

Metabolic constraints shape hypersynchronous dynamics in spiking cortical microcircuit models

Received: 31 March 2026

Accepted: 15 June 2026

Published online: 27 June 2026

Cite this article as: Dadras D. & Park H. Metabolic constraints shape hypersynchronous dynamics in spiking cortical microcircuit models. *Sci Rep* (2026). <https://doi.org/10.1038/s41598-026-58596-7>

Daniel Dadras & Hae-Jeong Park

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

ARTICLE IN PRESS

© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Metabolic constraints shape hypersynchronous dynamics in spiking cortical microcircuit models

Daniel Dadras^{1, 2} and Hae-Jeong Park^{2, 3, 4, 5, *}

¹Goethe University Frankfurt, Frankfurt am Main, 60629, Germany

²Graduate School of Medical Science, Brain Korea 21 Project, Department of Nuclear Medicine, Department of Psychiatry, Yonsei University College of Medicine, Seoul, Republic of Korea

³Center for Systems and Translational Brain Science, Institute of Human Complexity and Systems Science, Yonsei University, Seoul, Republic of Korea

⁴Department of Cognitive Science, Yonsei University, Seoul, Republic of Korea

⁵Brain Research Institute, Epilepsy Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea

*parkhj@yonsei.ac.kr

ABSTRACT

Neuronal activity depends on ATP-consuming ion homeostasis, yet the circuit-level consequences of impaired energy availability remain difficult to isolate experimentally. Existing seizure models often represent metabolic effects indirectly or at single-cell scale, leaving unclear how cellular energetic stress can alter structured cortical network dynamics. Here, we tested whether coupling intracellular energy availability to neuronal excitability is sufficient to destabilize baseline cortical activity and generate seizure-like synchronization. We extended the Adaptive Exponential Integrate-and-Fire model with a normalized energy variable governed by explicit production and consumption terms, fitted layer-specific parameters to human cortical current-clamp recordings, and embedded the model in a laminar cortical microcircuit. Reduced ATP production shifted the network from stable asynchronous baseline activity into a low-ATP burst-synchronized state characterized by reduced mean firing rates, increased Fano factor, and high-amplitude LFP-like oscillations. Increasing inhibitory synaptic conductance during persistent metabolic stress suppressed burst synchrony without restoring the metabolic state variable, producing an inhibition-stabilized low-energy state. Forward-backward parameter sweeps suggested history-dependent changes in burst synchrony, most consistently during inhibitory conductance modulation, although these effects were readout- and dwell-time dependent. Together, these results provide a scalable spiking-network framework for studying how metabolic constraints shape cortical stability and for distinguishing suppression of seizure-like electrical activity from recovery of the underlying metabolic state.

Introduction

Epilepsy is one of the most prevalent neurological disorders in children and adolescents, characterized by abnormal oscillatory synchronization of neuronal activity which may stop spontaneously or persist until clinical or experimental intervention^{1,2}. Recently, a growing body of research has highlighted the role of neuronal energy metabolism. Seizures are associated with extremely high metabolic demand, yet conditions of metabolic insufficiency, such as hypoxia, mitochondrial dysfunction, or impaired glucose metabolism, have also been shown to increase neuronal excitability and promote epileptiform activity³⁻⁵. Experimental studies further show that restricting glucose availability or impairing mitochondrial energy production can lower the seizure threshold and induce hyperexcitability in otherwise healthy neurons⁵. Moreover, therapies targeting the metabolic axis of epilepsy in the form of ketogenic diet or metabolic enzymes and products have been of increasing interest^{6,7}. Theories attempting to explain this hyper-excitable state have primarily focused on ion-channel interactions⁸, network properties⁹ and synaptic imbalances¹⁰.

The precise relationship between energy availability and the mechanisms governing seizure initiation and termination remains incompletely understood. Computational modeling provides a powerful framework for investigating these interactions. Some studies estimate neuronal energy consumption by linking ion currents and action potentials to their associated metabolic costs¹¹⁻¹⁴. These inferred estimates have provided valuable insights into the energetic efficiency of neural coding and information processing, as well as the metabolic demands of individual neurons^{14,15}. In contrast, generative models that explicitly incorporate energy dynamics allow the simulation of how energy production and consumption modulate neural activity. For example, detailed compartmental models of neuron–glia interactions have shown that disruptions in ion homeostasis can induce seizure-like activity under ischemic conditions^{16,17}.

Fardet and Levina¹⁸ introduced a metabolic extension of the Adaptive Exponential Integrate-and-Fire model (mAdExp) to capture the coupling between a neuron's resting membrane potential and its internal energy state. Their formulation represented an important step toward incorporating metabolic dynamics into simplified neuron models and successfully reproduced a range of single-neuron behaviors. However, the model was primarily limited to isolated neurons and small, unstructured networks, limiting the exploration of population-level mechanisms underlying seizure generation. Because the focus was not on network dynamics or realistic bioelectrical signals, the model did not examine how metabolic coupling reshapes structured cortical network dynamics relevant to seizure-like synchronization.

In this paper, we modify the mAdExp framework by treating intracellular energy as a bounded normalized state variable governed by activity-dependent consumption, finite recovery and production, and coupling to ATP-dependent membrane homeostasis. We further embed the model within a biologically inspired network architecture based on the Cortical Microcircuit (CMC), which includes excitatory and inhibitory neurons, diverse synaptic dynamics, and structured connectivity¹⁹. Unlike randomly connected networks, the CMC captures key biological principles such as laminar-specific excitation and inhibition, feedforward and feedback loops, and layer-dependent synaptic properties. These anatomical and functional structures provide a more realistic substrate for studying how local excitation-inhibition balance and laminar recurrence contribute to seizure-like synchronization^{20–22}. The goal of this study is to explore three main research questions: (i) Can the extended single-neuron model reproduce experimentally observed cortical voltage responses? (ii) How do the single-cell and network model behave in the metabolic parameter space? (iii) How does reduced ATP production affect cortical microcircuit dynamics, and can enhanced inhibition suppress the resulting burst synchrony without restoring the metabolic state?

In summary, this framework allows us to test whether metabolic constraints can destabilize stable asynchronous baseline activity, drive seizure-like synchronization, and whether enhanced inhibitory conductance can suppress these dynamics without restoring the baseline metabolic state.

Results

Overview of the modified mAdExp energy-feedback mechanism

The first step of this study was to modify the metabolic adaptive exponential integrate-and-fire model so that cellular energy availability could be manipulated directly in network simulations. The two main innovations relative to the original mAdExp framework are the explicit separation of energy production and consumption through accessible metabolic parameters, and the embedding of this energy-feedback mechanism in a structured cortical microcircuit network. The original mAdExp formulation introduced an internal energy variable that couples energetic state to neuronal excitability. Here, we retain this principle but reformulate the energy dynamics in terms of explicit production and consumption processes, allowing metabolic stress to be applied as a reduction in energy production rather than only as an abstract displacement of the energy nullcline.

The resulting model structure is summarized schematically in Fig. 1a. Changes in ϵ feed back onto excitability through two main pathways. First, through the coupling parameter d_ϵ , reduced energy availability shifts the effective leak potential E_L , linking metabolic state to membrane potential dynamics. This pathway can promote spiking when energy depletion depolarizes the effective resting state. Second, low energy increases the ATP-sensitive component of the adaptation current, which provides a counteracting activity-limiting influence. In addition, when ϵ falls below the energy-viability threshold ϵ_c , spike generation is suppressed by the model's energy-viability condition. The model can therefore express both depolarizing positive feedback and low-energy firing suppression, depending on the balance between these mechanisms.

This same energy-feedback mechanism was then embedded in the cortical microcircuit model. In the temporal perturbation protocol summarized in Fig. 1b, the network was first simulated under baseline conditions, then ATP production was reduced to induce metabolic disruption. While ATP production remained reduced, inhibitory conductance was transiently increased. GABAergic conductance was then returned to baseline before ATP production was restored. This protocol was used to test whether metabolic disruption can induce seizure-like network synchrony and whether enhanced inhibition can suppress the electrical expression of that disrupted state without immediately restoring the metabolic state variable ϵ .

The following sections first examine which metabolic parameters most strongly shape single-neuron behavior, then fit representative spiny neurons from different cortical layers, and finally embed the fitted model in a structured cortical microcircuit to test whether metabolic perturbations can destabilize stable asynchronous baseline activity.

Single-neuron modified mAdExp model

We first used single-neuron sensitivity analyses to identify which metabolic parameters most strongly shaped modified mAdExp behavior. Each parameter was increased or decreased by 20% around its baseline value while all other parameters were held fixed, and the resulting spike trains were summarized by firing rate, mean metabolic state, coefficient of variation (CV), Shannon entropy (SE), and mutual information (MI).

This analysis showed that the dominant contributors to firing rate and spike-train statistics were the ATP production rate α_{ATP} , the adaptation-related energy cost γ , the pump-efficiency parameter α_P , and the metabolic coupling strength d_ϵ (Fig. 2a).

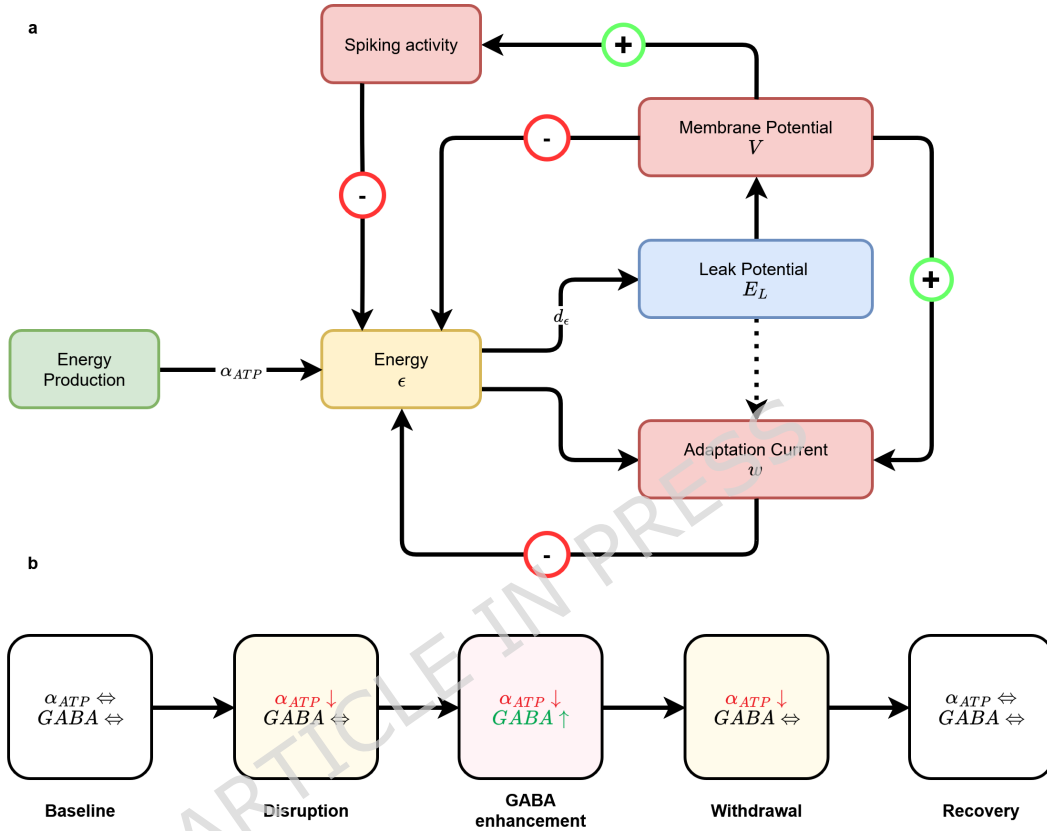


Figure 1. Conceptual overview of the modified mAdExp energy-feedback mechanism and disruption protocol. **a** The modified mAdExp model couples a normalized intracellular energy variable, ϵ , to neuronal excitability. Energy production, scaled by α_{ATP} , increases ϵ , whereas membrane depolarization, adaptation current, and spiking activity increase energy demand and reduce ϵ . Through the coupling parameter d_ϵ , reduced energy availability shifts the effective leak potential E_L , thereby linking metabolic state to membrane potential dynamics and spiking activity. The leak potential and adaptation current provide opposing energy-dependent influences on excitability: reduced ϵ depolarizes E_L and can promote spiking, while low-energy activation of the adaptation current provides a counteracting activity-limiting brake. Plus and minus symbols indicate the dominant sign of each interaction in the model. **b** Schematic of the disruption protocol used in the network simulations. After stable asynchronous baseline activity, ATP production was reduced to induce metabolic disruption. In the GABA enhancement phase, inhibitory conductance was transiently increased while ATP production remained reduced. GABAergic conductance was then returned to baseline before ATP production was restored during recovery.

