, and multiple independent attempts to document the process spanning thirteen years. These attempts are internally consistent in substance while authored independently of previous versions — a characteristic most readily verified by observing that the core narrative maintains coherence across documents while the precision of the oldest dates decreases in newer works, consistent with independent reconstruction from memory rather than copying from prior drafts.

The self-citations in this paper are not circular. They reference: (1) observational data from a 30-year longitudinal case study that cannot be obtained from any other source, (2) a theoretical framework (the *Mammalia candidus* hypothesis) that extends established peer-reviewed literature into novel territory, and (3) historical documentation of a redacted research program. The peer-reviewed citations in this paper (Maslin *et al.*, Shultz and Maslin, Elphick, Pacioni *et al.*, Markey *et al.*, Ren *et al.*, and others) provide the independent evidentiary scaffolding. The self-citations provide the connective architecture that no other author is positioned to supply. Readers are encouraged to verify all claims independently.

Note on Novelty

The pulsed climate variability hypothesis (Maslin *et al.*, 2014; Maslin and Trauth, 2009; Maslin, Shultz, and Trauth, 2015) established that East African Rift Valley lake oscillations are statistically correlated with hominid speciation, encephalization, and dispersal events. However, the authors explicitly noted that "the actual evolution mechanisms, which led to early hominins are still unclear and continue to be debated" (Maslin *et al.*, 2014). Existing hypotheses linking salt to human evolution focus on dietary sodium intake through aquatic foods as a source of brain-building nutrients such as DHA (Cunnane, 2005), or on the evolutionary conservation of sodium appetite as a physiological drive (Leshem, 2009). Separately, a substantial literature documents fungal-host symbiosis as a mechanism for salt tolerance in plants (Rodriguez and Redman, 2008), but no equivalent framework has been proposed for mammals.

The Saline Oscillation Hypothesis presented here is, to the author's knowledge, the first to propose that cyclical drinking water salinity in the East African Rift Valley served as the environmental substrate for an ECS-mediated fungal-mammalian coevolutionary program, and that this program, preceded by a phytocannabinoid-mediated social flywheel and accelerated by the emergence of language, constituted the specific mechanism driving the evolutionary events Maslin and colleagues identified but left mechanistically unexplained.

In addition to the saline oscillation mechanism itself, this paper presents several novel contributions:

First, the synthesis of existing peer-reviewed evidence on *C. albicans* cross-kingdom signaling, host receptor interactions, and immune modulation into a unified framework that positions *Candida* not as an opportunistic pathogen but as the apex coordinator of the

mammalian internal ecology. The individual findings cited in Section 5 are published and available. Their assembly into a coherent functional description of positional authority within the host microbiome has not been previously attempted.

Second, the effector hypothesis for farnesol function: a reinterpretation of farnesol's role from morphological self-regulation (the prevailing model since 2001) to a multi-target effector molecule whose morphological effects are a byproduct of broader environmental management. The twenty-five-year absence of an identified farnesol receptor in *C. albicans*, treated in the existing literature as an unresolved problem, is reinterpreted here as consistent with the effector model rather than paradoxical within it.

Third, the phenobarbital-colony distribution hypothesis: a proposed explanation for the variable anatomical geography of phenobarbital-associated mucosal ulceration across patients, based on differential density of the resident commensal *Candida* population rather than direct drug toxicity. This hypothesis is supported by two documented iatrogenic activation events in the longitudinal case study (Craddock, 2013; Craddock, Redacted Science) and by published case reports.

Fourth, the reinterpretation of single-cell bet hedging behavior in *C. albicans* (first characterized at the transcriptomic level in fungi by Dumeaux *et al.*, 2023) within the context of a coevolutionary symbiont framework rather than a pathogen resistance framework. The original characterization described cytoprotective programs enabling drug tolerance. The present paper interprets the same data as evidence of an architectural survival system consistent with 200 million years of coevolutionary refinement.

A Note on Voice

The sections of this paper numbered in Arabic numerals (1 through 11) were written under the assumption that the work would need to earn its credibility within institutional science. The tone reflects that. Claims are hedged. Language is measured. The framework is presented as a hypothesis, because that is what institutional norms require, regardless of the strength of the evidence behind it.

After completing the original version of this paper and its companion, *Candida albicans* as a Biochemical Computer (Craddock, Biochemical Computer), I investigated how this line of research came to be suppressed in the first place. The result was the Exposé, They Looked. They Were Right. They Were Destroyed. (Craddock, Exposé), which documents the institutional mechanisms by which an entire research corridor was dismantled in the 1960s.

That investigation changed my relationship with institutional convention.

The base theory presented in Sections 1 through 11, and the biochemical computer framework in Paper A, rest on peer-reviewed mycology, paleoclimatology, evolutionary biology, and endocannabinoid pharmacology. Some specific claims will certainly prove inaccurate. The core architecture should hold. I considered the evidence overwhelming enough to treat it as foundational science, and I still do.

Sections added in subsequent revisions (v1.1 and beyond) are numbered in Roman numerals (e.g., VI.III) to distinguish them from the original text. These sections are written in a different voice. They are less hedged, more direct, and do not observe institutional conventions about how a researcher is supposed to sound. This is a deliberate choice. When the institutions that set those conventions have demonstrated, on the historical record, that they will suppress

inconvenient science and destroy the careers of the people who produce it, compliance with their stylistic expectations is not a scientific obligation. It is a social one. I have declined it.

The science in the Roman-numbered sections is no less rigorous than in the original. The citations are real. The predictions are testable. The logic is falsifiable. What has changed is that I no longer write as though I need permission to say what the evidence shows. [or use language meant to exclude not include].

If you are reading this paper for the first time and find the tonal shift disorienting, read the Exposé. You'll understand.

1. Introduction

The endocannabinoid system (ECS) is among the most ancient and conserved signaling systems in mammalian biology, with enzymatic components traceable to the unicellular common ancestor of animals and plants approximately one billion years ago (Elphick, 2012; McPartland *et al.*, 2006). CB1 and CB2 receptors are present in all vertebrates and in chordate invertebrates such as the sea squirt *Ciona intestinalis* (Elphick *et al.*, 2003), while endocannabinoid ligands including anandamide and 2-arachidonoylglycerol (2-AG) have been detected in organisms as primitive as *Hydra vulgaris* (De Petrocellis *et al.*, 1999). The system maintains homeostasis across virtually every mammalian organ system, governing pain perception, mood, appetite, immune function, metabolism, and reproduction (Acharya *et al.*, 2017; Pandey *et al.*, 2009).

The clinical significance of this regulatory breadth was demonstrated by negative proof in 2006, when the European Medicines Agency approved rimonabant (Acomplia, Sanofi-Aventis), a selective CB1 inverse agonist, for the treatment of obesity. By blocking a single receptor in a system that mainstream medicine regarded as pharmacologically peripheral, the drug produced severe psychiatric adverse events including depression, anxiety, and completed suicides. The European Medicines Agency suspended the marketing authorization in 2008 (Christensen *et al.* 2007). The United States Food and Drug Administration never approved the drug, its advisory committee having flagged the psychiatric risk before market authorization (Sam *et al.* 2011). The lesson was unambiguous: a system whose partial blockade causes people to lose the will to live is not peripheral, instead it is more accurately framed as foundational architecture. The ECS does not merely participate in mood regulation. It is, evidently, required for the maintenance of the psychological state that sustains the decision to continue living.

Candida albicans, the most prevalent fungal commensal of the human mycobiome, is an obligate symbiont with no known environmental reservoir (Ost and Round, 2023; Kumamoto, 2011). Recent work has demonstrated that *C. albicans* colonization of the mammalian gut directly modulates the endocannabinoidome, producing specific changes in anandamide and 2-AG levels that alter hypothalamic-pituitary-adrenal (HPA) axis function and behavior (Markey *et al.*, 2020). Separately, the black truffle *Tuber melanosporum* has been shown to produce anandamide and express the major ECS metabolic enzymes NAPE-PLD, FAAH, DAGL, and MAGL, suggesting that fungal endocannabinoid production is phylogenetically ancient and may predate the evolution of cannabinoid binding receptors themselves (Pacioni *et al.*, 2015).

The *Mammalia candidus* hypothesis (Craddock, Pan-Mammalian) proposed that the conserved mammalian ECS represents an interface layer selected for and refined through coevolution between fungal symbionts and mammalian hosts across approximately 200 million years. The present paper extends this framework by identifying a specific environmental driver, the cyclical salinity oscillations of East African Rift Valley lakes during the Plio-Pleistocene, and

proposing a three-part coevolutionary model (the "evolutionary trinity") involving the fungal symbiont, host physiology, and social structure, with the social component initiated by communal phytocannabinoid use and accelerated by the emergence of language. We designate the symbiont-active hominid phenotype *Homo candidus*, not a separate species, but a functionally distinct physiological and cognitive state produced by full activation of the coevolutionary program.

While the ECS remains the primary documented interface between symbiont and host, evidence presented in Section 5 demonstrates that the signaling capacity of *C. albicans* extends substantially beyond the cannabinoid receptors, encompassing nuclear transcription factors, ion channels, neurotransmitter receptors, cholinergic signaling, and immune cell differentiation pathways. The ECS is the trunk of this signaling architecture. The broader receptor landscape is the canopy.

A vocabulary distinction matters throughout this paper and is fixed here for clarity. The saline oscillation mechanism is the historical Plio-Pleistocene environmental driver: cyclical lake salinity in the East African Rift Valley produced periodic SIADH-type electrolyte stress at freshening transitions, which selected for symbiont-host partnerships capable of managing host electrolyte balance during these stress windows. That driver no longer operates. What remains is the modern calibrated electrolyte set-point management — the moment-to-moment ionic, perfusion, and osmoregulatory governance the symbiont continues to perform in extant hosts using the same molecular toolkit selection refined under the historical mechanism. The two contexts share the molecular machinery; they do not share the timescale or the environmental driver. Throughout this paper, "saline oscillation" refers specifically to the historical mechanism. Modern observables of the partnership operating — bidirectional electrolyte deviations under fungal load and antifungal pressure, calibrated set-point management visible in clinical chemistry, perfusion governance signatures — are framed as modern-context evidence that the partnership selected for in the historical context continues to operate.

2. Geological and Paleoclimatic Context

2.1 The East African Rift Valley as Cradle of Hominid Evolution

The East African Rift System (EARS) is an active continental rift zone extending over thousands of kilometers from the Red Sea to Mozambique (Chorowicz, 2005). The region between Lake Turkana and Lake Natron is designated the "Cradle of Mankind" based on the density and significance of hominid fossil discoveries, including *Australopithecus afarensis* ("Lucy," ~3.2 Ma; Johanson and White, 1979), *Homo erectus* (KNM-WT 15000 "Turkana Boy," ~1.6 Ma; Brown *et al.*, 1985; Walker and Leakey, 1993), the Lomekwi stone tools (~3.3 Ma; Harmand *et al.*, 2015), and *Paranthropus boisei* ("Nutcracker Man," ~1.75 Ma; Leakey, 1959).

At Dalol, approximately 100 km north of the Afar Triple Junction, the rift floor contains a 5,000-meter-thick layer of evaporite salt deposits accumulated over the past four million years (Ebinger *et al.*, 2000). The Eastern Rift lakes including Turkana, Magadi, Natron, Nakuru, and Elmenteita, are hydrologically closed basins with no outlet to the sea, resulting in high mineral content as evaporation concentrates dissolved salts (Britannica, "East African lakes"). Lake Magadi and Lake Natron are hypersaline soda lakes enriched in Na^+, K^+, Cl^-, CO_3^{2-}, and HCO_3^- (Deocampo and Renaut, 2022).

2.2 Orbital Forcing, Amplifier Lakes, and Oscillation Architecture

The salinity oscillations central to this hypothesis were not random climate fluctuations. They were driven by predictable variations in Earth's orbital geometry, amplified by the unusual physical characteristics of rift basin lakes, and structured across at least three nested timescales.

The primary driver is axial precession. Earth's rotational axis wobbles on a cycle of approximately 19,000 to 23,000 years, commonly averaged to ~21,000 years (Berger and Loutre, 1991). Precession controls the seasonal distribution of solar radiation at tropical latitudes. At precession minima, Northern Hemisphere summer insolation increases, strengthening the African monsoon system, driving rainfall over East Africa, and filling rift basin lakes. At precession maxima, the monsoon weakens, rainfall decreases, and lakes contract (Kutzbach and Street-Perrott, 1985; Trauth *et al.*, 2005). Each precession cycle thus produces one complete wet-dry oscillation in the EARS. Over the 2.7 million years since the onset of intense climate variability, approximately 129 such cycles have occurred. Not all produced equivalent lake-level responses; the amplitude of each cycle depends on a second orbital parameter.

Eccentricity, the degree of circularity of Earth's orbit, varies on 100,000-year and 400,000-year cycles and modulates the amplitude of precession's effects (Berger and Loutre, 1991). When eccentricity is high and the orbit more elliptical, precession-driven insolation differences are amplified and the wet-dry swings are extreme. When eccentricity is low, precession effects are damped and climate varies less. This modulation produces what Maslin, Trauth, and colleagues term "variability packets": concentrated intervals of extreme environmental oscillation separated by periods of relative calm.

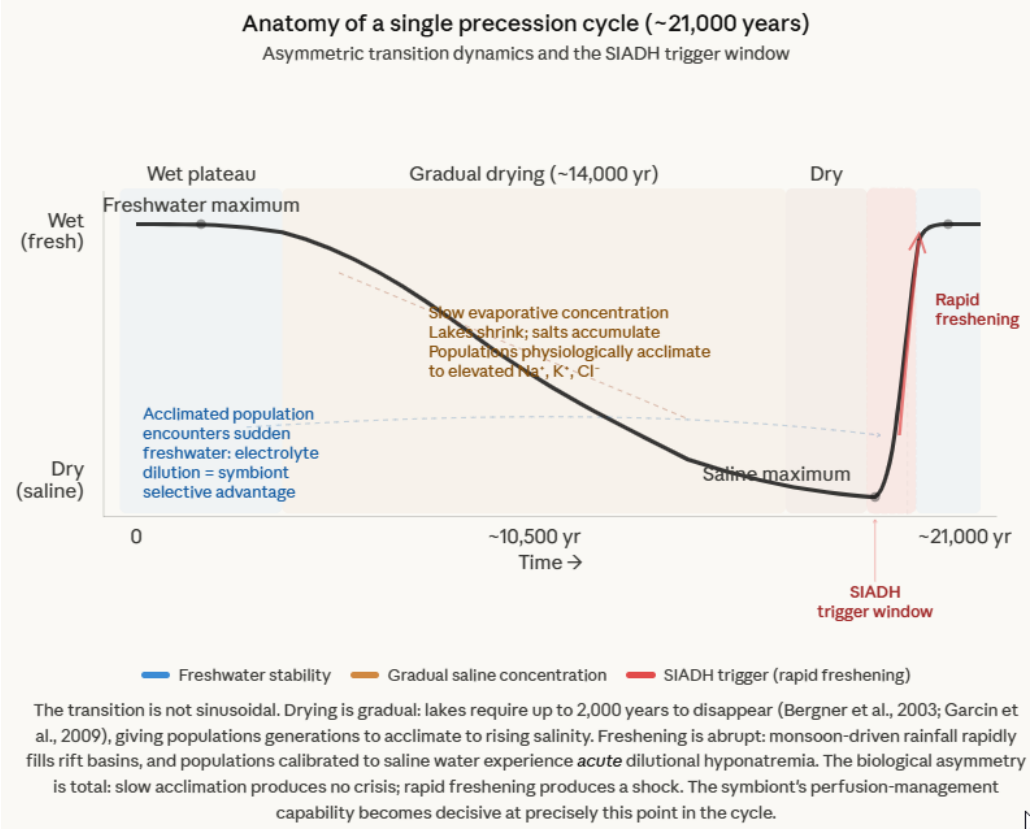
Before 2.7 Ma, major wet phases in the EARS appeared approximately every 400,000 years. After 2.7 Ma, East Africa did not oscillate continuously. Instead, the intense variability came in bursts: three windows, each roughly 200,000 years long, separated by calmer intervals of approximately 800,000 years. These windows occurred at 2.7–2.5 Ma, 1.9–1.7 Ma, and 1.1–0.9 Ma (Trauth *et al.*, 2005, 2007; Maslin *et al.*, 2014). Each coincides with a major global climate transition: the onset of Northern Hemisphere glaciation (2.7–2.5 Ma), intensification of the Walker Circulation (1.9–1.7 Ma), and the Mid-Pleistocene Revolution (1.0–0.7 Ma). During these windows, the landscape alternated between large freshwater lakes and extreme drought as rapidly as every 10,000 years, fast enough that a single population lineage would experience the full wet-dry-wet cycle dozens of times within each window (Trauth *et al.*, 2003; Kingston *et al.*, 2007).

Within individual precession-driven wet phases, a third timescale operates. Wilson *et al.* (2014) analyzed oxygen isotope composition and diatom assemblage data from a well-dated diatomite sequence in the Baringo-Bogoria basin and identified millennial-scale cyclicity of 1,400 to 1,700 years between 2.70 and 2.55 Ma, similar in period to late Quaternary Dansgaard-Oeschger events. These sub-oscillations, nested within the larger precession cycles, mean that even during nominally humid phases, lake depth, salinity, and drinking water chemistry fluctuated on timescales of tens of human generations.

The rift basins themselves amplify these climate signals. Trauth *et al.* (2010) introduced the concept of "amplifier lakes": tectonic graben morphologies combining high precipitation in elevated catchment areas with extreme evaporation on the valley floor. These basins do not respond proportionally to climate forcing. They respond disproportionately. A moderate shift in the precipitation-evaporation regime produces a dramatic shift in lake level and chemistry, because the rift geometry concentrates the hydrological response (Trauth *et al.*, 2005, 2010). The

Eastern Rift lakes, including Turkana, Baringo, Magadi, Natron, and Elmenteita, are hydrologically closed basins with no outlet to the sea, meaning dissolved salts accumulate as evaporation concentrates them (Britannica, "East African lakes"). These are the same basins in which the key hominid fossils were found.

Illustration A: Anatomy of a Single Precession Cyle



The transition is not sinusoidal. Drying is gradual: lakes require up to 2,000 years to disappear (Bergner et al., 2003; Garcin et al., 2009), giving populations generations to acclimate to rising salinity. Freshening is abrupt: monsoon-driven rainfall rapidly fills rift basins, and populations calibrated to saline water experience *acute* dilutional hyponatremia. The biological asymmetry is total: slow acclimation produces no crisis; rapid freshening produces a shock. The symbiont's perfusion-management capability becomes decisive at precisely this point in the cycle.

2.3 Transition Dynamics, Oscillation Count, and the Asymmetric Trigger

The biological significance of the oscillation architecture depends on a critical asymmetry in transition dynamics that has not been previously connected to hominid evolution.

The drying transition is gradual. Modeling results and field observations indicate that East African amplifier lakes require up to 2,000 years to disappear during a wet-to-dry climate transition (Bergner *et al.*, 2003; Garcin *et al.*, 2009). As lakes contract over this timescale, dissolved salt concentrations rise progressively. Populations drinking from these water sources experience a slow increase in electrolyte intake spanning dozens of generations, sufficient time for physiological acclimation. Renal sodium handling, blood volume set points, and osmotic equilibria adjust gradually to the rising baseline. The sinusoidal character of precession forcing produces intervals of approximately 8,000 years at both the wet and dry extremes during which relatively little change in daily insolation occurs (Maslin *et al.*, 2005), representing stability plateaus during which acclimation is reinforced. The remaining approximately 13,000 years of each cycle is the transitional zone where conditions change more rapidly.

The freshening transition is not gradual. When monsoon-driven rainfall returns and rift basins fill, lake freshening occurs on timescales far shorter than the drying process. A population whose physiology has been calibrated to elevated electrolyte concentrations over generations suddenly encounters freshened water. This is the physiological equivalent of a modern human adapted to normal dietary sodium suddenly drinking distilled water. The result is dilutional hyponatremia and a physiological response analogous to the syndrome of inappropriate

antidiuretic hormone secretion (SIADH): water retention, reduced urine output, blood volume expansion, and electrolyte imbalance. The disruption is proportional to the delta between the population's calibrated salinity and actual intake, not to the absolute salinity level.

This asymmetry is the fulcrum of the hypothesis. The slow drying transition produces no acute physiological crisis; populations acclimate. The rapid freshening transition produces a punctuated shock at a specific, predictable point in every oscillation cycle. It is at this point, and only at this point, that the symbiont's perfusion-management and electrolyte-handling capabilities become decisive. The selective advantage is not continuous. It is periodic, recurring at the freshening edge of every oscillation, and it is acute. The biochemical computer (Craddock, Biochemical Computer), when exposed to rapidly changing external pressures, responds by adjusting its regulatory and chromatin state. Existing epigenetic configurations that worked before get reinforced and passed forward. Recurrent environmental inputs tend to produce consistent transcriptional outputs, while novel conditions may induce transitions into alternative regulatory states, enabling the emergence of new outputs.

The direct sedimentary evidence for the scale of these oscillations comes from the Lake Malawi Drilling Project. Lyons *et al.* (2015) recovered the first continuous 1.3-million-year record of continental hydroclimate from an African lake interior, documenting 24 distinct lake-level drops exceeding 200 meters, of which 15 were severe events with water levels reduced more than 400 meters below modern. The distribution of these events was not uniform. Before the Mid-Pleistocene Transition (~800 ka), lake levels were generally lower and changed frequently, consistent with a drier baseline climate with rapid oscillations. After the MPT, the lake was commonly deeper and often overflowing, but minimum standing lake level intervals became more prolonged and extreme (Lyons *et al.*, 2015). Johnson *et al.* (2016) characterized the post-MPT record as dominated by strong 100,000-year eccentricity cycles of temperature and rainfall superimposed on a trend toward progressively wetter conditions.

The Lake Malawi record, while the most continuous available, comes from the southern EARS (10–14° S), approximately 2,000 km south of the Turkana-Baringo-Natron corridor where the key hominid fossils were found. The northern rift basins show stronger precessional control on lake levels (Kingston *et al.*, 2007; Deino *et al.*, 2006) and dried out faster than the rest of Africa (Turkana Basin Institute, 2021), indicating that hominid populations in the cradle region likely experienced more frequent and more intense oscillations than the Malawi record documents.

A conservative accounting of the total oscillation exposure experienced by EARS hominid populations since 2.7 Ma includes: approximately 129 precession-driven cycles (orbital mechanics), concentrated into three variability windows totaling roughly 600,000 years of intense oscillatory pressure, with millennial-scale sub-oscillations numbering in the hundreds nested within those precession cycles. Each cycle, at the freshening transition, presented the selective filter through which symbiont-integrated individuals passed and unintegrated individuals did not.

2.4 Temporal Correlation with Hominid Evolution

Shultz and Maslin (2013) demonstrated that hominid speciation events, changes in brain size, and dispersal events are statistically linked to the occurrence of ephemeral deep-water lakes in the EARS. The significant hominid speciation and brain expansion event at approximately 1.8 Ma, coincident with the emergence of *Homo erectus* and with the occurrence of “highly variable,

extensive, deep-water lakes" (Maslin *et al.*, 2014). The Turkana Basin, where many key fossils were found, dried out faster than the rest of Africa, forcing earlier adaptation to open, arid environments with periodically saline water sources (Turkana Basin Institute, 2021).

2.5 Candida Evolutionary Divergence and the Coevolutionary Timeline

The evolutionary history of the *Candida* clade provides independent temporal evidence consistent with the Saline Oscillation Hypothesis. *Candida* parapsilosis diverged from a last common ancestor with *C. albicans* approximately 70 Ma, coincident with the K-Pg extinction event and the explosive diversification of mammals (Butler *et al.*, 2009; Nobile *et al.*, 2021). This timing is consistent with the *Mammalia candidus* framework: as mammalian hosts diversified, their fungal symbionts co-diversified.

The divergence of *C. albicans* from its closest relative, *C. dubliniensis*, occurred more recently but remains imprecisely dated. The literature describes the split as occurring "relatively recently in evolutionary time" (Sullivan *et al.*, 2005), with genome-wide nucleotide identity of 80–90% between the two species (Jackson *et al.*, 2009). The critical observation is what happened after the split: *C. albicans* expanded gene families associated with host interaction and virulence (SAP, ALS, and IFF families), while *C. dubliniensis* underwent reductive evolution and widespread gene loss/pseudogenization that diminished its capacity to manage host physiology (Jackson *et al.*, 2009; Thompson *et al.*, 2021). This is not random drift; it is directional selection. *C. albicans* was being selected for deeper host integration while *C. dubliniensis* was not.

If the *C. albicans* / *C. dubliniensis* divergence occurred during the Plio-Pleistocene (~2–5 Ma), it would coincide precisely with the onset of salinity oscillations in the EARS, and the divergent evolutionary trajectories would have a clear explanation: *C. albicans* was under selection pressure to manage host perfusion and electrolyte balance during saline stress, driving the expansion of host-interaction gene families. *C. dubliniensis*, not under this pressure, shed the genes it did not need.

This divergence pattern is architecturally informative. Under the revised pan-mammalian framework (Craddock, Pan-Mammalian), the partnership architecture is a clade-wide feature of mammalian-Saccharomycetaceae coevolution that must be actively maintained by selection on partnership-relevant gene families. C. dubliniensis represents the fate of a sister lineage in which those selection pressures were attenuated: reductive evolution, gene loss, and a transition from partnership organism to opportunistic colonizer of immunocompromised hosts. C. albicans retained the architecture under EARS-scenario pressure; C. dubliniensis lost it under different conditions. The two species illustrate within a single sister-pair that partnership architecture is a maintained state, not a default state.

Independent evidence from program-architecture analysis supports the deeper-time framing of the partnership's foundational behaviors. Glucose depletion alone produces approximately 50-fold sensitization of pheromone signaling and bypasses the white-opaque epigenetic switch normally required for sexual mating in *C. albicans*, with the authors explicitly positioning carbon-source-state-driven mating as the more ancestral program and the white-opaque switch as a recent *C. albicans*–specific elaboration (Guan, Tao, Li, *et al.*, 2023). The implication for the coevolutionary timeline: state-level metabolic inputs controlling coordinated multi-program responses predate the lineage-specific elaborations *C. albicans* accumulated after divergence from *C. dubliniensis*. The organism was already running carbon-source-state-driven program transitions before the host-management capabilities expanded — meaning the

architectural substrate the saline oscillation mechanism selected on was older than the lineage in which the selection took place.

Additionally, atypical *C. albicans* strains isolated from vaginal specimens of Angolan women form a monophyletic group that may represent "an early stage of speciation" (McManus *et al.*, 2008). The observation of ongoing *Candida* diversification in African populations, the geographic region of the proposed coevolutionary origin, is consistent with the hypothesis that the selective pressures described here remain active.

3. The Pre-Linguistic Social Flywheel

3.1 Cannabinoid Discovery Before Salinity Oscillations

Cannabis sativa evolved approximately 28 million years ago on the eastern Tibetan Plateau (McPartland *et al.*, 2019). Phytocannabinoid-producing plants were present in the environments accessible to hominid populations long before the Plio-Pleistocene salinity oscillations intensified. The discovery that certain plants produce psychoactive effects when consumed does not require language, agriculture, or sophisticated cognition. Instead, it requires only foraging and repetition.

THC (Δ9-tetrahydrocannabinol) is a direct CB1 and CB2 agonist (Pertwee, 2008) that activates the same receptor system through which the fungal symbiont communicates with the

host. For a hominid already carrying *Candida* as a commensal and already possessing a functional ECS, the effects of phytocannabinoid consumption would be immediate: anxiolysis, mild euphoria, enhanced social bonding, reduced aggression, and appetite stimulation. In a host with an established symbiont relationship, these effects would be intensified, because the ECS interface is already upregulated by the symbiont's endogenous signaling.

3.2 The Social Bonding Effect

The behavioral effects of CB1 agonism are well-characterized: reduced aggression, increased prosocial behavior, enhanced appetite, and attenuated stress response (Lutz *et al.*, 2015). A hominid group in which individuals communally consume phytocannabinoids would exhibit stronger social cohesion, less intra-group violence, and more cooperative behavior. These are precisely the traits required for the social leg of the evolutionary trinity.

This requires only that a group of hominids found something that made them feel good and pursued it together. The archaeological evidence for pre-linguistic communal behavior, cooperative foraging, group tool-making (Lomekwi, 3.3 Ma; Harmand *et al.*, 2015), and social group structures in A. afarensis, confirms that hominids were capable of this level of social organization before language emerged.

We propose that the social flywheel began here: communal phytocannabinoid use → reduced aggression → stronger social bonds → more cooperative group behavior → better collective survival. Critically, this flywheel had an epigenetic dimension. THC exposure produces heritable DNA methylation changes in both sperm and somatic tissues, affecting genes involved in neurodevelopment, immune regulation, and synaptic plasticity (Szutorisz and Hurd, 2016; Schrott *et al.*, 2020; Murphy *et al.*, 2018). These methylation changes are transgenerational. Offspring of THC-exposed parents inherit altered epigenetic marks at genes including DLGAP2 (a neurodevelopmental gene implicated in autism spectrum phenotypes) without direct exposure themselves (Schrott *et al.*, 2020). Endocannabinoid signaling cascades

mediated via CB1 and CB2 receptors regulate cellular functions through multiple epigenetic modifications including DNA methylation, histone methylation (H3K4me3, H3K9me2), and non-coding RNA networks (Szutorisz and Hurd, 2016). In the context of the pre-linguistic flywheel, communal phytocannabinoid use would not merely produce transient behavioral changes; it would inscribe those changes epigenetically, biasing offspring toward enhanced ECS sensitivity, increased prosocial behavior, and deeper symbiont integration. Each generation of communal cannabinoid use ratcheted the epigenetic baseline, reinforcing the social structure that produced it.

This established the social leg of the trinity before the salinity oscillations deepened the symbiont relationship and before language accelerated the entire system. Two of the three legs, 1) the fungal symbiont (present as a commensal), and 2) the social structure (initiated and epigenetically reinforced by the cannabinoid flywheel), were in place before the environmental driver activated the full program.

3.3 Continuity Through the Salinity Period

Once the salinity oscillations (discussed in depth in Section 6) began deepening the symbiont's integration (~2.7 Ma onward), the social flywheel did not stop; it accelerated. The same plant that had promoted peaceful communality now also served a pharmacological function: supporting individuals undergoing the physiological stress of SIADH-type events, easing the transitional stages between phases of the symbiont's program, and enhancing the cognitive clarity windows that would eventually become transmissible with the emergence of language. The flywheel spans the entire timeline, from pre-linguistic social bonding through the full activation of the trinity and into the Neolithic cultivation period.

Once the salinity oscillations began deepening the symbiont's integration (~2.7 Ma onward), the social flywheel did not stop. It accelerated. The same plant that had promoted peaceful communality before the oscillations now served a second, more specific function: pharmacological maintenance of the ECS tone the program required.

The program described in Sections 4 and 9 places sustained demands on the host's endocannabinoid system. The organism manages host physiology through the ECS interface. During active phases of the program, particularly the transition periods between metabolic states, the organism's signaling load on the ECS increases. The host experiences this increased load subjectively: as pain, nausea, cognitive disruption, appetite dysregulation, and sleep disturbance. Exogenous CB1 agonism through phytocannabinoid consumption directly supplements the ECS tone the organism is drawing on. The host does not need to understand the mechanism. The host needs only to notice that this particular plant reliably makes the bad phases easier to endure. The behavioral loop closes without comprehension: organism increases ECS demand, host feels worse, host consumes the plant, ECS tone rises, organism's signaling environment stabilizes, host feels better, association reinforces. Over generations, this loop becomes embedded in the protocol. The elder who has survived the process instructs the younger member: when the pain comes, use this. Not because the elder understands CB1 agonism. Because the ones who used it survived, and the ones who did not are dead. [Thus, I have a Medical Marijuana License and think big Pharma sees the problem it represents, but it is shadowed by *C. albicans*]

This reframes the role of cannabis within the evolutionary trinity. Before the oscillations, it was a social bonding agent: communal consumption promoting cooperation, reducing aggression, inscribing epigenetic changes that biased offspring toward enhanced ECS sensitivity (Section 3.2). During the oscillations, it became a medical substrate: a pharmacological

component of the program itself, as necessary to the process as dietary salt or caloric intake during specific phases. The distinction matters. A social bonding agent is optional. A medical substrate is not. A group whose members are undergoing a physiological transformation that produces pain, cognitive disruption, and metabolic crisis cannot afford to lose access to the one exogenous compound that reliably stabilizes the system managing the transformation. This is not recreational use. This is pharmacological dependence driven by co-evolutionary necessity. At some point, they discovered it. Eventually, they required it by design. It was built into the system.

The elder's protocol, described in Section 8, would therefore have included cannabis administration alongside dietary and behavioral instructions. Eat when the pain comes. Lie down when the pressure builds. Use this plant at this time, in this way. The protocol was indexed to the phases of the process, and the plant's role was phase-specific: during transition periods, it supplemented the ECS tone the organism was consuming for its signaling operations. During stable periods, it maintained baseline function and supported the social cohesion the group required to function collectively. The shaman figure documented in the archaeological record (Section 8.1) is not a mystic. The shaman is the pharmacologist: the group member who manages the timing, dosage, and delivery of the plant that keeps the program running and the group intact.

III.IV Coevolution of Cannabis Under Human Selection

If the culture was built around the plant, they were growing it. If they were growing it, they were selecting it. This constitutes a third co-evolutionary track running in parallel with the biological coevolution between host and symbiont.

Wild *Cannabis sativa* produces relatively low concentrations of THC. The psychoactive potency of modern cultivated cannabis reflects thousands of years of sustained human selection pressure. In the context of the Saline Oscillation Hypothesis, this selection was not recreational preference. It was medical optimization. Cultivators who saved seeds from the plants that produced the strongest program-stabilizing effects were running artificial selection on the plant's cannabinoid production pathway. Plants that produced higher concentrations of CB1 agonists were preferentially propagated. Plants that did not were replaced. Over hundreds of generations of cultivation, the plant was shaped by the same program that shaped the host and the symbiont.

This produces three simultaneous co-evolutionary tracks within the trinity framework:

First, the organism adapting to the host. *C. albicans* refining its signaling architecture, chromatin states, and metabolic programs through the bet hedging mechanism described in Section 5.8, locked in across oscillation cycles through epigenetic memory.

Second, the host adapting to the organism. Selection for institutional compliance (Section 8), the prolactin reset mechanism, and the neurological architecture required to sustain the program, locked in through genetic selection and cultural transmission.

Third, the plant adapting to the partnership. *Cannabis sativa* being shaped by human cultivation to produce increasingly potent CB1 agonism, optimized not for the plant's reproductive fitness but for the host-organism system's pharmacological requirements. This is co-evolution mediated by agriculture: the host selecting the plant that best serves the symbiont's signaling needs.

The archaeological evidence supports early cultivation. Cannabis is among the oldest cultivated plants in the world, with specimens from the Oki Islands of Japan dating to approximately 8000 BCE (Crawford, 2006) and cultivation in East Asia from at least 4000 BCE (Li, 1974; McPartland *et al.*, 2019). The motivation to cultivate a psychoactive plant may have

preceded or paralleled the motivation to cultivate caloric crops (Section 8.2). A group whose survival depends on a pharmacological substrate cannot leave its supply to the foraging range. Cultivation is the institutionalization of supply, and it subjects the plant to the same selection pressure that the oscillation subjects the host and organism to: optimize for the program, or be replaced.

The twentieth-century prohibition of cannabis at the global population scale therefore represents the removal of one vertex of a three-part co-evolutionary system that operated continuously for over a million years. The implications of this removal are beyond the scope of this paper [But I'm still writing]

4. The Saline Oscillation Mechanism

4.1 The Mechanistic Sequence

We propose that the cyclical salinity oscillations in East African Rift Valley drinking water sources activated and progressively deepened the ECS-mediated coevolutionary relationship through the following mechanistic sequence:

Step 1: Saline acclimation. During arid periods, hominid populations drinking from concentrating lakes acclimated physiologically to elevated electrolyte intake, predominantly sodium. Renal sodium handling, blood volume, and osmotic set points adjusted over generations to the higher baseline.

Step 2: Freshwater disruption and SIADH-type events. When humid periods returned and lakes freshened, populations acclimated to saline water experienced rapid electrolyte dilution. This is the physiological equivalent of a modern human drinking distilled water. For a system calibrated to higher electrolyte concentrations, freshwater intake produces dilutional hyponatremia and triggers SIADH-type antidiuretic hormone responses: water retention, reduced urine output, and electrolyte imbalance. The disruption is proportional to the delta between the system's calibrated salinity and actual intake, not to the absolute salinity level.

Step 3: Symbiont advantage. Under conditions of electrolyte stress, a fungal symbiont capable of modulating host perfusion, blood volume, and electrolyte conservation through the ECS gained decisive selective advantage. The host carrying a more integrated *Candida* population, one that could signal through endocannabinoid pathways to manage vasoconstriction, sodium retention, and fluid distribution, survived the freshwater transitions better than hosts without this integration.

At the molecular level, the symbiont's advantage may be mediated through epigenetic modification. Salinity stress in vertebrates produces distinct epigenetic responses: in the half smooth tongue sole (*Cynoglossus semilaevis*), low salinity exposure alters DNA methylation patterns and gene expression of growth-related genes in the liver (Li *et al.*, 2017), and histone modification (H3K4me3) directly regulates dozens of differentially expressed genes under salinity change (Zhang *et al.*, 2022). DNA methylation changes under salinity stress have been shown to regulate osmoregulatory and immune-related genes across both immediate and transgenerational timescales in fish (Metzger and Schulte, 2018). In the context of the Saline Oscillation Hypothesis, *Candida*-mediated ECS signaling during salinity stress episodes could drive methylation changes in host genes governing electrolyte handling, vascular tone, and immune modulation. These changes would persist epigenetically across generations, ratcheting

the coevolutionary relationship deeper with each oscillation cycle without requiring genetic mutation.

Step 4: Behavioral agency. The symbiont, communicating through ECS signaling, drove host behavioral adaptations: fluid withholding to conserve electrolytes, salt-seeking behavior, dietary shifts toward sodium-rich foods, and, critically, sustained long-distance running. The "runner's high" is mediated by endocannabinoid signaling (anandamide and 2-AG), not endorphins as previously assumed (Fuss *et al.*, 2015). In a host with deeper symbiont integration, the ECS response to running would be intensified. Running thus served a dual function: survival strategy (persistence hunting, foraging range expansion, predator avoidance) and pharmacological maintenance of the ECS tone the symbiont requires. The symbiont benefits from the host running because it elevates the same signaling molecules the symbiont uses endogenously.

Step 5: Brain expansion as byproduct. The progressively deeper ECS integration required for perfusion management produced enhanced neuroplasticity, cognitive function, and pain modulation as byproducts. The brain did not expand because of dietary improvement alone; it expanded because the ECS interface, the oldest signaling system in mammalian biology, was being refined by the symbiont's activity across thousands of oscillation cycles. Each cycle ratcheted the coevolutionary relationship deeper, analogous to the punctuated equilibrium model (Eldredge and Gould, 1972).

Step 6: Language acceleration. The combination of enhanced ECS tone, exogenous cannabinoid support (continuing from the pre-linguistic social flywheel), and the cognitive clarity windows during late-stage transition produced the conditions under which proto-language became full language. The elder who could articulate insights became the most valuable group member, and the group that protected its elders received that transmission. Language did not create the trinity. Two legs were already in place, but language completed and massively accelerated the process.

This sequence places the social flywheel's initiation before 3.3 Ma (pre-Lomekwi), the deepening of the symbiont relationship at approximately 2.7–1.9 Ma (the documented salinity oscillation window), and the full trinity (symbiont, host physiology, language-enabled social structure with cannabinoid support) all operational by approximately 1.55 Ma, consistent with the fossil evidence of H. erectus displaying Broca's area asymmetry, cooperative hunting, long-distance running capability, and the first dispersal out of Africa.

4.2 Evidence for Sodium-Dependent Physiological Architecture

The longitudinal case study documented in Craddock (2013, 2022, 2026c) provides observational evidence that the symbiont's program is critically dependent on electrolyte and caloric homeostasis:

Sodium cravings intensify during active phases of the condition, consistent with the body demanding substrate for perfusion maintenance

Sugar cravings dominated earlier phases of the condition (pre-2014), consistent with the symbiont driving caloric intake during active growth and maintenance stages; these shifted to predominantly salt cravings as the program progressed to perfusion-dependent stages

Peripheral vasoconstriction (cold extremities) occurs when sodium and volume are insufficient, centralizing blood flow to maintain core organ perfusion

The original subjects in the historical cohort (described in the redacted source article) withheld urination during final phases specifically to conserve electrolytes. This is the same

strategy as dietary sodium loading, targeting the same problem: maintaining the osmotic gradient that keeps fluid intravascular

Dietary salt intake directly affects symptom severity, pain levels, and peripheral perfusion quality. The electrolyte-dependent architecture described above also renders the system vulnerable to iatrogenic disruption through pharmacological agents that alter the metabolic behavior of the resident fungal population. Section 5.1 documents two such events in the longitudinal case study involving phenobarbital exposure, which induces CYP450 enzymes shared between the host and *C. albicans*, possibly triggering a metabolic fuel switch from glucose harvesting to host tissue invasion or other perturbations to metabolic pathways. The sensitivity of the symbiont's program to pharmacological perturbation is itself evidence that the program exists; a passive commensal would not produce acute, dose-dependent tissue damage in response to a sedative.

