# Challenges and Frontiers in Computational Metabolic Psychiatry.

**Anthony G. Chesebro[a,b], Botond B. Antal[a,b], Corey Weistuch[c], and Lilianne R. Mujica-Parodi[a,b,d,1]**

[a]Department of Biomedical Engineering and Laufer Center for Physical and Quantitative Biology, Renaissance School of Medicine, State University of New York at Stony Brook, NY USA; [b]Martinos Center for Biomedical Imaging, Massachusetts General Hospital, MA USA; [c]Department of Medical Physics, Memorial Sloan Kettering Cancer Center, NY USA; [d]Santa Fe Institute, Santa Fe, NM USA

**One of the primary challenges in metabolic psychiatry is that the disrupted brain functions that underlie psychiatric conditions arise from a complex set of downstream and feedback processes spanning across multiple spatiotemporal scales. Importantly, the same circuit can have multiple points of failure, each of which results in a different type of dysregulation, and thus elicits distinct cascades downstream that produce divergent signs and symptoms. Here, we illustrate this challenge by examining how subtle differences in circuit perturbations can lead to divergent clinical outcomes. We also discuss how computational models can perform the spatially heterogenous integration and bridge *in vitro* and *in vivo* paradigms. By leveraging recent methodological advances and tools, computational models can integrate relevant processes across scales (e.g., *TCA-cycle*, *ion channel*, *neural microassembly*, *whole-brain macro-circuit*) and across physiological systems (e.g., *neural*, *endocrine*, *immune*, *vascular*), providing a framework that can unite these mechanistic processes in a manner that goes beyond the conceptual and descriptive, to the quantitative and generative. These hold the potential to sharpen our intuitions towards circuit-based models for personalized diagnostics and treatment.**

## 1. Clinical Motivation for Control Circuit Models

Functional neuroimaging of psychiatric disorders of any type often reveals underlying dysregulation of connections between the frontal cortex and the striatum, both hubs that integrate diverse inputs into a controllable output (1–6). While psychiatric disorders often involve diffuse dysregulation throughout the brain, the commonality of connections to the frontal cortex and striatum center on two circuits in particular: the prefrontal-limbic (PFL) and corticostriatal (CS) circuits (3, 5, 7). Dysregulation of the PFL circuit can give rise to a host of emotionally dysregulated symptoms, ranging from extreme anxiety in generalized anxiety disorder (4, 5, 8) to impulsivity in schizophrenia (9, 10). Similarly, dysregulation of the CS circuit leads to learning deficits in many disorders ranging from neurodegenerative disorders like Parkinson's (11–13) to psychiatric conditions like major depressive disorder (14, 15).

However, although disorders may share identical neurobiological and metabolic circuits, even small deviations in these circuits' feedback when perturbed from homeostasis, typically at the microscale, can lead to profound differences in their ability to maintain allostatic regulation of emotional stress and mood (3, 6, 7, 16–18). The properties inherent in these circuits pose an essential challenge: standard statistical approaches like multiple linear regressions are typically unable to correctly parse the complex feedback these loops entail (7). In systems with cyclical connections, correlations alone are insufficient to identify which elements are dysregulated. Adopting a circuit-based approach, however, accounts for the complex interactions among brain regions, enabling the identification of the key drivers and not only aiding in diagnosing the actual disorder but also informing targeted treatment strategies. This is where traditional experimental techniques can fruitfully combine with approaches from complex systems, control systems, and dynamical systems to probe these dynamics further.

Here, we provide examples of neural circuits that have diverging dynamics in the face of different regulatory processes. We also examine the metabolic circuits that support the energy demands faced by these circuits as they are perturbed and how these metabolic circuits can also feedback to the layers above them to create additional dynamical instabilities. Through these examinations, we note that traditional statistical analyses, focused on correlative, results are likely insufficient to characterize the phenomena that drive functional differences where two disorders arise from the same underlying circuit dysregulated in different ways (e.g., sensitivity to perturbation in different regions). Using this as a motivation for computational models, we then discuss how these microscale and macroscale circuits have been modeled in the past and what these models hold for the future of computational metabolic psychiatry.

[1]To whom correspondence should be addressed. E-mail: mujica@lcneuro.org.



