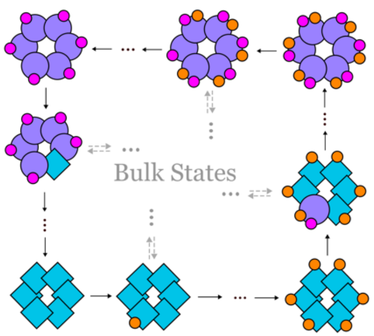
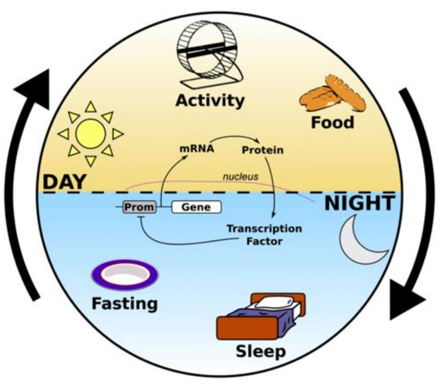
Topology protects long cycles in stochastic systems





Evelyn Tang
Center for Theoretical Biological Physics
Physics Department
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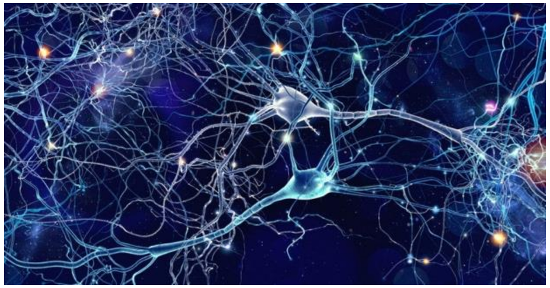
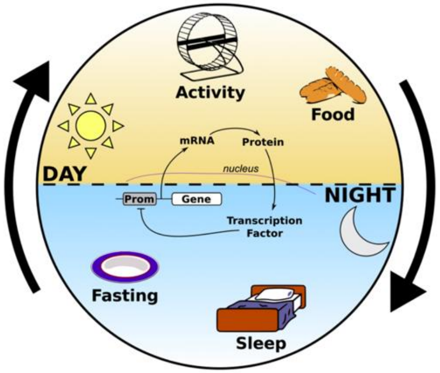
IUPAP Interdisciplinary Prize
IUPAP General Assembly
October 13, 2024

How do long and stable timescales and rhythms emerge?

Given heterogeneity and randomness,
how does robust function emerge?

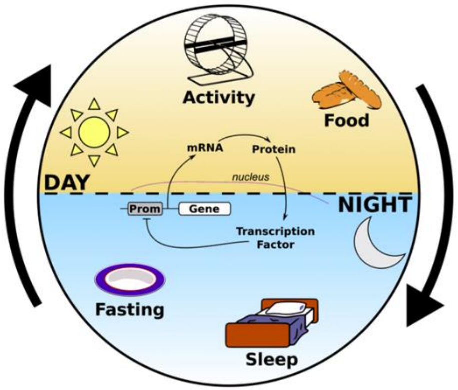


Long time-scales such as circadian cycles or memory, persist despite consisting of many faster reactions



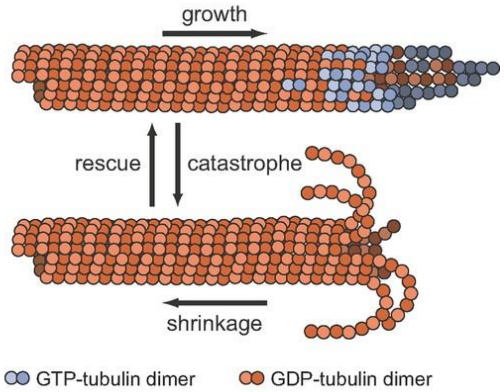
Can we predict such global dynamics analytically?

Biological systems show many types of robust self-organization



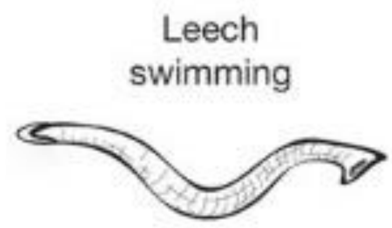
http://ieeecss.org

A global clock



Bioessays 2013

Gene replication



Churchland et al., *Nature* 2012

Rhythmic motion

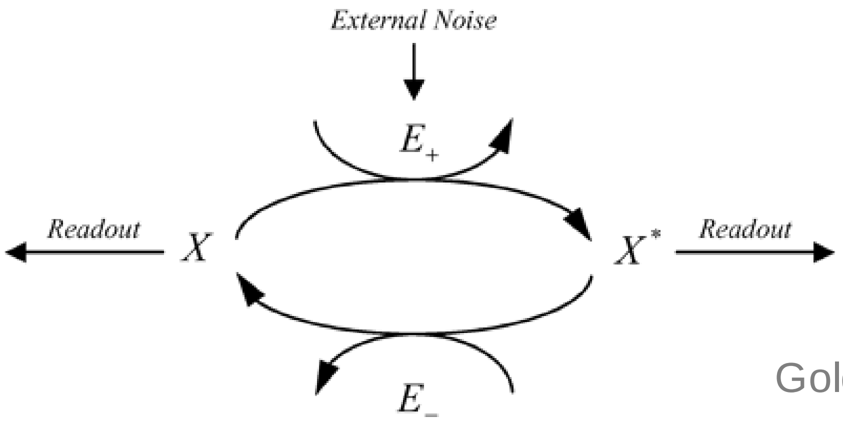
Many parts acting together to produce more than the sum of each part

Similar dynamics all hinge on the edge state of a topological phase, that consists of many non-reciprocal cycles

Living things show strong non-Hermiticity and dissipation which appears wasteful

Living systems exhibit many microscopic out-of-equilibrium transitions, e.g. by consuming fuel such as ATP or GTP

“Futile cycles” consume a lot of energy; ubiquitous in biology (metabolism, sensory systems, muscular contraction, protein synthesis)

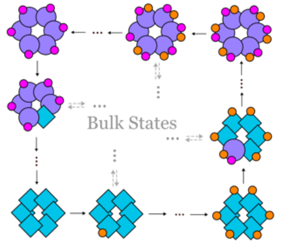


Hopfield, *PNAS* 1974

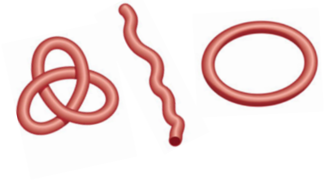
Goldbeter & Koshland, *PNAS* 1981

Could these “wasteful” motifs contribute to system robustness?

