

# 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:

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

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 caveat 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

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

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

### 1.1 General case

In the general case we can write

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

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

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

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

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

where  $\epsilon_t$  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 Ensemble. Thus for each microstate we are interested in what its energy is and how many ligands are bound in that microstate, denote these as  $E_\alpha$  and  $N_\alpha$ . Then the probabilities of microstates being occupied is given by their Gibbs factors so that

$$p_\alpha \propto \exp(-\beta(E_\alpha - \mu N_\alpha)) \quad (6)$$

with  $\mu$  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



we get

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

where each  $\mu_X = \epsilon_X + k_B T \ln(c_X)$  and we make a choice to split the terms so that

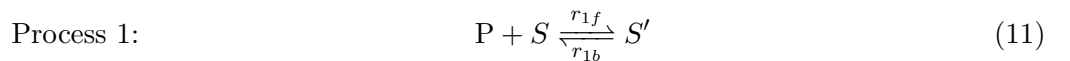
$$r_f = r c_{S_1} c_{S_2} \cdots \exp(\beta(\theta_f(\epsilon_{S_1} + \epsilon_{S_2} + \cdots) - (1 - \theta_b)(\epsilon_{P_1} + \epsilon_{P_2} + \cdots))) \quad (9)$$

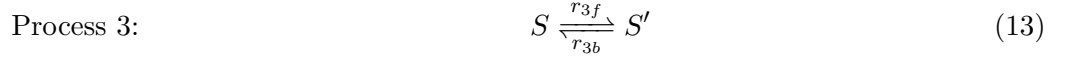
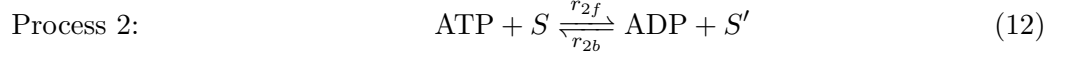
$$r_b = r c_{P_1} c_{P_2} \cdots \exp(\beta(\theta_b(\epsilon_{P_1} + \epsilon_{P_2} + \cdots) - (1 - \theta_f)(\epsilon_{S_1} + \epsilon_{S_2} + \cdots))) \quad (10)$$

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  $\mu$  between the forward and backward rates using the dimensionless  $\theta_i$  parameters.

### 3.1 Transition rates for Model 2.5

We still consider the following three processes





where the  $S$ s 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  $\epsilon_S$  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  $\mu_S$  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  $\epsilon_i^S$  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

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

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

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

and so

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

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

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

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

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

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

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

## 4 Parameters

The model has the following parameters

Where they come from	parameters	units
Energy parameters	$\epsilon_t, \Delta\epsilon_r, \epsilon_b$	E
Equilibrium statistics	$\mu, k_b T$	E
Rates: overall scaling	$r_{1/2}(c_i), r_3 - 2C + 1$ of these	rates – T <sup>-1</sup>
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

### 4.1 Reducing parameters

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

We can start off with setting all the  $\theta_i$  to one 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 to 0.

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

### 5.1 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  $\epsilon_t$ . 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

