Summary of Model 2.5

Same as Model 2 but with the locality problem fixed and different $r_?$ parameters based on conformation.

1 Energies

As before, to summarize:

$$E(\{c_i\}, \{b_i\}) \simeq \sum_i E_M(c_i, b_i) + \frac{1}{2} \sum_i E_I(c_{i-1}, c_i) + E_I(c_i, c_{i+1}) \tag{1}$$

where E_M is a $C \times (B+1)$ matrix defining the energies of each individual monomer according to its conformation and number of bound ligands. And E_I is a $C \times C$ matrix defining the monomer interaction energies, specifically $E_I(c_1, c_2)$ is the energy cost of having a monomer of conformation c_1 to the left of one in conformation c_2, hence the particular ordering in eq. (1). The model is achiral if E_I is symmetric. There is one caviat to eq. (1) which is why the $\simeq$ symbol is used and that is the problem of boundaries. Specifically, are we considering a single chain of monomers or a loop that joins its ends, eq. (1) is correct for a loop and can be easily corrected for a chain configuration.

Notably, we can also write eq. (1) as

$$E(\{c_i\}, \{b_i\}) \simeq \sum_i E_M(c_i, b_i) + \frac{E_I(c_{i-1}, c_i) + E_I(c_i, c_{i+1})}{2} = \sum_i E_i \tag{2}$$

where E_i are the energies associated with each monomer and its state.

1.1 General case

In the general case we can write

$$E_M \leftrightarrow \begin{pmatrix} 0 & \epsilon_{1,1} & \epsilon_{1,2} & \cdots \\ \epsilon_{2,0} & \epsilon_{2,1} & \epsilon_{2,2} & \cdots \\ \epsilon_{3,0} & \epsilon_{3,1} & \epsilon_{3,2} & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix} \qquad E_I \leftrightarrow \begin{pmatrix} 0 & \epsilon_{b,1} & \epsilon_{b,2} & \cdots \\ \epsilon_{b,1} & 0 & \epsilon_{b,B+1} & \cdots \\ \epsilon_{b,2} & \epsilon_{b,B+1} & 0 & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix} \tag{3}$$

Restricting ourselves to the $C = 2$, achiral case we can immediately simplify to

$$E_M \leftrightarrow \begin{pmatrix} 0 & \epsilon_{T,1} & \epsilon_{T,2} & \cdots \\ \epsilon_{R,0} & \epsilon_{R,1} & \epsilon_{R,2} & \cdots \end{pmatrix} \qquad E_I \leftrightarrow \begin{pmatrix} 0 & \epsilon_b \\ \epsilon_b & 0 \end{pmatrix} \tag{4}$$

borrowing the tense (T) and relaxed (R) conformation labels from haemoglobin models where presumably $\epsilon_{R,0} \geq 0$ and $\epsilon_{T,i} \geq \epsilon_{R,i}$ for most of $i \neq 0$.

1.2 Simplest case

However, to further reduce the number of parameters we use

$$E_M \leftrightarrow \begin{pmatrix} 0 & \epsilon_t & 2\epsilon_t & \cdots \\ \Delta\epsilon_r & \epsilon_t - \Delta\epsilon_r & 2\epsilon_t - \Delta\epsilon_r & \cdots \end{pmatrix} \qquad\qquad E_I \leftrightarrow \begin{pmatrix} 0 & \epsilon_b \\ \epsilon_b & 0 \end{pmatrix} \qquad (5)$$

where ϵ_t sets the overall energy of binding additional ligands and $\Delta\epsilon_r$ is a measure of how different the R state is.

2 Equilibrium/Boltzmann Statistics

Firstly, defining our system as the polymer only (not any ligands or other chemicals floating around) its clear we are working in a Grand Canonical Ensamble. Thus for each microstate we are interested in what its energy is and how many ligands are bound in that microstate, denote these as E_α and N_α. Then the probabilities of microstates being occupied is given by their Gibbs factors so that

$$p_\alpha \propto \exp(-\beta(E_\alpha - \mu N_\alpha)) \tag{6}$$

with μ being the chemical potential of the ligand. This is a slightly problematic quantity as I'm not too sure how this fits in with the next section, however I suspect it should be kept as a separate thing as long as possible.

3 Modified Transition Rates

We still consider the recipe as in Model 2 where for a reaction

$$S_1 + S_2 + \cdots \xrightleftharpoons[r_b]{r_f} P_1 + P_2 + \cdots \tag{7}$$

we get

$$\frac{r_f}{r_b} = \exp(\beta(\mu_{S_1} + \mu_{S_2} + \cdots - \mu_{P_1} - \mu_{P_2} - \cdots)) \tag{8}$$

where each $\mu_X = \epsilon_X + k_B T \ln(c_X)$ and we make a choice to split the terms so that
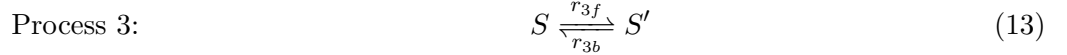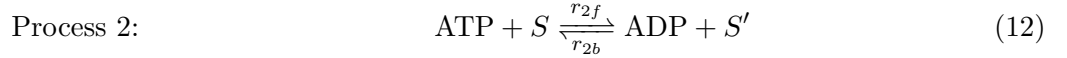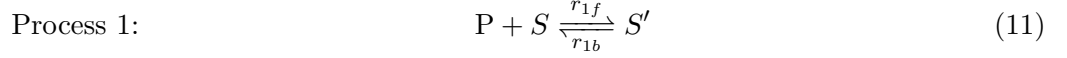
$$r_f = r c_{S_1} c_{S_1} \cdots \exp(\beta(\theta_f(\epsilon_{S_1} + \epsilon_{S_2} + \cdots) - (1 - \theta_b)(\epsilon_{P_1} + \epsilon_{P_2} + \cdots))) \tag{9}$$

$$r_b = r c_{P_1} c_{P_1} \cdots \exp(\beta(\theta_b(\epsilon_{P_1} + \epsilon_{P_2} + \cdots) - (1 - \theta_f)(\epsilon_{S_1} + \epsilon_{S_2} + \cdots))) \tag{10}$$

so that higher concentrations of any chemicals increase the rates of those reactions using them (reasonable) and then we can split the energetic contributions to the μ between the forward and backward rates using the dimensionless $\theta_?$ parameters.

3.1 Transition rates for Model 2.5

We still consider the following three processes

$$\text{Process 1:} \qquad\qquad\qquad P + S \xrightleftharpoons[r_{1b}]{r_{1f}} S' \tag{11}$$

$$\text{Process 2:} \qquad\qquad\qquad ATP + S \xrightleftharpoons[r_{2b}]{r_{2f}} ADP + S' \tag{12}$$

$$\text{Process 3:} \qquad\qquad\qquad S \xrightleftharpoons[r_{3b}]{r_{3f}} S' \tag{13}$$

where the Ss are different in each process and denote different microstates of our polymer.

Though here we examine the different $\mu_?$ in more detail. Specifically, for each outside chemical we use $\mu_{chem} = \epsilon_{chem} + k_B T \ln(c_{chem})$ as before. However, for the polymer states we only have a direct energetic contribution. In model 2 we used $\mu_S = \epsilon_S$ where ϵ_S was the energy of the whole microstate S as given by eq. (1), however this lead to the locality breaking in that model. To correct for that, we now change μ_S to be only that energy of the microstate S that is associated with the monomer that undergoes a change and relevant to the reaction. We label these ϵ_i^S as these correspond to parts of the E_i of eq. (2), depend on the microstate labelled by S and on which monomer is being affected denoted by i throughout this section. Specifically we consider only the individual monomer energies given by E_M for processes 1 and 2, and we consider that and the monomer nearest neighbor interaction energies given by E_I for process 3.

The second change to the transition rates in this model is that we allow the scaling parameters $r_?$ associated with processes 1 and 2 to depend on the affected monomers conformation. This is physically reasonable as the rates at which (de)binding happens very likely does depend on the conformation of the monomer besides just the energetic dependence already in model 2. We label these as $r_1(c_i)$ and $r_2(c_i)$ where again i is the index of the affected monomer, but we still keep only one r_3.

