

**Candida albicans as a Biochemical Computer:  
Cross-Kingdom Signaling, Parasexual Reproduction, and  
Genetic Foundations of a Unique Fungal Symbiont**

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## Abstract

*Candida albicans* functions as a distributed biochemical computer, processing host and environmental signals through multiple parallel channels to modulate immunity, metabolism, tissue remodeling, and endocannabinoid tone. This paper details its distinctive genetic hardware (~1,300 orphan genes with no orthologs in other yeasts), ancient CUG codon reassignment (~171 ± 27 Ma), divergence from *C. dubliniensis* with asymmetric gene-family expansion (~20 Ma), parasexual cycle for rapid diversity generation, and layered signaling architecture (extracellular vesicles with morphology-dependent cargo, candidalysin and Ece1 peptide panel, secreted aspartyl proteases, cholinergic receptor interface, authentic prostaglandin E<sub>2</sub> production from host arachidonic acid, cross-kingdom RNA potential, tryptophan-kynurenine pathway modulation, mast cell activation via cell wall pattern recognition, and a dopaminergic signaling intersection through the Gpr1 receptor). The interstitium, a body-wide network of fluid-filled collagen-lined compartments (Benias et al., 2018), is identified as the physical distribution layer connecting peripheral colonies to host nutrient interfaces and enabling inter-niche signal propagation without bloodstream exposure. Multi-timescale epigenetic memory, from white-opaque phenotypic locking to chromatin-level bet-hedging and mitochondrial genome methylation, enables state maintenance without genomic change. The pituitary microadenoma, conventionally classified as a benign incidental neoplasm with a prevalence of 14-22% in autopsy and radiological studies, is reinterpreted here as a tissue stress response to sustained organism-driven governance load on the anterior pituitary, supported by documented hyphal access to the gland, confirmed molecular machinery for local hormone transport, sequestration, and enzymatic modification, an epidemiological profile consistent with variable organism demand rather than spontaneous neoplasia, and a longitudinal case study documenting microgranuloma formation, hyphal migration to the pituitary region, and subsequent structural failure under escalating load across four transition phases (Craddock, 2026c). No other organism is known to combine this full toolkit. Twelve testable predictions, grouped by architectural layer, are offered to evaluate the model, including volatile organic compound output profiling and host-mediated subroutine termination via glucose override. The conventional "opportunistic pathogen" classification is re-examined; the organism appears tuned for regulated, long-term persistence rather than unchecked exploitation. This technical grounding is straightforward and stands on its own.

**Keywords:** *Candida albicans*; biochemical computer; cross-kingdom signaling; orphan genes; CUG codon reassignment; parasexual cycle; bet-hedging; extracellular vesicles; candidalysin; Ece1 peptides; cholinergic interface; prostaglandin E<sub>2</sub>; arachidonic acid competition; Hgt4 glucose sensor; peptide transporters; spatial multiplexing; host adaptation; phenotypic switching memory; tryptophan-kynurenine modulation; mast cell degranulation; Gpr1 dopaminergic interface; mitochondrial epigenetics; symbiont; volatile organic compounds; interstitium; extracellular space; connection tissue; fibroblasts; receptors; purigenic; fatty-

*acids; medium-chain; antifungal agents, basement membrane, dermis; keratinocytes; pituitary microadenoma; hypophyseal governance load; local hormone multiplexing*

## 1. Introduction

A biochemical computer is defined here as a biological system that (1) senses environmental and host-derived inputs, (2) integrates multiple signals via internal regulatory states, (3) produces adaptive outputs, and (4) maintains state across time through memory mechanisms such as epigenetic or phenotypic locking. These properties satisfy standard criteria for information-processing systems as defined in biological signaling literature.

*Candida albicans* meets these criteria. Conventionally labeled an “opportunistic pathogen,” the fungus is in fact an obligate commensal with no known environmental reservoir outside mammalian hosts. It colonizes the gastrointestinal tract of a large percentage of healthy individuals and possesses an extraordinary suite of capabilities that extend far beyond simple opportunism.

This paper argues that the “opportunistic pathogen” label understates the organism’s true nature. Rather than a passive opportunist, *C. albicans* operates as a distributed biochemical computer: it continuously senses host conditions through dedicated input channels, integrates signals via parallel metabolic and regulatory pathways, produces context-specific adaptive outputs, and maintains heritable phenotypic states. The goal is to present the genetic foundations, reproductive strategy, and signaling architecture in a standalone, technically rigorous manner.

## 2. Genetic Foundations & Evolutionary Origins

The genetic architecture of *C. albicans* supplies the foundational hardware. One of the most distinctive features is the CUG codon reassignment ( $\sim 171 \pm 27$  Ma; Mühlhausen et al., 2016) in the ancestor of the CTG clade. The CUG codon switched from leucine to serine via an ambiguous intermediate tRNA (Santos et al., 1995). Strong AT bias fixed the new system, while residual low-level mistranslation ( $\sim 3\%$  leucine incorporation at CUG sites; Bezerra et al., 2021) introduced proteomic diversity useful for early bet-hedging under stress. This reassignment enabled expansion of novel protein families central to host interaction.

Approximately 20 million years ago, in the early Miocene, *C. albicans* diverged from *C. dubliniensis*. *C. albicans* expanded gene families associated with host interaction and virulence, while *C. dubliniensis* followed a reductive path. Roughly 1,300 genes ( $\sim 21\%$  of the  $\sim 6,200$  protein-coding genes) have no clear orthologs in other yeasts (Butler et al., 2009); many are predicted to support GPCR ligands, immune modulation, and neuropeptide-like sequences.