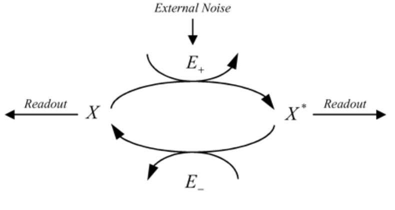
A topological mechanism for robust function in stochastic systems



Model for emergent oscillations

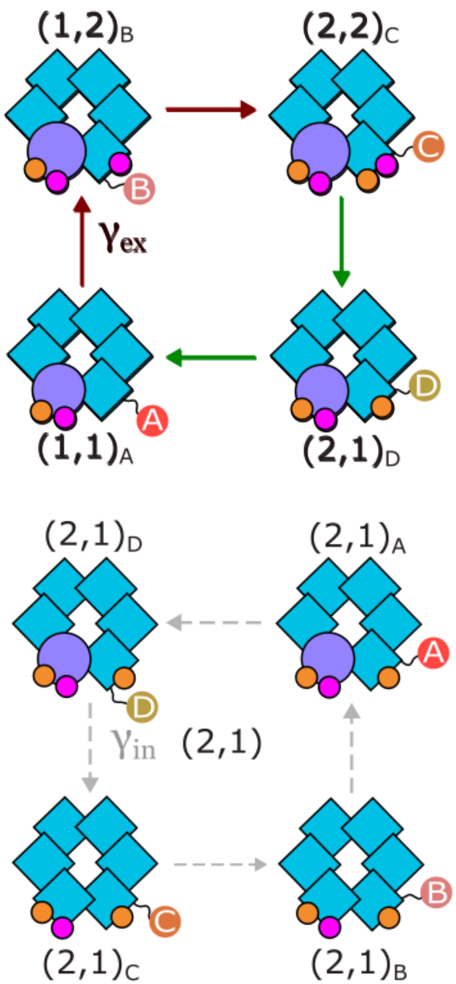


New physics and underlying topology



Non-reciprocity is a necessary condition

A two-dimensional reaction space with four internal states



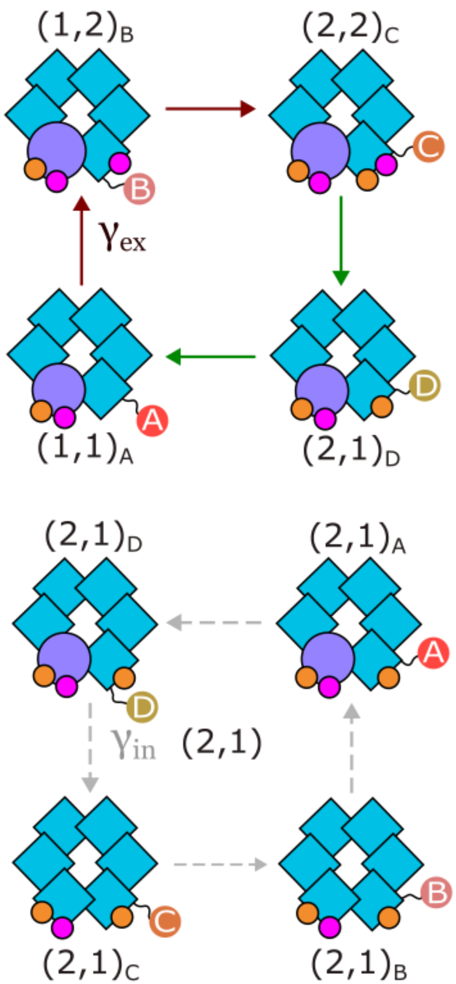
Phoshorylation — Dephosphorylation

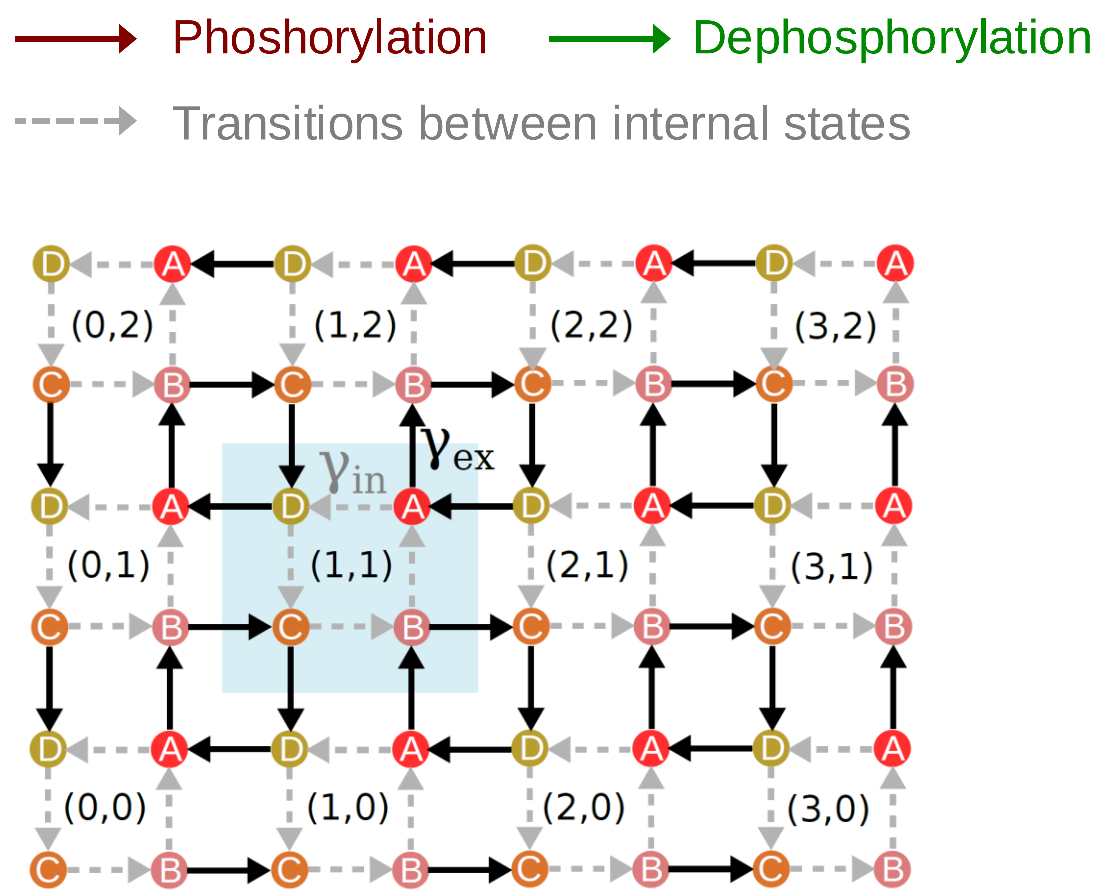
Another process primes system for next transition, i.e. 4 internal states which we can label

A: Pink phosphorylation
B: Orange phosphorylation
C: Pink dephosphorylation
D: Orange dephosphorylation

Transitions between internal states of the same phosphorylation level

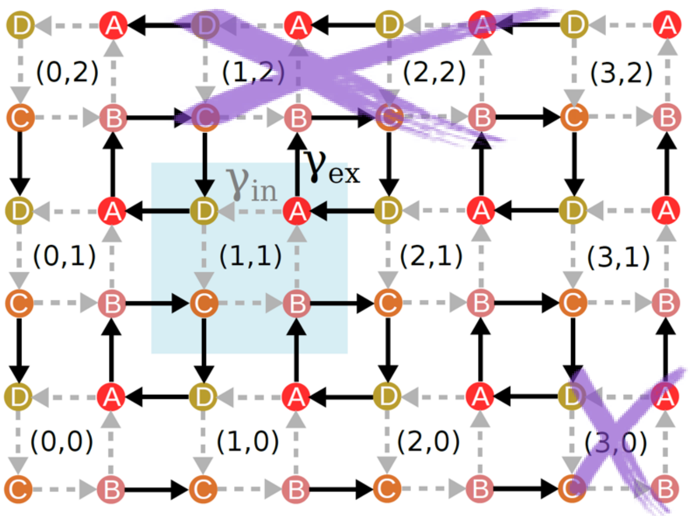
Repeating this motif of four internal states allows the tiling of a lattice

