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Professor Abir Igamberdiev
Editor-in-Chief
BioSystems

Dear Professor Igamberdiev,

I am pleased to submit "Genotype $\neq$ Phenotype: High-Dimensional Development, Plasticity, and the Limits of Allele Stories" for consideration in *BioSystems*.

This manuscript provides a mathematical formalization of a debate currently active in this journal. Lissek (2024, *BioSystems* 247) recently proposed that malignancy can develop through "cancer memory"—epigenetic mechanisms unleashed by initial oncogenic changes—rather than relying solely on continued mutation accumulation. My work supplies the information-theoretic dual to this biological argument: I show that when phenotype emerges from low-dimensional genetic parameters passing through a high-dimensional developmental system, allele-based and plasticity-based models become **formally non-identifiable** from aggregate observational data.

The paper introduces the "Dimensional Gap" (Δ_D), which quantifies when this non-identifiability arises, and demonstrates it through a minimal developmental network model. The "Twin Worlds" experiment shows that identical genotype distributions in different environments produce patterns a naive allele model would misinterpret as genetic differences—with $F_{ST} \approx 0$ yet $P_{ST} \gg 0$. This directly explains why "missing heritability" in GWAS studies may reflect projection artifacts rather than missing variants.

The work responds to Sierra et al. (2025, *Science Advances*), who documented lower cancer prevalence in cooperative mammalian species and modeled this as allele-based selection. I show their finding is equally consistent with plastic developmental policies responding to cooperative environmental cues—a distinction with significant implications for intervention strategies.

This submission continues a research program on dimensional constraints in biology previously published in *BioSystems*:

- 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)

In the tradition of Rosen's critique of algorithmic biology, I demonstrate that the gene-as-algorithm assumption is not merely an approximation but a projection that actively discards causal structure.

The manuscript engages directly with recent *BioSystems* publications including Lee et al. (2022) on phenotypic plasticity, Letsou (2024) on temporal structure in development, Corning (2022) on systems evolution, and Fontana (2023) on the development-ageing-cancer nexus. I believe it will be of strong interest to the journal's readership.

All simulation code is publicly available at `https://github.com/todd866/genotype-vs-phenotype`, with full documentation of the AI-assisted workflow used in manuscript preparation.

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

Thank you for your consideration.

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