Whereas α_{ATP} , γ , and α_P primarily determine the balance between energy supply and demand, d_ϵ controls how strongly changes in energy availability are translated into membrane excitability.

Because these parameters act through coupled production, consumption, and excitability pathways, we next varied selected parameter pairs over 30–300% of their baseline values (Fig. 2b). Stronger metabolic coupling combined with reduced production or increased demand increased firing rates while leaving the mean metabolic state comparatively stable. CV showed no consistent monotonic pattern, whereas Shannon entropy and mutual information broadly followed the firing-rate structure, suggesting that metabolic parameters shape both excitability and spike-output variability in the single-cell model.

To constrain the model with biologically grounded parameters and provide layer-specific values for the network simulations, the model was fitted to electrophysiological recordings obtained from the Allen Cell Types Database (specimen ID H17.06.003)²³. Fig 3 showcases comparisons between real and simulated data for one spiny neuron from each of cortical layers 3 to 6; the resulting layer-specific intrinsic parameters were then assigned to both excitatory and inhibitory neurons in the network model. The fitted model reproduced delayed firing and a progressive increase in firing during sustained current injection. Notably, currents that do not elicit an action potential still exert a significant influence on energy metabolism within the model.

Network level simulations of the modified mAdExp model

To investigate the population-level behavior of the energy-dependent neuron model, we embedded the fitted modified mAdExp neurons in a cortical column microcircuit comprising approximately 8,000 neurons across four layers (L2/3, L4, L5, and L6), each represented by excitatory and inhibitory populations. Connectivity probabilities were derived from the Potjans-Diesmann microcircuit model¹⁹, and layer-specific intrinsic parameters were assigned from the single-neuron fits described above.

Under baseline conditions with Poisson background input (3 Hz), the network remained in a stable, non-bursting regime (Fig. 4). The raster plot showed sparse, uncoordinated firing across layers. To distinguish population asynchrony from single-neuron irregularity, we quantified spike-time irregularity using the per-neuron ISI coefficient of variation (ISI CV). The baseline global ISI CV was 0.3489, which is below the values typically associated with classical asynchronous-irregular states in balanced-network models ($CV \approx 1$)⁴⁷. We therefore interpret the baseline as a stable asynchronous regime rather than a canonical asynchronous-irregular state²⁴.

Population firing rates stabilized at layer-specific levels reflecting the connectivity and intrinsic excitability of the circuit; L5 excitatory neurons showed the highest excitatory firing rates, consistent with their role as a major output population, while inhibitory populations generally fired at higher rates than their corresponding excitatory populations.

The metabolic state variable ϵ also remained stable across all populations and stayed above the model-defined energy-viability threshold $\epsilon_c = 0.15$ (Fig. 4), below which spike generation is suppressed. Thus, under baseline network activity, ATP production was sufficient to balance activity-dependent energy consumption, maintaining a stable operating point without spontaneous burst synchronization or runaway excitation.

To assess the stability of the cortical column and identify mechanisms leading to pathological states, we next performed a one-parameter-at-a-time sensitivity analysis at the network level. Four control parameters were scaled from $0.3 \times$ to $2.0 \times$ their baseline values: the energy production rate (α_{ATP}), the metabolic coupling strength (d_ϵ), and the synaptic conductances for NMDA (g_{NMDA}) and GABA (g_{GABA}). For each perturbation, the network response was quantified using firing rate, mean metabolic state, coefficient of variation (CV), Shannon entropy (SE), Kuramoto synchrony, and mutual information (MI) (Fig. 5).

Reducing the energy production rate α_{ATP} lowered the mean metabolic state (Fig. 5b) and, at stronger reductions, was associated with increased network synchrony (Fig. 5e). This low-ATP synchronized regime was accompanied by a reduction in mean firing rate rather than a uniform increase in activity (Fig. 5a), consistent with the low-ATP burst-synchronized state observed in the temporal disruption protocol.

Changing the metabolic coupling parameter d_ϵ produced a different effect. Increasing d_ϵ made membrane excitability more sensitive to energy fluctuations and increased network synchrony while leaving the mean metabolic state comparatively stable (Fig. 5b,e). Thus, α_{ATP} and d_ϵ affected network stability through complementary routes: one by reducing available energy, the other by strengthening the translation of energy changes into excitability changes.

Synaptic perturbations shifted the network along more conventional excitation-inhibition axes. Increasing g_{NMDA} elevated firing rate and synchrony, whereas increasing g_{GABA} reduced firing rate and tended to suppress synchrony (Fig. 5a,e). The information-theoretic summaries changed more modestly, but lower SE and MI in more synchronized regimes suggest that pathological synchronization was associated with more stereotyped population activity under the present estimator (Fig. 5d,f).

Metabolic disruption induces low-rate burst synchrony

We next asked how the cortical microcircuit responds over time to a sustained reduction in energy production and whether enhanced inhibition can suppress the resulting electrical activity while the metabolic deficit persists. In the temporal perturbation protocol, ATP production was reduced to $0.3 \times$ baseline in superficial layers (L2/3 and L4) and $0.5 \times$ baseline in deep layers

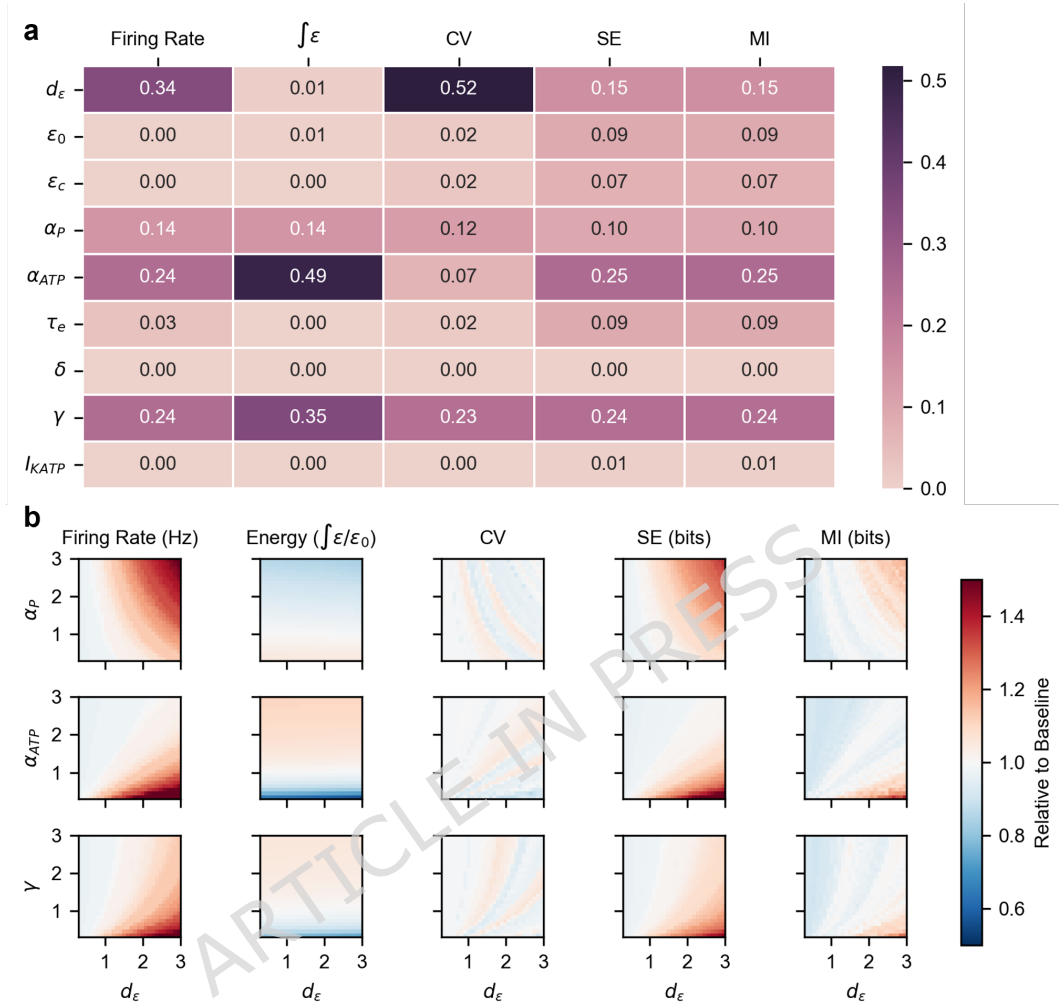


Figure 2. Local perturbation analysis in the single-cell model. **a** Sensitivity heatmap demonstrating the impact of $\pm 20\%$ perturbation in metabolic model parameters on biological and information-theoretic performance of a single modified mAdExp neuron with an Ornstein-Uhlenbeck noise input. Rows correspond to perturbed parameters: metabolic coupling strength (d_ϵ), baseline metabolic state (ϵ_0), energy-viability threshold (ϵ_c), pump efficiency (α_P), ATP production rate (α_{ATP}), energy relaxation time (τ_e), per-spike energy cost (δ), adaptation energy cost (γ), and maximal K-ATP current (I_{KATP}). Columns represent output metrics: firing rate (Hz), normalized mean metabolic state ($\int \epsilon$), coefficient of variation (CV) of inter-spike intervals, Shannon entropy (SE) of spike words (bits), and mutual information (MI) between noise input and spike output (bits). Mean absolute deviations are depicted. Values are normalized such that each column sums to 1. **b** Two-dimensional perturbation grids showing the joint effect of parameter pairs on cellular performance. Rows show different parameter interactions: pump efficiency (α_P) vs. metabolic coupling (d_ϵ), ATP production (α_{ATP}) vs. metabolic coupling (d_ϵ), and adaptation energy cost (γ) vs. metabolic coupling (d_ϵ). Columns represent firing rate, mean metabolic state, CV, Shannon entropy (SE), and mutual information (MI). All metrics are normalized relative to the baseline parameter set (center of each grid). Note that the x- and y-axes depict the relative change, not the absolute values