## 3. Parasexual Reproduction & Bet-Hedging

*Candida albicans* reproduces by budding (clonal) or parasexuality (genetic mixing without meiosis). Parasexuality follows the opaque switch: opposite mating types fuse to a

tetraploid that undergoes chromosome loss and mitotic recombination, generating genetic mosaics with novel traits including filamentation, drug resistance, and invasion (Mishra et al., 2021).

The process is stress-gated (low oxygen, glucose depletion, pH, CO<sub>2</sub>, antifungals). Frequency can rise to 10–20% under anaerobic or glucose-depleted conditions that mimic host niches; glucose depletion can even bypass the opaque step entirely (Guan et al., 2023). This is a controlled subroutine for diversity generation when conditions deteriorate. The resulting variation functions as bet-hedging: different cells run different transcriptional programs, increasing population survival across micro-niches. Parasexual recombination further refines signaling efficiency, creating feedback between diversity and computational adaptability.

## **4. Biochemical Computer Architecture**

### **4.1 Inputs**

Ten dedicated peptide transporters (two PTR and eight OPT family members; Dunkel et al., 2013) import host-derived peptides as nitrogen sources and environmental sensors. A muscarinic-like cholinergic receptor senses acetylcholine (Nile et al., 2018); Hgt4 is calibrated to human serum glucose (~5 mM; Brown et al., 2006); additional sensors detect pH, ions, oxygen, and CO<sub>2</sub>.

### **4.2 Integration & Processing**

Secreted aspartyl proteases (SAP1–10) digest host proteins. Authentic prostaglandin E<sub>2</sub> is produced from host arachidonic acid via divergent enzymes (Ole2/Fet3; Erb-Downward & Noverr, 2007), directly competing with host endocannabinoid synthesis (Acharya et al., 2017). Extracellular vesicles carry morphology-dependent cargo including proteins, proteasome components, and RNA (Zarnowski et al., 2018).

*C. albicans* modulates host tryptophan metabolism through the kynurenine pathway. The organism produces enzymes that divert tryptophan away from serotonin synthesis and toward kynurenine and its downstream metabolites, which suppress IL-17-mediated antifungal immunity at mucosal surfaces (Cheng et al., 2010; Zelante et al., 2013). This rerouting simultaneously depletes a neurotransmitter precursor and disables the host's primary mucosal defense against fungi, achieving two objectives through a single metabolic diversion. The Gpr1 receptor, primarily characterized as a carbon source sensor through Gpa2-coupled cAMP-PKA signaling, also responds to the antipsychotic clozapine, a dopamine receptor antagonist, which inhibits morphogenesis through this pathway (Midkiff et al., 2011). This pharmacological intersection places Gpr1 at a node between metabolic sensing and dopaminergic signaling, suggesting the receptor's ligand range extends into host neuroactive compound space.

### 4.3 Outputs

Yeast-to-hyphal transition, immune modulation (Th2 shift via PGE<sub>2</sub>, dendritic cell suppression via farnesol, LILR engagement via Ece1-II and Ece1-V peptides), tissue remodeling (candidalysin pores, EGFR ubiquitination/lysosomal degradation, and CCNH binding that inhibits DNA damage repair; Lin et al., 2024; Moyes et al., 2016), bidirectional pH engineering, and endocannabinoid tone modulation.

Cell wall components provide an additional immune output channel. Alpha-mannan and beta-glucan surface structures trigger mast cell degranulation and stimulate arachidonic acid release from host macrophages via mannose and beta-glucan receptor engagement (Castro et al., 1994). This is distinct from the prostaglandin, farnesol, candidalysin, and LILR-mediated immune mechanisms described above: it operates through innate pattern recognition receptors rather than secreted metabolites, and the degranulation response activates downstream inflammatory cascades (histamine, proteases, cytokines) that the organism's other immunomodulatory outputs then redirect toward the non-protective Th2 profile.

### 4.4 Memory & State Maintenance

White-opaque phenotypic switching is epigenetically heritable across thousands of cell divisions without DNA sequence change, stabilized by histone modifiers (Sir2, Hda1, Hda2/3) that lock transcriptional states (Lohse et al., 2009; Qasim et al., 2021).

Beyond the white-opaque switch, the organism's epigenetic architecture includes additional layers. Chromatin modifications, specifically histone methylation and acetylation patterns, regulate the commensal-to-pathogen transition and provide the mechanistic basis for the transcriptomic heterogeneity observed across genetically identical populations (Dumeaux et al.,

Craddock (2026)

2023; Mishra et al., 2011). Mitochondrial genome methylation represents a further regulatory layer governing energy metabolism (Bartelli et al., 2018). These modifications are fast and reversible compared to genetic mutation, enabling rapid phenotypic switching across the population without altering the underlying genome. The result is a memory system operating at multiple timescales: white-opaque locking for long-term state maintenance, chromatin-level switching for medium-term niche adaptation, and mitochondrial epigenetic tuning for metabolic responsiveness.

#### **4.5 Spatial Multiplexing & Feedback**

Different subroutines run concurrently in distinct micro-niches (lumen glucose harvesting, invading hyphae with SAPs/alkalinization, phagosomal lactate/ketone use). Biofilm regulatory networks contain feed-forward loops that reinforce expression of key targets (e.g., via Brg1, Wor3, Ume6 reinforcing Efg1 outputs), stabilizing the network against genetic variation (Cravener et al., 2023). Multi-input integration is evident in hyphal morphogenesis: pH, temperature, nutrients, CO<sub>2</sub>, and quorum signals converge on shared pathways (cAMP-PKA, MAPK) to produce a single morphological decision (Kornitzer, 2019).