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## 2. Neural Control Circuits in Psychiatric Disorders

**A. Prefrontal-limbic circuit dysregulation in schizophrenia and generalized anxiety disorder.** The prefrontal-limbic (PFL) circuit, as we discuss it in this context, can be thought of as comprising frontal regions (both dorsolateral and ventromedial prefrontal cortex (dlPFC and vmPFC, respectively) and orbitofrontal cortex (OFC)) and the connections they have with the hippocampus, amygdala, and thalamus (Figure 1A) (4, 5, 19, 20). Collectively, these regions coordinate evaluation and response to stimuli carrying emotional valence (19–22), and through the frontal pathways connected to the corticostriatal circuit (discussed further below), give secondary input to learning (23, 24).

In the context of schizophrenia, two different, interacting forms of circuit dysregulation have been noted in literature: neurotransmitter imbalance (9, 23, 25, 26) and functional circuit discontinuity (11–13, 27–29). Neurotransmitter imbalance, particularly striatal overabundance of dopamine with potential prefrontal underabundance, has long been a focus of both research and treatment options in schizophrenia (23, 25). This is intrinsically linked to the reduced inhibitory feedback from glutamatergic projections from the cortex, and the modulation of GABA or NMDA receptors can also aid in modifying the course of schizophrenia (26). As GABA and dopamine form antagonistic feedback loops in their activity, balancing them therapeutically can be difficult (26). Dopamine therapy, for example, alters the concentration of GABA – particularly in the thalamus (9) – meaning that the relationship between cause and effect, even in treatment, can be difficult to disentangle. At a functional level, these effects are observable as a loss of synchrony between circuit regions, more prominent at some frequencies than others (e.g., beta and gamma oscillation synchrony loss (28)). This loss of coordinated circuit activity is particularly noticeable during task paradigms (11, 12, 29), where a lack of regulatory synchronization from the thalamus is noted. The end-stage results of this circuit imbalance are the behavioral and emotional sequelae of schizophrenia: psychosis, hallucinations or delusions, and the classic patterns of disordered thinking (11).

Contrasting this functional dysregulation with that seen in generalized anxiety disorder (GAD), there are markedly different dynamics even when the same neurobiological circuit is involved in the dysregulation (4, 5, 8, 19, 20, 22). In GAD, a more common pattern is hyperactivity of the amygdala (4, 21), with decreased synchrony between the PFC and the amygdala (22), indicating a lack of normal attenuation of response to emotionally valent stimuli. There is also increased involvement of the inferior frontal gyrus, responsible for the processing of ambiguous stimuli (5), indicating once again a failure of regulation in making decisive evaluations and a corresponding increase in uncertainty.

Unlike schizophrenia, which has well-developed hypotheses of neurotransmitter dysregulation (23), the picture in GAD is not as clear. There are proposed roles for both glutamatergic and serotonergic pathway dysregulation (30), and the heterogeneity of these results is mirrored in the various efficacy (or lack thereof) of neurotransmitter-modulating therapies (19). This points, however, to a key feature in the complexity of studying psychiatric circuits: **the same underlying neural circuits can be dysregulated in subtly different ways that lead to drastically different behavioral outcomes.**

**B. Corticostriatal circuit dysregulation in Parkinson's disease and mood disorders.** The corticostriatal (CS) circuit comprises interconnected regions in the frontal cortex (dlPFC, vmPFC), striatum (caudate, putamen), the pallidum (both internal and external), subthalamic nucleus, substantia nigra, and thalamus, together with the inputs from other regions integrated by these areas (Figure 1B) (6, 24, 31–34). The CS circuit is intimately connected to the PFL circuit, as they share prefrontal cortex connections in common, allowing for integration of emotional processing and learning (6, 34, 35). The CS circuit, however, functions as a feedback system to integrate new information and control, particularly in carrying out tasks requiring learning through repetition (14, 31, 36). In real-world tasks, this circuit coordinates goal-directed behaviors, and receiving reward from achieving goals is how reinforcement learning is accomplished (14, 37). In experimental paradigms, ambiguous learning tasks are ideal for probing the function or potential dysregulation of this circuit under different conditions (14, 15).