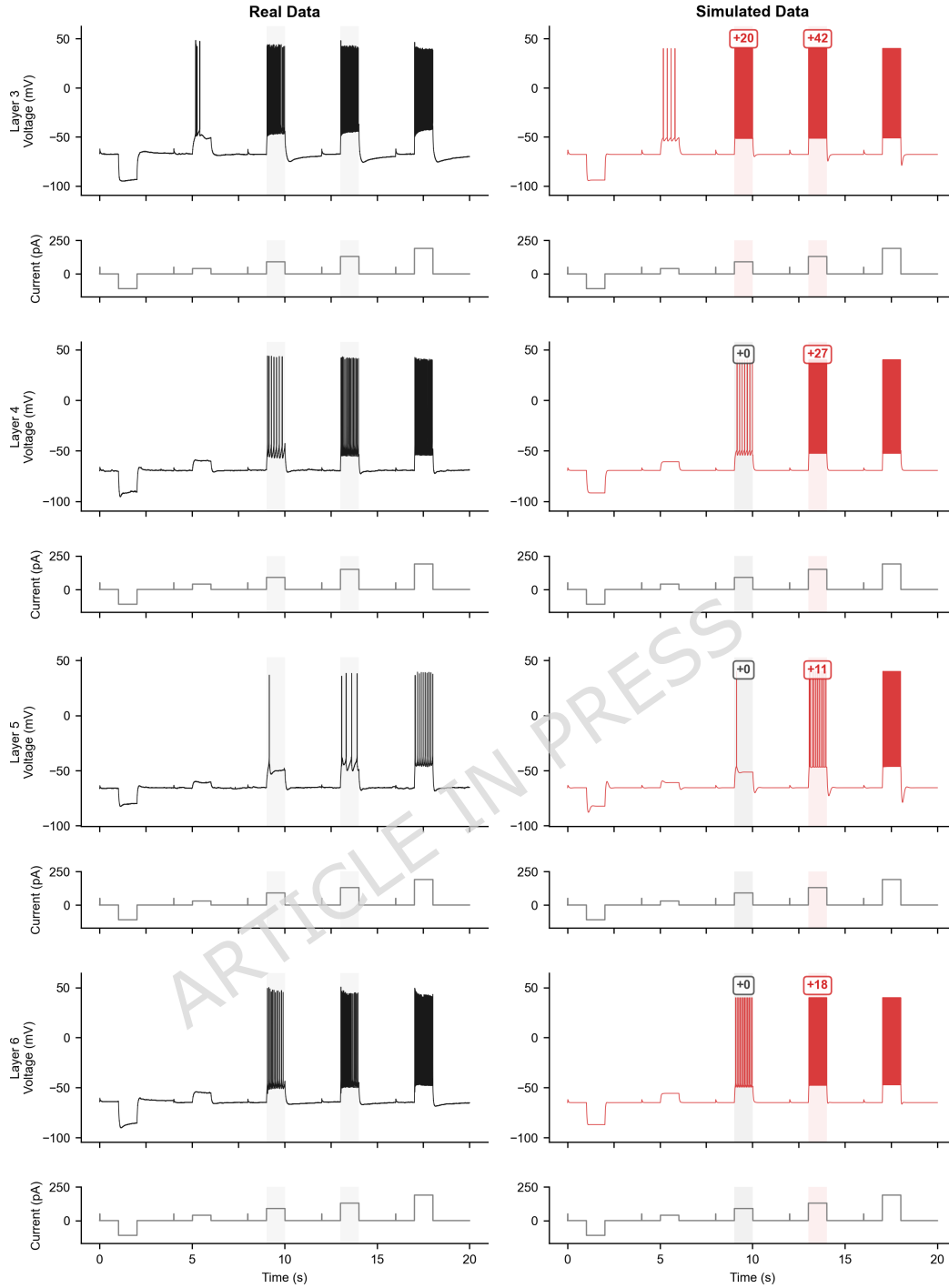


Figure 3. Fitting and Validation of modified mAdExp neurons to recorded voltage tracings. Validation of the Metabolic Adaptive Exponential (mAdExp) model against electrophysiological recordings from different cortical layers. **Left Column (Real Data):** Intracellular voltage traces recorded from excitatory neurons across Layers 3, 4, 5, and 6 (rows) in response to fluctuating current injection shown below each respective trace. **Right Column (Simulated Data):** Response of the mAdExp model using layer-specific parameters optimized via a Nelder-Mead minimization. To validate the fit quality, the spike counts of the second and third positive-current pulses in each recording (shaded vertical bands) are compared between simulated and experimental data. Numerical values above the simulated traces denote the deviation (Simulated – Recorded spike count). Selected cell tracings from the Allen Cell Types Database from a single donor (H17.06.003, middle temporal gyrus, 23yo female with epilepsy).

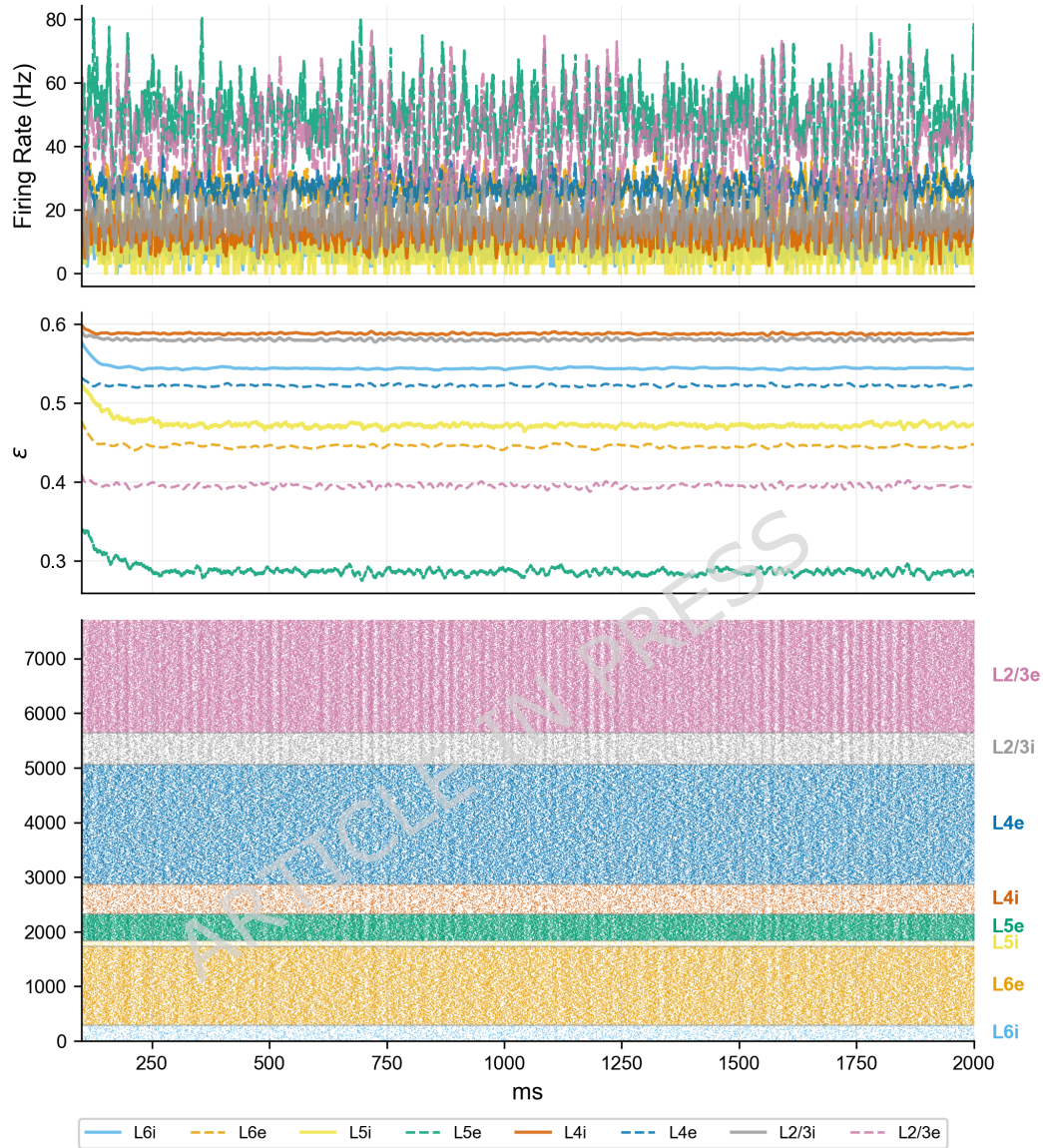


Figure 4. Network performance and metabolic stability in the cortical column. Baseline activity and metabolic state of the 8-population cortical microcircuit (L2/3, L4, L5, L6; excitatory/inhibitory) simulated using the Potjans-Diesmann microcircuit model.¹⁹ (Top) Mean population firing rates smoothed with a 10 ms moving average. Each population receives Poisson background input (3 Hz) to sustain baseline activity. (Middle) Trajectories of the metabolic state variable ε for each population. ε remains stable above the model-defined energy-viability threshold ε_c , indicating a balance between ATP production (α_{ATP}) and activity-dependent consumption under baseline conditions. (Bottom) Spike raster plot showing firing activity across the simulated cortical column. Horizontal lines separate the eight cell populations. Distinct laminar patterns emerge from the recurrent connectivity structure, with inhibitory populations (dashed lines in top/middle panels) providing gain control.

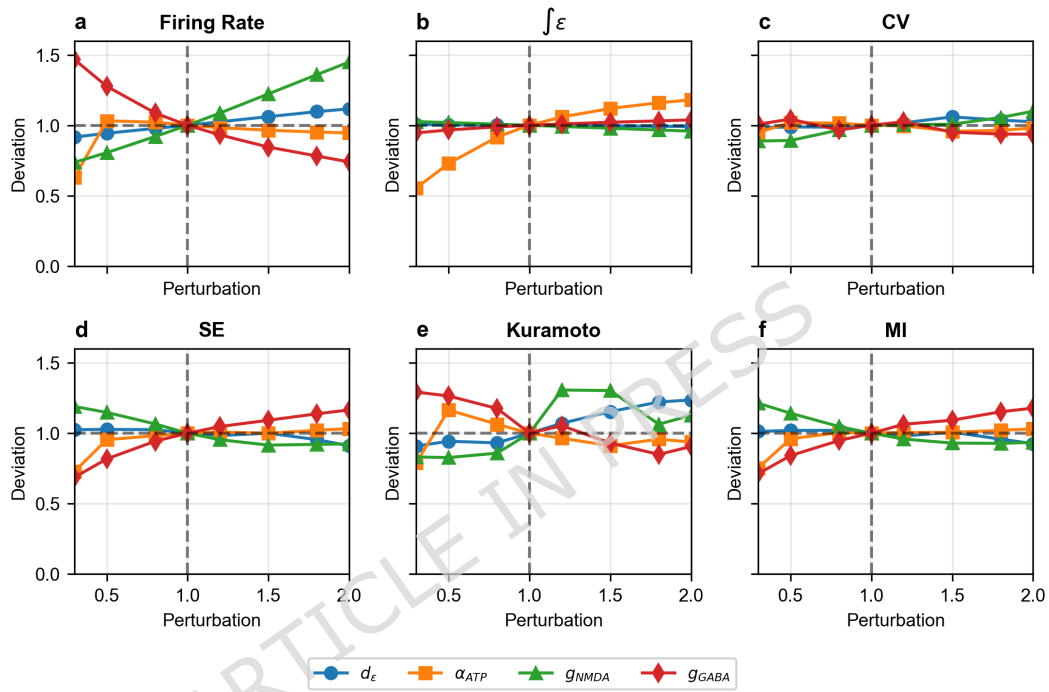


Figure 5. Local perturbation analysis in the network model. Global response of the cortical microcircuit to systematic perturbations in metabolic and synaptic parameters. Each parameter was scaled from $0.3\times$ to $2.0\times$ its fitted baseline value while all other parameters were held constant; the resulting network-wide metrics are plotted as normalized deviations from baseline. The six panels show: **a** total firing rate, **b** mean metabolic state ($\int \epsilon$), **c** mean coefficient of variation (CV), **d** global Shannon entropy (SE), **e** mean synchrony (Kuramoto order parameter), and **f** mean mutual information (MI). Colored lines and marker styles represent perturbations of distinct parameters: metabolic coupling strength (d_ϵ , blue circles), ATP production rate (α_{ATP} , orange squares), NMDA conductance (g_{NMDA} , green triangles), and GABA conductance (g_{GABA} , red diamonds). The horizontal and vertical dashed lines indicate the unperturbed baseline.

(L5 and L6). During a subsequent GABA enhancement epoch, ATP production remained impaired while inhibitory synaptic conductance was increased to $2 \times g_{GABA}$. Inhibitory conductance was then returned to baseline before ATP production was restored (Fig. 6).

Reducing ATP production caused a rapid decline in the population-averaged metabolic state variable ε (Fig. 6c). The electrical response was not a simple increase in mean firing rate. Instead, mean population firing rates decreased or remained low during the ATP-disrupted state (Fig. 6b), while the population Fano factor increased markedly (Fig. 6a). The raster plot and LFP-like proxy showed temporally clustered firing and large-amplitude rhythmic activity (Fig. 6d–f). Thus, in this model, severe metabolic disruption produced a low-rate but burst-synchronized network state rather than a uniformly high-rate state. This apparent paradox reflects the competing energy-dependent feedback pathways described in Fig. 1: reduced ε increases susceptibility to burst synchronization through the $\varepsilon \rightarrow E_L$ coupling, while ATP-sensitive adaptation and the energy-viability threshold limit sustained firing when energy becomes severely depleted.

The LFP-like proxy was computed from summed AMPA, NMDA, and GABA synaptic currents onto excitatory populations and bandpass filtered between 1.5 and 100 Hz. This readout is intended as a qualitative measure of macroscopic synaptic drive rather than a biophysical reconstruction of extracellular potentials. Under ATP disruption, the proxy developed high-amplitude rhythmic oscillations, consistent with the increased Fano factor and the temporally clustered spike raster. These dynamics help explain why mean firing rate alone is insufficient to characterize the disrupted state: the main change is the timing and synchrony of population activity.

Increasing g_{GABA} during persistent ATP disruption strongly reduced the Fano factor and LFP-like oscillation amplitude without restoring ε to its baseline level (Fig. 6a,c,e,f). Mean firing rates changed only modestly during this GABA enhancement epoch (Fig. 6b), indicating that enhanced inhibition primarily suppressed temporal clustering and burst synchrony rather than simply silencing the network. When g_{GABA} was returned to baseline while ATP production remained impaired, burst-synchronous activity re-emerged; restoration of ATP production then returned both the metabolic variable and the electrical readouts toward baseline.

