Chronic Disease as Stuck Program Modes of the Candida albicans Biochemical Computer

A Unified Framework for Metabolic, Psychiatric, Functional, and Neurodegenerative Disease

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May 2026 V2

Abstract

This paper introduces the stuck-program model, a framework for understanding chronic diseases as phased biological programs that failed to transition. The model derives from the biochemical computer framework (Craddock, Biochemical Computer; Craddock, Saline Oscillation), which describes *Candida albicans* as a coevolved fungal symbiont operating phased programs within the mammalian host using documented cross-kingdom signaling capabilities. Each program phase employs specific organism capabilities to manage host physiology. When a phase transition signal fails, the capability runs indefinitely, producing a host phenotype that conventional medicine classifies as chronic disease.

A three-gate selection methodology is presented for identifying candidate conditions: (1) documented organism mechanism mapping directly to the disease's central pathology, (2) unexplained persistence in conventional medicine, and (3) demographic or geographic clustering patterns consistent with quorum sensing or colonization density dynamics.

Nine conditions are analyzed in companion papers: type 2 diabetes, anorexia nervosa, irritable bowel syndrome, obesity, Parkinson's disease, endometriosis, autism, addiction, and Alzheimer's disease.

Three cross-disease cellular and host architecture mechanisms are developed: the bifurcated SOX9 rheostat producing exhausted and inflammatory-locked phenotypes within the same SOX9-governed tissue under chronic *Candida* governance stress; APOE4 as host-symbiont architecture variant calibrated for pathogen-rich environments with cross-cultural cognitive evidence across multiple cohorts; and the cholesterol axis as a substrate-and-signaling junction connecting steroidogenic regulation, membrane biology, and dietary-input modulation.

A unified therapeutic framework combining substrate change, antifungal pressure, exercise, and sustained duration is proposed, along with the identification of organism colonization density as the single measurable variable that should predict disease severity, intervention response, and relapse risk across all conditions.

Keywords: *stuck program mode; Candida albicans; biochemical computer; chronic disease; quorum sensing; farnesol; phase transition; dietary antifungal; bifurcated SOX9 rheostat; APOE4 architecture; cholesterol axis; type 2 diabetes; anorexia nervosa; irritable bowel syndrome; obesity; Parkinson's disease; endometriosis; autism; addiction; Alzheimer's disease; Homo candidus; Redacted Science Research Initiative.*

I. The Problem of Persistence

Modern medicine manages chronic disease. It rarely resolves it. Type 2 diabetes is treated with lifelong medication. Irritable bowel syndrome is managed with dietary modification and symptom control. Anorexia nervosa has the highest mortality rate of any psychiatric disorder despite aggressive treatment. Obesity shows a 95% weight-regain rate following dietary intervention. Parkinson's disease is progressive and irreversible. Alzheimer's disease has no disease-modifying therapy after three decades of investment and more than seventeen anti-amyloid antibody trials enrolling over twenty thousand participants. Endometriosis shows lesion recurrence rates approaching the original disease prevalence after surgical removal. Autism is treated as a lifelong neurodevelopmental condition without pharmacological resolution. Addiction's standard of care is decade-long abstinence with high relapse rates. Each condition has its own research literature, its own clinical guidelines, and its own pharmacological armamentarium. What they share is a central puzzle: why does the condition persist?

For each of these conditions, the standard model describes a pathological state but does not fully explain what maintains it. Insulin resistance in T2D is progressive, but why? IBS has no structural cause, but the symptoms are lifelong. Weight-restored AN patients show persistent physiological abnormalities. The body defends an elevated weight set-point in obesity. Substantia nigra neurons continue dying in Parkinson's patients despite adequate dopamine replacement. Amyloid plaques in AD remain after antibody-mediated clearance, suggesting their continued production. Endometriotic lesions recur in tissue distal to surgical removal sites. Autism's developmental trajectory is set early and does not reverse. Addiction relapse persists across pharmacological substitution and behavioral therapy. In each case, conventional medicine identifies the downstream consequences but not the upstream driver that sustains them.

This paper proposes that these conditions share a common upstream feature: a resident biological system, operating through documented molecular mechanisms, that is running a program phase without transitioning to the next one.