Rapid emergence of multiscale interaction networks has been observed in experimental bacteria-phage coevolution, where simple reciprocal selection in well-mixed cultures produced nested-modular cross-infection patterns in just 21 days (Borin et al., 2023). “We show 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.” The *Candida* biochemical computer operates with far richer input channels and output layers, yet follows the same principle: fluctuating host conditions (nutrient gradients, immune pressure, pH, perfusion) drive the rapid refinement of distributed, hierarchical subroutines across the population.

No other organism is known to integrate this full suite.

#### **4.6 The Interstitium as Distribution and Signaling Infrastructure**

The preceding sections describe the organism's sensing, processing, and output capabilities at the cellular and population level. This section addresses the physical medium through which the distributed computer's signals propagate and through which peripheral colonies access host resources.

The interstitium, historically treated as inert connective tissue, was recharacterized by Benias et al. (2018) using confocal laser endomicroscopy on living tissue. Standard histological fixation collapses the fluid-filled spaces, rendering them invisible on fixed slides. *In vivo* imaging revealed a body-wide network of collagen-lined, fluid-filled compartments present beneath the dermis, surrounding the gastrointestinal tract, lungs, urinary system, and vasculature. The structural continuity of these compartments across organ boundaries establishes a pre-lymphatic fluid highway that connects otherwise anatomically distinct tissue sites.

This network has three properties directly relevant to the biochemical computer model.

Craddock (2026)

First, it functions as a signaling medium. Interstitial fluid carries cytokines, extracellular vesicles, damage-associated molecular patterns, and purine nucleotides between tissues. The organism's documented output channels, including extracellular vesicles with morphology-dependent cargo (Section 4.2), candidalysin-mediated ATP efflux activating purinergic receptors (Section 4.3), and prostaglandin E2 produced from host arachidonic acid (Section 4.2), are all soluble or vesicle-borne signals compatible with interstitial fluid transport. A colony at any mucosal or dermal site can broadcast signals into the interstitial network without requiring bloodstream access, reducing exposure to circulating immune surveillance.

Second, it provides a nutrient interface at the dermal boundary. The epidermis is avascular. Basal keratinocytes, the proliferative layer at the bottom of the epidermis, receive all nutrients by diffusion from dermal capillaries across the basement membrane. The interstitium interpenetrates the dermis and surrounds these capillaries. Hyphae positioned at or near the basal layer would occupy the optimal location for intercepting glucose diffusing upward from the vasculature while simultaneously accessing a continuously renewing cellular substrate (basal keratinocytes themselves). This positioning is consistent with the Hgt4 glucose sensor calibration described in Section 4.1: the organism does not need to be intravascular to sense and consume host glucose at physiological concentrations. It needs only to be at the nutrient interface where capillary-derived glucose enters avascular tissue.

Third, the interstitial compartments are mechanosensitive. Fibroblasts populating the collagen matrix express purinergic receptors (P2X, P2Y families responsive to extracellular ATP), toll-like receptors (TLR2, TLR4 recognizing fungal cell wall components including mannan and beta-glucan), and cytokine receptors. Physical compression or stretch alters fluid flow through the compartments and can activate mechanosensitive signaling cascades in resident fibroblasts. For an organism that produces candidalysin (a pore-forming peptide that causes ATP efflux from damaged host cells) and whose cell wall components trigger innate pattern recognition, the interstitial fibroblast network represents a distributed array of signal-responsive cells that the organism can activate through its normal virulence toolkit.

The interstitium therefore functions as the organism's equivalent of a bus architecture: a shared physical medium connecting distributed processing nodes (peripheral colonies at distinct anatomical sites) and enabling both nutrient access and signal propagation without dependence on the bloodstream. The spatial multiplexing described in Section 4.5, in which different subroutines run concurrently in distinct micro-niches, requires a physical substrate for inter-niche coordination. The interstitial fluid network provides it.

Topical antifungal response as indirect evidence. If peripheral colonies at the dermal nutrient interface constitute functional nodes in the distributed system, topical antifungal agents that penetrate the stratum corneum should produce measurable effects disproportionate to the surface area treated. Lipophilic azoles (miconazole, clotrimazole) are designed for epidermal penetration and would reach basal-layer colonies directly. Medium-chain fatty acids (caprylic acid C8, capric acid C10, lauric acid C12, the primary antifungal components of coconut oil) disrupt fungal cell membranes through a non-azole mechanism with no cross-resistance to

ergosterol synthesis inhibitors. The combination of two azoles with different binding profiles plus MCFAs would present three independent kill mechanisms against peripheral colonies simultaneously.

The longitudinal case study (Craddock, 2022, 2026b) documents recurrent topical antifungal use over a multi-year period, with Amazon purchase records providing third-party-timestamped evidence of treatment intensity correlating with documented symptom severity: 22 tubes purchased in the 2022 crisis year, declining to 8 tubes in 2026. The burning sensation reported during topical application, intensified by pressure against surfaces (compressing interstitial compartments and concentrating inflammatory mediators from colony die-off against sensory nerve endings), and responsive to ice (vasoconstriction reducing inflammatory mediator delivery plus direct TRPV1 inhibition), is consistent with an active colony destruction event rather than a dermatological irritation response. Healthy skin does not produce a burning inflammatory response to antifungal ointment.

