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Endogenous Dimethyltryptamine Reconsidered

A Constraint-Based Trace Amine Ensemble Model

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ABSTRACT

Endogenous dimethyltryptamine (DMT) has been detected intermittently in mammalian systems, yet its physiological relevance remains unresolved due to low steady-state concentrations, rapid monoamine oxidase-mediated clearance, and inconsistent detection across tissues. This position paper argues that the prevailing single-molecule, tonic-neurotransmitter framing of endogenous DMT is misaligned with its metabolic biology. We propose that DMT functions as a transient component of a constraint-governed trace amine ensemble composed of indole- and phenyl-derived amines whose biological impact emerges from coordinated flux rather than sustained extracellular concentration.

Within this framework, ensemble configuration is determined by precursor partitioning, enzymatic gating, clearance dominance, and physicochemical membrane permeability. Central glial networks regulate volume transmission and degradation kinetics, while neuron-glia microdomains in the brain and high-surface-area neuroendocrine interfaces in the lung and gut are proposed as conditional relay architectures for localized indole methylation. The absence of the 5-hydroxyl group enables non-hydroxylated ensemble members to traverse lipid barriers that restrict canonical monoamines, linking peripheral metabolic shifts to central neural states.

Inflammatory activation amplifies constraint through coordinated tryptophan diversion into the kynurenine pathway, increased monoamine oxidase expression, and expansion of peripheral hydroxylation flux, collectively compressing ensemble amplitude and duration. This model reframes endogenous DMT not as a missing classical neurotransmitter, but as a pulse dependent state modulatory component within a distributed metabolic architecture. The framework generates experimentally falsifiable predictions concerning spatial enzyme adjacency, flux coupling, inflammatory compression, and transient pulse detection, providing a structured basis for future investigation. To aid interpretation of this systems-level framework, schematic figures are provided summarizing the proposed peripheral relay architectures, central neuron-glia relay model, and constraint logic governing ensemble-state transitions.

KEYWORDS endogenous dimethyltryptamine · DMT · trace amines · INMT · monoamine oxidase · neuroinflammation · neuroendocrine signalling · tryptophan metabolism

I. Introduction: The Failure of the Tonic Model

Endogenous dimethyltryptamine (DMT) occupies an unresolved position in neurochemistry (Barker, 2018). Although its biosynthetic pathway is established as tryptophan decarboxylation to tryptamine followed by N-methylation, its physiological role remains disputed (Chaves et al., 2024). For decades, investigations have centered on bulk concentration measurements and receptor agonism, implicitly assuming a model of tonic availability and classical synaptic neurotransmission. This serotonergic framing assumes that if DMT were relevant, it

would be stored in vesicles and maintained at a steady state (Vitale et al., 2011).

However, the persistent failure to detect sustained, behaviorally relevant extracellular levels suggests that the "missing neurotransmitter" model may be fundamentally misaligned with the molecule's biology. Recent transcriptomic evidence indicates colocalization of Indolethylamine N-methyltransferase (INMT) and Aromatic L-amino acid decarboxylase (AADC) mRNA within mammalian brain tissue, supporting the plausibility of central synthetic capacity within defined cellular compartments without, on its own, demonstrating active enzymatic flux (Dean et al., 2019). Peripheral tissues, however, show a more complex differential expression pattern. Lung tissue exhibits robust INMT expression (Ardini et al., 2025), while AADC appears restricted primarily to pulmonary neuroendocrine cells (PNECs) (Lauweryns and Van Ranst, 1988). A comparable architectural separation may exist within the gastrointestinal tract, where enterochromaffin (EC) cells exhibit neuroendocrine amine-handling features and express Aromatic L-amino acid decarboxylase (Tao et al., 2022). In this manuscript, references to neuroendocrine amine-handling phenotypes are used only to describe functional biochemical features, including amine precursor handling and decarboxylation capacity, not to imply a shared developmental lineage.

Beneath the epithelial layer, the intestinal lamina propria contains stromal, mesenchymal, vascular, and perivascular compartments, including myofibroblasts, fibroblasts, mesenchymal progenitor-like cells, capillary networks, and vascular mural or smooth-muscle-associated populations (Powell et al., 2011). These compartments provide an anatomical substrate for epithelial-stromal exchange and candidate relay partners for diffusible tryptamine generated by enteroendocrine or enterochromaffin cells (Powell et al., 2011). Independent tissue-level datasets indicate that INMT is expressed in human gastrointestinal tissues, including stomach and intestinal regions (Uhlén et al., 2015; Human Protein Atlas, 2025), while genetic association data link an INMT coding variant to Hirschsprung disease risk and aganglionosis extent (Kim et al., 2015). These observations support enteric relevance for INMT but do not identify the specific epithelial, neuronal, glial, endothelial, pericytic, or stromal populations responsible for the tissue-level signal. The enteric relay model therefore treats cell-type-resolved INMT localization as an explicit prediction requiring spatial transcriptomic, immunohistochemical, and functional validation.

These spatial arrangements are consistent with the possibility of compartmental specialization and transcellular relay architectures rather than uniform, bulk synthesis within single cells. In such systems, decarboxylation and methylation steps may occur across neighboring cellular compartments embedded within high-surface-area epithelial-stromal interfaces. This paper moves beyond single-molecule framing, proposing instead that DMT represents a fleeting biochemical condition: a pulse within a broader ensemble that is managed by distributed, state-dependent metabolic constraints operating across brain and peripheral interfaces.

A methodological caution is necessary at the outset. Much of the spatial logic developed in this framework rests on transcriptomic and atlas-level evidence, which can establish cellular plausibility and anatomical adjacency but does not by itself demonstrate protein abundance, enzymatic activity, substrate flux, or downstream product formation. Accordingly, references to pulmonary, enteric, and central relay architectures in the sections that follow should be read as transcriptomically and anatomically plausible models requiring protein-level and functional validation rather than as demonstrated biochemical pathways.

II. Re-categorization: DMT as a Trace Amine

To understand DMT, we must move it out of the category of classical neurotransmitter and into the category of trace amine. Unlike serotonin or dopamine, DMT lacks confirmed vesicular storage and is highly susceptible to rapid degradation by monoamine oxidase (MAO), particularly the MAO-A isoform (Colosimo et al., 2024).

These features align DMT with the biology of trace amines like Phenethylamine (PEA) and Tryptamine (Pei et al., 2016). Crucially, this classification is supported by the absence of confirmed vesicular monoamine transporter 2 (VMAT2)-mediated handling. This does not exclude the physicochemical possibility that a lipophilic weak base such as DMT could passively accumulate in acidic intracellular compartments through pH-gradient proton trapping. However, passive acidic-compartment sequestration is not equivalent to VMAT2-dependent vesicular loading for regulated exocytotic release. Unlike classical monoamines, which are actively concentrated into synaptic vesicles for quantal release, DMT lacks confirmed evidence of regulated vesicular storage and release (Palner et al., 2026). This supports its treatment as an intracellular-first and microdomain-limited molecule rather than a conventional synaptic transmitter. The relevant functional framework therefore shifts away from classical synaptic persistence and toward trace amine regulatory systems, including trace amine-associated receptor 1 (TAAR1), as well as other receptor and intracellular targets engaged within transient microdomains. Located on presynaptic terminals (Miller, 2011) and glial membranes or immune-associated

compartments (Fleischer et al., 2018), TAAR1 functions as a metabolic regulatory node (Revel et al., 2011), suggesting that trace amine ensemble members may modulate the responsiveness of the broader monoaminergic system rather than carrying discrete point-to-point signals.

This reclassification has functional consequences. If DMT is approached as a member of a trace amine ensemble rather than as a failed classical neurotransmitter, the relevant regulatory context shifts from vesicular release into the synaptic cleft toward microdomain-level modulation of monoaminergic tone. In that setting, TAAR1 functions as a plausible ensemble-integrating node. Phenyl-derived trace amines such as phenethylamine and tyramine are positioned to influence presynaptic excitability, transporter behavior, and monoaminergic responsiveness through TAAR1-linked signaling, while indole-derived methylamines may contribute state-specific signaling bias through partially overlapping but non-identical receptor and intracellular targets.

This suggests that synthesis and degradation are enriched in non-neuronal compartments, particularly glial cells. Glia are primary metabolic regulators of the brain, expressing significant MAO activity (Pallio et al., 2021; Jaisa-Aad et al., 2024) and contributing to interstitial chemical homeostasis. Within the brain, glial-associated microdomains provide a plausible environment for localized indole methylation and for transient interaction between ensemble generation, ensemble sensing, and rapid enzymatic termination. In this view, DMT functions not as a persistent signal-carrier, but as a transient state-shifter embedded within a broader trace amine regulatory field.

III. The Trace Amine Ensemble Hypothesis

3.1 Ensemble Composition and Flux Coupling

A core tenet of this framework is that biological relevance does not arise from DMT in isolation, but from the coincident availability of an ensemble of indole- and phenyl-derived trace amines. This ensemble includes tryptamine, N-methyltryptamine (NMT), dimethyltryptamine (DMT), phenethylamine (PEA), and tyramine. This collection of molecules shares structural similarities, rapid turnover kinetics, and susceptibility to monoamine oxidase degradation. They are metabolically unified by reliance on AADC as a shared enzymatic bottleneck (Parthasarathy et al., 2018).

