Functional dynamics in out-of-equilibrium allosteric assemblies

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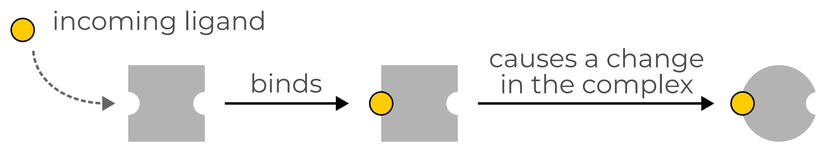
Allostery is the communication between distant sites of a macromolecule, such as binding sites on a protein



Equilibrium allostery

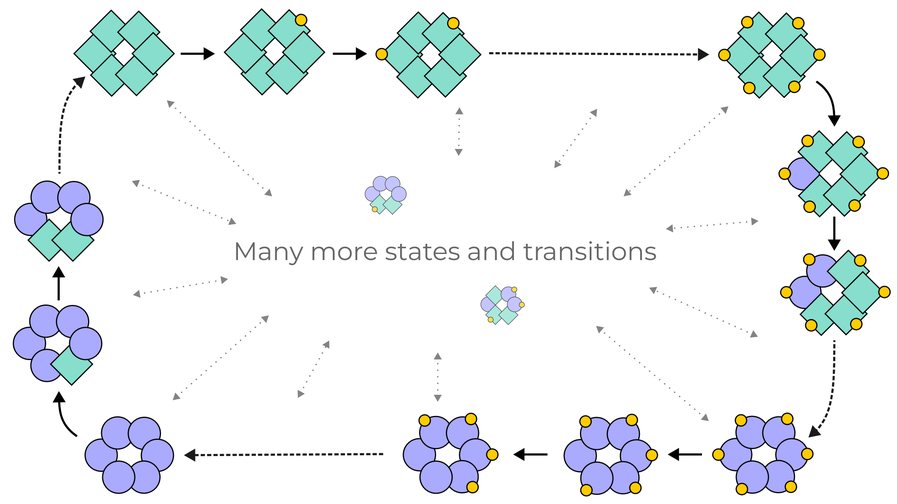
- MWC, KNF and the comprehensive Ensemble Allostery Model
- Cooperative binding, allosteric regulation/signalling

But there are **out-of-equilibrium** allosteric complexes like the AAA ATPases (*e.g.*, the cyanobacterial clock KaiC or the DNA clamp loader)

What new behaviour is possible out of equilibrium?

- Dynamic steady states
- Oscillations (such as in KaiC or other circadian clocks)
- Sensitivity to initial conditions (memory/ spontaneous symmetry breaking)
- Dimensionality reduction (constraining the dynamics to part of the state space)
- Topologically protected states
- Modified cooperative binding

Goal: We are xxx blah design blah...to find in biology and guide synthetic design



Our approach

- Model of **identical subunits** (polymer like)
- Statistical physics and graph theory methods
- **Local (nearest-neighbour) interactions**
- **Thermodynamically consistent** transitions between system states (satisfying local detailed balance)

$$\text{system} + \mathrm{R}_1 + \cdots \underset{r_b}{\overset{r_f}{\rightleftharpoons}} \text{changed system} + \mathrm{P}_1 + \cdots$$

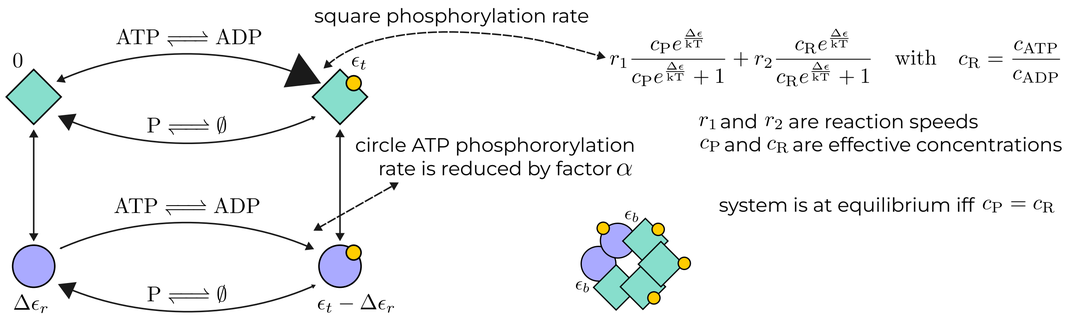
r_f

$$\frac{r_f}{r_b} = \exp(\beta(\Delta\epsilon + \mu_{R_1} + \cdots - \mu_{P_1} - \cdots))$$

change in system energy — chemical potentials of all reactants and products

Towards autonomous topological currents in non-eq blah

- Each subunit can be in one of **2 conformational states** (squares and circles) and **phosphorylate**
- Subunits interact through their conformations only, and in an equilibrium manner by an energy penalty of ϵ_b per square-circle boundary
- Drive the system out of equilibrium by allowing **two different phosphorylation reactions** which couple differently to each conformation
- Through that we implement **futile cycles** of phosphorylation and conformation change within monomers