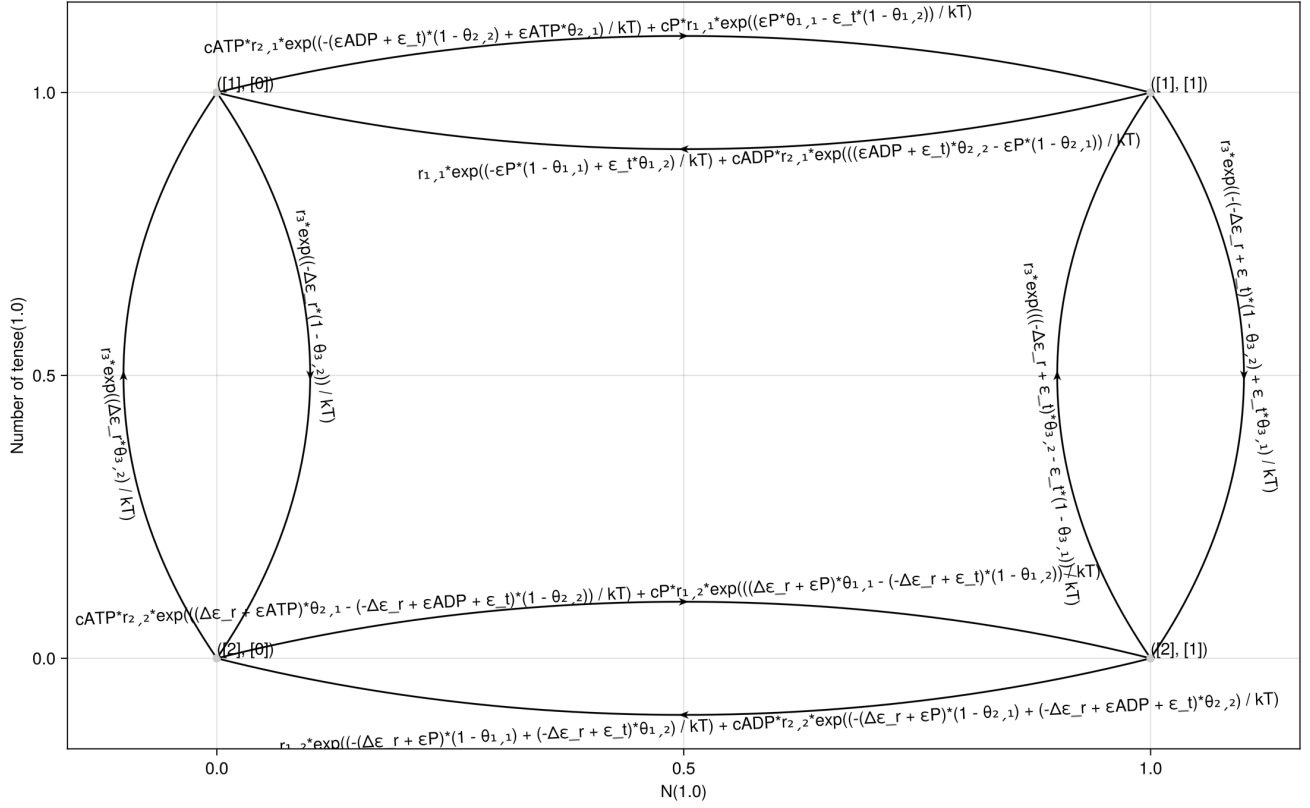


Figure 1: Diagram of single monomer transitions for  $C = 2, B = 1$ . Top row is the tense conformational states, bottom is the relaxed ones. Left column are without a ligand and right column with one ligand bound.

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  $\epsilon$  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  $\theta_i$  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.

## 5.2 Brute force approach

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

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

$$c_{ATP} r_2(2) e^{\frac{(\Delta \epsilon_r + \epsilon_{ATP}) \theta_{2f} - (-\Delta \epsilon_r + \epsilon_{ADP} + \epsilon_t)(1 - \theta_{2b})}{kT}} + c_P r_1(2) e^{\frac{(\Delta \epsilon_r + \epsilon_P) \theta_{1f} - (-\Delta \epsilon_r + \epsilon_t)(1 - \theta_{1b})}{kT}} < \\ r_1(2) e^{\frac{-(\Delta \epsilon_r + \epsilon_P)(1 - \theta_{1f}) + (-\Delta \epsilon_r + \epsilon_t) \theta_{1b}}{kT}} + c_{ADP} r_2(2) e^{\frac{-(\Delta \epsilon_r + \epsilon_P)(1 - \theta_{2f}) + (-\Delta \epsilon_r + \epsilon_{ADP} + \epsilon_t) \theta_{2b}}{kT}} \quad (24)$$

## 5.3 Choosing parameters

In order to move forward, we use the parameter reductions from section 4.1 and make some additional choices. Inspired from section 5.1, we let the rates  $r_1(?)$  all be the same, call it  $r_1$ , and we let  $r_2 = r_2(1)$  and  $r_2(2) = \alpha r_2$ , with presumably  $\alpha < 1$ . This makes the rates become

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

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

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

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

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

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

which from a slightly different perspective is

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

$$r_{b_i+1, c_i=2} = (r_1 c_P + \alpha r_2 c_{ATP}) \exp(\beta E_M(2, b_i)) \quad (32)$$

$$r_{b_i-1, c_i=1} = (r_1 + r_2 c_{ATP}) \exp(\beta E_M(1, b_i)) \quad (33)$$

$$r_{b_i-1, c_i=2} = (r_1 + \alpha r_2 c_{ATP}) \exp(\beta E_M(2, b_i)) \quad (34)$$

$$r_{c_i \rightarrow c'_i, b_i} = r_3 \exp(\beta (E_M(c_i, b_i) + \text{NN interaction energy})) \quad (35)$$