Under this model, physiological states are not defined by the concentration of a single trace amine, but by the relative ratios and temporal co-occurrence of ensemble members within defined microdomains. A DMT-dominant pulse does not imply sustained high extracellular concentration, but rather a transient ensemble configuration in which N-methylated indoles increase relative to hydroxylated indoles and phenyl-derived amines within a constrained spatial and temporal window and do so to a degree sufficient to alter downstream signaling within that microdomain.

Synergy rather than absolute concentration defines the functional output of this system. Because tryptamine, phenethylamine, and tyramine converge on AADC for decarboxylation, any physiological state that increases decarboxylase flux will proportionally increase the availability of multiple trace amines (Christian and Berry, 2018). Downstream methylation via INMT introduces a second regulatory gate, creating a layered architecture in which flux through shared enzymatic constraints determines ensemble composition.

3.2 Receptor Modulation and Threshold Conditions

We propose a model of metabolic co-operativity rather than simple receptor co-activation. While DMT may engage receptors such as 5-HT2A or Sigma-1 (Su et al., 2009), the concurrent presence of phenyl-derived amines acting at TAAR1 can alter neuronal excitability thresholds, transporter regulation, and intracellular signaling tone (Revel et al., 2011). In this framework, modulatory context refers to the local adjustment of system responsiveness before or during an indole pulse: TAAR1-active phenyl-derived amines bias the gain and regulatory state of the surrounding monoaminergic microenvironment, while indole-derived methylated species contribute state-specific signaling bias within that conditioned window. The resulting biological effect emerges from coordinated flux rather than isolated ligand binding.

This ensemble-based framing predicts non-linear physiological outcomes. Because all members are rapidly degraded by MAO (Premont et al., 2001) and lack confirmed regulated vesicular storage and release, their impact depends on momentary alignment of precursor availability, enzymatic permissiveness, and clearance restraint. Small shifts in constraint parameters may therefore produce disproportionate changes in ensemble configuration without large changes in bulk concentration.

A biologically consequential ensemble configuration should not be defined by dimethyltryptamine abundance alone, but by the coincidence of at least three threshold conditions within a constrained microdomain: first, a relative shift toward non-hydroxylated indoles over competing hydroxylated and phenyl-derived states; second, a pulse duration sufficient to outlast immediate monoamine oxidase-dominated collapse; and third, a spatial scale broad enough to influence local receptor or intracellular target engagement beyond a purely intracel-

lular transient. In this framework, a DMT-dominant pulse refers qualitatively to a transient state in which N-methylated indoles become disproportionately represented within a local ensemble for long enough, and across sufficient microdomain extent, to alter downstream signaling bias. The specific quantitative boundaries of ratio, duration, and spatial extent remain unknown and must be determined experimentally.

3.3 Conceptual Ensemble Ratio and Threshold Definition

For clarity, a DMT-dominant ensemble state can be defined conceptually as a local, time-bounded shift in the balance between methylated non-hydroxylated indoles and competing trace amine or hydroxylated pathways, normalized against local clearance pressure. This definition does not require sustained high absolute dimethyltryptamine concentration. Rather, it requires that methylated indoles become proportionally enriched within a constrained microdomain for long enough to alter downstream receptor-linked or intracellular signaling tone.

A simplified conceptual relationship can be expressed as:

$$E_{DMT} \propto [(DMT + NMT) / (\text{tryptamine} + PEA + \text{tyramine} + \text{hydroxylated indoles})] \times D_{pulse} \times A_{clearance}$$

where E_DMT represents the local DMT-weighted ensemble state, DMT and NMT represent methylated indole products, and tryptamine, phenethylamine, tyramine, and hydroxylated indoles represent competing ensemble members or pathway states. D_pulse represents pulse duration normalized to the relevant local signaling window, and A_clearance represents a dimensionless clearance-permissiveness term inversely related to local monoamine oxidase-mediated degradation pressure. This relationship is not proposed as a strict thermodynamic, pharmacokinetic, or kinetic rate equation. It is an operational scaffold intended to express proportional weighting among ensemble ratio, pulse persistence, and local clearance restraint.

Within this framework, an activation threshold would be crossed when E_DMT exceeds the minimum local value required to alter downstream signaling gain within that microdomain. Such effects could include Sigma-1-linked intracellular stress-response signaling, TAAR1-associated modulation of monoaminergic responsiveness, or combined changes in excitability, transporter regulation, and glial metabolic state. The threshold is expected to depend on microdomain geometry, receptor or intracellular target density, methyl-donor availability, local redox state, and clearance kinetics.

This formulation makes the ensemble hypothesis experimentally tractable. A predicted DMT-dominant state is not simply a condition in which dimethyltryptamine is detectable. It is a state in which methylated non-hydroxylated indoles rise relative to competing trace amines and hydroxylated products while local clearance pressure is sufficiently restrained to permit a biologically meaningful pulse duration. Conversely, a high precursor state with rapid MAO-mediated collapse, or a trace amine pulse dominated by unmethylated or hydroxylated products, would not qualify as DMT-dominant under this definition.

3.4 Relation to Competing Receptor-Centered Frameworks

This framework is proposed in the context of several existing interpretations of endogenous dimethyltryptamine biology rather than only as a rejection of the tonic classical neurotransmitter model. One interpretation emphasizes intracellular Sigma-1 receptor-mediated effects, particularly in relation to cellular stress response, calcium regulation, mitochondrial stability, ER-mitochondrial interface function, and neuroprotection (Su et al., 2009; Weng et al., 2017; Lee and Min, 2018). A second emphasizes trace amines as modulators of monoaminergic and serotonergic tone through receptors such as TAAR1 (Pei et al., 2016; Miller, 2011; Revel et al., 2011). Both views capture important elements of the biology discussed here, but neither alone fully addresses the spatially distributed, state-dependent, and metabolically constrained character of the present model.

A Sigma-1-centered account provides a plausible mechanism for downstream intracellular effects once endogenous dimethyltryptamine or related indole methylamines are present, but it does not by itself specify how transient endogenous availability is generated, spatially constrained, or differentially suppressed across peripheral and central compartments. A TAAR1-centered trace amine framework likewise explains how phenyl-derived trace amines and related compounds may regulate monoaminergic responsiveness but does not by itself explain why non-hydroxylated indole methylamines would emerge only under specific combinations of precursor partitioning, methylation permissiveness, membrane permeability, and clearance restraint.

The ensemble model proposed here is therefore intended as a higher-order organizational framework rather than a dismissal of receptor-mediated hypotheses. In this formulation, Sigma-1 receptor signaling and TAAR1-linked modulation are treated as plausible downstream or parallel functional components within a broader architecture governed by spatial enzyme distribution, physicochemical gating, shared upstream flux constraints, methyl-donor availability, and inflammatory compression. The question shifts from which single receptor defines endogenous dimethyltryptamine function to how transient indole methylamine states emerge, persist, and become biologically consequential within a regulated trace amine field.

The remainder of this paper examines the regulatory architecture governing this ensemble. Sections IV through VI describe how glial networks, peripheral relay nodes, oxygen-sensing mechanisms, and inflammatory gating collectively determine whether trace amine flux remains suppressed, transient, or crosses the proposed DMT-weighted ensemble threshold. The central question is not whether DMT is produced, but under what physiological constraints its contribution to the ensemble becomes biologically consequential. Within this formulation, TAAR1-linked phenyl trace amine signaling is best understood as part of the regulatory background that conditions ensemble responsiveness, rather than as a parallel hypothesis separate from the ensemble model itself.

IV. The Pan-Glial Network as a Distributed Metabolic Interface

To understand how this ensemble is managed, attention must shift to the glial network as a distributed metabolic interface. Glial cells outnumber neurons (Stevens, 2003) and participate in precursor allocation, immune signaling, neurotransmitter clearance, redox buffering, and maintenance of interstitial homeostasis. Within this framework, glia function as primary regulators of ensemble constraint rather than passive support cells (Tasker et al., 2012).

Because DMT and its precursors lack confirmed vesicular storage and exhibit high diffusibility, they are positioned to operate through volume transmission within the glial-interstitial space (Özçete et al., 2024). Unlike classical synaptic transmission, which is confined to the synaptic cleft, volume transmission permits ensemble members to diffuse across extracellular microdomains, integrating signals across neuronal and non-neuronal compartments.

The glial network regulates ensemble configuration through three interdependent mechanisms: precursor allocation, enzymatic permissiveness, and clearance dominance. Precursor allocation determines whether tryptophan is directed toward serotonin synthesis (Yin et al., 2022), the kynurenine pathway (Argolo et al., 2025), or decarboxylation into tryptamine (Juorio et al., 1993). Enzymatic permissiveness reflects the availability of cofactors such as S-adenosylmethionine (SAM), the methyl donor required for INMT-mediated N-methylation reactions that convert tryptamine into downstream indole methylamines. In this framework, methyl-donor availability is treated as one component of the broader constraint architecture governing whether decarboxylated indoles can proceed into methylated ensemble states. Clearance dominance is mediated primarily by monoamine oxidase activity within astrocytic and other glial compartments, constraining trace amine accumulation and limiting pulse duration.