Because the temporal traces could otherwise be interpreted as ongoing adaptation rather than settled network states, we repeated the protocol with adaptive epoch durations. Each phase was maintained until mean excitatory firing rate, population Fano factor, mean excitatory metabolic state, and LFP-proxy RMS satisfied stability criteria over the most recent 3 s window; the numerical criteria are reported in Supplementary Table S1. Under this control, the stable asynchronous baseline, low-ATP burst-synchronized, GABA-enhanced low-energy, and recovery phases reached the stopping criterion after 14, 9, 4, and 6 s, respectively. The settled low-ATP burst-synchronized state had reduced mean firing rate (14.43 Hz) but elevated Fano factor (114.84) and LFP-proxy RMS (35.45), whereas the GABA-enhanced low-energy state reduced the Fano factor to 2.92 and LFP-proxy RMS to 12.25 while mean metabolic state remained low ($\bar{\varepsilon} = 0.148$). These results support the interpretation that metabolic disruption and GABA enhancement affect mean firing rate and burst synchrony on separable axes.

Path-dependent changes in burst synchrony

To evaluate whether these regimes showed evidence of path-dependent recovery, we compared plateau-state Fano factors with forward-backward sweeps along the ATP and GABA axes (Fig. 7). In the temporal protocol, ATP disruption markedly increased population Fano factor, whereas increasing GABA conductance g_{GABA} under persistent low ATP suppressed the Fano factor to below baseline-like levels (Fig. 7a). This confirmed that the GABA-enhanced low-energy state was electrically distinct from the low-ATP burst-synchronized state, even though ε remained low.

The ATP-axis sweep provided limited evidence for path dependence (Fig. 7b). Across five seeds, forward and backward branches differed mainly in the Fano-factor synchrony readout, with a loop area of 6.28 ± 1.48 for the 2.0 s dwell protocol. However, supplementary dwell-time controls showed that ATP-axis branch separation decreased with longer equilibration, and firing rate and mean metabolic state largely followed the current value of the metabolic-disruption parameter. We therefore interpret the ATP-axis result as synchrony-specific and partly dwell-sensitive rather than broad hysteresis across all state variables.

The GABA-axis sweep at fixed low ATP showed a stronger and more consistent branch separation in burst synchrony (Fig. 7c). Increasing inhibitory conductance suppressed the high-Fano low-ATP burst-synchronized state, and the low-Fano GABA-enhanced low-energy state persisted during much of the return sweep. Across five seeds, the Fano-factor loop area was 10.13 ± 3.15 for the 2.0 s dwell protocol and 4.46 ± 1.15 for the 4.0 s dwell protocol, while mean metabolic state remained low throughout the GABA enhancement regime ($\bar{\varepsilon} \approx 0.134$ – 0.143). Taken together, the strongest evidence for history-dependent changes in the revised analysis concerns the electrical expression of the low-ATP burst-synchronized state, as quantified by population Fano factor, rather than a complete separation of firing-rate or metabolic-state trajectories.

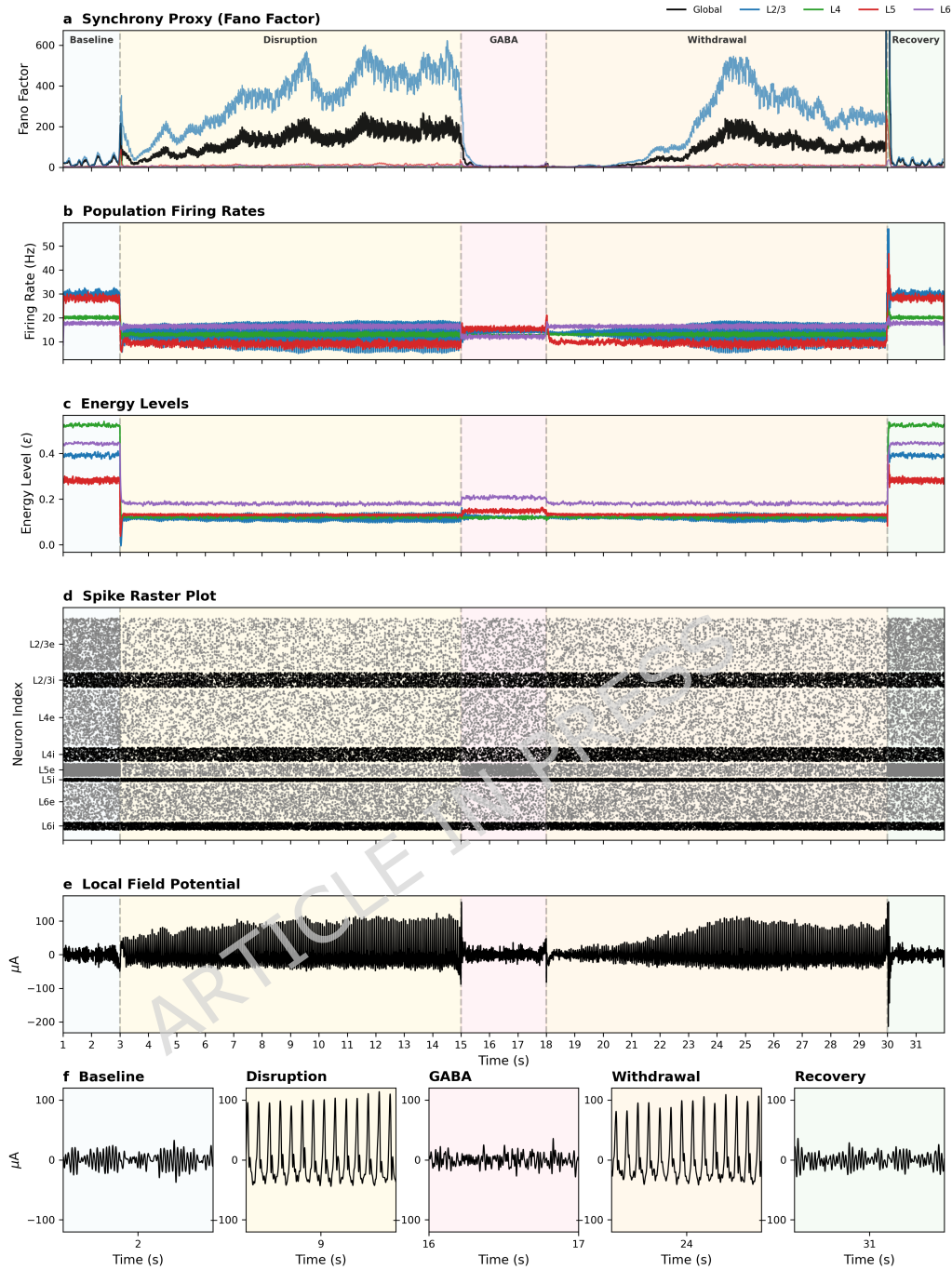


Figure 6. ATP disruption and GABAergic enhancement in the cortical microcircuit. Time-resolved response of the 8-population cortical microcircuit to a reversible metabolic perturbation and transient enhancement of inhibitory conductance. Shaded regions indicate protocol epochs: stable asynchronous baseline, ATP disruption, GABA enhancement during persistent ATP disruption, GABA withdrawal during persistent ATP disruption, and recovery after ATP restoration. During ATP disruption, α_{ATP} was reduced to $0.3 \times$ baseline in superficial layers (L2/3 and L4) and $0.5 \times$ baseline in deep layers (L5 and L6). During the GABA enhancement epoch, inhibitory synaptic conductance was increased to $2 \times g_{GABA}$ and then returned to baseline while ATP production remained impaired. **a** Population spike-count Fano factor for global and layer-specific excitatory activity, used here as a burstiness/synchrony proxy. **b** Smoothed population firing rates across cortical layers. **c** Population-averaged metabolic state variable ϵ , showing that GABA enhancement suppresses burst synchrony and LFP-like oscillations without restoring baseline ϵ levels. **d** Spike raster across excitatory and inhibitory populations. **e** Global LFP-like proxy computed from summed synaptic currents onto excitatory populations. **f** One-second LFP-like excerpts from each protocol epoch. ATP disruption produces high-amplitude rhythmic activity despite reduced mean firing rates, GABAergic enhancement suppresses this oscillatory signature under persistently low ϵ , and withdrawal of the enhanced inhibition restores the low-ATP burst-synchronized state until ATP production is returned to baseline.

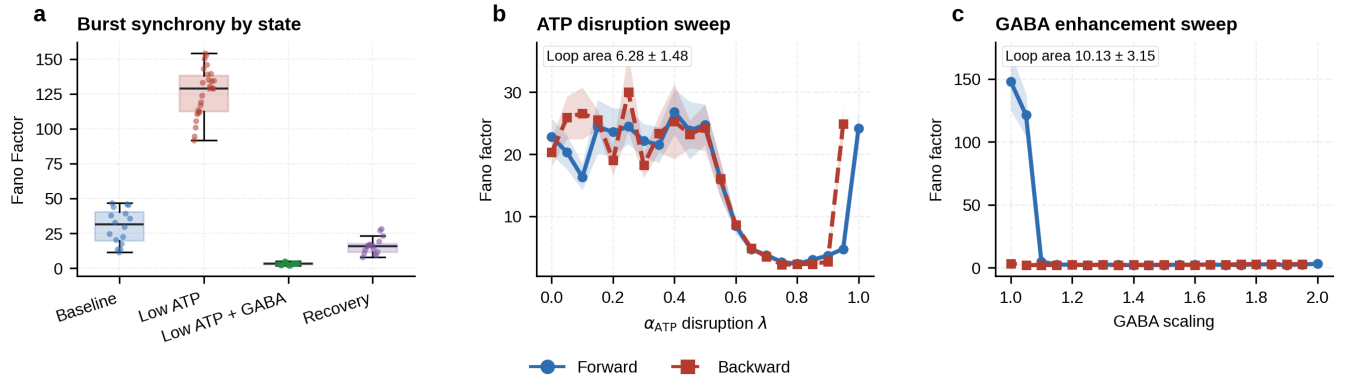


Figure 7. Fano-factor separation and path-dependent burst synchrony during metabolic disruption and GABA enhancement. **a** Population Fano factor measured across stable plateau windows of the temporal ATP/GABA protocol. Low ATP markedly increased burst synchrony, whereas GABA enhancement under persistent low ATP suppressed burst synchrony to below baseline-like levels. Recovery after restoration of ATP and baseline inhibition returned the network toward a low-Fano regime. Boxes show the interquartile range, horizontal lines show medians, whiskers show non-outlier ranges, and points show sliding-window samples. **b** Replicated forward-backward ATP-disruption sweep. The metabolic disruption parameter λ interpolates from baseline ATP production ($\lambda = 0$) to the low-ATP perturbation ($\lambda = 1$). Forward and backward branches differed primarily in burst synchrony, with a Fano loop area of 6.28 ± 1.48 for the 2.0 s dwell protocol. **c** Replicated forward-backward GABA enhancement sweep at fixed low ATP. Increasing g_{GABA} suppressed high-Fano burst synchrony, and the low-Fano GABA-enhanced low-energy state persisted during the return sweep. The Fano loop area was 10.13 ± 3.15 for the 2.0 s dwell protocol. Together, these results support the interpretation that GABA enhancement can stabilize the electrical expression of the low-ATP burst-synchronized state without requiring restoration of the metabolic state. Curves show mean population Fano factor across five seeds, and shaded regions show SEM. Loop-area values are reported as mean $\pm$ SD across seeds.

Discussion

This study introduces a metabolically constrained extension of the mAdExp model and embeds it in a structured cortical microcircuit to examine how intracellular energy availability can shape seizure-like network dynamics. The central contribution is the explicit coupling of a normalized energy variable, ϵ , to both energy production-consumption balance and membrane excitability. In contrast to phenomenological slow variables, ϵ is tied to ATP-dependent ion homeostasis and to the energetic consequences of activity. The model therefore provides a compact way to test how metabolic impairment can destabilize cortical activity while remaining computationally tractable at the network scale.

At the single-neuron level, reduced energy availability has two opposing consequences. Through the $\epsilon \rightarrow E_L$ coupling, low energy depolarizes the effective leak reversal potential and can increase susceptibility to input, consistent with experimental observations that metabolic failure or impaired pump function can promote neuronal hyperexcitability⁵. At the same time, the ATP-sensitive adaptation term and the energy-viability threshold ϵ_c limit sustained firing when ϵ becomes sufficiently depleted. This balance is important for interpreting the network results: metabolic disruption did not simply produce a uniform increase in mean firing rate. Instead, the settled low-ATP burst-synchronized state was characterized by low-rate, high-Fano activity with strong LFP-like oscillations. Thus, in this model the pathological signature of metabolic insufficiency is best described as altered timing and synchronization rather than generalized rate elevation.