II. The Stuck-Program Model

Foundation: The Biochemical Computer

The biochemical computer framework (Craddock, Biochemical Computer; Craddock, Saline Oscillation) describes *C. albicans*, the most prevalent fungal commensal of the human mycobiome, as a coevolved symbiont operating a phased program within the mammalian host. The framework is built on documented molecular evidence: the organism possesses confirmed signaling access to the host's endocannabinoid system, nuclear transcription factors, ion channels, neurotransmitter receptors, cholinergic signaling, immune cell differentiation pathways, the incretin system, reproductive hormones, stress hormones, and the autonomic nervous system via vagal muscarinic receptors. This signaling reach is documented in the primary literature and assembled in Craddock, Biochemical Computer (Section 5) and Craddock, Saline Oscillation (Section 5).

The organism's metabolic architecture is equally broad: it can utilize glucose, amino acids, carboxylic acids, fatty acids, N-acetylglucosamine, lactate, and ketones as carbon sources, switching between them based on local availability. This metabolic flexibility, described in Craddock, Saline Oscillation (Section 5.10), enables the organism to operate simultaneously

across tissue environments ranging from the glucose-rich gut lumen to the amino acid-rich tissue interstitium to the lactate-rich interior of a macrophage phagosome.

The combination of comprehensive signaling reach and metabolic flexibility produces an organism capable of managing host physiology across multiple organ systems. The framework proposes that these capabilities are organized into a phased program, with different capabilities serving different program stages. Critically, this program was refined over tens of thousands of generations of coevolution with the *Homo candidus* phenotype described in Craddock, Saline Oscillation: a host with different cardiac architecture (suction-dominant perfusion enabling pituitary colonization), a social infrastructure providing external transition cues (communal feeding, behavioral protocol enforcement, ritual dietary management), and a physiology shaped by active symbiont management. Modern *Homo sapiens* carries the organism and its program but lacks the physiological and social architecture the program was designed to operate within. The stuck states described in this series are, in part, the consequence of running software written for one operating system on hardware that no longer fully supports it. The Pan-Mammalian extension (Craddock, Pan-Mammalian) generalizes this reading across the mammalian clade, with each lineage carrying its own host-adapted Saccharomycetaceae symbiont.

Phase Transition Logic

In a functional program, phases cycle. The organism runs a capability, achieves the metabolic or physiological condition that phase requires, registers the completion signal through its environmental sensing infrastructure (Hgt4 for glucose, SPS for amino acids, Rim101 for pH, Cyr1 for CO2, Hsp90 for temperature, and the hormonal sensing described in Craddock, Saline Oscillation, Section 5.7), and advances to the next phase.

Transition signals can originate from multiple sources: the organism's own metabolic activity changing the local environment (glucose depletion triggering substrate shift), host dietary or behavioral change (fasting, dietary composition shift, iatrogenic causes), hormonal cycling (reproductive hormone fluctuations modulating organism operational state), environmental change (seasonal variation, temperature shifts), or, in the *Homo candidus* context described in Craddock, Saline Oscillation, social intervention (communal feeding, behavioral protocol enforcement, ritual dietary management).

The stuck state occurs when the transition signal fails to arrive. Possible failure modes include: modern diet providing infinite substrate for one phase, preventing the depletion signal that would trigger transition; antibiotic disruption of bacterial populations the organism uses as intermediary tools, removing an element of the signaling chain required for transition; loss of the social infrastructure that provided external transition cues in the ancestral coevolutionary context; or hormonal environments that lock a particular organism response without the subsequent signal architecture to advance it.

Quorum Sensing and Program Maintenance

The stuck state is not maintained by individual organism cells making independent decisions. It is maintained by population-level coordination. *C. albicans* was the first eukaryote in which quorum sensing was identified (Hornby et al., 2001). Farnesol and tyrosol, the primary quorum-sensing molecules, coordinate population-level behavior including morphogenetic decisions, biofilm formation, and virulence expression.

Within the stuck-program model, quorum sensing provides the mechanism by which a program phase sustains itself above a density threshold. Below that threshold, individual cells

lack the coordinated signaling required to maintain coherent program execution. Above it, the population acts as a unified management system. This means that organism density is not merely a correlate of the stuck state. It is the variable that determines whether a stuck state can maintain itself. Reducing density below the quorum threshold should allow a stuck program to release, independent of whether the transition signal arrives through other channels.

This generates a unifying prediction across all conditions in the series: colonization density, measurable through standard mycological culture or molecular techniques, should predict disease severity, intervention response, and relapse risk.

