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Dr. Abir Igamberdiev
Editor-in-Chief
BioSystems

Dear Dr. Igamberdiev,

I am pleased to submit "The Geometry of Biological Shadows: Quantifying Topological Aliasing in High-Dimensional Systems" for consideration in *BioSystems* as a computational companion to my recently published paper (Todd, 2025; vol. 258, 105608).

Context:

The earlier paper argued theoretically that Popperian falsifiability faces structural limits in high-dimensional biological systems. That work remained qualitative. This manuscript provides the computational framework to *measure* those limits.

The Central Contribution:

We introduce the "Topological Aliasing Rate"—the first standardized metric for quantifying how much 2D projections (t-SNE, UMAP) misrepresent high-dimensional neighborhood relationships. Our key empirical finding: across four standard single-cell benchmark datasets (90,300 cells total), **75.5% of apparent neighbors in 2D projections were NOT neighbors in the original high-dimensional space**.

This is not a property of any particular dataset. It is a geometric consequence of projecting $D_{sys} \approx 10$–40 dimensions into $D_{obs} = 2$.

The Deliverable:

The accompanying `falsifiability` Python library (pip-installable, archived on Zenodo: DOI 10.5281/zenodo.17791874) enables any researcher to compute aliasing rates on their own data. We provide practical calibration guidelines:

- Aliasing $< 30\%$: Visual clusters likely reflect high-dimensional topology
- Aliasing 30–60%: Clusters should be interpreted with caution
- Aliasing $> 60\%$: 2D is for visualization only; quantitative analysis must occur in high-dimensional space

Why BioSystems:

This work directly extends the epistemological framework of my earlier *BioSystems* paper, operationalizing philosophical arguments into measurable quantities. The audience that engaged with

"The Limits of Falsifiability" is precisely the audience for this computational companion. The work bridges systems biology, bioinformatics, and philosophy of science—the intersection that defines *BioSystems*.

Thank you for your consideration.

Sincerely,

Ian Todd
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