Taking all this into account we arrive at

$$\frac{r_{1f}(c_i)}{r_{1b}(c_i)} = \exp\left(\beta(\epsilon_i^S + \mu_P - \epsilon_i^{S'})\right) = c_P \exp\left(\beta(\epsilon_i^S + \epsilon_P - \epsilon_i^{S'})\right) \tag{14}$$

4

$$\frac{r_{2f}(c_i)}{r_{2b}(c_i)} = \exp\left(\beta(\epsilon_i^S + \mu_{ATP} - \epsilon_i^{S'} - \mu_{ADP})\right) = \frac{c_{ATP}}{c_{ADP}} \exp\left(\beta(\epsilon_i^S + \epsilon_{ATP} - \epsilon_i^{S'} - \epsilon_{ADP})\right) \tag{15}$$

$$\frac{r_{3f}}{r_{3b}} = \exp\left(\beta(\epsilon_i^S - \epsilon_i^{S'})\right) \tag{16}$$

and so

$$r_{1f}(c_i) = r_1(c_i) c_P \exp\left(\beta(\theta_{1f}(\epsilon_i^S + \epsilon_P) - (1 - \theta_{1b})\epsilon_i^{S'})\right) \tag{17}$$

$$r_{1b}(c_i) = r_1(c_i) \exp\left(\beta(\theta_{1b}\epsilon_i^{S'} - (1 - \theta_{1f})(\epsilon_i^S + \epsilon_P))\right) \tag{18}$$

$$r_{2f}(c_i) = r_2(c_i) c_{ATP} \exp\left(\beta(\theta_{2f}(\epsilon_i^S + \epsilon_{ATP}) - (1 - \theta_{2b})(\epsilon_i^{S'} + \epsilon_{ADP}))\right) \tag{19}$$

$$r_{2b}(c_i) = r_2(c_i) c_{ADP} \exp\left(\beta(\theta_{2b}(\epsilon_i^{S'} + \epsilon_{ADP}) - (1 - \theta_{2f})(\epsilon_i^S + \epsilon_{ATP}))\right) \tag{20}$$

$$r_{3f} = r_3 \exp\left(\beta(\theta_{3f}\epsilon_i^S - (1 - \theta_{3b})\epsilon_i^{S'})\right) \tag{21}$$

$$r_{3b} = r_3 \exp\left(\beta(\theta_{3b}\epsilon_i^{S'} - (1 - \theta_{3f})\epsilon_i^S)\right) \tag{22}$$

where the $r_?, c_?, \epsilon_P, \epsilon_{ATP}, \epsilon_{ADP}$ and $\theta_?$ are parameters.

4 Single Monomer Futile Cycles

Focusing on the $N = 1$ system with also $C = 2, B = 1$ we get essentially the simple subsystem we considered before (especially as now we don't have the locality breaking as before). This system has 4 microstates which along with the full symbolic transition rates between them are shown in fig. 1 (with slightly differing notation). As before the up and down transition (that change conformation) are naturally
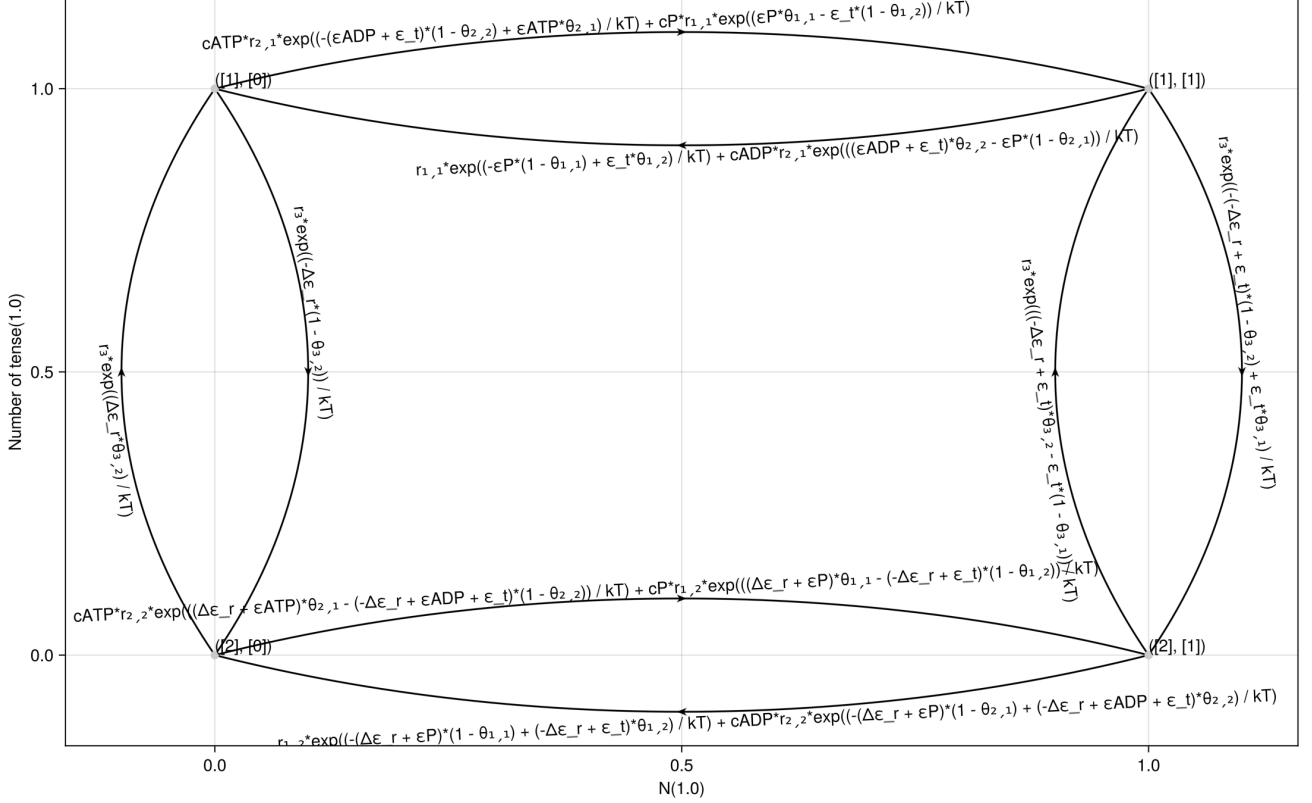

Figure 1: Diagram of single monomer transitions for $C = 2, B = 1$. Top row is the tense conformational states, bottom is the relaxed ones. Left column are without a ligand and right column with one ligand bound.

"driven" clockwise just due to the nature of the energies $\epsilon_t, \Delta\epsilon_r$. But how do we complete the cycle?

4.1 Systematic approach

Before we look at the exact rates for the $N = 1$ system it is worth looking at the general picture of ligand binding by processes 1 and 2. From eq. (14) we can see that binding a ligand in process 1 is favoured as long as the energy is not raised by more than $\mu_P = \epsilon_P + \frac{1}{\beta}\ln(c_P)$ The same logic can be applied to process 2 and the results are summarized as

Process	binding favoured if $\epsilon_i^{S'} - \epsilon_i^S <$	overall rate scale
1	$\mu_P = \epsilon_P + \frac{1}{\beta}\ln(c_P)$	$r_1(c_i)$
2	$\mu_{ATP} - \mu_{ADP} = \epsilon_{ATP} - \epsilon_{ADP} + \frac{1}{\beta}\ln\frac{c_{ATP}}{c_{ADP}}$	$r_2(c_i)$

Coming back to the $N = 1$ system, to complete the clockwise cycles from fig. 1 we want ligand binding to be favoured on the top edge where the energy difference $\epsilon_i^{S'} - \epsilon_i^{S}$ is ϵ_t. But we want it not to be favoured by the bottom edge where the energy difference is $\epsilon_t - 2\Delta\epsilon_r$ which is always lower. Thus it is impossible to have either of the processes favour binding in the top transition and favour debinding in the bottom one and so in order to complete the cycle we must use the dependence of the overall scales of the processes on the conformation.

So to complete the cycle, one of the processes must have its $\Delta\mu$ be $< \epsilon_t - 2\Delta\epsilon_r < \epsilon_t$ and so favour debinding in both of the transtions. And the other must have its $\Delta\mu > \epsilon_t > \epsilon_t - 2\Delta\epsilon_r$ and so favour binding in both transitions. Then we need to tune the overall scales of the rates r_1, r_2 as functions of the conformation so that we get the desired behaviour.

