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Professor Abir Igamberdiev
Editor-in-Chief
BioSystems

Dear Professor Igamberdiev,

I am pleased to submit "The Physics of Immune Cooperation: Dimensional Surveillance and Attractor Enforcement in Multicellular Systems" for consideration in *BioSystems*. This manuscript develops a theoretical framework supported by computational simulations and empirical validation.

This manuscript proposes a unified theoretical framework that resolves the "combinatorial explosion" paradox in immunology by reframing immune recognition as a problem of **dimensional surveillance**. Drawing on attractor dynamics, costly signalling theory, and the bioelectric frameworks of Levin et al., I argue that the immune system does not merely recognize molecular patterns but actively measures the dynamical complexity (D_{eff}) of target cells.

Cancer cells, virally-infected cells, and senescent cells share a common signature: reduced effective dimensionality, reflecting escape from high-dimensional organismal attractors into simpler replicative or dysfunctional states. Immune receptor interactions (CD molecules, MHC-TCR coupling) function as **synchronization probes** that couple to target cells and measure their dynamical complexity. This reframing unifies cancer immune evasion, T-cell exhaustion, autoimmunity, and chronic inflammation under a single dynamical principle.

Key Contributions:

1. **Dynamical Friction and Exhaustion:** I derive T-cell exhaustion not as a functional defect but as a thermodynamic consequence of "dynamical friction"—the metabolic cost of coupling a high-dimensional sensor to a low-dimensional target. Exhaustion time scales as $t_{exhaust} \sim E_0/k(\Delta D)^2$.

2. **Sensor Collapse and Inflamm-aging:** When the immune sensor itself loses dimensionality, distinct target states alias onto the same low-dimensional projection, producing either indiscriminate attack (autoimmunity) or indiscriminate tolerance (exhaustion)—explaining the paradox of inflamm-aging.

3. **Empirical Validation:** Crucially, I test this theory against single-cell RNA sequencing data from melanoma patients (GSE120575). T-cells from immunotherapy responders exhibit **2.3-fold higher effective dimensionality** (participation ratio ≈ 28) compared to non-responders (≈ 12).

The Dimensionality-Entropy Dissociation: Our analysis reveals a critical theoretical distinction. While responders have higher *dimensional structure* (D_{eff}), they do not have higher *transcriptomic entropy*—in fact, entropy is slightly higher in non-responders. This empirically distinguishes **coherent complexity** (health) from **incoherent noise** (disease), validating the core

premise that the immune system targets loss of functional degrees of freedom, not merely thermodynamic disorder.

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 substantially with Cohen et al. (2022, *Nature Aging*) on complex systems approaches to aging, and Levin (2021, *Cell*) on bioelectric signaling and morphogenetic fields. All simulation code and analysis scripts are available at `https://github.com/todd866/immune-cooperation`.

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

Thank you for your consideration.

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