Clearance dominance is further shaped by glymphatic system dynamics and interstitial fluid movement (Jessen et al., 2015). During periods of high metabolic activity, microglia and astrocyte-mediated MAO activity acts as a rapid enzymatic sink (Pallio et al., 2021; Lee et al., 2025), maintaining ensemble transience. Under hypoxic or stress-associated conditions, shifts in glial cell volume and interstitial space geometry may alter diffusion parameters, potentially prolonging ensemble dwell time within constrained microdomains.

This regulatory architecture is not confined to the brain. Glial and glia-like metabolic interfaces extend into peripheral neuroimmune tissues (Reed et al., 2022), allowing physiological shifts in organs such as the lung to influence central ensemble dynamics. In this view, a hypoxia-induced alteration in pulmonary trace amine flux can be integrated centrally through distributed metabolic coupling rather than classical synaptic signaling.

V. The Peripheral Conduit: Multimodal Transcellular Synthesis

While the brain possesses enzymatic machinery for DMT synthesis (Dean et al., 2019), the periphery offers high-surface-area interfaces that may act as generators of primary trace amine pulses (Schimmelpfennig and Jankowiak-Siuda, 2025). We propose two major peripheral nodes for this activity, the pulmonary relay and the enteric relay, alongside a central neuron-glial relay model for brain-localized ensemble assembly.

5.1 The Pulmonary Neuroendocrine Adjacent Relay Model: PNEC Integration

Human Protein Atlas and related transcriptomic resources indicate robust INMT associated signal in lung tissue (Zhou et al., 2022), whereas AADC signal appears comparatively limited in bulk transcriptomic datasets. This apparent mismatch is consistent with, but does not by itself establish, a transcellular relay architecture rather than

strict single-cell enzymatic co-expression. PNECs reside within the airway epithelium and express AADC, reflecting amine-handling and decarboxylation-associated neuroendocrine features that enable the local generation of tryptamine from tryptophan. These cells are positioned at the epithelial-stromal interface and are frequently found in close proximity to capillary networks within the subepithelial lamina propria (Noguchi et al., 2020).

Pulmonary neuroendocrine cells frequently occur in small clusters known as neuroepithelial bodies, which function as airway oxygen and chemical sensors (Adriaensen et al., 2006). These structures are commonly innervated by vagal afferent fibers projecting to the nucleus tractus solitarius in the brainstem (Kubin et al., 2006). Through this architecture, signaling within pulmonary neuroendocrine units can rapidly influence central autonomic and metabolic regulatory circuits, providing a potential physiological pathway by which pulmonary trace amine pulses could modulate central ensemble dynamics. Recent high-resolution anatomical mapping has also identified specialized pulmonary glial populations associated with airway sensory structures (Hall et al., 2024). These include terminal neurosensory glial cells positioned at the base of neuroepithelial bodies, where they facilitate communication between airway sensory cells and afferent nerve terminals. Additional pulmonary glial populations, including non-myelinating and satellite glial cells, form networks surrounding airway nerves and intrinsic pulmonary ganglia. The presence of these glial compartments suggests that pulmonary neuroendocrine signaling occurs within a broader neuro-glial microenvironment capable of integrating metabolic, sensory, and neural signals within airway microdomains.

Immediately subjacent to the epithelial layer, the pulmonary interstitium contains subepithelial interstitial fibroblasts, adventitial and perivascular fibroblasts, pulmonary mesenchymal stromal cells, pericytes, and pulmonary capillary microvascular endothelial cells (Zhang et al., 2022). Single-cell transcriptomic datasets indicate that subsets of these fibroblast, stromal, pericyte, and endothelial compartments may exhibit enriched INMT transcript signal. These data are consistent with the possibility of a microdomain in which an epithelial AADC-positive node is anatomically adjacent to INMT-positive mesenchymal and endothelial neighbors (Schupp et al., 2021), but they do not by themselves demonstrate active relay biochemistry.

Within this relay model, PNECs are proposed to generate tryptamine intracellularly. Due to its non-hydroxylated, lipophilic structure, tryptamine would be expected to diffuse across the relatively thin epithelial basement membrane and narrow interstitial space into adjacent INMT-expressing stromal or endothelial cells if the relevant enzymes are present and active. Under that proposed arrangement, methylation to N-methyltryptamine and subsequently dimethyltryptamine would be predicted to occur in a second cellular compartment rather than within the originating neuroendocrine cell.

This epithelial-mesenchymal-vascular coupling would eliminate the requirement for strict single-cell enzymatic colocalization and instead offers a plausible pulmonary microanatomical framework for localized, state-dependent indole methylation. Given the dense capillary network surrounding airway neuroendocrine units (Candeli and Dayton, 2024), methylated products generated within stromal, pericytic, or endothelial compartments would be positioned for relatively direct access to pulmonary venous circulation (Worrell and MacLeod, 2021). Figure 1 summarizes the proposed pulmonary relay architecture, including AADC-positive pulmonary neuroendocrine cells, candidate INMT-positive stromal, pericytic, and pulmonary microvascular endothelial relay compartments, local methylation, and pulmonary venous access.

(A) In the pulmonary relay, pulmonary neuroendocrine cells (PNECs) are proposed to generate tryptamine from tryptophan through aromatic L-amino acid decarboxylase (AADC). Tryptamine may then diffuse into adjacent subepithelial stromal, pericytic, or pulmonary microvascular endothelial compartments where candidate INMT-dependent methylation could generate N-methyltryptamine and dimethyltryptamine (DMT), pending protein-level and functional validation. This route is positioned for comparatively direct pulmonary venous access. (B) In the enteric relay, enterochromaffin/enteroendocrine cells may generate tryptamine, which could diffuse into candidate stromal, glial, pericytic, or vascular-associated relay compartments. Unlike the pulmonary route, portal entry is expected to encounter gut-wall and hepatic monoamine oxidase (MAO)-mediated first-pass degradation. Solid arrows indicate established biochemical direction; dashed arrows indicate hypothesized relay, diffusion, or transport steps requiring validation.

5.2 The Enteric Neuroendocrine Adjacent Relay: EC Cell Integration

Parallel to the pulmonary system, the gastrointestinal tract contains the body's largest population of dispersed neuroendocrine cells: enterochromaffin cells. Although best characterized for TPH1-mediated serotonin synthesis (Alcaino et al., 2025), EC cells share with PNECs a neuroendocrine amine-handling profile and retain decarboxylation capacity via AADC (Gunawardene et al., 2011). Under defined metabolic conditions including alterations in luminal metabolites, microbiota-derived signaling molecules, or local pH shifts, EC cells may divert

substrate toward tryptamine production rather than exclusive hydroxylation.

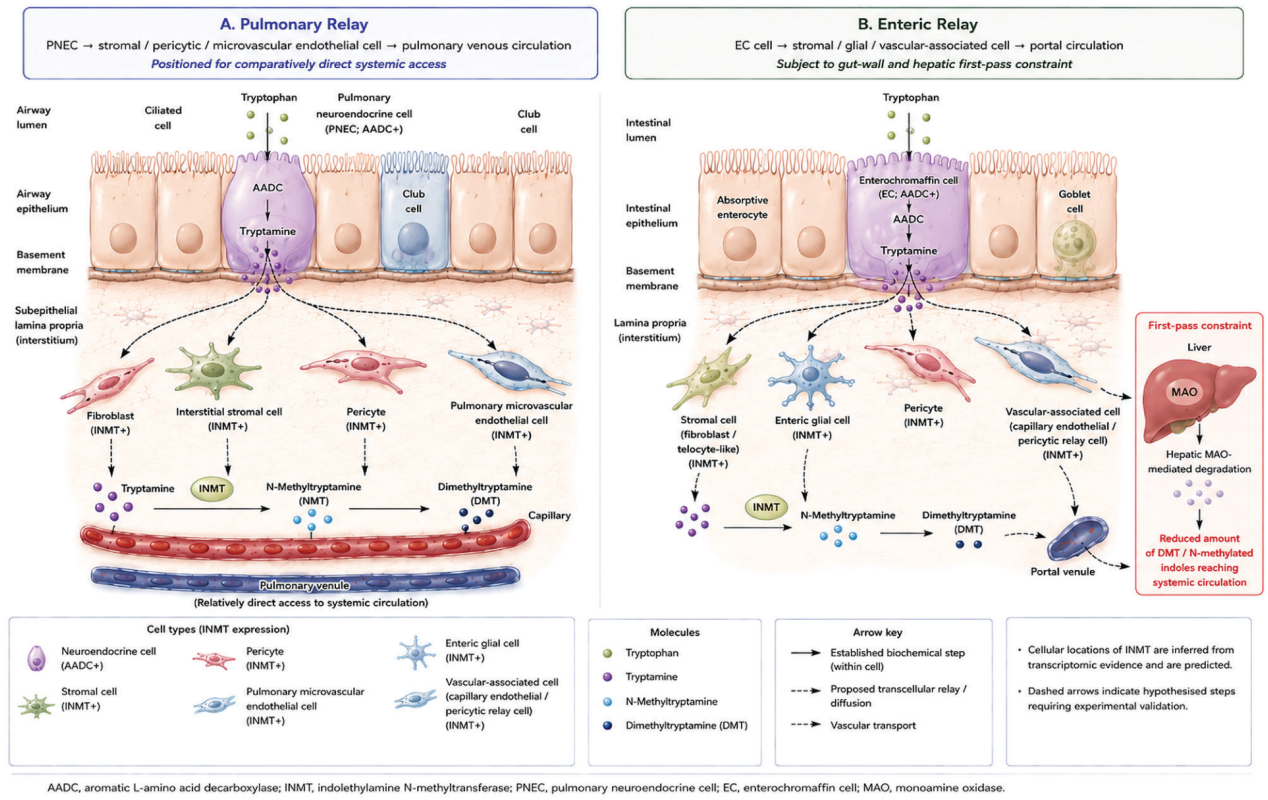

Figure 1. Proposed peripheral relay architectures for endogenous indole methylation.