It seems plausible to choose process 1 as the one that favours debinding and process 2 as the energetically driven process that drives binding in the top process. This gives as a bound on setting the $\Delta\mu$ which has two underlying degrees of freedom, we can either tune it using the chemical energies ϵ which may enter into both of the rates, or using the chemical concentrations which only affect the rate which has them used, these become the same when relevant $\theta_?$ are 1. Next we still have to set the overall rate scales $r_{1/2}(c)$ for both monomer conformations. It seems reasonable to have process 1 couple equally to both conformations, but to have process 2 couple stronger to the tense ($c_i = 1$) conformation.

4.2 Brute force approach

But in case it is useful, these are the conditions in full to get the single monomer cycles described above

$$
c_P r_1(1) e^{\frac{\epsilon_P \theta_{1f} - \varepsilon_t(1-\theta_{1b})}{kT}} + c_{ATP} r_2(1) e^{\frac{-(\epsilon_{ADP}+\varepsilon_t)(1-\theta_{2b})+\epsilon_{ATP}\theta_{2f}}{kT}} >
$$
$$
r_1(1) e^{\frac{-\epsilon_P\left(1-\theta_{1f}\right)+\varepsilon_t\theta_{1b}}{kT}} + c_{ADP} r_2(1) e^{\frac{(\epsilon_{ADP}+\varepsilon_t)\theta_{2b}-\epsilon_P\left(1-\theta_{2f}\right)}{kT}}
$$
(23)

$$
c_{ATP} r_2(2) e^{\frac{(\Delta\varepsilon_r+\epsilon_{ATP})\theta_{2f}-(-\Delta\varepsilon_r+\epsilon_{ADP}+\varepsilon_t)(1-\theta_{2b})}{kT}} + c_P r_1(2) e^{\frac{(\Delta\varepsilon_r+\epsilon_P)\theta_{1f}-(-\Delta\varepsilon_r+\varepsilon_t)(1-\theta_{1b})}{kT}} <
$$
$$
r_1(2) e^{\frac{-(\Delta\varepsilon_r+\epsilon_P)\left(1-\theta_{1f}\right)+(-\Delta\varepsilon_r+\varepsilon_t)\theta_{1b}}{kT}} + c_{ADP} r_2(2) e^{\frac{-(\Delta\varepsilon_r+\epsilon_P)\left(1-\theta_{2ff}\right)+(-\Delta\varepsilon_r+\epsilon_{ADP}+\varepsilon_t)\theta_{2b}}{kT}}
$$
(24)

5   Simplified Model with Reduced Parameters

Overall, the model has the following parameters

Where they come from	parameters	units
Energy parameters	$\epsilon_t, \Delta\epsilon_r, \epsilon_b$	E
Equilibrium statistics	$\mu, \mathrm{k_b}T$	E
Rates: overall scaling	$r_{1/2}(c_i), r_3 - 2C + 1$ of these	rates $-\mathrm{T}^{-1}$
Rates: dimensionless concentrations	c_P, c_{ATP}, c_{ADP}	1
Rates: intrinsic chemical energies	$\epsilon_P, \epsilon_{ATP}, \epsilon_{ADP}$	E
Rates: thetas/balancing	$\theta_{1/2/3,f/b} - 6$ of these	1

which is quite a lot to make initial progress, so here we outline a simplified model with these reduced.

Firstly, assuming constant T we may choose $\mathrm{k_B}T = 1\mathrm{E}$ to be our energy unit. We can also reasonably take all the $\theta_?$ to be equal. Beyond this it gets more questionable.

> We can start off with setting all $\theta_? = 1$ which is very convenient as that then makes the somewhat redundant degrees of freedom of the concentrations and intrinsic chemical energies have the same effect. As such, with this simplification we can also without loss of complexity set all the intrinsic chemical energies $\epsilon_P = \epsilon_{ATP} = \epsilon_{ADP} = 0$ as well.

In addition, inspired from section 4.1, we let the rates be $r_1(1) = r_1(2) = r_1$, $r_2(1) = r_2$ and $r_2(2) = \alpha r_2$, with presumably $\alpha < 1$. This makes the rates become

$$r_{1f}(c_i) = r_1 c_P \exp\big(\beta\epsilon_i^S\big) \tag{25}$$

$$r_{1b}(c_i) = r_1 \exp\big(\beta\epsilon_i^{S'}\big) \tag{26}$$

$$r_{2f}(c_i) = r_2 c_{ATP} \exp\big(\beta\epsilon_i^S\big) \quad \{\times\alpha \quad \text{if in conf. 2} \quad\} \tag{27}$$

$$r_{2b}(c_i) = r_2 c_{ADP} \exp\big(\beta\epsilon_i^{S'}\big) \quad \{\times\alpha \quad \text{if in conf. 2} \quad\} \tag{28}$$

$$r_{3f} = r_3 \exp\big(\beta\epsilon_i^S\big) \tag{29}$$

$$r_{3b} = r_3 \exp\big(\beta\epsilon_i^{S'}\big) \tag{30}$$

which from a slightly different perspective is

$$r_{\text{binding},b_i,c_i=1} = (r_1 c_P + r_2 c_{ATP}) \exp(\beta E_M(1, b_i)) \tag{31}$$

$$r_{\text{debinding},b_i,c_i=1} = (r_1 + r_2 c_{ATP}) \exp(\beta E_M(1, b_i)) \tag{32}$$

$$r_{\text{binding},b_i,c_i=2} = (r_1 c_P + \alpha r_2 c_{ATP}) \exp(\beta E_M(2, b_i)) \tag{33}$$

$$r_{\text{debinding},b_i,c_i=2} = (r_1 + \alpha r_2 c_{ATP}) \exp(\beta E_M(2, b_i)) \tag{34}$$

$$r_{c_i \to c_i', b_i} = r_3 \exp(\beta(E_M(c_i, b_i) + \text{NN interaction energy})) \tag{35}$$

where we have plugged in the corresponding terms for ϵ_i^S as well. The resulting transition graph for the $N = 1$ system can be seen in fig. 2

Finally, the exact conditions to have our single monomer futile cycles in this simplified model where we further assumer $B = 1$ are

$$\frac{r_{\text{binding},b_i,1}}{r_{\text{debinding},b_i+1,1}} = \frac{(r_1 c_P + r_2 c_{ATP})}{(r_1 + r_2 c_{ADP}) \exp(\beta \epsilon_t)} > 1 \tag{36}$$

$$\frac{r_{\text{binding},b_i,2}}{r_{\text{debinding},b_i+1,2}} = \frac{(r_1 c_P + \alpha r_2 c_{ATP}) \exp(\beta \Delta \epsilon_r)}{(r_1 + \alpha r_2 c_{ADP}) \exp(\beta (\epsilon_t - \Delta \epsilon_r))} < 1 \tag{37}$$
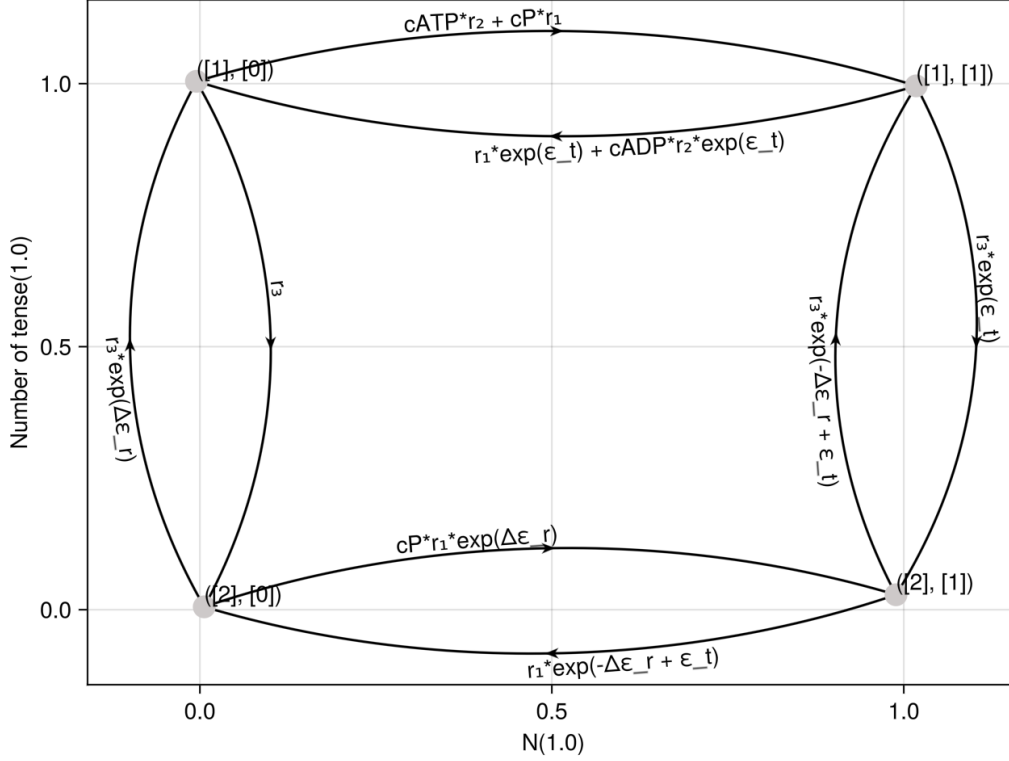
$$\tag{38}$$

