Topological States in Out-of-Equilibrium Allosteric Molecular Assemblies

Jan Kocka

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 are general features of a class of systems that are modified but persist as parameters of the system are changed or noise alters it. This persistence along with their ability to effectively reduce the dimensionality of the problem makes them a prime candidate for explaining this robustness. In this study we look for topological features in a non-equilibrium, thermodynamically consistent stochastic model of an allosteric molecular assembly where each subunit can change conformation and bind ligands. Our master equation model is based on considering multiple chemical reactions, the rates of which depend on chemical concentrations. We then investigate such environments where isolated subunits would undergo futile cycles of binding a ligand, changing conformation, debinding and changing conformation back to its original state. Such futile cycles are common in biological settings[5, 6] and can give rise to topological edge currents[2]. Upon joining the subunits with a nearest-neighbor interaction however, the small futile cycles fall apart, and we look for open of closed directed currents in the overall assembly dynamics (fig. 1). Such closed loops in the macroscopic dynamics could help understand highly robust, out-of-equilibrium systems such as the KaiABC molecular clock[4] or . . . .

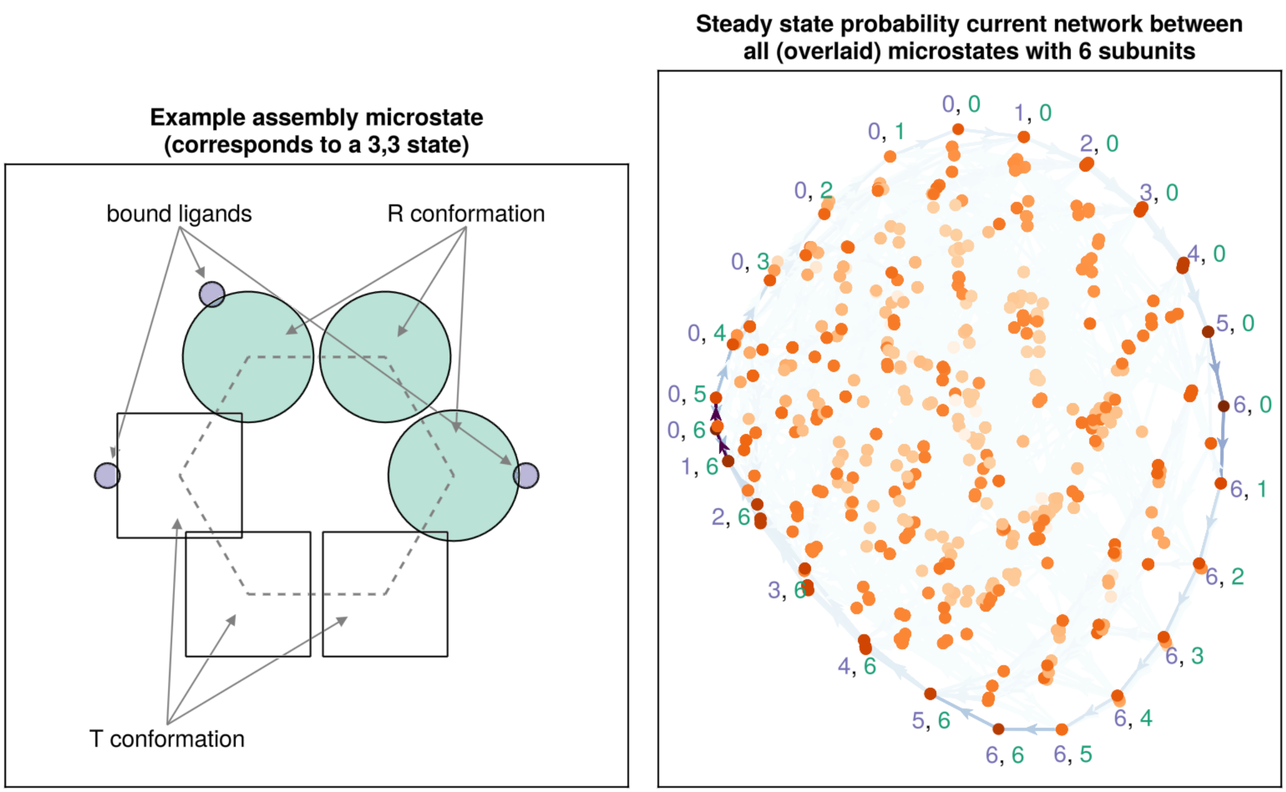

Figure 1:

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).

1 New Notes

1.1 Questions and things to discuss

- Title! Right now it is very clunky. Should it include "thermodynamically consistent"?
- Conclusion bit! Very much not sure about it as it is – is it too short? Should I specifically cite the paper I do there as that really proposes a similar but different model for it, or should I instead highlight the locality difference we add to it? Not sure
- In order to expand the conclusion I need to slightly cut down something.
- Should I reference the figure from the abstract?
- Little Things
  - Should I explicitly list what our futile cycle is? It's a bit long and perhaps obvious but I think it's nice to give a concrete, simple thing to visualize.
  - I should probably check that using "artificially" where I do is appropriate.
  - "this robustness" → "biological robustness"?
  - Is "We consider" acceptable language?

1.2 General

- So going for **Clocks, timers and cell cycle dynamics** topic
- Can I squeeze in "non-Hermitian topology" somewhere (I have some references for it, and it is relevant)?

2 Old 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

2.1 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]

2.2 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