Early-stage Parkinson's disease is associated with memory deficits and decreased striatal volume, particularly in the putamen (38, 39). This volume loss accompanies the classic loss of dopamine in the dorsal striatum that drives the motor symptoms classically associated with Parkinson's disease (38, 40, 41). In the CS circuit, this targeted neurodegeneration causes decreased performance in reward-based learning tasks, particularly in the putamen, which exhibited decreased activity and functional connectivity even during unperturbed dynamics (e.g., resting-state fMRI) (42–44). In the context of mood disorders, by contrast, particularly bipolar disorder (BD) and major depressive disorder (MDD), there is noticeable disruption of the CS circuit, particularly in connections between the frontal cortical regions and the caudate (2, 6, 15, 36, 45). While circuit function has



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been implicated in these disorders and shown to increase in response to successful therapy (24, 37), it is also observed to correlate both with symptom severity (32) and with potential response to treatment (6).

As with the PFL circuit, the CS circuit provides another example of how the same circuit, when dysregulated in different ways, produces distinctly different behavioral profiles. The CS circuit also offers a promising entry point for diagnostic and therapeutic targeting, as it can be probed by simple learning tasks with rewards that translate both to human imaging and can be adapted for use in other species (6, 31).

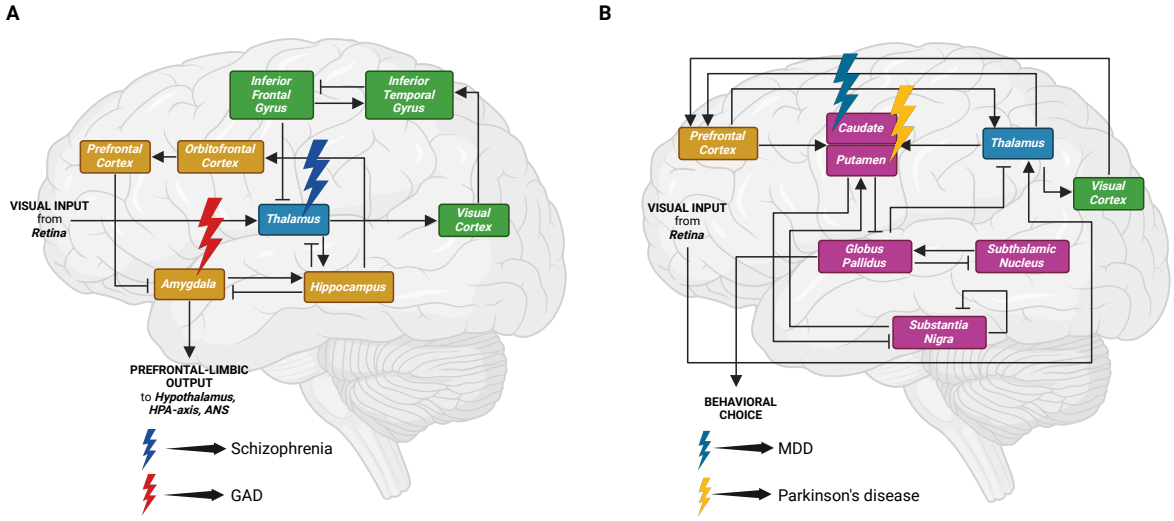


**Fig. 1. The same brain circuit can be disrupted in various ways, leading to different psychiatric conditions. A**: The prefrontal-limbic (PFL) control circuit (discussed in detail in Mujica-Parodi et al. (5)) modulates responses to perceived threats by moderating impulsive fear reactions through evaluative processes. Disruptions in this circuit have been implicated in both schizophrenia and generalized anxiety disorder (GAD). **B**: The corticostriatal (CS) control circuit (discussed in detail in Pathak et al. (31)) is responsible for decision-making processes by integrating sensory information and carrying associated motor control. Its dysfunction is associated with major depressive disorder (MDD) and Parkinson's disease, depending on how the circuit is compromised. Created with BioRender.com.

## 3. Microscale metabolic circuits

Neural circuits, which have been our focus, operate above subcellular mechanisms that form intricate networks of chemical reactions. These create a complex layer of metabolic circuits with close feedback with neuronal function. Because brain activity depends on both substantial energy and precise physiological conditions - conditions that are difficult to maintain simultaneously - neurons are highly sensitive to perturbations in these metabolic circuits. Consequently, metabolic pathologies can significantly contribute to the dysregulation of neuronal circuits underlying psychiatric conditions. This is evidenced by the three-fold higher odds of a chronic course of bipolar disorder in patients with Type 2 diabetes compared to those with normal glycemia (46). Therefore, metabolic regulatory circuits are essential to consider in the emergence of neurological dysfunction and psychiatric disorders.