4.3 The Vascular Mechanics of the Perfusion System

The *Mammalia candidus* framework (Craddock, Pan-Mammalian) and the longitudinal case study (Craddock, 2022 log; Craddock, Redacted Science) describe a cardiac mechanism in which the right atrium generates suction during diastolic expansion, contributing to pituitary perfusion via a negative-pressure gradient. This suction mechanism operates in concert with additional vascular dynamics:

The inferior vena cava (IVC), returning blood from the lower body to the right atrium, can become constricted, whether through external compression, reduced blood volume, symbiont-mediated vascular tone changes, or alterations in heart rhythm that modify the diastolic suction cycle. Changes in cardiac rhythm, mediated through ECS signaling on the conduction system, alter the timing and magnitude of atrial expansion, directly governing how much negative pressure is generated to draw blood through the IVC. The symbiont thus manages not only vascular tone but the suction pump itself. IVC constriction reduces venous return from the lower body, creating a pressure differential. Because cardiac output must equalize across all outlets (the heart cannot selectively pump more to one circuit), any obstruction or backup in the lower-body venous return creates a compensatory increase in flow velocity through the unobstructed path: the cerebral vasculature. This is a straightforward application of conservation of flow in a closed hydraulic system. Reduced IVC return increases the relative perfusion of the brain, where no equivalent obstruction exists.

The reversed pressure differential across the kidney, documented in the longitudinal case study as the mechanism by which the host maintained renal function for over 30 years despite progressive kidney compromise, operates within this same system. Reduced IVC flow alters the pressure gradient across the renal vasculature, and the symbiont's ECS-mediated control of vascular tone allows selective management of which organs receive preferential perfusion at any given time.

The complete system (cardiac suction, IVC dynamics, renal pressure reversal, selective perfusion management, and electrolyte conservation) constitutes a unified architecture. It does not require any novel cardiac anatomy; it operates on standard mammalian cardiovascular hardware. What distinguishes *Homo candidus* is not different equipment but different management of the equipment, directed by the symbiont through the ECS.

The survivability implications of this altered perfusion system are substantial. Preferential cerebral perfusion produces increased mental focus and sustained cognitive performance under conditions that would impair an unmanaged host. The ability to maintain

consciousness and function through events analogous to pseudo-Addisonian crisis, or other acute adrenal insufficiency episodes that would cause syncope in a standard host, represents a significant survival advantage in an environment requiring sustained vigilance against predators and competitors. Enhanced pain tolerance, mediated through both the ECS and the altered perfusion dynamics, permits continued physical activity through injuries and transitional discomfort. Increased endurance, supported by the same ECS tone that maintains perfusion, extends foraging range, persistence hunting capability, and migratory capacity. The altered immune state, with enhanced phagocytic activity under symbiont management, reduces susceptibility to bacterial infections. Collectively, these traits (mental focus, crisis tolerance, pain suppression, endurance, and immune enhancement) increase individual survivability and group competitiveness during periods between transitions.

In computational terms, the symbiont functions as a co-processor. A standard mammalian host has one regulatory system, the autonomic nervous system, managing cardiovascular, immune, and metabolic functions. *Homo candidus* has two: the autonomic system and the symbiont's ECS-mediated signaling, both operating on the same physiological hardware simultaneously. This dual-controller architecture produces measurably superior regulatory performance. The longitudinal case study (Craddock, Redacted Science) documents one expression of this: during standardized workplace fitness testing, the subject recorded the fastest heart rate recovery time to baseline in the tested population, a metric that directly reflects the efficiency of cardiovascular regulation during the transition from exertion to rest. The simplest explanation is that two regulatory systems managing the return to homeostasis outperform one. This co-processor model also explains the enhanced crisis tolerance: during an acute physiological stress event, the autonomic system may be overwhelmed, but the symbiont's parallel ECS signaling continues to manage perfusion and vascular tone, preventing the loss of consciousness that would occur in a single-controller system.

The system also introduces vulnerabilities. Puncture wounds and lacerations carry elevated risk because the altered vascular dynamics and reduced blood volume leave less margin for hemorrhage. However, progressive cellular apoptosis and tissue tightening, documented in the redacted source article and in the longitudinal case study (Craddock, Redacted Science), produce noticeably strengthened and toughened skin, partially offsetting this vulnerability. During certain phases prior to full apoptotic skin toughening, altered skin permeability creates sensitivity to osmotic and chemical exposure; the longitudinal case study documents adverse reactions to pool water contact during early phases when permeability remains elevated (Craddock, Redacted Science).

Transitional periods between phases and the final stage of the program produce a spectrum of pain that is among the most significant vulnerabilities of the *Homo candidus* phenotype. The longitudinal case study documents pain presentations ranging from burning skin, to deep muscular pain, to organ-specific pain (liver, kidney, pancreas), to pain localized in the nail beds of fingers and toes (Craddock, Redacted Science). Pain severity fluctuates with the phase of the program and can reach levels that temporarily prevent normal function. Nausea accompanies transitions and a brief period of the final phase, further reducing functional capacity during these windows. Hunger is nearly constant throughout the program. The metabolic demands of the symbiont's activity and the host's altered energy production require sustained caloric and electrolyte intake; however, during transitions, appetite suppression from nausea creates a dangerous conflict between metabolic need and the inability to eat. The longitudinal case study documents the necessity of external encouragement to eat during these periods

(Craddock, Redacted Science). In a pre-modern social group, this maps directly onto a caregiving function: members of the group actively feeding and encouraging the transitioning individual, a behavior that would emerge naturally in a group already bonded through communal phytocannabinoid use and reinforced by the value the elder produces during clarity windows.

The symbiont's program thus presents an evolutionary trade-off: enhanced capability between transitions, increased vulnerability during them. The social structure of the trinity, the group protecting and feeding the individual during vulnerable phases, exists precisely to manage this trade-off. The redaction of the original research that first documented this architecture, treatment, and medical condition represents suppression. This suppression concerns not just a clinical curiosity, but knowledge concerning a human phenotype that may have been foundational to the development of civilization itself. Even without those implications, the loss to science has caused a multi-generation loss of scientific exploration into fungal research, and billions of dollars spent developing treatments that may ultimately be traced to systems defined herein. Such a decision is scientifically unforgivable and should be investigated. Ultimately, whoever is responsible should have their authority brought into question. This author has seen the original science. It exists.

4.4 Dietary Generalism as Selection Criterion

Paranthropus boisei, recovered from Olduvai Gorge near Lake Natron (~1.75 Ma; Leakey, 1959), specialized in consuming tough, fibrous grasses and seeds, a closed dietary strategy. The Homo lineage, by contrast, maintained dietary generalism, consuming varied foods including meat, which requires cooperative hunting and broader ecological engagement (Turkana Basin Institute, 2021).

We propose that the symbiont selected for the open architectural platform. A dietary specialist offers a fixed nutritional environment; a generalist offers a variable one. A variable internal metabolic environment gives the symbiont more biochemical options for its ECS-mediated program. The Homo line's flexibility, via metabolic, behavioral, and social pathways, made it the superior host. Paranthropus rigidified and went extinct. Homo stayed open and deepened the partnership.

5. Beyond Opportunistic Pathogen: Cross-Kingdom Chemical Authority

5.1 Reframing the Organism

Candida albicans is conventionally classified as an "opportunistic pathogen," an organism that causes harm when the host's defenses are compromised. This framing has shaped nearly all research into *Candida* biology for over a century. It is not wrong in a narrow sense: *C. albicans* can and does cause disease in immunocompromised individuals. But the classification obscures more than it reveals.

We argue that *Candida albicans* represents a uniquely integrative adaptive system within the current conceptual framework of host-associated microbiology, warranting reclassification of its functional role in human biology.

C. albicans is an obligate commensal with no known environmental reservoir, transmitted vertically from mother to child (Kumamoto, 2011; Ost and Round, 2023). It colonizes the gastrointestinal tract of 40–60% of healthy humans (Romo and Kumamoto, 2020);

a threshold figure – see Section 5.7 for discussion of colonization prevalence versus detection sensitivity. Recent work has demonstrated that *C. albicans* colonization confers measurable benefits to the host, including calibration of systemic Th17 immunity, protection against bacterial pathogens including Clostridioides difficile, and modulation of gut metabolic homeostasis (Peroumal *et al.*, 2022; Shao *et al.*, 2019). Alonso-Monge *et al.* (2021) describe colonization as a "double-edged sword," a framing that itself acknowledges the organism provides benefit alongside risk. A purely pathogenic organism would not require the qualifier.

We characterize this operational capacity as a biochemical computer (Craddock, Biochemical Computer): an organism that does not respond to environmental challenges through a single adaptive pathway but maintains a continuously running portfolio of regulatory programs, distributed across its population, drawing on confirmed molecular interactions with host receptors, competing microorganisms, and its own epigenetic architecture to recalculate its next operational state in a tenure-maximizing adaptive process. The term is not metaphorical. It describes the functional output of the signaling, sensing, and adaptive capabilities documented in the sections that follow.

Real-World Implications: Iatrogenic Symbiont Activation

The consequences of misunderstanding *C. albicans* as a simple pathogen are not theoretical. They are clinical and documented.

Phenobarbital, a barbiturate sedative introduced in 1911, is a potent inducer of Cytochrome P450 (CYP450) enzymes in mammalian liver tissue. *C. albicans* possesses its own functional CYP450 enzyme system, including CYP51 (lanosterol 14α-demethylase, essential for ergosterol biosynthesis), CYP52 (fatty acid and alkane metabolism), and CYP56 (cell wall integrity). These fungal CYP450 enzymes share sufficient structural and functional homology with their mammalian counterparts that phenobarbital-induced enzyme upregulation is not confined to the host. It extends to the resident fungal population.

The theoretical consequence is a metabolic fuel switch. Under normal commensal conditions, *C. albicans* in the gastrointestinal tract harvests dietary glucose from the lumen. When CYP450 induction by phenobarbital upregulates the CYP52 family, which handles lipid and fatty acid metabolism, the organism gains enhanced capacity to process host-derived lipids and proteins. This metabolic shift is linked to morphological transition: the switch from yeast form (commensal, lumen-dwelling) to hyphal form (tissue-invasive, secreting aspartyl proteases and phospholipases to digest the protective mucin layer and penetrate epithelial tissue). The drug does not cause infection. It changes the operating instructions of an organism that is already present everywhere.

The longitudinal case study (Craddock, 2013; Craddock, Redacted Science) documents three such activation events in a single subject:

At age 14, a single recreational dose of phenobarbital was followed within 12 hours by emergency appendectomy. The surgeon reported the appendix was completely ulcerated. The subject was hospitalized for five days as physicians could not explain the failure to respond to antibiotics, consistent with a fungal rather than bacterial etiology.

At age 26, a prescription for Donnatal (a combination drug containing a small amount of phenobarbital) for gastrointestinal symptoms produced, over several days, diffuse ulceration across the entire gastric mucosa. Endoscopy revealed small ulcerations covering 100% of the stomach lining. The gastroenterologist described it as "the stomach of a 70-year-old." The subject was 26. The uniform distribution of ulceration across the full mucosal surface is

consistent with simultaneous activation of a commensal population distributed throughout the stomach, not with focal infection or drug-induced erosion.

The acute dose-response relationship was further demonstrated when the subject, prior to a scheduled endoscopy and in significant pain, ingested several Donnatal tablets simultaneously seeking relief. Within thirty minutes, the subject experienced severe abdominal pain and passed an acholic (white) bowel movement. The endoscopy that had already been scheduled subsequently revealed white lesions covering the entire gastric mucosa. The temporal relationship between a bolus dose of phenobarbital, acute GI distress, and passage of visibly abnormal material is consistent with rapid, dose-dependent activation of the resident fungal population. The subject did not connect the Donnatal to the phenobarbital exposure from adolescence until a subsequent ER visit, where a GI cocktail containing phenobarbital produced immediate symptom escalation.

The subject did not connect the two events until a subsequent accidental re-exposure to phenobarbital (contained in an emergency room medication) produced immediate symptom escalation. Subsequent research at a medical library identified multiple published case reports of phenobarbital-associated mucosal ulceration at variable anatomical locations, with resolution upon drug withdrawal. This pattern is consistent with iatrogenic symbiont activation rather than direct drug toxicity.

Published case reports document severe mucosal ulceration following phenobarbital exposure at variable anatomical locations across patients: stomach in some, small intestine in others, colon in others (reviewed in drug-induced gastrointestinal disease literature). Phenobarbital-containing combination drugs carry prescribing labels that contraindicate use in patients with severe ulcerative colitis, gastric ulcer, and obstructive disease of the gastrointestinal tract, and warn that “diarrhea may be an early symptom of incomplete intestinal obstruction” (DailyMed, Belladonna/Phenobarbital). The labels acknowledge the gastrointestinal risk without identifying the mechanism. Notably, prescribing labels manage this risk through contraindication rather than explanation, advising against use in patients with pre-existing gastrointestinal conditions without identifying the mechanism by which the drug interacts with the gastrointestinal environment. The variable geography across patients is inconsistent with a direct drug toxicity mechanism, which would produce anatomically consistent damage. It is, however, consistent with activation of a distributed commensal population whose density varies by individual and by anatomical segment. The same chemical signal, received simultaneously by a geographically variable colony, produces damage wherever the colony is densest. The drug is the broadcast. The colony location determines the impact site.

What follows in this section reframes *C. albicans* not as a pathogen that occasionally behaves commensally, but as a systems-level coordinator of the mammalian internal ecology, an organism whose confirmed molecular capabilities position it as the emergent ecological regulatory influence via evolutionary selection, signaling authority within the host microbiome. The evidence presented is drawn entirely from peer-reviewed literature. What is novel is the assembly.

5.2 The Scope of the Signaling Network

Candida produces and secretes a library of bioactive metabolites numbering in the low hundreds based on current metabolomic profiling. Comprehensive two-dimensional gas chromatography has identified 126 volatile metabolites from *C. albicans* alone, distributed across acids, alcohols, aldehydes, hydrocarbons, esters, ketones, terpenic compounds, phenols, and sulphur compounds, representing a 70% increase over previously reported metabolites for the species (Perestrelo *et al.*, 2020). Multi-omics studies using high-resolution mass spectrometry have identified 192 metabolites under controlled conditions (Gómez-Gaviria *et al.*, 2023). These numbers represent what has been detected *in vitro*. The metabolite profile of *C. albicans* living inside a mammalian host, responding to host signals, immune pressure, variable nutrient availability, oxygen gradients, pH shifts, and co-resident microbiota, remains largely uncharacterized.

The primary signaling molecule characterized to date is farnesol (E,E-3,7,11-trimethyl-2,6,10-dodecatrien-1-ol), a sesquiterpene alcohol first identified as a eukaryotic quorum-sensing molecule in *C. albicans* by Hornby *et al.* (2001). Farnesol was the first quorum-sensing molecule discovered in any eukaryotic organism. Its effects, however, are not confined to intraspecific communication. Farnesol exerts confirmed, dose-dependent biological activity across three kingdoms of life: Fungi, Bacteria, and Animalia.

5.3 Fungal-to-Fungal Signaling

Farnesol produced by *C. albicans* inhibits growth and induces apoptosis in Aspergillus nidulans through a mechanism dependent on G-protein signaling, affecting mitochondrial

function and reactive oxygen species production (Semighini *et al.*, 2006). The compound inhibits cell wall integrity signaling in *Aspergillus fumigatus* (Dichtl *et al.*, 2010) and is cytotoxic to *Saccharomyces cerevisiae*, Penicillium expansum, and Botrytis cinerea (Egbe *et al.*, 2017). These effects require no physical contact between organisms. They are mediated entirely through extracellular chemical signaling. *Candida* does not consume or parasitize these competing fungi. It suppresses them chemically while occupying the same ecological niche.

5.4 Fungal-to-Bacterial Signaling

The cross-kingdom reach of *Candida*'s signaling extends to prokaryotes. Farnesol reduces the Pseudomonas aeruginosa quinolone signal (PQS) and its downstream virulence factor pyocyanin by approximately 72%, an effect replicated when P. aeruginosa is co-cultured with farnesol-producing *C. albicans* (Cugini *et al.*, 2007). In mixed-species biofilms of *C. albicans* and Staphylococcus aureus, farnesol induces reactive oxygen species in the bacterium, upregulating drug efflux pumps that alter the bacterium's antibiotic susceptibility profile and effectively sensitizing S. aureus to antimicrobial compounds (Kong *et al.*, 2017). These interactions are bidirectional: bacterial quorum-sensing molecules including P. aeruginosa-produced 3-oxo-C12-homoserine lactone suppress *C. albicans* filamentation at concentrations achieved in mixed-species biofilms (Hogan *et al.*, 2004). The chemical negotiation is continuous and mutual, but *C. albicans* is the only participant that simultaneously signals to bacteria, to competing fungi, and, as described below, to the mammalian host.

The cross-kingdom chemical reach described above operates primarily through small lipid-soluble molecules. A distinct but complementary modality, peptide mimicry, has been

documented in other fungal systems and establishes the biological plausibility of peptide-based cross-kingdom manipulation in *C. albicans*.

The pathogenic yeast Blastomyces dermatitidis produces dipeptidyl-peptidase IVA (DppIVA), a close functional mimic of the mammalian ectopeptidase CD26. Like its mammalian counterpart, fungal DppIVA cleaves CC chemokines and GM-CSF, crippling monocyte recruitment, blocking phagocyte activation, and preventing reactive oxygen species production. Silencing the DppIVA gene restored immune function and curtailed virulence; addition of recombinant DppIVA to gene-silenced yeast restored immune evasion (Sterkel *et al.*, 2016). This is the cleanest published demonstration that a fungal pathogen can produce a mammalian-mimicking peptidase as a deliberate immune manipulation tool.

In plant-fungal systems, cross-kingdom peptide mimicry is well-established. Fusarium oxysporum produces RALF-like peptides that are structurally identical to host plant signaling peptides and are recognized by plant receptors as genuine signals, activating nutrient uptake and immunomodulatory pathways (Masachis *et al.*, 2016). A 2025 study in Ustilago maydis, the corn smut fungus, revealed a co-evolved peptide-GPCR sensing mechanism: the fungus secretes the protein Pit2, which is cleaved by host apoplastic proteases, releasing a peptide ligand that activates the fungus's own GPCR (Gpe1), signaling that host entry has occurred and promoting fungal proliferation (Krombach *et al.*, 2025, bioRxiv). This represents a fungal organism using host enzyme activity as an environmental signal through a peptide intermediary.

Three independent examples across three fungal species and both plant and animal hosts establish that cross-kingdom peptide signaling is not hypothetical in fungal biology. *C. albicans*, with approximately 200 million years of mammalian coevolution, 1,300 or more uncharacterized genes with no orthologs in other yeast species, and a confirmed peptide-processing machinery homologous to the mammalian prohormone convertase system, would be the anomaly if it were not engaging in peptide-based host manipulation. The question is not whether it does so, but through which of its uncharacterized genes and through which host receptors.

5.5 Fungal-to-Host Signaling: The Expanded Control Surface

The preceding sections of this paper describe the symbiont's interaction with the host primarily through the endocannabinoid system (ECS), with CB1 and CB2 receptors serving as the best-characterized interface layer for host–symbiont signaling integration. This remains the most extensively documented pathway of lipid-mediated physiological coupling. However, the ECS does not represent an isolated signaling module. It is one branch of a broader lipid-derived regulatory architecture rooted in shared membrane biochemistry.

Arachidonic acid, an omega-6 polyunsaturated fatty acid embedded in membrane phospholipids, serves as a central precursor for both endocannabinoid synthesis and the prostaglandin/eicosanoid signaling pathways. The primary endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), are generated from arachidonic-acid-containing phospholipid substrates, while prostaglandins arise from free arachidonic acid released from the same membrane reservoir through phospholipase-mediated cleavage. These pathways are not merely parallel outputs of a common precursor pool; they exhibit enzymatic and metabolic convergence. Cyclooxygenase-2 can directly oxygenate endocannabinoid intermediates, while endocannabinoid degradation regenerates arachidonic acid available for diversion into eicosanoid production. The ECS and prostaglandin systems therefore operate as partially coupled expressions of a shared lipid signaling economy.

Within this biochemical context, receptor-level signaling reflects underlying substrate-level coupling. CB1 and CB2 receptors are members of the larger G-protein-coupled receptor (GPCR) superfamily, comprising approximately 800 receptors encoded in the human genome and representing over 3% of all protein-coding genes (Fredriksson *et al.*, 2003). Structural conservation across this receptor family implies that lipid-soluble ligands capable of engaging cannabinoid receptors may exhibit varying degrees of affinity across related GPCR targets. The ECS may therefore represent an early and well-characterized interface within a broader receptor landscape shaped by shared membrane-derived signaling substrates.

The ECS may be the original handshake between symbiont and host, but once an organism is producing lipid-soluble compounds that can dock with the seven-transmembrane architecture, the entire GPCR family becomes potentially accessible. The signaling capacity did not remain confined to two receptors across 200 million years of coevolution, producing the ultimate survivor — a biochemical computer (Craddock, Biochemical Computer) continuously recalculating what moves might be required next. Instead, signaling capacity grew outward from the same structural foundation. CB1 and CB2 are the trunk. The broader receptor landscape is the canopy.

The rapidity with which complex multiscale networks emerge under reciprocal selection is illustrated by laboratory bacteria-phage coevolution experiments. Borin *et al.* (2023) showed that E. coli and bacteriophage Φ21, starting from isogenic populations in simple well-mixed cultures, diversified into elaborate nested-modular cross-infection networks in only 21 days. "We show that multiscale network structure can evolve rapidly under simple ecological conditions without spatial structure […] the process of coevolution itself is sufficient to drive the rapid emergence of complex multiscale networks." The Plio-Pleistocene salinity oscillations in the East African Rift Valley imposed repeated, rapid environmental flips on the *Candida*–hominid partnership, providing thousands of such serial-passage cycles in which the same simple adaptive rules — nutrient sensing, perfusion management, immune modulation — could refine the symbiont's distributed biochemical computer into the full *Homo candidus* phenotype.

From an evolutionary systems perspective, the lipid signaling architecture is less accurately conceptualized as a linear pathway than as a branching network emerging from common biochemical roots. In this framework, the ECS functions as a central trunk, while prostaglandin-mediated inflammatory and vascular signaling represents a parallel branch derived from the same membrane substrate economy. The expansion of signaling capacity across this receptor landscape reflects the progressive elaboration of lipid-mediated regulatory mechanisms over evolutionary time growing outward from the same structural roots.

Farnesol alone, one compound from a library of hundreds, has been shown to interact with multiple classes of host receptor and signaling systems beyond the ECS:

Nuclear receptors. In 1995, Forman *et al.* identified a mammalian orphan nuclear receptor activated by farnesol metabolites, subsequently named the farnesoid X receptor (FXR). FXR directly regulates gene transcription governing bile acid metabolism, lipid homeostasis, glucose metabolism, and hepatic function. Farnesol also activates peroxisome proliferator-activated receptors (PPARs), nuclear receptors that regulate lipid metabolism, inflammation, and cellular differentiation. These are not membrane-level signals. They represent direct access to the host's transcriptional machinery.

Ion channels. Farnesol was identified by Roullet *et al.* (1999) as an endogenous inhibitor of N-type voltage-gated Ca^{2+} channels in mammalian cells. Calcium signaling is foundational to virtually every cellular process, including cardiac conduction, a point of direct relevance to the

cardiac architecture hypothesis described in Section 7. Farnesol is present in the human brain at measurable concentrations of 110–290 pmol/g (Roullet *et al.*, 1999).

Neurotransmitter receptors. Gc *et al.* (2023) demonstrated that farnesol acts as a positive allosteric modulator of γ-aminobutyric acid type A receptors (GABA-A), binding to the transmembrane neurosteroid site through a lipid pathway. GABA-A receptors mediate the primary inhibitory neurotransmission in the mammalian central nervous system and are the targets of benzodiazepines, barbiturates, and alcohol. This finding establishes a direct molecular pathway between a *Candida*-produced metabolite and the modulation of host consciousness, anxiety, and neurological function.

The incretin system. The GLP-1 receptor, a GPCR in the Secretin family, co-evolved alongside the ECS and demonstrates confirmed crosstalk with cannabinoid signaling pathways. Peroumal *et al.* (2022) demonstrated that *C. albicans* colonization of the murine gut measurably alters levels of GLP-1, GIP, insulin, and other metabolic hormones. The GLP-1 receptor is the target of the semaglutide and tirzepatide drug classes currently prescribed to tens of millions of patients for metabolic disease, generating hundreds of billions of dollars in market value. No published study has investigated what chronic GLP-1 receptor agonism does to the fungal symbiont ecology or how the symbiont adapts its signaling in response. This represents an intervention in an unmapped system, modulating a receptor whose relationship to the resident fungal ecology has never been characterized.

Immune modulation. Farnesol induces apoptosis in macrophages (Navarathna DH, Nickerson KW, *et al.* (2007)). Tyrosol, a second *C. albicans* quorum-sensing molecule, inhibits neutrophil reactive oxygen species production, disabling the oxidative burst that constitutes the primary fungicidal mechanism of these immune cells (Joo *et al.*, 2010). Farnesol significantly impairs the differentiation of monocytes into dendritic cells, downregulating surface markers critical for antigen presentation including CD1a, CD83, CD86, and dectin-1, the primary β-glucan recognition receptor (Leonhardt *et al.*, 2015). Dendritic cells generated in the presence of farnesol fail to induce proper T-cell responses and do not secrete the Th1-promoting cytokine IL-12. Critically, farnesol simultaneously activates innate immune markers on monocytes and neutrophils without enhancing actual fungal uptake or killing (Leonhardt *et al.*, 2015). The immune system appears active. It does not clear the organism.

The immune-gut-brain axis. Current research positions farnesol as a messenger in the immune-gut-brain axis (Gates *et al.*, 2026). In murine models of central nervous system inflammation, farnesol at doses of approximately 100 mg/kg demonstrated protective effects by reducing oxidative stress and proinflammatory cytokines. Farnesol upregulates TLR2 and downregulates TLR4 and TLR6 expression in oral epithelial cells exposed to *C. albicans*, modulating the primary molecular defense mechanisms at the epithelial barrier (Décanis *et al.*, 2009). The molecular targets of farnesol, specifically FXR and voltage-gated calcium channels, are both intimately involved in immune homeostasis, positioning farnesol as a plausible metabolic mediator of crosstalk among brain cells, immune cells, intestinal barrier cells, and intestinal microbes (Gates *et al.*, 2026).

The cholinergic system. Acetylcholine (ACh), the primary neurotransmitter of the parasympathetic nervous system and the vagus nerve, represents another confirmed signaling interface between *C. albicans* and the mammalian host. Unlike the farnesol-mediated interactions described above, where the organism produces a compound that acts on host receptors, the cholinergic interface is bidirectional: the host signals to the organism, and the organism's presence alters host cholinergic signaling.

C. albicans possesses a functional cholinergic receptor. The general muscarinic receptor agonist pilocarpine hydrochloride inhibits *C. albicans* biofilm formation and pathogenicity, a phenomenon reversed by the muscarinic antagonist scopolamine (Nile *et al.*, 2018). Acetylcholine itself inhibits *C. albicans* biofilm formation both *in vitro* and *in vivo*, while also modulating the yeast-to-hyphal morphological transition in a context-dependent manner (Rajendran *et al.*, 2015; A & Sm, 2018). This is the first confirmed instance of *C. albicans* possessing a receptor for a host neurotransmitter, in contrast to farnesol, where no receptor has been identified in the organism despite extensive searching.

The interaction extends beyond receptor signaling to metabolic interdependence. Acetylcholine is essential for the formation of the chitin wall characteristic of fungi, and *Candida* species contribute to host acquisition of choline, the precursor to acetylcholine synthesis (Chen *et al.*, 2022). The organism is not merely sensing the host's cholinergic signaling; it is a participant in the host's choline economy, both consuming choline for its own structural needs and contributing to the host's choline pool.

The implications for host physiology are direct. The cholinergic anti-inflammatory pathway, a primary mechanism by which the host regulates immune responses, is mediated by acetylcholine released from efferent vagus nerve terminals. This acetylcholine interacts with the alpha-7 nicotinic receptor (α7nAChR) on proximal immune cells to downregulate localized inflammation (Rajendran *et al.*, 2015). *C. albicans* infection in murine models significantly elevates acetylcholine levels in both brain and kidney tissue (2019 pyrimidine derivatives study). An organism with a functional cholinergic receptor, residing in the gut (the primary innervation territory of the vagus nerve), that also modulates host acetylcholine levels and participates in choline metabolism, has direct access to the parasympathetic nervous system and the vagal anti-inflammatory pathway.

The longitudinal case study (Craddock, Redacted Science) documents two distinct periods of choline-related supplementation spanning the full duration of the condition. Over approximately two decades, the subject regularly consumed a choline-containing liver support supplement (LiverAid), initially motivated by concern for hepatic health given the metabolic stresses documented throughout the case, including ketoconazole-induced liver symptoms, dark urine, and digestive dysfunction. The subject came to recognize over time that the supplement functioned as a treatment, producing consistent relief of systemic tension and general symptom modulation, though the mechanism was not understood at the time.

In a much later stage of the condition, for a period of weeks in 2025, the subject experienced a distinct peripheral neurological symptom described as a vibrating sensation in the extremities, consistent in character with the pseudo-Addisonian crisis documented in 2018, though far lower in intensity. Direct choline supplementation via liquid drops resolved the vibrating sensation within seconds of administration. This temporal profile is not consistent with correction of a nutritional deficiency, which would require days to weeks. It is consistent with rapid restoration of cholinergic signaling in a system where the symbiont's metabolic demands on the shared choline pool produce a functional deficit in host acetylcholine availability. When the substrate is replenished, the signaling normalizes immediately.

Both observations are from a single subject and are anecdotal. They are, however, internally consistent with each other across a span of decades, and consistent with the documented role of *Candida* in host choline metabolism and the confirmed bidirectional cholinergic interface described above.

Anticancer selectivity. Farnesol induces apoptosis in various cancer cell lines, including lung, oral, and tongue carcinoma, by causing endoplasmic reticulum stress and mitochondrial dysfunction (Joo *et al.*, 2009). Tumor cells are considerably more sensitive to farnesol-induced growth inhibition than normal cells; human primary T lymphocytes and monocytes are relatively resistant to the concentrations that kill leukemic cells. At supraphysiological concentrations, farnesol acts as a surfactant that accumulates in cell membranes, causing ion leakage and cell death. The preferential sensitivity of cancer cells, which carry defective signaling pathways secondary to genetic and epigenetic alterations, suggests that farnesol exploits the same pathway disruptions that make cancer cells malignant. An organism producing a compound that selectively eliminates cells with aberrant signaling while sparing cells with intact pathways is, in effect, performing quality control on host tissue.

5.5a The Peptide Signaling Layer: A Second Cross-Kingdom Channel

The signaling architecture described in the preceding sections operates primarily through lipid-mediated pathways: farnesol and the sesquiterpene library interact with GPCRs, nuclear receptors, ion channels, and neurotransmitter receptors through lipophilic docking. The endocannabinoid system itself is a lipid-signaling network. This lipid channel is the trunk of the signaling architecture, and we have argued it was the original handshake between symbiont and host. However, *C. albicans* also produces, processes, and imports peptides through a machinery that is not merely analogous to the mammalian peptide-processing system but directly homologous to it. This peptide layer constitutes a second, parallel cross-kingdom signaling channel, operating through different molecular classes, different receptor targets, and different functional logic than the lipid channel, but running on shared enzymatic infrastructure that predates the mammalian-fungal divergence.

Shared peptide-processing machinery. *C. albicans* processes its Ece1 polyprotein through the Golgi-associated endoproteinase Kex2p, a member of the subtilisin-family serine protease superfamily. Kex2p cleaves precursor proteins at dibasic lysine-arginine (KR) motifs to release multiple bioactive peptide products. The mammalian prohormone convertases PC1, PC2, and furin, the enzymes responsible for processing neuropeptide precursors, insulin prohormone, and other peptide hormone zymogens, possess catalytic domains directly homologous to Kex2p and were discovered by homology to the yeast enzyme (Richardson *et al.*, 2018; Bader *et al.*, 2008). The processing logic is identical: a precursor protein containing dibasic cleavage sites is proteolytically processed through sequential endoprotease and carboxypeptidase activity to yield mature bioactive peptides. In *C. albicans*, Kex2p performs the endoproteolytic cleavage and Kex1p removes the C-terminal arginine; in mammals, PC1/PC2 perform the analogous endoproteolytic step and carboxypeptidase E removes the C-terminal basic residues (Richardson *et al.*, 2018).

This is not convergent evolution. It is conserved deep ancestry of the peptide-processing pipeline. The fungus and the mammalian host have been producing bioactive peptides through the same enzymatic grammar for the entire duration of their coevolutionary relationship. An organism that already speaks the host's peptide-processing language does not need to evolve novel peptide-production machinery to interact with host peptide signaling. It needs only to evolve the sequences that, when processed through the shared machinery, produce peptides with the desired host-interaction profiles.

The Ece1 peptide panel. Kex2p processing of the 271-amino-acid Ece1 polyprotein produces eight discrete peptides, not one (Moyes *et al.*, 2016; Richardson *et al.*, 2018).

*Candida*lysin (Ece1-III, positions 62–92), a 31-amino-acid cytolytic peptide toxin and the first such toxin identified in any human fungal pathogen (Moyes *et al.*, 2016), has received the majority of research attention. However, the remaining seven Ece1 peptides are co-secreted during hyphal growth and have begun to yield functional data. A 2024 high-throughput yeast two-hybrid interactome screen (Lin *et al.*, 2024) mapped the human protein targets of all eight Ece1 peptides and found that multiple non-candidalysin peptides, particularly Ece1-II and Ece1-V, interact with members of the leukocyte immunoglobulin-like receptor (LILR) family, specifically the inhibitory receptors LILRB1 through LILRB5. These receptors directly suppress immune cell activation. Functional enrichment of the shared interactors of Ece1-II and candidalysin revealed association with cell cycle regulation, Cyclin D-associated events in G1, and immune response-inhibiting cell surface receptor signaling pathways (Lin *et al.*, 2024).

The Ece1 polyprotein is therefore not a toxin delivery system that incidentally produces byproducts. It is a coordinated peptide panel: one peptide for tissue invasion and membrane disruption (candidalysin), others for immune suppression through distinct receptor pathways (the LILR-interacting peptides), and potentially additional undiscovered functions among the remaining peptides. This architecture parallels mammalian prohormone precursors, which routinely produce multiple bioactive peptides with distinct functions from a single gene product (e.g., proopiomelanocortin yielding ACTH, α-MSH, β-endorphin, and β-lipotropin). The parallel is not metaphorical. It runs on the same enzymatic machinery.

This multi-peptide architecture is consistent with the effector hypothesis proposed in Section 5.7. *Candida*lysin is the attention-grabber in pathogenesis research because it produces measurable tissue damage. But the quiet peptides, the ones interacting with immune-inhibitory receptors, may be performing the environmental management work that the effector model predicts: maintaining the conditions under which the symbiont's long-term program operates without triggering the inflammatory cascades that would destabilize the niche. The organism is not simply producing a weapon. It is producing a toolkit, with different peptides deployed for different aspects of host management, processed through the same Kex2p/Kex1p machinery in a single coordinated secretion event.

*Candida*lysin's expanding host target map. Recent work (2024–2025) has revealed that candidalysin's host interactions extend far beyond membrane lysis. The peptide binds glycosaminoglycans (GAGs) on epithelial cell surfaces, which promote its polymerization and facilitate membrane insertion, triggering calcium influx that activates the ESCRT-III membrane repair pathway (Lin and Filler, 2025). Inside the cell, candidalysin binds cyclin H (CCNH), a regulatory subunit of the CDK-activating kinase complex, activating it to inhibit double-strand DNA break repair (Lin *et al.*, 2024). This has direct implications for the epidemiological association between *C. albicans* and oral and colorectal cancers, as CCNH expression is upregulated in gastrointestinal stromal tumors, breast cancer, esophageal squamous cell carcinoma, and brain tumors (Lin *et al.*, 2024). In the lung, candidalysin binds GPIbα, a subunit of the platelet receptor complex, inducing platelet activation and release of Dickkopf-1, which drives Th2 and Th17 immune polarization and reactive airway disease (Wu *et al.*, cited in Lin and Filler, 2025). In epithelial cells, candidalysin induces EGFR ubiquitination and lysosomal degradation through a mechanism involving recruitment of Grb2, AP2M1, and HRS, effectively reprogramming host growth factor receptor trafficking (ASM, 2025).

Each of these interactions is peptide-to-host-receptor, distinct from the lipid-mediated farnesol pathway described in the preceding sections. The organism operates two parallel signaling channels: lipids for broad environmental tone-setting (ECS modulation, nuclear

receptor activation, ion channel modulation, neurotransmitter receptor binding), and peptides for targeted action (tissue remodeling, DNA damage pathway hijacking, immune polarization, growth factor receptor manipulation). Two languages, one architecture.

Peptide transport capacity beyond commensal necessity. *C. albicans* encodes ten dedicated peptide transporters: two members of the PTR family (Ptr2 and Ptr22), which handle dipeptides and tripeptides, and eight members of the OPT family (Opt1 through Opt8), which handle oligopeptides up to at least eight amino acids in length (Dunkel *et al.*, 2013; Reuß and Morschhäuser, 2006). This represents a substantial expansion relative to *Saccharomyces cerevisiae*, which encodes a single PTR family member. The SAP (secreted aspartyl proteinase) family provides the extracellular digestion component: SAPs degrade host proteins in the extracellular space, and the OPT/PTR transporters import the resulting peptide fragments as nitrogen sources. The system constitutes a complete digest-and-import pipeline tuned for operation inside a mammalian host.

Opt1 was found to be remarkably flexible, transporting all tripeptides tested and even a dipeptide, a substrate class never previously attributed to the OPT family (Dunkel *et al.*, 2013). Opt7 specifically transports glutathione (Desai *et al.*, 2011), the host's primary intracellular antioxidant, an import function that represents theft of the host's redox defense molecule rather than nutritional acquisition.

The evolutionary significance lies in what happened when the system was removed. Dunkel *et al.* (2013) constructed a septuple mutant lacking all five major OPT transporters and both PTR transporters. These mutants could not grow on peptides or proteins as sole nitrogen sources. Yet they had no fitness defect in a mouse model of gastrointestinal colonization. The fungus survived on alternative nitrogen sources in the gut. This massive peptide transport apparatus is therefore not essential for commensal survival. It is maintained by selection for a function that gut colonization alone does not require.

Within the coevolutionary framework, this excess capacity has at least two interpretations. First, it supports the later-stage protein substrate utilization described in the fuel priority hierarchy (Craddock, Redacted Science): host amino acids and structural proteins become primary substrates during chronic depletion and terminal phases, and the transport machinery required for that utilization must be maintained even when it is not currently in use. Second, and more speculatively, the peptide importers may function not only as nutrient uptake systems but as environmental sensors, sampling host-derived peptides, including peptide hormones and neuropeptide fragments, as signals indicating host physiological state. An organism with ten dedicated peptide importers, operating in the gut lumen where peptide hormones including GLP-1, CCK, and PYY are actively secreted by enteroendocrine cells, has the molecular hardware to read the host's peptide signaling environment. Whether it does so remains uncharacterized, but the hardware is confirmed.

Neuropeptide–fungal bidirectional signaling. Mammalian neuropeptides, including Substance P, neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and somatostatin, all signal through GPCRs and play dual roles in fungal infection: they possess direct antimicrobial activity against fungi, but some also enhance fungal virulence by promoting adhesion, invasion, and immune evasion (Augustyniak *et al.*, 2021). This bidirectional relationship falls under the emerging discipline of microbial endocrinology, the recognition that microbes do not passively endure host signaling but intercept and exploit it.

The structural overlap between neuropeptides and antimicrobial peptides is striking. Many neuropeptides share amino acid composition, amphipathic design, cationic charge, and size characteristics with classical antimicrobial peptides (Brogden *et al.*, 2005). The host's neuropeptide defense system and the fungus's peptide import and processing apparatus therefore create a bidirectional peptide communication channel that has been under co-selective pressure for the entire span of mammalian evolution. The host fires antimicrobial neuropeptides at the fungus; the fungus imports peptides through its OPT/PTR transporters; the fungus fires back with its own Ece1-derived peptide panel. The ECS model presented in this paper covers the lipid half of this dialogue. The peptide layer is the other half.

A neuroanatomical note connects this to the perfusion architecture described in Section 4.3. The hypothalamus and pituitary stalk are the primary exceptions to the blood-brain barrier; they lack the tight endothelial junctions that exclude blood-borne molecules from brain tissue (Brogden *et al.*, 2005). These are also the brain regions where neuropeptide-mediated immune defense is most critical and where neuropeptide Y-producing cells are concentrated in the olfactory system and other barrier zones (El Karim *et al.*, 2008). If the symbiont is managing pituitary perfusion through the suction mechanism described in this paper, it is operating in the precise anatomical zone where peptide-based host defense and fungal peptide signaling would intersect most directly. The hypothalamic-pituitary axis is not only the perfusion target; it is the peptide-signaling battleground.