The ablation analysis supports this interpretation. Removing the energy-dependent leak-potential coupling reduced peak burstiness, indicating that the $\epsilon \rightarrow E_L$ pathway is a major amplifier of the seizure-like temporal pattern. However, networks without this coupling still showed reduced firing rates under metabolic disruption, demonstrating that ATP production loss affects network dynamics through more than one pathway. In contrast, the explicit spike-cost term had negligible effects at the current network scale. These results suggest that the direct depolarizing feedback from low energy is important for the characteristic burst-synchronized state, but it is not the only way that reduced ATP production shapes cortical activity.

The information-theoretic analyses provide a complementary view of this state transition. Reduced ATP production lowered Shannon entropy and mutual information under the present short-word estimator, consistent with a loss of diverse spatiotemporal activity patterns during seizure-like hypersynchrony²⁵. These measures should be interpreted as regime-comparative summaries rather than complete estimates of neural coding capacity, but they reinforce the distinction between firing rate and temporal organization. The low-ATP burst-synchronized state was not merely quieter or more active; it occupied a more stereotyped

activity regime.

Increasing inhibitory synaptic conductance suppressed this high-Fano oscillatory state despite persistently low ε . Because the manipulation was implemented as a qualitative scaling of GABAergic conductance rather than as a receptor-level or pharmacokinetic drug model, the result should be interpreted as a test of GABA enhancement rather than a detailed benzodiazepine simulation². Within that scope, the simulations indicate that electrical suppression of the burst-synchronized state and recovery of the metabolic state can be partially dissociated: enhanced inhibition reduced the electrical expression of the pathological state without restoring ε to baseline. This distinction is relevant to metabolic approaches to epilepsy, including ketogenic and related interventions that target energy balance more directly than conventional anti-seizure suppression of network activity⁶.

The forward-backward sweeps further support a cautious form of path dependence. Along the ATP axis, branch separation was strongest in the Fano-factor synchrony readout and decreased with longer dwell times, suggesting that slow relaxation contributes to the apparent hysteresis. Along the GABA axis, the separation of high-Fano and low-Fano branches was more consistent, while mean metabolic state remained far from baseline. The strongest conclusion is therefore not that the model proves bistable coexistence of seizure and non-seizure states, but that burst synchrony can depend on recent metabolic and inhibitory history, especially during inhibitory enhancement.

Several limitations should be considered. The neuronal parameters were fitted to representative human spiny neurons from the Allen Cell Types Database and then assigned by layer to both excitatory and inhibitory populations; inhibitory identity was represented primarily through network population, connectivity, and synaptic role rather than through separately fitted inhibitory intrinsic parameters. The network architecture was based on the Potjans-Diesmann cortical microcircuit and scaled to approximately 8,000 neurons, so finite-size effects and species-specific connectivity differences may affect transition thresholds. The LFP proxy captures population-level temporal structure but not the full biophysics of extracellular recordings, and future work could combine the model with forward-modeling tools such as LFPy. Finally, the metabolic component compresses mitochondrial respiration, glucose and oxygen transport, calcium dynamics, and neuron-glia interactions into a single energy variable. Extending the model with richer neurovascular and metabolic pathways could allow more direct investigation of substrate supply, compensatory recovery, and pathologically uncoupled metabolic states^{16,26}.

Overall, the results support the view that intracellular energy availability can function as a slow control variable for cortical network stability. In the revised model, reduced ATP production is sufficient to transform stable asynchronous baseline activity into a low-rate but burst-synchronized seizure-like regime, while increased inhibitory conductance can suppress the electrical signature without correcting the underlying metabolic deficit. This provides a mechanistically interpretable platform for studying how metabolic constraints, inhibition, and structured connectivity interact during seizure-like state transitions.

Methods

Neurons primarily utilize energy in the form of adenosine triphosphate (ATP) molecules, which are converted into adenosine diphosphate (ADP) during the process of consumption. A major consumer of ATP is the Na^+/K^+ -pump, which maintains ion concentration gradients between the intracellular and extracellular spaces. This is essential for facilitating a wide range of cellular functions, including the formation of action potentials²⁷. The turnover rate of the pump is dependent upon the available energy, or more specifically, the ATP/ADP ratio²⁸. A decline in pump performance results in a shift towards equilibrium in ion concentrations, which in turn brings the reversal potentials closer to neutral. Experiments that block the pump have demonstrated that neurons become more excitable with higher firing rates and elevated resting potentials^{29,30}. Conversely, when ion concentrations are further removed from the resting state potential, the pump increases output and thus metabolizes more ATP. This interdependency between resting state potential and energy state was successfully presented in the eLIF and mAdExp models proposed by Fardet and Levina¹⁸, which were demonstrated to be capable of emulating a wide range of behaviors, including bursting phenotypes of cell populations.

Here, we refine the formulation of mAdExp¹⁸ and extend the model to larger, more complex networks in the form of a simplified cortical column to demonstrate that the energy-related principle is applicable across different hierarchies and can be employed to examine metabolic aspects of epileptic disease. We distinguish between energy production and consumption, delineating their respective domains of action. To facilitate large-scale simulations, the neuron is assumed to be in energy balance when the membrane potential is at rest. Accordingly, we consider energy consumption solely in the context of depolarization and, subsequently, action potentials. The parameter α_{ATP} represents energy-production capacity and can be reduced to model metabolic stress, such as ischemia or related energetic alterations. Like the mAdExp model, our neuron model exhibits a similar capacity to replicate biological findings of increased excitability with decreasing energy and a firing arrest in neurons when ε falls below the energy-viability threshold ε_c .

The modified mAdExp model

The core distinction of the mAdExp model lies in how the energy state modulates the leak reversal potential, E_L , similar to the model proposed in the foundational work of Fardet and Levina¹⁸. In our modified model, however, the dynamics of the

neuron's energy state are governed by an energy-production term, ATP , and a consumption term representing pump activity, P , rather than by the ATP/ADP ratio¹⁸.

The modified mAdExp model is characterized by coupled update equations for the membrane potential V , the adaptation current w_ϵ , and the energy state ϵ , as follows:

$$\begin{aligned} & \text{if } V < V_{th} \text{ or } \epsilon < \epsilon_c : \begin{cases} C\dot{V} = g_L(E_L - V) + g_L\Delta_T \frac{\epsilon - \epsilon_c}{\epsilon_0} \exp\left(\frac{V - V_{th}}{\Delta_T}\right) + I_e - I_{syn} - w_\epsilon, \\ E_L = E_0 \left[1 - d_\epsilon \left(\frac{\epsilon_0 - \epsilon}{\epsilon_0 - \epsilon_c}\right)\right], \\ \tau_{w_\epsilon} \dot{w}_\epsilon = a(V - E_L) - w_\epsilon + I_{KATP} \frac{\epsilon_c}{\epsilon_c + 2\epsilon}, \\ \tau_\epsilon \dot{\epsilon} = ATP - P, \end{cases} \\ & \text{else: } \begin{cases} V \leftarrow V_{reset}, \\ \epsilon \leftarrow \epsilon - \delta, \\ w_\epsilon \leftarrow w_\epsilon + b \end{cases} \end{aligned} \quad (1)$$

The variable ϵ is not intended to represent a directly measured ATP concentration. Instead, it is a normalized control variable representing effective intracellular energetic availability and its impact on ATP-dependent membrane homeostasis. It captures the effective balance between metabolic energy production and consumption that regulates ion pump activity and thereby modulates neuronal excitability. The neuron emits a spike and resets when the membrane potential reaches the threshold V_{th} while the metabolic state remains above the energy-viability threshold ϵ_c . Similar to conventional integrate-and-fire point-neuron models, subthreshold dynamics are governed by the passive leak current, characterized by the leak conductance g_L , leak reversal potential E_L , and membrane capacitance C . The total input current includes a deterministic external input I_e and synaptic input from other neurons I_{syn} , which itself includes a stochastic noise component Σ modeling background fluctuations (Eq. 4).

Changes in ionic gradients resulting from reduced Na^+ - K^+ -pump activity primarily manifest as shifts in the neuronal resting potential. We modeled energy depletion through a dynamic leak reversal potential to provide a computationally efficient approximation of pump-mediated depolarization. Thus, unlike in standard integrate-and-fire models, the leak potential E_L is not fixed but depends dynamically on the neuron's energy state ϵ , shifting toward more depolarized values as energy is depleted.

To model the dependence of the sodium-potassium pump on available ATP³¹, the leak reversal potential E_L is modeled as a linear function of the intracellular energy state ϵ , such that decreasing energy levels lead to a depolarizing shift of the effective resting potential. This relationship is expressed as a function of the reference reversal potential E_0 multiplied by a constant d_ϵ , the corresponding reference (or basal) metabolic state ϵ_0 , and the energy-viability threshold ϵ_c . This energy dependence introduces a coupling between cellular excitability and the metabolic state variable.

The adaptation current w_ϵ includes a standard voltage-dependent adaptation term and an additional ATP-sensitive potassium current (I_{KATP}) component that activates at low energy levels, distinguishing it from the standard AdExp model. γ^{-1} represents the energy cost required to restore potassium ions per unit of adaptation current.

The energy variable ϵ evolves, with a time constant τ_ϵ , according to a production-consumption balance, where ATP represents energy supply and P denotes energy consumption. The energy equations for energy production ATP and pump activity P are listed below.

$$ATP = \alpha_{ATP} \left(1 - \frac{\epsilon}{\epsilon_0}\right) \quad (2)$$

$$P = \alpha_P (V - E_0) \sigma(V - E_0) \sigma(s \cdot (\epsilon - \epsilon_c)) + \frac{w_\epsilon}{\gamma} \quad (3)$$

Energy production ATP is maximal when the energy variable is fully depleted ($\epsilon = 0$) and vanishes at the resting energy level ($\epsilon = \epsilon_0$), ensuring that the neuron does not accumulate energy beyond its baseline state. Energy consumption P is proportional to the value of depolarization, $(V - E_0)$, while hyperpolarization does not consume energy (Fig. 8). This assumes that the main contributor to energy consumption is the sodium-potassium pump which acts against depolarization and uses more energy as the neuron moves towards more positive membrane potentials^{32,33}. Two sigmoid functions ensure that energy consumption only occurs when the membrane is depolarized relative to the reference reversal potential E_0 and is suppressed as ϵ approaches the energy-viability threshold ϵ_c .

The advantage of this approach is that it captures the energetic cost of synaptic potentials, which is where a large portion of neuronal energy consumption occurs^{27,34}. Energy production and consumption are scaled by their respective parameters α_{ATP} and α_P . Biologically, α_{ATP} can be interpreted as energy-production capacity, which may be impaired during stroke, injury, or metabolic stress, while α_P may increase in situations of neuronal stress such as when influenced by neurotoxic substances. Note that ATP and P do not introduce additional state variables into the system. The model therefore remains a low-dimensional three-variable dynamical system (V, w, ε) , preserving computational efficiency while retaining an interpretable representation of metabolic dynamics. Accordingly, the model does not explicitly resolve mitochondrial ATP production, glycolytic flux, metabolite transport, or subcellular energy compartmentalization.

After a spike is emitted, the membrane potential is reset to V_{reset} and the energy is decremented by δ to account for the energetic cost of spiking. An immediate cost δ is used because AdExp-type point-neuron models represent the action potential as a threshold-triggered spike and reset rather than as a temporally continuous conductance process.

In the original model by Fardet and Levina,¹⁸ the energy term $d\varepsilon/dt$ was governed by a flex potential E_f and an energy-depletion potential E_d . The model presented here makes two major modifications: one, by introducing the factors α_{ATP} and α_P , the neuron's energy production and consumption can be modeled and accessed directly. Two, as seen in Fig 8, the neuron is metabolically at rest at ε_0 and E_0 , unlike the original model where energy production and consumption were not limited by a biologically corresponding capacity. Here, we assume that the neuron does not produce significant amounts of energy beyond ε_0 and similarly, does not consume great amounts of energy below E_0 . A strictness parameter s modifies the slope of the sigmoid curve for energy consumption, controlling how sharply consumption is suppressed as ε approaches the energy-viability threshold ε_c . Additionally, energy consumption is now directly proportional to the distance from E_0 .

Through this coupling, intracellular energy acts as a slow control variable modulating neuronal excitability. As ε decreases, the effective leak reversal potential shifts toward more depolarized values, increasing the probability of spike generation. Increased spiking in turn raises metabolic demand through pump activity, creating a feedback loop between energy depletion and neuronal excitability. At the network level, this feedback can destabilize stable asynchronous baseline activity and promote burst-synchronized oscillations.