Enterochromaffin cells are also positioned within a well-characterized gut-brain signaling interface (Martin et al., 2018). These neuroendocrine cells release serotonin and other signaling molecules in response to luminal and metabolic stimuli and are closely associated with afferent fibers of the enteric and vagal nervous systems. Activation of these pathways transmits signals to the nucleus tractus solitarius and other brainstem autonomic centers, forming a central component of the gut-brain axis (Grundeken and El Aidy, 2025). Through this architecture, enteric neuroendocrine signaling is capable of rapidly influencing central physiological state, providing a potential pathway through which enteric trace amine dynamics could modulate central ensemble regulation.

Unlike the airway epithelium, the intestinal mucosa is organized around a highly interactive epithelial-stromal interface (Asal et al., 2024). Beneath the EC cell layer, the lamina propria contains subepithelial myofibroblasts, telocytes (Shoshkes-Carmel, 2024), interstitial Cajal-like cells (López-Pingarrón et al., 2023), and additional mesenchymal fibroblast populations that together form an extended structural and signaling network. Human tissue-level datasets support INMT expression across gastrointestinal regions, while high-resolution enteroendocrine transcriptomic analyses define regional EC/EEC diversity along the gastrointestinal tract (Smith et al., 2024). However, the specific epithelial, neuronal, glial, stromal, vascular-associated, or pericytic cell populations responsible for the GI INMT signal remain unresolved, so these adjacent compartments are treated here as candidate methylation nodes rather than established INMT-positive sites. The intestinal mucosa also contains an extensive population of enteric glial cells, which represent the largest glial network outside the central nervous system (Santhosh et al., 2024). These cells form a distributed signaling and metabolic support system throughout the enteric nervous system and are closely associated with enterochromaffin cells, enteric neurons, and lamina propria stromal compartments. Enteric glia regulate neurotransmitter metabolism, barrier function, immune signaling, and extracellular chemical environments within the gut. Their proximity to neuroendocrine cells and enteric neurons positions them as plausible participants in local metabolic relay architectures capable of integrating neuroendocrine, immune, and neural signaling within intestinal microdomains.

Tryptamine generated within EC cells could diffuse basally into this mesenchymal scaffold, where sequential N-methylation to N-methyltryptamine and dimethyltryptamine would become anatomically plausible if adjacent INMT-positive cells are confirmed. Because the intestinal villi are penetrated by fenestrated capillary endothelial cells with direct access to the portal circulation, methylated indoles produced within this stromal domain would not require long diffusion paths before vascular entry. However, portal entry does not by itself imply efficient systemic or central delivery, because gut-wall and hepatic monoamine oxidase activity would be expected to impose substantial first-pass metabolic constraint on any methylated indoles generated in this compartment (Brito-da-Costa et al., 2020; van der Heijden et al., 2025).

In addition, INMT signal within elements of the myenteric (Auerbach's) plexus, including enteric neuronal and associated glial populations in available transcriptomic datasets (Spencer and Hu, 2020), raises the possibility that locally generated dimethyltryptamine may exert paracrine or neuromodulatory effects within the enteric nervous system prior to systemic distribution. This introduces a functional dimension distinct from the pulmonary relay: the enteric relay may be most relevant as a local mucosal, neuroimmune, and motility-associated signaling architecture rather than as a primary direct-delivery route to the central nervous system.

Under this interpretation, first-pass metabolism does not negate the enteric relay. Instead, it defines its likely biological scale. Methylated indoles generated within intestinal stromal, glial, pericytic, vascular-associated, or myenteric microdomains would be expected to encounter substantial gut-wall and hepatic monoamine oxidase-mediated degradation if they enter the portal circulation (Brito-da-Costa et al., 2020; van der Heijden et al., 2025). Therefore, robust systemic or central delivery from the enteric compartment should not be assumed. The more conservative prediction is that enteric methylated indole pulses, if generated, would act primarily within local volume-transmission fields affecting epithelial–stromal signaling, enteric glial activity, myenteric excitability, gut motility, and mucosal immune tone before hepatic passage (Santhosh et al., 2024; Spencer and Hu, 2020; Brandl et al., 2017).

A secondary systemic route remains anatomically plausible but should be treated as conditional and lower probability. Under conditions of high local production, reduced clearance dominance, favorable diffusion gradients, and sufficient microdomain dwell time, a fraction of methylated indoles could enter intestinal lymphatic drainage or local non-portal vascular routes before complete portal-hepatic degradation. Such escape would not be expected to match the pulmonary relay in efficiency, but it provides a plausible mechanism by which enteric production could contribute weak or intermittent systemic signals under permissive physiological states.

Together, the pulmonary and enteric relays illustrate pharmacokinetically distinct peripheral architectures. The pulmonary relay is better positioned for rapid systemic access through pulmonary venous outflow, whereas the enteric relay is more likely to operate as a local paracrine, neuroimmune, and motility-associated microdomain system with only limited and conditional systemic escape. This distinction strengthens rather than weakens the model, because it predicts different experimental signatures for each relay: pulmonary enrichment should be most evident in venous outflow and systemic circulation, while enteric enrichment may be strongest in local tissue, portal blood, mesenteric lymph, or myenteric-associated compartments and may fail to survive systemic dilution or hepatic clearance.

5.3 The Central Neuron–Non-Neuronal Relay: Neurovascular and Glial-Associated Microdomain Integration

While peripheral tissues provide large surface-area interfaces for trace amine generation, the brain presents a different architectural environment in which metabolic coupling between neurons, astrocytes, neurovascular cells, and other non-neuronal compartments forms tightly regulated microdomains (Bonvento and Bolaños, 2021). Within these domains, neurotransmitter metabolism, monoamine degradation, and interstitial diffusion occur in close spatial proximity. Such interfaces provide a plausible substrate for localized trace amine ensemble assembly through non-vesicular volume transmission rather than classical synaptic release. This framework does not privilege a single brain region a priori. Instead, it proposes neuron-to-non-neuronal metabolic microdomains as a general central architecture, with the hippocampus discussed below as an illustrative candidate rather than an exclusive locus.

Central non-neuronal populations across the nervous system express receptor systems and intracellular signaling complexes known to interact with trace amines and dimethyltryptamine, but these populations should not be treated as a single undifferentiated glial category. Among these systems, the sigma-1 receptor is widely expressed in glial cells (Weng et al., 2017) and functions as an intracellular chaperone located at endoplasmic reticulum-mitochondrial interfaces, where it regulates calcium signaling, mitochondrial stability, and cellular stress responses (Lee and Min, 2018). In addition to intracellular signaling systems, trace amine-associated receptors are expressed in glial and immune-associated compartments

(Miller, 2011; Fleischer et al., 2018), providing a possible mechanism for detecting and responding to locally generated indole and phenyl trace amines within extracellular microdomains. Astrocytes are especially relevant as extracellular homeostatic and monoamine-regulatory interfaces because they regulate extracellular monoamine dynamics through enzymatic degradation and interstitial control (Tasker et al., 2012). Microglia, by contrast, are most relevant to inflammatory gating, cytokine signaling, and IDO-linked tryptophan diversion rather than baseline methylation relay unless direct INMT expression or close spatial adjacency is demonstrated. Through these differentiated signaling and clearance systems, central non-neuronal microdomains may possess the molecular machinery necessary to detect, modulate, and terminate transient trace amine ensemble dynamics within local extracellular environments.

Evidence from transcriptomic datasets indicates that AADC expression is broadly associated with neuronal populations, including hippocampal and other central neural compartments. In contrast, INMT signal appears more restricted and should not be generalized to glia as a single category. The most conservative interpretation is that candidate INMT-positive central relay compartments may include specific non-neuronal or neurovascular-associated populations, such as astrocyte-associated, endothelial, pericytic, mural, or other glial-adjacent cell types, depending on dataset and regional context. This differential distribution raises the possibility that indole decarboxylation and subsequent methylation may occur across adjacent cellular compartments rather than exclusively within single cells, but the exact methylating compartment remains unresolved.

In this proposed neuron-glia relay architecture, neuronal aromatic L-amino acid decarboxylase activity provides a plausible source of tryptamine generated from tryptophan within central neural compartments, consistent with evidence that endogenous tryptamine occurs in mammalian brain and exhibits rapid turnover (Juorio and Durden, 1984). Due to its non-hydroxylated structure and moderate lipophilicity, tryptamine would be expected to diffuse across short interstitial distances into neighboring glial microdomains. Within adjacent INMT-expressing non-neuronal or neurovascular-associated cells, sequential methylation could then generate N-methyltryptamine and dimethyltryptamine locally, although the proposed neuron-glia compartmental relay requires direct spatial and functional validation.