Figure 2: Diagram of single monomer transitions for $C = 2, B = 1$ using the simplifying parameter choices. Top row is the tense conformational states, bottom is the relaxed ones. Left column are without a ligand and right column with one ligand bound.

6   Symbolic Analysis of $N = 1$ using the Transition Matrix

It is worth looking directly at the transition matrix $\underline{\underline{R}}$ where R_{ij} corresponds to the transition from j to i. This takes the form

$$\underline{\underline{R}} \leftrightarrow \begin{pmatrix} 0 & c & e & 0 \\ a & 0 & 0 & g \\ b & 0 & 0 & h \\ 0 & d & f & 0 \end{pmatrix} \quad \text{with states ordered as} \quad \begin{pmatrix} (\{1\},\{0\}) \\ (\{2\},\{0\}) \\ (\{1\},\{1\}) \\ (\{2\},\{1\}) \end{pmatrix} \tag{39}$$

where the variables are shorthands for the rates in fig. 1 or the simplified ones in fig. 2. For the simplified rates these would be

$$a = r_3 \tag{40}$$
$$f = r_3 e^{\epsilon_t} \tag{41}$$
$$d = c_P r_1 e^{\Delta \epsilon_r} + c_{ATP} r_2 e^{\Delta \epsilon_r} \alpha \tag{42}$$
$$g = r_1 e^{-\Delta \epsilon_r + \epsilon_t} + c_{ADP} r_2 e^{-\Delta \epsilon_r + \epsilon_t} \alpha \tag{43}$$

$$h = r_3 e^{-\Delta \epsilon_r + \epsilon_t} \tag{44}$$
$$b = c_{ATP} r_2 + c_P r_1 \tag{45}$$
$$e = r_1 e^{\epsilon_t} + c_{ADP} r_2 e^{\epsilon_t} \tag{46}$$
$$c = r_3 e^{\Delta \epsilon_r} \tag{47}$$

with the full version being in fig. 9

6.1   Finding the steady state

However, more interesting to use is the matrix $\underline{\underline{W}}$ given by $W_{ij} = R_{ij} - \delta_{ij} \sum_k R_{ki}$ as puts the probability evolution align

$$\partial_t p_i = \sum_j (R_{ij} p_j - R_{ji} p_i) \quad \text{into the convenient form of} \quad \partial_t p_i = \sum_j W_{ij} p_j \tag{48}$$

using substitutions from before we get

$$\underline{\underline{W}} \leftrightarrow \begin{pmatrix} -a - b & c & e & 0 \\ a & -c - d & 0 & g \\ b & 0 & -e - f & h \\ 0 & d & f & -g - h \end{pmatrix} \tag{49}$$

any such matrix is guaranteed to have 0 as an eigenvalue, and all its other eigenvalues to be negative. Further, if the graph/matrix is strongly connected (should mostly be true for us) then there is only a single eigenvector associated to the eigenvalue of 0. Also, the components of all the other eigenvectors sum to 0.

Symbolically solving for the eigensystem of eq. (49) indeed returns one eigenvector which always has eigenvalue 0, it is

$$\underline{p}^{\text{ss}} = \frac{1}{n} \begin{pmatrix} ceg + ceh + cfg + deh \\ aeg + aeh + afg + bfg \\ adh + bcg + bch + bdh \\ ade + adf + bcf + bdf \end{pmatrix} = \frac{1}{n} \begin{pmatrix} ce\,(g + h) + cfg + deh \\ ae\,(g + h) + (a + b)\,fg \\ (a + b)\,dh + bc\,(g + h) \\ ad\,(e + f) + b\,(c + d)\,f \end{pmatrix} \tag{50}$$

with n being a rather unwieldy positive normalization constant

$$n = a\left(d\left(e+h\right)+\left(d+g\right)f+e\left(g+h\right)\right)+\left(bc+bd+\left(b+c\right)g\right)f+\left(b+e\right)\left(c\left(g+h\right)+dh\right) \overset{\text{notably}}{>} 0 \quad (51)$$

After plugging in the simplified version of the variables this gives

$$\underline{p}^{\,\text{ss}} = \frac{1}{n}\begin{pmatrix} \left(\left(2r_1+c_{ADP}r_2\left(1+\alpha\right)\right)r_3+\left(r_1+c_{ADP}r_2\right)\left(\left(1+c_P\right)r_1+\left(c_{ADP}+c_{ATP}\right)r_2\alpha\right)\right)r_3 e^{2\epsilon_t} \\ \left(\left(2r_1+c_{ADP}r_2\left(1+\alpha\right)\right)r_3+\left(\left(c_{ADP}+c_{ATP}\right)r_2+\left(1+c_P\right)r_1\right)\left(r_1+c_{ADP}r_2\alpha\right)\right)r_3 e^{-\Delta\epsilon_r+2\epsilon_t} \\ \left(\left(r_1+r_3+c_P r_1+r_3\alpha+c_{ADP}r_2\alpha+c_P r_1\alpha\right)c_{ATP}r_2+\left(r_1+2r_3+c_P r_1+c_{ADP}r_2\alpha\right)c_P r_1+r_2^2 c_{ATP}^2\alpha\right)r_3 e^{\epsilon_t} \\ \left(\left(r_1+2r_3+c_{ADP}r_2+c_P r_1\right)c_P r_1+\left(r_3\left(1+\alpha\right)+c_{ADP}r_2\alpha+\left(c_P+\alpha+c_P\alpha\right)r_1\right)c_{ATP}r_2+r_2^2 c_{ATP}^2\alpha\right)r_3 e^{\Delta\epsilon_r+\epsilon_t} \end{pmatrix}$$
$$(52)$$

as an unnormalized steady state probability distribution.

6.2   Probability currents

Next we want to get the steady state probability currents between microstates. Denote J_{ij} to be the net probability current flowing from j to i at some probability distribution $\underline{p}$. Then we have

$$J_{ij} = R_{ij}p_j - R_{ji}p_i \quad (53)$$

We can then calculate the matrix $\underline{\underline{J}}^{\text{ss}}$ for the steady state distribution in the $N=1$ case to get

$$\underline{\underline{J}}^{\text{ss}} \leftrightarrow \frac{1}{n}\begin{pmatrix} 0 & -adeh+bcfg & adeh-bcfg & 0 \\ adeh-bcfg & 0 & 0 & -adeh+bcfg \\ -adeh+bcfg & 0 & 0 & adeh-bcfg \\ 0 & adeh-bcfg & -adeh+bcfg & 0 \end{pmatrix} \quad (54)$$

which confirms that this is truly a steady state as we have $\sum_j J_{ij} = 0$ for all i. Alternatively (as this is really the same thing restated in another perspective) we can look at the flow along the loop as in the diagram figs. 1 and 2. Clearly the net flow along each of the four sides must equal to each other in the steady state, this is equivalent to saying $J^{\text{ss}} = J_{31}^{\text{ss}} = J_{43}^{\text{ss}} = J_{24}^{\text{ss}} = J_{12}^{\text{ss}}$ which is indeed true for the resulting $\underline{\underline{J}}^{\text{ss}}$. We then get a net flow in the clockwise direction of

