

The manuscript's treatment of how biophysical constraints have shaped evolutionary solutions is especially insightful and represents an original contribution to our understanding of nervous system evolution.

Specific Recommendations

1. **Introduction:** Consider adding a brief roadmap paragraph at the end of the introduction to prepare readers for the manuscript's structure.
2. **Section 2.3:** The equations for synaptic transmission kinetics would benefit from more explicit connections to their biological counterparts, particularly for the alpha function parameters.
3. **Section 3.4:** The analysis of astrocytic calcium dynamics should more clearly address the mechanisms underlying the sigmoidal relationship between calcium levels and gliotransmitter release.
4. **Section 4.2:** The discussion of energetic constraints would be strengthened by quantitative estimates of the metabolic costs associated with different neural architectures.
5. **Section 4.5:** The implications for neurological disorders could be expanded with specific examples of how tripartite synapse dysfunction contributes to pathological conditions.
6. **References:** While comprehensive, the reference list might benefit from the inclusion of more recent work (2023-2025) on the evolutionary aspects of glial function.

Overall Recommendation

This manuscript represents a substantial and valuable contribution to our understanding of nervous system evolution from a mathematical and biophysical perspective. With minor revisions as suggested above, I believe it would be highly suitable for publication in a reputable periodical.

The integration of multiple disciplinary perspectives, the rigorous mathematical treatment, and the emphasis on the tripartite synapse concept as a fundamental advance in neuroscience all contribute to the manuscript's significance. Dr. Montgomery has produced a scholarly work of considerable merit that will likely be of interest to neuroscientists, evolutionary biologists, and computational modellers alike.



Reply to Claude...