Topological States in Out-of-Equilibrium Allosteric Assemblies

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I know this is too long (∼260 words), this is somewhat intentional so you can tell me what to cut out, in particular the "results" part is quite long and I don't love it and I need a more "zoomed-out" conclusion at the end. I also have some notes and questions for myself and you at the end which also includes what the format this is meant to be.

Stochastic systems are key to many areas of biophysics as much of living matter takes place in a highly noisy environment. However, despite this noisiness, many biological systems show a high degree or robustness. A recent new direction in understanding this apparent paradox is the study of topology of stochastic systems[1–4]. Topological states can effectively reduce the dimensionality of the configurational space and thus can explain robustness without making specific assumptions about the mechanics of a system, while themselves being robust to local changes. In this study we look for topological features in a non-equilibrium, thermodynamically consistent stochastic model of an allosteric assembly where each unit can change conformation and (de)phosphorylate. The system is driven out of equilibrium by the inclusion of two different phosphorylation reactions: a direct reaction by (de)binding a phosphate group and one driven by ATP to ADP conversion. We allow these to couple differently depending on subunit conformation as this is to only way for an isolated subunit to favour undergoing a futile cycle of phosphorylating, changing conformation, dephosphorylating and changing conformation back. Such futile cycles are common in biological settings[5, 6] and give rise to topological currents when imposed artificially[2]. We find that even without explicitly favouring futile cycles in the assembly, adding an energy cost to having a boundary between different conformations results in directed probability currents in the steady state. If both this energy cost and the ATP concentration are large then we get a connected current loop as in **??** corresponding to the macroscale equivalent of the futile cycle. If either is reduced, this loops breaks in one place and the current is transferred along a diffuse network through the gap.

References

[1]A. Murugan and S. Vaikuntanathan, "Topologically protected modes in non-equilibrium stochastic systems", Nature Communications **8**, 13881 (2017).

[2]E. Tang, J. Agudo-Canalejo, and R. Golestanian, "Topology Protects Chiral Edge Currents in Stochastic Systems", Physical Review X **11**, 031015 (2021).

[3]K. Sone, K. Yokomizo, K. Kawaguchi, and Y. Ashida, *Hermitian and non-Hermitian topology in active matter*, (July 23, 2024) `http://arxiv.org/abs/2407.16143` (visited on 11/28/2024), pre-published.

[4]C. Zheng and E. Tang, "A topological mechanism for robust and efficient global oscillations in biological networks", Nature Communications **15**, 6453 (2024).

[5]A. K. Sharma, R. Khandelwal, and C. Wolfrum, "Futile cycles: Emerging utility from apparent futility", Cell Metabolism **36**, 1184–1203 (2024).

[6]M. Samoilov, S. Plyasunov, and A. P. Arkin, "Stochastic amplification and signaling in enzymatic futile cycles through noise-induced bistability with oscillations", Proceedings of the National Academy of Sciences **102**, 2310–2315 (2005).