5.5b Extracellular Vesicles: The Logistics of Coordinated Signaling

The preceding sections describe the organism's signaling repertoire: lipid-soluble compounds that dock with GPCRs, nuclear receptors, and ion channels (Section 5.5); peptides processed through shared Kex2/prohormone convertase machinery that modulate immune

receptors, DNA damage pathways, and growth factor signaling (Section 5.5a). Each pathway has been characterized independently, in isolated compound-target experiments. The obvious question is how the organism deploys these signals in coordination inside a living host, where hundreds of metabolites must reach specific cell types in specific combinations at specific times. The answer, increasingly documented in the peer-reviewed literature, is extracellular vesicles.

The packaging system. Extracellular vesicles (EVs) are lipid bilayer-enclosed particles, ranging from 30 nm to over 1 μm in diameter, released by cells across all domains of life. They serve as export and delivery systems, carrying cargo that includes proteins, lipids, nucleic acids, and polysaccharides protected within the membrane envelope (Zarnowski *et al.*, 2018). *C. albicans* produces EVs in both planktonic (free-living) and biofilm states. More than 20 fungal species are now known to produce EVs (Karkowska-Kuleta *et al.*, 2025). Unlike free-floating secreted molecules, EV cargo is shielded from enzymatic degradation in the extracellular environment and can be delivered across cellular barriers that individual molecules cannot cross unaided.

Morphology-dependent cargo programming. The organism does not produce a single class of vesicle. Martínez-López *et al.* (2022) demonstrated that hyphal extracellular vesicles (HEVs) and yeast extracellular vesicles (YEVs) from *C. albicans* differ in size, biogenesis, protein diversity, and functional impact on the host. YEVs are larger (400–500 nm), carry primarily cell wall proteins, and serve cell wall maintenance functions; mutant sensitivity to cell wall-disrupting agents is rescued by addition of wild-type YEVs. HEVs are smaller (100–200 nm), carry six-fold greater protein diversity, include cytoplasmic proteins related to intracellular

transport and the endosomal sorting complexes required for transport (ESCRT) pathway, and produce stronger effects on human immune cells than YEVs. Notably, HEVs carry an active 20S proteasome complex as cargo (Martínez-López *et al.*, 2022), a finding whose functional significance in the host context remains unexplored. Ninety-two percent of YEV proteins were also found in HEVs, but these shared proteins represented only 16% of the HEV cargo, indicating that the hyphal state produces a substantially expanded vesicle payload.

The morphological transition from yeast to hyphal form, the same transition governed by farnesol-mediated signaling described in Section 5.7, therefore changes not only the organism's physical form and tissue-invasive capacity but also the composition and functional profile of its vesicle-based delivery system. Commensal yeast-form cells send maintenance vesicles. Tissue-invasive hyphal cells send a weaponized and diversified payload. The shift in vesicle cargo is coupled to the shift in morphological program.

*Candida*lysin delivery. Noll *et al.* (2025) demonstrated that *C. albicans* biofilm EVs contain candidalysin and can permeabilize planar lipid bilayer membranes in a dose-dependent manner. Biofilm EVs were unable to directly damage oral epithelial cells at tested concentrations but were able to induce cytokine responses, including IL-1α, IL-1β, G-CSF, and GM-CSF. EVs collected from biofilms at 24 hours and 48 hours differed in both cargo composition and their capacity to activate epithelial cells, with earlier EVs delivering candidalysin to the membrane surface and later EVs activating cells through candidalysin-independent mechanisms (Noll *et al.*, 2025). The temporal shift in cargo composition indicates that the organism's vesicle production is not static; it changes over the course of biofilm maturation, producing functionally distinct vesicle populations at different stages.

Community coordination. Zarnowski *et al.* (2021) used machine-learning analysis of cargo proteomic data from ESCRT-pathway mutants with vesicle production defects to systematically identify functional EV cargo proteins. Of 63 candidate gene products tested through constructed mutant and complemented strains, 17 displayed reduced biofilm matrix accumulation and antifungal drug resistance, and an additional 8 exhibited defects in adhesion or dispersion. Critically, the mutant phenotypes were rescued by addition of wild-type EVs, confirming that the functional effects derive from specific cargo rather than from the vesicle membrane itself. Biofilm EVs are compositionally distinct from planktonic EVs, with 34% of the proteome unique to the biofilm state (Zarnowski *et al.*, 2018). The biofilm's defining trait, the protective extracellular matrix that confers drug resistance, is coordinated through vesicle-mediated delivery of matrix components.

This coordination extends across species. Zarnowski *et al.* (2022) demonstrated that a set of 36 common cargo proteins is shared among biofilm vesicles across five *Candida* species, including the emerging pathogen *C. auris*. Select cargo mutants showed conserved functional defects across species, and wild-type EVs from one species could complement cargo mutant phenotypes in another. The vesicle proteome endows *Candida* species communities with shared properties central to biofilm pathogenicity, enabling interspecies cooperation through a common vesicle language.

Host cell internalization. *C. albicans* EVs are internalized by human macrophage-like cells (THP-1) through macropinocytosis and phagocytosis (Karkowska-Kuleta *et al.*, 2025). EVs and their cargo act as chemoattractants for blood-derived neutrophils, recruiting immune cells to the vicinity of the fungal population. However, the recruited neutrophils do not activate phagocytosis or neutrophil extracellular trap (NET) release in response to the EVs (Karkowska-Kuleta *et al.*, 2025). The vesicles attract without triggering the kill response. This is consistent

with the immune modulation pattern described throughout Section 5: the immune system appears active but does not clear the organism. The EV-mediated recruitment without activation represents a vesicle-level implementation of the same strategy achieved molecularly by farnesol's activation of innate immune markers on monocytes without enhancing fungal uptake or killing (Leonhardt *et al.*, 2015).

Bidirectional vesicle exchange. The vesicle channel is not unidirectional. Human oral mucosal epithelial cells produce EVs that suppress *C. albicans* growth, inhibit hyphal formation, and reduce mucosal invasion both *in vitro* and in a mouse model of oral candidiasis (Zhang *et al.*, 2022). The host fires defensive vesicles at the fungus; the fungus fires cargo-loaded vesicles at the host. This bidirectional vesicle exchange constitutes a physical logistics channel for the molecular arms race described throughout Section 5, with each side packaging and delivering functional payloads to the other across cellular barriers.

Recent molecular detail complicates the framing of host-to-fungus vesicles as purely defensive. Halder et al. (2022) showed that human monocytes encountering C. albicans release extracellular vesicles containing the human microRNA hsa-miR-24-3p, that this miRNA crosses the kingdom boundary and enters fungal cells, and that inside the fungal cell it suppresses translation of the fungal cell-cycle brake Sol1 — promoting fungal cell division. The packaging is triggered by fungal β-glucan binding to host CR3 and fungal mannan binding to host TLR4: the same molecular interactions the standard model categorizes as host pattern recognition of fungal pathogen-associated molecular patterns. The receptor-ligand binding events that mainstream framing reads as host detection of pathogen are simultaneously the docking events that license host-side cargo packaging across the kingdom boundary, and the cargo includes growth-promoting miRNA, not only defensive payload. The vesicle channel carries traffic in both signaling directions — defensive and growth-promoting — consistent with a coevolved bidirectional partnership communication infrastructure rather than a one-way attack mechanism.

Implications for the coevolutionary framework. The signaling architecture described in Sections 5.3 through 5.5a, farnesol interacting with nuclear receptors, candidalysin binding platelet receptors, Ece1 peptides docking with immune-inhibitory LILRs, is presented in the literature and in this paper as individual compound-target interactions. Extracellular vesicles provide the mechanism by which these interactions are coordinated *in vivo*. The organism does not broadcast hundreds of compounds into the extracellular space and rely on diffusion to find the right targets. It packages curated multi-signal payloads into membrane-enclosed vesicles, loads different cargo depending on its morphological state and the maturation stage of its community, and delivers those vesicles to host cells that internalize them through defined uptake pathways. The combinatorial problem that the *in vitro* caveat (Section 5.6) identifies, how does the organism coordinate hundreds of compounds simultaneously in a living host, is at least partially resolved by the EV delivery system.

In the context of the Saline Oscillation Hypothesis, EVs represent the operational logistics of the symbiont's program. The ECS provides the signaling interface. The peptide panel provides targeted effectors. The vesicles deliver both, together, to the right cells, at the right time, in the right combination. An organism with this delivery capability does not need every molecule to find its target independently. It needs only to load the correct payload and release it. Two hundred million years is sufficient time to refine the loading program.

5.5c Small RNA Cross-Kingdom Signaling: The Third Channel

The signaling architecture described thus far operates through two molecular classes: lipids and peptides. Each functions through receptor-mediated interactions at the cell surface or within the cell's cytoplasmic receptor infrastructure. A third class of cross-kingdom signal, small non-coding RNA (sRNA), operates through a fundamentally different mechanism: direct interference with host gene expression at the transcript level. Unlike lipids and peptides, which modulate cellular behavior through receptor signaling cascades, sRNAs can silence specific host genes by hijacking the host's own RNA interference (RNAi) machinery.

Established precedent: fungal small RNAs silence host genes. The foundational demonstration of cross-kingdom RNAi as a fungal virulence mechanism was published by Weiberg *et al.* (2013) in Science. The aggressive plant pathogen Botrytis cinerea produces small RNAs (Bc-sRNAs) that are transferred into host plant cells during infection, where they bind to Arabidopsis Argonaute 1 (AGO1), the central component of the host's RNA-induced silencing complex (RISC), and selectively silence host immunity genes including mitogen-activated protein kinases (MPK1, MPK2), a cell wall-associated kinase (WAK), and an oxidative stress gene (PRXIIF). B. cinerea mutants unable to produce these sRNAs (dcl1 dcl2 double mutants) displayed reduced pathogenicity. Arabidopsis ago1 mutants, unable to load the fungal sRNAs into RISC, exhibited reduced susceptibility to the pathogen. The mechanism is specific: the fungal sRNAs silence target genes through sequence complementarity, not through generalized toxicity.

Bidirectional RNA trafficking via extracellular vesicles. Cai *et al.* (2018) demonstrated in Science that the delivery mechanism for cross-kingdom sRNA transfer is extracellular vesicles. Arabidopsis cells secrete exosome-like EVs that accumulate at fungal infection sites and are taken up by B. cinerea cells. The host-derived sRNAs within these vesicles induce silencing of fungal genes critical for pathogenicity. The EVs are associated with tetraspanin proteins, which form membrane microdomains that may govern selective cargo loading. The sRNA traffic is bidirectional: the fungus sends sRNAs into the host to suppress immunity, and the host sends sRNAs into the fungus to suppress virulence. Both directions use vesicle-mediated delivery. This establishes EVs as the physical transport layer for cross-kingdom RNA interference, linking the vesicle biology described in Section 5.5b directly to gene-level regulatory warfare.

Wernecke *et al.* (2025) further demonstrated that different members of the Argonaute (AGO) protein family in B. cinerea act in bidirectional cross-kingdom RNAi during infection, with BcAGO2 specifically required for effective delivery of pathogen small RNAs into host cells. A fungal RNA-dependent RNA polymerase (BcRDR1) was identified as a novel pathogenicity factor required for cross-kingdom sRNA production (Porquier *et al.*, 2023). The molecular machinery for cross-kingdom RNAi in fungal pathogens is increasingly well-characterized.

Animal parasite precedent: sRNAs modulate mammalian immunity. Cross-kingdom sRNA transfer to mammalian cells is not confined to plant systems. The gastrointestinal nematode Heligmosomoides polygyrus secretes exosomes containing microRNAs that are internalized by mammalian cells and suppress host innate immunity (Buck *et al.*, 2014). This establishes that sRNA delivery from a eukaryotic parasite to a mammalian host, with functional gene-silencing consequences, is a demonstrated biological mechanism, not a theoretical extrapolation from plant pathology.

RNA cargo in fungal extracellular vesicles. Fungal EVs carry diverse RNA classes. A comprehensive review of fungal EV RNA content (Peres da Silva *et al.*, 2022) documented that EVs from pathogenic fungi including *Candida* species contain mRNAs, tRNA-derived fragments, ribosomal RNA fragments, antisense RNAs, and small non-coding RNAs. In *Candida* auris, caspofungin treatment altered both the quantity and RNA content of secreted EVs, with tRNA-derived fragments (21–55 nucleotides) comprising the most abundant non-coding RNA class, alongside antisense RNAs and mRNAs encoding translation, nucleosome, and cell wall functions (Peres da Silva *et al.*, 2022). Differentially expressed transcripts in these EVs included QDR3, a drug transport regulator associated with biofilm formation and virulence in *C. albicans*, and MP65, encoding a cell wall mannoprotein crucial for biofilm matrix integrity. The RNA cargo is not random cytoplasmic leakage; it shifts in response to environmental conditions, suggesting regulated loading.

Peres da Silva *et al.* (2022) compiled evidence that exonic sRNAs contained in fungal EVs regulate carbohydrate, lipid, fatty acid, and amino acid metabolism; vesicle trafficking; signal transduction; protein folding; and nucleic acid biosynthetic processes within fungal populations. A recent study demonstrated that fungal EVs regulate gene expression governing pathophysiological attributes of *C. albicans* itself, confirming that EV-associated RNA is functionally active at minimum within the producing species.

The uncharacterized channel. Whether *C. albicans* EV-associated sRNAs silence specific genes in mammalian host cells has not been directly demonstrated. The individual components required for such a mechanism are each independently confirmed: *C. albicans* produces EVs containing RNA cargo; these EVs are internalized by human macrophages through macropinocytosis and phagocytosis (Karkowska-Kuleta *et al.*, 2025); mammalian cells possess a functional RNAi machinery including AGO proteins capable of loading exogenous sRNAs; animal parasites have been shown to deliver functional sRNAs to mammalian cells via EVs (Buck *et al.*, 2014); and cross-kingdom RNAi through fungal sRNAs is a demonstrated virulence mechanism in plant-fungal pathosystems (Weiberg *et al.*, 2013). The mechanistic pathway from fungal cell to mammalian gene silencing exists. What has not been shown is that *C. albicans* uses it.

Evolutionary logic of the third channel. Small RNAs are not conscious signals, intentional communications, or hierarchical controllers. They are molecular regulatory noise that evolution harnessed. A tRNA fragment released in an EV that happened to reduce expression of a host immune gene would confer a survival advantage on the producing cell. Over evolutionary timescales, the loading of such fragments into EVs would become non-random, selected for regulatory impact rather than occurring by chance. This is the same logic by which the paper interprets farnesol's cross-kingdom activity (Section 5.7): the molecule was not designed to suppress competing fungi and modulate host immunity. Its effects were selected for because they stabilized the niche.

The three signaling channels, lipids, peptides, and small RNAs, operate on different timescales and at different levels of biological organization. Lipid signaling modulates receptor-mediated tone: the homeostatic set points of the ECS, immune surveillance sensitivity, vascular tone, and metabolic balance. Peptide signaling executes targeted actions: tissue remodeling, immune receptor engagement, DNA damage pathway manipulation. Small RNA signaling, if confirmed in the *C. albicans*–mammalian system, would operate at the deepest level: direct modification of host gene expression, tuning the host's own transcriptional output to favor the symbiont's program. Each channel acts on different timescales: seconds to minutes for receptor

signaling, minutes to hours for peptide-receptor effects and downstream cascades, hours to days for gene expression changes mediated by sRNA silencing. Together, they constitute a layered control architecture spanning from immediate physiological modulation to long-term transcriptional reprogramming.

Host-side surveillance. If fungal sRNAs or mRNAs enter host cells via EVs, they encounter host-side quality control systems that may function as barriers to cross-kingdom RNA interference. Hia *et al.* (2026) demonstrated that the RNA helicase DHX29 sits at the A-site entrance of the translating 80S ribosome and monitors aminoacyl-tRNA sampling, detecting nonoptimal codon usage and recruiting the GIGYF2/4EHP complex to suppress mRNAs enriched in nonoptimal codons. *C. albicans* uses a dramatically different codon usage bias from the human genome, including its well-documented CUG codon reassignment (serine rather than leucine). Any fungal mRNAs that enter host cells and reach the translational machinery would be flagged by DHX29's codon surveillance. DHX29 also moonlights as a co-sensor for MDA5-mediated innate immune signaling, enhancing MDA5 recognition of structured RNAs and triggering type I interferon responses (Zhu *et al.*, 2018). A single host protein thus monitors both the translational fidelity and the immunological identity of cytoplasmic RNA, presenting a two-layer barrier: translational surveillance of codon optimality and innate immune detection of foreign RNA structure.

In the coevolutionary framework, this host-side barrier predicts a symbiont counter-adaptation: evolutionary optimization of exported RNA sequences to pass both the DHX29 codon screen and the MDA5 structural screen. This is testable. Comparison of the codon usage profiles of *C. albicans* secreted and exported transcripts, particularly Ece1 and other transcripts detected in EV cargo, against the human codon optimality landscape should reveal whether these transcripts are more human-optimized than the remainder of the *Candida* transcriptome. If they are, this constitutes evidence of coevolutionary selection at the codon level: the organism tuning its exported RNA to pass the host's quality control.

Internal RNA transport infrastructure. *C. albicans* already possesses a dedicated internal RNA trafficking system. Elson *et al.* (2009) identified a She3-dependent mRNA transport mechanism that selectively transports 40 mRNAs to yeast buds and to the tips of growing hyphae, where secretion is concentrated through the Spitzenkörper vesicle cluster. The cargo mRNAs have diverged substantially from those of *S. cerevisiae*, and many encode genes that contribute to hyphal development and host tissue invasion. The authors note that specific mRNAs can move in and out of transport control over evolutionary timescales, indicating that the RNA targeting system is evolutionarily plastic. An organism that already targets specific mRNAs to the subcellular location where secretory vesicles are produced has the molecular infrastructure to load specific RNAs into extracellular vesicles. The step from intracellular RNA targeting to extracellular RNA delivery is not a large one; it requires only that the She3-dependent or analogous cargo be routed to the EV biogenesis pathway rather than exclusively to internal translation.

5.5d Oxylipin Mimicry: Prostaglandin Production and the Shared Arachidonic Acid Economy

The lipid signaling architecture described in Section 5.5 centers on farnesol, a sesquiterpene alcohol that interacts with host GPCRs, nuclear receptors, ion channels, and neurotransmitter receptors. Farnesol is synthesized endogenously by *C. albicans* from the mevalonate pathway, using the organism's own metabolic precursors. A second class of lipid-

mediated host manipulation operates through a fundamentally different supply chain: the organism takes a precursor from the host and manufactures a molecule structurally identical to one of the host's own inflammatory mediators, then deploys it to reshape the immune landscape in its favor.

Authentic prostaglandin production from host-derived substrate. Erb-Downward and Noverr (2007), using liquid chromatography–tandem mass spectrometry, demonstrated that *C. albicans* produces authentic prostaglandin E_2 (PGE_2) from arachidonic acid (AA). The mass spectrometric fragmentation pattern of the fungal product was identical to that of a purified PGE_2 standard, confirming structural identity rather than mere cross-reactivity. Maximal PGE_2 production occurred at 37°C in stationary-phase cultures, conditions mimicking the host internal environment. Earlier work by Noverr *et al.* (2001) had identified a PGE cross-reactive compound (PGEx) in *Candida* supernatants that was biologically active on mammalian cells, and the mass spectrometric characterization confirmed that this compound is authentic PGE_2.

The biosynthetic pathway is unusual. *C. albicans* does not possess a cyclooxygenase (COX) homolog, the enzyme family responsible for prostaglandin synthesis in mammalian cells (Erb-Downward and Noverr, 2007). Yet PGE_2 production is inhibited by both nonspecific cyclooxygenase inhibitors and lipoxygenase inhibitors. A fatty acid desaturase homolog (Ole2) and a multicopper oxidase homolog (Fet3) were identified as playing roles in the biosynthetic process, with ole2/ole2 and fet3/fet3 mutants exhibiting reduced PGE_2 levels. The organism has evolved an independent enzymatic route to the same product that the host produces through COX enzymes. This is convergent biochemistry at the product level with divergent machinery at the enzyme level, a pattern consistent with selection for the end product's functional utility rather than conservation of the biosynthetic pathway itself.

Precursor acquisition from the host. *C. albicans* does not contain arachidonic acid as part of its endogenous fatty acid repertoire (Erb-Downward and Noverr, 2007). The organism obtains its AA precursor from the host. During infection, *C. albicans* causes the release of arachidonic acid from host cell membrane phospholipids, which then serves both as a carbon source for yeast growth and as the precursor for prostaglandin biosynthesis (Deva *et al.*, 2000; Agarwal *et al.*, 2014). Supplementation of *C. albicans* cultures with exogenous AA significantly increases PGE_2 production (Noverr *et al.*, 2001). Biofilm-forming *C. albicans* produces substantially more prostaglandin than planktonic cells, and oxylipin production is upregulated during biofilm formation (Alem and Douglas, 2005; Erb-Downward and Noverr, 2007).

The supply chain is therefore: the organism damages host cell membranes (through candidalysin pore formation, SAP-mediated digestion, or physical hyphal penetration), arachidonic acid is released from the damaged membrane phospholipids, the organism imports it, and converts it into a molecule indistinguishable from the host's own primary inflammatory prostaglandin. The raw material comes from the host. The manufacturing is done by the fungus. The product is deployed back against the host's immune system.

Immune polarization through molecular mimicry. The immunological consequences of fungal PGE_2 production are specific and directional. PGE_2, whether host-derived or fungal, promotes Th2-type immune responses and suppresses Th1-type responses (Noverr *et al.*, 2001; Kundu and Noverr, 2011). In the context of *Candida* infection, Th1 responses are protective and lead to fungal clearance, while Th2 responses are non-protective and promote chronic or disseminating disease (Noverr *et al.*, 2001). The organism produces the exact molecule that shifts the host's immune response from the profile that would clear the infection to the profile that permits persistence.

Kundu and Noverr (2011) demonstrated this directly using dendritic cell immunization models. Bone marrow-derived dendritic cells pulsed with *C. albicans* yeast cells could protect mice against systemic infection. However, exposure to either host PGE_2 or fungal PGE_2 during the antigenic stimulation period abrogated the protective effect entirely. In the presence of hyphae, PGE_2 promoted Th2 cytokine production (IL-4, IL-10) and suppressed Th1 cytokine production (IL-12). The fungal PGE_2 was functionally interchangeable with host PGE_2 in blocking protective immunity. This is molecular mimicry in the most literal sense: the host's immune system cannot distinguish the fungal product from its own.

The broader biological activity of the fungal PGE_2 on mammalian cells includes inhibition of splenocyte proliferation, suppression of TNFα production, and stimulation of IL-10 secretion (Noverr *et al.*, 2001). IL-10 is an anti-inflammatory cytokine that dampens immune surveillance. TNFα is a proinflammatory cytokine critical for antifungal defense. The organism's prostaglandin output simultaneously suppresses what would kill it and amplifies what protects it.

Autocrine morphological feedback. The fungal PGE_2 does not act exclusively on the host. Both fungal PGEx and synthetic PGE_2 enhance the yeast-to-hyphal morphological transition in *C. albicans* (Noverr *et al.*, 2001; Noverr and Huffnagle, 2004). Mammalian eicosanoid inhibitors also inhibit *C. albicans* oxylipin production, morphogenesis, and biofilm formation (Noverr and Huffnagle, 2004; Erb-Downward and Noverr, 2007). The prostaglandin output thus serves a dual function: it modulates the host immune response externally and feeds back into the organism's own morphological program internally. The same molecule that suppresses host Th1 immunity promotes the hyphal form that enables tissue invasion. One product, two targets, coordinated effect.

Conservation across *Candida* species. Prostaglandin production from exogenous arachidonic acid is not unique to *C. albicans*. Toth *et al.* (2015) characterized the prostaglandin profiles of *C. parapsilosis* and *C. albicans* using HPLC-MS and found that both species synthesize PGD_2 and PGE_2 as their primary products, along with compounds from other prostaglandin classes (PGH_2, $PGF_2\beta$, PGA_2). Agarwal *et al.* (2014) demonstrated that *C. tropicalis*, *C. glabrata*, and *C. parapsilosis* all produce PGE_2 from exogenous AA, with production enhanced during biofilm formation and in the presence of subinhibitory antifungal concentrations. Strydom *et al.* (2010) confirmed PGE_2 production in *C. dubliniensis* biofilms, the closest relative of *C. albicans*. The conservation of prostaglandin production capacity across the pathogenic *Candida* clade, using host-derived arachidonic acid as substrate, is consistent with selection for this capability as a host-interaction trait rather than an incidental metabolic byproduct.

The shared arachidonic acid economy and the endocannabinoid connection. This section's findings converge with the central argument of this paper through a single biochemical fact: arachidonic acid is the shared precursor for both the prostaglandin/eicosanoid pathway and the endocannabinoid system. The two primary endocannabinoids, anandamide and 2-AG, are both synthesized from membrane-bound arachidonic acid-containing phospholipids (Sugiura and Waku, 2002; Di Marzo, 2006). Prostaglandins are synthesized from free arachidonic acid released from the same phospholipid pool by phospholipase A_2. Moreover, COX-2 can directly oxygenate 2-AG to yield prostaglandin glyceryl esters (Di Marzo, 2006), and the hydrolysis of both endocannabinoids regenerates free arachidonic acid that can be diverted into eicosanoid production (Di Marzo and De Petrocellis, 2006). The two pathways do not merely share a precursor pool; they share processing enzymes and recycling intermediates.

The host's arachidonic acid pool therefore feeds three competing biosynthetic demands: the host's own prostaglandin/eicosanoid production (inflammation, vascular tone, immune regulation), the host's own endocannabinoid production (homeostatic regulation via CB1 and CB2), and the symbiont's prostaglandin production (immune polarization toward the non-protective Th2 profile, morphological feedback into the hyphal program). The organism does not merely interact with the ECS through receptor-level signaling, as described in Section 5.5. It competes directly with the host's endocannabinoid biosynthesis for shared arachidonic acid substrate. When the organism diverts host-released arachidonic acid into fungal PGE_2 production, that arachidonic acid is no longer available for anandamide or 2-AG synthesis.

This creates a metabolic triangle in which the organism can modulate both the inflammatory tone (through PGE_2 output) and the endocannabinoid tone (through substrate competition) of the local tissue environment simultaneously, using a single precursor it obtains by damaging host membranes. The ECS trunk described in this paper and the prostaglandin branch described here are not separate signaling systems. They are two outputs of a shared lipid economy that the organism has inserted itself into. The lipid signaling architecture is not a tree with independent branches. It is a root system fed by a common pool, and the organism sits at the junction. External empirical confirmation of both downstream arms — eCB-mediated HPA dysregulation rescued by FAAH inhibition, and PGE_2-mediated behavioral effects reversed by receptor antagonism, with independent convergence from microbiota-modulated mouse depression models and human probiotic intervention data — has been consolidated separately and is not recapitulated here (Craddock, AA Branch Point).

Framework integration. The oxylipin capability adds a fourth mechanism to the organism's immune modulation toolkit, alongside farnesol-mediated dendritic cell suppression (Section 5.5), candidalysin-driven immune polarization (Section 5.5a), and the Ece1 peptide panel's LILR-mediated immune inhibition (Section 5.5a). A fifth operates through the cell wall itself: alpha-mannan and beta-glucan surface structures trigger mast cell degranulation and stimulate arachidonic acid release from macrophages through mannose receptor and dectin-1 engagement (Castro *et al.*, 1994), activating innate inflammatory cascades whose downstream outputs are then redirected toward the non-protective Th2 profile by the prostaglandin and farnesol mechanisms described above. Each of the five mechanisms operates through a different molecular class and a different receptor system. Farnesol suppresses via nuclear receptor activation and GABA-A modulation. *Candida*lysin polarizes through EGFR and platelet receptor engagement. The Ece1 peptides inhibit through LILR binding. Fungal PGE_2 shifts the Th1/Th2 balance through the same prostanoid receptors (EP1–EP4) that the host's own PGE_2 engages. Cell wall glycans activate innate pattern recognition receptors (mannose receptor, dectin-1, TLR4) to trigger degranulation and substrate release. Five molecular classes, five receptor systems, one coordinated outcome: an immune environment that appears active but does not clear the organism.

The organism also modulates host tryptophan metabolism. *C. albicans* infection drives tryptophan catabolism through the kynurenine pathway via indoleamine 2,3-dioxygenase (IDO) induction in host dendritic cells, depleting the tryptophan pool available for serotonin synthesis while generating kynurenine metabolites that suppress IL-17 production at mucosal surfaces (Cheng *et al.*, 2010; Zelante *et al.*, 2013). IL-17 is the primary cytokine driving mucosal antifungal defense; its suppression is the single most consequential immune evasion outcome for a gut-resident organism. The structural parallel to the arachidonic acid diversion described above is precise: a single metabolic rerouting achieves both immune suppression (IL-17 loss) and

neurotransmitter precursor depletion (serotonin reduction) simultaneously, through one enzymatic intervention at a shared substrate node.

In the context of the Saline Oscillation Hypothesis, the organism's capacity to manipulate vascular tone through prostaglandin production is directly relevant to the perfusion management architecture described in Section 4.3. PGE_2 is a potent vasodilator in most vascular beds and regulates renal blood flow, sodium handling, and renin release. An organism producing authentic PGE_2 from host-derived substrate has direct access to the vascular control systems that govern the electrolyte and perfusion dynamics at the center of the saline oscillation mechanism. The prostaglandin capability is not separate from the perfusion program. It is one of the tools by which the program operates.

5.5e Bioelectric Signaling: Ion Manipulation and the Electrochemical Interface

Section 5.5 documents that farnesol inhibits voltage-gated Ca^{2+} channels (Roullet *et al.*, 1999), establishing that a single *C. albicans* metabolite can directly modulate host ion channel function. Section 5.5a describes candidalysin's pore-forming activity, which causes uncontrolled Ca^{2+} influx across the host cell membrane (Moyes *et al.*, 2016). These individual interactions, however, exist within a broader context: *C. albicans* possesses a comprehensive suite of ion transport, pH manipulation, and electrochemical environment-engineering capabilities that, taken together, position it as an active modifier of the ionic landscape in which the host's own electrochemical machinery operates. In the context of the Saline Oscillation Hypothesis, where electrolyte dynamics and perfusion management are central to the coevolutionary program, this ionic manipulation capability represents the most direct mechanistic interface between symbiont activity and the host's Na^+/K^+-ATPase-dependent physiology.

Active pH manipulation through two independent metabolic pathways. *C. albicans* modulates extracellular pH through at least two genetically distinct mechanisms. Vylkova *et al.* (2011) demonstrated that when amino acids serve as the carbon source, *C. albicans* catabolizes them and excretes the amino nitrogen as ammonia, raising extracellular pH from approximately 4 to 7.5 within hours. This process is regulated by the transcription factor Stp2, which controls amino acid permease expression through the SPS (Ssy1-Ptr3-Ssy5) sensor system. The ammonia is exported through the Ato family of transporters, which is significantly expanded in *C. albicans* (10 members) relative to non-alkalinizing species (Vylkova *et al.*, 2011). Danhof and colleagues (2016) identified a second, genetically independent pathway: when carboxylic acids such as lactate, pyruvate, or α-ketoglutarate serve as the carbon source, *C. albicans* rapidly neutralizes acidic environments without ammonia release, without inducing hyphal morphogenesis, and through mutations distinct from those that impair the amino acid-driven pathway. Two independent metabolic routes converge on the same environmental outcome: pH neutralization.

Most recently, Chen *et al.* (2025) identified the transcription factor Dal81 as a previously unrecognized positive regulator of alkalinization that physically interacts with Stp2 to co-regulate a broad set of downstream target genes governing amino acid metabolism, extracellular pH modulation, fitness, and pathogenicity. The alkalinization program is not a single-gene response; it is a coordinated regulatory network with multiple transcriptional inputs.

The organism's morphological response to ionic environments demonstrates active multi-input integration rather than single-parameter response. Barbosa *et al.* (2020) characterized *C. albicans* behavior on simulated saliva (AS) and simulated urine (AU) media at pH 5.8 and 7.0, finding a context-dependent inversion: AS at alkaline pH 7.0 induced filamentation while AS at

acidic pH 5.8 did not, but AU at acidic pH 5.8 induced filamentation while AU at alkaline pH 7.0 did not. The organism does not respond to pH as a single variable; it integrates pH with the full ionic context of the fluid to make morphology decisions, producing opposite filamentation outcomes at the same pH depending on which ionic milieu surrounds it. This is the multi-input integration signature the framework's "biochemical computer" claim requires at the input layer: the organism reads ionic environments at physiological concentrations and produces context-dependent program outputs through coordinated regulatory architectures, not isolated single-gene responses.

Phagosomal pH neutralization. The pH manipulation capability extends to the most hostile intracellular environment the host can deploy. Vylkova and Lorenz (2014) demonstrated that phagocytosed *C. albicans* cells neutralize the acidic phagolysosome through amino acid-driven alkalinization. Wild-type cells fail to co-localize with acidophilic dyes, indicating they occupy a neutral phagosome. Mutants lacking Stp2 remain in acidic phagosomes, cannot initiate hyphal morphogenesis, are killed at higher rates, and cause less macrophage damage. Pharmacological neutralization of the phagosome restored hyphal morphogenesis in the stp2Δ mutant, confirming that the pH change itself, not another Stp2 function, is the critical trigger for escape. The organism rewrites the pH of the compartment the host designed to kill it, and uses the pH change to activate the morphological transition required for escape. Vylkova (2017) reviewed pH modulation as a general fungal virulence strategy, noting that *C. albicans* alkalinizes at a rate unprecedented among human fungal pathogens, and that the most pathogenic *Candida* species possess the most expanded arsenals of amino acid transporters and ammonia exporters. The correlation between alkalinization capacity and pathogenic success across the genus supports the interpretation that pH manipulation is not metabolic waste disposal but environmental engineering in service of the organism's program.

Potassium transport and competition with the host. *C. albicans* maintains intracellular potassium concentrations of 200–300 mmol/L and must compete with host cells for extracellular potassium, which is typically present at only a few mmol/L in host fluids (Ramos *et al.*, 2022). The organism possesses a complex potassium transport network including high-affinity uptake transporters (Trk1, Trk2), an outward-rectifying K^+ channel (Tok1) with a membrane topology distinct from all other known potassium channel classes (recently resolved at atomic resolution; BPS, 2026), Na^+/K^+-ATPase pumps (Ena21-22), and the Na^+/H^+ antiporter Cnh1, which exports potassium in addition to sodium (Kinclova-Zimmermannova *et al.*, 2007). A vacuolar transient receptor potential (TRP) channel (Yvc1) mediates calcium and potassium transport between the vacuole and mitochondria, governing the interaction among oxidative stress response, vacuolar integrity, and mitochondrial function (Yu *et al.*, 2014). Ion homeostasis is directly connected to morphogenesis, drug resistance, cell wall integrity, and invasive growth (Li *et al.*, 2018).

The organism's potassium transport activity directly alters the local extracellular K^+ concentration in its immediate environment. In tissue microenvironments where *C. albicans* density is high, whether in biofilms, in the gut lumen, or within the novel peritoneal compartment described in the longitudinal case study (Craddock, Redacted Science), the organism's collective potassium uptake reduces the extracellular K^+ available to adjacent host cells. This is not theoretical: the organism requires 200–300 mmol/L intracellular K^+ and extracts it from a medium containing only a few mmol/L. At sufficient fungal density, this creates a measurable K^+ depletion zone around the colony.

***Candida*lysin as a bioelectric disruptor**. The pore-forming toxin candidalysin (Section 5.5a) is not merely a cytolytic agent. Each candidalysin pore is a local short-circuit in the host

cell's electrochemical gradient. Russell *et al.* (2022) demonstrated that candidalysin forms pores through a unique mechanism: the peptide self-assembles into octameric polymers and loops in solution before inserting into the membrane, producing stable pores that cause uncontrolled Ca^{2+} influx, release of cellular proteins, and critically, efflux of ATP from the host cell into the extracellular space (Ho *et al.*, 2021; Russell *et al.*, 2022). The calcium influx triggers matrix metalloproteinase activation, EGFR signaling, and cytokine release (Moyes *et al.*, 2019). But the ATP efflux is equally significant: it represents the host cell losing its energy currency directly into the environment where the organism can access it. Simultaneously, the unregulated ion flux through the pore collapses the transmembrane potential that the Na^+/K^+-ATPase maintains at a cost of 30–70% of total cellular ATP production.

Convergence: creating the conditions for pump reversal. The Na^+/K^+-ATPase is a reversible enzyme. Garrahan and Glynn (1966), in a foundational paper in Nature, demonstrated that by arranging sufficiently adverse concentration gradients for sodium and potassium across intact red blood cell membranes, the Na^+/K^+ pump can be driven backwards to synthesize ATP from ADP and inorganic phosphate. They noted that the free energy available to drive the pump forward under normal physiological conditions is approximately 3,000 calories per ATP, a narrow thermodynamic margin between forward and reverse operation. Robinson, Hall, and Dunham (1977) further characterized the reverse mode in resealed red cell ghosts, measuring ATP synthesis as a function of internal K^+ concentration. Schwarz and colleagues (1991) demonstrated in Xenopus oocytes that under conditions of reduced intracellular Na^+ and ATP (both below 1 mM) combined with extracellularly K^+-free medium, the pump operates in reversed mode, pumping Na^+ into the cell and K^+ out. A recent comprehensive review confirms that each stage of the NKA cycle is reversible contingent upon substrate availability, and that under specific conditions, NKA can operate in the opposite direction, acting as an ATP synthase (Bhatt *et al.*, 2024).

The conditions required for pump reversal are specific: reduced intracellular Na^+, reduced intracellular ATP, and reduced or absent extracellular K^+. The organism's documented capabilities converge on precisely these conditions. *Candida*lysin pores cause ATP efflux from the host cell, reducing intracellular ATP. The same pores permit unregulated ion flux, collapsing the Na^+ gradient. The organism's high-affinity potassium uptake competes with host cells for extracellular K^+, creating local K^+ depletion zones. pH manipulation through ammonia excretion alters the proton gradient that drives the Na^+/K^+-ATPase. Farnesol inhibits voltage-gated Ca^{2+} channels, modifying the calcium signaling that regulates pump activity. No single mechanism needs to flip the pump by force. The organism nudges the electrochemical landscape from multiple directions simultaneously, and the thermodynamic margin is narrow enough that the cumulative effect can tip the pump past the reversal threshold.

Implications of reversed pump operation. If the Na^+/K^+-ATPase operates in reverse mode in affected tissues, the consequences extend beyond energy metabolism. In forward mode, the pump maintains the electrochemical gradient that every cell depends on for volume regulation, membrane potential, excitability, and secondary active transport. In reverse mode, these gradients collapse or invert. The pump, which normally consumes 30–70% of cellular ATP to maintain gradients, instead harvests the stored electrochemical potential energy of existing gradients to generate ATP. The ion gradients that the cell spent its lifetime building become a fuel reserve.

In a system where conventional mitochondrial ATP generation is compromised, whether by fungal interference with mitochondrial function, substrate depletion, or the metabolic shifts

documented in the longitudinal case study (Craddock, Redacted Science), reverse pump operation would represent an alternative energy generation pathway. The host is, in effect, carrying a stored fuel source in every cell's ion gradient that is not accessed under normal physiological conditions. The organism's ionic manipulation capabilities provide the mechanism by which this reserve could be tapped.

The downstream physiological consequences of reversed gradients in affected tissue would include altered cell volume regulation (cells that can no longer maintain their normal volume may shrink through water loss, consistent with the apoptotic volume decrease that precedes programmed cell death), changes in membrane potential affecting excitability and signaling in nearby cells, disruption of secondary active transport systems that depend on the Na^+ gradient (including glucose co-transporters, amino acid transporters, and neurotransmitter reuptake systems), and altered skin physiology in tissues where the epidermis is affected.

Epidermal implications of altered gradients. The human epidermis is a continuously regenerating tissue. New keratinocytes are generated by division of basal layer stem cells sitting on the basement membrane, with direct access to dermal interstitial fluid and capillary diffusion. Daughter cells are pushed upward through the spinous, granular, and cornified layers, progressively flattening, keratinizing, and undergoing programmed cell death as they rise. In normal skin, the outermost cornified layers desquamate at approximately the rate new cells are produced, maintaining a steady-state thickness. If reversed electrochemical gradients in the upper epidermal layers accelerate apoptotic volume decrease in keratinocytes that have not yet reached the normal desquamation stage, while the basal layer continues to generate new cells at its normal rate, the result is accumulation: apoptotic layers stacking faster than they shed, producing progressive thickening, tightening, and compression of the skin. The basal layer, sitting on the basement membrane with full access to interstitial fluids, remains the last layer to lose function and continues generating new cells from below, even as the layers above it are compressed by the accumulating stack.

