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November 30, 2025

Professor Abir Igamberdiev
Editor-in-Chief
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Dear Professor Igamberdiev,

I am pleased to submit “Nonergodic Development: How High-Dimensional Systems with Low-Dimensional Anchors Generate Phenotypes” for consideration in *BioSystems*.

This manuscript develops a theoretical framework for understanding why genotype does not algorithmically determine phenotype. The core insight is that biological development is **nonergodic**: the state space of a developing organism is too vast to explore in biological time. Developmental trajectories are trapped in attractor basins, and the phenotype reflects which basin was entered—not an algorithmic genotype-to-phenotype mapping.

The genome functions as a low-dimensional *anchor* that constrains which attractor basins are accessible, while environmental history determines which basin the developmental trajectory enters. I formalize this via the **Dimensional Gap** (Δ_D), which quantifies the mismatch between anchor dimensionality and developmental degrees of freedom. When $\Delta_D \gg 0$, allele-based and trajectory-based models become non-identifiable from aggregate data.

The “Twin Worlds” experiment demonstrates this dramatically: identical genotype distributions in different environmental regimes produce patterns that naive genetic analysis would misinterpret as allele frequency differences ($F_{ST} \approx 0$ yet $P_{ST} \gg 0$). This provides a formal explanation for “missing heritability” in GWAS—the heritability is not missing variants but missing trajectory information.

I apply this framework to Sierra et al. (2025, *Science Advances*), who found that cooperative mammalian species have lower cancer prevalence. Their allele-based interpretation is compelling, but my framework shows it is not uniquely supported: cooperative environments enable slower, more coordinated development with fewer cellular bifurcations—cancer being, in this framing, attractor bifurcation rather than repair failure.

This work provides formal foundations for Lissek’s (2024, *BioSystems*) “cancer memory” hypothesis: in nonergodic terms, epigenetic memory *is* the trapped state—the system cannot spontaneously return to its previous attractor basin.

This submission continues a research program on dimensional constraints in biology:

- Todd (2025a): “The limits of falsifiability” (DOI: 10.1016/j.biosystems.2025.105608)
- Todd (2025b): “Timing inaccessibility and the projection bound” (DOI: 10.1016/j.biosystems.2025.105632)

The manuscript engages with recent *BioSystems* publications including Lee et al. (2022) on plasticity, Letsou (2024) on temporal development, Corning (2022) on systems evolution, and Fontana

(2023) on development-ageing-cancer connections. All simulation code is available at <https://github.com/todd866/nonergodic-development>.

This manuscript is original and not under consideration for publication elsewhere.

Thank you for your consideration.

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