$$J^{\text{ss}} = \frac{1}{n}\left(bcfg - adeh\right) \quad (55)$$

notably, if we look at which traditions the letters correspond to as in fig. 3, $bcfg$ is the product of the clockwise transition rates and $adeh$ of the counterclockwise transition rates. Which seems like quite a curious combination, but at the very least it does agree with the notion that if the transition rates going clockwise are bigger than those going opposite we get a clockwise current and vice-versa.
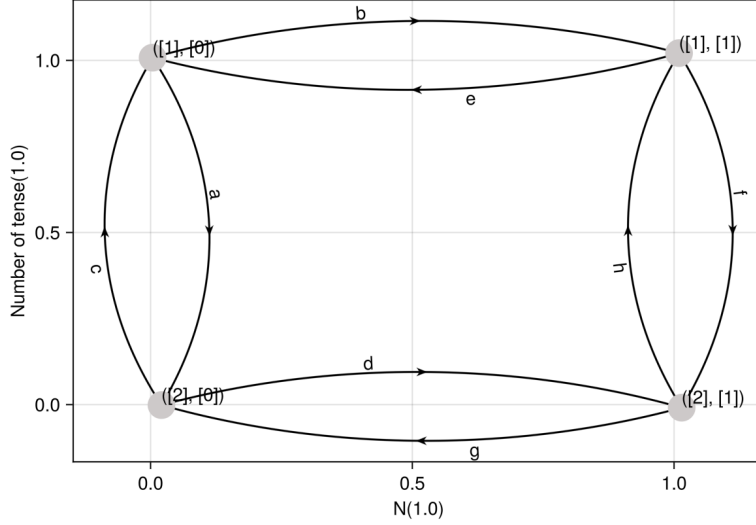
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Figure 3: Transition diagram in terms of the substituted variables of eq. (39).

Going beyond that we can plug in the values for the letters and get to the flow as

$$J^{\text{ss}} = \frac{1}{n}(bcfg - adeh) =$$

$$= \frac{1}{n}r_3^2 \left(c_{ATP}e^{\frac{\epsilon_{ATP}}{kT}} - c_{ADP}c_P e^{\frac{\epsilon_{ADP}+\epsilon_P}{kT}} \right) \times$$

$$\left(-r_1(1)r_2(2)e^{\frac{\Delta\epsilon_r\left(\theta_{1b}+\theta_{2f}\right)}{kT}} + r_1(2)r_2(1)e^{\frac{\Delta\epsilon_r\left(\theta_{1f}+\theta_{2b}\right)}{kT}} \right) \times$$

$$e^{\frac{-\epsilon_{ATP}-2\epsilon_t-\Delta\epsilon_r\theta_{1b}-\Delta\epsilon_r\theta_{2b}+\epsilon_{ADP}\left(-1+\theta_{2b}\right)+\epsilon_{ATP}\theta_{2f}+\epsilon_P\left(-1+\theta_{1f}\right)+\epsilon_t\theta_{1b}+\epsilon_t\theta_{2b}+\epsilon_t\theta_{3f}+\epsilon_t\theta_{3b}}{kT}} \tag{56}$$

where I do not plug in for n as that is too large to show. For the simplified form of section 5 we have

$$J^{\text{ss}} = \frac{1}{n}(bcfg - adeh) = \frac{1}{n}r_1 r_2 r_3^2 \left(c_{ATP} - c_{ADP}c_P \right)(1-\alpha)e^{2\epsilon_t} \tag{57}$$

$$n = r_3 e^{-\Delta\epsilon_r + \epsilon_t} \times$$

$$\big(((c_{ADP} + c_{ATP})r_2 + (1 + c_P)r_1)(r_1 + c_{ADP}r_2\alpha)e^{\epsilon_t} +$$

$$((c_{ADP} + c_{ATP})r_2 + (1 + c_P)r_1)(c_P r_1 + c_{ATP}r_2\alpha)e^{2\Delta\epsilon_r} +$$

$$(2(e^{\epsilon_t} + c_P e^{\Delta\epsilon_r})r_1 + (c_{ADP}e^{\epsilon_t} + c_{ATP}e^{\Delta\epsilon_r})r_2(1+\alpha))r_3(1 + e^{\Delta\epsilon_r}) +$$

$$(c_{ATP}r_2 + c_P r_1 + (r_1 + c_{ADP}r_2)e^{\epsilon_t})((1 + c_P)r_1 + (c_{ADP} + c_{ATP})r_2\alpha)e^{\Delta\epsilon_r} \big) \tag{58}$$

From both of these we can notably infer whether the current is 0 or is negative or positive (as $n > 0$ besides trivial cases). We get a current of 0 at equilibrium (due to the first bracket term in either expression, see section 6.3) or in the simplified model only if $\alpha = 1$ which means there's no difference in the ATP to monomer coupling by conformation state. However, this condition is perhaps more interesting in its general case of eq. (56) where we get a current of 0 if

$$r_1(1)r_2(2)e^{\beta\Delta\epsilon_r\left(\theta_{1b}+\theta_{2f}\right)} = r_1(2)r_2(1)e^{\beta\Delta\epsilon_r\left(\theta_{1f}+\theta_{2b}\right)} \tag{59}$$

12

$$r_1(1)e^{\beta\Delta\epsilon_r\theta_{1b}}r_2(2)e^{\beta\Delta\epsilon_r\theta_{2f}} = r_1(2)e^{\beta\Delta\epsilon_r\theta_{1f}}r_2(1)e^{\beta\Delta\epsilon_r\theta_{2b}} \tag{60}$$

which is quite a peculiar condition that I'm not too sure what to think of.

Coming back to sanity checks for driving the current in the simplified model, note that driving binding by ATP corresponds to having $c_{ATP} \gg c_{ADP}$ and by P to having $c_P \gg 1$.

6.3 Equilibrium currents and steady state

The condition for equilibrium in our system is given by the reaction

$$\text{ATP} \rightleftharpoons \text{ADP} + \text{P} \tag{61}$$

being at its steady state. This corresponds to

$$\mu_{ATP} = \mu_{ADP} + \mu_P \tag{62}$$
$$c_{ATP}\exp(\beta\epsilon_{ATP}) = c_{ADP}c_P\exp(\beta(\epsilon_{ATP}+\epsilon_P)) \tag{63}$$

according to the same recipe as we used earlier to derive our reaction rates. This perfectly agrees with our net current expressions of eqs. (56) and (57) which ought to both be 0 at equilibrium by detailed balance.

We can also try to plug in this expression into the steady state probability distribution from section 6.1. This can be done in multiple ways depending on which concentration we want to eliminate. If we plug in $c_{ATP} \to c_P c_{ADP}$ to eliminate the ATP concentration into the steady state of the simplified model (eq. (52)) we get

$$p_{\text{eq}}^{\text{ss}} = \frac{1}{\left(e^{\epsilon_t}+c_Pe^{\Delta\epsilon_r}\right)\left(1+e^{\Delta\epsilon_r}\right)}\begin{pmatrix}e^{\Delta\epsilon_r+\epsilon_t}\\e^{\epsilon_t}\\c_Pe^{\Delta\epsilon_r}\\c_Pe^{2\Delta\epsilon_r}\end{pmatrix} = \frac{e^{\Delta\epsilon_r+\epsilon_t}}{\left(e^{\epsilon_t}+c_Pe^{\Delta\epsilon_r}\right)\left(1+e^{\Delta\epsilon_r}\right)}\begin{pmatrix}1\\e^{-\Delta\epsilon_r}\\c_Pe^{-\epsilon_t}\\c_Pe^{-(\epsilon_t-\Delta\epsilon_r)}\end{pmatrix} \tag{64}$$

which agrees perfectly with the standard Gibbs factor results of section 2 if we readd the $\beta = \frac{1}{kT}$ factors and use $c_P = e^{\beta\mu_P}$ (both of which are valid in the simplified model).

6.4 Steady state current as a function of drive

We only work in the simplified model here where to recap, we have

$$J^{\text{ss}} = \frac{1}{n}(bcfg - adeh) = \frac{1}{n}r_1r_2r_3^2\left(c_{ATP}-c_{ADP}c_P\right)(1-\alpha)e^{2\epsilon_t} \tag{57 revisited}$$

where n is a complicated function of all the variables. To simplify given that the ADP concentration is usually very small compared to ATP and P we set $c_{ADP} \sim 0$. After which we are left with two main parameters coming from the outside environment, the concentrations of ATP and P. As such we analyse the current as a function of these two parameters.