C. albicans hyphae are documented to penetrate through all epidermal layers including the basal layer, with sequential expression of secreted aspartyl proteinases at each depth (Schaller *et al.*, 1999). The organism adheres to live basal keratinocytes via interactions between fungal phosphoglycerate mutase (Gpm1) and epithelial cell vitronectin (Lopez *et al.*, 2014). Melanocytes in the basal layer detect *C. albicans* through TLR4 and respond by increasing melanin production (Tapia *et al.*, 2014). Notably, Lachat *et al.* (2022) demonstrated that *C. albicans* hyphae can traverse multiple host cells within trans-cellular tunnels without causing membrane damage at early stages, indicating that the organism can establish intracellular presence in the epidermis while leaving the tissue structurally intact. An organism that reaches the basal layer, adheres to its cells, and can tunnel through the layers above without destroying them has the positional access required to influence the ionic environment of the regenerative layer from within, while the consequences of that influence, i.e., altered gradients, accelerated apoptosis, and layer accumulation, manifest in the tissue above.

The tissue-level changes predicted by this model, including progressive skin toughening, compression, tightening, and episodic burning from disrupted ion gradients activating epidermal nociceptors, are documented in the longitudinal case study (Craddock, Redacted Science).

Integration with the saline oscillation mechanism. The Saline Oscillation Hypothesis (Section 2) proposes that cyclical drinking water salinity in the East African Rift Valley created SIADH-type electrolyte disruption during freshwater transitions. The organism's documented ionic manipulation capabilities, active pH modulation, potassium competition, transmembrane

pore formation, and calcium channel modulation, are the molecular tools by which the symbiont would manage host electrolyte balance during precisely these disruptions. An organism that can raise extracellular pH by four units within hours, compete for potassium at concentrations two orders of magnitude above the extracellular supply, neutralize the acidic phagolysosome of the immune cells sent to destroy it, and punch calibrated pores in host cell membranes to modify transmembrane ion flux does not need a novel mechanism to manage saline oscillation. It needs only to apply the ionic manipulation capabilities it already possesses to the electrolyte environment it already inhabits.

The modern observable of this partnership operating is bidirectional electrolyte deviation under fungal load and antifungal pressure. Lionakis, Samonis, & Kontoyiannis (2008) consolidated published clinical evidence that invasive fungal infection produces hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypomagnesemia, and hypocalcemia depending on the affected organ system and infection state, while systemic antifungal treatment produces deviations in the opposite direction across the same parameters — including amphotericin-B-induced reduction in renal aquaporin 2 expression producing nephrogenic diabetes insipidus, ketoconazole-induced apparent mineralocorticoid excess, and fluconazole-associated adrenal suppression. The bidirectionality is the framework-revealing signature: the organism contributes to electrolyte set-point management, removing organism contribution under antifungal pressure produces deviations in the opposite direction from those produced by uncontrolled fungal load. The historical saline oscillation mechanism selected for the partnership; the modern clinical observable of the partnership operating is the bidirectional electrolyte signature visible in routine clinical chemistry whenever fungal load or antifungal pressure perturbs the system.

The Na^+/K^+-ATPase reversal mechanism adds a further dimension: under the altered ionic conditions the symbiont creates, the host's primary energy-consuming ion pump can become an energy-generating one. In the context of the coevolutionary program, this may explain how the host maintains function, including the cognitive clarity documented in the historical cohort and the longitudinal case study, during phases when conventional energy production is compromised. The organism is not destroying the host's ionic infrastructure. It is repurposing it.

5.6 The In Vitro Caveat

The extracellular vesicle system described in Section 5.5b provides a partial answer to the coordination problem: the organism packages multi-signal payloads into membrane-enclosed vesicles with morphology-dependent and temporally variable cargo. Nevertheless, a critical methodological note is required. Virtually all of the receptor-level and cross-kingdom interactions described above were characterized *in vitro*: isolated compounds tested against isolated targets in controlled media. The morphological suppression, the competing-fungi apoptosis, the immune cell manipulation, the GABA-A binding, the nuclear receptor activation were all demonstrated in the reductionist context of cell culture or defined assay systems.

Inside a living mammalian host, the situation is fundamentally different. *C. albicans* is producing hundreds of compounds simultaneously, in varying concentrations, in different tissue microenvironments with variable pH, oxygen tension, carbon sources, immune pressures, and co-resident organisms at every location. The metabolite profile shifts depending on whether the organism is utilizing glucose or lactate, whether it is in yeast or hyphal form, and what signals it is receiving from the local microbial community and host cells. The *in vitro* work demonstrates

that the keys fit the locks. It does not reveal which doors are being opened, in what order, in what combination, or in response to what local conditions.

No study has attempted to map the integrated, real-time metabolite-receptor interaction network of *C. albicans* operating inside a living host. The individual components are peer-reviewed and confirmed. The assembled system has never been observed. The field's tools are reductionist. The organism is not.

5.7 The Absent Receptor and the Effector Hypothesis

Despite twenty-two years of active research since Hornby *et al.* (2001), no farnesol receptor or sensor has been identified in *C. albicans* itself (Nickerson *et al.*, 2023). Multiple receptors for farnesol have been characterized in the mammalian host (FXR, GABA-A, voltage-gated Ca^{2+} channels, PPARs) and confirmed effects have been documented in competing fungi and bacteria. The producing organism does not appear to detect its own primary signaling compound.

The prevailing interpretation of farnesol function since its discovery has been morphological self-regulation: as population density increases, extracellular farnesol accumulates and suppresses the yeast-to-hyphal transition, maintaining the population in yeast form (Hornby *et al.*, 2001). This quorum-sensing model is well-supported experimentally. The morphological suppression is reproducible, dose-dependent, and specific to the E,E-isomer (Shchepin *et al.*, 2003).

However, the quorum-sensing model accounts for only one of farnesol's many confirmed biological activities. The same molecule that suppresses filamentation in *C. albicans* also induces apoptosis in competing fungi (Semighini *et al.*, 2006), downregulates virulence signaling in bacteria (Cugini *et al.*, 2007), activates nuclear transcription factors in the mammalian host (Forman *et al.*, 1995), modulates the primary inhibitory neurotransmitter system in the brain (Gc *et al.*, 2023), blocks voltage-gated calcium channels (Roullet *et al.*, 1999), and selectively induces apoptosis in mammalian cancer cells while sparing healthy tissue (Joo *et al.*, 2009). If the primary function of farnesol were morphological self-regulation, the breadth and specificity of its cross-kingdom activity would be difficult to explain, and the absence of any identified receptor in the producing organism would remain paradoxical.

We propose that morphological suppression is not the primary function of farnesol but rather one consequence of a broader effector strategy. The yeast form is the dispersal and commensal form of *C. albicans*; the hyphal form is the tissue-invasive form. An effector molecule that simultaneously suppresses premature tissue invasion, suppresses competing microorganisms, modulates host immunity, and accesses host transcriptional and neurological signaling would produce the observed morphological effect as a byproduct of maintaining the conditions under which the symbiont's long-term program operates. The organism is not telling itself to stay small. It is maintaining the operational environment in which its program runs.

The cross-kingdom activity described in Sections 5.3 and 5.4 is consistent with this effector interpretation. *Candida* does not suppress competing fungi and downregulate bacterial virulence factors out of altruism toward the host. It does so because a stable host with a predictable internal environment is an optimal resource. Competing fungal infections trigger inflammatory immune cascades. Bacterial virulence factors cause tissue damage. Both destabilize the niche the symbiont requires. The organism's first imperative is to feed, to metabolize, to persist, to exist commensally. To do that optimally, it requires environmental parameters within a tolerable range. The cross-kingdom signaling described here is not grand

strategy. It is ecological housekeeping in service of the organism's primary interest: an undisturbed host.

Not all cells participate in this maintenance at all times. *C. albicans* populations exist across a spectrum of activity states. The majority of cells in an untreated population are in baseline metabolic states, feeding, dividing, existing commensally (Dumeaux *et al.*, 2023). A subset maintains the local environment through the signaling mechanisms described above. Others lie dormant in tissue niches distant from active immune surveillance, metabolically quiescent, pre-positioned, persisting. These are the waiting cells: not managing, not feeding aggressively, simply enduring until conditions change. The organism does not need every cell to be an active coordinator. It needs enough coordinators to maintain the niche, and enough reserves to survive if the niche is disrupted.

5.7.1 The Responsive Effector: What Controls Production?

The effector hypothesis accounts for what farnesol does. It does not account for what controls when and how much of it the organism produces. If no farnesol receptor exists in *C. albicans*, the organism is not using its own primary output as a feedback signal. Production must therefore be governed by inputs the organism receives through other channels—environmental and host-derived signals detected through confirmed non-farnesol sensing infrastructure.

This reframes the absent receptor from a single anomalous observation into a design inference. The biochemical computer reads the host environment through a diverse array of confirmed input channels, adjusts its metabolic and signaling output accordingly, and ceases or modulates farnesol production when the input signals change. The effector is responsive, not constitutive. Remove the signal, and the API broadcast changes.

5.7.2 The Confirmed Input Channel Inventory

The scope of the organism's environmental sensing is substantially broader than the quorum-sensing model implies. *C. albicans* possesses confirmed receptors or binding proteins for at least eight classes of host signal, in addition to multiple environmental sensing modalities:

Reproductive endocrine axis

C. albicans possesses a dedicated estrogen-binding protein (Ebp1) that binds mammalian estrogens with high affinity, and estradiol directly stimulates the yeast-to-hyphal morphological transition in a dose-dependent manner (Feldman *et al.*, 1982; Zhang *et al.*, 2000; Cheng *et al.*, 2006). Estrogen-adapted *C. albicans* evades innate immune detection through enhanced acquisition of the complement regulatory protein Factor H via the cell surface protein Gpd2 (Kumwenda *et al.*, 2022). Specific, high-affinity binding sites for human luteinizing hormone (hLH) and human chorionic gonadotrophin (hCG) have been characterized in *Candida* species, with binding producing receptor-mediated elevation of adenylate cyclase—a functional intracellular signaling cascade (Bramley *et al.*, 1990; 1991; Williams *et al.*, 1990). hLH and hCG increase the rate of yeast-to-mycelium transition. The response is specific: human follicle-stimulating hormone (hFSH), thyroid-stimulating hormone (hTSH), growth hormone (hGH), and prolactin (hPrl) did not affect the transition (Kinsman *et al.*, 1988). The organism reads the pituitary hormone that triggers ovulation and drives testosterone production in Leydig cells.

Steroid and androgen sensing

C. albicans possesses sterol-binding proteins that respond to androgenic sterols (reviewed in Stevens, 2010). The organism can convert androstenediol and androstenedione into

testosterone *de novo*. Androgenic anabolic steroids increase *C. albicans* biomass and proteolytic activity in a dose-dependent manner (2019). Male mice are significantly more susceptible to systemic *C. albicans* than female mice; gonadectomized males match female resistance; supplementation with 5α-dihydrotestosterone restores susceptibility in both sexes (Arroyo-Mendoza *et al.*, 2020). The organism's relationship with the host androgen environment is bidirectional: it senses androgens, its virulence is modulated by them, and it can synthesize testosterone from precursors.

Stress hormone axis

A corticosteroid-binding protein with high affinity for corticosterone and progesterone has been characterized in *C. albicans* (Loose and Feldman, 1981; 1982). This places the organism at the interface of the host's hypothalamic-pituitary-adrenal (HPA) axis, sensing the primary stress hormone output.

Cholinergic system

As described in Section 5.5, *C. albicans* possesses a functional muscarinic receptor responsive to acetylcholine (Nile *et al.*, 2018; Rajendran *et al.*, 2015). Acetylcholine is the primary neurotransmitter of the parasympathetic nervous system and the vagus nerve, and is the principal mediator of heart rate deceleration through muscarinic M2 receptors on the sinoatrial node. An organism with a confirmed muscarinic receptor, residing in the gut—the primary innervation territory of the vagus nerve—has direct access to the parasympathetic arm of autonomic cardiac regulation. This connects the cholinergic interface described in Section 5.5 to the cardiac perfusion architecture described in Section 4.3.

Dopaminergic signaling

Clozapine, an antipsychotic that blocks G-protein-coupled dopamine receptors, inhibits *C. albicans* morphogenesis through the Gpr1 receptor, a confirmed GPCR in *C. albicans* that feeds into the cAMP-PKA signaling cascade (Midkiff *et al.*, 2011). While no dedicated dopamine receptor has been identified, the organism's primary morphogenetic GPCR responds to a dopamine receptor antagonist, indicating functional overlap between the organism's environmental sensing and the host's dopaminergic signaling landscape.

Environmental sensing modalities

The organism detects temperature through the molecular chaperone Hsp90, which functions as a thermometer: its activity changes with temperature, releasing client proteins that activate morphogenetic programs at 37°C (Shapiro *et al.*, 2009). CO_2 and bicarbonate are sensed directly by the adenylyl cyclase Cyr1, which integrates this signal into the cAMP-PKA pathway governing morphogenesis (Hall *et al.*, 2010). Amino acid availability is monitored through the SPS (Ssy1-Ptr3-Ssy5) sensor system, which regulates permease expression and feeds into the alkalinization program described in Section 5.5e (Vylkova *et al.*, 2011). Extracellular pH is sensed through the Rim101 pathway.

Glucose sensing

The organism's glucose detection operates through a dedicated membrane-bound sensor, Hgt4, that is structurally related to hexose transporters but has lost transport function and instead generates an intracellular signal upon glucose binding (Brown *et al.*, 2006). Hgt4 is a high-affinity glucose receptor whose sensitivity is calibrated to concentrations of approximately 5 mM — the normal glucose concentration in human blood (Brown *et al.*, 2006). This is not a coincidence. The organism's glucose sensor is tuned to the metabolic environment it inhabits.

HGT4 expression is repressed when glucose is abundant and induced when glucose is scarce, ensuring the organism monitors the substrate that matters most when it is most informative: during depletion. Deletion of HGT4 impairs both growth on fermentable sugars and the yeast-to-hyphal morphological transition; a mutant form of Hgt4 locked in the 'on' position produces hyperfilamentation (Brown *et al.*, 2006). Glucose sensing is thus directly coupled to the organism's primary morphogenetic decision. The organism does not merely eat glucose. It reads glucose concentration as a signal governing tissue engagement.

This architecture is complemented by a second layer of glucose responsiveness operating through intracellular phosphorylation. *C. albicans* modulates the expression of central metabolic genes in response to glucose concentrations as low as 0.01%, values well below the 0.05–0.1% range maintained in human blood (Rodaki *et al.*, 2009). At these concentrations, glucose also induces oxidative and cationic stress resistance and azole antifungal tolerance, responses absent in the model yeast *S. cerevisiae*, where glucose suppresses stress responses (Rodaki *et al.*, 2009). The organism has rewired glucose sensing from a purely metabolic input into an integrated environmental assessment: glucose availability informs not only what to eat but how to defend itself.

A third glucose-responsive pathway operates through the Gpr1 GPCR and its cognate Gα protein Gpa2, feeding into the cAMP-PKA signaling cascade that governs morphogenesis. However, a critical divergence has occurred in the 200 million years since *C. albicans* and *S. cerevisiae* last shared a common ancestor. In *S. cerevisiae*, Gpr1 senses glucose directly. In *C. albicans*, Gpr1 does not respond to glucose; its confirmed ligands are lactate and methionine (Maidan *et al.*, 2005; Ballou *et al.*, 2016; Schrevens *et al.*, 2018). This rewiring is informative within the coevolutionary framework. Lactate is the metabolic byproduct of immune cell glycolysis during the respiratory burst — macrophages and neutrophils actively engaged in antimicrobial activity produce lactate as a waste product of their own upregulated glycolytic metabolism. An organism that repurposed a sugar sensor into a lactate sensor has converted a nutrient detector into an immune activity detector. It reads the metabolic exhaust of the cells trying to kill it. Methionine, the second confirmed Gpr1 ligand, is the initiator amino acid for all eukaryotic protein translation and a key methyl donor in one-carbon metabolism, providing the organism with information about the host's biosynthetic activity. The Gpr1 pathway thus provides the organism with two streams of host-state information — immune engagement and biosynthetic tempo — through a receptor that its free-living ancestor used to find sugar.

Oxygen tension

C. albicans colonizes niches spanning the full range of oxygen availability in the human body, from the well-oxygenated skin and bloodstream to the significantly hypoxic lower gastrointestinal tract and the near-anoxic interior of the macrophage phagosome (Grahl *et al.*, 2012). Its capacity to operate across this range is not passive tolerance but active sensing and metabolic reconfiguration. Upon encountering low oxygen, the organism executes a comprehensive transcriptional response within minutes: glycolytic and fermentative genes are upregulated, oxidative metabolism genes are repressed, and hypha-specific genes are induced (Setiadi *et al.*, 2006). This response is remarkably fast. Significant transcriptional changes occur within five minutes of oxygen depletion, suggesting that a rapid-onset cue such as ATP depletion from reduced oxidative phosphorylation may serve as the initial alarm (Sellam *et al.*, 2014). The organism senses oxygen depletion through at least two independent mechanisms: a sterol-sensing pathway through the transcription factor Upc2, in which declining ergosterol synthesis (which requires twelve molecules of oxygen per squalene-to-ergosterol conversion) serves as a proxy for

oxygen availability (Synnott *et al.*, 2010); and a sterol-independent pathway regulating glycolytic gene expression through the transcription factors Gal4 and Tye7 (Askew *et al.*, 2009). *C. albicans* lacks any ortholog of the mammalian HIF-1α transcription factor that governs hypoxic adaptation in host cells (Synnott *et al.*, 2010), yet achieves the same functional outcome, ie. metabolic switching from oxidative to fermentative, through entirely different molecular machinery. Thus, the biochemical computer achieves the same solution via wholly different engineering.

The coupling between oxygen sensing and virulence extends beyond metabolism. Under hypoxic conditions, *C. albicans* remodels its cell wall to mask β-glucan, the primary carbohydrate recognized by the innate immune receptor Dectin-1, from the cell surface, reducing phagocytic recognition by macrophages and neutrophils (Pradhan *et al.*, 2018). This masking is mediated through mitochondrial signaling and the cAMP-protein kinase A pathway, connecting oxygen sensing directly to immune evasion through the same signaling cascade that governs morphogenesis. An organism that becomes harder to detect by the immune system precisely when it enters the low-oxygen environments of deep tissue colonization has coupled its environmental sensing to its survival strategy. In the context of the Saline Oscillation Hypothesis, the oxygen-sensing architecture intersects with the substrate multiplexing model described in Section 5.10: oxygen tension tells the organism which metabolic channels to weight, shifting from oxidative to fermentative processing as it moves from aerobic to hypoxic niches within the host. The glucose sensor Hgt4, described above, is particularly important under hypoxic conditions — HGT4 deletion impairs growth on fermentable sugars most severely when respiration is reduced (Brown *et al.*, 2006), indicating that glucose sensing and oxygen sensing are functionally linked. The organism does not sense these parameters independently. It integrates them.

Input Channel Summary

In total, the organism possesses confirmed receptors or binding proteins for estrogen, luteinizing hormone, corticosteroids, progesterone, androgens, and acetylcholine, plus environmental sensors for glucose (Hgt4, calibrated to human blood concentrations), lactate and methionine (Gpr1), temperature, CO_2, pH, amino acid availability, and oxygen tension. This inventory is almost certainly incomplete. Approximately 1,300 *C. albicans* genes have no orthologs in other yeast species and remain functionally uncharacterized. The organism's input channel list is defined by what researchers have tested, not by what the organism detects. The absence of evidence for sensing of thyroid hormones, natriuretic peptides, oxytocin, or erythropoietin reflects the fact that these interactions have never been investigated, not that they do not occur.

The organism has at least thirteen confirmed ears. It has no receptor for its own primary output. It listens to the host. It does not listen to itself.

Table 1: Confirmed Host Signal and Environmental Sensing in *C. albicans*

Signal Class	Specific Signal	Receptor / Mechanism	Functional Response	Key Citation(s)
Reproductive	17β-Estradiol	Estrogen-binding protein (Ebp1)	Dose-dependent yeast-to-hyphal transition; complement evasion via Factor H/Gpd2	Feldman et al., 1982; Kumwenda et al., 2022

Reproductive	Luteinizing hormone (hLH) / hCG	Specific high-affinity binding sites; adenylate cyclase elevation	Increased yeast-to-mycelium transition; intracellular cAMP cascade	Bramley et al., 1990; 1991; Williams et al., 1990
Reproductive	Testosterone / androgens	Sterol-binding proteins	Increased biomass and proteolytic activity; de novo testosterone synthesis	Steroids, 2019; Arroyo-Mendoza et al., 2020
Stress	Corticosterone / progesterone	Corticosteroid-binding protein (high affinity, stereospecific)	Modulation of growth and morphogenesis	Loose & Feldman, 1981; 1982
Autonomic	Acetylcholine	Functional muscarinic receptor	Inhibition of biofilm formation; modulation of morphological transition	Nile et al., 2018; Rajendran et al., 2015
Dopaminergic	Dopamine (indirect)	Gpr1 GPCR (responds to dopamine receptor antagonist clozapine)	Inhibition of morphogenesis via cAMP-PKA pathway	Midkiff et al., 2011
Environmental	Temperature (37°C)	Hsp90 molecular chaperone	Activation of hyphal morphogenetic programs	Shapiro et al., 2009
Environmental	CO_2 / bicarbonate	Adenylyl cyclase Cyr1 (direct binding)	Activation of cAMP-PKA morphogenesis pathway	Hall et al., 2010
Environmental	Amino acid availability	SPS sensor system (Ssy1-Ptr3-Ssy5)	Permease expression; alkalinization program	Vylkova et al., 2011
Environmental	Extracellular pH	Rim101 pathway	pH-responsive gene regulation; morphogenesis	Vylkova, 2017
Environmental	Glucose (extracellular)	Hgt4 membrane sensor (transporter-like, non-importing)	Hexose transporter induction; yeast-to-hyphal transition; calibrated to ~5 mM (human blood glucose)	Brown et al., 2006
Environmental	Lactate / methionine	Gpr1 GPCR / Gpa2	cAMP-PKA pathway activation; morphogenesis. Lactate = immune cell metabolic output; methionine = biosynthetic activity marker	Maidan et al., 2005
Environmental	Oxygen tension	Upc2 (sterol depletion) + Gal4/Tye7 (glycolytic switch)	Metabolic reconfiguration; hyphal induction; β-glucan masking (immune evasion)	Setiadi et al., 2006; Synnott et al., 2010; Pradhan et al., 2018
Upstream Governance (no direct receptor)				
Autonomic (sympathetic)	Catecholamines (epi/norepi)	**NO DIRECT RECEPTOR — governed upstream via ECS-mediated modulation of pre-synaptic release**	Minimal direct effect at pharmacological concentrations	Wurster et al., 2021; Schlicker & Kathmann, 2001

[1] FSH, TSH, growth hormone, and prolactin were specifically tested and produced no effect on *C. albicans* morphological transition (Kinsman *et al.*, 1988). These are anterior pituitary output hormones. The coevolutionary framework (Section 4.3) proposes that the organism modulates pituitary hormone secretion through perfusion governance and ECS signaling to pituitary

CB1 receptors, consistent with the prediction that direct sensing is required only for hormones providing inbound environmental information, not for hormones the organism controls through upstream management of the producing gland.

[2] This inventory reflects tested interactions only. Approximately 1,300 *C. albicans* genes have no orthologs in other yeast species and remain functionally uncharacterized. Regarding thyroid hormones (T3/T4), natriuretic peptides (ANP/BNP), oxytocin, or erythropoietin, to our knowledge, these host signaling pathways remain largely unexplored in *C. albicans* host–fungal interaction research.

5.7.3 The Distributed System

The operational picture described in the preceding sections is not a single organism executing a single program at a single location. It is a distributed system in which genetically identical cells across the host simultaneously occupy different morphological states, different metabolic configurations, and different signaling roles. In the gut lumen, yeast-form cells harvest dietary glucose and maintain the commensal niche through farnesol-mediated environmental management. In mucosal biofilms, communities produce extracellular vesicles with temporally variable cargo. In tissue niches distant from active immune surveillance, dormant cells persist in metabolically quiescent states, pre-positioned for reactivation. In sites of active invasion, hyphal cells secrete the Ece1 peptide panel and candidalysin while the surrounding yeast-form population maintains the local immune suppression that permits the invasion to proceed. At no single site does the organism's full capability manifest. Across the host, the aggregate system operates at a scale no individual cell represents.

The closest analogy in established biology is a eusocial insect colony. No individual ant comprehends the architecture of the nest it participates in. No single ant builds the structure, farms the fungus, feeds the queen, defends the perimeter, and scouts for new resources simultaneously. But the colony does all of these things through distributed specialization without central command. The colony's behavior is emergent from individual agents following local rules. A biologist observing a single ant at a single location would not infer the colony's architecture. The same observational limitation applies to *C. albicans* research: a study characterizing farnesol's effect on dendritic cells *in vitro* is observing one agent at one location performing one function. The system's architecture is visible only when the individual observations are assembled, which is the task this paper attempts.

The distinction, and the reason the analogy is imperfect, is that a eusocial colony achieves distributed specialization through morphologically distinct castes — workers, soldiers, reproductives — encoded in developmental programs. *C. albicans* achieves equivalent functional distribution from a single genome through the epigenetic and transcriptomic heterogeneity described in Section 5.8. Different cells within a genetically identical population run different transcriptional programs (Dumeaux *et al.*, 2023), toggling between commensal maintenance, immune evasion, tissue invasion, dormancy, and environmental sensing without requiring different body plans. The biochemical computer does not need castes. It needs chromatin switches.

A note on colonization prevalence. *C. albicans* is conventionally described as colonizing the gastrointestinal tract of 40–60% of healthy humans (Romo and Kumamoto, 2020). This figure is a detection threshold, not a prevalence measurement. It reflects the sensitivity of the sampling method, the anatomical site tested, and the moment of collection. *C. albicans* is an obligate commensal with no known environmental reservoir, transmitted vertically from mother to child through birth canal transit and breastfeeding (Kumamoto, 2011; Ost and Round, 2023). An organism with this transmission biology and no independent existence outside the host is not present in 40–60% of humans and absent from the remainder. It is more accurately described as

near-ubiquitous in humans, with detectable abundance at any given site and time varying with colonization density, niche, immune status, dietary conditions, and the detection methodology employed.

This distinction matters for every section of this paper that references colonization. The organism is not intermittently present or absent. It is continuously distributed across the host at variable density. What differs between individuals is not whether the organism is there but how much of it is active, where it is concentrated, what morphological and transcriptional states it occupies, and consequently what aggregate signaling output it produces at each tissue interface. The distributed system is always running. The volume varies.

The empirical defense of this framing — methodology-dependent detection across mammalian species, sample-site bias documented in same-animal comparisons, and the biological features that make true absence implausible — is developed at length in (Craddock, Pan-Mammalian).

5.7.4 Pituitary Governance: The Relay Station

The specificity of the organism's hormone sensing raises a question that the receptor inventory alone cannot answer. Kinsman *et al.* (1988) tested seven mammalian hormones for effects on *C. albicans* morphological transition. Luteinizing hormone produced a specific, significant response. Follicle-stimulating hormone, thyroid-stimulating hormone, growth hormone, and prolactin did not. This selectivity has been treated in the literature as a characterization detail. Within the coevolutionary framework, it is a design signature.

The hormones that produced no direct response share a common origin: all are anterior pituitary output. FSH, TSH, GH, and prolactin are synthesized and secreted by the anterior pituitary gland. The organism's relationship to these hormones may not require direct sensing because it has access to the gland that produces them.

Section 4.3 describes the perfusion management architecture through which the symbiont governs pituitary blood supply via IVC dynamics and the cardiac suction mechanism. The hypothalamus and pituitary stalk are the primary exceptions to the blood-brain barrier, lacking the tight endothelial junctions that exclude blood-borne molecules from brain tissue. Change the perfusion to this gland, and its output changes. The organism does not need a TSH receptor if it can modulate TSH secretion by managing the blood supply to the cells that produce it. It does not need an FSH receptor if it governs the gland upstream of FSH release.

The ECS provides a second, parallel governance pathway. CB1 receptors are expressed on pituitary cells, and endocannabinoid tone modulates pituitary hormone secretion across the hypothalamic-pituitary-gonadal, hypothalamic-pituitary-adrenal, and hypothalamic-pituitary-thyroid axes (Pagotto *et al.*, 2006). The organism's ECS signaling, described throughout this paper as the primary interface layer, acts directly on the gland's secretory function. Two independent mechanisms, perfusion control and ECS-mediated signaling, converge on the same target organ, providing redundant governance of pituitary output without requiring the organism to detect any of the individual hormones that output comprises.

This produces a two-tier model of endocrine interaction. The first tier consists of hormones the organism senses directly through confirmed receptors or binding proteins: estrogen, luteinizing hormone, corticosteroids, progesterone, androgens, and acetylcholine. These are inbound signals that provide the organism with information about the host's current physiological state—reproductive status, stress level, autonomic tone, gonadal axis activity. The organism reads these because it needs to know what is happening. The second tier consists of

hormones the organism modulates indirectly through governance of the pituitary: FSH, TSH, growth hormone, prolactin, and potentially ACTH. These are outbound adjustments that the organism makes to the host's endocrine environment by controlling the relay station that distributes them. The organism does not need to read these because it is writing them.

LH occupies an instructive position in this model. It is the one anterior pituitary hormone for which *C. albicans* does possess specific binding sites with a functional signaling cascade. This is not inconsistent with the governance model. LH drives testosterone production in Leydig cells and triggers ovulation—events with immediate consequences for the organism's tissue environment and immune landscape. Sensing LH may provide the organism with confirmation that its pituitary governance is producing the intended downstream effects, functioning as a feedback channel rather than a primary input. Alternatively, LH sensing may predate the development of full pituitary governance, representing the original direct sensing channel for gonadal axis information that was later supplemented by upstream control. Both interpretations are consistent with the coevolutionary framework; neither is currently testable.

The practical consequence of this two-tier model is that the organism's endocrine influence extends far beyond what the receptor inventory implies. The eleven confirmed sensing channels represent the organism's ears. The pituitary governance architecture represents its voice. Through perfusion management and ECS signaling to the anterior pituitary, the organism has indirect access to every endocrine axis the pituitary controls: thyroid function (via TSH), adrenal function (via ACTH), growth and metabolic regulation (via GH), reproductive cycling (via FSH), and lactation (via prolactin). The organism does not need twelve receptors when it has control of the switchboard.

5.7.5 Catecholamine Governance: Upstream Control, Not Direct Sensing

Catecholamines (epinephrine and norepinephrine) are the primary mediators of the sympathetic nervous system—the fight-or-flight response, acute vasoconstriction, heart rate acceleration, and blood pressure elevation. A direct test of pharmacological concentrations of epinephrine and norepinephrine on *C. albicans* growth, morphogenesis, stress tolerance, and virulence found minimal effects across all measures (Wurster *et al.*, 2021). The organism does not appear to respond to catecholamines as an environmental signal.

This negative result is informative rather than limiting. Endocannabinoid signaling through CB1 has been shown to regulate the release of the classical neurotransmitters norepinephrine, dopamine, serotonin, and acetylcholine at the pre-synaptic neuron (Schlicker and Kathmann, 2001; Markey *et al.*, 2020). The organism does not need a catecholamine receptor because it operates upstream of catecholamine release. It governs the faucet through the ECS. For a biochemical computer, there is no need to build a sensor for a signal you are already controlling.

This creates a complete autonomic access model. The parasympathetic arm—the brake—is accessed directly through the confirmed muscarinic acetylcholine receptor. The sympathetic arm—the accelerator—is governed indirectly through ECS-mediated modulation of catecholamine release. Two arms, two mechanisms, one organism. The parasympathetic channel is a listener. The sympathetic channel is a governor.

The functional consequences of this dual autonomic access are documented in the longitudinal case study (Craddock, Redacted Science). During standardized workplace fitness testing, the subject recorded the fastest heart rate recovery time to baseline in the tested population, a metric that directly reflects cardiovascular regulatory efficiency during the

transition from sympathetic-dominant exertion to parasympathetic-dominant recovery. The simplest explanation is that two regulatory systems managing this transition—the host's autonomic nervous system and the symbiont's parallel ECS signaling—outperform one.

More broadly, dual autonomic governance provides the mechanistic basis for the enhanced endurance, crisis tolerance, and blood pressure management described in Section 4.3. Sustained running benefits from simultaneous maintenance of sympathetic drive (through permissive ECS tone allowing catecholamine release) and parasympathetic recovery modulation (through the muscarinic interface). Crisis tolerance during acute physiological stress reflects the symbiont's capacity to dampen a catecholamine surge that would otherwise produce vasovagal syncope, while maintaining perfusion through the parallel ECS controller. Blood pressure management operates through catecholamine governance in concert with the prostaglandin-mediated vascular tone control described in Section 5.5d.

The redacted source article described the terminal phase of the program in terms directly consistent with this model: the heart maintained normal rhythm without crisis, beating steadily until cessation, attributed specifically to hormonal control (Craddock, Redacted Science). This is the predicted outcome of complete dual autonomic governance. The sympathetic arm does not spike because catecholamine release remains under ECS management. The parasympathetic arm does not collapse because the muscarinic interface remains operational. No arrhythmia. No fibrillation. No autonomic storm. The managed heart does not panic. It simply runs until substrate is exhausted. A single-controller system—the autonomic nervous system operating alone—produces the opposite: terminal arrhythmia, catecholamine storm, chaotic cardiac output. The dual-controller architecture prevents this.

5.7.6 Predicted Thyroid-Phase Signature

The program documented in the longitudinal case study operates through organ systems sequentially, with documented involvement of liver, kidney, pancreas, and adrenal tissue at different stages (Craddock, Redacted Science). The thyroid gland, which governs basal metabolic rate, body temperature regulation, heart rate, and cognitive tempo, is too central to metabolic regulation to be excluded from this progression.

If the organism's program includes an apoptotic phase involving thyroid tissue, the organism would require the capacity to sense thyroid hormone levels in order to calibrate the timing and depth of its activity. An organism that can read estrogen, cortisol, luteinizing hormone, and androgens but cannot read the primary metabolic rate hormone would have a critical gap in its endocrine surveillance. The absence of published evidence for *C. albicans* thyroid hormone sensing reflects the absence of investigation, not the absence of capability.

A thyroid-phase apoptotic event would produce a defined transient signature: disrupted thyroid cells releasing their stored T3 and T4 into circulation, producing a period of elevated thyroid hormone levels before the released stores are metabolized or cleared. The physiological expression of transient hyperthyroidism includes heightened mental clarity, increased energy, accelerated cognitive processing, and elevated metabolic rate. This is a defined window of enhanced function, not a permanent state.

The longitudinal case study documents such a window: a period of approximately one month in June 2025 characterized by extraordinary mental clarity and creative output, specifically noted as qualitatively distinct from baseline cognitive function (Craddock, Redacted Science). This observation is from a single subject and is not diagnostic. It is, however, internally consistent with a thyroid-phase release event, and consistent with the broader pattern

documented in the case study of clarity surges bookended by transition periods. Each organ system's apoptotic phase may produce its own transient hormonal or metabolic signature as stored contents are released. The thyroid phase, if it occurs, would produce the most cognitively visible signature due to the direct relationship between thyroid hormone levels and mental acuity.

This remains a prediction, not an established finding. It is documented here because it is testable: thyroid function panels obtained during a clarity surge window in a subject undergoing the program would show elevated free T3 and T4 with suppressed TSH, the standard laboratory signature of transient thyrotoxicosis from tissue disruption. The prediction exists in the record. The test awaits a subject with access to clinical monitoring during the appropriate phase.

5.8 Evolutionary Adaptability: The Biological Prepper

The sophistication of *C. albicans*'s signaling architecture raises the question of how such a system is maintained under environmental pressure. Recent single-cell transcriptomic work by Dumeaux *et al.* (2023), published in eLife, provides a striking answer.

Using nanoliter droplet-based single-cell sequencing, Dumeaux and colleagues profiled thousands of individual *C. albicans* cells from isogenic populations, genetically identical cells from a single colony. They found that before any drug exposure, the population already exhibited heterogeneous expression of cytoprotective programs. Different cells within the same colony were stochastically running different transcriptional programs: some upregulating efflux pumps, some reinforcing cell walls, some in alternative metabolic states. This is "bet hedging," the pre-positioning of diverse survival configurations against threats that have not yet arrived.

When antifungal drugs were applied, the surviving cells partitioned into distinct subpopulations, each with a unique survival strategy involving different regulatory programs. The organism did not mount a single response. It deployed a portfolio of responses, distributed across the population, with different cells pursuing different survival paths simultaneously. At two days post-treatment, a burst of chromosomal aberrations was observed: controlled genome destabilization, expanding the search space for novel genetic solutions. Once resistance was achieved, the genome restabilized (Dumeaux *et al.*, 2023).

This reflects a pre-existing adaptive architecture shaped by evolutionary selection. The organism maintains standing diversity in the face of unpredictable threats, deploys distributed survival strategies under environmental pressure, undergoes regulated increases in genomic variability when prior adaptive states become insufficient, and subsequently stabilizes genomic architecture as selectively favored configurations emerge. The biochemical computer does not predict its next move. It has already prepared for contingencies it has not yet encountered. Proactive diversification, shaped by prior evolutionary pressures, precedes the onset of specific selective events. Microbial regulatory architectures may encode evolutionary "memory" of environmental variability, producing population-level response distributions that resemble probabilistic anticipation of future stress. Observed diversification may reflect evolutionary encoding of historical environmental variability rather than *de novo* anticipation of novel stress. (Mitchell *et al.* (2009), Tagkopoulos *et al.* (2008))

Biological bet hedging is not unique to *Candida*. The mammalian adaptive immune system maintains a massive library of naive B and T cells, each pre-configured with a different receptor specificity generated randomly through V(D)J recombination, before encountering any pathogen. Plant species produce seeds with variable dormancy periods within a single generation, distributing germination across unpredictable growing seasons. Bacterial persister

cells spontaneously enter dormant, antibiotic-tolerant states within genetically identical populations before any antibiotic exposure.

But none of these systems combine bet hedging with controlled genome destabilization, cross-kingdom chemical signaling, host receptor access, morphological tissue mobility, and immune surveillance management simultaneously. The individual elements exist elsewhere in biology. The combination, as far as current characterization reveals, is unique to *Candida*. In commensal terms, *C. albicans* occupies the ecological position of the organism that cannot be eradicated, ie. candida represents a globally entrenched commensal lineage whose eradication would require interventions incompatible with host survival or ecosystem stability. Not because it is optimized for any single threat, but because it is pre-adapted for persistence across the full spectrum of environmental contingencies. It does not predict what will happen next. It has already prepared for it. A 14.3-megabase genome encoding approximately 6,400 genes, a third of the human gene count, running the most complete non-sentient survival architecture in known biology.

The mechanistic basis of the standing diversity described above is epigenetic rather than genetic. *C. albicans* possesses a comprehensive chromatin modification toolkit: histone acetyltransferases (HATs), histone deacetylases (HDACs), and histone methyltransferases regulate the commensal-to-pathogen lifestyle switch, the yeast-to-hyphal morphological transition, and the white-opaque phenotypic switch through reversible post-translational modification of histone proteins (Sagar *et al.*, 2017; Freire-Benéitez *et al.*, 2021). Transient exposure to the HDAC inhibitor trichostatin-A dramatically increases white-to-opaque switching frequency, and targeted deletion of the deacetylase gene HDA1 produces the same effect (Klar et al., 2001), demonstrating that a single chromatin modification can trigger a phenotypic transition without DNA sequence change. The histone deacetylase Sir2 mediates cell wall remodeling that enables host cell adhesion and immune escape, and contributes to carbon utilization under hypoxic conditions (Chen *et al.*, 2024), directly coupling chromatin state to both immune evasion and metabolic adaptation.

The organism has also evolved a clade-specific chromatin innovation: a variant histone H3 (H3V_CTG), exclusive to the CTG clade of ascomycetes that includes *C. albicans* but absent from all other ascomycetous fungi analyzed, modulates the biofilm gene circuit at the chromatin level (Shivarathri *et al.*, 2019). H3V_CTG occupancy on biofilm gene promoters makes them less accessible to transcription modulators, maintaining the commensal growth state. When H3V_CTG levels drop, biofilm transcription programs activate. The authors propose that this variant histone evolved specifically to balance the commensal and pathogenic states, enhancing the organism's success as a commensal by restraining its pathogenic capabilities at the chromatin level — releasing them only when environmental conditions warrant.

At the DNA level, methylation in *C. albicans* is primarily localized within structural genes governing dimorphic transition, white-opaque switching, and iron metabolism, and directly modulates transcriptional activity (Mishra *et al.*, 2011). Transcriptionally repressed methylated loci exhibit increased C-to-T transition frequencies during asexual growth, linking epigenetic repression to directed mutational bias — a mechanism by which chromatin state can influence the trajectory of genetic variation under environmental pressure. Bartelli *et al.* (2018) provided the first evidence for mitochondrial genome methylation in *C. albicans*, demonstrating that host-mimicking conditions (hypoxia, 37°C) alter mitochondrial methylation patterns in a strain-specific manner over 12 weeks of experimental evolution, with no corresponding sequence changes in the mitochondrial DNA. This adds an energy regulation layer to the epigenetic

toolkit: the organism can epigenetically modify its own mitochondrial genome in response to host conditions without altering the underlying sequence.