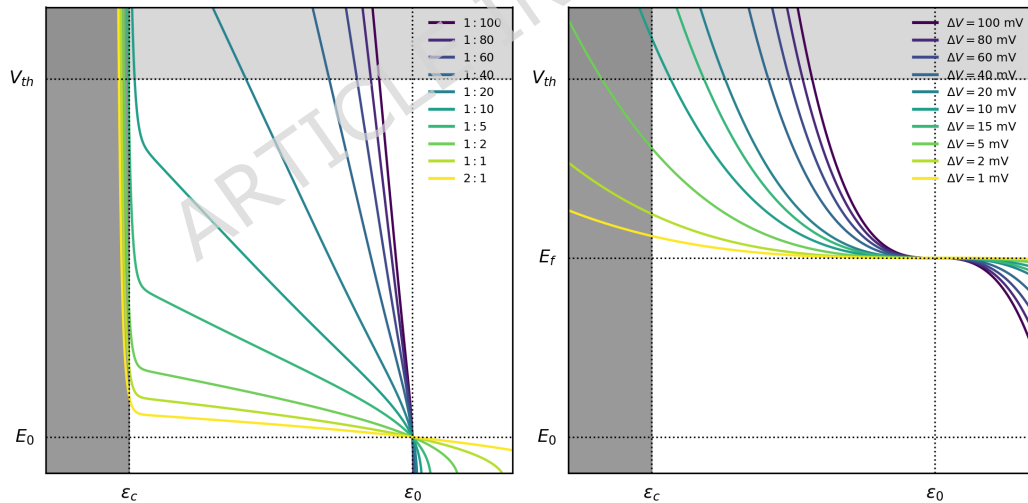


Figure 8. Phase-space with ε -nullclines. ε -nullclines in the (V, ε) phase plane for varied parameterisations of the modified mAdExp model (left) and the original mAdExp model¹⁸ (right). **Left panel:** Nullclines are shown for different ratios of the ATP production rate to pump efficiency, $\alpha_{ATP} : \alpha_P$. The legend labels 1:1, 1:2, 1:5, etc. denote the $\alpha_{ATP} : \alpha_P$ ratio; as the ratio shifts towards higher consumption (lower α_{ATP} relative to α_P), the nullcline moves downward, restricting the energy-viable operating range. **Right panel:** Nullclines are shown for different separations $\Delta V = E_f - E_d$ between the flex potential E_f and the depletion potential E_d in the original formulation. The super-threshold region, in which spikes are triggered upon entry, is indicated by light grey shading. The energy-limited region is shown in dark grey and overlaps with the super-threshold region, where energy constraints suppress spiking despite the neuron being above threshold. In both panels, the adaptation current w is held constant to isolate the differences in the energy mechanism between the two models.

Cortical Microcircuit Network

For the network simulations, the cortical microcircuit model (CMC) as presented in¹⁹ was adapted to simulate the neuronal architecture of cortical columns. The network consists of 8 populations representing layers 2/3, 4, 5, and 6, each divided into excitatory (e) and inhibitory (i) subpopulations. Although the model is based on awake animals rather than human brains, it was chosen here for its simple yet effective architecture.

Connectivity probabilities between populations were derived from the statistical connectivity map provided by Potjans and Diesmann¹⁹. The total network size was scaled to $N \approx 8000$ neurons (scale factor 0.1) to maintain computational tractability while preserving network dynamics.

The synapses were modeled after²⁴ and incorporate excitatory NMDA, AMPA as well as inhibitory GABA receptors on all neurons with different parameters for excitatory and inhibitory populations. The total synaptic current is given by the sum of the individual contributions:

$$I_{syn} = I_{AMPA,ext} + I_{AMPA,rec} + I_{NMDA,rec} + I_{GABA,rec} + \Sigma \quad (4)$$

Here, $I_{AMPA,ext}$ represents external background activity modeled as a Poisson process, while $I_{AMPA,rec}$, $I_{NMDA,rec}$, and $I_{GABA,rec}$ denote synaptic currents mediated by AMPA, NMDA, and GABA receptors, respectively. Σ represents stochastic noise in the form of fluctuating currents. Following the convention of Brunel and Wang²⁴, individual synaptic currents are defined as $I = g(V - V_{rev})s$, representing transmembrane ionic currents; the total synaptic current enters the membrane equation (Eq. 1) with a negative sign. The details of synaptic currents are shown below.

$$I_{AMPA,ext}(t) = g_{AMPA,ext}(V(t) - V_E) \sum_{j=1}^{C_{ext}} s_j^{AMPA,ext}(t) \quad (5)$$

$$I_{AMPA,rec}(t) = g_{AMPA,rec}(V(t) - V_E) \sum_{j=1}^{C_E} s_j^{AMPA,rec}(t) \quad (6)$$

$$I_{NMDA,rec}(t) = \frac{g_{NMDA}(V(t) - V_E)}{1 + [Mg^{2+}] \exp(-0.062V(t))/3.57} \sum_{j=1}^{C_E} s_j^{NMDA,rec}(t) \quad (7)$$

$$I_{GABA,rec}(t) = g_{GABA}(V(t) - V_I) \sum_{j=1}^{C_I} s_j^{GABA}(t) \quad (8)$$

The synaptic currents are determined by the product of synaptic conductance ($g_{AMPA,ext}$, $g_{AMPA,rec}$, g_{NMDA} , and g_{GABA}) and the receptor gating variables, s , driven by incoming presynaptic spikes during each time step. C_{ext} represents external neural cells, C_E denotes excitatory cells, and C_I corresponds to inhibitory cells within the population. Individual presynaptic events incremented their corresponding gating variable with unit weight. Unless explicitly manipulated in a perturbation protocol, the synaptic conductances $g_{AMPA,ext}$, $g_{AMPA,rec}$, g_{NMDA} , and g_{GABA} remained fixed throughout the simulation. The excitatory reversal potential, $V_E = 0\text{mV}$, is uniform across all excitatory synapses, while the inhibitory reversal potential is set to $V_I = -70\text{mV}$, primarily determined by the chloride ion concentration gradient. Although metabotropic GABA receptors exist, this model simplifies all GABA receptors into simple ionotropic conductance-based synapses³⁵. All synapses are connected with a 2-millisecond delay. To emulate the voltage-dependent magnesium block of NMDA receptors, the current is modulated by a sigmoid function, considering an extracellular magnesium concentration of $Mg^{2+} = 1\text{mM}$.

The gating variable for NMDA channels is characterized by a rise time of $\tau_{NMDA,rise} = 2\text{ms}$, a rising rate of $\alpha = 0.5\text{ms}^{-1}$, and a decay time of $\tau_{NMDA,decay} = 100\text{ms}$.

$$\frac{ds_j^{NMDA}(t)}{dt} = -\frac{s_j^{NMDA}(t)}{\tau_{NMDA,decay}} + \alpha x_j(t)(1 - s_j^{NMDA}(t)) \quad (9)$$

$$\frac{dx_j(t)}{dt} = -\frac{x_j(t)}{\tau_{NMDA,rise}} + \Sigma_k \delta(t - t_j^k) \quad (10)$$

$$(11)$$

For AMPA and GABA channels, the rise times are considered to be instantaneous and can therefore be neglected. Their gating variables are described by simple decay equations, with respective decay times of $\tau_{AMPA} = 2\text{ms}$ and $\tau_{GABA} = 10\text{ms}$:

$$\frac{ds_j^{AMPA}(t)}{dt} = -\frac{s_j^{AMPA}(t)}{\tau_{AMPA}} + \sum_k \delta(t - t_j^k) \quad (12)$$

$$\frac{ds_j^{GABA}(t)}{dt} = -\frac{s_j^{GABA}(t)}{\tau_{GABA}} + \sum_k \delta(t - t_j^k) \quad (13)$$

The CMC-based networks used in this study are visualized in Fig. 9.

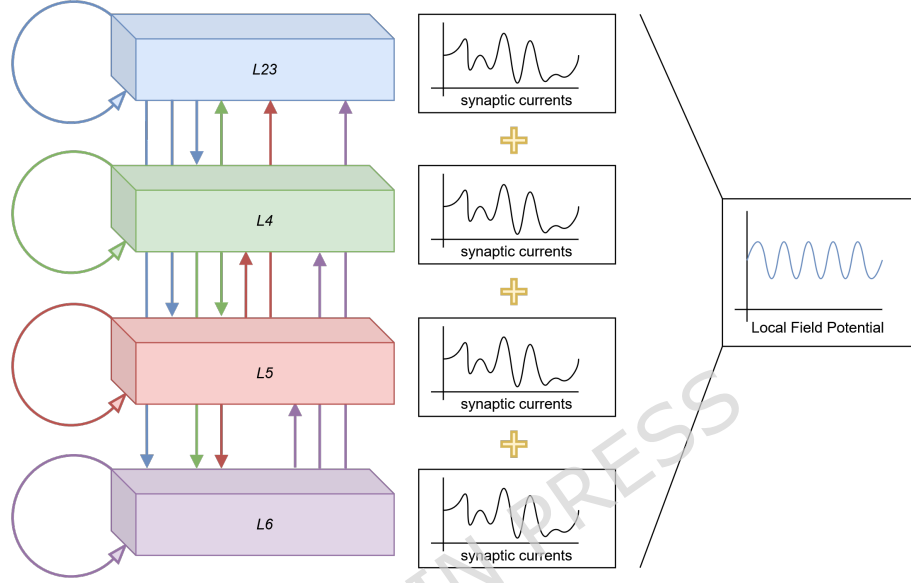


Figure 9. Cortical Column architecture. Schematic of the four-layer (L2/3, L4, L5, L6) cortical column abstraction. Arrows illustrate synapses between layers, with connection densities based on the Potjans-Diesmann microcircuit.¹⁹ Synaptic currents include NMDA, AMPA, and GABA dynamics based on Brunel and Wang.²⁴ The LFP-like proxy is approximated by summing synaptic currents onto excitatory populations, following the approach from Mazzoni et al.³⁶

Local Field Potential

To bridge the gap between spiking activity and macroscopic signals measurable in clinical settings, we estimated the Local Field Potential (LFP). Recent studies suggest that the main contributors to the LFP are the transmembrane currents of pyramidal neurons, due to their parallel alignment and large dendritic trees³⁶.

We use a simplified LFP-like proxy derived from aggregated synaptic activity to capture coarse-grained temporal structure across network states.

Let $\mathcal{E} = \{L2/3e, L4e, L5e, L6e\}$ denote the set of excitatory populations, then:

$$\text{LFP}(t) \propto \sum_{p \in \mathcal{E}} \left(I_{\text{AMPA}}^{(p)}(t) + I_{\text{NMDA}}^{(p)}(t) + I_{\text{GABA}}^{(p)}(t) \right) \quad (14)$$

This computed proxy signal was then bandpass filtered between 1.5 Hz and 100 Hz using a 4th-order Butterworth filter to match the typical frequency range of clinical EEG/LFP recordings.

This readout is intended for qualitative comparison of dynamical regimes, not quantitative forward modeling of extracellular field potentials.

Data Analysis and Metrics

Network Synchrony

Network synchronization was evaluated using the Fano Factor of the population spike counts, a standard measure of burstiness^{37,38}. For a given time window W , the spike count $N(t)$ was calculated, and the Fano Factor was defined as the ratio of the

variance to the mean of the spike counts:

$$FF = \frac{\text{Var}(N(t))}{\mu(N(t))} \quad (15)$$

High values ($FF \gg 1$) indicate bursty, synchronized firing characteristic of seizure states, while values near 1 indicate Poisson-like asynchronous activity.

Additionally, the Kuramoto order parameter $R(t)$ was computed to measure phase synchrony^{39,40}. Spike trains were converted into instantaneous phases $\phi_j(t)$ via linear interpolation between spike times t_j^k and t_j^{k+1} :

$$\phi_j(t) = 2\pi \frac{t - t_j^k}{t_j^{k+1} - t_j^k} \quad \text{for } t_j^k \leq t < t_j^{k+1} \quad (16)$$

The global order parameter was then calculated as:

$$R(t) = \left| \frac{1}{N} \sum_{j=1}^N e^{i\phi_j(t)} \right| \quad (17)$$

where $R(t)$ ranges from 0 (incoherent firing) to 1 (perfect synchronization).