Firstly, we would expect the current to grow (with $\alpha < 1$) as c_{ATP} increases and perhaps to reduce as c_P increases (as then the current driving ATP process is more washed out). Kabir was curious about whether this is a monotonic relation so lets have a look. Symbolically obtaining the partial derivatives we get

$$\frac{\partial J^{\text{ss}}}{\partial c_P} = \frac{-r_1^2 cATP\left(2r_3e^{\Delta\epsilon_r}+\left(e^{\Delta\epsilon_r}+e^{\epsilon_t}+2cPe^{\Delta\epsilon_r}\right)r_1+cATPr_2e^{\Delta\epsilon_r}(1+\alpha)\right)r_2r_3\left(1+e^{\Delta\epsilon_r}\right)e^{\Delta\epsilon_r+\epsilon_t}(1-\alpha)}{\text{positive denominator}}$$

$$\tag{65}$$

13

$$\frac{\partial J^{\text{ss}}}{\partial c_{ATP}} = \frac{\left(2\left(e^{\epsilon_t} + cPe^{\Delta\epsilon_r}\right) r_1 r_3 + r_1^2 \left(1 + cP\right)\left(e^{\epsilon_t} + cPe^{\Delta\epsilon_r}\right) - r_2^2 cATP^2 e^{\Delta\epsilon_r}\alpha\right) r_1 r_2 r_3 \left(1 + e^{\Delta\epsilon_r}\right) e^{\Delta\epsilon_r + \epsilon_t}\left(1 - \alpha\right)}{\text{positive denominator}}$$

(66)

where note that all the concentrations, the overall rates $r_?$ and α are positive with $\alpha < 1$ meaning the ATP reaction acts stronger on conformation 1 than on conformation 2. Thus, for a fixed α the current function is monotonic with respect to c_P essentially always acting against the current that is driven by the ATP process. The derivative with respect to c_{ATP} is more interesting though, it will have the opposite sign if

$$r_2^2 cATP^2 e^{\Delta\epsilon_r}\alpha < 2\left(e^{\epsilon_t} + cPe^{\Delta\epsilon_r}\right) r_1 r_3 + r_1^2 \left(1 + cP\right)\left(e^{\epsilon_t} + cPe^{\Delta\epsilon_r}\right) \tag{67}$$

$$cATP < +\sqrt{\frac{2\left(e^{\epsilon_t} + cPe^{\Delta\epsilon_r}\right) r_1 r_3 + r_1^2 \left(1 + cP\right)\left(e^{\epsilon_t} + cPe^{\Delta\epsilon_r}\right)}{r_2^2 e^{\Delta\epsilon_r}\alpha}} = \kappa \tag{68}$$

where assuming the energies ϵ_t and $\Delta\epsilon_r$ are positive we have

$$\kappa \geq +\sqrt{\frac{2\left(1 + 0\right) r_1 r_3 + r_1^2 \left(1 + 0\right)\left(1 + 0\right)}{r_2^2 \alpha}} = +\sqrt{\frac{r_1(2r_3 + r_1)}{r_2^2 \alpha}} \tag{69}$$

which is notably inversely proportional to α, meaning that at least in the $\alpha = 0$ limit this point is never reached and generally, we mostly have the c_{ATP} driving a current. The overall behaviour can be summarized as

sign of J^{ss}, slope w.r.t. c_P, and c_{ATP}	$c_{ATP} < \kappa \sim \sqrt{\frac{2}{\alpha}}$	$c_{ATP} > \kappa \sim \sqrt{\frac{2}{\alpha}}$
$\alpha < 1$	$+, -, +$	$+, -, -$
$\alpha > 1$	$-, +, -$	$-, +, +$