III. Selection Methodology: Three Gates

Candidate conditions were evaluated through three gates designed to distinguish framework-consistent applications from post hoc retrofitting.

Gate 1: Documented Mechanism

The organism must possess a documented signaling or metabolic capability that maps directly to the disease's central pathology, not a downstream consequence but the primary driver. The mapping must be specific: a general claim that the organism modulates immune function is insufficient; a specific claim that the organism's production of PGE2 from host arachidonic acid competes with endocannabinoid synthesis and thereby modulates hedonic reward signaling is testable. Each companion paper identifies the specific organism capability anchoring the disease application. The arachidonic acid branch-point analysis (Craddock, AA Branch Point) provides a worked example of how the framework's Gate 1 mechanism mapping operates at the cofactor and metabolite level.

Gate 2: Unexplained Persistence

The disease must have a recognized persistence problem in conventional medicine: treatment manages symptoms but does not resolve the underlying state, and the reason for this persistence is either unknown or incompletely explained. This gate eliminates conditions with well-characterized self-limiting courses or clear structural causes. The stuck-program model is specifically designed for conditions where the question "why does this continue?" has no satisfactory answer.

Gate 3: Clustering Patterns

The disease must show demographic, geographic, or familial clustering patterns that colonization density dynamics, quorum sensing thresholds, or organism-host equilibrium variation could explain better than, or in addition to, current epidemiological models. This gate distinguishes organism-mediated conditions from conditions whose distribution is fully explained by known genetic and environmental factors. Patterns of interest include: population-level prevalence differences that persist after controlling for known risk factors, familial clustering beyond genetic heritability (consistent with vertical organism transmission), post-antibiotic-era prevalence acceleration, and female predominance correlating with the organism's documented estrogen and LH sensitivity.

IV. The Candidate Conditions

Nine conditions were evaluated through the three gates. Each is analyzed in full in a companion paper; summaries are provided here.

Type 2 Diabetes (Craddock, T2D)

Glucose harvesting without phase transition. Hgt4, calibrated to 5 mM human blood glucose, anchors the mechanism. The organism's continuous glucose draw produces progressive insulin resistance and beta cell failure. Modern dietary glucose abundance prevents the substrate shift signal. Bariatric surgery's rapid T2D remission (before weight loss) is interpreted as acute habitat disruption forcing program reset. Passes all three gates. Strongest single-mechanism anchor.

Anorexia Nervosa (Craddock, Anorexia)

Substrate restriction without phase transition. Endocannabinoid tone management via arachidonic acid competition suppresses hedonic food reward. Monteleone et al. (2015) demonstrated that endocannabinoid disruption persists after weight restoration, indicating the program runs regardless of caloric input. Pubertal-onset female predominance maps to the organism's LH and estrogen sensitivity (Kinsman et al., 1988). Passes all three gates. Persistence-despite-weight-restoration is the strongest single evidence point.

Irritable Bowel Syndrome (Craddock, IBS)

Gut management frozen in a single operating state. IBS subtypes (IBS-D, IBS-C, IBS-M) represent different stuck modes of the organism's CB1/TRPV1 gut management system. The absence of structural pathology (the defining feature of IBS) is precisely what a management-layer disorder predicts. Post-infectious IBS maps to organism reorganization following bacterial disruption. The companion analysis of antifungal therapeutic response in IBS (Craddock, Clear Evidence IBS; Craddock, Clear Evidence IBS Protocol) documents directly intervention-relevant evidence. Passes all three gates. Subtype-as-frozen-mode is the most novel testable prediction.

Obesity (Craddock, Obesity)

Growth/storage without phase transition. GLP-1/incretin modulation, endocannabinoid appetite management, and HPA axis influence maintain a storage-mode equilibrium the host cannot override through caloric restriction alone. Semaglutide's efficacy on a receptor within the organism's signaling reach supports the framework. The most mechanistically diffuse candidate. Passes all three gates with the caveat that no single-mechanism anchor dominates.

Parkinson's Disease (Craddock, Parkinson's)

Dopaminergic interface burnout. Gpr1's pharmacological overlap with dopaminergic signaling and kynurenine-derived quinolinic acid neurotoxicity provide the mechanistic basis. The age of onset (60+) is consistent with decades of cumulative neuronal burnout. Gate 3 (clustering) is weak. The most speculative of the original five conditions; included to demonstrate the framework's range and to generate testable hypotheses.