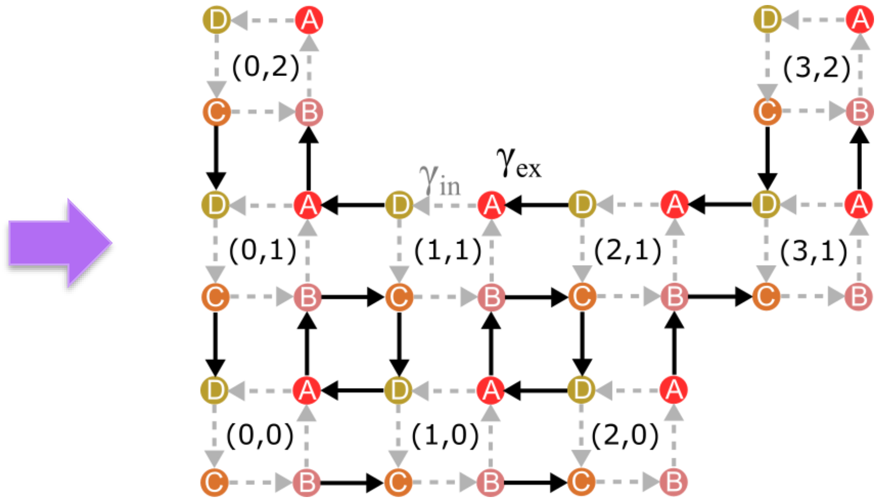




Square lattice

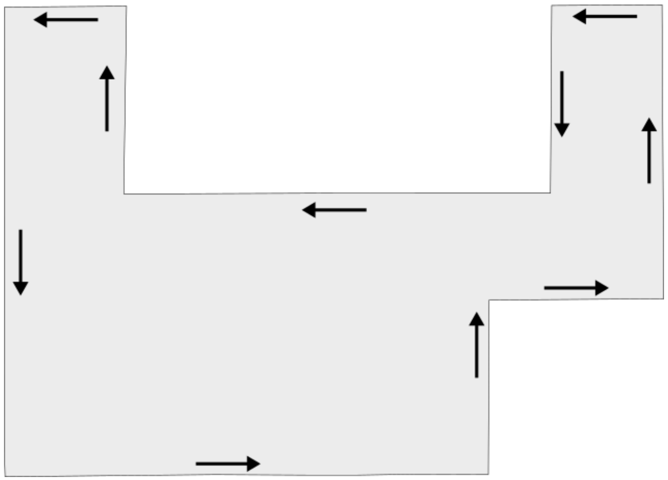
When large external transitions dominate, the system will stay on the edge





Edge current is robust to inaccessible or missing states

Random matrix theory:
robustness to random perturbations



ET et al., *Phys Rev X* 2021

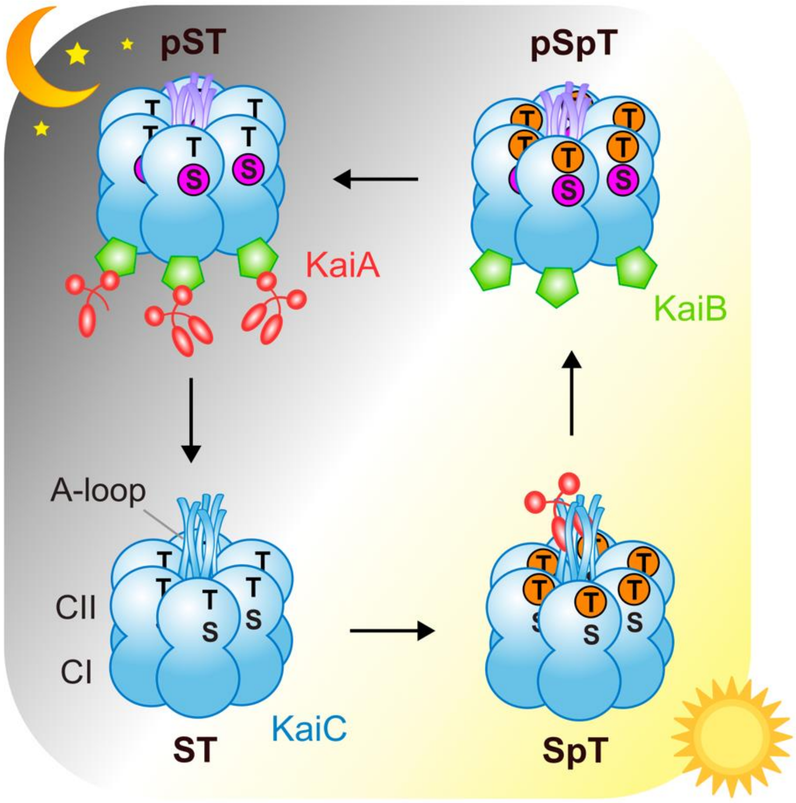
Can describe emergent cycles in biological oscillators

24hr cycle in KaiC hexamers arises from sequential phoshorylation of T and S sites

KaiC monomers can take different conformations, e.g., with exposed or buried A-loops

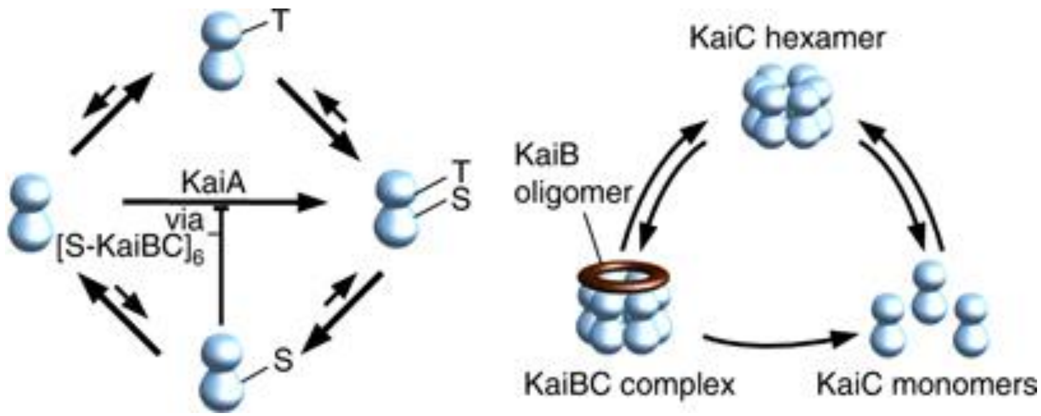
Cohen & Golden, *Microbio & Mol Bio Rev* 2015

Given the large reaction space, why does a global and robust cycle emerge?