There are two key aspects of this regulation we will consider here: the energetic demands of neuronal activity and the processes that fuel neurons. Through these pathways, **biochemical reactions can be dysregulated in ways that propagate to the abnormal neural functioning considered in the previous section and therefore are a key component of future computational models**.

**A. Energetic requirements of neuronal activity.** The primary energy-consuming processes of neuronal activity are maintaining ion gradients with ATP-dependent pumps and sustaining neurotransmitter pools (51, 52). To ensure an adequate energy supply for these functions, neurons tightly couple energy production with activity, extending beyond mere energy availability. This tight linkage is manifested in several processes, including an increase in regional blood flow in response to heightened brain activity, known as neurovascular coupling (53), and the approximately 1:1 coupling between neurotransmitter cycling and glycolysis via cytosolic redox balance (54) (Figure 2).

In addition to satisfying the overall high energy demands, the close coupling between neuronal activity and energy metabolism also accommodates the rapidly fluctuating energy requirements of neurons over time. During intense periods of activity, neurons must quickly increase their firing rate, leading to substantial



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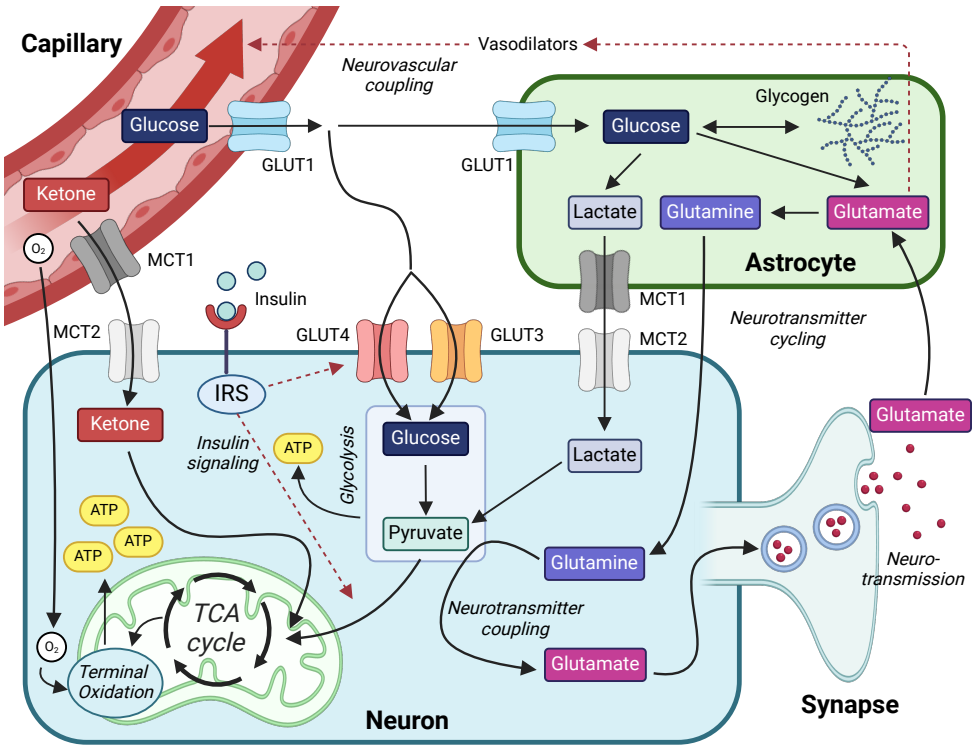


**Fig. 2. Energy metabolic pathways underlying neuronal function.** The brain relies on a continuous supply of energy substrates and oxygen from the blood. Glucose is the primary energy source for neurons (47), delivered through capillaries and taken up by neurons via various glucose transporters. In glycolysis, glucose is metabolized to pyruvate, producing a net gain of 2 ATP per glucose molecule. Pyruvate is then transported into the mitochondria, where it undergoes oxidation involving the TCA cycle and terminal oxidation, generating an additional 34-36 ATP molecules per glucose. Astrocytes have significant glycogen reserves that they can use to meet their own energetic needs. They also produce lactate from glucose, which can be shuttled to neurons for oxidation. After neurotransmitters are released into the synapses as part of neuronal signaling, about 80% of these neurotransmitters are recaptured by astrocytes and converted to glutamine (48). The reconversion of glutamine to glutamate is tightly coupled with neuronal glycolysis. Neurons have insulin receptors that regulate glucose uptake via insulin-dependent GLUT4 transporters and influence pyruvate metabolism following glycolysis (49, 50). Additionally, ketones serve as an alternative fuel for neurons. Their utilization bypasses glycolysis and directly enters the TCA cycle. Created with BioRender.com.