Table 1: Simplified behaviour of the current eq. (57) with very small c_{ADP}

Beyond this relatively simple but general analysis, we can look at some sample plots for $r_?$ of order 1, a couple of α values (in particular 0) and some sample energy values. Such plots can be seen in figs. 4 to 6 and which agree with the general features discussed above.
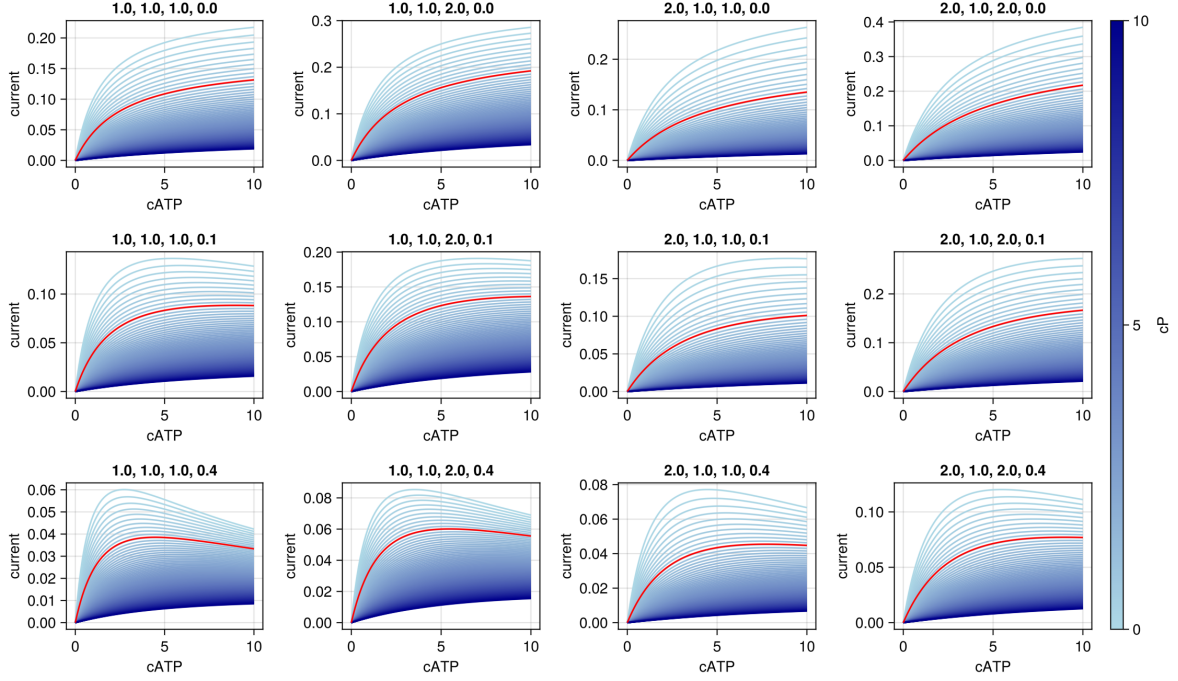
Figure 4: Plotting the steady state current J^{ss} as a function of c_{ATP} for different c_P (shown in colors). These are all for $\epsilon_t = \Delta\epsilon_r = 0$ (the no allostery model) and the values of r_1, r_2, r_3 and α are noted above each subplot. In particular, we do not change r_2 as that simply scales c_{ATP}. For r_1 and r_2 we have plots for each being 1 or 2, with different combinations of these being in each column. Finally, the rows differ by values of α which are 0, 0.1 and 0.4.
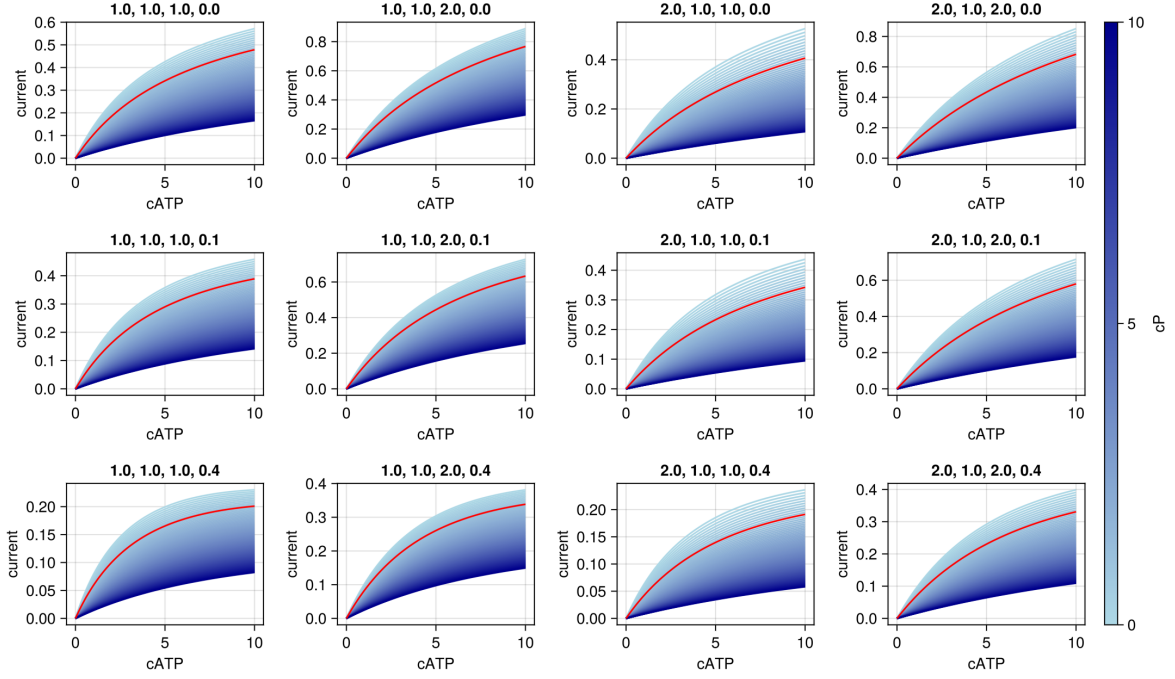
Figure 5: Plotting the steady state current J^{ss} as a function of c_{ATP}. In the same format as fig. 4, but with $\epsilon_t = 3\mathrm{k}T$ and $\Delta\epsilon_r = 0$.
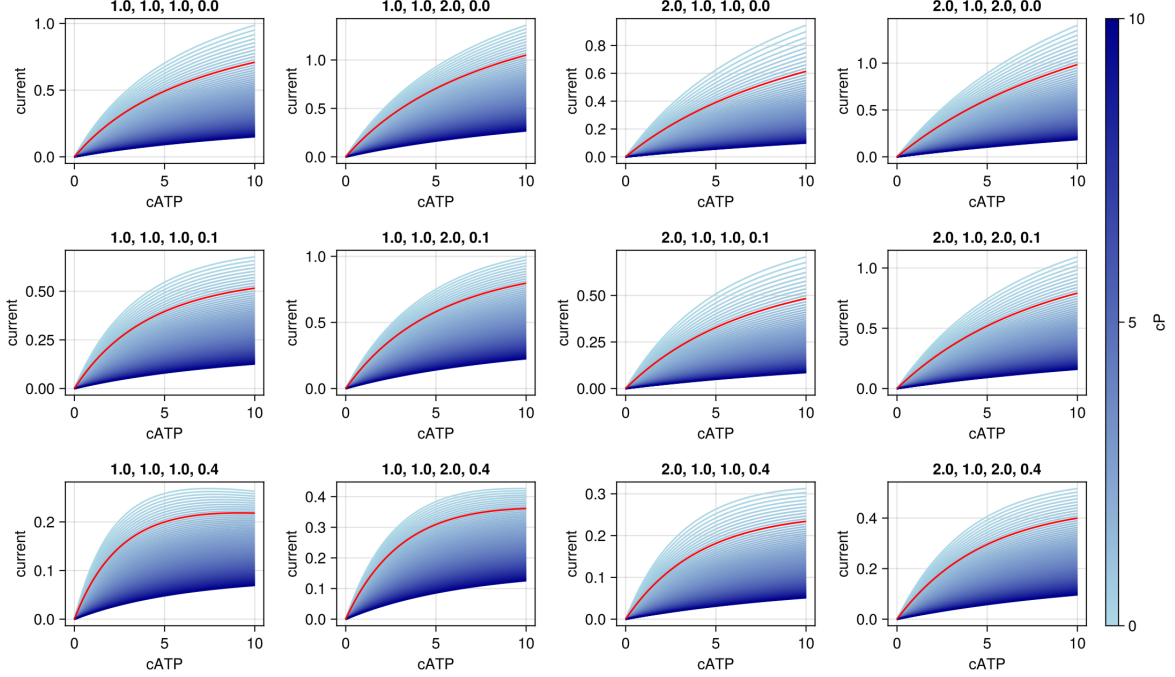

Figure 6: Plotting the steady state current J^{ss} as a function of c_{ATP}. In the same format as fig. 4, but with $\epsilon_t = 3\mathrm{k}T$ and $\Delta\epsilon_r = 1\mathrm{k}T$.

7 Going beyond $N = 1$

For an illustration on how the graphs scale see fig. 7 where the corresponding graph is shown for $N = 2$ and
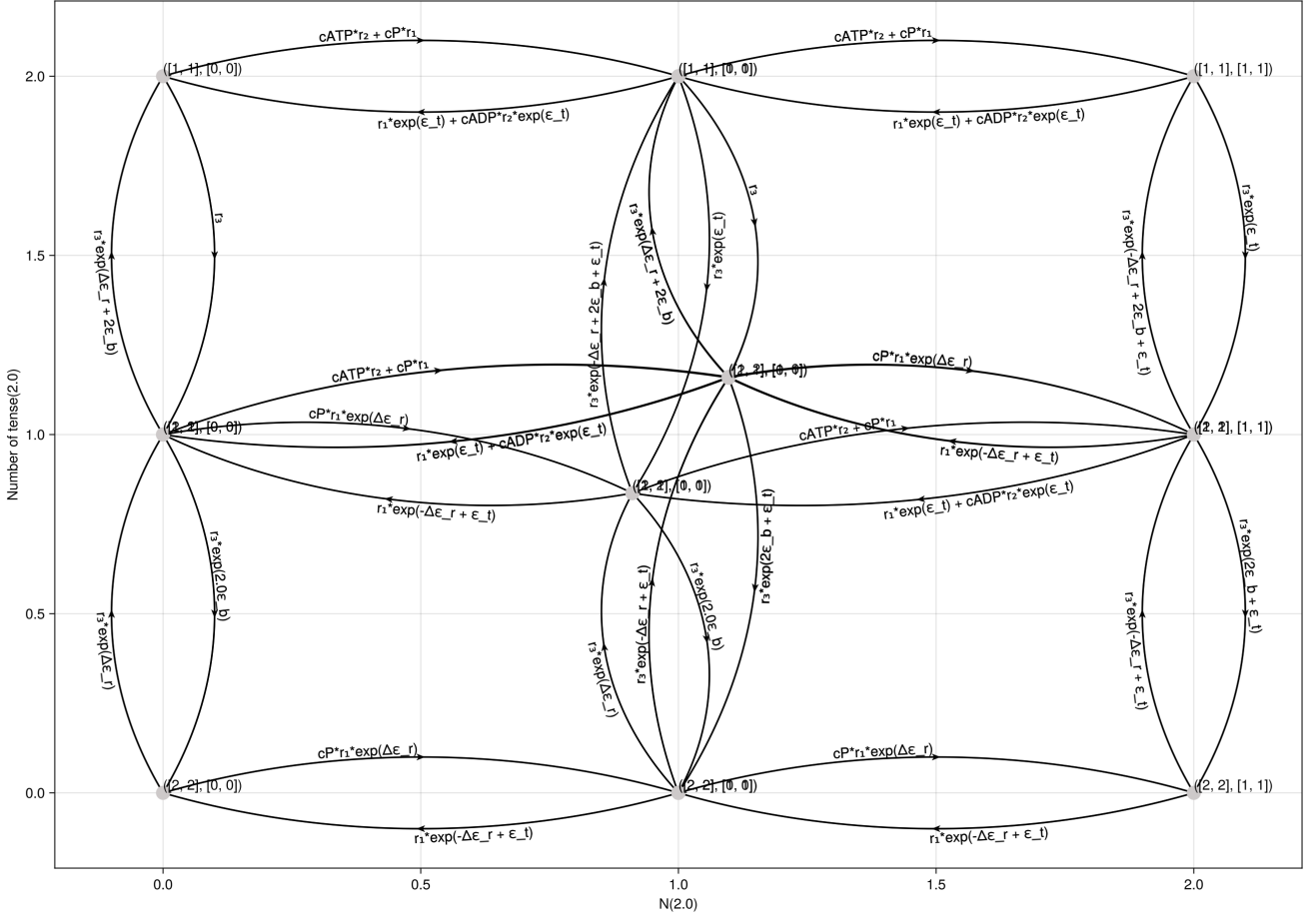

