Trade-offs between energetic cost and excitability in compartmental models of juvenile rat CA1 pyramidal cells

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Abstract

Neurons face fundamental trade-offs between competing demands: they must respond reliably to inputs while minimising metabolic cost. The relationship between excitability and energy efficiency is influenced by morphological diversity and degeneracy – the ability of structurally distinct ion channel configurations to produce equivalent firing behaviour. In the present study, we investigate whether such a trade-off emerges in a population of biophysically detailed models of hippocampal CA1 pyramidal neurons constrained by electrophysiological features extracted from patch-clamp recordings in acute slices from juvenile rats. We identify a global Pareto front of models that simultaneously minimise energy cost and maximise excitability, as measured by the input-output gain for somatic current injection. Additionally, we demonstrate that the absolute ATP cost of compartmental models scales with neuronal surface area, in agreement with the expected role of cell size in shaping metabolic burden.

1 Introduction

The hippocampal CA1 region plays a central role in spatial navigation, episodic memory formation, and cognitive flexibility. Neurons in this region exhibit highly diverse electrophysiological properties yet reliably encode and transmit information. This is partly attributed to neural degeneracy – the ability of structurally distinct ion channel configurations to produce functionally equivalent outputs [1-4]. Understanding how degeneracy in modelling space and in biological space is constrained by biophysical trade-offs is essential for linking cellular-level variability to cognitive function.

One fundamental trade-off in neural computation is between excitability and energy efficiency. More excitable neurons can respond to weaker inputs and fire at higher rates, but action potentials are metabolically costly, primarily due to Na^+/K^+-ATPase activity required to restore ionic gradients and calcium extrusion following each spike [5].

Here, we present an analysis of a large population of biophysically detailed compartmental models of CA1 pyramidal neurons, constrained by electrophysiological features from experimental patch-clamp recordings in acute slices from juvenile rats. We quantify the excitability-energy efficiency trade-off across the model population and identify Pareto-optimal configurations [3], asking which morphologies and parameter regimes produce neurons that are simultaneously most excitable and most efficient. These results represent a first preliminary step towards a systematic characterisation of functional and energetic trade-offs in this population of data-driven compartmental models.

2 Methods

A population of 3,500 valid compartmental models of CA1 pyramidal neurons, instantiated across 10 distinct reconstructed morphologies of juvenile rat hippocampus, was generated using a population-based data-driven modelling framework. In total, 182 electrophysiological features were used for optimisation, reliably capturing the key characteristics of experimental voltage responses [6].

ATP consumption per spike was estimated from charge carried by Na^+ and Ca^{2+} currents during a single action potential elicited by a 5 ms somatic current injection, assuming 3 Na^+ per ATP for the Na^+/K^+-ATPase and standard Ca^{2+} pump stoichiometry. Excitability was quantified as the gain of a linear fit to the F/I curve with respect to somatic current injections and somatic firing rates. Both metrics were normalised by total membrane capacitance (pF) derived from surface area, yielding size-independent measures (ATP/pF and gain/pF).

A global Pareto front was computed across all models, simultaneously minimising ATP/pF and maximising gain/pF. A model was considered Pareto optimal if no other model in the population simultaneously

achieved equal or higher excitability and equal or lower ATP cost, with at least one of these conditions holding strictly. The collection of all such non-dominated models constitutes the Pareto front. Prior to Pareto analysis, a Spearman correlation between gain/pF and ATP/pF was computed to confirm the existence of a population-level trade-off. Morphology overrepresentation on the Pareto front was assessed by a permutation test (10,000 permutations, $p < 0.05$). The relationship between surface area and median ATP cost per morphology was characterised by linear regression.

3 Results

Figure 1 shows that the total number of ATP molecules consumed per spike varied substantially across 10 morphologies. Black horizontal lines in boxplots represent the median, while dots represent individual models. Results are consistent with the expectation that larger neurons with greater membrane surface area require more energy per spike.

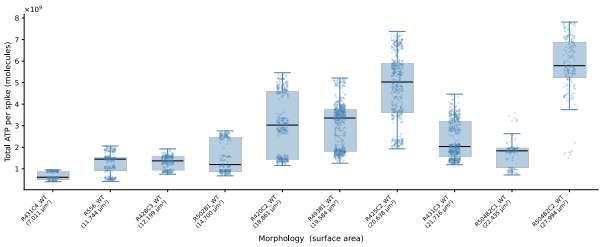

Fig. 1. Total ATP consumed per spike across 10 morphologies of different sizes, ordered by surface area.

Figure 2 shows the relationship between neuronal surface area and ATP cost, with each morphology represented by its median ATP value (filled marker) and minimum ATP value (hollow marker), connected by a vertical line. The length of the line reflects within-morphology variability: morphologies with longer lines show greater dispersion in ATP cost across their model populations. The relationship between surface area and median ATP was significant (Pearson $r = 0.78$, $p = 0.007$), as captured by the regression line, confirming that surface area is a major determinant of absolute metabolic cost.