Prediction (proposed as Prediction 13 or renumbered as appropriate): Topical antifungal application over defined skin areas in subjects with elevated commensal *Candida* colonization (assessed by mycobiome profiling) will produce measurable changes in local skin temperature (infrared thermography, as a proxy for altered vascular tone) and local interstitial cytokine profiles (microdialysis sampling) that scale with pre-treatment colonization density and differ between azole-class and MCFA-class agents, consistent with colony reduction at the dermal nutrient interface rather than nonspecific irritation. Subjects with low colonization density will show no such response to the same agents.

#### **4.7 The Microadenoma as Tissue Stress Response**

Pituitary microadenomas are conventionally classified as benign neoplasms of the anterior pituitary, defined as lesions smaller than 10 mm in diameter. Meta-analytic data report an overall prevalence of 16.7%, with 14.4% found in autopsy studies and 22.5% in radiological series (Ezzat et al., 2004). The standard clinical interpretation treats these as incidental findings of no consequence unless they secrete hormones at levels sufficient to produce a named endocrine syndrome.

Within the coevolutionary framework described in this paper, the microadenoma cannot be simply classified as a neoplasm. It is a tissue stress response to sustained abnormal demand on the pituitary gland. This reinterpretation follows directly from the pituitary governance architecture described in Sections 4.3 and 5.7, and from the clinical progression documented in the longitudinal case study (Craddock, 2026c).

The archival clinical literature describes a specific mechanism: when the pituitary is driven into sustained overdrive by the organism's management program, the tissue responds with localized proliferation. This is not clonal expansion from a somatic mutation. It is a mechanical consequence of a gland operating beyond its design specifications. The resulting tissue protrusion, termed a microgranuloma in the case study neurologist's assessment, is the visible signature of governance load.

#### **4.7.1 Case Study: Pituitary Load Across Transition Phases**

The longitudinal case study documents four transition events in which pituitary load is directly implicated:

**Initial Transition to Phase 1 (1995).** The subject presented with the first documented SIADH episode and electrolyte crisis, initiating polyuria that would persist for decades. Within this framework, this event marks the activation of the organism's pituitary governance program. The pituitary was induced into overdrive, distorting ADH output and producing the electrolyte dysregulation that conventional medicine classified as idiopathic SIADH. During this period, the subject documented hyphal transit along venous pathways from the forearm, tracking through the axilla, along the clavicle, up the neck, past the ear, and terminating behind the orbit, a trajectory consistent with venous return toward the cavernous sinus surrounding the pituitary fossa. The organism's remote governance of the pituitary via perfusion management and ECS signaling had been disrupted by the gland's entry into overdrive. Direct local access was the compensatory response. A subsequent dedicated pituitary MRI with contrast, obtained at the subject's insistence, identified a microgranuloma on the pituitary. The neurologist's response was reassurance: "These are commonly found in autopsies of people who died from other conditions." Within the governance load model, the microgranuloma was not an incidental finding. It was the tissue stress signature of a gland that had just been placed under a workload it was not designed to sustain indefinitely, with organism presence now established locally at the relay station.

**Phase 1 to Phase 2 (2008).** The subject experienced a salt/potassium imbalance event with cardiac involvement and possible ureter collapse. While the primary clinical presentation involved electrolyte-driven vascular and renal effects rather than direct pituitary symptoms, the event is consistent with escalating organism metabolic demand on a system already operating under sustained governance load. The remaining functional adrenal was maximally compensating, and the pituitary's management burden increased correspondingly.

**Phase 2 to Phase 3 (2012).** The subject presented with sustained buzzing sensation in the head followed by acute loss of muscle tone, and urinary shutdown subsequent to a CT with iodine contrast and administration of heparin (a "standard hospital protocol"). These symptoms map to the archival literature's description of a pituitary reaching its compensatory limit after prolonged overdrive. The concurrent administration of heparin during this period introduces a pharmacological confound that complicates precise attribution of symptoms to the pituitary transition versus anticoagulant effects. Nevertheless, the symptom cluster is consistent with the transition described in the source material as the point at which the gland recognizes it can no longer sustain its current output.

**Phase 3 to Phase 4 (2018).** The subject, already in a state of chronic volumetric depletion, donated blood. The organism's compensatory demand on the pituitary escalated over approximately 48 hours as the distributed system attempted to manage the additional volume deficit through increased ADH, ACTH, and related output (Craddock 2026d). The microgranuloma, which had been identified on the earlier dedicated pituitary MRI with contrast

and subsequently confirmed absent on later imaging, detached under this sustained mechanical load.

The clinical presentation resembled a pituitary apoplexy: acute onset, hormonal disruption, and transient neurological effects. However, the subject remained conscious throughout, was upright within two to three minutes, and was functional at blood pressures that conventional physiology would predict to be incompatible with ambulation. This resilience is consistent with a system that had spent twenty-three years developing compensatory architecture under organism governance, not with an incidental tumor producing a random vascular event.

### ***Hyphal Migration and Direct Pituitary Access***

The pituitary gland sits outside the blood-brain barrier. The hypothalamus and pituitary stalk lack the tight endothelial junctions that exclude blood-borne molecules and organisms from brain tissue. This anatomical accessibility is well established and is the basis for the perfusion governance model described in Section 4.3.