energy needs within short durations. Under such conditions, it has been shown that neurons adjust their metabolic processes to prioritize rapid ATP production over efficiency (55). Through the described coupling mechanism, where increased neurotransmitter cycling drives up glycolysis, neurons may shift their reliance toward aerobic glycolysis as the main source of ATP, also known as the "Warburg effect," instead of the slower-yield mitochondrial respiration (56).

The same coupling between neurotransmitter cycling and glycolysis is implicated in pathological conditions when neuronal energetic supply is impaired. Existing hypotheses suggest that a low-energy state due to impaired neuronal metabolism may increase glycolysis, leading to excessive glutamate cycling through this coupling mechanism (18). This abnormally high glutamate cycling results in hyperactivity, imposing elevated energy demands, further depleting energy levels, and creating a vicious cycle. This cascade may ultimately lead to a collapse of neuronal energetics, potentially underlying psychiatric conditions.

**B. Maintenance of neuronal energy supply.** Astrocytes, outnumbering neurons by approximately 1.5:1 in humans, play a crucial role in maintaining neuronal energy homeostasis and function (57). While neurons are highly specialized and sensitive compartments of the nervous system, astrocytes have evolved as more resilient and versatile compartments that support neurons in maintaining their precise conditions. Unlike neurons, astrocytes utilize a wider range of substrates, including acetate and fatty acids, and absorb harmful fatty acids from neurons to protect against oxidative stress (58). Astrocytes facilitate neurotransmitter cycling, which constitutes about 80% of the neurotransmitter flux, and synthesize the remaining 20% de novo from glucose (48). Furthermore, in contrast to neurons, astrocytes possess significant glycogen reserves that they can quickly utilize to fuel ion buffering and provide glucose for neurons (59). Additionally, through the lactate shuttle, they may provide lactate to neurons for oxidation (60). As such, impaired astrocytic function has profound implications for the metabolic homeostasis of the central nervous system.

A major candidate mechanism behind compromised neuronal energy supply is deficient oxidative mitochon-



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drial metabolism. While a definitive mechanistic link remains unclear, prolonged hyperinsulinemia leading to neuronal insulin resistance may contribute to diminished mitochondrial metabolism in neurons (61). Dysregulation of mitochondrial oxidative phosphorylation has been implicated in several psychiatric disorders and neurodegenerative pathologies, implicating this mechanism as a key feature for future study (16, 62–65). In addition to oxidative phosphorylation, insulin resistance may also hinder the cellular uptake of energy substrates. Neurons are limited in their ability to utilize various substrates for energy and primarily depend on glucose as their main energy source. Disruptions in insulin signaling can compromise glucose transport mechanisms, particularly affecting insulin-dependent uptake via GLUT4 in synaptic compartments where energy demands are highest (49, 50). This vulnerability exposes neuronal energy supply to dysregulated peripheral insulin homeostasis.

Ketones are a group of organic compounds that serve as an alternative energy source for neurons while using uptake processes that do not rely on insulin-dependent transporters (66, 67). This characteristic could mitigate challenges associated with impaired glucose uptake (68). Additionally, since ketone utilization bypasses glycolysis, ketones may help prevent neuronal energetic exhaustion caused by excessive neurotransmitter cycling due to hyperglycolysis (18, 69). Another potential consequence of decreased glycolysis is the activation of ATP-sensitive potassium channels, which can lead to hyperpolarization of the membrane potential (70). This hyperpolarization reduces neuronal excitability, helping to stabilize neuronal energetics. These phenomena may explain the observed therapeutic effects of ketones in patients with bipolar disorder (65, 71) or in age-related functional decline (72), although the exact mechanisms require further elucidation.