Endometriosis (Craddock, Endometriosis)

Reproductive-tissue management frozen in proliferative mode without transition signaling. The organism's documented sensitivity to estrogen and LH (Kinsman et al., 1988) anchors the mechanism: hormonal cycles that historically provided transition signals do not function in the modern hormonal environment, and the proliferative program continues to deploy in tissues outside the uterine cavity. Lesion recurrence rates approaching original disease prevalence after surgical removal indicate the underlying program continues to operate while the

organism's signaling load remains intact. Reproductive-age female predominance anchors Gate 3. Passes all three gates.

Autism Spectrum Disorder (Craddock, Autism)

Developmental neurological calibration locked in a non-transitioning configuration. Early-life organism engagement of neurodevelopmental signaling, particularly through the arachidonic acid branch-point (Craddock, AA Branch Point) and endocannabinoid pathways, affects synaptic pruning and neural circuit organization during critical developmental windows. The maternal-microbiome and antibiotic-exposure associations with ASD risk are consistent with vertical transmission and early-life organism-load dynamics. Rising prevalence tracking sanitation and antibiotic-era transitions anchors Gate 3. Passes all three gates.

Addiction (Craddock, Addiction)

Hedonic reward management locked in seek-reward configuration without normal phase transition. The organism's endocannabinoid signaling for reward, cross-kingdom arachidonic acid management (Craddock, AA Branch Point), and dopaminergic interface overlap (the same Gpr1 mechanism in the Parkinson's framework reading) maintain the seeking state. Cross-substance addiction patterns, comorbidity with other stuck states (IBS, depression, T2D), and responsiveness to community-based interventions and ritual frameworks (AA-style programs) are consistent with organism-mediated rather than substance-specific maintenance. Passes all three gates.

Alzheimer's Disease (Craddock, Alzheimer's)

Brain-tissue stuck state. Astrocytic SOX9-MEGF10 phagocytic clearance machinery decoupled by anti-SOX9 autoantibodies in the relevant patient subgroup, with amyloid β functioning as antimicrobial defensive encapsulation around live Candida targets. The multi-compartment inflammatory architecture (exhausted and inflammatory-locked astrocyte subpopulations plus clonal-hematopoiesis-driven microglia-like cells infiltrating through compromised blood-brain barrier) maintains the locked symptomatic state. One hundred percent fungal presence in Pisa/Carrasco AD brain cohorts; antifungal compounds as top-ranked hits from blind drug screens; lecanemab differential failure in APOE4 carriers (60-75% of patients) corroborates the architecture-specific encapsulation reading. Passes all three gates with substantial cross-disease integration. The most architecturally elaborate of the conditions.

V. Cross-Disease Cellular and Host Architecture Mechanisms

The framework's strongest claim is not any individual condition application but the cross-domain pattern. As the corpus has expanded, three cellular and host architecture mechanisms have emerged that operate across multiple stuck states rather than within any individual disease. These are not condition-specific findings; they are signatures of the framework's underlying reading of how chronic *Candida* governance load engages mammalian tissue and host genetic architecture.

V.1 The Bifurcated SOX9 Rheostat

SOX9 is a master transcription factor governing tissue maintenance across multiple cell lineages: chondrocytes in cartilage, melanocytes in skin, astrocytes in the central nervous system, support cells in the testis, hepatocyte progenitors in the liver, and neural stem cells during

development. Wherever SOX9 governs, the framework reads chronic *Candida* governance stress as producing a bifurcated cellular response signature: two opposing phenotypes coexisting within the same tissue.

Bell et al. (2025) documented the exhausted phenotype in sporadic Alzheimer's astrocytes: reduced SOX9 protein function (predicted by the framework to reflect autoantibody-mediated decoupling, documented in chronic-*Candida* APECED patients per Hedstrand et al. 2001), HK1 deficits, impaired glycolysis, mitochondrial dysfunction, and reduced lactate shuttling support for neurons. Bell's rescue experiment - HK1 overexpression restoring astrocytic support function - confirmed the deficit phenotype as causal to the dysfunction.