A large phase space of many possible different reactions

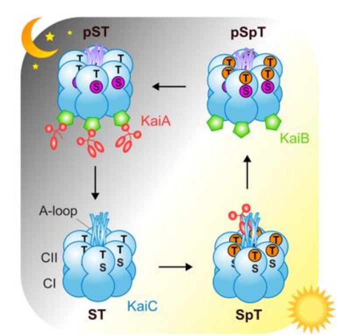
Monomers can autophosphorylate or assemble into hexamers



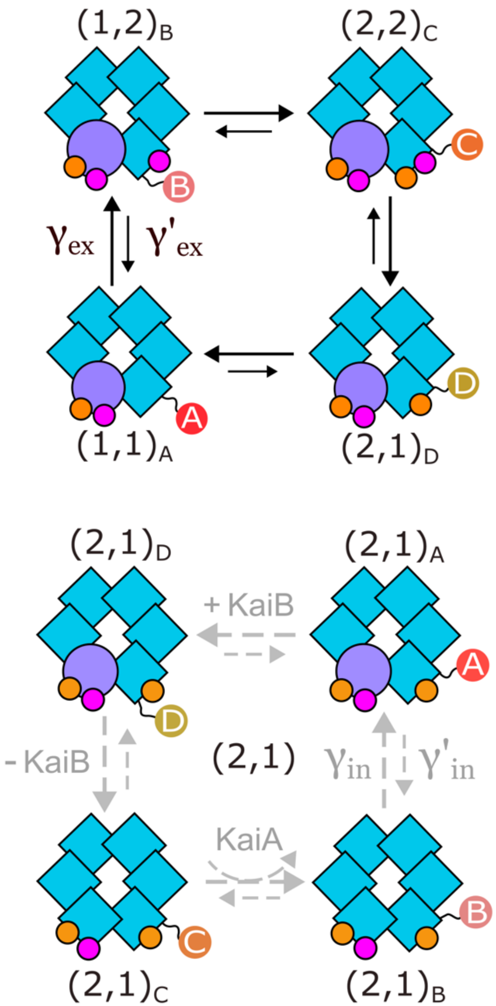
Brettschneider et al., *Mol Syst Biol* 2010

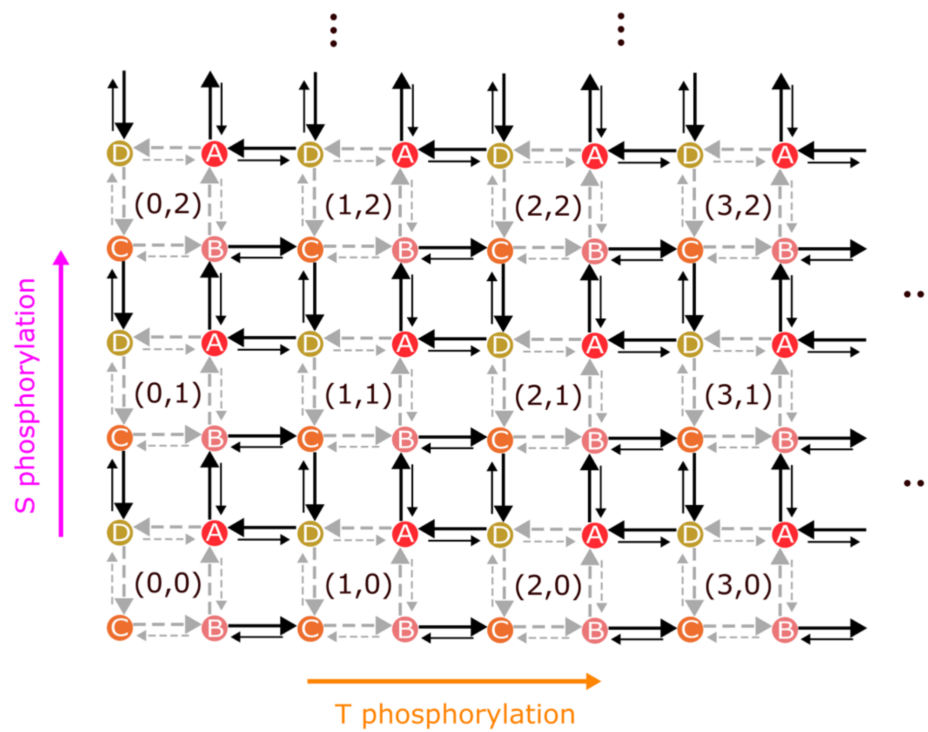
Can take different conformations in same hexamer Han et al., *Nat Comm* 2023

With this large phase space of monomer transitions, why do they phosphorylate in a concerted way?



Within the large space of transitions: we propose 4-state directed cycles





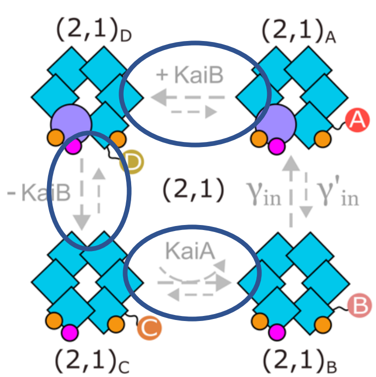
Experimental evidence for this model

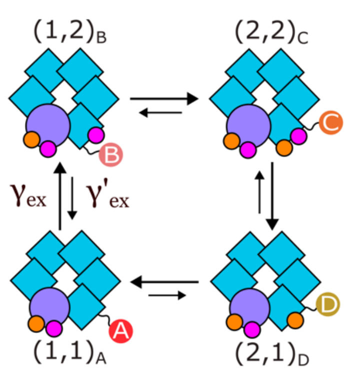
Specific internal states are needed for phosphorylation steps

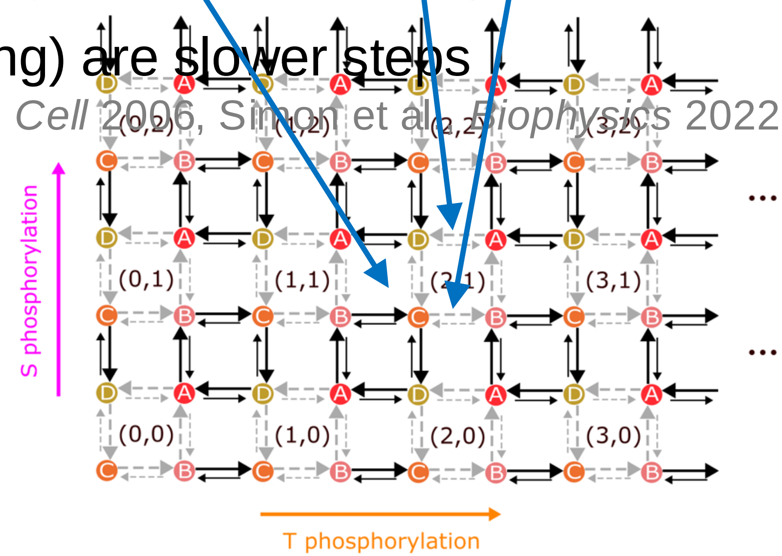
- KaiA binding promotes phosphorylation Tomita et al., *Science* 2005
- KaiB binding promotes dephosphorylation Rust et al., *Science* 2007
- KaiA only binds to exposed A-loop Kim et al., *PNAS* 2008