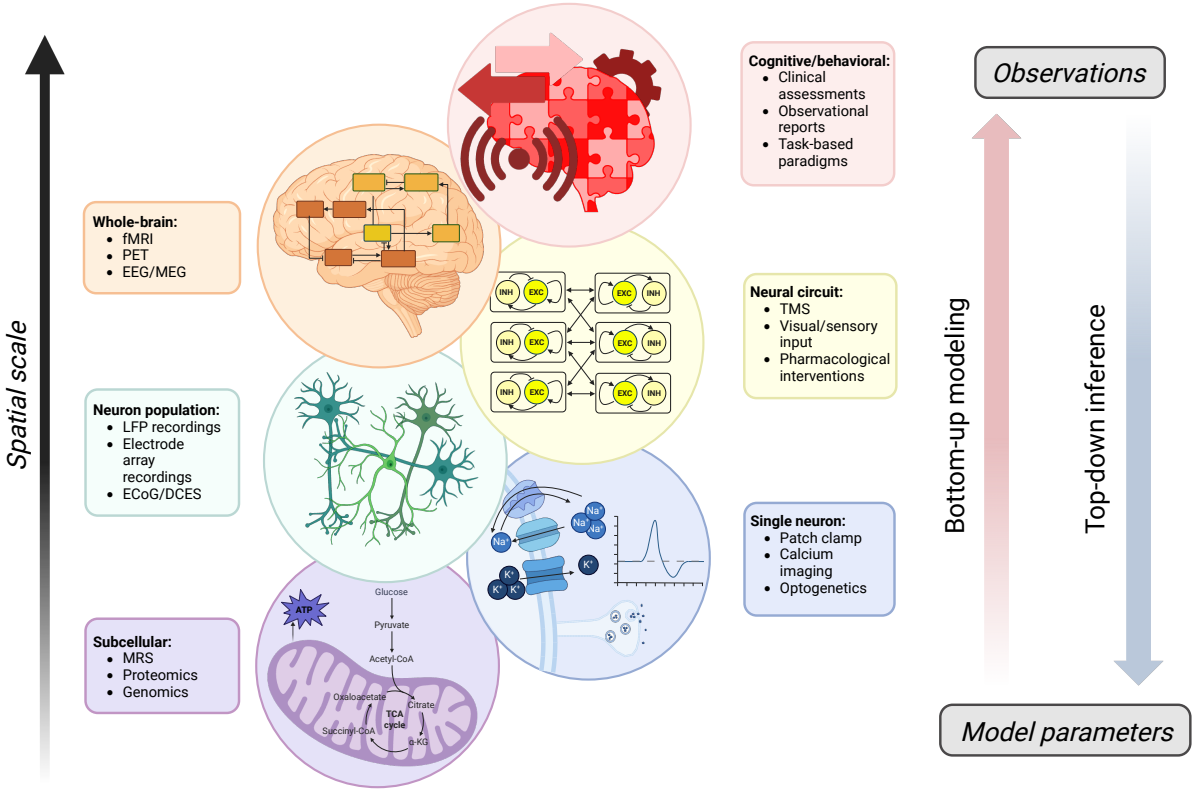


**Fig. 3. Diagram illustrating the multi-scale processes underlying brain function and behavior, with corresponding measurement modalities and fundamental modeling paradigms.** Abbreviations: fMRI: functional magnetic resonance imaging; PET: positron emission tomography; EEG: electroencephalography; MEG: magnetoencephalography, TMS: transcranial magnetic stimulation; LFP: local field potentials; ECoG: electrocorticography; DCES: direct cortical electrical stimulation; MRS: magnetic resonance spectroscopy. Created with BioRender.com

## 4. Computational Models of Psychiatric Control Circuits

Linking clinical conditions to their underlying cellular mechanisms is difficult because of inherent observational limitations *in vivo*. Instead, mechanisms are often investigated in more accessible experimental paradigms, often losing, however, translational applicability. To bridge the gap between candidate mechanisms and clinical conditions, mechanistic hypotheses must be translated to the scale of emergent, clinically observable features.



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**Computational models become essential in capturing the complex interactions among processes at different scales, as they provide a range of approaches for integrating disparate circuit elements and offering a framework for rapid testing.**

Multi-scale brain models, based on the premise of linking neuronal function with metabolism and scaling up to brain circuits, facilitate the comparison of candidate mechanisms with behavioral outcomes and neuroimaging data (73, 74). Additionally, the intermediate outputs of these models can be validated through metabolic assays (75). To be scientifically and translationally useful, models must make falsifiable predictions that can be tested with experimental data while giving mechanistic insights that were previously not directly observable. Broadly speaking, there are two categories of modeling approaches that can achieve this data-model synergy (Figure 3): **bottom-up modeling**, where models created from biological principles produce experimentally-testable predictions and **top-down modeling**, where data-driven techniques are used to directly fit model parameters to determine their functional form.