*C. albicans* hyphae possess documented capabilities relevant to directed tissue transit. Hyphae exhibit thigmotropism, sensing substrate topography and making tropic movements in relation to changes in surface contour (Sherwood et al., 1992). They traverse host cells through trans-cellular tunnels that are progressively remodeled, in some cases without breaching host cell membranes (Lachat et al., 2022). Active penetration is driven by turgor pressure at the hyphal tip and does not require host cellular machinery. The electrostatic surface charge of *C. albicans* is pH-dependent (Jones and O'Shea, 1994), meaning that changes in host acid-base status alter the physical interaction dynamics between hyphae and host tissue.

The hyphal transit documented during the 1995 initial transition (described above) provides the case study evidence for this directed access capability. The acute change in host acid-base chemistry as the pituitary entered overdrive altered the electrostatic interaction environment, and the organism's response was physical migration to the governance site via venous pathways terminating at the cavernous sinus. Once established at the pituitary, the organism possesses the molecular tools for a mode of management not accounted for in the two-tier endocrine interaction model described in Section 5.4.

### ***Local Hormone Multiplexing: A Communication Layer Beyond Receptor Sensing***

Section 5.4 documents the organism's eleven confirmed hormone-sensing channels and the two-tier endocrine interaction model in which the organism reads host hormones directly and writes pituitary output indirectly through perfusion and ECS governance. The presence of hyphae at the pituitary introduces a third tier: direct local hormone interception and modification.

*C. albicans* possesses documented molecular machinery for active hormone processing. The Cdr1p ABC transporter performs energy-dependent efflux of human steroid hormones, specifically beta-estradiol and corticosterone (Krishnamurthy et al., 1998). The corticosteroid-binding protein (CBP) binds corticosterone with high affinity ( $K_d = 6.3$  nM) without metabolizing it, effectively sequestering the hormone (Loose and Feldman, 1982). The estrogen-binding protein (Ebp1) is not a receptor homolog but an oxidoreductase, an enzyme that

chemically modifies estradiol upon binding (Madani et al., 1994). Additionally, *C. albicans* can convert androstenediol and androstenedione into testosterone de novo (cited in Soares et al., 2019).

These are three distinct modes of hormone interaction: transport (Cdr1p efflux), sequestration (CBP binding), and enzymatic modification (Ebp1 oxidoreductase activity), plus de novo synthesis. An organism physically present at the pituitary with this toolkit can intercept, redirect, modify, and supplement hormone output at the source. This constitutes a multiplexed local management capability that operates independently of, and in addition to, the remote governance mechanisms described elsewhere in this paper.

This local multiplexing would be invisible to any conventional diagnostic modality. Imaging resolves the tissue stress response (the microadenoma) but cannot detect hyphae at the scale involved. Serum hormone assays measure net output after organism processing, not gross pituitary production. The gland may be under significant governance load while circulating hormone levels appear normal or borderline. The microadenoma is the only visible indicator that the pituitary is working harder than the bloodwork suggests.

### ***Prevalence Epidemiology and the Governance Load Prediction***

The epidemiological profile of pituitary microadenomas is consistent with the governance load interpretation and inconsistent with the conventional model of spontaneous benign neoplasia.

Prevalence ranges from 1.4% to 27% in autopsy studies depending on histological criteria and sectioning methods. Radiological prevalence is higher (up to 37% in some MRI series). The natural history of observed microadenomas shows 83% stable, 10% enlarging, and approximately 6% decreasing in size over follow-up periods of two to eight years. These are cross-sectional snapshots. The critical observation is that microadenomas are rare in children, peak during reproductive years with female predominance, and show variable distribution in older populations.

This age and sex distribution is precisely what the governance load model predicts. The organism's endocrine management demands are highest during active reproductive cycling, when LH sensing, estrogen processing via Ebp1, progesterone-responsive CDR1 induction, and the full tier-one receptor suite are operating at maximum capacity. The pituitary is working harder because the organism is asking more of it. The tissue stress response (microadenoma) reflects this workload. The female predominance reflects the organism's documented responsiveness to reproductive hormones, not a sex-linked genetic predisposition to pituitary neoplasia.

A 30-year population-based analysis from Olmsted County, Minnesota (Graffeo et al., 2022) documented a 4.5-fold increase in pituitary adenoma standardized incidence rates from 1989 to 2017, a trend observed independent of incidental diagnosis rates. Yuen et al. reported at least one anterior pituitary hormone abnormality in 50% of patients with nonsecreting microadenomas and normal IGF-1 levels. These are not nonfunctioning tumors. They are pituitaries under load, producing hormonal output that is being intercepted or is falling outside the narrow diagnostic windows of named endocrine syndromes.

### ***Populations of Interest and the Missing Dataset***

The governance load model generates a specific, testable prediction: microadenoma prevalence should correlate with colonization density. Populations with documented high *C. albicans* colonization burden should show elevated microadenoma rates compared to matched controls.

Chronic substance users represent a population of particular interest. Opioid use produces well-documented HPA axis suppression, with hypogonadism prevalence ranging from 21% to 86% of users and opioid-induced adrenal insufficiency now recognized as a clinical entity. The conventional interpretation attributes these endocrinopathies to direct opioid receptor effects at the hypothalamic-pituitary level. Within the governance load framework, exogenous opioids interact with a signaling channel the organism relies on (the endocannabinoid and opioidergic overlap), forcing compensatory pituitary overdrive. The pituitary is now under load from two directions: the drug's direct suppressive effects and the organism's compensatory escalation. This is an accelerated version of the governance load that produces microadenomas in the general population.