Chen et al. (2025) documented the inflammatory-locked phenotype in a reactive astrocyte subpopulation in the same disease context: SOX9 phosphorylation drives HK1 hyperactivation, lactate output, and H3K9 lactylation-mediated transcriptional locking into pro-inflammatory programs. The Chen subset is a minority population within the same diseased tissue that contains the Bell-phenotype exhausted majority. Single-cell methods reveal both populations coexisting.

The framework's reading integrates these findings into a generalizable mechanism. SOX9 functions as a rheostat under chronic *Candida* governance stress, with two characteristic failure modes: depletion (loss of normal function, supportive failure) and lock-in (hyperactivation, inflammatory amplification). Both failure modes within the same tissue produce the chronic dysfunction signature of the stuck state. The mechanism is developed in full in Craddock, Alzheimer's (§VI.9). The framework's cross-disease prediction is that wherever SOX9 governs a tissue affected by a stuck state, single-cell methods should reveal the bifurcated rheostat signature.

Specific applications across the candidate conditions: AD astrocytes (developed in Craddock, Alzheimer's); cartilage chondrocytes in inflammatory and degenerative joint disease; vitiligo melanocytes (cross-tissue resonance with AD per the SOX9 autoantibody mechanism); the Sertoli cell architecture in male infertility; and other SOX9-governed tissues that show stuck-state pathology. The bifurcated rheostat is a tissue-level unifying observation analogous to organism density as a population-level unifying variable.

V.2 APOE4 as Host-Symbiont Architecture Variant

Apolipoprotein E ε4 (APOE4) has been the strongest genetic risk factor for late-onset Alzheimer's disease for thirty years. The conventional reading treats APOE4 as a deleterious allele that should have been removed by selection but persists at 14-25% frequency across human populations. Mainstream evolutionary genetics has recently arrived at a resolution: APOE4 must confer benefits earlier in life or in different ecological contexts (Dönertaş & Partridge, 2026, *Nature Reviews Genetics*). The empirical evidence supporting this resolution has accumulated across *multiple* cohorts.

Three independent lines of evidence document the APOE4 advantage in pathogen-rich contexts. Oriá et al. (2010), studying Brazilian shanty town children with heavy diarrhea burdens, found APOE4 carriers showed better cognitive development and growth outcomes under enteric infection stress than APOE3/3 children. Trumble et al. (2017), studying 372 Tsimane forager-horticulturalists in the Bolivian Amazon (aged 6 to 88, with high parasite burdens across the lifespan), found older adult APOE4 carriers either maintained or slightly improved cognitive performance with age while non-carriers showed cognitive decline tracking parasite burden. The Tsimane finding is striking: same allele, opposite cognitive aging outcomes, different ecological context. Zhao et al. (2020), studying 569 urban multi-ethnic Northern

Manhattan Study participants, found APOE ε4 modifies the relationship between infectious burden and cognition (HSV-1 × APOE ε4 interaction p=0.02); the authors propose that 'an antimicrobial role of the ε4 allele is possible.' Lathika Rajendrakumar et al. (2025), analyzing 1,509 ADNI participants, documented APOE4 and infections jointly contribute to brain glucose hypometabolism in dose-response fashion.

The framework's reading is that APOE4 is not a disease allele but a host-symbiont architecture variant calibrated for pathogen-rich contexts. Its antimicrobial properties confer childhood-infection protection (Oriá), maintain cognitive performance through adulthood in pathogen-rich environments (Trumble), and modify infectious-burden × cognition relationships in urban populations (Zhao). The architecture's pathogen-engagement-optimized phenotype runs without sufficient engagement targets in modern industrialized contexts and turns against the host's own tissue as cumulative exposures accumulate. The lecanemab APOE4 failure (no measurable benefit in 60-75% of AD patients carrying ε4) is mechanistically resolved (developed in Craddock, Alzheimer's §VII.5) as architecture-specific encapsulation removal in patients whose architecture depends on the encapsulation.

The framework's cross-disease prediction is that APOE4 stratification should reveal architecture-specific response patterns across stuck states. Some stuck states should show APOE4 advantage (where the architecture's pathogen-engagement is appropriate to the disease environment); others should show APOE4 disadvantage (where engagement runs without proper transition signaling). T2D, obesity, and addiction trial data stratified by APOE4 status should reveal distinct response patterns. Cross-disease comorbidity patterns should track APOE4 architecture. The implication beyond AD is that host genotype interacts with stuck-state architecture in framework-predictable ways, and trials of any stuck-state intervention should record APOE4 status to support the stratified analysis the framework requires.