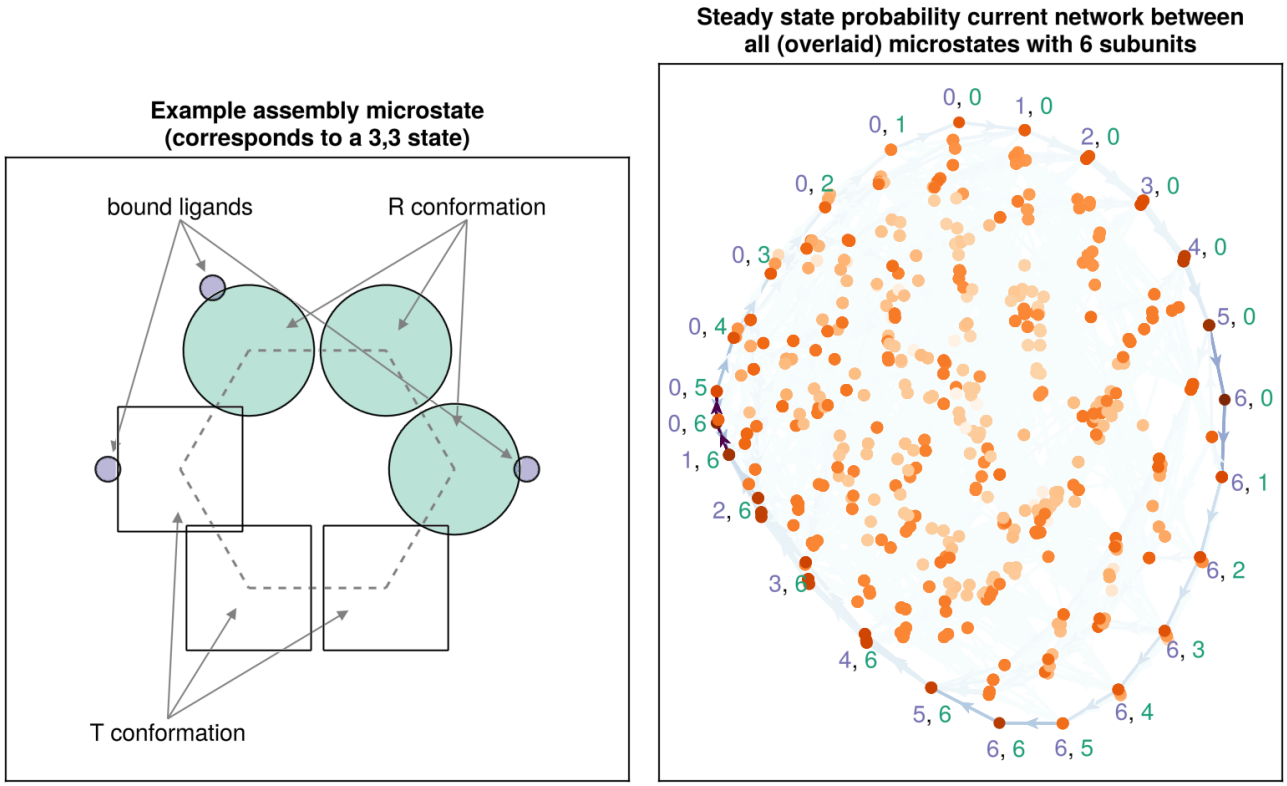
Example assembly microstate
(corresponds to a 3,3 state)
bound ligands
R conformation
T conformation
Steady state probability current network between
all (overlaid) microstates with 6 subunits
0, 0
1, 0
2, 0
3, 0
4, 0
5, 0
6, 0
6, 1
6, 2
6, 3
6, 4
6, 5
6, 6
5, 6
4, 6
3, 6
2, 6
1, 6
0, 6
0, 5
0, 4
0, 3
0, 2
0, 1

Figure 1:

1 Notes

Format For POL2025 (the one due on the 6th) it should be 250 words, include references and up to 1 figure.

Topic I need to choose one of a list of topics. Perhaps the closest might be: **"Biomolecular assemblies and condensates"** given that the main model is of an allosteric assembly? Others that may be relevant:

- "Patterns, waves, transport, collective phenomena, and microswimmers" – there's collective phenomena! but idk about microswimmers
- "Clocks, timers and cell cycle dynamics" – if we lean into KaiABC then maybe
- "Protein structure, dynamics and interactions" – cause I guess the polymer as I've been calling it would realistically be a protein?
- "Emerging Areas in the Physics of Life" – idk what this is but probably not

1.1 Questions

- Approach to talk about a project that has only just started?
- Should I be talking about allostery or not so much? It seems relevant and as an interesting topic but it's not really a core ingredient in it.
- I'm a bit worried that the only "result" is a bit obvious once you think about it. If we add a penalty for NN having different conformation then of course the ones with all the same conformation will be preferred. Then if all are in conformation 1 (tense) then they are ATP driven to bind ligands so they do so. After that they are by our choice of parameters not favoured to debind hence the only thing they can do is change conformation. The same sort of reasoning then completes the cycle.
- Is an ArXiV citation admissible here?[3]

1.2 Key points to cover

- stochastic systems
- futile cycles
- non-equilibrium dynamics
- allostery
- system features
  - complex – high dimensional network, not pen-and-paper tractable
  - locality – unlike the previous models, have NNs, can model waves along the polymer
  - discrete configurational space
  - Thermodynamically consistent? idk if this is the right wording

- Search for topological states/patterns in realistic systems (this means starting from the ground up with (non-equilibrium) statphys, LDB, no arbitrary choices) with futile cycles
- the futile cycle is implemented via physical parameters by coupling to two physically reasonable asymmetrical processes