SARC Research Proposal

Bifurcation Analysis of Complement-Mediated Synaptic Pruning: Deriving the Critical Threshold for E/I Balance Failure in Cortical Networks

Anoushka Chandra

anoushka.chandra5@gmail.com

Grade 11, IB Diploma Programme

Hyderabad, India

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1. Research Problem and Introduction

Elevated expression of *C4A* — a complement gene driving microglial tagging and elimination of excitatory synapses — is one of the strongest identified genetic risk factors for schizophrenia (Sekar et al., 2016). Excessive complement-mediated pruning shifts cortical excitation–inhibition (E/I) balance toward inhibition, producing hallmark features including reduced gamma-band synchrony and prefrontal hypoactivity (Uhlhaas & Singer, 2010). The brain partially compensates via homeostatic plasticity, scaling up remaining synaptic weights to restore firing rates (Turrigiano, 2011). However, the precise threshold of excitatory synapse loss at which homeostatic compensation fails has never been analytically derived — nor has its dependence on the relative timescales of pruning and compensation been characterized. This gap matters clinically: if the failure threshold is sharp, small increases in C4A copy number could produce disproportionately large jumps in pathological risk, explaining the observed non-linear dose-response relationship.

2. Literature Review

The Wilson-Cowan (1972) rate model governs coupled excitatory (E) and inhibitory (I) population dynamics and is the standard framework for cortical E/I analysis. Strogatz (2015) established that such systems undergo saddle-node bifurcations — stable fixed points annihilate at critical coupling values — but this has not been applied to complement-driven pruning, such as the one in schizophrenia. Hertäg & Sprekeler (2019) modeled inhibitory stabilization in E/I circuits without incorporating progressive synapse loss or homeostatic dynamics. Turrigiano (2011) characterized synaptic scaling as a compensatory mechanism but did not identify its failure regime analytically. The gap is specific: no study has derived the critical wEE threshold — the excitatory coupling strength below which homeostatic gain α cannot prevent network destabilization — nor expressed this threshold as a function of the pruning-rate-to-compensation-speed ratio β/α.

3. Research Question

At what critical level of complement-mediated excitatory synaptic pruning does homeostatic compensation fail to maintain stable cortical E/I balance, and how does this threshold depend on the ratio of pruning rate (β) to homeostatic plasticity timescale (α)?

4. Methodology

The study augments the Wilson-Cowan system with a homeostatic term $h(t) = \alpha \cdot (E^* - E)$ and a pruning dynamic $wEE(t) = wEE_0 - \beta \cdot t$, giving: $\tau \cdot dE/dt = -E + F(wEE \cdot E - wEI \cdot I + P + h(t))$ and $\tau \cdot dI/dt = -I + F(wIE \cdot E - wII \cdot I + Q)$, where $F(\cdot)$ is a sigmoid transfer function. The analytical core is a bifurcation analysis: nullclines are derived by setting both derivatives to zero; fixed points are located at their intersections; the Jacobian J is computed at each fixed point; and the Routh-Hurwitz stability conditions ($tr(J) < 0$ and $det(J) > 0$) are applied. Setting $det(J) = 0$ and solving for wEE yields the critical threshold wEE^* as a closed-form function of β/α. This analytical result is then validated numerically: Python (NumPy, SciPy, Matplotlib) is used to integrate the system across a parameter grid and generate bifurcation diagrams. Predicted threshold behavior is compared qualitatively to published EEG data on

gamma-band synchrony reduction in schizophrenia (Uhlhaas & Singer, 2010) and to C4A copy number dose-response data (Sekar et al., 2016).

5. Conclusion and Feasibility

This project will produce a novel analytical result: a closed-form expression for the critical pruning threshold wEE* and its dependence on β/α, providing a mechanistic explanation for why C4A risk scales non-linearly and why rapid adolescent pruning is disproportionately dangerous. The mathematical tools required — partial differentiation, Jacobian analysis of 2×2 systems, and the Routh-Hurwitz criterion — are accessible to a student completing IB Mathematics Analysis and Approaches HL and AP Calculus BC. Computational work requires only Python with no laboratory access or specialized resources. Broader significance: the framework may generalize to other complement-related neurodevelopmental conditions and provide a computational basis for future biomarker research targeting the pruning-compensation ratio.

References

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