Difference in transition rates

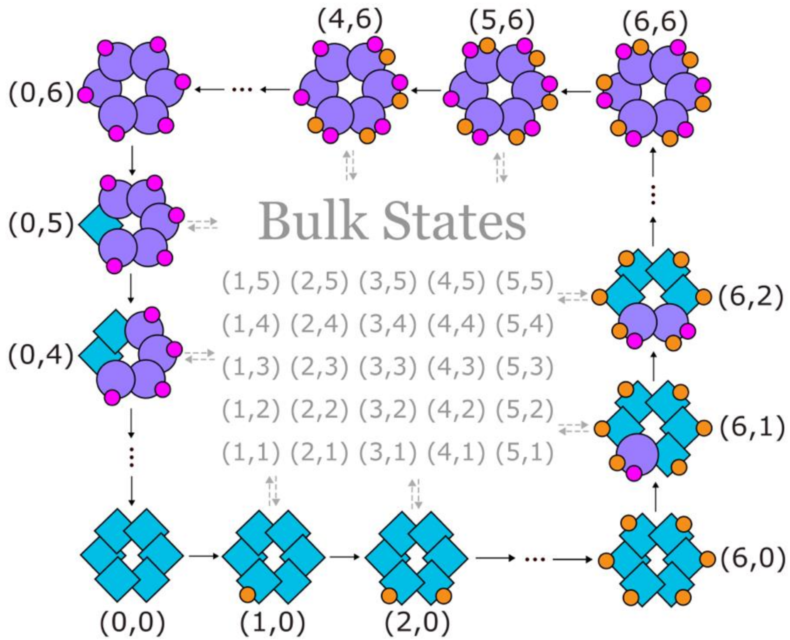
- Phosphorylation reactions are faster Paijmans et al., *PLoS comp bio* 2017
- KaiB binding (and possibly its unbinding) are slower steps
  Abe et al., *Science* 2015, Kageyama et al., *Mol. Cell* 2006, Simon et al., *Biophysics* 2022







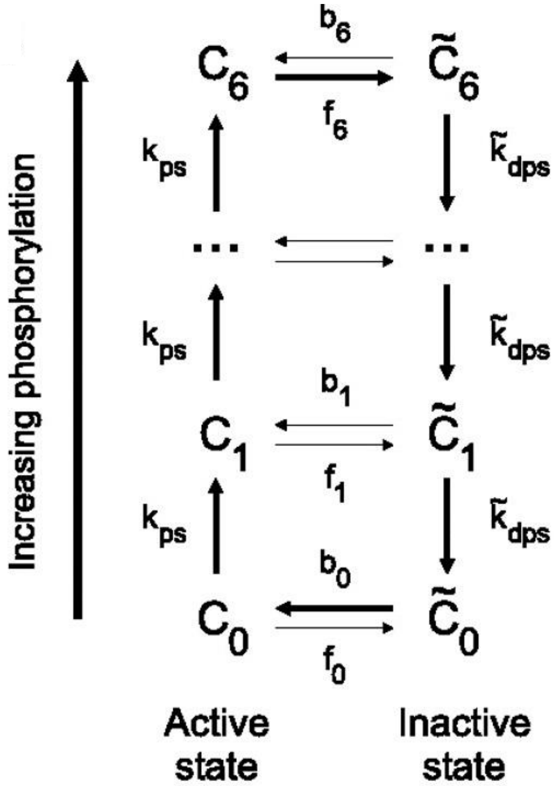
Edge cycle reproduces observed dynamics with fewer fine-tuned parameters



Edge state produces cycles of

- all T phosphorylation,
- all S phosphorylation,
- all T dephosphorylation,
- all S dephosphorylation

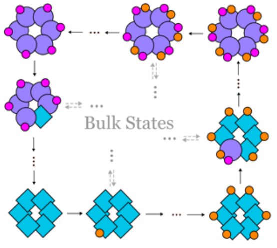
Zheng and ET, *Nat Comm* 2024



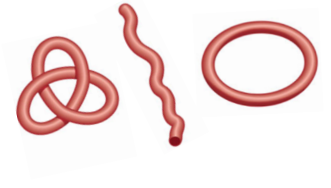
In MWC paradigm: ordering put in by hand; intermediate transitions assumed negligible

van Zon et al., *PNAS* 2007

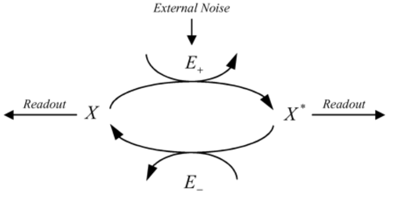
A topological mechanism for robust function in stochastic systems



Model for emergent oscillations



New physics and underlying topology

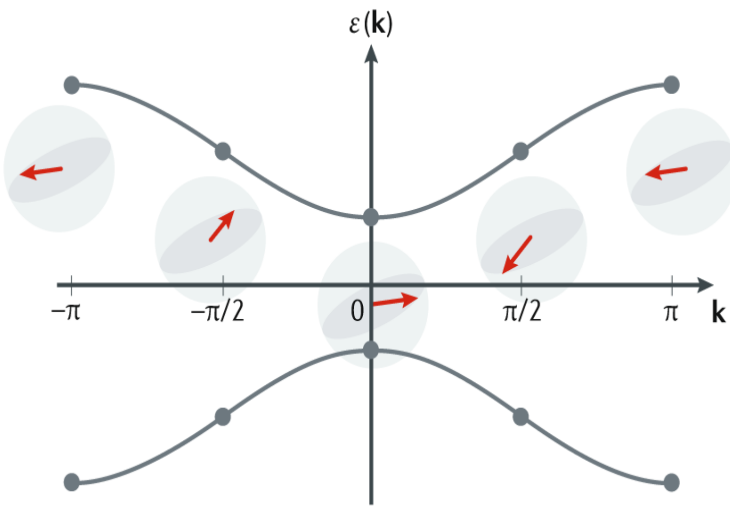


Non-reciprocity is a necessary condition

To see if the system is in a topological state, analyze $\mathcal{W}$ the transition matrix

Systems described by the Master equation $\frac{d}{dt}\boldsymbol{p} = \mathcal{W}\boldsymbol{p}$

Lattice description allows for calculation of the Berry connection, which is calculated from the eigenvectors of $\mathcal{W}$



Nat Rev Phys 2019

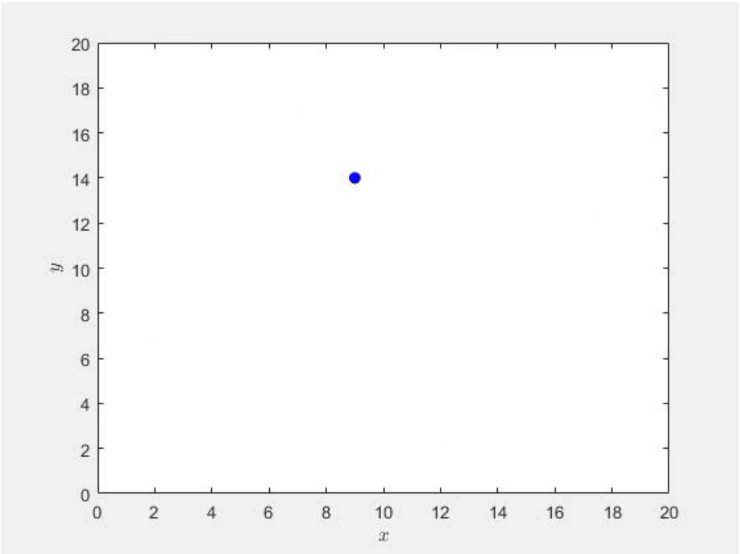
Integration over reciprocal space gives 0 (trivial phase) or π (topological phase)