In this section, we discuss existing and emerging variations of both approaches. At the microscale level, we consider computational models of metabolic circuits: how these are tied to experimental data and how they lead to the emergent dysregulation of ion gradients at the spiking neuron level. At the macroscale level, we discuss how neural mass models - representations of the average activity of large neuronal populations that facilitate simulations at the whole-brain level - can be directly used to predict clinically observable outcomes in scenarios ranging from ion gradient depletion to pathologic plaque accumulation. Finally, we discuss new top-down modeling approaches that provide novel ways to fit mechanistic parameters from clinical datasets, laying the groundwork for greater accuracy in future models.

## A. Bottom-up approach: building models from microscale to macroscale.

***A.1. Microscale metabolic models.*** As discussed earlier, linking neuronal function with underlying metabolic pathways requires integrating processes across multiple scales (Figure 2). At the scale of subcellular metabolic reactions, representing chemical processes with ordinary differential equations ensures both accuracy and interpretability (**?** ). One method for constructing these differential equations involves using kinetic rate constants (**?** ). However, obtaining accurate estimates of these constants is challenging, as they can vary significantly across different species, phenotypes, and conditions (**? ?** ).

A more practical approach, given the current state of the field, is to utilize metabolic fluxes instead. Metabolic fluxes integrate kinetic rates and substrate concentrations to quantify the rate at which metabolites flow through a biochemical network, assuming steady-state conditions where metabolite concentrations are constant (**?** ). While the steady-state assumption limits their applicability, the primary advantage of metabolic fluxes is that they are readily measurable, unlike kinetic constants. The most commonly used techniques for this purpose are carbon labeling experiments, with $^{13}$C magnetic resonance spectroscopy (MRS) being the most widely employed for studying brain metabolism (**?** ). $^{13}$ MRS has consistently provided reliable estimates of neurotransmitter cycling, glycolysis, and the TCA cycle in humans (48).

Estimating metabolic fluxes relies on understanding stoichiometries, which describe the relative amounts of reactants in key energetic pathways (76). Stoichiometries are relatively well-established and consistent across species and conditions. By combining stoichiometric information with the assumption of steady-state conditions, metabolic fluxes within a reaction network can be constrained to the extent where measurements from $^{13}$C MRS can provide specific values (**?** ). Additional constraints can be applied using objective functions, such as maximizing ATP production, a core principle of flux balance analysis (FBA) (76), or maintaining the 1:1 ratio between neurotransmitter cycling and glycolysis (59).

A key limitation of metabolic fluxes is their reliance on the steady-state assumption, which makes them unsuitable for describing transient behaviors. Nevertheless, metabolic fluxes can be integrated with differential equation-based frameworks, and if used with an understanding of their limitations, they have significant potential to describe the mechanistic coupling between metabolic pathways and neuronal activity. This approach could remain valuable until advancements in the field enable more accurate estimation of kinetic rates.

The quantitative link between metabolism and neuronal activity can be established through ion concentrations and neurotransmitter fluxes. Ion gradients, determined by these ion concentrations, are essential for neuronal spiking, as described by Hodgkin-Huxley channel dynamics (77). Neuronal spiking depletes these gradients, requiring restoration by ATP-consuming pumps, thus providing feedback on energy metabolism (78). Additionally, the coupling of synaptic signaling with glycolysis creates a mutual feedback loop.

New models can also incorporate neurovascular metabolic coupling; for instance, a dynamic model of neurovascular coupling developed using flux balance analysis (79) enables the exploration of cerebrovascular dysfunction effects and their interactions with metabolic processes. These models also facilitate the accurate



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simulation of the hemodynamic response function, allowing comparison of simulated signals with blood oxygen level-dependent signals measured by fMRI.