This process would not require vesicular packaging or classical synaptic release. Instead, it would operate through non-vesicular volume transmission within the glial-interstitial space (Syková and Chvátal, 2000), consistent with the broader ensemble model proposed in this work. Because glial cells also express significant monoamine oxidase activity, such microdomains would naturally enforce rapid degradation, ensuring that trace amine pulses remain transient and spatially constrained.

The hippocampus represents one relevant candidate site for this architecture rather than an exclusive or uniquely established locus. Neuron-astrocyte coupling in hippocampal circuits tightly regulates metabolic flux, neurotransmitter clearance, and interstitial diffusion, creating microdomains well suited for transient chemical signaling through volume transmission. Within the dentate gyrus, which is one of the few regions of the adult brain where neural stem cell populations and plasticity-related signaling pathways remain active (Kempermann, 2022), such neuron-glia metabolic interfaces may provide a plausible environment for transient trace amine ensemble pulses. Other regions with strong monoaminergic integration, trace amine relevance, or dense neuron-glia metabolic coupling may also prove important and should not be excluded by the present formulation.

Under this framework, localized dimethyltryptamine formation within neuron-glial microdomains would represent a conditional biochemical state rather than a persistent signaling molecule. The emergence of such pulses would remain governed by the same constraint architecture described throughout this manuscript: precursor partitioning, enzymatic permissiveness, and rapid clearance dominance.

Peripheral trace amine pulses generated within pulmonary and enteric relays may influence central ensemble dynamics through multiple routes. Non-hydroxylated indoles such as tryptamine and dimethyltryptamine possess physicochemical properties that permit limited passive diffusion across the blood-brain barrier. However, direct transport may represent only one component of the interaction. Pulmonary and enteric neuroendocrine systems are tightly coupled to central physiology through autonomic, immune, and metabolic signaling pathways. Transient peripheral trace amine pulses may therefore act not only as circulating signals but also as physiological triggers that alter precursor availability, enzymatic permissiveness, and glial metabolic state within the brain. Under this framework, peripheral relays do not merely deliver trace amines to the central nervous system; they may prime neuron-glia microdomains to assemble localized ensemble pulses.

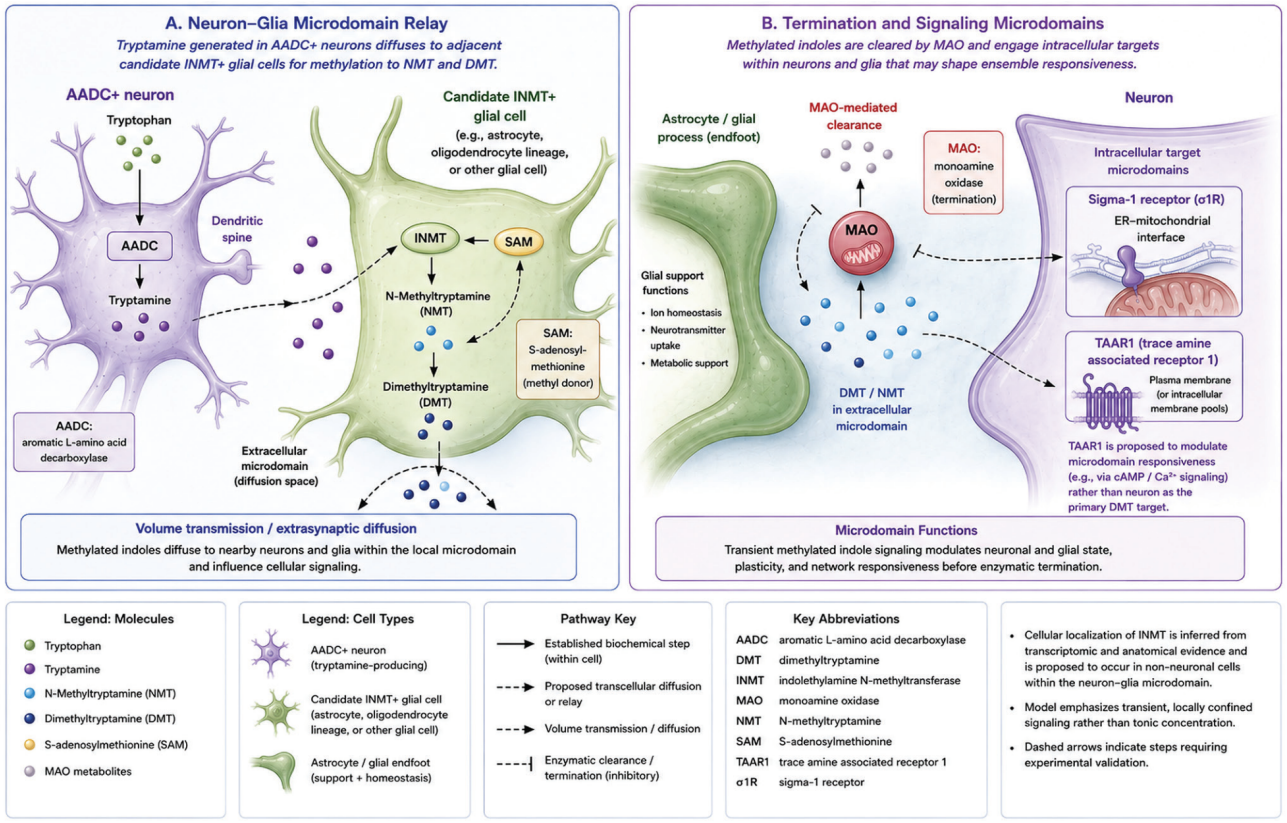

Figure 2. Proposed central neuron-glia microdomain relay for endogenous indole methylation.

Figure 2 summarizes the proposed central neuron-glia microdomain relay architecture, including neuronal decarboxylation, short-range tryptamine diffusion, candidate glial or non-neuronal INMT-dependent methylation, volume transmission, intracellular or receptor-linked target engagement, and MAO-mediated termination.

This schematic illustrates a proposed central relay in which AADC-positive neurons generate tryptamine from tryptophan within local neural compartments. Tryptamine may diffuse across the extracellular microdomain into adjacent candidate INMT-positive glial or non-neuronal cells, where SAM-dependent methylation could generate N-methyltryptamine and dimethyltryptamine (DMT), pending spatial and functional validation. Locally produced methylated indoles are proposed to act through volume transmission within constrained extrasynaptic microdomains, influencing nearby neurons and glia before rapid enzymatic termination. Astrocytic or glial processes are shown as clearance and homeostatic interfaces, with monoamine oxidase (MAO) limiting pulse amplitude and duration. Sigma-1 receptor and TAAR1-associated compartments are depicted as potential downstream or modulatory targets rather than proof of established endogenous DMT signaling. Solid arrows indicate established biochemical direction; dashed arrows indicate proposed diffusion, relay, volume-transmission, or clearance steps requiring experimental validation.

5.4 The 5-Hydroxyl Advantage: Physicochemical Gating and Passive Diffusion

A critical chemical distinction allows the pulmonary- and enteric-derived trace amine pulses to reach the brain while sequestering canonical monoamines in the periphery. Dimethyltryptamine and its primary precursor, Tryptamine, lack the 5-hydroxyl group that characterizes serotonin (5-HT) and bufotenine. In classical biochemistry, the presence of a hydroxyl group significantly increases molecular polarity, rendering the molecule a target for active transport systems while simultaneously creating a barrier to passive lipid-membrane penetration.

This physicochemical distinction can be quantified using Topological Polar Surface Area (TPSA) and lipophilicity, commonly expressed as the partition coefficient (LogP). The Blood-Brain Barrier (BBB) restricts passive diffusion based in part on molecular polarity, hydrogen bonding capacity, and lipid solubility. Compounds with a TPSA exceeding approximately 60-70 Å² generally demonstrate limited passive BBB penetration and often require carrier-mediated transport, particularly when highly polar or charged at physiological pH (Pajouhesh and Lenz, 2005).

Serotonin (5-HT), due to the presence of its 5-hydroxyl group, exhibits a TPSA of approximately 62.2 Å² (National Center for Biotechnology Information, 2026a) and low lipophilicity (LogP ≈ 0.2). In combination with predominant protonation at physiological pH, these properties confer poor passive membrane permeability, effectively restricting serotonin to peripheral compartments unless transported by specialized carrier systems.

In contrast, dimethyltryptamine (DMT) lacks the 5-hydroxyl group and incorporates N,N-dimethylation of the amine side chain, reducing TPSA to approximately 17.3 Å² (National Center for Biotechnology Information, 2026b) and increasing lipophilicity (LogP ≈ 2.5). Although DMT remains substantially protonated at physiological pH, protonation exists in dynamic equilibrium with a smaller unprotonated free-base fraction. Passive transcellular diffusion would be expected to occur primarily through this uncharged fraction rather than through the charged species. As the unprotonated fraction partitions into lipid membranes and crosses the barrier, the protonated and unprotonated pools re-equilibrate, allowing additional free-base molecules to become available for continued diffusion along the concentration gradient. However, this equilibrium is highly sensitive to local tissue pH. Microdomain-specific acidosis under hypoxic, ischemic, or inflammatory stress may shift a larger fraction of the pool toward the protonated state, creating localized proton-trapping effects. Such trapping would be expected to prolong intracellular or local tissue dwell time and potentially increase local intracellular target engagement, while simultaneously reducing immediate passive transcellular escape or systemic clearance. Therefore, DMT's low TPSA and higher lipophilicity support greater membrane partitioning potential despite partial protonation, while local pH state remains an important determinant of whether a pulse is locally retained or systemically transmitted (National Center for Biotechnology Information, 2026b; Spielvogel et al., 2025).