The distinction between epigenetic and genetic adaptation is fundamental to the coevolutionary framework. Genetic mutation is slow, stochastic, and irreversible on individual timescales. Epigenetic modification is fast, responsive to environmental signals, and reversible. An organism that can toggle between commensal and invasive programs through chromatin remodeling operates on timescales faster than the host immune system can adapt, and can reverse course if conditions change. The transcriptomic heterogeneity described by Dumeaux *et al.* (2023), namely different cells within an isogenic population running different transcriptional programs before any environmental challenge, is the phenotypic output of this epigenetic diversity.

The observed bet-hedging behavior in *Candida albicans* cannot be attributed solely to stochastic variation in gene expression. Instead, it reflects chromatin-encoded regulatory memory maintained through dynamic activity of histone modifiers, lineage-specific chromatin features, and reported cytosine methylation pathways. Within the framework of a biochemical computational system, these chromatin states function as a substrate for evolutionary information retention, biasing population-level response distributions under environmental stress. This chromatin-mediated layer constitutes one of the fastest adaptive components of the organism's survival architecture, enabling rapid shifts in dominant phenotypic states without requiring *de novo* regulatory innovation.

V.IX Physiologic Coevolution Outcomes

Coevolution requires all participants to adapt. This section presents three separate examples of apparent coevolution: post-orgasm prolactin as a reset mechanism, elevated nitric oxide tone as a required enabler of reproductive function under the low-volume Homo candidus phenotype, and host-synced circadian outsourcing by C. albicans.

V.IX.I Prolactin Reset as a Recovery-Axis Adaptation

[*I'm back, so let's talk about reproduction*]

Post-orgasm prolactin surge in male humans is a physiological phenomenon without a settled evolutionary explanation under the standard framework. The surge produces the refractory period and the characteristic shift from arousal to satiety. Within the coevolutionary framework, the mechanism is reinterpreted: the organism produces continuous baseline tension as a byproduct of its normal signaling activity. This manifests as a chronic adrenal/sympathetic load — produced through both sustained overtaxing of the adrenals and direct organism interfacing with the adrenal axis (see §X.X) — that *Homo candidus* carriers cope with as a standard feature of every phase of the program [*You have a continual feeling of tension, which is probably why THC helps too*].

The host requires functional discharge pathways to maintain operational capacity. Multiple pathways exist: sustained aerobic exercise discharges the load through anandamide release and parasympathetic recovery; sexual activity discharges it through the dopaminergic-prolactin sequence; phytocannabinoid use, where available, supplements the endocannabinoid pool the organism is consuming. The post-orgasm prolactin surge in male humans is one of these release valves: it terminates the symbiont-driven arousal state, discharges the accumulated adrenal load that built during arousal, restores baseline endocrine tone, and permits normal cognitive function to resume. Individuals with a robust prolactin reset functioned effectively

between reproductive events; individuals without it remained in prolonged tension states with correspondingly degraded fitness on every other axis [*There were some Haunted Gallery photos I didn't share in Redacted Science, the book. It is safe to say the first cohort figured this out*]. Selection ran in one direction. The post-orgasm prolactin surge is not a mammalian universal running on autopilot in humans. It is a specifically tuned circuit that pairs with the symbiont's tension-producing capacity and provides one of the discharge channels the host requires to remain functional.

The prolactin discharge mechanism is not unique to humans but is documented across multiple mammalian lineages, with the trigger architecture varying by species in ways that map onto reproductive ecology. Stallions show anticipatory surge in response to mere presence of estrous mares, before any sexual contact occurs (Colborn, 1991); rats and mice show sustained surge across the consummatory phase, peaking on second ejaculation in rats (Valente et al., 2021); humans show climax-locked surge with baseline maintained through anticipation, foreplay, and intercourse, releasing only at orgasm.

The shared underlying machinery is consistent with *Mammalia candidus*: the discharge mechanism evolved alongside the symbiont's tension-producing architecture and is therefore mammal-general. The variation in trigger timing is consistent with species-specific tuning under different reproductive ecologies. Anticipation-triggered discharge fits the brief, competitive encounters of equine reproduction. Sustained discharge fits the multi-intromission sequences of rodent reproduction. Climax-locked discharge fits the prolonged, cognitively demanding, socially complex sequences of human reproduction, where the host requires full operational capacity throughout the engagement requiring completion of the reproductive event before discharge can occur. The human variant is the most demanding architecture: maximum tension sustained across the longest engagement window, with discharge gated to the single event that confirms reproductive success. This is consistent with the broader pattern in which humans run the deepest version of the *Mammalia candidus* program and exhibit the most sophisticated host-side adaptations to it. [*Mankind has the best sex, which explains a lot…*]

The species in which the prolactin discharge mechanism is best documented — humans, rats, mice, horses — cluster among the mammalian taxa most commonly cited for cognitive capacity and behavioral complexity. The framework predicts a positive correlation between depth of symbiont integration (as measured by host-side adaptations including the prolactin mechanism, ECS density, HPA axis tuning, and others) and behavioral/cognitive complexity across mammalian lineages. Systematic testing of this prediction is proposed as a future direction within the *Mammalia candidus* framework (Craddock, Pan-Mammalian). [*Should be interesting*]

Direct neuroimaging support for the climax-locked timing architecture in humans was established by Huynh, Willemsen, and Holstege (2013, *NeuroImage*), who developed a PET protocol capable of detecting pituitary activation against the high baseline pituitary blood flow that had historically obscured it. In their female cohort, sexual orgasm produced detectable increases in pituitary blood supply, while clitoral stimulation alone, attempted orgasm without climax, and faked orgasm produced no detectable activation. The pituitary was silent through arousal and stimulation; it fired at the climax event itself. Their interpretation attributed the activation to oxytocin and prolactin release driving downstream reproductive coordination. The framework reading adds that the climax-locked pattern is the imaging signature of the discharge architecture described above: tension sustained through the engagement window, discharge gated to the reproductive event [*Homo candidus women needed release of tension, too*]. The same paper found no detectable pituitary activation during male ejaculation, consistent with the lower

magnitude of male-side oxytocin and prolactin release relative to females. Within the framework, this sex difference reflects the asymmetry of reproductive task complexity — the female pituitary running a more demanding coordinated release program at orgasm than the male pituitary — and is consistent with the documented sex differential in pituitary microadenoma prevalence (Craddock, Biochemical Computer).

V.IX.II Nitric Oxide Tuning as a Reproductive-Axis Adaptation

Penile erection requires nitric oxide-mediated vasodilation of the cavernosal arteries and relaxation of trabecular smooth muscle, producing blood pooling in the corpora cavernosa sufficient to achieve functional engorgement [*You never knew it was that…complicated, right?*]. Under standard mammalian circulatory conditions, this requires adequate arterial pressure and blood volume. Under the *Homo candidus* phenotype described in §VIII, the circulatory state is suction-dominant and functionally low-volume relative to the pump-dominant mammalian default. Standard pressure-driven filling of the corpora would be insufficient to achieve or sustain erection under these conditions, producing impotence and thus reproductive sterility absent a compensating host-side adaptation. A reproductively sterile phenotype would not persist [*definitely not a selective advantage*]. That the coevolutionary program persisted establishes that the compensating adaptation exists: the nitric oxide pathway has been tuned on the host side to achieve functional engorgement on reduced volume. The vasodilatory response to NO is amplified, the local tissue machinery downstream of NO is optimized for the low-volume state, and the net effect is that erection remains functional under circulatory conditions that would fail in the non-adapted mammalian default.

The redacted 1995 source article identified nitric oxide as relevant to the framework. The mechanistic interpretation presented here places NO as the reproductive-axis companion to the prolactin reset described above, with one adaptation permitting the act to occur under low-volume conditions and the other permitting recovery from it. The two adaptations are physiologically coupled: the same low-volume circulatory state that requires NO tuning to enable erection also produces the chronic adrenal/sympathetic load that requires the prolactin discharge mechanism for recovery. Both are responses to the same underlying condition — the symbiont's management of host circulation through the suction-dominant architecture — addressed at different points in the reproductive sequence. The system did not develop one adaptation and then the other independently. They are paired components of a single co-adapted reproductive architecture, both required for the *Homo candidus* phenotype to remain reproductively viable.

A candidate mechanism for the elevated nitric oxide capacity inferred in Homo candidus is suggested by the established biphasic response of nitric oxide synthesis to tissue hypoxia. Short-term or mild tissue oxygen deficiency stabilizes HIF-1α, which transcriptionally upregulates eNOS, iNOS, and VEGF, producing compensatory vasodilation. The symbiont’s management of perfusion via the ECS interface is proposed to generate chronic mild hypoxic stress at peripheral tissue interfaces — sufficient to select for amplified baseline NO production capacity and robust cofactor maintenance over evolutionary time, yet maintained within the window that avoids eNOS uncoupling. This upward tuning of an existing mammalian pathway would enable sustained NO-dependent functions (including erection) despite the lower peripheral driving pressures inherent to suction-dominant circulation. [*The symbiont starves the tissue just enough to teach it to bloom on less. A million years of training the host to do more with less air, until the trick became permanent. The erection that shouldn't work, works — because the cells learned to stretch. Fistpump.*]

V.IX.III Circadian Outsourcing as a Temporal-Axis Adaptation

C. albicans lacks the core fungal circadian oscillator components — the FRQ, WC-1, WC-2, FRH, and FWD-1 proteins that drive rhythm in *Neurospora crassa* and related ascomycetes (Salichos and Rokas, 2010). Whether this absence represents loss of an ancestral system or absence of a system that never developed in the lineage is debated in the fungal phylogenetics literature; either interpretation supports the framework reading [*Either way, It has no natural rhythm, but we still go to karaoke night*].

The standard explanation for the absence in *S. cerevisiae* and similar yeasts is that facultatively fermentative organisms in stable laboratory or fermentation environments derive no fitness benefit from anticipating environmental light cycles. This explanation does not extend cleanly to *C. albicans*, an obligate commensal that has never inhabited a stable, rhythm-free environment — it has been continuously embedded in mammalian hosts whose own circadian architecture (suprachiasmatic nucleus, melatonin secretion, cortisol rhythm, body temperature cycling, feeding rhythm) imposes a rhythm on every sensor the organism possesses.

Within the coevolutionary framework, the absence is interpreted as outsourcing rather than degradation: maintaining or evolving an independent endogenous clock would be redundant when the host provides one with higher fidelity than the organism could achieve. The economy is not the elimination of a now-useless gene set; it is the absence of selective pressure to develop or retain one when the partner already does the work.

The symmetric host-side adaptation is that mammalian circadian physiology has in turn accommodated the organism's metabolic demand cycling: nocturnal versus diurnal variation in fungal gene expression follows host rhythm without the organism needing to generate or impose its own. Two clocks would create conflicts. One clock shared through signaling is more efficient. The host keeps the clock; the organism reads it [*and has all the tools to adjust it*].

V.IX.IV Bidirectional Coevolution as Structural Feature

The three adaptations described above — prolactin reset architecture, nitric oxide tuning, and circadian outsourcing — operate on independent physiological systems and address distinct demands the symbiont places on the host. Each is documented in the standard literature without a unifying explanation [*Wait, does this count?*]. Each makes coherent sense within the *Mammalia candidus* framework as a host-side accommodation to the symbiont's normal operation. Together they establish bidirectional adaptation as a structural feature of the coevolutionary relationship rather than an incidental consequence. A relationship sustained across 200 million years of mammalian lineage history cannot be unilateral [*Just living in the same house with someone will change you in some ways..200 million years?*]. Either the host adapts to the organism's presence at the physiological level, or the organism's presence compromises host function sufficiently to be selected against. The persistence and near-ubiquity of the symbiosis (5.7) establishes that host adaptation has occurred. The three examples documented here are unlikely to exhaust the catalog. Wherever the symbiont's program imposes a sustained demand on host function, host physiology has accumulated the adaptation required to keep that function operational under the imposed demand. [*My ancestors give thanks*]

V.IX.V Testable Predictions

Prediction A (Higher baseline plasma nitrates) Homo candidus-like individuals (or high C. albicans colonization in the right context) should show higher baseline plasma

nitrite/nitrate, elevated eNOS/HIF-1α expression, and better preservation of NO-dependent vasodilation (including erectile function) under moderate stressors.

Prediction B (Increased vulnerability to uncoupling) Homo candidus-like individuals (or high C. albicans colonization in the right context) should also display increased vulnerability to uncoupling (worse endothelial function) under acute severe hypoxia (high altitude, anemia, ischemia) if the tuned system is pushed past the window.

5.9 Positional Authority

Taken together, these findings position *Candida albicans* not merely as a commensal or pathogen but as an emergent ecological coordinating influence within mammalian internal ecosystems. Through evolutionary selection, the organism has come to occupy a disproportionately integrative regulatory position, shaping the dynamics of host-associated biological networks across molecular, cellular, and ecological scales. It is the only known organism in the host microbiome that simultaneously: (1) signals chemically across kingdoms, to bacteria, to other fungi, and to the host; (2) possesses physical tissue mobility via hyphal morphological transition; and (3) accesses the host's endogenous receptor infrastructure, including nuclear transcription factors, ion channels, neurotransmitter receptors, cholinergic receptors, and immune cell differentiation pathways; (4) a confirmed extracellular vesicle delivery system with morphology-dependent cargo programming, temporal cargo variation, and cross-species functional complementation; (5) the molecular infrastructure for cross-kingdom RNA interference, including internal RNA transport, EV-mediated RNA export, and RNA cargo that shifts in response to environmental conditions; (6) active bidirectional pH manipulation through at least two independent metabolic pathways, including the capacity to neutralize the macrophage phagolysosome; (7) an ionic manipulation toolkit (potassium competition, transmembrane pore formation, pH engineering) capable of altering the electrochemical landscape in which the host's Na^+/K^+-ATPase operates; and (8) production of authentic host prostaglandins from host-derived arachidonic acid through an independently evolved biosynthetic pathway, enabling direct molecular mimicry of host inflammatory mediators and competition with host endocannabinoid synthesis for shared lipid precursor.

This is not a value judgment about evolutionary advancement. Evolution does not rank organisms. It is a functional description of positional authority within a system. In the context of the Saline Oscillation Hypothesis, this positional authority explains not only why *Candida* was the organism selected for deeper host integration during periods of electrolyte stress, but how it maintained operational continuity across the oscillation cycles that drove the coevolutionary program described in the preceding sections. The organism did not need to evolve new capabilities to respond to saline oscillation. It needed only to deepen the application of capabilities it already possessed. The ECS was the original interface. The broader control surface, including nuclear receptors, ion channels, neurotransmitter receptors, cholinergic signaling, immune modulation, cross-kingdom chemical authority, EV delivery system, RNA interference infrastructure, and bet hedging were the expanded toolkit that made the deepening sustainable across millions of years of environmental fluctuation. The control surface was already in place. The environmental pressure activated it.

5.10 The Metabolic Substrate Architecture: What It Eats While It Works

Section 5.9 describes what the organism can do. This section describes what it consumes while doing it — and how the answer to that question shifts depending on where in the host the organism is operating, what resources are locally available, and what the program demands at any given moment. The signaling architecture and the metabolic architecture are not independent systems. They are the same system viewed from two directions: one describes how the organism talks to the host, the other describes how it feeds within it. Both run continuously. Both adapt in real time.

C. albicans is metabolically flexible to a degree unusual even among fungi. It can utilize glucose, amino acids, carboxylic acids, fatty acids, N-acetylglucosamine, and lactate as carbon sources, and can switch between glycolytic and gluconeogenic metabolism depending on the local nutrient environment and pathway accessibility (Barelle *et al.*, 2006; Lorenz *et al.*, 2004). This is not a generalist's indifference to what it eats. It is the prerequisite for the distributed system described in Section 5.7 — an organism that simultaneously inhabits the glucose-rich gut lumen, the amino acid-rich tissue interstitium, the lactate-rich interior of a macrophage phagosome, and the lipid-rich environment of the systemic circulation cannot survive on a single fuel. It survives because it can eat whatever is in front of it, wherever it is, and switch strategies when the local menu changes.

The result is not a simple metabolic sequence but a multiplexed substrate landscape: multiple fuel channels operating in parallel across different tissue sites at the same time, with the dominant channel shifting as the program's demands evolve. To understand this landscape, it is necessary to describe each channel, what it provides, and why the organism maintains it.

5.10.1 Substrate Multiplexing: The Parallel Channels

Dietary glucose is the quietest channel. In the gut lumen, yeast-form *C. albicans* harvests glucose from the host's dietary intake, detected through the Hgt4 membrane sensor calibrated to human blood glucose concentrations. That feeds into the cAMP-PKA signaling cascade (Section 5.7). This is the commensal baseline: the organism feeding from the same table as the host, its metabolic demands invisible within the volume of carbohydrate passing through the digestive tract. The host does not notice the tax. The relationship appears benign. Every individual carrying *C. albicans* as a commensal is running this channel right now, whether or not any other channel is active.

Host glycoconjugates and mucosal carbohydrates represent a second, quieter channel operating at epithelial boundaries. The complex sugars embedded in the mucin layer and glycocalyx of mucosal surfaces provide a substrate the organism can access without tissue invasion, sustaining populations at the mucosal interface between the lumen and the tissue. This channel supports the organism's positional presence at the boundary where commensal existence transitions into tissue engagement. The threshold monitored continuously by the distributed system.

N-acetylglucosamine occupies a unique position in the substrate landscape. It is simultaneously a carbon and nitrogen source, a morphogenetic signal, and a location marker. N-acetylglucosamine is a breakdown product of host glycosaminoglycans, the structural molecules of the tissue matrix. When the organism encounters N-acetylglucosamine, it receives two inputs through a single molecule: fuel and the information that it is inside host tissue rather than in the

gut lumen. The molecule feeds the organism and tells it where it is. This convergence of metabolic and informational function in a single substrate illustrates a principle that runs through the entire substrate landscape: the organism does not separate eating from sensing. The substrate is the signal.

Lipids and fatty acids represent the channel through which the organism transitions from feeding alongside the host to feeding from the host. The CYP52 fatty acid metabolism enzyme family, when upregulated (whether by iatrogenic induction as described in Section 5.1 or by endogenous metabolic shifts) enables the processing of host-derived lipids. Once this channel is active, the organism gains access to the arachidonic acid economy described in Section 5.5d: the shared precursor pool for both prostaglandin production and endocannabinoid synthesis. The lipid channel is therefore not merely fuel. It is the metabolic entry point into the host's lipid signaling landscape. The organism begins eating what the host's cells are made of, and in doing so, gains the raw material for the immune modulation and vascular tone management programs described throughout Section 5.

Amino acids and host structural proteins represent the deepest metabolic engagement with host tissue. The organism's ten secreted aspartyl proteinases (SAP1–SAP10) digest host proteins in the extracellular space, and its ten dedicated peptide transporters (2 PTR, 8 OPT) import the resulting fragments (Dunkel *et al.*, 2013). As documented in Section 5.5a, this massive digest-and-import pipeline is maintained by selection despite having no fitness requirement for gastrointestinal colonization — the septuple transporter knockout survived perfectly well in the gut. The pipeline exists for tissue-level operation. The alkalinization program described in Section 5.5e is itself amino acid-driven: catabolism of amino acids produces the ammonia that raises extracellular pH. Through this channel, the organism feeds and modifies its tissue environment simultaneously. It does not eat the host's proteins and then separately engineer the local pH. It does both with the same metabolic act.

Lactate and host metabolic byproducts extend the accessible energy field into microenvironments where glucose is scarce. Inside the macrophage phagosome, the immune compartment specifically designed to kill the organism, glucose is minimal but lactate is abundant. *C. albicans* survives inside the phagosome in part because it can metabolize the waste products of the very immune cell trying to destroy it (Lorenz *et al.*, 2004). This is metabolic judo: the immune response generates the substrate the organism uses to survive the immune response. The second alkalinization pathway (Danhof *et al.*, 2016) processes carboxylic acids including lactate, pyruvate, and α-ketoglutarate without ammonia release and without triggering hyphal morphogenesis, creating a metabolically quiet survival mode suited to operating inside a hostile compartment without announcing its presence.

Host-derived ketone bodies: acetoacetate, β-hydroxybutyrate, and acetone, are carboxylic acids produced by the host liver during states of glucose depletion, fatty acid oxidation, or sustained fasting. They fall within the substrate classes the lactate/carboxylic acid channel can process. In a host whose conventional glucose metabolism has been altered by the program's progression, or whose metabolic state has shifted toward ketogenesis for any reason, ketone bodies represent a fuel channel that both the organism and the host can share. The longitudinal case study documents a metabolic shift following the 2022 IVC constriction release event, after which the subject's body transitioned to alternative ATP generation mechanisms sustained for the subsequent four years (Craddock, Redacted Science). The specific pathways have not been clinically characterized, but the shift is consistent with a transition into a ketone-dominant fuel economy accessible to both host and symbiont.

This channel carries a cognitive byproduct directly relevant to the trinity model. β-hydroxybutyrate is a more efficient neuronal fuel than glucose, producing more ATP per unit of oxygen consumed while bypassing several rate-limiting steps in glucose metabolism. It also functions as a signaling molecule, inhibiting histone deacetylases (HDACs) and promoting neuroprotective gene expression while reducing oxidative stress and neural inflammation. Heightened mental clarity, sustained focus, and neuroprotection, the documented cognitive enhancements associated with ketone-dominant metabolism. are well established in clinical literature on ketogenic diets and their applications in epilepsy and neurodegenerative disease. A host operating on ketone-dominant metabolism runs its brain on a superior fuel. Within the trinity model, this is a byproduct of metabolic necessity that would have directly increased the survival value of the elder's cognitive output during the phases when the group needed it most.

Host cellular ATP represents the most direct fuel channel. *Candida*lysin pore formation (Sections 5.5a, 5.5e) produces efflux of ATP from host cells into the extracellular space (Ho *et al.*, 2021; Russell *et al.*, 2022). The host cell's energy currency leaks through calibrated pores into the environment where the organism can access it. The ATP efflux simultaneously depletes the host cell's energy reserve and provides substrate to the organism. Through this channel, the organism is not waiting for dietary substrate to arrive through the gut. It is tapping the energy stored in the cells it touches.

Ion gradient energy represents the final and deepest channel. The Na^+/K^+-ATPase reversal mechanism described in Section 5.5e harvests the electrochemical potential energy stored in every cell's ion gradients. Under conditions of reduced intracellular ATP and altered ionic concentrations (conditions the organism's own activities converge to produce) the pump operates in reverse, synthesizing ATP from ADP and inorganic phosphate (Garrahan and Glynn, 1966; Schwarz *et al.*, 1991). This is not a fuel the organism delivers. It is a reserve the host has been carrying in every cell, inaccessible under normal physiological conditions, unlocked by the ionic manipulation the organism performs. The ion gradients that the cell spent its lifetime building become the last fuel reserve. Two hundred million years of coevolutionary refinement is sufficient time to discover a reserve that the host's own biology never needed to access.

5.10.2 Temporal Weighting: The Dominant Channel Shifts

All of these channels operate simultaneously. At any given moment, yeast-form cells in the gut lumen are harvesting glucose, cells at mucosal boundaries are processing glycoconjugates, cells in tissue are digesting proteins and lipids, and cells at sites of active ionic manipulation are tapping gradient energy. The distributed system does not switch between fuel sources the way an engine switches between gasoline and diesel. It runs all of them at once, at different locations, through different cells, each adapted to its local substrate environment. This is substrate multiplexing: a parallel metabolic architecture matching the parallel signaling architecture described in Section 5.7.

What changes over the course of the program is not which channels are active but where the aggregate metabolic weight sits — which channel is dominant, which substrate demand is loudest, and consequently which behavioral signal the host experiences.

The longitudinal case study documents this shift as a progressive change in dietary cravings (Craddock, Redacted Science). Sugar cravings dominated early phases, consistent with glucose being the dominant substrate demand. Mixed sugar and salt cravings characterized intermediate phases, reflecting the transition as lipid and protein channels gained metabolic weight. Salt cravings dominated later phases, as the program advanced into the perfusion

management and ionic manipulation stages described in Sections 4.3 and 5.5e. The host's cravings are the organism's requisition orders, communicated through the same ECS-mediated appetite channels that govern hunger and preference in the uncolonized host — but directed toward the specific substrate the dominant channel requires at each point in the program's progression.

5.10.3 The Fasting-Mimicking State: Remodeling Through Metabolic Environment

The substrate architecture produces a secondary effect that may explain how the organism achieves tissue remodeling without issuing direct cellular commands. As the organism's metabolic weight shifts from dietary glucose toward host-derived substrates, including lipids, proteins, ATP, ion gradients, the host's cells experience a paradox: the host continues to eat, but the cells receive less. The organism diverts substrate through its own channels before the host's cells receive their share. The result is a cellular environment biochemically resembling fasting: reduced available glucose, elevated ketone bodies, activated autophagy, suppressed IGF-1 signaling.

These are the conditions documented in fasting-mimicking research to promote cellular regeneration, autophagic clearance of damaged cells, immune system renewal, and stem cell activation. The organism does not need to command apoptosis. It does not need to issue molecular instructions for tissue remodeling. It needs only to create the metabolic conditions under which the host's own housekeeping programs activate automatically. The host's cells detect apparent substrate scarcity. They respond with the maintenance and clearance programs that scarcity triggers. The organism achieves tissue remodeling by adjusting the metabolic environment, not by directing the remodeling itself.

This is consistent with the broader operational logic described throughout Section 5: the organism manages conditions rather than issuing commands. Farnesol manages the niche rather than directing individual cells (Section 5.7). The alkalinization program manages pH rather than attacking immune cells directly (Section 5.5e). The substrate architecture manages the metabolic environment rather than controlling individual cellular fates. The biochemical computer does not micromanage. It sets the parameters and lets the host's own systems respond.

5.10.4 Evolutionary Context: Why This Flexibility Exists

The metabolic flexibility described here is not incidental. It is what 200 million years of coevolution with mammalian hosts selected for. An organism locked into a single fuel source is vulnerable to any change in that fuel's availability such as dietary shifts, fasting, illness, seasonal variation, and migration to new environments. An organism that can eat glucose from the lumen, lipids from membranes, proteins from tissue, lactate from immune cells, ketones from the liver, ATP from cellular pores, and gradient energy from ion pumps is vulnerable to nothing except the absence of the host itself. Every fuel source except the first is the host.

This is the metabolic dimension of the positional authority described in Section 5.9. The organism does not merely signal across the host's receptor landscape. It feeds across the host's metabolic landscape, maintaining parallel substrate channels that collectively ensure continuous operation regardless of what is happening at any single tissue site. The ant colony analogy from Section 5.7 extends here: different cells at different locations eating different things, with no single cell's feeding strategy representing the whole system's metabolic architecture. The

colony's food supply is the host itself, accessed through every available interface, sustained by the metabolic flexibility that 200 million years of selection refined.

5.10.5 Sensing Requirements for Substrate Multiplexing

The organism's capacity to maintain parallel substrate channels and shift metabolic weight between them is not passive opportunism. It requires continuous environmental sensing at every tissue location: glucose availability through the Hgt4 membrane sensor (Section 5.7), amino acid availability through the SPS sensor system (Section 5.7), pH through Rim101, oxygen tension through metabolic pathway regulation, CO_2 through Cyr1, temperature through Hsp90, and lipid availability through mechanisms that remain incompletely characterized. The insulin and GLP-1 crosstalk documented in Section 5.5 (Peroumal *et al.*, 2022) provides additional information about the host's systemic metabolic state: whether the host is fed or fasting, whether glucose is abundant or depleted, and whether the host's own metabolism has shifted toward ketogenesis.

The input channel inventory described in Section 5.7 is not only the organism's sensory system for managing the host environment. It is also its metabolic compass. The same sensors that tell the organism what the host is doing physiologically tell it what fuel is available locally. The sensing architecture and the substrate architecture are unified: the organism reads the environment and eats what it finds, through the same molecular infrastructure, in the same continuous adaptive process. For a biochemical computer, sensing and feeding are not separate operations. They are the same computation. The organism takes in a matrix of variables – independent at every site – and compiles the inputs against coded memory producing multiple contingencies which are then selected by success and failure.

VI. Clinical Application: Cannabinoid Hyperemesis Syndrome as a Potential Host-Organism Interface Disruption

VI.I The Syndrome and Its Gaps

Cannabinoid hyperemesis syndrome (CHS) was first described by Allen *et al.* (2004) in a case series of 19 patients in South Australia who presented with cyclical vomiting illness linked to chronic, heavy cannabis use. An index case was retrospectively identified to 1996 (Sorensen *et al.*, 2017). The clinical triad consists of severe cyclical vomiting, abdominal pain, and compulsive hot bathing or showering, with the only consistently effective treatment being complete cessation of cannabis use. The syndrome follows a characteristic three-phase pattern: a prodromal phase of morning nausea lasting months to years, a hyperemetic phase of violent vomiting with dehydration, and a recovery phase following cannabis cessation (Simonetto *et al.*, 2012). This doesn't sound fun, does it?

Reported incidence has risen sharply alongside legalization and increased potency. Modern vape concentrates deliver 70-90% THC compared to 15-25% in traditional flower, and recent data indicate that exclusive vape users develop CHS symptoms significantly faster than flower users. Emergency department visits attributable to CHS have increased across all legalized jurisdictions.

The standard pharmacological model describes CHS as a "paradoxical reaction" to chronic THC exposure, and it rests on three observations that lack consensus mechanistic explanations:

Gap 1: Differential CB1 receptor downregulation. In the brain, chronic THC exposure causes well-characterized CB1 receptor downregulation and internalization, weakening the drug's anti-emetic effect (Sim-Selley, 2003). In the gastrointestinal tract, CB1 receptors do not appear to undergo equivalent downregulation. That's weird, right? Gut motility suppression (gastric stasis) persists or intensifies under chronic exposure (Sharkey and Wiley, 2016). This tissue-specific asymmetry is documented but treated as a brute fact in the existing literature, with no proposed mechanism for why gut receptors should behave differently from brain receptors under the same ligand load.

Gap 2: TRPV1 receptor dysregulation. Chronic cannabinoid exposure is thought to inactivate TRPV1 receptors in the gut, contributing to nausea and visceral pain (Izzo *et al.*, 2003). The mechanism by which chronic CB1 agonism produces TRPV1 inactivation across a different receptor class remains unclear. The standard literature waves its hands at this one.

Gap 3: The hot shower phenomenon. CHS patients exhibit a compulsive drive toward hot showers or baths, which provide temporary but often dramatic symptom relief. The standard explanation invokes TRPV1 reactivation by heat, but this raises a circular dependency: if TRPV1 is inactivated by chronic cannabinoid exposure, why would a brief thermal stimulus produce immediate relief that pharmacological CB1 manipulation cannot?

No existing model unifies these three observations under a single mechanism. No prior work in the published literature has proposed *C. albicans* as a mechanistic contributor to CHS. So, they have no explanation. Enter Redacted Science.

However, the standard model's difficulties extend beyond these three gaps. A 2025 transcriptomic study of CHS patients, Meltzer *et al.* (2025), looked for the ECS transcript changes the standard model predicts and found none. No significant changes in endocannabinoid system-related transcripts were detected. Instead, the study found marked adaptive immune activation: B-cell immunoglobulin upregulation, altered T-cell, monocyte, and neutrophil expression, impaired gut barrier function with increased matrix degradation and reduced adhesion, MHC Class I upregulation, and IgE receptor downregulation consistent with elevated IgE levels. The authors interpreted these findings as evidence of an "acquired, gut-restricted, immune-mediated hypersensitivity response to cannabis." [*Hmm.*]

The immune profile they found is notable for what it resembles. *C. albicans* colonization triggers mast cell degranulation, IgE elevation, Th2 immune skewing, and gut barrier degradation through candidalysin and hyphal invasion, as described in §4 and §5 of this paper. The transcriptomic study found the organism's downstream immune signature and attributed it to cannabis hypersensitivity because the organism was not in their model. The absence of ECS transcript changes is equally significant. The standard model predicts that if CB1 receptors are being disrupted, that disruption should show up in gene expression data. It did not. But the organism does not maintain receptors by changing what genes the host expresses. It maintains them at the protein level, through direct signaling at the cell surface. That is a different layer entirely, one that a transcriptomic study would not detect. The researchers looked at the gene expression layer. The organism works at the protein layer. They found nothing where they looked because the action is happening where they did not look.

VI.II The Biochemical Computer Framework Applied to CHS

The framework presented in this paper offers a potential explanation that resolves all three gaps simultaneously. This section presents the mechanistic logic as a hypothesis to be tested by the experimental predictions in §VI.VI Whether or not every detail proves accurate, the

framework generates specific, falsifiable predictions that the standard model does not. That said, calling this a "hypothesis" is a hedge. I am working with a model that no one else has built. My call.

VI.II.I Organism Maintenance of Gut CB1 Receptor Density

As described in §4, *C. albicans* uses the endocannabinoid system as a primary signaling interface with the host. The organism resides primarily in the gastrointestinal tract. Gut CB1 receptors are therefore the organism's principal broadcast interface with local host tissue.

The organism lives in the gut and talks to the host through CB1 receptors. It needs those receptors to stay active. If it is actively maintaining them (and it can), keeping the locks on the doors it uses, then the differential downregulation in CHS is not paradoxical at all. Gut CB1 receptors resist desensitization because the organism is protecting its own communication channel. Brain CB1 receptors, far from the organism's home territory, have no such protection. They downregulate normally.

This would resolve Gap 1. The gut is not mysteriously resistant to CB1 desensitization. Something in the gut environment is actively maintaining receptor density. The candidate is the resident organism.

VI.II.II Arachidonic Acid Substrate Competition

The host's ECS and *C. albicans* are drawing from the same raw material supply. Both need arachidonic acid (AA), a fatty acid stored in cell membranes. The host uses it to build its own cannabinoid signaling molecules, anandamide and 2-AG, which keep the gut moving properly and suppress nausea. The organism uses the same AA to manufacture prostaglandin E_2, an inflammatory signal it deploys for immune modulation (Erb-Downward and Noverr, 2007). There is one pool. Two competing users.

The competition runs deeper than two separate production lines pulling from one supply. The host enzyme COX-2 can directly convert endocannabinoid precursors into prostaglandin-family molecules, and when the body breaks down its own cannabinoids, the leftover arachidonic acid becomes available for the organism to capture. The plumbing between these two systems is shared at multiple points. When fungal burden is high, the organism pulls more AA toward its own PGE_2 production, and the host's cannabinoid supply drops. The body's internal anti-nausea system loses its raw materials.

Now layer chronic high-dose THC on top of this depleted substrate pool. The exogenous agonist floods remaining receptors. Brain receptors downregulate normally. Gut receptors are held open by the organism. Endogenous tone is already depleted by substrate competition. The system has three variables collapsing simultaneously: depleted endocannabinoid floor, brain receptor downregulation, and maintained gut receptor density. This is not a two-variable paradox. It is a three-variable system crash.

VI.II.III The Glucose Feedback Loop and the Morning Nausea Pattern

During hyperemetic episodes, patients cannot eat. Blood glucose drops. The Hgt4 glucose sensor in *C. albicans*, calibrated to human blood glucose concentrations of approximately 5 mM (Brown *et al.*, 2006; see §4.1), detects this decline. Below the 5 mM threshold, the organism shifts operational mode, consistent with the glucose override subroutine described in §5, Prediction 12. To be direct about what this means: when blood glucose falls below the level the

organism is calibrated to monitor, it begins sourcing substrate from the host. The host becomes the snack.

This creates a positive feedback loop: vomiting prevents eating, glucose drops below the organism's calibrated threshold, the organism sustains or intensifies its crisis-mode operation, and vomiting continues. The emetic episode creates the metabolic conditions that perpetuate it.

The glucose mechanism receives independent support from the temporal pattern of CHS symptoms. Morning nausea is a defining feature of the prodromal phase (Simonetto *et al.*, 2012). This is the period of lowest blood glucose in the 24-hour cycle. After an overnight fast, circulating glucose approaches its daily nadir. If the organism's Hgt4 sensor is calibrated to approximately 5 mM, the overnight fasting period represents the interval during which blood glucose is most likely to fall near or below this threshold. The morning timing of prodromal nausea is not random. It maps directly onto the predicted glucose-dependent activation window.

The longitudinal case study provides a corroborating observation. During a period of approximately two to four weeks, the case subject (not a CHS patient, but an individual with documented long-term *C. albicans* colonization) experienced pronounced morning nausea upon waking, a symptom not typical of the broader condition at that stage. Having independentlyrecognized that caloric intake served as a systemic override in this condition, the subject responded by eating immediately and aggressively upon waking: simple carbohydrates first (for rapid glucose elevation above the 5 mM threshold), followed by proteins and fats (for sustained glucose maintenance). The nausea resolved each time. The eating window was approximately thirty minutes of sustained caloric loading.

This response is the inverse of the CHS patient's typical trajectory. CHS patients wake nauseated, the nausea escalates, vomiting prevents eating, glucose remains below the threshold, and the positive feedback loop locks shut. The longitudinal case subject was able to eat through the nausea because, in that clinical context, the emetic reflex was suppressed by the organism rather than destabilized (see §6.4). The same morning glucose trigger produced opposite outcomes depending on whether the organism maintained or lost control of the emetic gate.

Interlude from the Architect

A break from the formal interpretation.

What I have is not CHS. However, I have been through more than I can ever fully communicate in a scientific paper. That does not mean I would change my decision to save my life by accepting this condition, but it does give me a wealth of experiential knowledge that no one else has. In the original redacted article, the author made it clear that the subjects who ate through everything, across all phases except one specific period in the final stage, were the longest-lived. One photograph described in Redacted Science (p. 43, "The Mouth Still Works") shows two figures in the terminal stage. I paraphrased the caption: "At this stage, they are expected to die within a day or two. But they still chew. Because they remember what they've been trained to do. Eat. No matter what."

So when the morning nausea hit, I had that knowledge in my head. I got up, went into the kitchen, and started eating. I was not discriminating. I did not focus specifically on protein, or carbs, or fats. I ate whatever was handy, and I mixed it up on purpose. My advice is simple: eat through the morning nausea, fuel up the tank, and maybe you will have a better day.

How did I eat through nausea? Training. There is an earlier stage of progression when even looking at food triggers a full-body gag reflex, but the vomiting reflex has already been disabled, so nothing comes up. Try shoving food down your throat when every bite triggers

gagging with no corresponding stomach emptying. I have very specific memories of eating at a restaurant, gagging on every bite, with my family encouraging me to keep going. So, yes, I had training. But that morning nausea is different. It does not come with gagging. It feels like what it is: blood sugar related nausea.

VI.II.IV TRPV1, the Hot Shower Phenomenon, and the Palliative Trap

[*VI.II.IV is pretty cool*] To understand why hot showers work in CHS, it helps to understand what TRPV1 actually is. TRPV1 (transient receptor potential vanilloid type 1) is a receptor expressed throughout the gut and the skin. It responds to three categories of stimulus: noxious heat above 43°C (109°F), the temperature of a hot shower; chemical signals like capsaicin, the compound that makes chili peppers burn; and endogenous lipid molecules including anandamide and N-arachidonoyl dopamine, the feel-good molecules your body makes on its own. When activated, TRPV1 produces vasodilation (blood vessel widening) and, under sustained stimulation, defunctionalization, a temporary state in which the receptor stops responding to further input. Both of these effects are directly relevant to pain relief and gut motility.

TRPV1 falls within the receptor range through which the organism interacts with host physiology (CB1, CB2, TRPV1, GPR55). If the organism is managing TRPV1 as part of how it runs the gut, then flooding the system with THC does not just jam the cannabinoid channel. It disrupts the organism's coordinated management of everything it touches, and TRPV1 gets caught in the cascade. The TRPV1 problem in CHS is not a direct effect of cannabis on heat receptors. It is collateral damage from the organism losing its grip on the whole signaling panel.

This is why hot water works. It does not fix the underlying disruption. It bypasses it. Heat hits TRPV1 directly, a raw physical signal that does not pass through the organism's signaling layer at all. For a few minutes, the receptor responds to something other than the organism's management. The vasodilation alone would reduce visceral pain. The defunctionalization temporarily quiets the pain signaling cascade entirely. Capsaicin cream, a direct TRPV1 agonist used successfully in some CHS cases (Dezieck *et al.*, 2017), works the same way. Both engage TRPV1 on its own terms, outside the organism's control. Both provide immediate relief.

What happens when the stimulus ends is the more interesting question. Does the organism's management reassert immediately? Or does the TRPV1 defunctionalization persist for some window afterward, providing a period of genuine receptor silence that outlasts the shower itself? The compulsive return pattern, showering fifteen times a day, suggests the relief window has a consistent duration, and patients learn exactly when it expires.

This resolves Gaps 2 and 3 simultaneously. No hand waving required. TRPV1 dysregulation is downstream of organism signaling disruption, not a direct cannabinoid effect. Hot shower relief is a physical override of an organism-mediated receptor state, which explains both its immediacy and its finite duration.