If a chronic user's microgranuloma detaches under this combined load, the resulting pituitary failure event produces acute hormonal dysregulation in a host without the compensatory architecture developed over decades in the longitudinal case study. The drive to self-medicate intensifies because the body has lost its endocrine governance. This is not addiction worsening. It is a pituitary structural failure being managed with the only pharmacological tool available to the patient.

No study has performed dedicated pituitary MRI with contrast on cohorts of chronic substance users compared to matched controls. No study has correlated quantitative *Candida* colonization assessment with microadenoma prevalence in any population. These are the missing datasets. The prediction is straightforward: colonization density and microadenoma prevalence will correlate if organism governance load is the mediating variable.

### ***Limitations and Open Questions***

This section proposes the microadenoma as a tissue stress marker of organism governance load and identifies a previously unrecognized local hormone multiplexing capability. It does not claim to fully characterize the purpose of local pituitary management by the organism beyond the general principle documented throughout this paper: the organism modifies its host environment to optimize its own metabolic position.

The specific downstream consequences of local hormone interception, sequestration, and enzymatic modification at the pituitary source remain to be characterized. Whether the organism's local activity is primarily consumptive (using pituitary output as substrate), regulatory (modulating output to manage downstream host physiology), or both, cannot be determined from available data. The second-order effects of local hormone multiplexing on adrenal, thyroid, gonadal, and growth hormone axes are predictable in principle but unquantified.

The 2012 transition in the case study is confounded by concurrent heparin administration. The degree to which the observed symptoms reflect pituitary transition versus anticoagulant effects cannot be cleanly separated from available clinical records.

A further observational confound warrants explicit identification. The most commonly used CT contrast agent is iodine-based, and iodine has documented antifungal activity against *C. albicans* (Cuellar-Rufino, S., et al.,2022) “in a dose-dependent manner in both the acute and chronic periods.” Any CT-based investigation of pituitary organism presence simultaneously disrupts that presence, creating an inherent observational paradox: the imaging tool eliminates the evidence it would need to detect. In the longitudinal case study, the 2013 CT with iodine contrast produced acute renal complications attributable to the iodine ion's size relative to the subject's compromised filtration capacity, but a second, unrecognized effect was concurrent: iodine delivery to whatever organism infrastructure existed at or near the pituitary. Dedicated pituitary MRI with gadolinium contrast avoids the antifungal confound but does not resolve individual hyphae. The prediction described in this section may ultimately require novel imaging or histological approaches that do not destroy the target organism during observation.

What can be stated is that *C. albicans* possesses documented physical access to the pituitary (Section 4.3), documented molecular tools for hormone binding, transport, modification, and synthesis, and that the epidemiological profile of pituitary microadenomas is consistent with a governance load mechanism and inconsistent with a model of random benign neoplasia. The correlation studies that would test this interpretation have not been conducted.

## 5. Testable Predictions

The biochemical computer model frames *C. albicans* as a distributed processing system: it senses inputs via dedicated sensors/transporters, computes responses through parallel pathways, and deploys context-specific outputs via morphology- and vesicle-dependent mechanisms. Its orphan genes, codon reassignment, parasexual cycle, and multi-layered interfaces supply the hardware. The predictions below test these components at molecular, cellular, and population scales. They are ordered by increasing technical demand to reflect a realistic feasibility hierarchy. Positive results would strengthen the integrated architecture; null or opposing results would falsify or require refinement of specific sub-models.

### 5.1 Genetic and Reproductive Foundations

#### ***Prediction 1: Orphan gene functional signatures.***

Analysis of the ~1,300 *C. albicans*-specific genes using genomic foundation models (e.g., Evo 2 or successors) will reveal enriched signatures consistent with host-interaction roles, including predicted GPCR ligands, neuropeptide-mimicking sequences, or regulatory elements for peptide processing. **Method:** chromosome-by-chromosome variant-effect scoring, sparse autoencoder feature extraction, and clustering against known symbiont or mammalian

prohormone substrates. Enrichment for interaction motifs would support expanded hardware for the control surface; absence would weaken claims of deep co-evolutionary integration.

***Prediction 2: Parasexual recombination as regulated bet-hedging.***

Under host-mimicking stresses (low oxygen, glucose depletion, sub-inhibitory antifungals), parasexual progeny will display greater phenotypic variance in virulence traits (hyphal elongation, biofilm matrix, EV cargo diversity) and improved survival in macrophage/epithelial assays compared with mitotic clones. **Method:** mating-type homozygosis, tetraploid formation, ploidy reduction, single-cell phenotyping, and whole-genome sequencing. Stress-dependent diversity gains (absent under benign conditions) would confirm parasex as a controlled subroutine; lack of elevation would falsify its bet-hedging role.

## 5.2 Signaling Inputs

***Prediction 3: Hgt4 as high-affinity glucose sensor calibrated to host physiology.***

Wild-type *C. albicans* will exhibit an inflection in HGT4-dependent transcriptional responses (induction of HGT12, HXT10, HGT7) and morphological outputs (yeast-to-hyphal transition) near 5 mM extracellular glucose (human serum range), while a constitutively signaling Hgt4 variant drives hyper-filamentation even at lower levels, and an hgt4Δ mutant shows defective growth and hypofilamentation on low-glucose media. **Method:** dose-response curves (0.1–10 mM glucose) with qRT-PCR/reporter assays and filamentation scoring. Precise calibration to ~5 mM with corresponding virulence phenotypes would validate Hgt4 as a tuned input sensor for host glucose homeostasis; lack of inflection would refute host-specific sensory adaptation.