***A.2. Macroscale models of emergent properties.*** Models informed by microscale metabolic parameters can be used to simulate activity across the entire brain in a variety of metabolic states, providing insight into how subcellular processes propagate to emergent phenomena that are clinically observable. Recent work (73) leveraged the Larter-Breakspear neural mass model (80, 81), which has been shown to capture ion gradient dynamics reflecting metabolic deficits (82), to demonstrate potential mechanisms of ketosis in the aging brain. When a variety of ion gradient imbalances were simulated to provide whole-brain EEG data, only potassium dynamics fully captured the loss of synchrony seen with aging in human EEG data as well as the synchrony following the administration of exogenous ketones (73). Previous work has shown that potassium channels are sensitive modulators of neuronal activity, particularly in the context of oxidative stress, and are implicated in many neurodegenerative conditions (83, 84). This modeling approach provides compelling evidence that this underlying neuronal phenomenon can propagate to observable changes in EEG synchrony, while ruling out similar ion-linked membrane changes.

Models can also be created to achieve more personalized medicine, where the underlying parameters are directly tuned to individual cases. Recent work has taken a traditional (Wilson-Cowan) neural mass model and tuned specific parameters to regional $\beta$-amyloid and tau deposition based on PET imaging in a cohort of patients with varying degrees of Alzheimer's disease (74). These models were then used to predict how cellular pathophysiology would impact individual whole-brain functioning, simulated as neuronal activity coupled with a BOLD observation function. Comparing the simulated results with fMRI measurements from the same individuals showed striking overlap, with regional differences between $\beta$-amyloid and tau being of particular interest as they contribute directly to theta and alpha band activity changes associated with the clinical presentation of Alzheimer's disease. As spatial maps of gene expression and receptor distribution become more widely available, they can further inform this process and enable the testing of hypotheses related to specific pathways (85, 86).

**B. Top-down approach: fitting microscale parameters from macroscale experiments.** While bottom-up modeling effectively tests whether hypothesized mechanisms lead to observed outcomes, it relies on strong *a priori* assumptions about model structure and relevant parameters. This can be a major limitation when not all parameters are observable, or of known functional form, as is frequently the case with multi-scale brain models. To overcome these limitations, a top-down approach can be employed to learn parameters and model structure directly from experimental data. Advanced optimization algorithms can facilitate an efficient exploration of possible parameter and model combinations, leading to a data-derived model rather than a more hand-crafted approach.

A common challenge for top-down approaches is that computational models are often overparameterized. Redundant parameters result in complex optimization landscapes that hinder convergence to the underlying solutions. A recently developed framework leverages deep learning to understand the entire landscape of a given model and reparameterize it with uniquely inferable composite parameters (75). This approach offers several benefits: it helps design future experiments by indicating which microscopic properties are expected to be resolvable through different experimental modalities, provided they can be simulated. Additionally, the method can be used to identify critical parameters in a circuit model and thus highlight the likely contributors to clinical outcomes before experiments are conducted. Finally, the composite representation obtained can be used with state-of-the-art optimizers to acquire unique parameter estimates from real data.

Taking lead from techniques in complex systems analysis, several emerging approaches to fitting microscale parameters from noisy macroscale data have been brought to bear in neuroscience domains (87, 88). One powerful approach is simulation-based inference, which leverages repeated simulations across a broad variety of parameter regimes to train a neural network that can then be used to give a probabilistic estimate of the underlying microscopic parameters given a specific observed timeseries (88–90). This approach has been successfully applied to estimating neural membrane parameters from patch-clamp data (88), and is actively being extended to include larger-scale data, including cognitive and behavioral timeseries, as additional inputs (91).

Finally, novel methods to extend more traditional circuit discovery techniques are emerging as ways to integrate microscale information into pipelines for fMRI data. As an example, dynamic causal modeling (DCM) techniques continue to be refined (92–95) to improve speed and flexibility on large datasets to integrate information from many different sites. Additionally, DCM has continued to prove fruitful in probing excitation-inhibition balance in the context of aging and dementia (96), and leveraging simultaneous fMRI and FDG-PET



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imaging has shown direct metabolic-involved circuits that can become dysregulated (97, 98), opening new avenues for future exploration.

## 5. Conclusion

One of the most enduring challenges in understanding the dysregulation of neural circuits in different psychiatric disorders is the fundamental conundrum of complex system interactions, where the same system dysregulated in subtly different ways gives rise to vastly different macroscale phenomena, observable both as neurovascular dynamics (EEG, fMRI) and cognitive symptoms. By shifting experimental and analytic paradigms to focus on computational modeling, techniques from complex systems analysis can finally be brought to bear on psychiatric problems, bringing in powerful new ways of disentangling tightly coupled pathways that have eluded complete characterization and harmonizing techniques to tie microscale changes to macroscale observables.

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