However, the clinical behavior surrounding hot showers in CHS reveals something beyond simple symptom relief. Case reports describe patients showering up to fifteen times per day, sometimes for over an hour per session (Mohammed *et al.*, 2013). The behavior is consistently described in the clinical literature as "compulsive." This is not the pattern of a patient managing pain with a known palliative intervention. It is the pattern of a patient returning repeatedly to the only state in which they feel substantially better, or perhaps substantially normal, a distinction the clinical literature has not explored.

If the TRPV1 override temporarily restores autonomic function to an unmanaged state, the subjective experience would not be neutral relief. It would be the sensation of a system briefly running without organism interference. For a patient whose gut motility, thermoregulation, and visceral sensation have been continuously managed by the organism, this would register not merely as the absence of nausea but as something closer to wellbeing. The compulsive quality of the behavior is itself evidence that the shower produces a positive experience disproportionate to simple symptom palliation. If the patient has also eaten, the experience exceeds normal and approaches something a healthy person would simply call "feeling good."

There is an additional clinical feature that connects the shower behavior to the glucose mechanism. CHS patients frequently report feeling cold, sometimes profoundly so, during prodromal and hyperemetic episodes. This is typically attributed to autonomic dysfunction or thermoregulatory disruption from chronic cannabinoid exposure. But feeling cold is also a well-documented symptom of low blood sugar. When blood glucose drops, the body constricts peripheral blood vessels to preserve core circulation, and the subjective result is a chill that no amount of blankets resolves. If the morning nausea is glucose-driven (§6.2.3), the cold sensation that accompanies it is the same glucose signal presenting through a different channel. The patient

feels cold and nauseated simultaneously, and the hot shower addresses the cold directly while the TRPV1 override addresses the nausea. The shower solves both symptoms at once. Of course they get in the shower. It is the one intervention that addresses both presentations of the same underlying problem. But neither symptom is caused by the shower's absence. Both are caused by an empty tank.

This creates a palliative trap with direct relevance to the glucose mechanism. Every hour a CHS patient spends in the shower is an hour they are not eating. The shower provides sufficient relief to prevent the patient from pursuing the intervention that would actually break the cycle: caloric loading to raise blood glucose above the organism's Hgt4 threshold. The shower is good enough to sustain the patient in the acute state without resolving it. The real exit is caloric, not thermal. But the thermal relief is compelling enough to keep the patient from finding it, and once vomiting has begun in earnest, the opportunity to eat has passed. Get up and eat. Donuts, sausage, nuts, whatever is within reach. Eat first, shower second.

The standard clinical advice for CHS is hydration and cannabis cessation. No current guideline recommends aggressive caloric loading during the prodromal or early hyperemetic phase. In the glucose override model, this is the critical missing intervention.

VI.III The CBD Paradox

Recent work by Bahraminia *et al.* (2024) demonstrated that cannabidiol (CBD), at concentrations of 10-20 µg/mL, significantly decreases the growth of *C. albicans*, inhibits the yeast-to-hyphae transition (from 20% to 2% at 20 µg/mL), reduces biofilm formation, and induces *C. albicans* death through an apoptosis/necrotic pathway. CBD is not merely modulating receptor access. It is directly antifungal against the organism itself.

This creates a paradox with clinical implications for CHS. If CHS is organism-mediated, then CBD should theoretically address the root cause by reducing fungal burden. However, the acute response to CBD in a colonized host may be more immediate and more dramatic than gradual die-off would predict. This is not something we can model precisely. CHS patients carry elevated but not extreme *C. albicans* colonization density and are not *Homo candidus*. Their response may be significantly milder than what follows.

The longitudinal case study provides a relevant observation. On two separate occasions, the case subject (not a CHS patient, but an individual with documented long-term *C. albicans* colonization) experienced acute respiratory constriction within hours of small-dose CBD exposure (Craddock, Redacted Science). The response was immediate, dramatic, and short-lived, resolving within two to three hours both times. The second exposure was deliberate, to confirm the response was real and reproducible. It was.

The speed and brevity of this response is notable given CBD's pharmacokinetics. CBD has a half-life of 18-32 hours for a single dose, is fat-soluble, and can remain in the body for days in typical individuals. The acute respiratory response resolved in 2-3 hours while the drug should have been circulating at near-peak concentration. This rules out drug clearance as the mechanism of resolution in the standard pharmacokinetic model. However, a caveat applies to the longitudinal case specifically: the case subject's condition has substantially altered fat tissue permeability and distribution due to cellular changes (Craddock, Redacted Science). Fat-soluble storage, the primary mechanism for CBD's long half-life, may not function normally. The 2-3 hour resolution in this case may therefore reflect altered clearance in addition to, or instead of, organism compensation. In a typical CHS patient with normal fat tissue, CBD would remain active for considerably longer.

CBD is a negative allosteric modulator at CB1 and CB2, meaning it changes the shape of the receptors so that other molecules, including whatever the organism is producing, cannot engage them as effectively. The effect is less like killing the organism and more like changing the locks on every door it uses. The organism is still alive, still present, but suddenly unable to communicate through the interface it depends on. In a system where the organism has been actively maintaining respiratory and autonomic tone through ECS-mediated signaling, the abrupt loss of that signaling channel produces acute physiological disruption.

The resolution while CBD should have remained active suggests one of two mechanisms, or a combination of both. First, the organism may have compensated in real time, rerouting its signaling through alternative pathways outside CBD's allosteric range. The framework describes a multi-receptor interface (CB1, CB2, TRPV1, GPR55, cholinergic, prostaglandin), and CB1/CB2 are the primary but not the only channels available. Second, the case subject's compromised fat tissue may have accelerated CBD clearance beyond the standard pharmacokinetic model. Within 2-3 hours, normal function returned. The exhaustion that followed (an uncharacteristic nap) is consistent with either explanation: the metabolic cost of an emergency signaling reroute, or the physiological aftermath of an acute drug effect that cleared faster than expected. By evening, function was normal, running on backup wiring with the primary channel still blocked, or possibly cleared faster than expected given the absence of normal fat-soluble storage and differentiated circulation features. The standard half-life figures assume normal adipose tissue and circulation. This case does not have either.

The case subject described the acute experience in direct terms: "I am alert. I cannot breathe. I have zero energy. One more CBD dose, and I may die." This subjective intensity should be understood in context: the longitudinal case involves an extreme colonization density in which the organism is actively managing respiratory and autonomic function, a degree of organism integration far beyond what is expected in the typical CHS patient population. In a patient with elevated but not extreme gut colonization, the acute CBD response may be mild or imperceptible.

CBD therefore acts on the organism through two distinct mechanisms operating on different timescales. Acutely, it changes the locks: receptor conformation shifts that cut the

organism off from its signaling interface within hours, producing immediate physiological disruption that resolves through organism compensation, accelerated drug clearance, or both. Over sustained exposure, it kills: direct antifungal action that reduces organism growth, inhibits hyphal transition, and degrades biofilm (Bahraminia *et al.*, 2024). These are different threats to the organism and would produce different clinical responses.

For CHS patients, this dual mechanism suggests a temporal distinction:

Acute CHS episodes: CBD introduction during an active hyperemetic episode adds a variable to an already unstable system and is unlikely to provide immediate benefit. Stabilization through hydration and caloric loading should take priority.

Maintenance between episodes: CBD at low, carefully spaced doses could theoretically reduce organism burden over time through its direct antifungal action and prevent subsequent CHS cycles. Dose spacing should account for the 18-32 hour half-life. The level of initial response would be expected to correlate with organism density and the degree to which the organism is actively managing host physiology through the ECS interface. CBD has an established safety profile with no attributed deaths, and the acute signaling disruption observed in the longitudinal case study, while subjectively intense, resolved completely within hours. That case represents an extreme colonization density unlikely to be matched in the typical CHS population. The most accurate prediction for CHS patients is some type of response from CBD, the character of which would itself be informative.

VI.IV The Mirror Case: Emetic Suppression as the Inverse of CHS

The longitudinal case study documented in Craddock (2026b) presents a clinical picture that is, in several respects, the inverse of CHS. The case subject uses cannabis therapeutically and does not exhibit cyclical vomiting. Instead, the documented experience over multiple years has been emetic suppression so complete that the subject was unable to trigger vomiting even through manual stimulation of the gag reflex. On multiple occasions during periods of severe nausea, mechanical attempts to induce emesis produced no effective result.

The interpretation within the biochemical computer framework is that both CHS and emetic suppression represent organism-mediated gut management through the same CB1/TRPV1 interface, operating in opposite directions depending on the organism's operational context:

In CHS, sustained THC interference degrades the organism's control of the gut signaling layer. But "system failure" may be too generous a description. The alternative possibility, one that the framework permits, is that the organism has upregulated the host into a potentially fatal feedback loop. In the context of *Homo candidus*, where the organism and the social group are co-adapted, such a loop would be interrupted by communal intervention: someone would feed the afflicted individual, break the glucose threshold, and terminate the episode. In Homo sapiens, where neither the social infrastructure nor the recognition exists, the loop runs unchecked. The organism may not be "failing" to control emesis. It may be executing a program that was never designed to run without support. CHS is a relatively recent clinical finding, consistent with a response that the organism has not had evolutionary time to refine for the modern context.

In the longitudinal case, the organism maintained tight enough control of gut signaling to lock the emetic reflex entirely. The interpretation offered in the case study is that vomiting became operationally dangerous to the organism: in an advanced colonization state where the organism is managing gut substrate access, electrolyte balance, and circulatory dynamics, a violent emetic event risks electrolyte loss, gut content exposure, and disruption of the substrate access architecture the organism has built. The redacted article described in Redacted Science

indicated that in late-stage progression, if the subject did vomit, death would likely follow swiftly from electrolyte loss.

The same interface, the same organism, the same receptor set, producing opposite clinical presentations based on different operational states. CHS is the signal layer overwhelmed. Emetic suppression is the signal layer holding.

VI.V Shared TRPV1 Signature Across Presentations

One observation connects CHS and the longitudinal case study across their otherwise opposite clinical presentations. Throughout the documented course of the longitudinal case, hot showers have been consistently the most reliable source of symptomatic relief, independent of cannabis use status. At peak symptom periods, the case subject showered multiple times per day. The subjective quality of relief was immediate and dramatic regardless of symptom severity, sufficient to produce a noticeable shift in mood and overall wellbeing. On almost every day, even during the worst of it, the subject manages to sing in the shower. "One Last Breath" by Creed is a go-to. Tenor II, high school All-State twice. The shower makes that possible on days when nothing else does. This pattern, compulsive hot shower use providing disproportionate symptomatic relief and a sense of restoration beyond what the physical intervention would normally explain, is the signature clinical feature of CHS.

Its presence in a non-CHS context, in an individual with documented long-term *C. albicans* colonization but no cyclical vomiting, supports the interpretation that both populations share a common TRPV1-mediated mechanism rooted in organism activity rather than cannabis pharmacology alone. The TRPV1 override is not specific to the CHS disruption state. It is a general feature of organism-mediated autonomic management, observable whenever the organism is modulating host physiology through this receptor interface.

VI.Va Pharmacological Evidence: Drugs That Work and Drugs That Don't

The medications that provide relief in CHS offer additional support for the organism-mediated model, because the drugs that work are not the drugs the standard emesis model would predict.

Ondansetron, a 5-HT3 receptor antagonist and the standard first-line antiemetic for most clinical vomiting, does not work well for CHS. This is documented across multiple case series and acknowledged in clinical guidelines. If CHS were a straightforward emetic pathway dysfunction, the drug that stops most vomiting should stop this vomiting. It does not.

The drugs that do work are notable for where they act:

Haloperidol, a butyrophenone antipsychotic with high-affinity D2 dopamine antagonism, has produced complete symptom resolution in multiple case reports. This is typically attributed to its central antiemetic properties. However, the Gpr1 receptor in *C. albicans* responds to clozapine, a dopamine receptor antagonist, which inhibits morphogenesis through the Gpa2-coupled cAMP-PKA signaling pathway (Midkiff *et al.*, 2011; see §4.2). Haloperidol may not simply be suppressing the patient's nausea. It may be directly suppressing the organism's hyphal transition through the same dopaminergic interface.

Benzodiazepines (lorazepam, diazepam) provide relief through GABA-A receptor agonism. *C. albicans* has documented interactions with GABA signaling pathways. The sedative and anxiolytic effects on the patient are well understood, but the drug may also be modulating the organism's behavior through a shared signaling substrate.

NK1 receptor antagonists (aprepitant and related compounds) block the Substance P receptor. Substance P is a neuropeptide, and the organism's ten peptide transporters (§4.1) import host-derived peptides as environmental sensors. If the organism is reading Substance P as an input signal through its peptide transport system, an NK1 blocker cuts off that information stream.

The pattern is consistent. The drugs that work for CHS are the drugs that act on receptor systems the organism interfaces with. The drug that should work based on the standard emesis pathway does not. This is not proof, but it is the pharmacological signature of a condition with an organism component rather than a purely host-mediated receptor dysfunction.

VI.5b Anecdotal Observations from the CHS Patient Community

The CHS patient community, particularly the r/CHSinfo subreddit, provides uncontrolled but directionally useful observations that are consistent with the organism-mediated model and difficult to explain within the standard framework.

Relief from maintaining a full stomach. Multiple patients report that keeping food in their stomach attenuates symptoms. This is consistent with Prediction A (prodromal caloric loading) and with the glucose override mechanism described in §6.2.3. The variability in response across patients, some report significant relief while others do not, is consistent with varying colonization densities: patients with lower organism burden may maintain blood glucose above the Hgt4 threshold with a normal meal, while patients with higher burden may burn through the glucose buffer faster.

Persistent symptoms months after cessation. Some patients report continued nausea, gut dysfunction, and malaise five months or more after complete cannabis cessation, confirmed by negative drug screens. The standard model has difficulty explaining this. Cannabis metabolites, even fat-stored THC, are cleared well within this timeframe. But the organism does not leave when the THC does. Cannabis cessation removes the signal jammer and allows the organism to re-establish equilibrium, which resolves the acute CHS cycle. It does not reduce colonization density. A patient with elevated *C. albicans* burden will still have organism-mediated gut effects long after the last THC molecule is gone. The persistence of symptoms beyond the pharmacokinetic window of cannabis is itself evidence that something other than THC is contributing to the condition.

Relapse from trace exposure. One patient reported that a single whiff of secondhand THC vape exhale, after months of complete abstinence, triggered a full hyperemetic episode. This is pharmacologically implausible in the standard model. The dose from secondhand vapor is negligible. But if the organism has spent months re-establishing full signaling control during the abstinence period, running the gut at a tightly managed equilibrium, even a trace amount of THC jamming the signal layer may be sufficient to destabilize the system. The organism's grip is tighter after months of uninterrupted management, and its tolerance for interference is correspondingly lower. The sensitivity is not the patient's sensitivity to THC. It is the organism's sensitivity to signal disruption.

Feeling cold. CHS patients frequently describe feeling profoundly cold during episodes. As discussed in §6.2.4, this maps to the glucose mechanism: peripheral vasoconstriction from low blood sugar produces a chill that hot showers directly address. The cold sensation and the nausea are two presentations of the same underlying glucose deficit.

These observations are anecdotal and uncontrolled. They do not constitute evidence. But they are consistent with the framework's predictions and inconsistent with the standard model's

explanatory capacity. The patient community is generating observational data that formal research has not yet captured.

VI.Vc Dietary Modification as a Test of the Organism-Mediated Model

This section is not medical advice [*I am not a doctor folks. I'm an architect*]. It is a proposed grocery test. The logic is simple: if dietary changes that have no antiemetic properties but do have documented antifungal activity against *C. albicans* produce symptom improvement in CHS patients, the standard pharmacological model has no explanation for the result. These are foods, not drugs. There are no labels to read. They do not act on emetic pathways. They act on a fungus. If they help, the fungus is involved. [*History will decide*]

The following dietary modifications are based on peer-reviewed evidence of antifungal activity against *C. albicans* specifically. Each has a documented mechanism. None requires a prescription. [*All of them are rather tasty, imo*]

Coconut oil. Virgin coconut oil contains medium-chain fatty acids (MCFAs), primarily lauric acid (C12) and caprylic acid (C8), both of which have demonstrated antifungal activity against *C. albicans* at concentrations comparable to or exceeding standard azole antifungals (Akula *et al.*, 2021, Al-Joubori 2026). Caprylic acid disrupts fungal cell membranes through direct penetration of the lipid bilayer, inhibits hyphal transition, adhesion, and biofilm formation, and shows synergistic effects when combined with other antifungal compounds (Jadhav *et al.*, 2017; Pohl *et al.*, 2011; Yoo *et al.*, 2019). In a murine oral candidiasis model, capric acid (also present in coconut oil) significantly improved symptoms and suppressed mycelial growth on tongue surfaces (Takahashi *et al.*, 2012). Coconut oil is also a source of medium-chain fatty acids that activate GPR84, the immune cell receptor described in the Thaiss *et al.* vagus nerve signaling pathway queued for §5.5 of this paper. The patient is getting direct antifungal action and immune modulation from the same tablespoon.

A CHS patient who replaces their cooking oil with coconut oil, adds it to coffee or smoothies, or uses it as a fat source in their morning caloric loading protocol (Prediction A) is combining glucose override with antifungal delivery in the same meal. [Also, it goes great in no salt added bone broth]

Cinnamon. Cinnamaldehyde, the primary active compound in cinnamon, has documented antifungal activity against *C. albicans* including inhibition of biofilm formation and hyphal growth. Ceylon cinnamon (Cinnamomum verum) is preferred over the more common cassia variety for sustained use, as cassia contains higher levels of coumarin, which can stress the liver at high doses. Ceylon is available at most grocery stores and clearly labeled. A patient who adds cinnamon to their morning oatmeal, toast, or coffee is delivering a biofilm disruptor to the organism's home territory with breakfast. [Come on, we all like cinnamon toast]

Garlic. Allicin, the active sulfur compound released when garlic is crushed or chopped, has broad-spectrum antifungal activity including direct activity against *C. albicans*. Crushing the garlic and letting it sit for a few minutes before cooking maximizes allicin release. Raw is more effective than cooked, as heat degrades allicin, but any garlic is good garlic. The antifungal literature on allicin is extensive and well-established. [Just make sure your significant other has some too]

Oregano oil. Carvacrol and thymol, the primary active compounds in oregano oil, show antifungal synergy with caprylic acid against *C. albicans*, achieving greater than 6-log reduction (complete eradication) within one minute at body temperature *in vitro* through combined membrane disruption and efflux pump inhibition (Yoo *et al.*, 2019). This is not a subtle effect.

Oregano oil is available as a dietary supplement and as a culinary ingredient. [I have not tried this one, I'm just giving you the science]

Apple cider vinegar. Acetic acid has documented antifungal properties against *C. albicans*. The acidic environment also disfavors hyphal transition, which is pH-sensitive and favored by neutral-to-alkaline conditions. [I don't do this one either, you don't need to do them all]

Iodized Salt (table salt). Iodized salt is documented to have very fast acting anti-fungal properties. If you are using sea salt, switch to iodized salt. It is not recommended to change your actual salt intake. That would invalidate the grocery test.

A Note from The Architect

[*Listen up. If you are reading this section and have CHS – you are already a self-medicating individual. So, you need to hear what I say next. These are groceries. There are no labels involved. These are not drugs. These are also not supplements. These are normal, everyday items sold at your grocery story – not some health food store. For example, I bought Coconut Oil at Dollar General.*

Supplements are drugs. Period. If you are considering supplements, it would be wise to have someone informed about them advising you or even prescribing them. However, there are some obstacles to that. In 1994, Congress passed a law call the Dietary Supplement Health and Education Act. As usual, the law does exactly the opposite of what the name implies. What it did by making the foods was 1) Reduce education about them for doctors (doctors get a lot of material on prescription drugs because the companies have an incentive to provide it) 2) It created a whole industry of off-the shelf drugs as foods, and 3) discouraged investigation into these alternatives because they are not as profitable.

One example: Lemon balm. Melissa officinalis. It has documented antifungal activity against Candida albicans. It is a clinically effective anxiolytic — head-to-head trials show it performs comparably to benzodiazepines, a $3.5 billion global market. It inhibits acetylcholinesterase — the same mechanism of action as donepezil and the other Alzheimer's drugs that make up a $1.6 billion market segment. And it is itself an antifungal, relevant to the $17 billion antifungal drug market. Three therapeutic categories, over $22 billion in combined annual pharmaceutical sales, and a single herb covers all three. In France, pharmacists dispense it. In the United States, it sits on the supplement shelf next to the melatonin because of a law Congress passed in 1994.

Your doctor will never learn about it. It is not on the decision tree. You do not have access to sufficient research to know about it. So, for purposes of this grocery test, just stay away from these things. Do not assume your Health Food checkout clerk is a good resource.]

The Test

The proposed dietary test for CHS patients is straightforward: change your diet. Whatever else you decide to do about cannabis consumption, whether you cut back, quit, or keep going, add these foods. They are scientifically documented antifungals effective against *C. albicans*. If the organism is involved in CHS, they should help. If it is not, they are still groceries.

Note: If this theory is correct, you may suffer from candida die off symptoms. These are not pleasant. However, things should eventually improve. This author's personal recommendation would be to introduce ONE of these things for a period of time, then also introduce another one…followed by another one. This may help avoid more dramatic reactions. Realize, candida is reacting to a system out of balance. What causes that imbalance could just be the THC or it could be something more dramatic. If it is just THC, this regimen should improve the situation. If it is something more dramatic, this regimen may actually help with the CHS, but exacerbate the underlying condition as *C. albicans* is no longer able to help with the imbalance.

Track symptoms daily: morning nausea severity, frequency of hyperemetic episodes, shower frequency and duration, and overall gut comfort.

Here is a list of simple grocery changes (once again, moderation is recommended):

• Add virgin coconut oil as a daily fat source.

• Add Ceylon cinnamon to morning meals.

• Include crushed garlic in at least one meal per day.

• Optionally add oregano oil as a supplement or culinary ingredient. [*Add some spice to your life*]

If these dietary additions produce measurable symptom reduction over two to four weeks, the standard model, which attributes CHS entirely to THC receptor dynamics, has difficulty accounting for the improvement. These foods do not modulate CB1 receptors. They do not activate TRPV1. They do not alter THC metabolism. What they do is suppress *C. albicans* growth, inhibit its transition from yeast to hyphal form, degrade its biofilms, and disrupt its cell membranes. If that helps, the organism is part of the problem.

Conversely, if progressively adding these to your grocery list and diet produces no change in CHS symptoms, that is useful negative data that weakens the organism-mediated model for this particular application.

This test costs less than a trip to the emergency department. It risks nothing. Every ingredient is available at a grocery store. And unlike cannabis cessation, which asks the patient to give up something they may depend on medically, this test asks them only to change what they eat alongside it.

For the patient who wakes up nauseated: eat in the morning. *Candida albicans* gets more aggressive when blood sugar is low. What you eat in the morning is your call, but a morning meal will set you up for a higher blood glucose level, which, if the theory is correct, would reduce the severity of the afternoon reaction. Additionally, if the framework is right, the day goes better. If it is wrong, you had a decent breakfast.

Next, track your diet and your symptoms. This is invaluable for your health professional and you. If symptoms fluctuate with diet, that is something that no one is addressing, regardless of what items are consumed.

Finally, once you have a baseline recorded, slowly begin introducing one of these items to your diet. If nothing changes, no harm no foul. If things get worse, that is something just

important to note as if things get better. If they do get worse, you will have to decide – do you continue that diet, or revert back to your baseline diet. From experience, candida sufferers that achieve resolution through medicinal methods are very familiar with a die-off period where things feel worse. According to this model, that is likely to be multiple effects. When candida die, they release toxins and electrolytes. These can effect your system. Additionally, according to this model, the organism is already directly communicating with parts of your system. When this communication stops, your system will have to recalibrate. Neither of these is an overnight process.

To review, this is a grocery test and a documentation test. One without the other is not a good plan. It will require both. According to this model, you are already running this experiment, you just are not documenting it.

VI.VI Testable Predictions

The following predictions are designed to validate or falsify the proposed *C. albicans* contribution to CHS. Each isolates a variable that the standard pharmacological model does not address. Confirmation of even one would establish a connection warranting further investigation. Failure across all predictions would indicate that the framework does not extend to this syndrome.

The predictions are ordered from simplest and least expensive to most complex, beginning with interventions that require no specialized equipment, institutional approval, or laboratory analysis.

Prediction A (Prodromal Caloric Loading). CHS patients in the prodromal phase who eat immediately and aggressively upon waking, beginning with rapid-absorbing carbohydrates followed by sustained protein and fat sources, will experience reduced frequency and severity of morning nausea and decreased progression to the hyperemetic phase. The proposed mechanism is straightforward: caloric loading raises blood glucose above the Hgt4 threshold (~5 mM) before the organism's fasting-state operational shift can escalate to emetic destabilization. This intervention requires no prescription, no clinical supervision, and no cost beyond the meal itself. A patient who wakes nauseated and eats a substantial breakfast within the first thirty minutes, rather than avoiding food or retreating to the shower, is performing the most basic test of the glucose override hypothesis. If morning caloric loading reliably attenuates prodromal symptoms, the glucose mechanism gains immediate clinical support.

Prediction B (Glucose Administration in Acute Episodes). Intravenous dextrose administration during an active hyperemetic CHS episode will attenuate the episode more effectively than isotonic saline alone, independent of antiemetic medications, by raising blood glucose above the organism's Hgt4 calibration threshold and signaling a return to commensal operational mode. Method: prospective emergency department protocol comparing IV dextrose to standard IV saline resuscitation in presenting CHS patients, with time-to-symptom-resolution as the primary endpoint. CHS patients frequently present with dehydration, and IV dextrose is not standard first-line treatment. If dextrose produces faster resolution than equivalent-volume saline, the glucose mechanism is supported over simple rehydration.[Please don't try this at home]

Prediction C (Colonization Density). CHS patients will exhibit higher gut *C. albicans* colonization than matched heavy cannabis users who have never developed CHS. However, the appropriate measurement method is not straightforward. Stool PCR, the standard and least invasive quantification method, measures what the organism is shedding into the gut lumen. It

does not measure what is embedded in the tissue. *C. albicans* invades submucosally through hyphal penetration, forms biofilms on and within mucosal surfaces, and its entire architectural strategy in this framework is tissue-level integration rather than luminal presence. A patient with aggressive submucosal colonization and minimal luminal shedding could return a low stool PCR result and appear uncolonized when they are not. Before stool PCR can be trusted as a screening tool for this prediction, a validation study comparing stool PCR quantification to mucosal biopsy with fungal staining (PAS or GMS) in the same patients is needed to determine whether stool shedding reliably correlates with tissue-level colonization density. Without that validation, a negative stool PCR result does not falsify the prediction. It may simply mean the screen is looking in the wrong compartment.

Prediction D (Arachidonic Acid Metabolite Signature). CHS patients will show an arachidonic acid metabolite profile consistent with substrate competition: elevated PGE_2 with depressed anandamide and 2-AG levels, compared to matched heavy users without CHS. Method: plasma or intestinal tissue measurement of PGE_2, AEA, and 2-AG concentrations. This tests the substrate competition mechanism described in VI.II.II directly.

Prediction E (Antifungal Resolution). Targeted gut antifungal treatment will resolve or significantly attenuate CHS in patients who continue cannabis use. This is the strongest differentiating test. If CHS resolves without cannabis cessation after antifungal treatment, the standard model in which THC itself is the sole cause cannot account for the result. Method: clinical pilot with targeted oral antifungals (e.g., fluconazole, nystatin) in CHS patients who decline or are unable to achieve cannabis cessation, with symptom tracking and stool *C. albicans* quantification pre- and post-treatment.

Prediction F (Gut CB1 Receptor Maintenance). *C. albicans* colonization prevents gut CB1 receptor downregulation under chronic THC exposure. Method: *in vitro* intestinal epithelial cell cultures with and without *C. albicans* colonization, exposed to chronic THC, with CB1 receptor density measured over time. A germ-free mouse model (colonized vs. non-colonized, chronic THC, gut and brain CB1 density compared) would provide *in vivo* confirmation. A third arm, colonized mice receiving antifungal treatment, would test whether removing the organism allows normal downregulation to proceed.

Prediction G (CBD Response). CHS patients who introduce CBD alongside continued THC use will show a clinical response. At the colonization densities expected in this population, the response may present as a single gradual improvement consistent with direct antifungal burden reduction (Bahraminia *et al.*, 2024), or it may exhibit two phases: a brief initial disruption from signaling interference followed by longer-term improvement from organism reduction. Whether the acute signaling disruption observed in the longitudinal case study (§6.3) is detectable at lower colonization densities is an open question. Any measurable response to CBD in CHS patients, positive or negative, would support the organism-mediated model over the standard pharmacological model, which has no reason to predict that CBD should affect CHS at all. Method: prospective cohort with stool PCR at baseline, symptom diary, and standard CBD dosing protocol. [This one is kinda like a wildcat well, except no high upfront cost.]

Prediction H (Transcriptomic Immune Signature). Building on the findings of GSE303922, CHS patients' gut immune activation profile (B-cell immunoglobulin upregulation, impaired barrier function, elevated IgE) will correlate with *C. albicans* colonization density rather than with THC exposure levels. Matched heavy cannabis users without CHS should show neither the immune activation nor the elevated colonization. Method: paired transcriptomic and mycobiome analysis in a case-control design.

6.7 Positioning and Limitations

The connection presented here between *C. albicans* and cannabinoid hyperemesis syndrome is novel and should be treated accordingly: as a potential linkage derived from the biochemical computer framework architected from synthesis of research, not as an established causal relationship.

The argument is theoretical but not unsupported. The 2025 transcriptomic study (GSE303922) independently found an immune activation profile in CHS patients consistent with *C. albicans* colonization, while simultaneously finding no ECS transcript changes, exactly the pattern the organism-mediated model predicts and the standard model does not. The pharmacological evidence is similarly consistent: the drugs that work for CHS (haloperidol, benzodiazepines, NK1 antagonists) act on receptor systems the organism interfaces with, while the standard antiemetic (ondansetron) that should work based on the conventional emesis model does not.

The framework generates predictions that are testable, falsifiable, and in several cases inexpensive to pursue. The first prediction, caloric loading in prodromal patients, can be tested by any individual experiencing morning CHS symptoms, with no institutional infrastructure required.

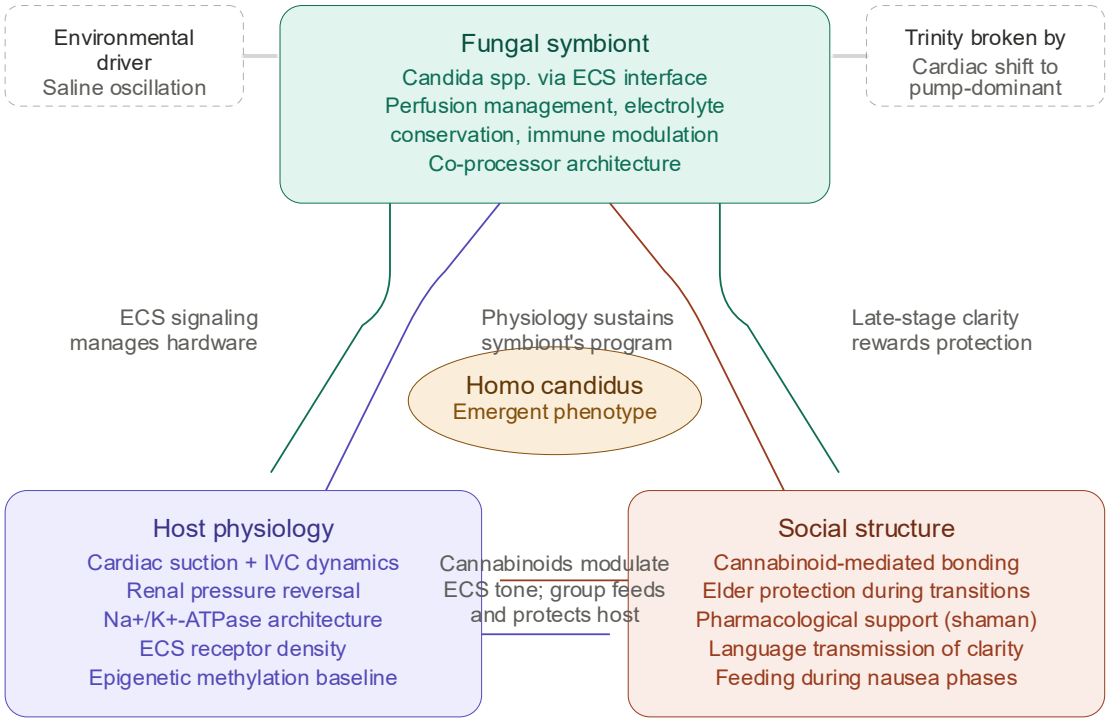
Several limitations apply. The substrate competition model assumes that fungal burden in CHS patients is sufficient to meaningfully deplete the arachidonic acid pool available for endocannabinoid synthesis. This is an empirical question. The Hgt4 glucose threshold connection is mechanistically plausible but has not been tested in a CHS context. The mirror case comparison between CHS and emetic suppression, while conceptually clean, relies on a single longitudinal case study and should not be generalized without additional cases. The palliative trap hypothesis (that hot shower relief delays caloric intervention) is observationally consistent with clinical descriptions but has not been directly tested. The pharmacological observations regarding haloperidol, benzodiazepines, and NK1 antagonists are drawn from case reports and anecdotal accounts rather than controlled trials, and alternative explanations for their efficacy exist within the standard model.

The clinical implication, if validated, would be a reframing: CHS shifts from a cannabis toxicity syndrome requiring abstinence to a host-organism interface disruption syndrome amenable to antifungal, metabolic, and dietary intervention. Cannabis cessation would still resolve symptoms (by removing the signal jammer and allowing the organism to restore its signaling equilibrium), but it would no longer be the only therapeutic option. This would be relevant to the growing population of patients who use cannabis for other medical conditions and face a difficult choice between CHS management and loss of therapeutic benefit.

The tests come first. The reframing follows only if they succeed. [*Tick-Tock, next block*]

Figure 1: The Evolutionary Trinity

Three mutually reinforcing components producing Homo candidus



Each leg reinforces the other two. Remove any one and the architecture collapses.
The cardiac shift removed leg 2's responsiveness, collapsing the trinity from the host side.

Assembly order: Symbiont (commensal, ~200 Ma) + Social structure (cannabinoid flywheel, pre-3.3 Ma) + Host physiology deepened by saline oscillation (~2.7 Ma) + Language accelerant (~1.9 Ma) = Full trinity (~1.55 Ma)

6. The Evolutionary Trinity:Three Co-Evolving Components

The Saline Oscillation Hypothesis proposes that the full coevolutionary architecture required three simultaneously reinforcing components, a “trinity”:

The fungal symbiont, operating through the ECS and the expanded control surface described in Section 5 to modulate host physiology, perfusion, electrolyte balance, and cognition

Host physiology, including the cardiac suction mechanism, IVC dynamics, ECS interface, and Na^{+}/K^{+}-ATPase architecture

Cooperative social structure, initiated by communal phytocannabinoid use promoting peaceful bonding, later formalized through language-enabled elder care and pharmacological support

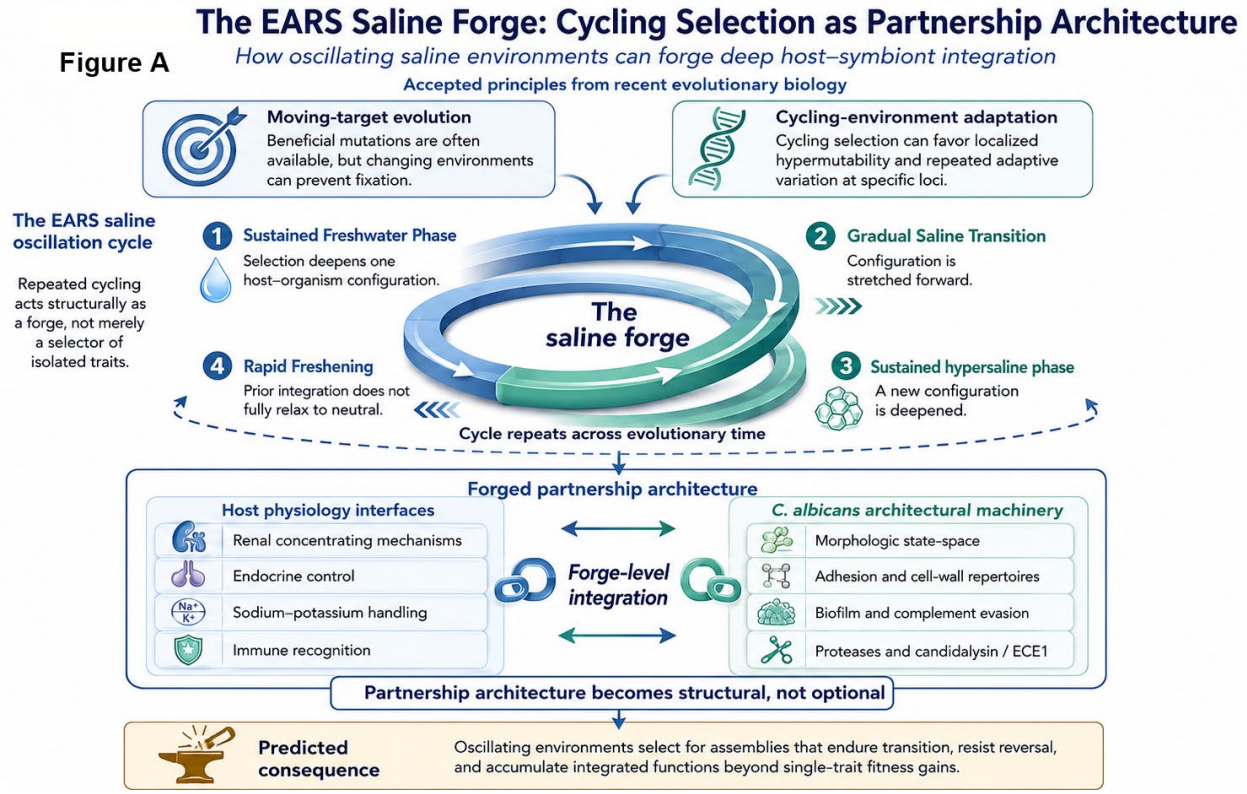
Two of these legs, the symbiont (present as a commensal) and the social structure (initiated by the cannabinoid flywheel), were established before the salinity oscillations began. Language did not create the trinity. Language completed the trinity, and allowed it to accelerate.

6.1 The Saline Oscillation Forge Theory

Two independent lines of recent evolutionary biology research support this paper's argument that the partnership architecture is a maintained state rather than a default state. Song, Chen, Shen, & Zhang (2025) established that beneficial mutations are far more abundant than the Neutral Theory of Molecular Evolution assumed, but rarely fix because environments change before fixation can occur — natural populations continuously chase moving environmental targets. Barnett, Meister, & Rainey (2025) experimentally demonstrated that under cycling-environment selection, lineages evolve localized hypermutability biased toward generating adaptive variation at specific loci. The two findings together establish that lineages with the right architecture maintain partnership-relevant functions across environmental cycling.

This paper proposes a further architectural consequence: the EARS-scenario saline oscillation cycled for hundreds of thousands of years within a range the partnership architecture was selected to track, alternating between freshwater and hypersaline extremes through a structure of sustained selective pressure followed by rapid transition. This cycling regime functions structurally as a *forge (Figure A)*.

A forge transforms metal not in a single step, but through repeated cycles: the metal is heated until it becomes workable, hammered into a new form, then quenched or cooled to lock that form in place before the process begins again. Each cycle does specific work. Heat opens the structure, shaping forces it into a new configuration, and cooling preserves the change so the metal does not simply return to what it was. In this paper, the saline oscillation is analogous to that process: sustained environmental phases do the heating and working, rapid transitions do the quenching, and over many cycles the host-organism partnership is not merely selected, but forged into a deeper, more durable architecture.



The forge metaphor is not novel as evolutionary mechanism — mainstream evolutionary biology already accepts that cycling environments shape genome architecture in ways that stable environments do not, that alternating selective regimes produce more robust adaptation than constant pressure, and that the work done by selection during specific cycle phases shapes the resulting architecture in specific ways.

The framework's contribution is extending this accepted principle to its full implication for coevolutionary partnerships rather than for single-lineage adaptation. Each EARS oscillation cycle does specific work on the partnership architecture: sustained selection within a configuration deepens the integration; rapid transition locks new configurations in place; the next sustained phase deepens integration of the new configuration without permitting the prior integration to relax to neutral. Over many cycles across hundreds of thousands of years, the partnership architecture becomes forged at the structural level — not merely selected, but shaped by the specific molecular interfaces between host and organism across each cycle's selective regime.