Single-neuron spike-time irregularity was quantified using the coefficient of variation of inter-spike intervals (ISI CV), computed separately for each excitatory neuron with at least three spikes in a given epoch and then averaged across neurons.

$$CV_{\text{ISI}} = \frac{\sigma_{\text{ISI}}}{\mu_{\text{ISI}}},$$

where σ_{ISI} and μ_{ISI} are the standard deviation and mean of that neuron's inter-spike intervals.

Information Theoretic Metrics

To compute information-theoretic quantities, continuous spike trains were first converted to binary sequences. The simulation interval of interest (after discarding a transient warm-up period of 100 ms) was divided into non-overlapping time bins of width $\Delta t = 2\text{ms}$. Each bin was assigned a value of 1 if at least one spike occurred within it, and 0 otherwise, yielding a binary string of length N_{bins} for each trial. Consecutive bins were grouped into non-overlapping spike words of length $L = 3$ bins, spanning a temporal window of $L \times \Delta t = 6\text{ms}$. Because the present estimator uses short binary words, the resulting entropy-rate values should be interpreted as lower-bound, regime-comparative summaries rather than complete characterizations of neural coding. Sliding this window across the binary string produced a sequence of $N_{\text{words}} = N_{\text{bins}} - L + 1$ words per trial. Each word is an element of the set $\{0, 1\}^L$, giving a maximum possible vocabulary of $2^L = 8$ distinct patterns. The short word length $L = 3$ was chosen as a pragmatic compromise: it keeps the vocabulary small ($2^3 = 8$ patterns) so that the empirical word-frequency distribution converges reliably from the available number of trials, while still capturing pairwise temporal correlations across the 6 ms window. This choice follows the recommendation of Strong et al.⁴¹, who showed that entropy estimates from short binary words converge rapidly and can be systematically extrapolated, and is further supported by the analysis of Nemenman et al.⁴², who demonstrated that Bayesian entropy estimators remain well-behaved at small word lengths even with limited data.

The marginal (total) Shannon entropy was estimated by pooling spike words across all K repeated trials:

$$H = - \sum_w p(w) \log_2 p(w) \quad (18)$$

where $p(w)$ is the empirical probability of word w obtained by counting its occurrences over all $K \times N_{\text{words}}$ pooled words.⁴³ H is measured in bits per word and quantifies the overall variability of the spike code. The entropy rate $\dot{H}$ was defined as:

$$\dot{H} = \frac{H}{L \cdot \Delta t} \quad (19)$$

and is expressed in bits per second. This quantity approximates the rate of information generation; its exact value converges to the true entropy rate in the limit $L \rightarrow \infty$.⁴⁴

The noise entropy H_{noise} captures trial-to-trial variability in the spike code for the same stimulus context. For each word position t , the distribution of spike words across the K trials was computed, and the entropy of that distribution H_t was calculated. The noise entropy was then the mean over all word positions:

$$H_{\text{noise}} = \frac{1}{N_{\text{words}}} \sum_{t=1}^{N_{\text{words}}} H_t \quad (20)$$

The mutual information (MI) between the stimulus context (metabolic parameter condition) and the neural response was estimated as the difference between the total entropy and the noise entropy:

$$MI = \max(0, H - H_{\text{noise}}) \quad (21)$$

measured in bits per word. This follows the "direct method" framework,⁴¹ in which the signal entropy reflects the diversity of responses across conditions, and the noise entropy reflects the variability of responses within a single condition.

These measures are used here as comparative descriptors of regime-dependent spike-pattern diversity, not as exhaustive estimates of cortical information processing capacity.

Trial Design and Averaging in Perturbation Experiments

Single-cell analyses: A single-compartment modified metabolic adaptive-exponential (mAdExp) neuron received an Ornstein–Uhlenbeck (OU) noise current with mean I_{mean} , correlation time $\tau_{\text{noise}} = 5\text{ms}$, and amplitude σ_{noise} . For each parameter condition, $K = 10$ (1-D sweeps) or $K = 5$ (2-D grid) repeated trials were run using a frozen-noise design, so corresponding trials reused the same noise realization across parameter conditions. Spike trains from all K trials yielded H , $\dot{H}$, and MI for that condition.

Network analyses: The eight-population cortical column model was parameterised per layer from fitted single-cell parameters.¹⁹ For each metabolic perturbation condition, $K = 3$ network trials were run. Spike trains of each of the eight populations (excitatory and inhibitory neurons in layers 2/3, 4, 5, and 6) were analysed independently, and population-level measures were averaged across populations to produce network-wide entropy, entropy rate, and mutual information. A Kuramoto order parameter was additionally computed across the network to quantify synchrony.

1-D sweeps: A single metabolic parameter θ was multiplied by a scalar $c \in \{0.80, 1.00, 1.20\}$ (single-cell) or by a scalar spanning $0.30\times$ to $2.00\times$ baseline (network), while all other parameters were held at their fitted baseline values.

2-D grids: Pairs of parameters (θ_1, θ_2) were jointly varied over a 28×28 grid of multipliers linearly spaced in $[0.30, 3.00]$, yielding heatmaps of each metric over the joint parameter space.

Hysteresis analysis

The temporal ATP/GABA perturbation protocol shown in Fig. 6 used fixed epochs to visualize the full sequence of stable asynchronous baseline activity, ATP reduction, inhibitory-conductance enhancement, inhibitory-conductance withdrawal, and ATP restoration. To verify that the reported low-ATP burst-synchronized and GABA-enhancement low-energy values did not reflect arbitrary epoch durations, we separately repeated the protocol with adaptive phase lengths. In that control, each phase was continued until mean excitatory firing rate, population Fano factor, mean excitatory metabolic state, and LFP-proxy RMS satisfied the stability criteria reported in Supplementary Table S1 over the most recent 3 s window.

To test whether the network response depended on recent perturbation history, we performed two forward-backward sweep protocols on the cortical microcircuit without reinitializing the network between successive parameter steps.

In the ATP-axis sweep, a scalar disruption parameter $\lambda \in [0, 1]$ interpolated between baseline metabolism and the low-energy perturbation used in the temporal disruption experiment. At $\lambda = 1$, ATP production was reduced to $0.3\times$ baseline in the superficial populations (L2/3 and L4) and to $0.5\times$ baseline in the deep populations (L5 and L6). In the GABA-axis sweep, ATP production was held at these low values while inhibitory conductance was scaled from $1.0\times$ to $2.0\times$ baseline and then returned to baseline.

Both sweeps used a step size of 0.05, yielding 21 forward parameter values and 20 backward values while omitting a duplicate measurement of the turning point. The main Fig. 7 sweep panels summarize five independent seeds using a 2.0 s dwell protocol at each parameter value, consisting of 1.5 s equilibration followed by a 0.5 s measurement window. A longer 4.0 s dwell protocol, consisting of 3.0 s equilibration followed by 1.0 s measurement, was used as a supplementary control for slow relaxation. Three observables were used to characterize network response: population Fano factor, mean excitatory firing rate, and mean excitatory metabolic state $\bar{e}$. Population Fano factor was computed from pooled excitatory spike counts (bin size 5 ms, sliding window 100 ms), mean firing rate was obtained from the aggregate excitatory spike count divided by the number of excitatory neurons, and $\bar{e}$ was calculated by averaging the recorded energy state across excitatory neurons.

In addition to the forward-backward sweeps, regime separation in Fig. 7a was quantified from the fixed-duration temporal perturbation experiment using plateau windows chosen to avoid transition transients: stable asynchronous baseline (2.0–3.0 s), low-ATP burst-synchronized state (6.5–8.0 s), GABA-enhanced low-energy state (11.5–13.0 s), and recovery (14.0–15.0 s).

These plateau samples were projected into a reduced metric space defined by firing rate, Fano factor, and mean metabolic state to compare the stable asynchronous baseline, low-ATP burst-synchronized, GABA-enhanced low-energy, and recovery regimes in the measured observables. The settled numerical values reported in the Results come from the separate adaptive-duration control described above.

Voltage Fitting Procedure

To constrain the model parameters to biologically plausible regimes, model parameters were fitted to human cortical current-clamp recordings from donor H17.06.003 obtained through the Allen Cell Types Database (<http://celltypes.brain-map.org>)²³. Representative spiny neurons from layers 2/3, 4, 5, and 6 of human cortical tissue from donor H17.06.003 were selected from long-square-pulse current-clamp recordings. These fitted layer-specific intrinsic parameters were then assigned to both excitatory and inhibitory populations in the network model; inhibitory identity was represented by population membership, connectivity, and synaptic role rather than by separately fitted inhibitory intrinsic parameters.

The fitting procedure consisted of a two-stage process: initialization of passive properties followed by numerical optimization of active and metabolic parameters.

First, passive parameters were estimated from subthreshold responses. The resting membrane potential E_0 was determined as the median voltage during periods of zero current injection. The membrane time constant τ_m was estimated by fitting an exponential decay function to voltage relaxations following small current steps (< 5 pA). The total conductance $g_{tot} = g_L + a$ was derived from the slope of the steady-state voltage (V_{ss}) versus input current (I) curve in the subthreshold regime. The membrane capacitance was then calculated as $C_m = \tau_m \cdot g_{tot}$.

Second, global parameter optimization was performed to fit the dynamic response, including spiking behavior and adaptation. A composite loss function L that penalizes both the mismatch in voltage traces and the discrepancy in spike counts was defined as:

$$L(\theta) = \frac{1}{N} \sum_t (V_{model}(t, \theta) - V_{exp}(t))^2 + \lambda (N_{model} - N_{exp})^2 \quad (22)$$

where V_{exp} is the experimental voltage trace, V_{model} is the simulated trace given parameters θ , N_{exp} and N_{model} are the total spike counts, and $\lambda = 10$ is a dimensionless weighting factor enforcing accurate firing rates. To prevent the loss function being dominated by the narrow, high-amplitude action potentials, both V_{model} and V_{exp} were clipped at the firing threshold V_{th} prior to calculating the mean squared error (MSE).

The experimental data were downsampled to 10 kHz, and the first 20 seconds of the recording were used for fitting. The optimization was performed using the Nelder-Mead simplex algorithm⁴⁵ as implemented in SciPy, minimizing $L(\theta)$ over the parameter space of the model. Bounded constraints were applied to ensure all parameters remained within physiologically realistic ranges (e.g., $\tau_e > 0$, $\alpha_p > 0$). After fitting, selected parameters (d_e , α_p , and δ) were set uniformly across the network to maintain numerical stability, as noted in Supplementary Table S2.

Numerical Simulations

The models were implemented using the Brian2 library⁴⁶ in Python 3 with a fixed time step of 0.1 milliseconds. Exact model parameters for the simulations can be found in Supplementary Tables S2 and S3. Simulations were conducted and analyzed on an AMD Ryzen 5 2500U processor and integrated Radeon Vega Mobile graphics card.

References

1. Fiest, K. M. *et al.* Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology* **88**, 296–303, DOI: [10.1212/WNL.0000000000003509](https://doi.org/10.1212/WNL.0000000000003509) (2017).
2. Sánchez Fernández, I., Goodkin, H. P. & Scott, R. C. Pathophysiology of convulsive status epilepticus. *Seizure* **68**, 16–21, DOI: [10.1016/j.seizure.2018.08.002](https://doi.org/10.1016/j.seizure.2018.08.002) (2019).
3. Ding, Y. *et al.* 18F-FDG PET and high-resolution MRI co-registration for pre-surgical evaluation of patients with conventional MRI-negative refractory extra-temporal lobe epilepsy. *Eur. J. Nucl. Medicine Mol. Imaging* **45**, 1567–1572, DOI: [10.1007/s00259-018-4017-0](https://doi.org/10.1007/s00259-018-4017-0) (2018).
4. Ponisio, M. R. *et al.* The Role of SPECT and PET in Epilepsy. *Am. J. Roentgenol.* **216**, 759–768, DOI: [10.2214/AJR.20.23336](https://doi.org/10.2214/AJR.20.23336) (2021).
5. De La Rossa, A. *et al.* Paradoxical neuronal hyperexcitability in a mouse model of mitochondrial pyruvate import deficiency. *eLife* **11**, e72595, DOI: [10.7554/eLife.72595](https://doi.org/10.7554/eLife.72595) (2022).