Consequently, the non-hydroxylated members of the ensemble are capable of greater passive diffusion across cellular membranes than hydroxylated indoles. While peripheral serotonin is constrained by polarity, protonation state, and BBB transport requirements, DMT exhibits greater membrane partitioning and passive diffusion potential relative to hydroxylated indoles (Spielvogel et al., 2025). This physicochemical profile would allow pulses generated in the pulmonary microdomain, specifically within the proposed PNEC-stromal relay, to access systemic circulation more efficiently than hydroxylated amines. By reducing dependence on vesicular storage or protein-mediated transport for membrane traversal, the proposed pulmonary relay architecture may function as a relatively efficient state-dependent delivery route for non-hydroxylated indoles. The absence of the 5-hydroxyl group is therefore best understood as a key determinant of the ensemble's membrane permeability profile, enabling peripheral non-hydroxylated indole pulses to more readily influence central neural states than hydroxylated counterparts while remaining subject to the broader metabolic constraints described throughout this manuscript (Wu et al., 2023).

VI. The Mechanics of Physiological Constraint

The trace amine ensemble described in the preceding sections does not arise from sustained synthesis, but from transient shifts in physiological constraint. Within this framework, the emergence of a DMT-dominant configuration reflects coordinated changes in metabolic partitioning, enzymatic permissiveness, and degradation pressure rather than tonic production. The pulmonary and enteric relay systems, neuron-glial metabolic microdomains, and physicochemical permeability constraints described above therefore define a continuous, distributed architecture governing ensemble formation. Figure 3 illustrates the constraint-based ensemble model as a state-space diagram in which precursor partitioning, enzymatic gating, methyl-donor availability, clearance dominance, inflammatory compression, hydroxylation bias, and peripheral routing determine whether trace amine flux remains suppressed, transient, or DMT-dominant.

This schematic summarizes how distributed physiological constraints are proposed to shift trace amine ensemble configuration between non-hydroxylated, DMT-favoring states and hydroxylated, serotonin-dominant states. The model treats ensemble output as a ratio-dependent state rather than a function of DMT abundance alone, with DMT-dominant configurations defined conceptually by enrichment of methylated non-hydroxylated indoles relative to competing trace amines and hydroxylated products, adjusted by local pulse duration and monoamine oxidase-mediated clearance pressure. Parameters such as tryptophan availability, AADC activity, INMT activity, S-adenosylmethionine availability, TPH activity, inflammatory tone, monoamine oxidase activity, redox state, and pulmonary versus enteric routing collectively bias pathway direction. Conditions favoring decarboxylation, methyl-donor sufficiency, lower inflammatory compression, and pulmonary relay access are predicted to increase non-hydroxylated indole representation. In contrast, inflammatory activation, increased TPH or MAO activity, low methylation permissiveness, and gut-wall or hepatic first-pass exposure are predicted to shift the ensemble toward hydroxylated indoles and degradation-dominant states.

Dashed arrows indicate predicted or context-dependent regulatory relationships requiring experimental validation.

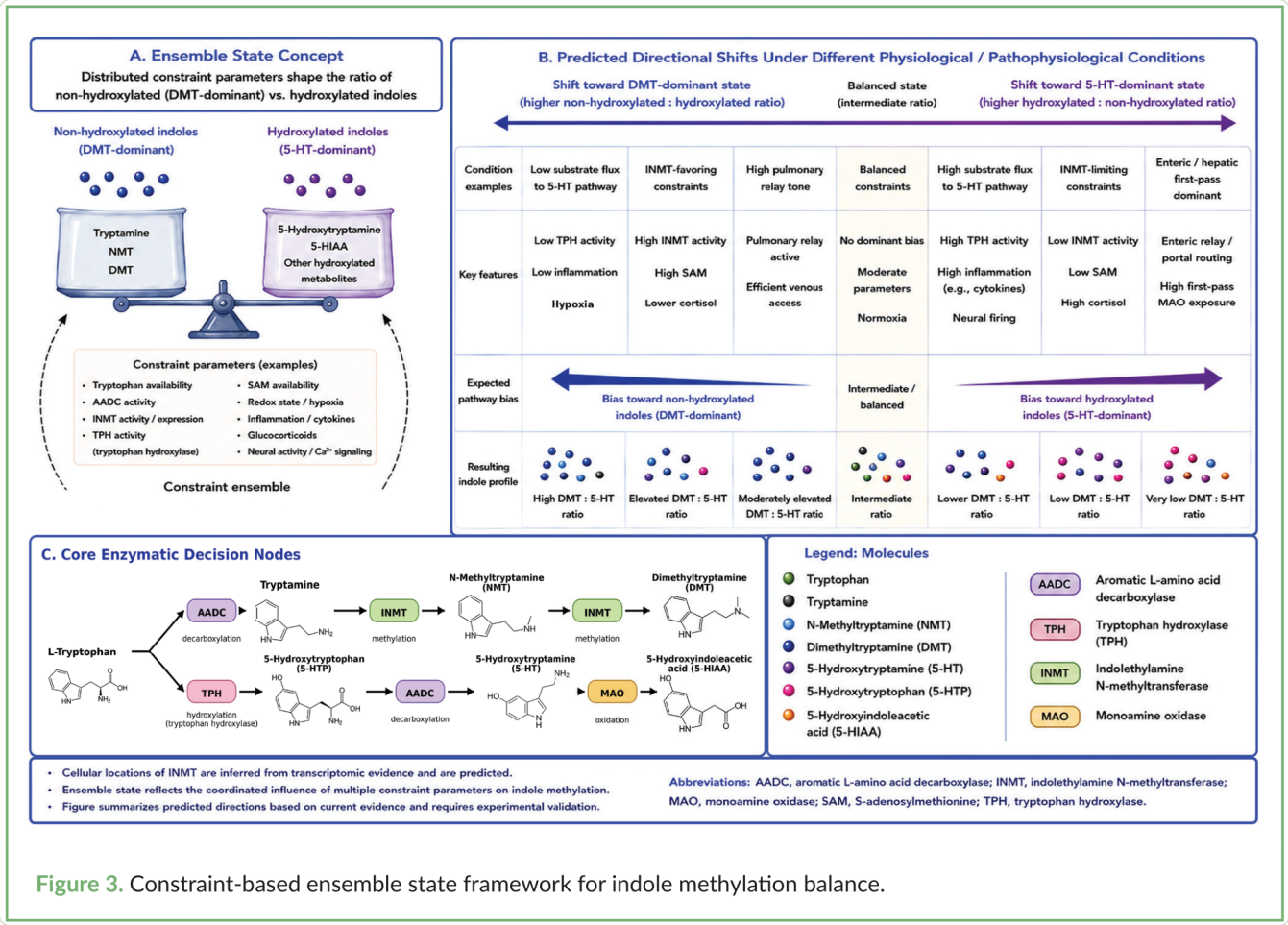

Figure 3. Constraint-based ensemble state framework for indole methylation balance.

6.1 Precursor Diversion and Flux Partitioning

Under baseline conditions, tryptophan is preferentially diverted toward the kynurenine pathway via indoleamine 2,3-dioxygenase (IDO), limiting availability for trace amine synthesis. During acute hypoxia or metabolic stress (Tsuji et al., 2023), this metabolic partition shifts away from competing pathways, permitting increased substrate flux toward decarboxylation and subsequent trace amine production (Mohapatra et al., 2021). Thus, ensemble emergence depends not solely on synthetic capacity, but on competitive pathway partitioning at the level of precursor allocation.

6.2 Enzymatic Gating and Oxygen Sensitivity

Synthesis is further constrained by oxygen-sensitive regulatory nodes. In the pulmonary relay model, AADC activity within PNECs is coupled to oxygen-sensing mechanisms (Gu et al., 2014). Under normoxic conditions, decarboxylation flux remains limited; under hypoxic stress, enzymatic permissiveness increases, allowing transient amplification of tryptamine production and downstream methylation (Bertoldi and Borri Voltattorni, 2000).

6.3 Methyl-Donor Availability as a Constraint on Methylation Flux

Enzymatic permissiveness depends not only on expression of the relevant enzymes and oxygen-sensitive regulatory states, but also on availability of the methyl donor S-adenosylmethionine. Because INMT-mediated conversion of tryptamine into N-methyltryptamine and dimethyltryptamine requires methyl transfer, local methyl-donor sufficiency represents a plausible constraint on whether increased decarboxylation flux can propagate into a methylated indole pulse (Tasker et al., 2012). Within this framework, SAM availability is not treated as a sole determinant of ensemble state, but as one gating variable that may interact with oxidative stress, nutritional state, and broader one-carbon metabolic conditions to influence methylation capacity. A physiological state that increases decarboxylation without supporting methyl-donor availability would therefore be expected to favor upstream trace

amine accumulation more than downstream dimethylated products.