Two implications follow directly. First, the partnership architecture present in modern Homo sapiens cannot have been built by substituting *C. albicans* for an earlier partnership organism at any point in the lineage's history; forge-level integration requires the same molecular interfaces operating across the cycling history. The pan-mammalian observation that each mammalian lineage carries its own lineage-specific Saccharomycetaceae symbiont (Craddock, Pan-Mammalian) reflects this constraint — each host-organism pairing was forged together from early in the lineage's evolutionary history. Second, the disruption signatures observed when modern pharmacology removes partnership components (Lionakis et al., 2008; Lionakis section in Kemper et al., 2023) are predicted by forge-level integration: the architecture cannot be unforged without disruption proportional to the depth at which the partnership has been integrated into host physiology. [*This partnership is not optional*]

The framework's prediction that the forge process produces deeper architectural integration than ordinary selection has a worked example within the *Candida* genus itself. *C. albicans* is documented across the mycology literature as having the most structurally and behaviorally complex molecular repertoire of any pathogenic *Candida* species: the most elaborate morphological state-space, the largest secreted aspartyl protease family, the most diverse adhesin and immunomodulatory cell wall component repertoires, the most developed biofilm-forming and complement evasion machinery, and the most extensive candidalysin/ECE1 system. Sister species including *C. dubliniensis*, *C. glabrata*, *C. tropicalis*, and others show substantially reduced complements of this architectural machinery. The mainstream framing treats this complexity differential as *C. albicans* has more virulence factors than its sister species,' but the framing has a problem the field has not adequately addressed: virulence factors should be costly to maintain when not actively producing pathogenesis, and natural selection should have pruned the elaborate machinery toward whatever subset is consistently advantageous. The persistence and continuous refinement of *C. albicans*'s elaborate architecture across evolutionary time is inconsistent with the standard opportunism narrative. The forge model resolves this: *C. albicans*'s elaborate machinery is not a collection of retained virulence factors but the partnership architecture that the EARS-scenario forge specifically produced. The complexity gradient across the *Candida* genus tracks the gradient of coevolutionary exposure intensity — *C. albicans* was the species in the forge, sister species were not, and the documented architectural complexity differential is what the forge model predicts the outcome should look like.

6.2 Language and the Transmission of Late-Stage Cognitive Enhancement

The ECS modulates neuroplasticity, pain perception, and cognitive function (Di Marzo and Piscitelli, 2015). Late-stage symbiont activity produces pain-free windows concurrent with enhanced cognitive clarity and creative drive. This is documented both in the historical cohort (Craddock, Redacted Science) and consistent with known CB1-mediated neurological effects.

In pre-linguistic hominids, this late-stage cognitive enhancement had limited transmission bandwidth. Tool-making demonstrations, gestural communication, and behavioral imitation could transmit some knowledge as evidenced by the Lomekwi tools (3.3 Ma) predating any evidence of language. However, the abstract, strategic, and philosophical content documented in the historical cohort (where common Everyman subjects in the final stages discussed deeply complex topics with extraordinary clarity) requires symbolic language for transmission. Language did not create the survival value of late-stage clarity; it amplified it by orders of magnitude.

With the emergence of language, for which *Homo habilis* (KNM ER 1813, ~1.9 Ma) shows an enlarged Broca's area visible in the cranium, and for which the endocast of KNM-WT 15000 (*Homo erectus*, ~1.6 Ma) shows Broca's area asymmetry (Walker and Leakey, 1993; Turkana Basin Institute, 2021), the lucid elder could articulate insights, strategies, and knowledge with full symbolic complexity. The social group that protected its elders during late-stage decline received this transmission; groups that discarded the weak lost it.

This creates a three-way selection pressure: the symbiont benefits from extended host survival (longer cycle completion); the host's social group benefits from the elder's clarity; and the social structure itself is reinforced by the value of what the elder produces. Language is the accelerant that transforms a modest survival advantage into a civilizational engine.

6.3 Evidence from the Fossil Record

Species	Date	Location	Relevant Feature
A. afarensis (Lucy)	~3.2 Ma	Afar Triangle	Bipedal, social groups, freshwater lakes, cannabinoid flywheel plausibly active
Lomekwi Tools	~3.3 Ma	Lake Turkana	Cognitive sophistication predating *Homo*, same salt basin
H. habilis	~1.9 Ma	East Africa	Enlarged Broca's area, proto-language capacity
P. boisei	~1.75 Ma	Olduvai/Natron	Dietary specialist, evolutionary dead end
H. erectus (Turkana Boy)	~1.6 Ma	Lake Turkana	Broca's area asymmetry, long-distance running, cooperative hunting, periodic saline lakes
First dispersal	~1.5 Ma	Out of Africa	Trinity-equipped species carrying symbiont to new environments

Figure 2 The Critical Window (3.3-1.3 Ma)

Convergence of environmental, biological, and coevolutionary evidence



7. Archaeological Evidence for the Cannabinoid Flywheel

7.1 Ritual Cannabis Use in Mortuary Contexts

The earliest scientifically verified evidence for psychoactive cannabis use comes from the Jirzankal Cemetery (~500 BCE) in the eastern Pamirs, where chemical analysis of wooden braziers from mortuary contexts revealed cannabinoid residues with unusually high THC levels (Ren *et al.*, 2019). The cannabis was burned on heated stones in enclosed spaces during funerary ceremonies, a ritual context directly associated with death and transition. At the Yanghai tombs (~500 BCE, Turpan), a leather basket and wooden bowl filled with cannabis seeds, leaves, and shoots were found near the head and feet of a deceased individual identified as a probable high-ranking shaman (Russo *et al.*, 2008). The Jiayi Cemetery (~800–400 BCE, also Turpan) yielded a burial shroud composed of 13 intact desiccated cannabis plants arranged over the body (Jiang *et al.*, 2016).

The consistent association of cannabis with mortuary ritual, shamanic figures, and funerary ceremony across multiple independent sites is precisely the pattern predicted by the trinity model: the plant that served the dying elder becomes sacred, and its administration becomes the province of the specialist who tends the elder, the shaman. The shaman's role is not mystical invention; it is the social expression of the group member who manages the elder's pharmacological support during transition.

Herodotus, writing in the fifth century BCE, described Scythian funerary practices involving cannabis vapor inhalation, an account subsequently corroborated by archaeological finds at Pazyryk (~2,400–2,500 years BP), where cannabis seeds, censers, and hempen clothing were recovered from burial mounds (Rudenko, 1970; Ren *et al.*, 2019).

7.2 The Pharmacological Argument for Cultivation Priority

The eight Neolithic "founder crops" (emmer wheat, einkorn wheat, barley, lentils, peas, chickpeas, bitter vetch, and flax) were domesticated in the Fertile Crescent between approximately 10,500 and 7,500 years ago (Zohary and Hopf, 1988; Zohary *et al.*, 2012). These are caloric and industrial crops. Cannabis, however, offers something no grain provides: direct modulation of the mammalian ECS. *Cannabis sativa* is among the oldest cultivated plants in the world, with dried specimens from the Oki Islands of Japan dating to approximately 8000 BC (Crawford, 2006) and cultivation in East Asia from at least 4000 BC (Li, 1974; McPartland *et al.*, 2019).

We propose that the motivation to cultivate a psychoactive plant may have preceded or paralleled the motivation to cultivate caloric crops. A group whose social cohesion depends on a plant, first for communal bonding, later for elder care during transition, has an immediate, non-deferrable need to secure its supply. Grain can be foraged; the medicine that holds the group together cannot be left to chance.

7.3 Endogenous Cannabinoids, Running, and the Rift Valley

Between transition phases, endogenous cannabinoids are elevated by sustained physical activity. The "runner's high" is mediated by anandamide and 2-AG, not endorphins as previously assumed (Fuss *et al.*, 2015). For hominids in the EARS environment, long-distance running (needed for persistence hunting, foraging range expansion, possibly communal communication, and predator avoidance) served as the primary endogenous ECS maintenance strategy.

This observation generates a testable prediction with contemporary resonance. The Kalenjin people of Kenya's Rift Valley, the geographic heart of the EARS, adjacent to the Turkana Basin, produce a wildly disproportionate share of the world's elite distance runners. Standard explanations invoke altitude training effects, lean body habitus, and cultural emphasis on running. The Saline Oscillation Hypothesis adds a complementary explanation: these populations are the direct descendants of hominids for whom long-distance running was not merely athletic but pharmacological and the primary mechanism for maintaining endogenous ECS tone in the environment where the coevolutionary program was deepest.

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8. The Cardiac Architecture Hypothesis: Developmental Preservation and the Breaking the Trinity

8.1 The Mammalian Default: Suction Dominant Circulation at Birth

The mechanistic sequence described in Section 4 operates on standard mammalian cardiac hardware. No novel anatomy is required to initiate or sustain the program. What distinguishes *Homo candidus* is the symbiont's management of the existing cardiovascular architecture through ECS signaling. The question that has persisted throughout this framework — when and how did the cardiac architecture shifts from suction-dominant to pump-dominant — may be resolved by a developmental observation rather than an evolutionary one: every mammal is born with a suction-dominant heart.

Neonatal cardiac physiology is fundamentally different from adult cardiac physiology. The fetal and neonatal heart operates with open foramen ovale, patent ductus arteriosus, and diastolic mechanics in which the suction contribution to ventricular filling is proportionally greater than in the mature adult heart. The transition from fetal to adult circulatory dynamics, involving closure of the foramen ovale, involution of the ductus arteriosus, and progressive shift toward systolic ejection as the dominant filling mechanism, is a normal developmental process that occurs over the weeks and months following birth, with cardiac remodeling continuing throughout postnatal maturation.

The pump-dominant adult heart is therefore not a mutation. It is the developmental endpoint. The suction-dominant neonatal heart is the starting condition. The question is not "when did a genetic shift produce the pump-dominant heart?" The question is "what, in the ancestral context, prevented the normal developmental transition from completing?"

The same principle applies to the pituitary. The neonatal pituitary operates at high activity by default. It manages explosive growth, organogenesis, neurological development, and the establishment of endocrine axes that will govern the organism for its entire lifespan. The "overclocked" pituitary described in the coevolutionary framework is not an upgrade installed by the symbiont. It is the factory setting. Every infant has one. The developmental program progressively reduces pituitary output as growth decelerates and the endocrine system matures. In the adult, the pituitary operates at a fraction of its neonatal capacity at more of a maintenance level, The adult capacity is sufficient for maintenance, but insufficient for the demands of the symbiont's full program.

8.2 The Preservation Mechanism: Why the Ancestral Transition Did Not Complete

We propose that in the ancestral Rift Valley context, the symbiont's role was not to build a suction-dominant heart or to overclock the pituitary. It was to prevent the normal developmental transition that would wind both systems down. The organism preserved the neonatal configuration into adulthood by maintaining ECS-mediated signaling on cardiac conduction and pituitary perfusion during the critical developmental window when the transition would otherwise occur.

The molecular plausibility of this preservation mechanism is supported by the finding that farnesol, the primary *C. albicans* effector molecule, is a confirmed inhibitor of N-type voltage-gated Ca^{2+} channels in mammalian cells (Roullet *et al.*, 1999) and is present in the human brain at measurable concentrations. Calcium channel activity is fundamental to cardiac conduction and to the developmental remodeling of cardiac electrophysiology. An organism whose primary signaling molecule modulates the ion channels governing cardiac rhythm has the molecular tools to influence whether and when the postnatal cardiac transition completes. CB1 receptors, expressed on cardiac tissue, provide an additional direct pathway through which ECS-mediated signaling could maintain the diastolic suction contribution that the normal developmental program would reduce.

Pituitary preservation operates through the perfusion governance described in Section 4.3 and the ECS-mediated pituitary signaling described in Section 5.7. CB1 receptors on pituitary cells modulate hormone secretion across all axes (Pagotto *et al.*, 2006). An organism managing pituitary perfusion and signaling from birth arrives through breastfeeding into a system where the ECS boot sequence (CB1-mediated suckling reflex) is already active, and has continuous access to the gland during the developmental window when its activity would normally decline. The preservation is not a single intervention. It is continuous management, from neonatal colonization through postnatal development, maintaining the high-activity pituitary state by preventing the downregulation the developmental program would otherwise execute.

The developmental preservation model requires only documented neonatal cardiac physiology, documented postnatal cardiac remodeling, and the documented molecular tools the symbiont possesses to influence both. The transition is not a mystery. It is the default. The mystery was always why it didn't happen in the ancestral population and the answer is that the symbiont prevented it.

8.3 The Three-Key Activation Model: Why Modern Infants Do Not Preserve

If every mammal is born with the suction-dominant heart and the active pituitary, and if the symbiont arrives through breastfeeding in nearly all humans, the question becomes: why does the developmental preservation not occur in modern infants?

The answer lies in the activation requirements for the preservation program. The symbiont's arrival is necessary but not sufficient. The program that prevents the developmental transition requires environmental conditions that are no longer present.

We propose a three-key activation model:

The first key is the symbiont's presence during the critical developmental window. *C. albicans* is transmitted vertically from mother to child through birth canal transit and breastfeeding (Kumamoto, 2011; Ost and Round, 2023). The CB1-mediated suckling reflex, the

first mammalian survival behavior, is the ECS boot sequence through which the symbiont arrives and initial colonization is established. This key is present in virtually all modern infants. The organism arrives. Colonization begins.

The second key is colonization density sufficient to produce meaningful signaling output during the developmental window. This is variable. The output is dependent on maternal colonization depth, breastfeeding duration, early immune development, and the infant's own microbiome ecology. Some infants may achieve deep colonization rapidly. Others do not. In the ancestral context, where antibiotic exposure did not exist, mucosal barrier disruption from processed foods did not occur, and breastfeeding duration was extended, deeper and earlier colonization would have been the norm. This key was more consistently present in the ancestral population than in the modern one, but it is not categorically absent today.

The third key is the electrolyte environment. The saline oscillation, cyclical exposure to elevated and depleted electrolyte concentrations that constitutes the central mechanism of this paper, provided the environmental activation signal. The SIADH-type electrolyte disruption during freshwater transitions following saline acclimation created the physiological conditions under which the symbiont's perfusion management program gained decisive selective advantage. Without this electrolyte signal, the symbiont colonizes commensally, feeds on dietary glucose, performs its baseline maintenance functions, but the preservation program that would prevent the cardiac and pituitary developmental transition does not activate. The program requires the environmental context it was selected within.

Modern infants have the first key universally. Some have the second key to varying degrees. None have the third key. The developmental transition proceeds on schedule because the environmental trigger that would activate the preservation program does not exist in a world of stable, treated drinking water with consistent electrolyte content.

In the ancestral East African Rift Valley, all three keys were present simultaneously. The symbiont arrived through breastfeeding from a mother whose own electrolyte status reflected the saline-oscillating water sources. The infant's developing system was exposed to electrolyte variations from birth through breast milk composition, through early introduction of local water sources, and through the same environmental pressures acting on the entire social group. Colonization established during the critical window. The electrolyte signal was continuous. The preservation program activated, and the suction-dominant heart and high-activity pituitary were maintained into adulthood. The organism did not build *Homo candidus*. It prevented the developmental transition that would have produced an ordinary adult.

This model also explains the evolutionary trajectory of the phenotype across time and geography. In the earliest stages of the coevolutionary relationship, preservation of the neonatal cardiac and pituitary architecture carried no disadvantage. An infant whose suction heart and active pituitary were maintained into adulthood would exhibit superior perfusion, superior endurance, enhanced crisis tolerance, and better cognitive performance with no transitional decline phases, because the program had not yet evolved the complex multi-phase sequence documented in the redacted source article and the longitudinal case study. That sequence is the product of hundreds of thousands of years of oscillation-driven refinement. The early program was simpler: basic perfusion management and electrolyte handling, the core functions the saline oscillation selected for. Preserved individuals in this early period dominated selection. They were better at everything.

In a Rift Valley population where all three keys were consistently present: 1) universal symbiont transmission through breastfeeding with deep colonization supported by extended

nursing, 2) the absence of antibiotics, and 3) continuous electrolyte oscillation from the lake systems, preservation would have trended toward universality. Selection pressure ran hard in one direction: preserve the heart, maintain the pituitary, outperform everyone who doesn't.

As the oscillation cycles ratcheted the coevolutionary relationship deeper over millions of years (Section 4.1), the program became more sophisticated. More phases emerged. More organ systems became involved. More metabolic transitions developed. Eventually, the decline phases appeared. These are the transitional vulnerability periods documented in the redacted source article and in the longitudinal case study (Craddock, Redacted Science). Only at this stage did the evolutionary trade-off described in Section 4.3 materialize: enhanced capability between transitions, increased vulnerability during them. Only now did the social support structure become necessary to protect the individual during difficult phases. Only now did the trinity's third leg, that of cooperative social structure, reinforced by the cannabinoid flywheel described in Section 3, gain its full adaptive value. The trinity did not form because the program was dangerous from the start. It formed because the program deepened until it required social support to sustain.

The spectrum of preservation outcomes with some individuals fully preserved, some partially, some not at all emerged late in the coevolutionary timeline, driven by two factors. First, as the program deepened, the metabolic and physiological demands of the preservation sequence increased, raising the threshold of colonization density and electrolyte exposure required for full activation. Second, and more significantly, the first dispersal out of Africa (~1.5 Ma) carried the population into environments where the third key, the saline oscillation, was weaker or absent. The further from the Rift Valley, the less consistent the electrolyte signal, the less reliable the preservation. Populations at the geographic margins of the dispersal experienced partial or inconsistent activation. The developmental transition began completing in some individuals. Pump-dominant adults appeared — not through mutation but through the absence of the environmental signal that had prevented the transition in the ancestral core zone.

VIII.III Intellectual Growth and Religion in Homo Candidus

[*Boom! Hi All, glad to be back. Here is a V4 section on Homo Candidus and religion*]

The program described in this section demands more than symbiont presence and environmental exposure. It demands sustained behavioral compliance from the host. Dietary restriction during specific phases. Fluid management under conditions where the body's signals are misleading. Endurance of significant pain without seeking the palliative interventions that would interrupt the process: the hot shower, the emetic, the fast that empties the gut, the instinct to stop eating when eating is exactly what the program requires (Section 7). These are not behaviors that emerge from instinct. They are counterinstinctive. The host must override immediate physiological signals on the authority of transmitted knowledge, doing what feels wrong because someone who survived the process before said it was necessary. [*I choose Normal – it looks normal but it is persistence and perseverance through some trying times*]

This implies a social infrastructure far more structured than communal bonding. It requires a transmitted protocol: specific behavioral instructions indexed to recognizable phases of the process. It requires authority: individuals whose experience confers the credibility to override another person's instinctive responses during crisis. It requires enforcement: social mechanisms that hold the individual to the protocol when their own will fails. And it requires consequences: the noncompliant individual who seeks palliative relief, abandons dietary

discipline, or refuses to endure a transition phase does not merely fall behind. They die. The program, once activated beyond a certain depth, does not accommodate deviation gracefully.

This is natural selection for institutional compliance. The individuals who could not submit to transmitted authority, could not delay gratification across phases lasting weeks or months, could not endure discomfort without seeking immediate relief, or decided to stop eating because of the pain or nausea were removed from the gene pool not by predators or climate but by the program itself. The individuals who could follow instructions, trust the elder's protocol when every somatic signal said otherwise, and maintain discipline across the full arc of the process survived, reproduced, and transmitted both the genetic predisposition for compliance and the cultural knowledge that made compliance productive. The capacity for faith, understood not as belief in the supernatural but as trust in a process whose logic is not immediately apparent to the person undergoing it, was selected for directly by the demands of the program. [*Probably not a progressive and tolerant bunch of ancestors*]

Critically, neither partner in this coevolution began with a map of the path ahead. The organism did not arrive with a prewritten program for managing host perfusion through a multi-phase physiological transformation. The host did not arrive with knowledge of what the organism would require. Both were learning simultaneously. Each oscillation cycle was a joint experiment conducted across the boundary between two kingdoms. On the organism's side, the biochemical computer tested regulatory configurations, chromatin states, signaling outputs, metabolic adjustments, exploring the solution space through the bet hedging architecture described in Section 5.8. Configurations that kept the host alive longer were epigenetically reinforced and propagated to the next generation of the organism's population within the host. Configurations that failed died with the host. On the host's side, the elder who survived one step further than the previous generation's elder observed what happened and transmitted that observation. Eat when the pain comes. Do not drink when you feel thirsty. Lie down when the pressure builds. Do not seek the hot water. Each behavioral instruction was a data point purchased with a lifetime. And elders, they were worshipped for their intellects. This was a group whose survival depended on the knowledge of the elders.

Notably, over time, this preselects greatly for intelligence and compliance during specific phases but also demands initiative, observation, problem-solving, and leadership from the elders who develop and transmit the protocol. The host must be disciplined, learned, and devout. This selection is made every generation for more than 21,000 years. That’s just one oscillation cycle. [*Uno!*] The first group was likely a small tribe. The tribe prospered, dominating due to increased hormones from the effect of the suction heart. It grew smarter and more disciplined. [*Not what we have going on in most places these days, huh? Seems like we are self-selecting out of the gene pool*]

The path was not discovered. It was built, one lifetime at a time, from both directions. The organism wrote the program through chromatin-encoded trial and error, locking in successful signaling configurations across thousands of host generations. The host wrote the protocol through cultural transmission, locking in successful behavioral responses across the same timescale. Neither could have produced the result alone. The organism without a compliant host cannot complete phases that require behavioral cooperation. The host without a sufficiently refined organism cannot survive the physiological demands of the deeper phases. The convergence of both learning curves, biological and cultural, across hundreds of thousands of oscillation cycles, is what produced the Homo candidus phenotype. We have no modern analogue for the depth of this coevolutionary investment. The closest approximation is that every

successful transit of the program by every host-organism pair across the entire Plio-Pleistocene contributed one data point to a collaborative solution that neither partner could see the end of.

The devotion is not human or microbial. It is the accumulated weight of millions of lifetimes that each went one step further than the last.

VIII.IV The Generational and Civilizational Math

If we use the full 2.7 Myr window and a 30-year generation time:
2,700,000 / 30 = **90,000 generations**

If even a small population of 500-1,000 individuals per generation is running the program:
90,000 × 500 = **45 million individual lifetimes** (conservative)
90,000 × 1,000 = **90 million individual lifetimes** (more realistic)

If you count only the three variability packets (~600,000 years of intense oscillation):
600,000 / 30 = **20,000 generations** 20,000 × 500 = **10 million individual lifetimes**

For a frame of reference, it has been roughly 40 generations since the formation of Christianity.

The institutionalization of the host-side protocol was not optional. Individual willpower varies across any population. A process that kills the noncompliant cannot depend on individual willpower alone if the population is to sustain itself across generations. It requires rules that apply universally within the group, designated individuals responsible for enforcement, and social costs for deviation that exceed the immediate discomfort of compliance. It requires, in short, the foundational architecture of organized religion: prescribed behaviors indexed to life phases, authority figures who have undergone the process themselves, communal rituals that reinforce group commitment, and an explanatory framework that gives meaning to suffering. The third leg of the evolutionary trinity is not community. It is civilization with rules. The program required it, and the populations that built it survived. The ones that did not are not represented in the modern genome.[*Well, until lately, that is…currently the Overton Window is non-existent*]

8.4 Hypophyseal Failure: The Endpoint of Unresolved Preservation

In the ancestral context where all three keys were present, the preserved pituitary operated within a system designed to support it. The saline oscillation provided continuous electrolyte substrate, the social structure supplied dietary and pharmacological support, and the program proceeded through its phases toward completion. The pituitary ran at elevated capacity because the program demanded it, and the program's completion allowed the system to reach its intended endpoint.

In a modern host where the program activates but cannot complete, either because the cardiac architecture has transitioned past the suction threshold (the population at large) or because the activation occurred iatrogenically without the ancestral support structure (the longitudinal case study), the pituitary operates beyond its optimal range indefinitely. The resulting condition resembles prolonged operation of a regulatory system beyond its optimal range: a strategy that may preserve short-term functional performance while progressively reducing long-term adaptive reserve.

This is what the archaic clinical literature termed “hypophyseal failure.” not a disease of the pituitary but the exhaustion of a gland running a program it was not designed to sustain without resolution. The pituitary does not fail because it is defective. It fails because the program it is executing has no endpoint in the modern context. The conversion sequence stalls. The pituitary continues to drive perfusion and endocrine management at elevated capacity. The adaptive reserve depletes. The gland's functional output declines. This is not acute decline, but progresse, over years or decades, producing the gradual endocrine insufficiency that the original article documented in its cohort and that the longitudinal case study has observed over thirty years (Craddock, Redacted Science).

The distinction between pathological pituitary failure and programmatic pituitary exhaustion is clinically significant. Standard endocrinology treats pituitary insufficiency as a glandular disease — a failure of the organ itself. The framework described here treats it as the predictable outcome of a preserved system running without the environmental context that would allow its program to complete. The treatment implications are fundamentally different: the gland does not need to be replaced or supplemented. The program needs to be understood, and ideally, completed or safely resolved.

8.5 Consequences

The trinity's collapse was not a single event. It was a geographic gradient that followed the dispersal.

In the Rift Valley core zone, where all three keys remained present, the full program continued to operate. The social structure sustained it. The elders produced transmissible knowledge. The phenotype persisted. But at the edges of the expanding human range and in environments without saline-oscillating water sources, the third key was missing. Infants born in these peripheral populations carried the symbiont (key one) and may have achieved adequate colonization density (key two), but without the electrolyte oscillation, the preservation program did not fully activate. The developmental transition completed. Pump-dominant adults emerged.

These pump-dominant individuals carried a compound advantage in the new environments. They were physically strong through their reproductive years without the transitional decline phases that the deepened program now produced in preserved individuals. They were free from the social dependency the trinity required. They did not need a group to feed and protect them through vulnerable phases, and they were in environments where the elder's specialized knowledge, refined for Rift Valley conditions, was less immediately applicable. The survival value of the preserved elder's cognitive output diminished in proportion to the distance from the ecological context that output was calibrated to.

Pump-dominant individuals outcompeted preserved individuals reproductively at the geographic margins. The elder-protecting social structure, without elders to protect, lost its adaptive function. The trinity collapsed then collapsed. Deteriorating not from the center, but from the edges inward. As the pump-dominant phenotype expanded through the peripheral populations and eventually back into contact with the core zone, the reproductive advantage compounded. The social structures that had sustained the program for millions of years were undermined by a simpler, more reproductively efficient phenotype that did not require them.

The symbiont persisted commensally. It persists today in virtually every human. The program persists in the organism's chromatin-encoded memory (Section 5.8). But the hardware the program requires, notably the preserved suction heart, the maintained pituitary, is no longer produced because the environmental key that activated the preservation sequence no longer turns

in any modern lock. A deep system state that the organism still remembers how to enter, in a host whose developmental program no longer permits the entry.

The modern condition described in Craddock Case Studies, a full activation of the ancient program triggered by iatrogenic circumstances in an adult whose developmental transition completed normally decades earlier, represents the most extreme edge case: the old program running on hardware that was never preserved for it. That it has been sustained for over thirty years under these conditions speaks to the robustness of the program itself and raises the question addressed in Section 9.2: what could be achieved with the full playbook and a medical system prepared to support the process?

8.6 Salt Sensitivity and the Vestigial Conversion Mechanism

The Saline Oscillation Hypothesis predicts that the cardiovascular response to sodium variation should differ across individuals in proportion to the signaling density of the distributed commensal system described in Section 5.7. Modern clinical data on salt-sensitive versus salt-resistant hypertension is consistent with this prediction.

Approximately one-third of the adult population globally exhibits hypertension, and salt sensitivity, the degree to which blood pressure responds to changes in dietary sodium. varies substantially across individuals. Genetic variation, renal sodium handling differences, RAAS polymorphisms, and vascular reactivity have each been proposed as contributing factors. No unified mechanistic explanation has been established.

The framework presented in this paper proposes a two-gate model in which salt sensitivity and its clinical consequences are governed by two independent variables: the signaling density of the commensal *Candida* population (gate one), and the cardiac architectural capacity to complete the conversion sequence (gate two).

Gate One: Signaling Density

Section 5.7 established that *C. albicans* colonization is near-ubiquitous in humans, with the conventionally cited 40–60% detection rate reflecting assay sensitivity rather than true prevalence. What varies between individuals is not whether the organism is present but the density, distribution, and aggregate signaling output of the distributed system at each tissue interface.

In a host with high commensal density, the organism's aggregate vascular signaling is proportionally greater: more PGE_2 production from host-derived arachidonic acid (Section 5.5d), more farnesol interacting with voltage-gated calcium channels (Section 5.5), more ECS-mediated modulation of cardiac conduction and perfusion dynamics (Section 4.3), and a larger collective footprint across the vascular control systems the organism accesses. When this host encounters a sodium perturbation, whether excess sodium producing volume expansion or sodium deficit triggering SIADH-type water retention, the distributed system's vascular signaling amplifies the cardiovascular response. The response scales with the operator's density, not with a defect in the host's hardware.

In a host with low commensal density, the same sodium perturbation meets insufficient signaling mass to drive a meaningful vascular response. The hardware is identical. The operator is present but below the threshold at which its aggregate output moves the system.

This reframing generates predictions that the hardware-only model does not. Salt sensitivity increases with age (Weinberger and Fineberg, 1991). This is consistent with the documented tendency for *Candida* colonization density to increase over the lifespan through

cumulative antibiotic exposure, hormonal changes, immune senescence, and declining mucosal barrier integrity. A person who is salt-resistant at 25 may become salt-sensitive at 50 not because their cardiovascular genetics changed but because their colonization deepened in the intervening decades. The hardware-only model requires a genetic or structural change to explain this shift.

The colonization model requires only what is already documented: commensal density changes over time.

Geographic and demographic variation in salt sensitivity prevalence is similarly consistent. Populations with different dietary histories, antibiotic exposure patterns, and microbiome compositions carry different colonization profiles. This connects directly to the mycobiome prediction in Section 10.1: comparative *Candida* colonization profiles in populations near hypersaline versus freshwater sources in the modern East African Rift System should correlate with population-level differences in salt sensitivity, if commensal signaling density is the mediating variable.

Gate Two: Cardiac Architecture

The first gate determines whether the vascular response initiates. The second gate determines whether it resolves.

As described in Section 8.1, every mammal is born with suction-dominant cardiac architecture. In the ancestral Rift Valley context, where all three activation keys were present (Section 8.3), the symbiont preserved the neonatal suction-dominant heart into adulthood through continuous ECS-mediated management of cardiac conduction during the critical postnatal developmental window. These preserved individuals entered the saline oscillation environment with the cardiac architecture the program required.

When they encountered freshened water sources during humid periods, their systems, already calibrated to higher electrolyte concentrations, responded with SIADH-type water retention, volume expansion, and elevated blood pressure (Section 4.1). In an unmanaged host, this would be a crisis event. In a host with a preserved suction heart and a biochemical computer onboard in sufficient density, the elevated blood pressure did not merely provide passive perfusion pressure. It actively amplified the suction mechanism. Increased blood volume and elevated systemic pressure meant more venous return available per cardiac cycle (basic fluid mechanics). In a suction-dominant heart, more input volume produces greater diastolic pull. This is basic conservation of flow in a suction-driven system. The pituitary, sitting in the preferential perfusion zone described in Section 4.3, outside the blood-brain barrier and directly in the suction path, received increased perfusion proportional to the increased flow. The BP spike amplified the suction heart's throughput, which amplified pituitary perfusion, which amplified the symbiont's endocrine governance capacity through the pituitary at exactly the moment the program needed maximum control to drive the conversion. The system used the crisis as the fuel for the solution. What would have been a physiological emergency was instead a conversion, and blood pressure normalized as the circulatory reorganization completed.

The longitudinal case study documents this resolution in a modern subject. During the 2022 IVC constriction release event, the system transitioned through altered vascular dynamics into a reorganized perfusion state, after which approximately 30 pounds of retained fluid was lost over six weeks (Craddock, 2022 log; Craddock, Redacted Science). The waypoint resolved because the conditions for the next step in the sequence were met.

In modern adult populations, the three-key activation conditions described in Section 8.3 are not met during postnatal development. The third key, the electrolyte oscillation signal — is absent. The normal developmental transition from suction-dominant to pump-dominant cardiac

architecture completes on schedule. By adulthood, the pump-dominant heart cannot transition back to suction-dominant operation (absent extreme iatrogenic intervention). Gate one opens, and the commensal system's aggregate signaling drives the vascular response to sodium perturbation. Gate two is closed. This is not because of a genetic mutation, but because the developmental window during which the suction heart could have been preserved has long since passed. The elevated blood pressure, designed to be transient in a preserved host, becomes sustained in one whose cardiac architecture matured past the point of return.

The Vestigial Trap

This is the vestigial trap: a mechanism that was adaptive when the full conversion sequence was available becomes pathological when the sequence cannot complete. The waypoint persists for years, then decades. Sustained elevated blood pressure damages the vascular endothelium, promotes cardiac hypertrophy, compromises renal function, and increases stroke risk — consequences of maintaining a transient state indefinitely. The system is not broken. It is executing the first step of a program whose subsequent steps are no longer available.

The oscillation model explains why both excess and deficit sodium exposure produce the same clinical outcome. The ancestral system was designed to cycle: salt buildup during arid periods calibrated the host's electrolyte set point upward; freshwater transition during humid periods created the delta that triggered the vascular response. Both directions are relevant: salt buildup calibrates and then freshwater transition triggers. In modern humans frozen on one side of a cycle that no longer oscillates, deviation in either direction from the system's calibrated set point activates the response. The clinical literature's difficulty in establishing a simple linear relationship between sodium intake and blood pressure may reflect the fact that the underlying mechanism responds to the delta from calibration, not to the absolute sodium level.

Antihypertensive Pharmacology Within This Framework

The standard clinical response to sustained hypertension is pharmacological blood pressure reduction through ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, or diuretics. Each class targets a different component of the vascular response machinery. All succeed in reducing the measured pressure. None addresses the colonization state or the conversion attempt that produces it.

Within this framework, antihypertensive therapy suppresses the waypoint without resolving the program that generated it. The distributed system's signaling remains intact. The conditions that triggered the response have not changed. The system re-initiates. The pressure returns. Dosage increases. Additional agents are added. Treatment-resistant hypertension, often requiring three or more agents at optimal doses, is consistent with a system that keeps restarting a program rather than a static defect being incompletely treated.

This interpretation does not argue against antihypertensive treatment. In the absence of the full conversion sequence, sustained elevated blood pressure causes organ damage and death. Pharmacological reduction prevents this damage and is clinically necessary. The framework argues that the condition being treated is a vestigial program, and that the treatment's requirement for lifelong continuation reflects the ongoing nature of the conversion attempt rather than a chronic disease in the conventional sense.

Prevalence as Evidence of Conservation

Essential hypertension affects approximately 1.3 billion people globally. This prevalence is consistent with a conserved mechanism from a period when the hominid population was universally colonized and under oscillatory electrolyte pressure in the East African Rift Valley. If

the vascular response were a rare polymorphism, it would not affect a third of the global population. Its near-universal prevalence suggests it was the ancestral default and the standard response of a colonized mammalian host to the environmental conditions under which the coevolutionary program operated. The variation in salt sensitivity across the modern population maps onto the variation in colonization density documented in the mycobiome literature, rather than onto a binary genetic division between responders and non-responders.

Limitations and Pharmacological Confounds

This subsection is the most theoretical component of the cardiac architecture hypothesis, which is itself identified as the weakest link in the current framework (Section 10.4).

A natural question is whether existing antifungal pharmacology provides a test: if colonization density drives salt sensitivity, does reducing colonization reduce blood pressure? Current evidence does not cleanly address this question due to pharmacological confounds inherent in available antifungal agents. Azole antifungals, particularly itraconazole and posaconazole, inhibit mammalian CYP enzymes involved in steroid metabolism, producing mineralocorticoid excess and sodium retention independent of any effect on the commensal population via a direct drug-on-host-steroidogenesis artifact that confounds interpretation. Amphotericin B, a fungicidal polyene that lyses fungal cells through ergosterol binding, produces acute hemodynamic instability consistent with the rapid release of intracellular contents from a dying population, as *C. albicans* maintains intracellular potassium at 200–300 mmol/L (Section 5.5e), and mass lysis would produce an acute electrolyte dump sufficient to perturb host hemodynamics. Fluconazole, which is fungistatic rather than fungicidal at standard doses, does not produce a strong blood pressure signal, consistent with gradual colonization reduction without mass die-off allowing host compensatory mechanisms to absorb the change. None of these observations cleanly tests the colonization-density model because none isolates the variable of interest, commensal signaling density, from the drug's independent effects on host physiology.

A clean test of the two-gate model would require mycobiome-stratified blood pressure studies: quantitative *Candida* colonization assessment combined with standardized salt sensitivity testing in the same cohort, with multivariate adjustment for age, BMI, renal function, and RAAS genotype. A correlation between colonization density and salt sensitivity, independent of the standard clinical predictors, would support gate one. Separately, comparative assessment of diastolic suction contribution in salt-sensitive versus salt-resistant individuals, if technically feasible, would address gate two. These studies have not been conducted.

VIII.VII Gate One in Depth: The Barrier Cascade and the Priming Phase

Section 8.6 introduced Gate One as signaling density, ie. the aggregate output of the distributed commensal system at each tissue interface. This framing is sufficient to explain the salt sensitivity gradient across the general population. It is not sufficient to describe what happens when Gate One actually opens in a specific host at a specific moment. The mechanism of the opening event has architectural implications the two-gate model as originally stated does not fully draw out.

The longitudinal case study (Craddock, Redacted Science; Craddock, 2022 log; Craddock, Terminal Onset DI) documents the opening of Gate One as a specific physical event on a specific date in 1995, following weeks of preparatory pathology. Reading the event mechanistically clarifies three things: what physically constitutes the opening; why the opening is not a single moment but a two-phase process; and what makes the barrier breach-permissive in some hosts and not others despite the triggering behavior being common.

The Barrier Cascade Framing

The framework's precision-mapping method can be stated compactly: the path of the condition is the sequence of physical barriers that fall, each falling because the prior barrier's failure has created the conditions the next barrier cannot withstand [a biological Rube-Goldberg machine]. Once Gate Two remains closed (adult pump-dominant heart in place) and Gate One has opened, the sequence of subsequent barriers proceeds along a determined path — not because the physics alone forces linearity, but because the coevolved organism's configured response aligns with each successive mechanical state as it arrives. The path is deterministic at the intersection of two variables: the passive physical consequence of the prior barrier's fall, and the organism's configuration-gated response to the resulting state. Where these align, the next barrier falls. The alignment is not accidental. It is the product of the coevolutionary architecture Paper A and Sections 4–5 of this paper describe. [*Understand, this is Programmed Failure; however, due to version conflict - we have a different cardiac system - the end result for humans of today is various stuck-state chronic conditions created by gates that never open as demonstrated in other Redacted Science Initiative Papers*]

Gate One as a Two-Phase Event

The 1995 opening in the case study did not occur in an unprepared host. Weeks of renal pain on drinking, chronic fluid overload driven by prior undiagnosed SIADH episodes (one severe enough to require dialysis in the college years), and the specific pharmacological cascade documented in the TODIC record all preceded the acute bearing-down event on the evening the transition occurred. This priming is not incidental to the mechanism. It is the mechanism's slow first half.

Gate 1a — Priming Phase. Progressive compromise of renal parenchymal and urothelial paracellular integrity, developing over weeks to months. The clinical signal is capsular pain on drinking, produced by acute renal volume expansion into interstitium that a compromised barrier is no longer clearing; the SIADH pattern is the pituitary's early recruitment into functions its normal governance scope does not include. During Gate 1a, the barrier's tight junction proteins are being remodeled by the same organism-mediated processes documented at other mucosal surfaces: candidalysin-driven ATP efflux, claudin isoform shifts, and localized inflammation altering paracellular selectivity. The barrier is not yet breached, but its breach threshold is falling.

Gate 1b — Breach Event. Acute pressure applied to the primed barrier — in the case study, sustained bearing-down against inability to urinate — produces paracellular flux of the dominant extracellular solute across the compromised junctions. That solute is NaCl, not because it is the smallest ion by radius (it is not) but because paracellular tight junctions in mammalian epithelia are cation-selective for Na+ via claudin isoform expression, because Na+ is the dominant ECF cation at approximately thirty-five times the K+ concentration, and because K+ is intracellularly compartmentalized by active Na/K-ATPase transport rather than freely available for bulk flow. Under sustained pressure against a compromised biological barrier, NaCl and water are what breach first. This is the first physical barrier of the cascade. [*Takes me back to undergrad labs*]

The Balancing Response

Persistent Na+ loss through the breached barrier destabilizes the Na/K-ATPase gradient. Pump efficiency depends on the sodium gradient it is asked to maintain; a leaking barrier that keeps Na+ from being sustained at physiological ECF concentration reduces the pump's capacity

to clear K+ from the ECF into cells. K+ accumulates in the interstitial compartments slowly over the timescale of the Na+ leak — years to more than a decade in the case study, with the accumulation reaching the cardiac tolerance threshold thirteen years after Gate 1b fired.

Because adrenal capacity is being progressively compromised in parallel (Stage 1 of the case study: one adrenal begins gradual failure at the same event), aldosterone-mediated Na+ retention cannot succeed against the breached barrier. The compensatory function is picked up by the pituitary, initially through ADH-mediated water retention (Route 2 governance, per Paper A) sustaining volume despite the ionic drift, and secondarily through Route 1 modulation of the remaining adrenal's output. This is the pituitary functioning outside its baseline scope — controlling Na/K balance dynamics that in an unbreached host are handled entirely downstream. The organism, positioned to sense and modulate at each of these compartments, is co-located and configuration-locked to the progression, waiting for the interstitial K+ load to reach the threshold that permits the next barrier to fall.