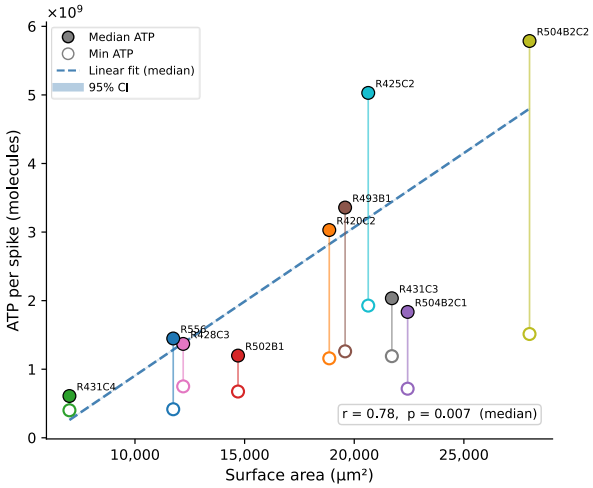

Fig. 2. Relationship between surface area and ATP consumption per morphology.

A weak but highly significant positive correlation was found between gain/pF and ATP/pF across all models (Spearman $r = 0.24$, $p < 0.001$), confirming a population-level trade-off between excitability and energy efficiency. Figure 3 shows the global Pareto analysis identifying models with an optimal trade-off between energy consumption and excitability. The analysis yielded 14 Pareto-optimal models forming a well-defined front in ATP/pF-gain/pF space, distributed across four morphologies: R420C2_WT (5 models), R502B1_WT (1 model), R504B2C1_WT (5 models), and R556_WT (3 models). A permutation test revealed that R504B2C1_WT and R420C2_WT were significantly overrepresented on the Pareto front ($p < 0.05$), indicating that these morphologies are particularly well-suited to achieving favourable excitability-efficiency trade-offs.

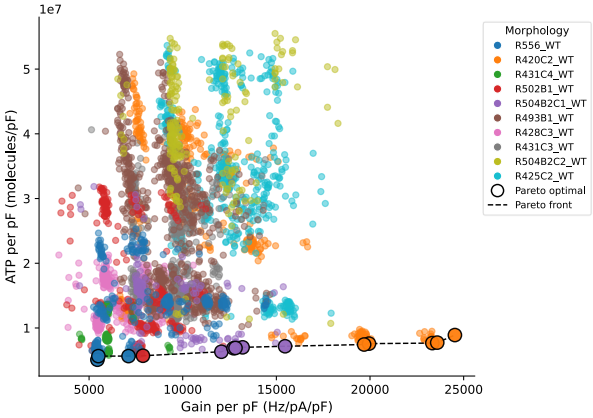

Fig. 3. Trade-off between energy efficiency and excitability across all models.

4 Discussion

The global Pareto front identified here, comprising 14 models forming a well-defined linear structure in ATP/pF-gain/pF space, represents neurons that achieve an optimal balance between metabolic cost and excitability. Pareto optimality may provide a principled way to identify such subpopulations within degenerate model ensembles with optimal solutions for the two objectives tending to occupy geometrically simple low-dimensional manifolds in parameter space [3]. The two-objective nature of our analysis naturally yields a continuum of solutions that trade off excitability and metabolic cost, with no single model dominating across both dimensions.

The substantial within-morphology variability in ATP cost reflects ion channel degeneracy. All models were optimised against identical electrophysiological targets and produce similar firing behaviour, so differences in ATP cost must arise from distinct ion channel configurations that are functionally equivalent but metabolically different. Migliore et al. showed that the conductance space of CA1 pyramidal neurons contains multiple such solutions, where different channel subsets contribute independently to firing characteristics [2]. The discrete ATP clusters in R420C2_WT suggest that this morphology permits several such distinct regimes, each valid from a functional standpoint but separated in energetic cost. If the distribution of ion channel parameters in our model population matched that in recorded CA1 pyramidal cells, this would be consistent with the concept of biological degeneracy, namely that compensatory mechanisms in neurons can sustain similar outputs across very different underlying parameter combinations [1].

The morphology R504B2C1_WT presents a particularly interesting case. Despite having the second-largest surface area, it achieves ATP per spike comparable to that of half-size surface-area morphologies. In addition, five of its models contribute to the global Pareto front, despite this morphology having the fewest valid models from optimisation overall. This suggests that the geometry of this morphology restricts the accessible parameter space to a narrow but energetically privileged region, implying that morphology and ion channel composition jointly constrain the metabolic phenotype of a neuron.

Several limitations must be acknowledged. First, excitability was characterised by a single metric. This captures only one dimension of neural responsiveness. Neurons in vivo must simultaneously satisfy multiple functional demands. Incorporating additional objectives into a multi-task Pareto framework would better reflect the true constraints shaping neuronal phenotypes [3]. Second, our models received only somatic current injection rather than distributed synaptic input. This distinction is consequential: It has been shown that while smaller neurons are more excitable under somatic stimulation due to reduced input conductance, excitability in the form of firing rates driven by distributed synaptic inputs is largely independent of dendrite length or complexity, depending instead on average dendritic diameter and intrinsic membrane conductivity [7]. The gain metric used here, therefore, reflects somatic integration capacity and may not generalise to synaptically driven conditions. Furthermore, synaptic currents contribute substantially to the energy budget of real neurons as well as their simulated counterparts, so simulations of synaptically driven neuronal responses would be more realistic and informative.

Future work will aim to extend this framework by incorporating additional excitability features and by simulating models under in vivo-like synaptic inputs, moving towards a more complete multi-objective characterisation of the excitability–efficiency trade-off in juvenile rat CA1 neurons.

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