6.4 Clearance Dominance and MAO Regulation

Monoamine oxidase activity within glial and peripheral compartments imposes rapid degradation pressure on indole and phenyl trace amines. Astrocytes, which express significant MAO-B activity and occupy much of the extracellular interface of neuronal circuits (Levitt et al., 1982), form extensive contacts with neuronal synapses and extracellular diffusion spaces and function as a distributed metabolic sink capable of rapidly degrading diffusible monoamines within interstitial microdomains.

Under lower-inflammatory conditions, this sink function remains present as part of baseline monoamine regulation but is expected to operate under less amplification than in reactive inflammatory states. The relevant contrast in this model is therefore not clearance versus no clearance, but baseline clearance dominance versus inflammation-amplified clearance dominance. Inflammatory amplification would be expected to shorten pulse duration, reduce pulse amplitude, and lower the probability that local ensemble states cross biologically consequential thresholds.

6.5 Amplification of Constraint

Pro-inflammatory cytokines, particularly IL-1β and TNF-α, induce reactive astrocytic phenotypes (Hyvärinen et al., 2019), and this shift toward astrogliosis is associated with increased monoamine oxidase-B expression and activity (Jaisa-Aad et al., 2024), effectively enhancing glial-mediated monoamine clearance within extracellular microdomains. Glial activation during inflammatory states is associated with altered monoamine metabolism, increased oxidative burden, and enhanced enzymatic degradation of trace amines. Concurrently, inflammatory activation of IDO initiates a profound metabolic pivot, shunting tryptophan toward the kynurenine pathway (Huang et al., 2020). Because the kynurenine cascade consumes large quantities of tryptophan and generates multiple downstream metabolites involved in redox regulation and NMDA receptor signaling, its activation represents a dominant metabolic sink for substrate that would otherwise be available for trace amine synthesis. This diversion does not merely deplete the substrate available for trace amine synthesis; it establishes a competing metabolic signature characterized by the accumulation of kynurenine pathway metabolites. Kynurenine itself functions as a signaling molecule through aryl hydrocarbon receptor activation (Grishanova and Perepechaeva, 2024), reinforcing inflammatory tone and stabilizing pathway activation, while downstream metabolites such as quinolinic acid contribute neurotoxic and excitotoxic pressure (Ting et al., 2009).

These reactive astrocytes act as the primary clearance regulators of the system, further compressing the ensemble through upregulation of MAO-B and alteration of interstitial geometry (Lei et al., 2017). By narrowing the volume of distribution and increasing enzymatic "sink" activity, this coordinated glial response ensures that any transient trace amine pulse is rapidly neutralized before it can achieve a DMT-dominant configuration.

These processes converge to amplify clearance dominance. The coordinated interaction between microglial substrate diversion into the kynurenine pathway and astrocytic upregulation of monoamine oxidase activity compresses the ensemble along both upstream and downstream axes. Reduction in available substrate limits synthesis, while increased enzymatic degradation shortens the temporal window of any transient pulse. In parallel, reactive astrocytes alter interstitial geometry, reducing diffusion volume and increasing effective sink strength. Under sustained inflammatory tone, trace amine pulses are therefore expected to be shorter in duration, lower in amplitude, and less likely to reach DMT-dominant configurations, reflecting a shift toward persistent degradation dominance rather than absence of synthesis.

If this framework is correct, chronic inflammatory conditions characterized by elevated microglial cytokine signaling (Zhang et al., 2010), persistent IDO activation (Wang et al., 2010), and increased monoamine oxidase expression (Beucher et al., 2024) are expected to suppress the probability, amplitude, and duration of transient state-shifting pulses. This reflects not an absence of synthesis, but sustained constraint at the level of ensemble ratio and temporal dynamics.

Such compression may represent a metabolic correlate of reduced adaptive flexibility within stressed systems. Whether this ensemble suppression contributes to clinical phenomena associated with chronic inflammatory states remains an open and testable question. In this context, the absence of detectable dimethyltryptamine in bulk measurements reflects constraint-driven suppression rather than absence of synthesis.

6.6 Peripheral Hydroxylation Bias as an Ensemble Suppressor

Inflammatory tone may also exert upstream constraint through preferential hydroxylation of tryptophan within peripheral neuroendocrine amine-handling systems. Enterochromaffin cells represent a major hydroxylation node via TPH1-dependent conversion of tryptophan to 5-hydroxytryptophan and subsequently serotonin. Inflammatory signaling has been associated with upregulated TPH1 expression and increased serotonergic output in peripheral neuroendocrine compartments (Kiziltug et al.,

2025), biasing substrate allocation toward hydroxylated indoles.

Pulmonary neuroendocrine cells, which share amine-handling and decarboxylation-associated neuroendocrine features with EC cells, are similarly capable of serotonergic synthesis and are responsive to hypoxic and inflammatory stress states (Pan et al., 2006; Wang et al., 2026). While quantitative shifts in hydroxylase expression within PNECs under inflammation require spatial validation, their stress reactivity suggests that peripheral hydroxylation flux may increase during inflammatory activation.

Under these conditions, tryptophan allocation becomes doubly constrained: diversion toward the kynurenine pathway reduces total substrate availability, while increased hydroxylation within neuroendocrine amine-handling compartments reduces the pool of non-hydroxylated intermediates such as tryptamine required for subsequent N-methylation. Even in the presence of INMT-positive endothelial or stromal microdomains, diminished non-hydroxylated substrate would suppress production of N-methyltryptamine and dimethyltryptamine.

This produces a coordinated ensemble shift in which hydroxylated indoles increase, while non-hydroxylated trace amines decline proportionally both upstream through substrate competition and downstream through MAO-mediated clearance. The net effect is compression of the non-hydroxylated ensemble and reduced probability of DMT-dominant pulses under sustained inflammatory tone.

6.7 Distributed Pulmonary Control of Tryptophan Metabolism Under Inflammatory Stress

Beyond epithelial neuroendocrine amine-handling compartments, inflammatory lung environments may expand hydroxylation capacity across multiple cellular populations. TPH1 expression has been identified not only in pulmonary neuroendocrine cells, but also in pulmonary arterial endothelial cells under stress-associated conditions (MacLean, 2018). Activated alveolar macrophages in inflammatory models further contribute to local tryptophan sequestration through IDO overexpression (Sadee et al., 2025). These findings suggest that serotonergic synthesis within the lung may become distributed across vascular compartments, while immune compartments reinforce substrate depletion during inflammatory activation.

Under such conditions, total pulmonary hydroxylation flux may increase via activation of existing PNECs, expansion of neuroendocrine cell populations, inducible TPH1 expression in endothelial cells, and inflammatory activation of resident macrophages. This distributed serotonergic capacity would further bias tryptophan allocation toward hydroxylated intermediates and away from non-hydroxylated indole substrates required for methylation pathways.

Importantly, inflammatory lung states are also associated with altered monoamine oxidase expression and increased oxidative stress within endothelial and immune compartments (Sommer and Schulz, 2021). The convergence of increased hydroxylation flux and elevated clearance activity creates a dual constraint on the non-hydroxylated trace amine ensemble. Even in the presence of INMT-positive stromal or endothelial microdomains, reduced availability of non-hydroxylated substrate combined with accelerated degradation would be predicted to suppress DMT-dominant pulses under sustained inflammatory tone.

VII. Testable Predictions

The constraint-based ensemble model generates experimentally testable predictions organized across spatial, metabolic, clearance, relay, and functional domains. These predictions are intended to test not merely whether ensemble members co-vary, but whether local ensemble states cross qualitative thresholds of ratio, duration, and spatial extent consistent with biologically consequential pulse configurations. For each domain, the relevant question is not only whether supporting observations can be obtained, but whether the results distinguish this framework from competing explanations. Accordingly, the predictions below specify both the outcomes expected if the model is correct and the findings that would weaken or refute specific components of the model.

7.1 Spatial Architecture Validation

In pulmonary and enteric tissues, high-resolution spatial mapping should reveal reproducible adjacency between AADC-positive epithelial or neuroendocrine compartments and INMT-positive stromal, endothelial, or glial-associated compartments if transcellular relay architecture is a valid component of the model.

A finding of widespread single-cell co-expression in the relevant peripheral cell populations would weaken the specific necessity of the relay formulation, even if it would still support local synthetic plausibility.

Conversely, failure to identify either reproducible adjacency or relevant co-expression in the proposed tissues would substantially weaken the peripheral relay component of the model.

In central tissue, spatial mapping should identify constrained neuron-glia or non-neuronal microdomains consistent with partitioned decarboxylation and methylation capacity. Failure to identify such compartmentalization would weaken the proposed central relay architecture.

7.2 Flux Coupling and Ensemble Co-Variation

During experimentally induced physiological state transitions such as hypoxia or metabolic stress, indole-derived trace amines and phenyl-derived trace amines should exhibit temporally coupled fluctuations consistent with shared upstream decarboxylase constraint.