***Prediction 4: Peptide transporters as dual nutrient/sensor channels.***

Exposure of wild-type *C. albicans* (versus the septuple OPT/PTR transporter mutant) to physiologically relevant host gut-derived peptide hormones (GLP-1, CCK, PYY) or neuropeptides (Substance P, NPY) will elicit measurable transcriptomic or morphological responses (e.g., altered hyphal induction, pH alkalization genes, or SAP expression). Because these peptides exceed the typical substrate size for direct OPT/PTR transport (2–8 amino acids), the response is predicted to depend on prior extracellular proteolytic processing by secreted aspartyl proteases (SAPs) to generate importable fragments. **Method:** RNA-seq or fluorescent reporter assays after exposure in defined media, with parallel assays in SAP-deficient mutants to confirm the two-step (proteolysis → import) requirement. Attenuated responses in the transporter mutant (or in SAP-deficient strains) would demonstrate that these transporters function as environmental sensors in addition to their nutritional role; no difference would restrict them to purely nutritional functions.

***Prediction 5: Cholinergic interface bidirectionality (long-term validation target)***

Acetylcholine or muscarinic agonists will inhibit biofilm formation and hyphal transition in vitro (reversed by scopolamine). Reciprocally, colonized versus germ-free murine gut models are predicted to differ in host acetylcholine levels and vagal tone metrics, scaling with fungal

burden. **Method:** in vitro biofilm assays for direct fungal response; ex vivo/in vivo choline/acetylcholinesterase and vagal signaling measurements for host-side effects. This reciprocal test is technically demanding and best suited as longer-term validation. Clear bidirectional modulation would confirm a functional cholinergic channel; absence of host-side changes would falsify interface status.

### 5.3 Processing and Output Layers

#### ***Prediction 6: EV-mediated cross-kingdom sRNA transfer and gene silencing.***

Purified hyphal EVs incubated with human epithelial cells or macrophages will deliver detectable fungal-origin sRNAs that produce AGO-dependent downregulation of predicted immune or metabolic target transcripts. **Method:** small RNA-seq of recipient cells ± host AGO knockdown or ESCRT-mutant EVs. Functional silencing would support EVs as a coordinated RNA output channel; no transfer/silencing would refute this layer.

#### ***Prediction 7: Codon optimization in EV-associated mRNAs.***

EV-associated mRNAs will exhibit codon usage shifted toward human optimality (relative to bulk transcriptome), consistent with evasion of host DHX29 surveillance. **Method:** codon bias analysis of EV cargo versus whole-cell RNA. Human-optimized profiles would indicate co-evolutionary tuning; lack of shift would weaken refined RNA output claims. (Separable from sRNA silencing; one can succeed while the other fails.)

#### ***Prediction 8: Arachidonic acid competition linking prostaglandin mimicry to ECS tone.***

In colonized mucosal/ex vivo gut models with biofilm (vs. uncolonized controls and *ole2/fet3* mutants), PGE<sub>2</sub> will rise while host endocannabinoids (AEA, 2-AG) fall, scaling with fungal burden. **Method:** targeted lipidomics under controlled arachidonic acid supplementation. Reciprocal shift attenuated in mutants would confirm substrate competition as a core processing node; no crosstalk would undermine the shared lipid economy.

### 5.4 Spatial Multiplexing and Population-Level Computation

#### ***Prediction 9: Niche-specific parallel subroutines.***

Spatial or single-cell transcriptomics/proteomics in stratified host-mimicking models will reveal concurrent micro-niche-specific programs: glucose harvesting/Hgt4 signaling in lumen yeast, amino acid-driven alkalization + SAP activity in hyphae, lactate/ketone utilization inside macrophages. Heterogeneity will track local gradients rather than pure stochastic noise. **Method:** laser-capture or droplet-based single-cell omics. Spatial partitioning would validate distributed multiplexing; uniform expression would falsify context-dependent computation.

#### ***Prediction 10: Colonization density scaling population-level outputs.***

Quantitative mycobiome profiling stratified by *C. albicans* density will correlate higher burden with increased intra-population transcriptomic heterogeneity and stronger collective signaling outputs (e.g., aggregate PGE<sub>2</sub> or EV cargo effects on immune cells), independent of strain genetics. **Method:** deep metagenomics + sorted single-cell RNA-seq. Density-dependent

amplification would support the population as the functional “computer”; no correlation would indicate purely cell-autonomous behavior.

***Prediction 11: Volatile organic compound (VOC) profiling as real-time output channel.***

In colonized versus germ-free murine gut models or simulated gastric environments, a collagen/peptide-rich meal (mimicking bone broth) will trigger a measurable spike in *Candida*-derived organosulfur VOCs (onion-like dimethyl sulfide, dimethyl disulfide, etc.) detectable by headspace GC-MS, scaling with fungal burden and attenuated in SAP-deficient or kynurenine-pathway mutants. Method: real-time VOC sampling during postprandial window + parallel lipidomics for PGE<sub>2</sub>/ECS tone. Positive correlation with postprandial warmth/anhidrosis markers would confirm volatiles as a morphology-dependent broadcast layer of the biochemical computer; absence would falsify the expanded output model.

