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Editorial Office
Progress in Biophysics & Molecular Biology

Dear Editors,

I am pleased to submit the manuscript "The Code-Constraint Problem in Biological Systems: How Low-Dimensional Interfaces Shape High-Dimensional Dynamics" for consideration as a Perspective article in *Progress in Biophysics & Molecular Biology*.

Summary. Biological systems operate in high-dimensional state spaces, yet experimental readouts—order parameters, expression markers, population codes—are inevitably low-dimensional. This dimensional mismatch creates systematic interpretive challenges across molecular, cellular, and systems biology. The manuscript proposes a unifying framework: low-dimensional interfaces function as *stabilizing constraints* rather than information channels. Using coupled oscillator simulations, we demonstrate a distinctive signature—complexity collapse in responding systems with bounded tracking—that appears only for structured projections capturing coherent collective variables.

Why PBMB? This work bridges multiple domains that your journal integrates:

- *Molecular biophysics*: We connect to protein conformational dynamics and the reliability of order-parameter descriptions (folding funnels, reaction coordinates).
- *Systems biology*: The framework addresses when coarse-grained models are reliable versus when they become "shadows" of latent dynamics—a question central to gene regulatory network modeling.
- *Bioelectricity and morphogenesis*: We explicitly connect to Michael Levin's work on bioelectric control of pattern formation, where low-dimensional voltage gradients constrain high-dimensional cellular dynamics.
- *Theoretical synthesis*: The paper positions the constraint framework relative to synergetics, information bottleneck theory, and Markov blanket formalism, offering a new quantitative dimension (bandwidth) to these established approaches.

Novel contribution. The central claim is testable and distinct from existing frameworks: we propose a *dynamical regime diagnostic*—complexity collapse in responding systems while tracking error remains bounded with respect to coarse-grained reconstruction. This signature discriminates effective biological codes (structured collective variables) from arbitrary dimensional reductions (which fail to induce constraint). The minimal model is intentionally abstract to emphasize generality; we include a concrete translation to protein-ligand binding with experimentally testable predictions.

Broader significance. The framework offers practical criteria for evaluating when low-dimensional

models are reliable, with implications for experimental design across scales—from choosing reaction coordinates in molecular dynamics to interpreting single-cell manifolds to understanding neural population constraints.

I confirm that this work is original, has not been published elsewhere, and is not under consideration at another journal. All simulation code and data are publicly available at `https://github.com/todd866/code-formation-jtb`.

Thank you for considering this submission. I look forward to your response.

Sincerely,

Ian Todd
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