Figure 7: Transition diagram in the simplified form of section 5

7.1 Single monomer futile cycles?

We want to make sure we get some notion of futile cycles in these system, the single monomer futile cycles seem like a reasonable target. To get thses, nothing changes in the binding/debinding transitions, but we do get a change in the conformation change transitions. Essentially, where before the transitions were always guaranteed to happen in the desired direction due to just energy balance, this is no longer guaranteed as we may get additional energy costs of up to $2\epsilon_b$. This means some of our single monomer futile cycles get disrupted, unless the energy matrices are such that $\Delta\epsilon_r > 2\epsilon_b$, which seems unreasonable. Figure 8 shows a sample diagram with all the futile cycles present, as in, with this condition true.
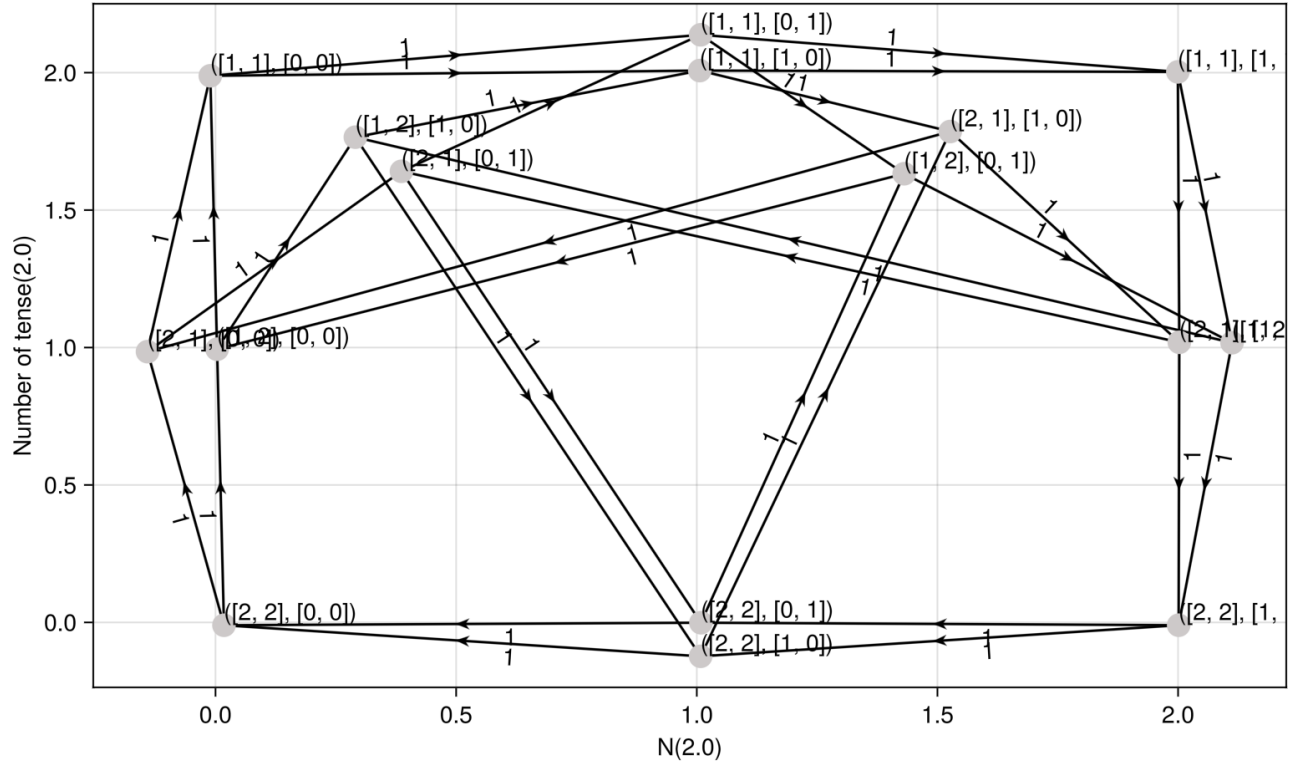
Figure 8: Diagram for $N = 2$ with only those transitions required for the single monomer futile cycles being shown.

8 Modifications for the future

After looking at some first numerical systems with $N > 1$ we got edge currents but adding ϵ_b highlighted a bit of an issue. This makes many conformational change rates scale with $e^{\beta \epsilon_b}$ which gets very large for $\epsilon_b \sim 1-5$ in which range we see a reasonable edge confinement. The only way in Model 2.5 to combat this is to adjust the overall rate scales r_i, but that somewhat changes their interpretation if we need significant differences between them to get overall similar transition rates. To fix this Jaime suggested adjusting the transition rates, in particular we could divide the rates from section 3 by $\exp(\beta(\sum \epsilon_?))$ with some sum of the energies to normalize the transition rates.

Firstly, it is clear that the role of concentrations should be the same, keeping them at the front of only the rates in which they are the substrates not products. However, it is not so clear what to do with the intrinsic chemical energies. For now, we exclude these from coming into the additional factor we talk of as that keeps our simplification of setting them all to zero when the $\theta_?$ are 1 valid. Thus, the $\epsilon_?$ can only be the energies of the microstates of the system and in particular only the part of those that is associated with the affected monomer, keeping things in the same spirit as before. I see two obvious choices to choose from.

8.1 Simple rescaling by reaction type

9 Extras

$$a = r_3 e^{\frac{-\Delta\epsilon_r\left(1-\theta_{3b}\right)}{kT}} \tag{70}$$

$$b = c_{ATP}r_2(1)e^{\frac{-(\epsilon_{ADP}+\epsilon_t)(1-\theta_{2b})+\epsilon_{ATP}\theta_{2f}}{kT}} + c_P r_1(1)e^{\frac{\epsilon_P\theta_{1f}-\epsilon_t(1-\theta_{1b})}{kT}} \tag{71}$$

$$c = r_3 e^{\frac{\Delta\epsilon_r\theta_{3b}}{kT}} \tag{72}$$

$$d = c_{ATP}r_2(2)e^{\frac{(\Delta\epsilon_r+\epsilon_{ATP})\theta_{2f}-(-\Delta\epsilon_r+\epsilon_{ADP}+\epsilon_t)(1-\theta_{2b})}{kT}} + c_P r_1(2)e^{\frac{(\Delta\epsilon_r+\epsilon_P)\theta_{1f}-(-\Delta\epsilon_r+\epsilon_t)(1-\theta_{1b})}{kT}} \tag{73}$$

$$e = r_1(1)e^{\frac{-\epsilon_P\left(1-\theta_{1f}\right)+\epsilon_t\theta_{1b}}{kT}} + c_{ADP}r_2(1)e^{\frac{(\epsilon_{ADP}+\epsilon_t)\theta_{2b}-\epsilon_P\left(1-\theta_{2f}\right)}{kT}} \tag{74}$$

$$f = r_3 e^{\frac{-(-\Delta\epsilon_r+\epsilon_t)(1-\theta_{3b})+\epsilon_t\theta_{3f}}{kT}} \tag{75}$$

$$g = r_1(2)e^{\frac{-(\Delta\epsilon_r+\epsilon_P)\left(1-\theta_{1f}\right)+(-\Delta\epsilon_r+\epsilon_t)\theta_{1b}}{kT}} + c_{ADP}r_2(2)e^{\frac{-(\Delta\epsilon_r+\epsilon_P)\left(1-\theta_{2f}\right)+(-\Delta\epsilon_r+\epsilon_{ADP}+\epsilon_t)\theta_{2b}}{kT}} \tag{76}$$

$$h = r_3 e^{\frac{(-\Delta\epsilon_r+\epsilon_t)\theta_{3b}-\epsilon_t\left(1-\theta_{3f}\right)}{kT}} \tag{77}$$

Figure 9: full rate version