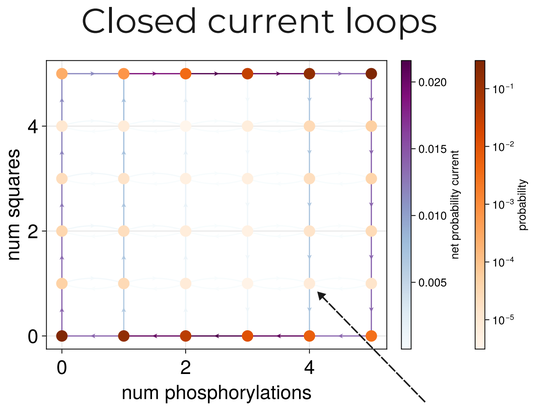
$$r_1 \frac{c_\mathrm{P} e^{\frac{\Delta\epsilon}{\mathrm{kT}}}}{c_\mathrm{P} e^{\frac{\Delta\epsilon}{\mathrm{kT}}} + 1} + r_2 \frac{c_\mathrm{R} e^{\frac{\Delta\epsilon}{\mathrm{kT}}}}{c_\mathrm{R} e^{\frac{\Delta\epsilon}{\mathrm{kT}}} + 1} \quad \text{with} \quad c_\mathrm{R} = \frac{c_\mathrm{ATP}}{c_\mathrm{ADP}}$$

r_1 and r_2 are reaction speeds
c_P and c_R are effective concentrations

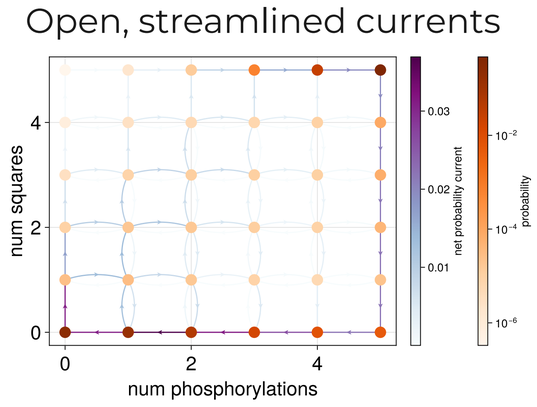
system is at equilibrium iff $c_\mathrm{P} = c_\mathrm{R}$

What types of dynamical steady states can we get?

Closed current loops



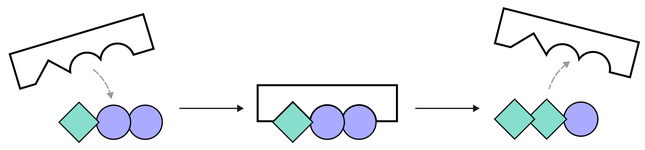
Open, streamlined currents



each node is a group of system states with the same number of bound ligands and the same number of squares/circles

Realising *molecular automata* with site-specific enzymes

- **Bring out-of-equilibrium drive directly into the nearest neighbour interactions**
- Stochastic dynamics on **binary strings** (or general digit strings)
- Adding transitions reactions that differ based on neighbours leads to



$$\text{enzyme } E + \overline{\cdots \mathrm{i0j} \cdots} \underset{r_{E,1\to0,ij}}{\overset{r_{E,0\to1,ij}}{\rightleftharpoons}} \text{changed } E + \overline{\cdots \mathrm{i1j} \cdots}$$

$$r_{E,0\to1,ij} = K_{E,ij} \frac{\exp(\beta\mu_E)}{\exp(\beta\mu_E) + 1}$$

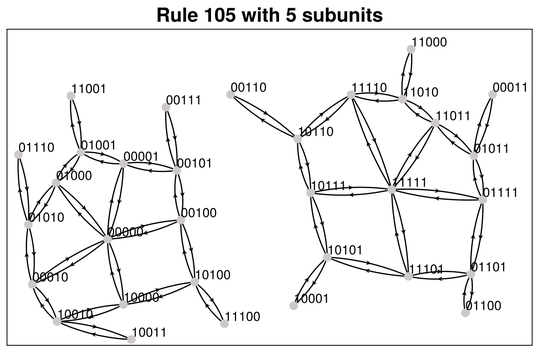
$$r_{E,1\to0,ij} = K_{E,ij} \frac{1}{\exp(\beta\mu_E) + 1}$$

- For each enzyme K_E **determines how it discriminates based on neighbours** and a μ_E **whether it is biased towards 0s or 1s**
- Out-of-equilibrium drive requires at least 2 reaction mechanisms

Minimal, maximally driven model has two enzymes, one for 0 to 1 transitions the one for the inverse

- This is the limit of one μ going to $+\infty$ and the other to $-\infty$
- A model is then fully specified by the two K
- This model can be seen as a stochastic version of 1D cellular automata and we can map any combination of K to a CA rule number
- Accounting for the symmetries of exchanging 0s and 1s and reversal wehave 88 distinct rules

Rule 105 with 5 subunits



Rule 105 with 6 subunits