If these compounds fluctuate independently across repeated state transitions, or if only one molecular subset changes while the others remain uncoupled, the ensemble formulation would be weakened in favor of more molecule-specific explanations.

This prediction distinguishes a coordinated trace amine ensemble model from a framework in which dimethyltryptamine, tryptamine, phenethylamine, and tyramine fluctuate as unrelated metabolic byproducts.

7.3 Hydroxylated versus Non-Hydroxylated Ratio Shifts

Under hypoxic versus inflammatory conditions, the ratio of non-hydroxylated indoles to hydroxylated indoles is predicted to shift in opposite directions. Hypoxic or acute metabolic stress states should favor relative expansion of the non-hydroxylated ensemble, while inflammatory states should favor compression through increased kynurenine diversion, hydroxylation bias, and enhanced clearance pressure.

Failure to detect directionally distinct ratio shifts under controlled perturbation would weaken the constraint-based ensemble model.

If hydroxylated and non-hydroxylated indoles change only in proportion to total tryptophan availability, rather than shifting according to state-dependent pathway allocation, the precursor-partitioning component of the model would require revision.

7.4 Clearance Dominance and Inflammatory Compression

In microdomain-resolved sampling paradigms, localized endogenous dimethyltryptamine or related indole methylamine signals should vary inversely with local monoamine oxidase activity more strongly than with precursor abundance alone.

If pulse amplitude and duration are explained primarily by precursor availability with little relationship to local clearance markers, the clearance-dominance component of the model would be weakened.

Acute inflammatory activation is predicted to reduce pulse duration and peak amplitude without fully abolishing synthetic plausibility, as assessed by INMT expression, spatial enzyme adjacency, or upstream flux markers.

If inflammatory activation fails to compress pulse-like signatures, or instead increases detectable persistence of the non-hydroxylated ensemble, the inflammatory compression component of the model would require revision.

Sustained inflammatory states are predicted to shift ensemble ratios toward degradation dominance, producing shorter, lower-amplitude pulses that may evade detection in bulk tissue assays.

7.5 Pulmonary Relay Validation

Under controlled hypoxic or stress paradigms, pulmonary venous blood should demonstrate transient enrichment of non-hydroxylated indoles relative to matched arterial samples if pulmonary microdomain synthesis contributes measurably to systemic flux.

This enrichment should be temporally restricted and should correlate with conditions favoring increased decarboxylation, reduced inflammatory compression, or altered pulmonary neuroendocrine activity.

Failure to detect any reproducible pulmonary venous enrichment under such conditions would weaken the pulmonary relay component of the model.

If pulmonary venous enrichment occurs without corresponding evidence of local AADC-INMT adjacency or relevant enzyme expression, the source of the signal would require alternative explanation.

7.6 Enteric Relay Validation

In enteric sampling paradigms, local enrichment of methylated indoles within intestinal tissue, myenteric-associated compartments, lamina propria microdomains, or portal circulation following defined luminal or metabolic perturbations would support enteric generation. However, absence of downstream systemic enrichment despite local or portal detection would remain compatible with strong gut-wall and hepatic first-pass degradation and would therefore weaken direct CNS-delivery interpretations more than local enteric generation itself.

The enteric relay should therefore be tested primarily as a local paracrine, neuroimmune, and motility-associated relay, with systemic escape treated as a secondary conditional possibility. Under conditions of high local production, reduced clearance dominance, favorable diffusion gradients, and sufficient microdomain dwell time, methylated indoles may enter intestinal lymphatic drainage or local non-portal capillary routes at low probability, partially bypassing hepatic first-pass monoamine oxidase exposure.

Detection of methylated indoles in intestinal lymph, mesenteric lymphatic outflow, non-portal systemic

capillary drainage, or myenteric-associated microdomains under defined perturbation would support the possibility of limited hepatic-bypass escape or local enteric signaling.

Failure to detect portal, lymphatic, non-portal, tissue-localized, or myenteric-associated enrichment under conditions predicted to favor enteric production would weaken the enteric relay component of the model.

If enrichment is detected locally but does not survive systemic dilution or clearance, the enteric relay would remain more consistent with local neuroimmune, motility-associated, or volume-transmission effects than with robust direct CNS delivery.

7.7 Functional Integration

In models of induced hypoxic stress, pharmacologic or genetic attenuation of Sigma-1 receptor signaling should reduce any neuroprotective effects that co-occur with transient increases in endogenous indole methylamine flux if Sigma-1-linked signaling is a functional downstream component of the ensemble state.

If such attenuation has no effect on the relevant physiological outcome despite preserved trace amine fluctuations, then Sigma-1-mediated functional integration would be weakened as an explanatory component of the model.

Similarly, perturbation of TAAR1-linked signaling should alter the modulatory context of ensemble activity if phenyl-derived trace amines contribute to local excitability or monoaminergic responsiveness.

If TAAR1 perturbation fails to affect ensemble-associated physiological outputs despite measurable phenyl trace amine fluctuation, the TAAR1-modulatory component of the model would require revision.

7.8 Pulse-Based Detection

Localized sampling methods such as microdialysis or other high-temporal-resolution detection techniques should detect transient ensemble spikes that are absent in bulk homogenate measurements if the system is genuinely pulse-based rather than tonic.

These spikes should be brief, spatially restricted, and state-dependent, with stronger detection probability during defined windows of reduced clearance dominance, increased decarboxylation flux, or altered pulmonary, enteric, or central microdomain activity.

If high-resolution local sampling fails to reveal transient spikes under conditions where the model predicts them, the pulse-based formulation would be substantially weakened.

If bulk homogenate measurements detect stable tonic elevations instead, the model would require revision away from a pulse-dominant framework and toward a more sustained concentration-based account.

VIII. Limitations and Conclusion

This manuscript presents a systems-level framework rather than a definitive mechanistic proof. Although transcriptomic evidence supports enzymatic colocalization in central compartments, peripheral microdomain methylation remains a hypothesis requiring high-resolution spatial and functional validation. The proposed pulmonary and enteric relay architectures depend on reproducible AADC-INMT adjacency, inducible flux conditions, and measurable downstream enrichment. In the enteric case specifically, even successful local or portal generation would need to be interpreted against expected gut-wall and hepatic first-pass degradation, which may sharply limit systemic or central availability. Failure to demonstrate such adjacency or conditional flux would directly challenge the relay component of this model. The regional emphasis within the central nervous system is also provisional. Although the hippocampus provides a useful exemplar of tightly coupled neuron-glia metabolic microdomains, the present framework does not establish it as the exclusive or primary locus of endogenous trace amine ensemble dynamics relative to other monoaminergic or integrative brain regions.

Similarly, the ensemble framework depends on demonstrable co-variation of indole- and phenyl-derived trace amines under defined physiological transitions and on evidence that these fluctuations cross biologically consequential thresholds of ratio, duration, and spatial extent. If ensemble members fluctuate independently, fail to exhibit ratio-based shifts under constraint manipulation, or remain confined to amplitudes or durations too limited to support local signaling effects, the central thesis would require revision.

This model is not intended to replace receptor-mediated accounts such as 5-HT2A engagement or intracellular Sigma-1 receptor modulation, but to explain the conditions under which such mechanisms would become endogenously relevant. Receptor-centered hypotheses remain plausible at the level of downstream effect, yet they do not by themselves resolve the upstream problem of when, where, and under what metabolic constraints endogenous indole methylamines are generated, preserved, or suppressed. The present framework therefore situates receptor interactions within a broader regulatory architecture governed by precursor partitioning, enzymatic gating, methyl-donor availability, clearance dominance, and inflammatory compression. Methyl-donor availability is included as part of enzymatic permissiveness, but the model does not yet quantify how one-carbon metabolic

state, nutritional variables, or oxidative stress affecting methylation capacity modulate local INMT-dependent flux across tissues. This methylation constraint is distinct from local monoamine oxidase-mediated clearance pressure, which acts downstream by shortening the amplitude and duration of any generated trace amine pulse. The emphasis shifts from sustained concentration to transient configuration, from isolated ligand activity to distributed metabolic constraint.

Physicochemical permeability constraints also require further qualification. Although the unprotonated free-base fraction of dimethyltryptamine is expected to drive passive membrane partitioning, this equilibrium is likely to be highly sensitive to local tissue pH. Microdomain-specific acidosis during hypoxic, ischemic, or inflammatory stress could shift the pool toward protonated species, creating localized proton-trapping effects that modulate diffusion, intracellular sequestration, or barrier transit.

Endogenous dimethyltryptamine is therefore best understood not as a missing classical neurotransmitter, but as a transient component of a regulated trace amine ensemble whose biological relevance emerges only when spatial architecture, metabolic permissiveness, and clearance restraint align. The explanatory power of this framework lies in its integration: central and peripheral synthesis, physicochemical gating at the blood-brain barrier, glial-mediated degradation, and inflammatory modulation converge to determine whether ensemble pulses remain suppressed, transient, or functionally consequential.

Reframing the question from "Is DMT present at meaningful concentrations?" to "Under what constraints does the ensemble become configuration-dominant?" offers a coherent path forward for experimental interrogation. By shifting focus from abundance to architecture, this model seeks to resolve longstanding ambiguities surrounding endogenous DMT and to ground its proposed biological relevance within measurable metabolic parameters.

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