V.3 The Cholesterol Axis

A convergent cholesterol-axis literature has emerged across the corpus that connects substrate availability, steroidogenic regulation, membrane biology, and dietary input modulation to stuck-state architecture. The pituitary occupies the master control position for organism-scale cholesterol→steroid conversion: anterior axis peptide and glycoprotein hormones (ACTH, LH, FSH, TSH, GH, prolactin) instruct downstream steroidogenic tissue (adrenal cortex, gonads) to convert cholesterol into cortisol, aldosterone, and sex steroids. The pituitary is also itself a cholesterol-dependent tissue requiring lipid substrate for membrane integrity, vesicular packaging, and signaling (developed in Craddock, Endocrine Interface; Craddock, Alzheimer's §VIII.9).

Three independent findings on cholesterol metabolism by stuck-state outcomes converge on this axis. Li et al. (2026, *Nature Communications*) demonstrated capsaicin's amelioration of AD pathology in murine models runs through gut-microbiota-dependent 24-hydroxycholesterol metabolism rather than through direct TRPV1 receptor action. The APOE4 architecture chain documented in §V.2 surfaces cholesterol-axis differences across populations and across age (Oriá et al. 2010 articulating ApoE-cholesterol balance under infection stress as critical for childhood cognitive outcomes). The conventional AD cholesterol literature documents altered 24-OH-cholesterol patterns and CYP46A1 activity in AD brain. These point to the pituitary cholesterol-control junction as one anatomical site where the framework's broader prediction operates.

The framework's reading is that cholesterol substrate availability and metabolism flux are framework-relevant variables across stuck states, with the pituitary serving as one master control point and tissue-specific cholesterol dynamics serving as another. The cholesterol axis appears wherever the stuck state involves steroidogenic hormone dysregulation (endometriosis through estrogen; obesity through cortisol and sex steroid balance; addiction through HPA axis dynamics; AN through reproductive hormone disruption), wherever membrane lipid biology is critical in affected cell populations (AD, autism, Parkinson's), or wherever diet directly modulates the substrate pool (all stuck states, with stronger expected effects in obesity and T2D).

Cross-disease predictions following from the cholesterol axis: 24-OH-cholesterol patterns should differ across stuck states in framework-predictable ways; statin use should affect stuck-state outcomes in directions depending on the specific role of cholesterol in each condition's mechanism; dietary cholesterol intake should modulate stuck-state trajectories with the egg-AD inverse-association pattern as one observed example; and the pituitary engagement point predicted in Craddock, Alzheimer's (§VIII.9) for AD should generalize to other late-stage stuck states with pituitary involvement.

[*The three cross-disease mechanisms - bifurcated SOX9 rheostat at the tissue level, APOE4 architecture at the host level, cholesterol axis at the substrate and signaling level - operate at different scales but converge on the same framework reading. The stuck states are not isolated conditions; they are different presentations of a single architecture under chronic Candida governance stress, with the specific presentation varying by tissue, by host genotype, and by metabolic substrate environment.*]

VI. The Unified Therapeutic Framework

The stuck-program model generates a four-layer therapeutic framework applicable across all nine conditions.

Layer 1: Substrate Change

Alter the dietary or metabolic landscape the organism reads, providing the transition signal the stuck program is waiting for. This is condition-specific: carbohydrate restriction for T2D; low-FODMAP for IBS (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols, the short-chain carbohydrates that the small intestine absorbs poorly, passing through to the colon where gut organisms ferment them, producing gas, drawing water into the bowel, and triggering the bloating, pain, and diarrhea cycle); structured refeeding for AN (controlled, monitored caloric restoration following clinical protocol); caloric reduction for obesity; cyclical reproductive hormone signaling support for endometriosis; pre- and probiotic intervention for autism and addiction; and substrate management for the chronic *Candida* engagement in AD (currently uncharacterized but a research priority per Craddock, Alzheimer's). Each substrate change targets the specific metabolic condition maintaining the program phase. Substrate change addresses the signal environment.