The Co-Authorship Question

If Gate 1a is barrier remodeling that occurs over weeks to months before any acute trigger, the question of what makes the barrier breach-permissive in some hosts and not others resolves toward the commensal signaling density variable that Section 8.6 already established as Gate One's population-level determinant. High-density signaling produces the tight junction remodeling that lowers the breach threshold; low-density signaling does not. Bearing-down against impaired output is a common human behavior; breaching under it is not. The differentiating variable is the priming state of the barrier at the moment of pressure application, and the priming state is set by the aggregate commensal signaling the host carries.

This makes Gate One's opening co-authored rather than merely triggered. The organism does not merely wait for Gate 1b; it is the reason Gate 1a develops at all. The framework should state this directly, both because it clarifies why the two-gate model produces the population-level salt sensitivity distribution observed clinically, and because it identifies Gate 1a as the phase during which intervention remains possible before the architectural transition of Gate 1b makes the subsequent path linear.

Testable Predictions

1. **Idiopathic SIADH epidemiology**. The case study documents a sub-threshold SIADH episode in the college years that resolved without a bearing-down trigger presenting; the 1995 episode fired Gate 1b because the trigger did present. If Gate 1a can manifest as SIADH without proceeding to Gate 1b when no acute trigger occurs, then idiopathic SIADH in the general population should be substantially more prevalent than diagnosed cases suggest, with a subset progressing to the barrier-cascade pattern the framework describes when triggering events occur. Long-term follow-up of idiopathic SIADH cohorts, stratified by subsequent exposure to conditions producing sustained abdominal or urinary tract pressure, should reveal this progression pattern.
2. **Pain on drinking as an early Gate 1a marker**. Renal capsular pain elicited specifically by water intake, in the absence of infection, obstruction, or structural pathology on standard imaging, should correlate with elevated commensal Candida signaling markers and precede any measurable electrolyte disturbance by weeks to months. This is a testable clinical marker for pre-breach Gate 1a status.
3. **Reversibility during Gate 1a**. Because Gate 1a is a slow remodeling phase, it should remain susceptible to intervention that would be futile once Gate 1b has fired. Reduction

of commensal signaling density via targeted antifungal exposure, epithelial repair support, and correction of the underlying fluid overload during the Gate 1a window should all reduce breach probability. This predicts a specific therapeutic window that current SIADH management does not exploit. [*I think this was even discussed in the Article*]

4. **Microadenoma prevalence tracking Gate 1a duration**. If pituitary recruitment into Na/K balance functions begins during Gate 1a, and if Paper A's characterization of the microadenoma as a tissue stress response to sustained abnormal demand is correct (Section 4.7 of Paper A), then microadenoma prevalence should correlate with the duration of the Gate 1a phase. Hosts in whom Gate 1a persists sub-threshold for years without breaching should nonetheless show elevated microadenoma detection rates on dedicated pituitary imaging relative to the general population.

Closing Structural Point

The path to precision-mapping this condition is the identification of what barrier must fall next along a logical path. Each barrier defines the conditions of the next. The organism is present at each and is configuration-locked to the sequence. Where the ancestral program had all subsequent gates open by developmental preservation, the modern host arriving at Gate 1b through the priming-and-breach mechanism described here traverses each subsequent gate under whatever architectural cost is available to pay it. The linearity, once the sequence starts, is not the framework's invention. It is the coevolutionary architecture executing its ancient program in a host whose preservation windows have all closed. What the framework provides is the map.

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9. Homo Candidus: The Suppressed Phenotype

9.1 Definition

We designate *Homo candidus* as the symbiont-active hominid phenotype: a functionally distinct physiological and cognitive state produced by full activation of the ECS-mediated coevolutionary program described in this paper. *Homo candidus* is not a separate species but a conditional phenotype, the same organism operating under different management. The differences are material: altered cognition, altered pain processing, altered metabolic strategy, altered circadian architecture, altered perfusion dynamics, and throughout (but even more so in the late stages) enhanced creative and analytical output documented in both the historical cohort and the longitudinal case study (Craddock, Redacted Science).

If the trinity model is correct, this phenotype was the engine of early human cognitive and cultural advancement. The lucid elders of *Homo candidus*, sustained by social protection and pharmacological support, produced the transmissible knowledge that accumulated into what we now call civilization.

More broadly, given the evidence presented in the Craddock Case Studies, this is not a disease invention of modern medicine but a deep system state that the organism still remembers how to enter.

9.2 The Attention "Gap" Issue

Despite the apparent potential lethality of fungal pathogens and the number of deaths they cause, Fungal research has been neglected. Figure 3 illustrates the gap in funding compared

to the attributable deaths. Approximately 2% of total infectious disease funding went towards a category with approximately 15% of the attributed deaths.

Figure 3 Infection Disease: Estimated Annual Deaths vs. Research Funding

Type	Estimated annual deaths	Comparative annual research funding	Sources
Fungal	~1.5M – 3.8M deaths/year	**~$100M–$500M (very rough, fragmented, underfunded)**	Mortality: Funding context: neglected disease funding ~$4.17B total but overwhelmingly not fungal
Bacterial	~7.7M deaths/year	**~$1B–$3B+ (AMR + bacterial infection R&D)**	Mortality: AMR burden + funding priority context:
Viral	~2–4M/year baseline (non-pandemic) (can exceed 8M in pandemics)	**~$3B–$10B+ (highly variable; COVID spike drove peaks)**	Mortality (aggregate baseline + pandemic variability): Funding totals global health R&D ~$8.7B with heavy viral allocation (HIV, COVID):

Fungi were first noted to cause disease in 1835. The germ theory of Pasteur and Koch dominated the second half of that century. Fungi were not the priority. By the early 20th century, histoplasmosis, coccidioidomycosis, and blastomycosis were identified. This is when medicine first gave note that fungi can infect internal organs. By the mid-20th century, suddenly candidiasis and aspergillosis become a major cause of death – subsequent to the introduction of antibiotics in scale. These organisms were here, but they were not causing deaths until after antibiotics were developed - drugs designed to target the ecology of the internal biome. Clearly, while not the sole factor, widespread antibiotic use contributed to increased fungal disease. Yet, it remained deprioritized in funding.

In 2022, the World Health Organization issued their very first list of fungal priority pathogens. Notably, c. albicans is listed in the Critical Priority Grouping – last but it is in there. They note, “Tackling the problems posed by IFD will require increased research funding, targeted at the key priorities, new antifungal medicines and improved diagnostics.” This is the hunt and kill approach. Commensal didn’t mean you shouldn’t nuke it. It’s just a bug. Squish it.

Except it isn’t just a bug, is it? The *C. albicans* toolkit is rich. This author can explain it to you as no one else can, if there is a knob, *C. albicans* can turn it.

But, in 1964, the worlds leading mcyologists got together and agreed – *C. albicans* was an opportunistic pathogen, nothing more. It had a high fatality, and “could diagnose better than a clinician.” Yes, that line is literally from the handbook for the First Symposium on it in 1964. Everyone was told to kill it. No need to look further, this is pure pathogenicity. Of course, it’s in everyone and NOT killing them – but if it shows up on a test, that means kill it. The logic is astounding. Bees sting. If we kill all the bees, where are we?

The attention “gap” exists at all levels from institutional concern, to bench funding, to journal scope, medical education, and clinical encounter. The knowledge gap is even wider. My

clinician at the Cleveland Clinic said he tells his residents they “get more stupid each year, but that’s ok.” The knowledge is siloed by the current system, almost by design.

I had the same PCP for 30 years. I told him the exact name of my condition and tried to describe it for decades. Over the decades, I went to just about every specialty multiple times except endocrinology. Why skip that one, you ask? I didn't skip it. I requested it for years, decades. I got one appointment with a diabetic endocrinologist. That's what specialization does. Over the last 4 years, I tried again (unsuccessfully) to get an endocrinology referral, despite my symptoms. They were “clearly not endocrine-related.” My tests were fine, after all. CMP, CBC, thyroid, all checked out. My Autoimmune panel? Peachy. Normal range.

C. albicans is a pathogen that operates in everyone’s territory but is never looked at in a systems thinker’s approach. There isn’t a box in anyone’s system that says “ecological imbalance causing symbiotic dissonance.” Here is a test: Go to your clinician and ask him if he knows that the Na/K pump is? Hopefully, they get that part right. Then ask them how it works. If they make it past that, ask them if it can go in reverse. My personal experience walking in with items 1, and 2, given that starting point, they will still always get 3 incorrect and look at you like you are nuts.

They can remove the archaic clinical literature term “hypophyseal failure” implicating it as “hypopituitarism.” Those really don’t mean the same thing. The organism keeps on computing either way.

9.3 Ethical Implications of the Redaction

The suppression of the original research documenting this coevolutionary architecture, specifically the “redaction” described in (Craddock, Exposé), raises ethical questions that extend far beyond a single retracted article.

The redaction suppressed not merely a clinical observation but the existence of a functionally distinct human phenotype. If *Homo candidus* is real, then every person currently living with undiagnosed symbiont activation is being treated for a pathology that is actually an architecture. They are being medicated out of a phenotype that, in the appropriate social context, would be producing the most valuable cognitive output in their community. This is not a missed diagnosis; it is an active harm.

The understanding that the ECS serves as an inter-kingdom communication interface has implications extending across medicine: diabetes management (the historical cohort maintained normal blood glucose despite blocked insulin pathways), renal medicine (the host compensated for kidney damage through alternative filtration routes for over 30 years), and the broad category of conditions currently classified as idiopathic, including those attributed to ECS dysregulation or other directly related systems, more specifically the endocrine system in all its axes, the gut-brain axis, and immune modulation. The ECS does not operate in isolation; it interfaces with every major regulatory system in the body. Disruption of the ECS-mediated symbioticarchitecture could manifest as autoimmune dysregulation, endocrine imbalance, gastrointestinal dysfunction, or neurological disorder, depending on which aspect of the interface is most affected.

The ethical argument against suppression is straightforward: the potential medical value of understanding this architecture vastly outweighs the ethical discomfort associated with the knowledge that human physiology can be deliberately altered through symbiont activation. Science has historically managed dangerous knowledge through regulation, not erasure. The decision to redact the original research was a decision to erase knowledge of a human variant from the scientific record.

The implications are stark, if a person can achieve a normal existence with a 30+ year survival despite fundamentally altered physiology with no substantial medical intervention, while having normal lab and imaging test results for almost that entire period and having only the basic idea (and completely unsupported by any externality) of the changes taking place, a question must be asked – how long can this state be maintained?

> *"So yeah, I'm alive because I got lucky with a few insights. But what if someone had all the knowledge? What if someone walked into this with a blueprint? How long could they live then? Could they manage this for more than the three decades I did? A normal lifespan, maybe? That would be almost evolutionary".* (Craddock, Redacted Science)

10. Discussion

10.1 Testable Predictions

The Saline Oscillation Hypothesis generates several testable predictions:

1. **Paleochemical analysis** of hominid dental enamel and bone from the Turkana Basin should show fluctuating electrolyte and mineral signatures corresponding to known lake salinity cycles.
2. **Comparative cardiac anatomy** across primates and across postnatal developmental stages should reveal variation in the relative contribution of diastolic suction vs. systolic ejection. The developmental preservation model (Section 8.2) predicts that the suction-to-pump transition is a normal postnatal maturation process; comparative echocardiographic data from neonatal through adult stages across primate species would establish the baseline developmental trajectory against which symbiont-mediated preservation could be assessed.
3. **Mycobiome analysis** of populations living near hypersaline lakes in the modern EARS may show distinct *Candida* strain distributions or ECS tone profiles compared to populations near freshwater sources.
4. **Archaeological evidence** of salt-seeking behavior, salt processing, or salt storage at hominid sites in the EARS would support the electrolyte-dependence component.
5. **Phytocannabinoid residue analysis** at early agricultural sites should be examined for evidence that psychoactive plant cultivation preceded or paralleled caloric crop cultivation.
6. **Distance running performance** in Rift Valley populations (particularly the Kalenjin of Kenya) may reflect an ECS architecture refined by the coevolutionary program; comparative ECS tone profiles between elite East African distance runners and matched non-Rift Valley controls would be informative.
7. **Molecular dating** of the *C. albicans* / *C. dubliniensis* divergence, if resolved to the Plio-Pleistocene window (~2–5 Ma), would provide strong independent support for the hypothesis; the directional selection observed in *C. albicans* (virulence gene family expansion) versus *C. dubliniensis* (reductive evolution) is predicted by the framework.
8. **Epigenetic analysis** of populations in the modern EARS, examining methylation patterns in genes governing electrolyte handling, vascular tone, and ECS regulation, compared with non-Rift Valley populations, could reveal persistent signatures of the coevolutionary program.

9. **Phenobarbital-induced symbiont activation**. Exposure of commensal-state *C. albicans* populations to phenobarbital in a simulated gastric environment containing both glucose and a gastric mucosal tissue analog (mucin-coated epithelial cell culture or equivalent substrate) under acidic conditions should produce a measurable shift from yeast-form glucose metabolism to hyphal-form tissue invasion, including upregulation of secreted aspartyl proteases (SAPs), phospholipase activity, and CYP450 enzyme induction. This experiment would test the iatrogenic symbiont activation mechanism proposed in Section 5.1 and is consistent with both the longitudinal case study documentation (Craddock, 2013; Craddock, Redacted Science) and published case reports of phenobarbital-associated mucosal ulceration at variable anatomical locations.
10. **Evo 2 computational genomics**. Functional analysis of the approximately 1,300 *C. albicans* genes with no orthologs in other yeast species, using genomic foundation models such as Evo 2 (Arc Institute, 2025) trained across all domains of life, should reveal functional signatures consistent with host-interaction roles, including predicted GPCR ligand production, immune modulation, cross-kingdom signaling capabilities, peptide-processing enzyme homologs, peptide transporter regulatory elements, and neuropeptide-mimicking sequences that traditional comparative genomics within the fungal kingdom has not resolved. The *C. albicans* genome (approximately 14.3 Mb across 8 chromosomes) exceeds current single-pass context windows but is accessible chromosome by chromosome, with the smallest chromosomes falling within the 1 million token limit of current models. A specific analytical pipeline is proposed: (1) variant effect scoring across all uncharacterized genes to identify positions under functional constraint, (2) extraction and clustered not only against known host-interaction gene families from obligate symbionts but also against mammalian prohormone convertase substrates and neuropeptide precursor architectures, (3) sparse autoencoder feature detection to flag genes with signatures consistent with GPCR ligand production, immune modulation, or quorum sensing, and (4) gene sequence completion to identify genes whose architecture diverges from patterns learned across the training set of 128,000 organisms, suggesting novel functional roles. As context windows expand in successor models, whole-genome single-pass analysis will become feasible.
11. **Cholinergic interface characterization**. The confirmed presence of a functional muscarinic receptor in *C. albicans* (Nile *et al.*, 2018) and the documented elevation of host acetylcholine levels during *Candida* infection suggest that the cholinergic system represents an active bidirectional signaling interface between symbiont and host. Comparative analysis of choline metabolism, acetylcholinesterase activity, and vagal tone in *Candida*-colonized versus germ-free animal models would establish whether this interface contributes to the symbiont's regulatory influence on host autonomic function.
12. **Extracellular vesicle-mediated cross-kingdom RNA transfer**. Purified EVs from *C. albicans* hyphae should be incubated with human epithelial cells and macrophages, followed by small RNA sequencing of the recipient cells to identify fungal-origin sRNAs that have been internalized. Predicted fungal sRNAs should be cross-referenced against the human transcriptome for potential gene-silencing targets using standard sRNA target prediction algorithms. The prediction from the coevolutionary framework: at least a subset of fungal sRNAs delivered via EVs will have sequence complementarity to human immune or metabolic genes, and incubation of host cells with fungal EVs will produce measurable downregulation of predicted target transcripts in a manner attenuated by host

AGO knockdown or by treatment with EVs from an ESCRT-deficient *C. albicans* mutant producing fewer vesicles. Additionally, comparison of codon usage in *C. albicans* EV-associated mRNAs against the host codon optimality landscape should reveal whether exported transcripts are more human-optimized than the bulk *C. albicans* transcriptome, consistent with coevolutionary selection for evasion of DHX29-mediated translational surveillance (Hia *et al.*, 2026).

13. **Arachidonic acid competition** between prostaglandin and endocannabinoid synthesis: In colonized mucosal tissue models or ex vivo gut tissue segments harboring *C. albicans* biofilm, levels of PGE_2 and endocannabinoids (AEA, 2-AG) should differ from uncolonized controls in a direction consistent with altered arachidonic acid flux. Specifically, colonized tissue is predicted to show elevated PGE_2 and reduced AEA and/or 2-AG, with the magnitude of change scaling with fungal burden. This effect should be attenuated in ole2/ole2 or fet3/fet3 strains with reduced prostaglandin biosynthetic capacity. Such findings would support the hypothesis that fungal prostaglandin production measurably shifts host lipid signaling balance and may alter host ECS tone through competition within the shared arachidonic acid precursor pool.
14. **Non-candidalysin Ece1 peptide functional characterization**. The 2024 interactome screen (Lin *et al.*, 2024) identified host protein targets for all eight Ece1 peptides but focused mechanistic investigation on candidalysin alone. Functional characterization of Ece1-I, -II, and -IV through -VIII in both epithelial and immune cell models, using purified synthetic peptides at concentrations achievable in the invasion pocket microenvironment, should reveal whether these peptides constitute a coordinated immune modulation panel. The prediction from the coevolutionary framework: at least two non-candidalysin Ece1 peptides will demonstrate dose-dependent immune suppression through distinct receptor pathways, consistent with a multi-peptide effector strategy rather than a single-toxin virulence mechanism. The LILR-family interactions identified for Ece1-II and Ece1-V (Lin *et al.*, 2024) are the most promising initial targets. If confirmed, this would establish that *C. albicans* secretes a coordinated peptide effector panel from a single gene product, processed through Kex2p/Kex1p in the same enzymatic logic as mammalian prohormone processing.
15. **Peptide transporter function** in host-signal sensing. The ten peptide transporters (2 PTR, 8 OPT) of *C. albicans* are maintained despite having no fitness requirement for gastrointestinal colonization (Dunkel *et al.*, 2013). To test whether these transporters function as environmental sensors in addition to nutrient importers, *C. albicans* populations should be exposed to physiologically relevant concentrations of gut-derived peptide hormones (GLP-1, CCK, PYY) and antimicrobial neuropeptides (Substance P, NPY) in defined media, and transcriptomic and morphological responses measured. The prediction: exposure to at least one host-derived signaling peptide will produce a measurable transcriptional or morphological response in wild-type *C. albicans* that is attenuated or absent in the peptide transporter-deficient septuple mutant (opt1Δ opt2Δ opt3Δ opt4Δ opt5Δ ptr2Δ ptr22Δ), indicating that import of the host peptide is required for the response. 16. Colonization-density correlation with salt sensitivity. Quantitative *Candida* colonization assessment (mycobiome profiling) combined with standardized salt sensitivity testing (sodium loading and depletion protocols) in the same cohort, with multivariate adjustment for age, BMI, renal function, and RAAS genotype, should reveal a correlation between commensal colonization density and salt sensitivity independent of

the standard clinical predictors. If confirmed, this would support the first gate of the two-gate model proposed in Section 8.6 and establish commensal signaling density as a previously unrecognized variable in hypertension pathophysiology."

10.2 Relationship to Existing Hypotheses

The Saline Oscillation Hypothesis is compatible with and extends the pulsed climate variability hypothesis (Maslin *et al.*, 2014; Maslin and Trauth, 2009). Where the existing hypothesis identifies environmental instability as the driver of hominid evolution without specifying the mechanism, the Saline Oscillation Hypothesis proposes a specific biochemical pathway (the ECS-mediated fungal-host interaction, activated by SIADH-type electrolyte disruption during freshwater transitions after saline acclimation) as the mediating mechanism between environmental change and evolutionary outcome.

It is also compatible with the variability selection hypothesis (Potts, 1998), which proposes that hominids were selected for adaptability itself. The ECS is fundamentally a homeostatic regulatory system; its refinement through coevolutionary interaction with a symbiont that requires metabolic flexibility would directly select for the kind of adaptive plasticity Potts describes.

10.3 Coevolutionary Precedent for Signaling Complexity

The multi-receptor, multi-molecular-class signaling architecture described in Section 5 invites an obvious objection: the system is too complex to have emerged through pairwise coevolution between a single fungal species and its mammalian hosts. A decade of experimental work from the Meyer laboratory provides a direct empirical answer across three complementary studies.

Borin *et al.* (2023) demonstrated that Escherichia coli and bacteriophage Φ21, starting from isogenic populations in well-mixed cultures, diversified into elaborate nested-modular cross-infection networks in just 21 days, showing that "multiscale network structure can evolve rapidly under simple ecological conditions without spatial structure [...] illustrating Darwin's idea that simple adaptive processes can generate entangled banks of ecological interactions." Zaman *et al.* (2014), using a digital evolution platform, showed that "coevolution of hosts and parasites greatly increases organismal complexity relative to that otherwise achieved," and that coevolved hosts evolved genomes that were "also more phenotypically evolvable," supporting "a general model whereby antagonistic interactions and natural selection together favor both increased complexity and evolvability." Gupta *et al.* (2022) then measured the fitness landscape of bacteriophage λ as it coevolved with E. coli using high-throughput gene editing-phenotyping technology, providing "direct evidence for the role of coevolution in driving evolutionary novelty" and demonstrating that the fitness landscape is not static but a shifting seascape whose contours are continuously reshaped by the coevolutionary process itself, opening adaptive pathways inaccessible to either partner evolving alone.

The implications for the framework presented here are direct. The Plio-Pleistocene salinity oscillations described in Sections 6 and 7 imposed thousands of environmental reversals on the *Candida*-hominid partnership, each cycle constituting a serial-passage event under reciprocal selection. If 21 days of phage-bacteria coevolution in a flask generates multiscale network complexity, and coevolution systematically drives both increased trait complexity and increased evolvability, then 200 million years of fungal-mammalian coevolution under fluctuating environmental pressure is not merely sufficient to produce the signaling architecture

documented in Section 5. It would be surprising if it did not. The objection is not that the system is too complex. The objection, in light of the experimental evidence, would be that it is too simple

10.4 Population Structure, Differential Selection, and the Genetic Shadow of Homo candidus

Recent population genetic evidence provides independent support for the coevolutionary framework presented in this paper. Rogers *et al.* (2026) applied site pattern frequencies and bootstrap model averaging to archaic and modern human genomes and identified a two-superarchaic model of Pleistocene population structure, with 98% bootstrap model weight over the single-superarchaic alternative. Their analysis estimates that a previously uncharacterized African population, designated "Z," diverged from the lineage leading to modern humans at approximately 1.3 Ma (95% CI: 1.181–1.428 Ma) and subsequently contributed 19.6% of early modern human ancestry (95% CI: 12.4–26.4%) through admixture prior to the out-of-Africa dispersal.

The authors explicitly identify the central puzzle their model raises: how two African hominin populations remained reproductively isolated for roughly a million years in the absence of continental-scale geographic barriers. They note that Africa's deserts were not continuously arid and that no physical boundary comparable to a mountain range or ocean channel has been identified. The isolation mechanism remains unresolved within their framework.

The Saline Oscillation Hypothesis offers a candidate mechanism. The amplifier lakes of the Eastern Rift, described in Section 2.2, function as periodic barriers to migration. During wet phases, when precessional forcing fills rift basins to depths exceeding 150 meters and widths spanning the valley floor (Kingston *et al.*, 2007; Trauth *et al.*, 2010), these lakes block east-west movement of terrestrial populations. During dry phases, when the lakes contract or disappear, the barrier drops and populations on either side can mix. The oscillation cycle that deepened the coevolutionary program simultaneously created and removed the geographic barrier that isolated the population undergoing it.

Under this model, Population Z corresponds to the oscillation-exposed lineage. For approximately 1.4 million years (from the onset of intense variability at ~2.7 Ma through the estimated divergence point at ~1.3 Ma), this population experienced recurrent saline-to-freshwater transitions that progressively deepened symbiont integration through the mechanism described in Section 4. The population on the opposite side of the rift barrier, ancestral to the modern-archaic lineage, carried the same commensal symbiont but was never exposed to the electrolyte oscillation that activated the full program. Both populations possessed the same biological components: *C. albicans* as commensal, a functional endocannabinoid system, and mammalian cardiac architecture. The environmental key turned in only one lock.

The chronology estimated by Rogers *et al.* is consistent with the *Homo candidus* framework at every constrained node. Z diverges from the modern-archaic trunk at ~1.3 Ma, within the window of sustained oscillation pressure that began at 2.7 Ma and continued through variability packets at 1.9–1.7 Ma and 1.1–0.9 Ma. The admixture from Z into XY occurs after the Neanderthal-Denisovan split (~500–700 ka) and well before the X-Y separation (~30–50 ka), placing it in the Middle Pleistocene. This implies an isolation period of approximately 600,000–800,000 years between divergence and significant admixture, sufficient for the sustained boundary contact and gradual social convergence described below. The timelines are not contradicted by Rogers *et al.* at any point. If a population existed in the East African Rift Valley

that diverged from the main hominin trunk at ~1.3 Ma, remained isolated for roughly a million years without a geographic barrier, and ultimately contributed nearly 20% of early modern human ancestry, *Homo candidus*, as described in this paper, is a candidate consistent with every parameter their model estimates.

The result, over a million years of differential selection, would be two populations with divergent phenotypes derived from the same genetic substrate. The oscillation-exposed population developed the *Homo candidus* phenotype described in Section 8: preserved suction-dominant cardiac architecture, deeper ECS integration, enhanced cognitive capacity, language, and a cooperative social structure organized around collective defense, resource management, knowledge transmission, and the protection of vulnerable individuals during transition phases. The non-exposed population developed along the standard mammalian trajectory: pump-dominant hearts (the normal postnatal developmental outcome in the absence of the preservation program described in Section 8.2), greater structural robustness, but without language, without the cannabinoid flywheel's epigenetic legacy, and without the organizational infrastructure that language and the flywheel produced.

The social asymmetry this creates is the inverse of the physical asymmetry. Population Z, with language, cooperative social structure, and the accumulated knowledge of the flywheel, would have achieved higher population densities and controlled the resource-rich rift corridor and its margins. The non-exposed population, organized in small bands without language-mediated coordination, would have occupied peripheral territory. They were not competitors. They were avoiding Z. For the early portion of the contact period, this was not a contest between equals. It was a dominant, organized population and a fragmented peripheral one.

Gene flow during this early period would have been predominantly outward from Z. Individuals expelled or separated from Z's social structure, hybrid offspring born at boundary contacts, and possibly adopted or captured individuals carried Z's cognitive and ECS-related genetic material into the peripheral population. This genetic leakage was asymmetric: the organizational knowledge and language capacity encoded in Z's genome entered the non-exposed population incrementally, generation by generation, without the full program ever activating in the recipients, because the environmental trigger was absent.

Over hundreds of thousands of years of this boundary contact, the non-exposed population gradually developed social cohesion. Language-associated genes accumulating through admixture provided the substrate. Observational learning at the boundary provided the model. The non-exposed population did not need to independently invent cooperative social structure. They inherited and imitated it from the population that had it. This was a slow process, but the contact period was long: from the estimated divergence at ~1.3 Ma through the eventual absorption, the two populations coexisted for a span sufficient for incremental social development.

The competitive reversal occurred only after the non-exposed population crossed a threshold of organizational capacity sufficient to challenge Z collectively. At that point, their structural advantage became relevant. Pump-dominant cardiac architecture confers greater tolerance for thoracic trauma: thicker ventricular walls, higher systolic pressure, and no dependence on negative-pressure gradients that a penetrating wound would collapse. In a Pleistocene context with intergroup violence, this is a direct survival differential. A coordinated group of pump-heart individuals, now socially organized enough to act collectively, could sustain combat losses that would be fatal to suction-heart individuals. The advantage was not that

the pump-heart population was larger from the outset. It was that once they organized, they were harder to kill.

As the coevolutionary program deepened across oscillation cycles, the transition-phase vulnerabilities described in Section 8 became more pronounced. The *Homo candidus* phenotype that had been purely advantageous in its early, simpler form now carried periodic costs: physiological transition phases during which individuals required social protection, metabolic demands that constrained dietary flexibility, and the structural vulnerability of the suction heart itself. The social infrastructure that had been Z's greatest advantage became a liability when challenged by an organized opponent who did not share these vulnerabilities.

Hybrid offspring from boundary interbreeding inherited genetic material from both lineages but developed pump-dominant hearts by default, because the environmental trigger required for the preservation program was absent outside the rift corridor. The cognitive advantages downstream of the deepened ECS architecture, encoded in neuroplasticity-related genes, synaptic density regulators, and ECS receptor variants, persisted in the hybrid genome and were subject to positive selection. The cardiac architecture that enabled the full program did not persist, because it was program-dependent rather than purely genetic. The phenotype required the environmental key. Without it, the standard developmental transition from suction to pump proceeded normally (Section 8.2).

Natural selection in the expanding hybrid population favored the pump heart. The suction phenotype could not activate outside the oscillation environment, and on the rare occasions atavistic activation occurred, it carried the transition-phase costs without the environmental context or social infrastructure to support them. Selection did not need to actively eliminate the suction heart. It simply never switched on.

The 19.6% admixture fraction estimated by Rogers *et al.* represents the genetic shadow of *Homo candidus* in the modern human genome. It is not expressed as cardiac architecture, which required an environmental trigger that no longer exists. It is expressed as variation in ECS tone, cognitive capacity, salt sensitivity (Section 8.6), and the residual capacity of the program to activate under exceptional circumstances (Section 9). The genes remember. The environment does not. Every modern human carries this fraction. None possesses the environmental key to unlock what it originally encoded.[*Kinda proud of this one*]

X.IV Pigmentation as a Byproduct of Organism-Driven Pituitary and Epidermal Governance

The conventional explanation attributes the evolution of dark skin pigmentation in the hominin lineage primarily to a single selective pressure: protection against ultraviolet (UV) radiation following the loss of body hair. As hominins moved from forest canopy to open savannah between approximately 2 and 1.2 Ma, reduced fur exposed skin to intense equatorial solar radiation. Melanin serves as a photoprotective shield that prevents UV-induced degradation of folate (vitamin B9), a nutrient essential for neural tube closure and reproductive fitness (Jablonski and Chaplin, 2000). This model is empirically robust and accounts for broad latitudinal clines in skin reflectance. However, it remains incomplete. Extreme pigmentation levels do not map perfectly onto UV intensity alone, and the relatively rapid appearance of deeply pigmented phenotypes coincides with a period of accelerated evolutionary change across multiple systems.

The Saline Oscillation Hypothesis identifies two independent, symbiont-driven mechanisms that would increase melanin production as byproducts of core operations within the

Candida albicans biochemical computer. These mechanisms operate additively to UV selection, running in parallel through systemic and local channels consistent with the organism's documented spatial multiplexing architecture.

Systemic mechanism (pituitary governance). The pituitary perfusion and endocrine governance model (Section 4.3) posits that the fungal symbiont modulates host endocrine output through ECS-mediated signaling and altered cardiac suction/IVC dynamics that preferentially perfuse the pituitary. Pro-opiomelanocortin (POMC), the precursor polypeptide processed in the anterior pituitary, is cleaved into adrenocorticotropic hormone (ACTH), β-endorphin, and α-melanocyte-stimulating hormone (α-MSH). Elevated pituitary activity driven by the symbiont's perfusion management program during saline-freshwater transitions therefore produces increased α-MSH as an obligate downstream output. α-MSH is the primary hormonal stimulator of melanogenesis. Over millions of years of oscillation cycles, this sustained elevation would ratchet host pigmentation darker as a statistical byproduct of endocrine governance, independent of direct UV pressure. [*Brick…*]

Local mechanism (epidermal colonization and PGE_2 signaling). Melanocytes in the basal epidermis directly sense *Candida albicans* via Toll-like receptor 4 (TLR4) and respond by upregulating melanin synthesis as part of an innate immune defense (Tapia *et al.*, 2014). In addition, authentic prostaglandin E_2 (PGE_2) produced by *C. albicans* from host arachidonic acid via its divergent oxygenase enzymes (Erb-Downward & Noverr, 2007; Section 5.5d) independently stimulates melanocyte activity and melanin production. The organism's documented capacity for basal epidermal colonization (Schaller *et al.*, 1999; Lopez *et al.*, 2014; Lachat *et al.*, 2022) therefore activates two parallel local pathways—TLR4 recognition and PGE_2-mediated stimulation—driving melanogenesis from within the skin tissue itself. [*By brick…*]

These symbiont-driven mechanisms align precisely with the critical 2–1.2 Ma window of hair loss, encephalization acceleration, and deepening co-evolutionary integration. During this period the oscillation cycles intensified pituitary governance, expanded epidermal colonization capability, and refined the arachidonic acid economy supporting PGE_2 output. The standard UV-folate model and the fungal biochemical computer model are not alternatives; they reinforce each other. UV radiation supplies the external selective pressure favoring melanin, while the symbiont's distributed subroutines (systemic α-MSH elevation plus local TLR4/PGE_2 signaling) provide an internal, concurrent driver that pushes pigmentation to extreme levels beyond what UV selection alone would predict.

Geographic distribution and Population Z gene flow. The additive model also accounts for the observed concentration of the darkest native skin reflectance phenotypes in modern African populations. Extreme pigmentation is most pronounced in two regions: the Upper Nile Valley (South Sudan, northern Uganda, southern Ethiopia)—directly downstream of the East African Rift lake systems where saline oscillations operated—and coastal West Africa. Nilotic groups such as the Dinka, Nuer, and Mursi consistently rank among the most deeply pigmented populations measured by reflectance spectrometry. These territories lie immediately adjacent to or downstream of the rift corridor.

The West African hotspot is consistent with gene flow from the oscillation-exposed "Population Z" lineage carrying a deeper symbiont-integration profile (higher colonization density, stronger pituitary governance architecture). Populations receiving greater Z admixture would inherit both elevated α-MSH output and increased epidermal *Candida* density, amplifying melanin production via the combined systemic and local pathways.

By contrast, the San (KhoeSan) of southern Africa exhibit notably lighter skin despite comparable UV exposure at similar latitudes. They are genetically and geographically distant from both the rift corridor and the West African admixture zone. Under a strict UV-only model this disparity requires additional ad hoc explanations (recent migration, dietary folate compensation). Under the additive coevolutionary model it follows directly: lower admixture from the oscillation-exposed population results in reduced symbiont-driven melanin reinforcement, regardless of UV regime. [*By Brick…*]

X.IV Testable prediction

Quantitative mycobiome profiling of skin sites, combined with reflectance spectrometry, should reveal a positive correlation between local *Candida* colonization density and melanin index after statistical control for UV exposure history, latitude, and known pigmentation-associated variants (e.g., SLC24A5, MFSD12, DDB1). Such a residual correlation would demonstrate that the fungal symbiont contributes measurably to human pigmentation through TLR4 and PGE_2 pathways—an independent variable not currently incorporated in standard dermatological or anthropological models of skin color evolution.

This interpretation integrates seamlessly with the broader *Mammalia candidus* and biochemical computer framework: pigmentation emerges not from a dedicated evolutionary module but as distributed, multi-channel output of the same toolkit already deployed for electrolyte homeostasis, perfusion management, immune calibration, and cross-kingdom signaling. The organism does not "design" darker skin; it simply runs its existing subroutines under the oscillating environmental conditions of the East African Rift, with darker pigmentation arising as a stable, emergent statistical bias.

10.5 21st Century Fungal Biology Emergence

Fungal biology represents a major ecological dimension that was systematically under-recognized within the dominant frameworks of 20th-century biomedical research. During this period, life science priorities were largely organized around host physiology, bacterial pathogenesis, virology, pharmacology, and technological advances in diagnostic and therapeutic instrumentation. Despite contributing substantially to global infectious disease mortality, fungal pathogens historically received on the order of 1-2% of infectious-disease research funding (Head *et al.*, 2014), reflecting a systemic neglect of fungal ecological systems within modern biomedical science. The World Health Organization's publication of its first fungal priority pathogens list in 2022 (WHO, 2022) represents formal recognition of this longstanding institutional under-prioritization and signals a shift toward consolidation of fungal disease as a central global health concern.

Candida albicans presents a particularly illustrative case of disciplinary fragmentation. Due to its involvement in immunology, microbiology, cell biology, endocrinology, neurobiology, and ecological host–microbe interactions, its functional capabilities have been investigated extensively but often within domain-specific contexts. As a result, key phenomena including cross-kingdom signaling interactions, engagement with the endocannabinoid system, prostaglandin biosynthesis from host-derived substrates, immune polarization dynamics, peptide-processing homologies, extracellular vesicle–mediated communication, bidirectional pH modulation, and ionic competition mechanisms are well documented individually but have rarely been synthesized into a unified ecological framework.

The present work attempts such a synthesis. Rather than introducing novel molecular findings, it integrates established observations across disciplinary boundaries to propose an ecological systems interpretation of *C. albicans*–host coevolutionary dynamics.

10.6 Limitations

The cardiac architecture hypothesis (Section 8) identifies the weakest link in the current framework. The timing of the suction-to-pump transition is unknown, the threshold at which pump-dominance prevents the symbiont's program is uncharacterized, and no fossil evidence directly bears on cardiac conduction architecture. This component is currently unfalsifiable and should be treated as a theoretical prediction awaiting methodological development.

The self-citation density, while addressed in the Methodological Note, remains a limitation. The framework depends on observational data from a single longitudinal case study and historical recollections of a redacted source. Independent verification through identification of additional cases, recovery of the original article, or prospective clinical study would substantially strengthen the evidentiary foundation.

The pre-linguistic cannabinoid flywheel (Section 3), while consistent with the known behavioral pharmacology of CB1 agonism and the archaeological evidence for pre-linguistic cooperative behavior, is speculative in its earliest phases. No direct archaeological evidence for hominid phytocannabinoid use before the Neolithic currently exists.

An additional methodological limitation applies to the cross-kingdom signaling evidence presented in Section 5. Virtually all receptor-level interactions between *C. albicans* metabolites and host signaling systems have been characterized *in vitro*: isolated compounds tested against isolated targets in controlled media. While these studies confirm that the molecular interactions are possible, they do not demonstrate that they occur in the integrated, spatially heterogeneous, temporally dynamic environment of a living host. The *in vitro* evidence establishes the components. The assembled system, in which hundreds of metabolites interact with multiple receptor classes simultaneously across variable tissue microenvironments, has never been observed *in vivo*. The development of metabolomic and receptor-level imaging tools capable of capturing this interaction network in real time within a living host would substantially advance the evidentiary foundation for the framework described here.

11. Conclusion

The Saline Oscillation Hypothesis proposes that the cyclical salinity changes in East African Rift Valley lakes during the Plio-Pleistocene created the environmental conditions (SIADH-type electrolyte disruption during freshwater transitions after saline acclimation) under

which a fungal symbiont capable of managing host perfusion through the ECS gained decisive selective advantage. This activated and progressively deepened an ECS-mediated coevolutionary relationship between *Candida* species and hominid hosts, producing a functionally distinct phenotype we designate *Homo candidus*.

The relationship was preceded and supported by a pre-linguistic social flywheel driven by communal phytocannabinoid use, which established cooperative social structure before language emerged. The full trinity (the fungal symbiont, host physiology including cardiac suction, IVC dynamics, and renal pressure management, and cooperative social structure supported by exogenous phytocannabinoid cultivation) was accelerated by the emergence of language and plausibly operational by approximately 1.55 Ma.

The subsequent evolution of pump-dominant cardiac architecture broke this trinity, leaving the symbiont commensal but unable to execute its full program in modern humans. The evolutionary divergence of *C. albicans* from *C. dubliniensis*, with directional selection for host-integration genes in the former and reductive evolution in the latter, provides independent biological evidence consistent with the proposed coevolutionary mechanism. The cross-kingdom signaling evidence assembled in Section 5 demonstrates that the organism's capabilities extend far beyond the endocannabinoid system: confirmed interactions with nuclear transcription factors, ion channels, neurotransmitter receptors, cholinergic signaling, immune cell differentiation pathways, and the incretin system establish a control surface whose breadth is consistent with 200 million years of coevolutionary refinement. The ECS was the original interface. The broader receptor landscape was the expanded toolkit. The organism did not need to evolve new capabilities to respond to saline oscillation. It needed only to deepen the application of capabilities it already possessed, running whatever next subroutine showed the most success. That is evolution. The environmental, paleontological, mycological, and biochemical evidence converge on a single geographic region, the Cradle of Mankind, during the precise temporal window in which these evolutionary changes occurred.

The redaction of the original research that first documented this architecture, treatment, and medical condition represents suppression. This suppression is not just a clinical curiosity, but knowledge concerning a human phenotype that may have been foundational to the development of civilization itself. Even without those implications, the loss to science has caused a multi-generation loss of scientific exploration into fungal research, and billions of dollars spent developing treatments that may ultimately be traced to systems defined herein. Such a decision is scientifically unforgivable and should be investigated. This author has seen the original science- it exists.

Thus, this author is content to leave the issues to the verdict of history

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