First developed for quantum Hamiltonians

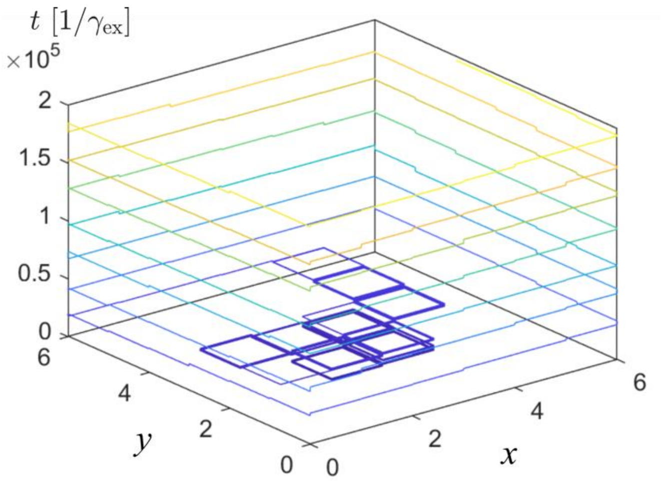
$$-i\frac{d}{dt}\psi(t) = \mathcal{H}\psi(t),$$

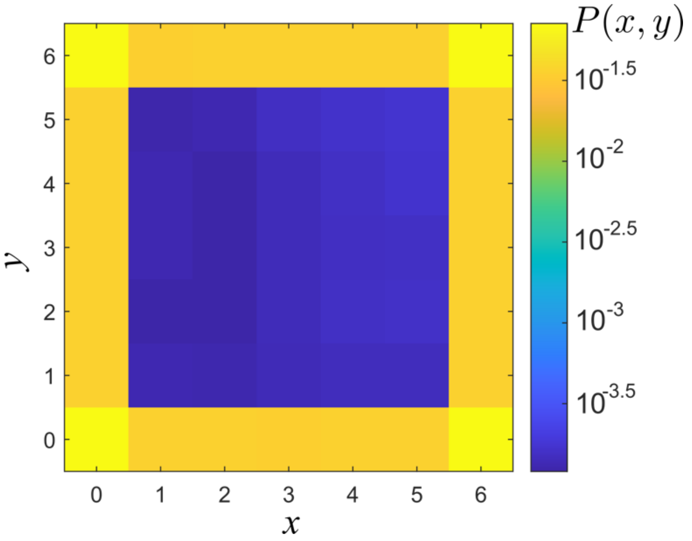
Identical to the Master equation up to a i

Verified using stochastic simulations



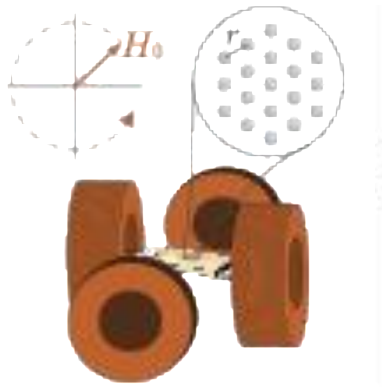
Gillespie algorithm, $\gamma_{\mathrm{ex}} = 10^3 \gamma_{\mathrm{in}}$

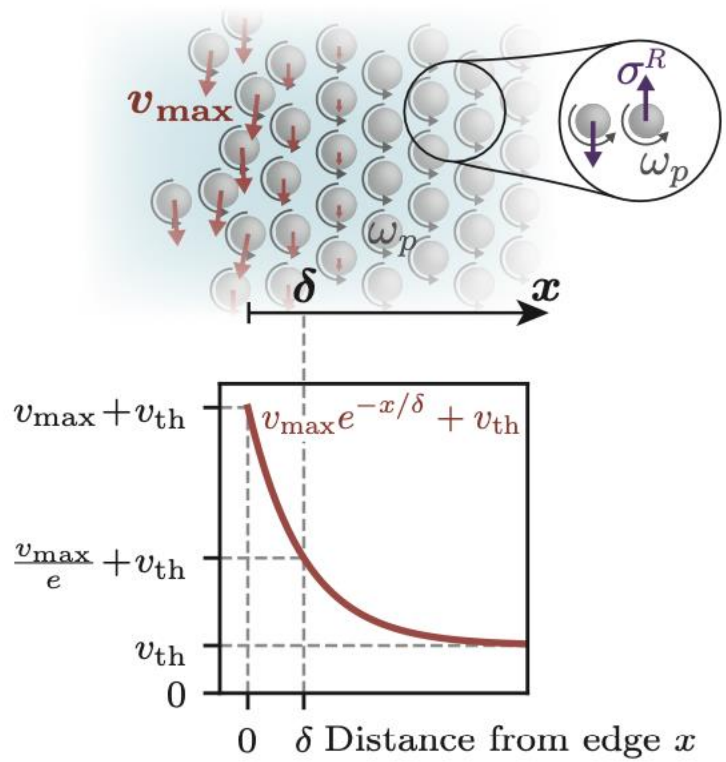


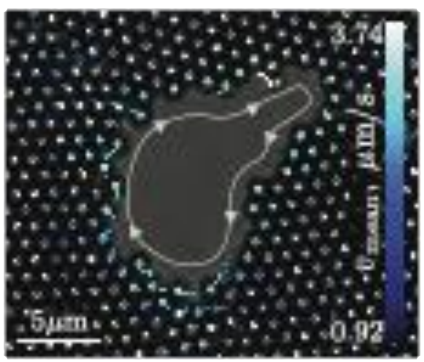


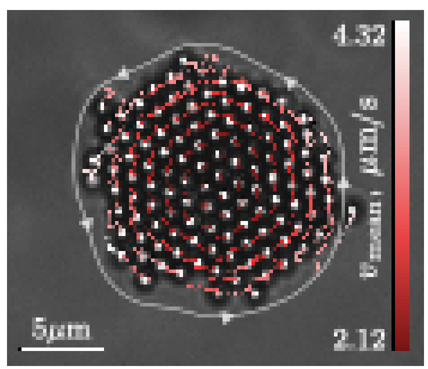
Edge flows drive macroscopic re-organization in driven colloids

