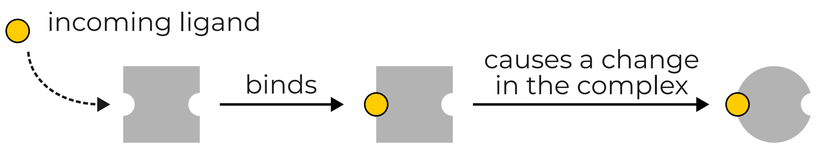
Functional dynamics in out-of-equilibrium allosteric assemblies

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



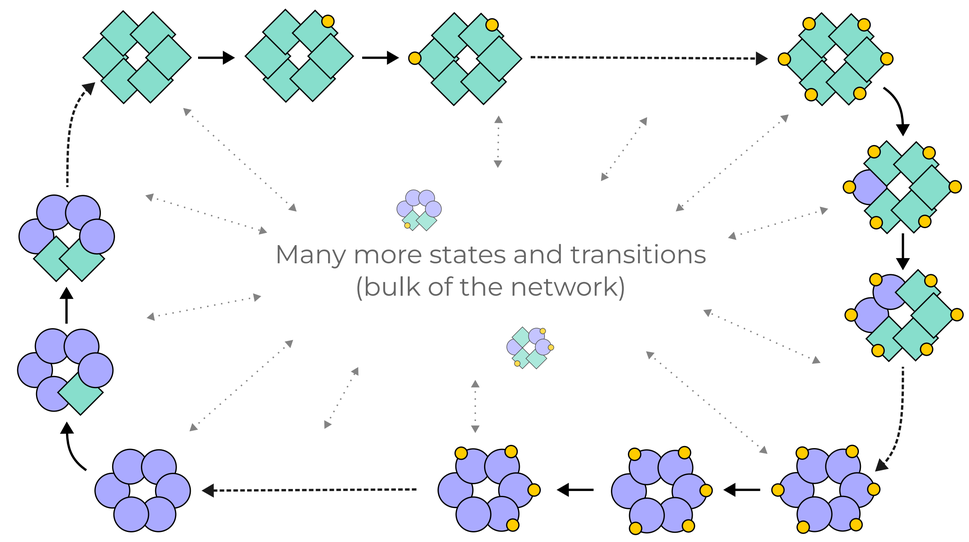
Equilibrium allostery

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

But there are **out-of-equilibrium** allosteric complexes such as AAA ATPases (*e.g.* cyanobacterial circadian 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



We build models to identify classes of behaviour in biology and guide synthetic designs

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

$$\text{system} + \mathrm{R}_1 + \cdots \underset{r_\mathrm{b}}{\overset{r_\mathrm{f}}{\rightleftharpoons}} \text{changed system} + \mathrm{P}_1 + \cdots$$

$$\frac{r_\mathrm{f}}{r_\mathrm{b}} = \exp((\Delta\epsilon + \mu_{\mathrm{R}_1} + \cdots - \mu_{\mathrm{P}_1} - \cdots)/\mathrm{kT})$$

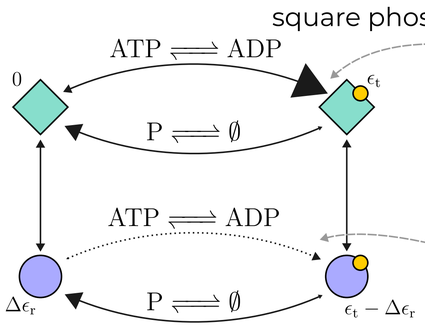
change in system energy

chemical potentials of all reactants and products

Towards topological edge currents in non-equilibrium assemblies

2 conformation states — each can **phosphorylate**, at different rates, through **two different reactions**

This brings the system out of equilibrium and allows individual subunits to perform **futile cycles**



square phosphorylation rate

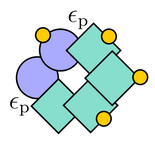
$$r_1 \frac{c_\mathrm{P} e^{\frac{\Delta\epsilon}{\mathrm{kT}}}}{c_\mathrm{P} e^{\frac{\Delta\epsilon}{\mathrm{kT}}} + 1} + r_2 \frac{c_\mathrm{R} e^{\frac{\Delta\epsilon}{\mathrm{kT}}}}{c_\mathrm{R} e^{\frac{\Delta\epsilon}{\mathrm{kT}}} + 1} \quad \text{with} \quad c_\mathrm{R} = \frac{c_\mathrm{ATP}}{c_\mathrm{ADP}}$$

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

equilibrium iff $c_\mathrm{P} = c_\mathrm{R}$

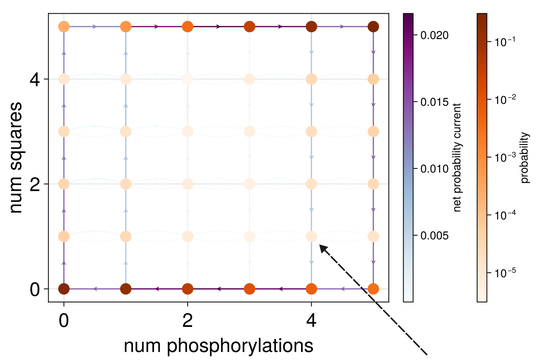
circle ATP phosphororylation rate is reduced by factor α

Subunits then interact in an equilibrium manner through an energy penalty of ϵ_p for each square-circle boundary

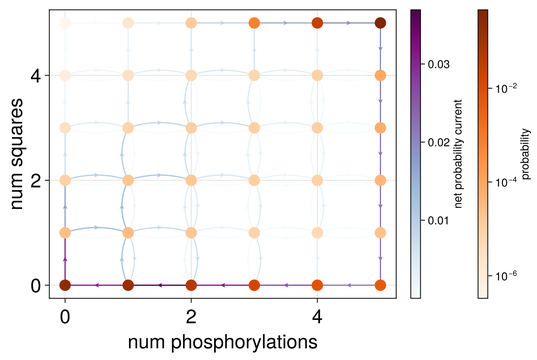


What types of dynamical steady states can we get?

Closed current loops



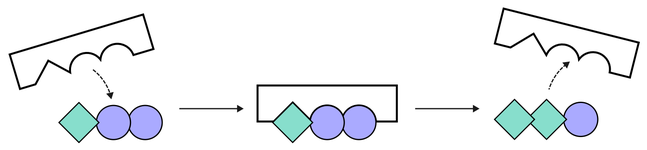
Open, streamlined currents



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

Realizing 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 E, $K_{E,ij}$ **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

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