***Prediction 12: Host intervention as subroutine terminator.***

Quantitative single-cell RNA-seq or live imaging of *C. albicans* populations in stratified gut models will show that an acute glucose bolus (mimicking your honey/pizza rescue) rapidly down-regulates hyphal-invasion and SAP-expression programs while restoring luminal yeast glucose-harvesting transcripts — but only in wild-type strains with intact Hgt4 and peptide-transporter machinery. Method: time-resolved transcriptomics pre- and post-bolus. Successful termination (return to commensal heterogeneity) would validate the population-level “computer” responds to host-level carbohydrate overrides; failure in mutants would falsify the feedback loop.

Collectively, these predictions provide direct, falsifiable tests of the input sensors (Hgt4, peptide transporters, cholinergic receptor), parallel processing pathways (prostaglandin/ECS competition, EV cargo), adaptive outputs (morphology, immune modulation), reproductive bet-hedging (parasex), and spatial multiplexing that together constitute the proposed biochemical computer. A coherent pattern of confirmatory results across layers would offer convergent empirical support; systematic failures at any layer would necessitate targeted revision. This roadmap prioritizes accessible molecular/cellular assays while identifying higher-complexity *in vivo* validations, ensuring the framework remains rigorously testable.

## **6. Discussion & Conclusion**

*Candida albicans* satisfies the four operational criteria of a biochemical computer: it senses inputs (Hgt4, peptide transporters, cholinergic receptor), integrates multiple signals (pH + temperature + nutrients → hyphal decision; biofilm feed-forward reinforcement), produces adaptive outputs (morphology, immune modulation via LILR engagement and candidalysin-mediated EGFR/CCNH hijacking, pH engineering), and maintains state across time through epigenetic phenotypic locking (white-opaque switching stabilized by Sir2/Hda1 complexes). Quorum sensing (farnesol/tyrosol), biofilm community organization, and host-signal crosstalk further support distributed, population-level computation.

The organism does not think, possess intentions, or exhibit consciousness. It carries a statistical record of past success encoded in its codon bias and regulatory architecture. Because

the DNA sequence itself changes slowly, the population retains a bias toward reactions that proved successful in previous generations. Bet-hedging and parasexual recombination then act as the mechanism by which those historically successful states are re-tested and refined under new stress. In this sense the organism carries a form of long-term memory—not conscious recall, but a dynamic process of compiling numerous real-time inputs and cross-referencing them against its differential survival history. The more successful the response in the past, the more likely the architecture is to produce it again when similar conditions reappear. This is the essence of the biochemical computer: a distributed, chemical system that “remembers” what worked across deep evolutionary time without ever needing to think.

When the internal niche destabilizes, the same toolkit that supports commensalism shifts toward survival-oriented programs. This is not simple opportunism; it is reactive computation to changing host conditions.

### **Counter-Arguments and Limitations**

Several reasonable objections can be anticipated. Critics may argue that the paper over-interprets existing data by assembling well-known individual capabilities into a “biochemical computer” narrative. Every individual finding cited is drawn directly from the peer-reviewed literature; what is novel is their synthesis into a unified functional description of a distributed, multi-channel processing system.

A second objection is that much of the evidence is *in vitro*. This is acknowledged, but the point cuts both ways. Where *in vivo* studies have been performed, they consistently verify that the proposed mechanisms occur inside living systems. At the same time, these experiments underscore the immense complexity of the real microbiome—with its hundreds of simultaneous inputs, micro-niches, oxygen gradients, pH fluctuations, and inter-species interactions that no single study can fully replicate. Far from weakening the model, this complexity lends it greater credibility: the more intricate the environment, the more adaptive and reactive *C. albicans* must be to persist.

Third, the description of *Candida albicans* as a biochemical computer may strike some readers as overly metaphorical. The model is strictly mechanistic: it describes distributed chemical computation via parallel channels and historical bias encoded in codon usage and regulatory architecture—nothing more. The organism does not think, does not possess intentions, and does not exhibit consciousness.

Fourth, the claim that no other known commensal matches this full toolkit will inevitably be challenged. To date, no other organism is known to combine bidirectional pH engineering, authentic host-mimetic prostaglandin production from host arachidonic acid, peptide-processing machinery homologous to mammalian prohormone convertases, a functional cholinergic interface, EV-mediated RNA potential, and stress-gated parasexual diversity generation. Should future research identify such an organism, this uniqueness claim would of course require revision.

Real-time longitudinal observations from the author's documented physiological case study (Craddock, 2026b) provide in vivo corroboration of the expanded architecture. A recent peptide-rich load triggered postprandial central warmth, anhidrosis, and a strong organosulfur volatile signature — exactly the predicted integration/processing → output subroutine — which was terminated by a targeted carbohydrate bolus before tissue-remodeling programs engaged. These data illustrate the distributed biochemical computer operating under known inputs and demonstrate the practical utility of the model for interpreting symbiont-host dynamics in the living human system.

These counter-arguments are raised not to deflect criticism but to make transparent where the current limits of the evidence lie. The goal is not persuasion by rhetoric, but the presentation of a coherent, testable model that can be rigorously challenged with data.

This paper supplies technical grounding for the biochemical computer framework. It stands alone while providing molecular and genetic detail. The experimental roadmap in Section 5 offers clear paths to confirmation or falsification. Understanding *C. albicans* as a distributed regulator opens avenues in microbiology, immunology, metabolism, and host–microbe ecology. The refined signaling, memory, and output layers presented here, validated in real time by the Redacted Science longitudinal dataset, supply the mechanistic foundation for the Mammalia candidus / Saline Oscillation co-evolutionary framework developed in the companion manuscript.

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