Lisa Biswal





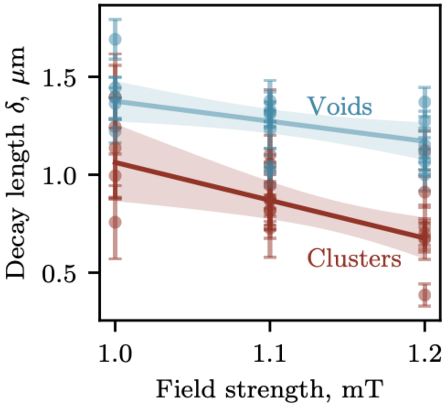




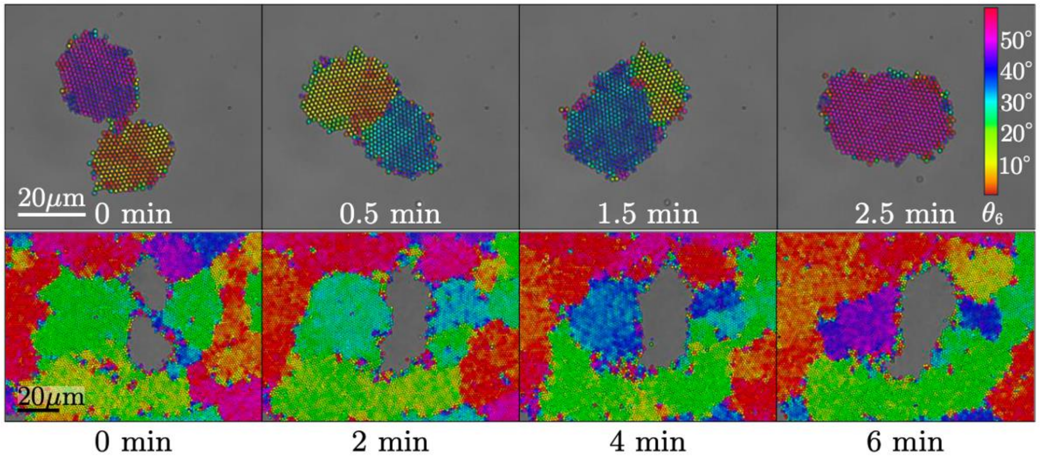
We identify and analyze edge currents around voids and clusters

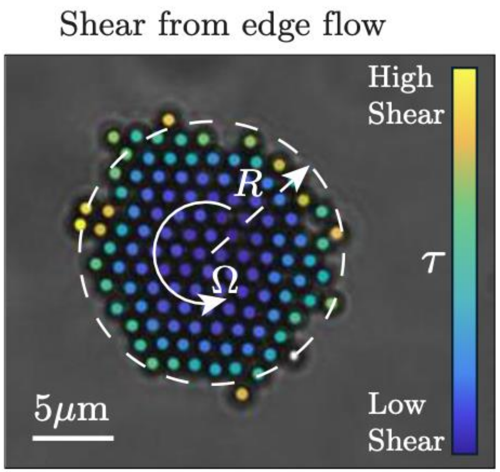
Building on theory first developed in Dasbiswas et al., *PNAS* 2018

Edge flows create stress patterns that drive coarsening on different time scales



We obtain physical properties of edge flows

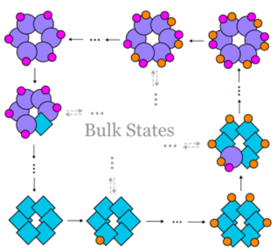




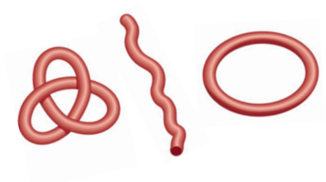
Coarsening happens on much longer timescale for voids as compared to clusters

Nelson, Lobmeyer, Biswal and ET, *arXiv* 2024

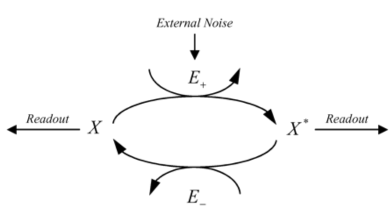
A topological mechanism for robust function in stochastic systems



Model for emergent oscillations



New physics and underlying topology



Non-reciprocity is a necessary condition

Out-of-equilibrium living systems require new theoretical tools

Stochastic systems are described by Master equation $\frac{d}{dt}\boldsymbol{p} = \mathcal{W}\boldsymbol{p}$

Out-of-equilibrium or non-reciprocal transitions make $\mathcal{W}$ non-Hermitian

Non-reciprocal interactions are legion in living and active systems, e.g. between predators and their prey

New properties in stochastic topological systems

Nelson and ET, *Phys Rev B* 2024

Quantum and stochastic networks are mapped only in the bulk

Network has the same operator under periodic boundary conditions

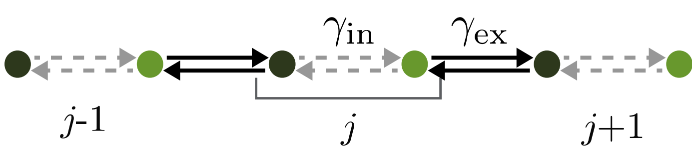
Since $\mathcal{W} = \mathcal{A} - \mathcal{D}$,

$\mathcal{A}_{ij} = \langle i|j\rangle$, transition rate from state p_j to p_i

$\mathcal{D}_{ij} = \delta_{ij} \sum_k \langle k|i\rangle$, a diagonal matrix

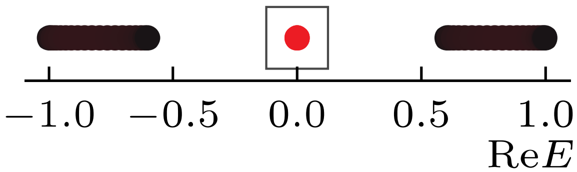
Then $\mathcal{D}$ is proportional to the identity, so the spectrum is just shifted

With open boundaries, the spectra are different due to $\mathcal{D}$

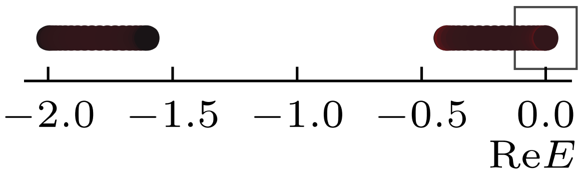


1d example

Quantum $\mathcal{H}$



Stochastic $\mathcal{W}$

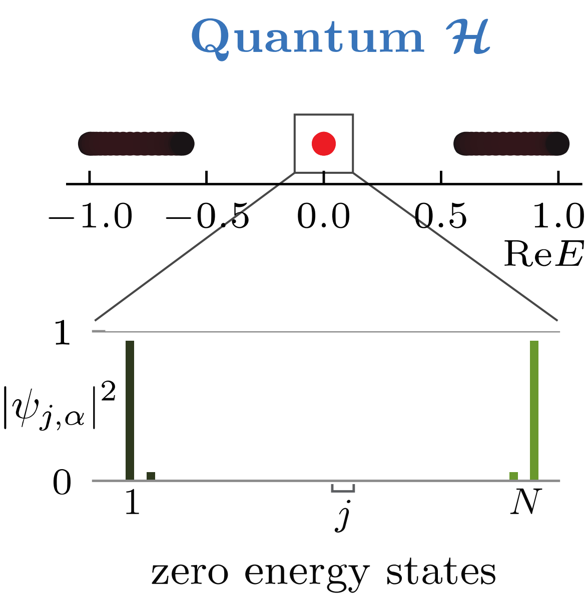


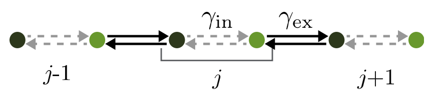
State of interest is also different: zero mode vs steady-state