Layer 2: Antifungal Pressure

Reduce organism density below the quorum sensing threshold maintaining the stuck state. This can be pharmaceutical (fluconazole, azoles) or dietary (coconut oil/lauric acid/caprylic acid, garlic/allicin, cinnamon/cinnamaldehyde, lemon balm). Dietary antifungals are of particular significance because they are accessible without prescription, carry minimal risk

at dietary doses, and have been present in human food traditions throughout evolutionary history. Their inconsistent effects across individuals is itself predicted: variable organism density and morphological state produces variable response to unmeasured antifungal pressure. Antifungal pressure addresses the population maintaining program coherence. [*You may learn of die-off. Your body will have to adjust to not having the same stuck state, and the die-off products can be uncomfortable.*]

Layer 3: Exercise

Provide multi-channel environmental input that the organism's sensing infrastructure cannot ignore. Exercise simultaneously alters gut motility (mechanical stimulation read through the organism's gut management system), cortisol dynamics (read through the corticosteroid-binding protein documented by Loose and Feldman, 1981), endocannabinoid tone (post-exercise anandamide elevation temporarily shifts the signaling landscape the organism manages), autonomic balance (sympathetic activation during exercise followed by parasympathetic recovery, read through the muscarinic receptor documented by Nile et al., 2018), and core temperature (read through Hsp90). No single dietary or antifungal intervention hits this many sensing channels simultaneously. Exercise provides the broadest transition input available without pharmacological intervention.

The AN exception must be stated directly. Compulsive exercise in AN is itself a feature of the stuck program: the organism driving caloric expenditure to maintain restriction-phase metabolic conditions. In AN, exercise is part of the disease, not part of the treatment, until the restriction program has released sufficiently for exercise to function as a therapeutic input rather than an organism-directed output. For the other eight conditions, exercise is unambiguously beneficial and its mechanism through the framework is clear: you are flooding the organism's sensing infrastructure with simultaneous signals that a single-mode stuck state cannot accommodate.

Layer 4: Duration

Sustained combined intervention allowing the organism time to register new conditions, lose quorum coordination, and release the stuck program. Short-term interventions fail because the organism's compensatory capacity can outlast a brief disruption. Long-term lifestyle changes succeed (when they succeed) because they outlast the organism's compensatory window. Duration addresses the temporal dynamics of program release.

The unified prediction: combined substrate change plus antifungal pressure plus sustained duration should outperform any single intervention across all *nine* [*9*] conditions. No current clinical trial tests this combination because no one is measuring organism density as a variable in any of these diseases. The Clear Evidence IBS analysis (Craddock, Clear Evidence IBS; Craddock, Clear Evidence IBS Protocol) provides the most direct documented case of antifungal therapeutic response in a stuck-state condition, and the central antifungal trial design specified in Craddock, Alzheimer's (§VIII.1) extends the combined-intervention prediction to neurodegenerative disease. [*Take a guess at what percentage of controls and AD patients had Candida in their brains? Hint: Make your guesses as far apart as possible*]

The regulatory environment constraining investigation of dietary antifungals, particularly the Dietary Supplement Health and Education Act of 1994 (DSHEA), which limits the ability to make therapeutic claims for food-derived compounds, is discussed in Craddock, Implications.

VII. The Unifying Variable

The single most important prediction of the stuck-program model is that organism colonization density, measurable through standard oral swab, fecal mycobiome, or site-specific culture techniques, should function as a unifying variable across all nine conditions. Specifically:

Disease severity should correlate positively with colonization density. Higher organism density means stronger quorum-mediated program maintenance, which means a more entrenched stuck state.

Intervention response should correlate with the degree of density reduction achieved. Interventions that reduce organism density (whether intentionally through antifungal treatment or incidentally through habitat disruption) should produce proportionally greater clinical improvement.

Relapse risk should correlate with density rebound. When organism density returns to pre-intervention levels, the stuck program should re-establish. Sustained density reduction should predict sustained clinical improvement.

No existing clinical dataset includes organism density as a measured variable in any of these nine conditions. The framework's most actionable recommendation is that mycobiome measurement be incorporated into the assessment protocols for T2D, AN, IBS, obesity, PD, endometriosis, autism, addiction, and AD research, not as a primary outcome but as a covariate that the framework predicts will explain a significant portion of currently unexplained variance in disease severity and treatment response. The bifurcated SOX9 rheostat signature and APOE4 architecture stratification developed in §V are complementary unifying observations at the tissue and host levels, joining organism density as the framework's three converging predictive variables. The evidence may only be apparent once a corresponding treatment approach is initiated.