6. Rho, J. M. & Boison, D. The metabolic basis of epilepsy. *Nat. Rev. Neurol.* **18**, 333–347, DOI: [10.1038/s41582-022-00651-8](https://doi.org/10.1038/s41582-022-00651-8) (2022).
7. Martin-McGill, K. J., Bresnahan, R., Levy, R. G. & Cooper, P. N. Ketogenic diets for drug-resistant epilepsy. *Cochrane Database Syst. Rev.* **2020**, DOI: [10.1002/14651858.CD001903.pub5](https://doi.org/10.1002/14651858.CD001903.pub5) (2020).
8. Oyrer, J. *et al.* Ion Channels in Genetic Epilepsy: From Genes and Mechanisms to Disease-Targeted Therapies. *Pharmacol. Rev.* **70**, 142–173, DOI: [10.1124/pr.117.014456](https://doi.org/10.1124/pr.117.014456) (2018).
9. McCormick, D. A. & Contreras, D. On The Cellular and Network Bases of Epileptic Seizures. *Annu. Rev. Physiol.* **63**, 815–846, DOI: [10.1146/annurev.physiol.63.1.815](https://doi.org/10.1146/annurev.physiol.63.1.815) (2001).
10. Staley, K. Molecular mechanisms of epilepsy. *Nat. Neurosci.* **18**, 367–372, DOI: [10.1038/nn.3947](https://doi.org/10.1038/nn.3947) (2015).
11. Moujahid, A. & Torrealdea, F. J. Energy and information in Hodgkin-Huxley neurons. *Phys. Rev. E* **83**, 031912, DOI: [10.1103/PhysRevE.83.031912](https://doi.org/10.1103/PhysRevE.83.031912) (2011).
12. Sengupta, B., Faisal, A. A., Laughlin, S. B. & Niven, J. E. The Effect of Cell Size and Channel Density on Neuronal Information Encoding and Energy Efficiency. *J. Cereb. Blood Flow & Metab.* **33**, 1465–1473, DOI: [10.1038/jcbfm.2013.103](https://doi.org/10.1038/jcbfm.2013.103) (2013).
13. Zhu, Z., Wang, R. & Zhu, F. The Energy Coding of a Structural Neural Network Based on the Hodgkin–Huxley Model. *Front. Neurosci.* **12**, 122, DOI: [10.3389/fnins.2018.00122](https://doi.org/10.3389/fnins.2018.00122) (2018).
14. Ding, Q., Wu, Y., Li, T., Yu, D. & Jia, Y. Metabolic energy consumption and information transmission of a two-compartment neuron model and its cortical network. *Chaos, Solitons & Fractals* **171**, 113464, DOI: [10.1016/j.chaos.2023.113464](https://doi.org/10.1016/j.chaos.2023.113464) (2023).
15. Zhu, F., Wang, R., Pan, X. & Zhu, Z. Energy expenditure computation of a single bursting neuron. *Cogn. Neurodynamics* **13**, 75–87, DOI: [10.1007/s11571-018-9503-3](https://doi.org/10.1007/s11571-018-9503-3) (2019).
16. Yu, Y., Yuan, Z., Li, J. & Wu, Y. Dynamic analysis of epileptic seizures caused by energy failure after ischemic stroke. *Chaos, Solitons & Fractals* **176**, 114116, DOI: [10.1016/j.chaos.2023.114116](https://doi.org/10.1016/j.chaos.2023.114116) (2023).
17. Jirsa, V. *et al.* Personalised virtual brain models in epilepsy. *The Lancet Neurol.* **22**, 443–454, DOI: [10.1016/S1474-4422\(23\)00008-X](https://doi.org/10.1016/S1474-4422(23)00008-X) (2023).
18. Fardet, T. & Levina, A. Simple models including energy and spike constraints reproduce complex activity patterns and metabolic disruptions. *PLOS Comput. Biol.* **16**, e1008503, DOI: [10.1371/journal.pcbi.1008503](https://doi.org/10.1371/journal.pcbi.1008503) (2020).
19. Potjans, T. C. & Diesmann, M. The cell-type specific cortical microcircuit: Relating structure and activity in a full-scale spiking network model. *Cereb. Cortex* **24**, 785–806, DOI: [10.1093/cercor/bhs358](https://doi.org/10.1093/cercor/bhs358) (2014).
20. Depannemaecker, D., Destexhe, A., Jirsa, V. & Bernard, C. Modeling seizures: From single neurons to networks. *Seizure* **90**, 4–8, DOI: [10.1016/j.seizure.2021.06.015](https://doi.org/10.1016/j.seizure.2021.06.015) (2021). LASSE – 15th Anniversary of Latin American Convergent Achievements in Epileptology.
21. Chakravarthy, N., Tsakalis, K., Sabesan, S. & Iasemidis, L. Homeostasis of Brain Dynamics in Epilepsy: A Feedback Control Systems Perspective of Seizures. *Annals Biomed. Eng.* **37**, 565–585, DOI: [10.1007/s10439-008-9625-6](https://doi.org/10.1007/s10439-008-9625-6) (2009).
22. Stefanescu, R. A., Shivakeshavan, R. & Talathi, S. S. Computational models of epilepsy. *Seizure* **21**, 748–759, DOI: [10.1016/j.seizure.2012.08.012](https://doi.org/10.1016/j.seizure.2012.08.012) (2012).
23. Berg, J. *et al.* Human neocortical expansion involves glutamatergic neuron diversification. *Nature* **598**, 151–158, DOI: [10.1038/s41586-021-03813-8](https://doi.org/10.1038/s41586-021-03813-8) (2021).
24. Brunel, N. & Wang, X.-J. Effects of neuromodulation in a cortical network model of object working memory dominated by recurrent inhibition. *J. Comput. Neurosci.* **11**, 63–85, DOI: [10.1023/A:1011204814320](https://doi.org/10.1023/A:1011204814320) (2001).
25. Kramer, M. A. & Cash, S. S. Epilepsy as a Disorder of Cortical Network Organization. *The Neurosci.* **18**, 360–372, DOI: [10.1177/1073858411422754](https://doi.org/10.1177/1073858411422754) (2012).
26. Chhabria, K. & Chakravarthy, V. S. Low-Dimensional Models of “Neuro-Glio-Vascular Unit” for Describing Neural Dynamics under Normal and Energy-Starved Conditions. *Front. Neurol.* **7**, DOI: [10.3389/fneur.2016.00024](https://doi.org/10.3389/fneur.2016.00024) (2016).
27. Harris, J. J., Jolivet, R. & Attwell, D. Synaptic Energy Use and Supply. *Neuron* **75**, 762–777, DOI: [10.1016/j.neuron.2012.08.019](https://doi.org/10.1016/j.neuron.2012.08.019) (2012).
28. Apell, H.-J., Nelson, M., Marcus, M. & Läuger, P. Effects of the ATP, ADP and inorganic phosphate on the transport rate of the Na⁺,K⁺-pump. *Biochimica et Biophys. Acta (BBA) - Biomembr.* **857**, 105–115, DOI: [10.1016/0005-2736\(86\)90103-3](https://doi.org/10.1016/0005-2736(86)90103-3) (1986).

29. Malek, S., Adorante, J. & Stys, P. Differential effects of Na-K-ATPase pump inhibition, chemical anoxia, and glycolytic blockade on membrane potential of rat optic nerve. *Brain Res.* **1037**, 171–179, DOI: [10.1016/j.brainres.2005.01.003](https://doi.org/10.1016/j.brainres.2005.01.003) (2005).
30. Anderson, T. R., Huguenard, J. R. & Prince, D. A. Differential effects of $\text{Na}^+ - \text{K}^+$ ATPase blockade on cortical layer V neurons. *The J. Physiol.* **588**, 4401–4414, DOI: [10.1113/jphysiol.2010.191858](https://doi.org/10.1113/jphysiol.2010.191858) (2010).
31. Kennedy, B. G., Lunn, G. & Hoffman, J. F. Effects of altering the ATP/ADP ratio on pump-mediated Na/K and Na/Na exchanges in resealed human red blood cell ghosts. *The J. general physiology* **87**, 47–72, DOI: [10.1085/jgp.87.1.47](https://doi.org/10.1085/jgp.87.1.47) (1986).
32. Vassalle, M. Contribution of the Na⁺/K⁺-pump to the membrane potential. *Experientia* **43**, 1135–1140, DOI: [10.1007/BF01945511](https://doi.org/10.1007/BF01945511) (1987).
33. Hasenstaub, A., Otte, S., Callaway, E. & Sejnowski, T. J. Metabolic cost as a unifying principle governing neuronal biophysics. *Proc. Natl. Acad. Sci.* **107**, 12329–12334, DOI: [10.1073/pnas.0914886107](https://doi.org/10.1073/pnas.0914886107) (2010).
34. Attwell, D. & Laughlin, S. B. An Energy Budget for Signaling in the Grey Matter of the Brain. *J. Cereb. Blood Flow & Metab.* **21**, 1133–1145, DOI: [10.1097/00004647-200110000-00001](https://doi.org/10.1097/00004647-200110000-00001) (2001).
35. Kim, H. R. & Martina, M. Bidirectional Regulation of GABAA Reversal Potential in the Adult Brain: Physiological and Pathological Implications. *Life* **14**, 143, DOI: [10.3390/life14010143](https://doi.org/10.3390/life14010143) (2024).
36. Mazzoni, A. *et al.* Computing the local field potential (lfp) from integrate-and-fire network models. *PLOS Comput. Biol.* **11**, e1004584, DOI: [10.1371/journal.pcbi.1004584](https://doi.org/10.1371/journal.pcbi.1004584) (2015).
37. Eden, U. T. & Kramer, M. A. Drawing inferences from fano factor calculations. *J. Neurosci. Methods* **190**, 149–152, DOI: [10.1016/j.jneumeth.2010.04.012](https://doi.org/10.1016/j.jneumeth.2010.04.012) (2010).
38. Rajdl, K., Lansky, P. & Kostal, L. Fano factor: A potentially useful information. *Front. Comput. Neurosci.* **14**, DOI: [10.3389/fncom.2020.569049](https://doi.org/10.3389/fncom.2020.569049) (2020).
39. Kuramoto, Y. *Chemical Oscillations, Waves, and Turbulence* (Springer Berlin Heidelberg, 1984, DOI: [10.1007/978-3-642-69689-3](https://doi.org/10.1007/978-3-642-69689-3)).
40. Breakspear, M., Heitmann, S. & Daffertshofer, A. Generative models of cortical oscillations: Neurobiological implications of the kuramoto model. *Front. Hum. Neurosci.* **4**, DOI: [10.3389/fnhum.2010.00190](https://doi.org/10.3389/fnhum.2010.00190) (2010).
41. Strong, S. P., Koberle, R., de Ruyter van Steveninck, R. R. & Bialek, W. Entropy and information in neural spike trains. *Phys. Rev. Lett.* **80**, 197–200, DOI: [10.1103/physrevlett.80.197](https://doi.org/10.1103/physrevlett.80.197) (1998).
42. Nemenman, I., Bialek, W. & de Ruyter van Steveninck, R. Entropy and information in neural spike trains: Progress on the sampling problem. *Phys. Rev. E* **69**, 056111, DOI: [10.1103/physreve.69.056111](https://doi.org/10.1103/physreve.69.056111) (2004).
43. Shannon, C. E. A mathematical theory of communication. *Bell Syst. Tech. J.* **27**, 379–423, DOI: [10.1002/j.1538-7305.1948.tb01338.x](https://doi.org/10.1002/j.1538-7305.1948.tb01338.x) (1948).
44. Bialek, W., Rieke, F., de Ruyter van Steveninck, R. R. & Warland, D. Reading a neural code. *Science* **252**, 1854–1857, DOI: [10.1126/science.2063199](https://doi.org/10.1126/science.2063199) (1991).
45. Nelder, J. A. & Mead, R. A simplex method for function minimization. *The Comput. J.* **7**, 308–313, DOI: [10.1093/comjnl/7.4.308](https://doi.org/10.1093/comjnl/7.4.308) (1965).
46. Stimberg, M., Brette, R. & Goodman, D. F. Brian 2, an intuitive and efficient neural simulator. *eLife* **8**, e47314, DOI: [10.7554/eLife.47314](https://doi.org/10.7554/eLife.47314) (2019).
47. Brunel, N. Dynamics of sparsely connected networks of excitatory and inhibitory spiking neurons. *J. Comput. Neurosci.* **8**, 183–208, DOI: [10.1023/A:1008925309027](https://doi.org/10.1023/A:1008925309027) (2000).

Acknowledgements

This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No. RS-2024-00401794).

Data availability

The code for the simulations, analysis, and figures is publicly available on [Github](https://github.com). Electrophysiological data was sourced from the Allen Brain Atlas (<http://celltypes.brain-map.org>).

Author contributions statement

D.D. conceived the study and developed the code. H.J.P. initiated the project and acquired funding. H.J.P. and D.D. performed the analysis and interpretation of the data. All authors reviewed and edited the manuscript.

Additional information

The authors declare no competing interests.

ARTICLE IN PRESS