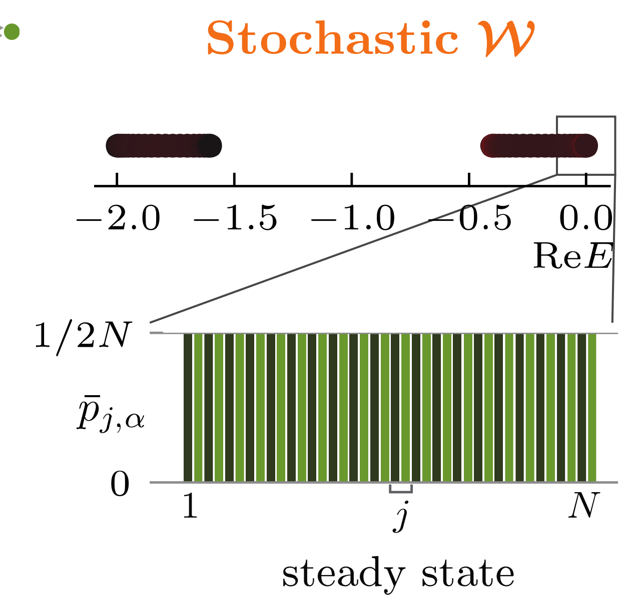
Stochastic systems break the bulk boundary correspondence

Quantum and stochastic networks have same operator and topological invariant under periodic boundaries, or in the bulk

With open boundaries, longest-lived states in each system look different

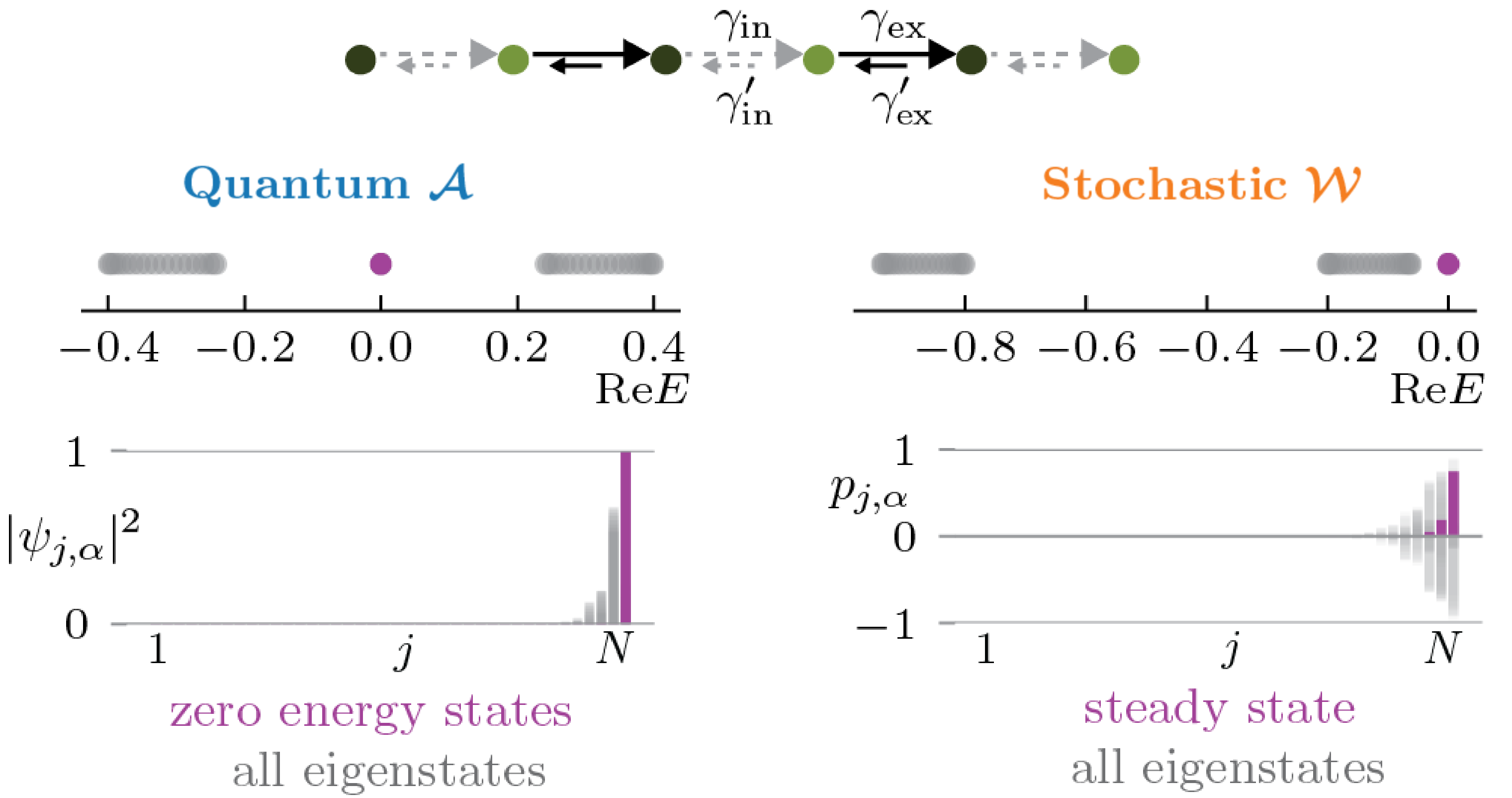






Despite same bulk topological invariant, reciprocal stochastic systems do not have edge states even when the quantum one does

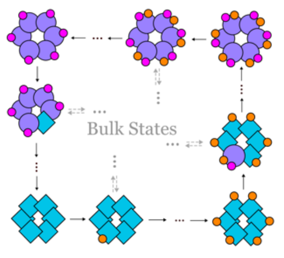
Stochastic topological systems are necessarily non-Hermitian



More generally: unlike in quantum systems, stochastic systems require non-Hermiticity to have edge states

We can prove this for any geometry and dimension

A topological mechanism for robust function in stochastic systems



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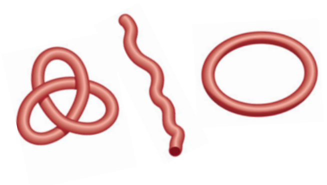

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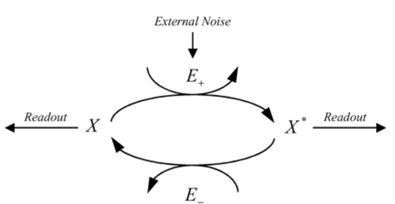

Non-reciprocity is a necessary condition

A topological mechanism for robust function in biological networks

1. Using simple repeated motifs such as phosphorylation cycles, we propose a topological framework that predicts the emergence of robust global dynamics, such as a global clock.

   ET et al., *Phys Rev X* 2021

2. We demonstrate the relevant biophysical mechanisms in KaiC which regulates the circadian rhythm.

   Zheng and ET, *Nat Comm* 2024

3. Topological edge flows can drive macroscopic re-organization in colloids.

   Nelson, Lobmeyer, Biswal and ET, *arXiv* 2024

Invited review: Agudo-Canalejo and ET, *arXiv* 2024

Acknowledgements

Chongbin Zheng

Alexandra Nelson

RICE UNIVERSITY
Center for Theoretical Biological Physics

Jaime Agudo-Canalejo, UCL

Lisa Biswal, Rice University

Student and postdoc positions available!