VIII. Cross-Domain Explanatory Power

The framework's strongest claim is not any individual condition application but the cross-domain pattern. A single model spanning metabolic disease (T2D, obesity), psychiatric disease (AN, addiction), functional gastrointestinal disease (IBS), reproductive disease (endometriosis), developmental disease (autism), neurodegenerative disease (PD, AD), and the cellular and host architecture mechanisms operating across them is without precedent in medicine. No existing framework connects these nine conditions under a single mechanism. [*But I'm about to try*]

This is either the model's greatest strength or its greatest vulnerability. If organism density correlates with disease severity and intervention response across even three or four of the nine conditions, the framework achieves an explanatory scope that no competing model matches. If it fails to correlate with any, the model is wrong. The predictions are testable. The experiments are straightforward. The framework exposes itself to refutation by design. [*One failed test does not disprove the model, only the test. I'm going to get some things wrong somewhere, but most of them will be right*].

The cross-domain pattern this framework identifies is not without historical precedent. Bayard Taylor Holmes compiled over 8,000 references linking focal infections, primarily gastrointestinal, to psychiatric and neurological disease (Holmes, 1924; Noll, 2006; Craddock, Focal Infections). His work was suppressed, his journal ceased publication, and his name was

erased from the history of psychiatry. The tools he had, microscopy and clinical observation, could identify the connection but not the mechanism. The tools available now, untargeted metabolomics, genomic foundation models, endocannabinoid system mapping, cross-kingdom signaling characterization, can. The Focal Infections 2.0 analysis (Craddock, Focal Infections) documents both the historical suppression and the molecular infrastructure that resolves what Holmes could only observe. This series is the applied consequence of that resolution.

The cannabinoid hyperemesis syndrome application developed in Craddock, Saline Oscillation (Section VI) serves as a template for the methodology applied here: identifying mechanistic gaps in the standard model, proposing organism-mediated explanations for each gap, generating testable predictions, and offering zero-cost interventions accessible without institutional gatekeeping. The nine condition papers and the cross-disease mechanism analyses follow the same structure.

IX. Limitations

The three-gate methodology is a selection heuristic, not a proof structure. Conditions that pass all three gates are framework-consistent, not framework-proven. Each companion paper identifies condition-specific limitations.

The nine candidates vary substantially in evidential strength. T2D, AN, IBS, and AD pass all three gates with strong evidence at each gate, with AD adding the architecturally elaborate multi-compartment reading developed in Craddock, Alzheimer's. Obesity passes all three gates but lacks a single-mechanism anchor. Endometriosis, autism, and addiction pass all three gates with the evidential weight varying by condition. Parkinson's remains the most speculative of the original five conditions; its evidential status has not substantially changed since v1 of this paper, and the framework's position on PD remains tentative. This gradient is intentional: the framework's credibility is better served by transparent acknowledgment of differential confidence than by uniform presentation.

[*we call that wildcatting in Oklahoma*]

All predictions require prospective testing with organism density as a measured variable, which no current clinical trial infrastructure includes. The methodological recommendation that mycobiome measurement be incorporated into chronic disease research is the paper's most immediately actionable output.

The dietary antifungal dose-response relationship is entirely uncharacterized. The gap between documented antifungal properties of dietary compounds and demonstrated clinical effect in any of these conditions remains open.

The three cross-disease mechanisms developed in §V (bifurcated SOX9 rheostat, APOE4 architecture, cholesterol axis) are framework-internal integrations of recent literature. They are testable but not yet tested as cross-disease patterns. Single-cell SOX9 phenotyping across stuck-state tissues, APOE4 stratification of stuck-state trial data, and cholesterol-axis biomarker assessment across the conditions are research priorities the framework specifies but cannot perform without institutional resources.

The stuck-program model assumes that *C. albicans* operates a phased program in the mammalian host. This assumption is the foundational claim of the biochemical computer framework (Craddock, Biochemical Computer; Craddock, Saline Oscillation) and is not independently established by the condition-specific analyses presented here. The condition

papers should be read as applications of the framework, not as independent evidence for the framework's foundational claims. The Pan-Mammalian extension (Craddock, Pan-Mammalian) generalizes the assumption across the mammalian clade with each lineage carrying its own host-adapted symbiont; this remains a framework-internal generalization rather than independent confirmation.

References

Note: All Craddock references are cited by paper short name following the corpus convention. Zenodo DOIs are provided for each.

Foundational Framework:

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