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

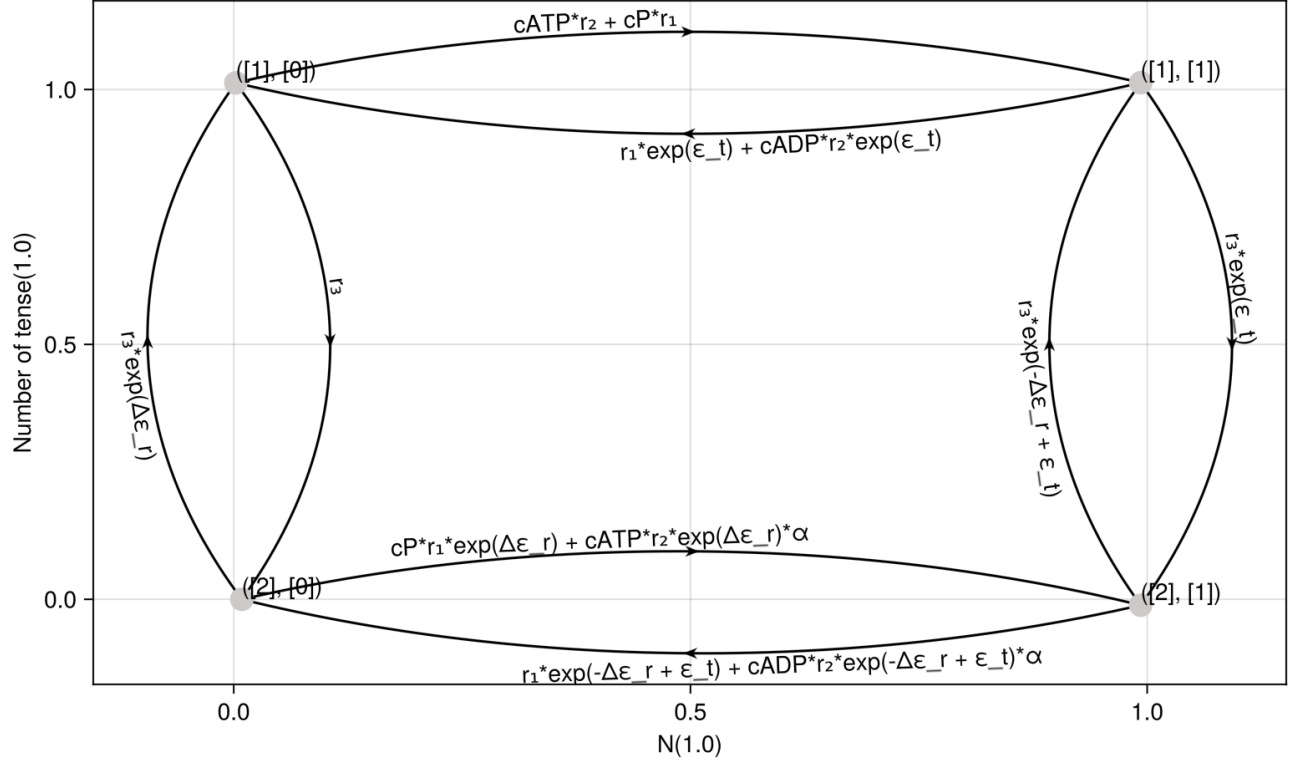


Figure 2: Diagram of single monomer transitions for  $C = 2, B = 1$  using the simplifying parameter choices. Top row is the tense conformational states, bottom is the relaxed ones. Left column are without a ligand and right column with one ligand bound.

#### 5.4 Looking at 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

$$\underline{\underline{R}} \leftrightarrow \begin{pmatrix} 0 & c & e & 0 \\ a & 0 & 0 & g \\ b & 0 & 0 & h \\ 0 & d & f & 0 \end{pmatrix} \quad \text{with states ordered as} \quad \begin{pmatrix} (\{1\}, \{0\}) \\ (\{2\}, \{0\}) \\ (\{1\}, \{1\}) \\ (\{2\}, \{1\}) \end{pmatrix} \quad (36)$$

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

$$a = r_3 \quad (37)$$

$$f = r_3 e^{\epsilon_t} \quad (38)$$

$$d = c_P r_1 e^{\Delta \epsilon_r} + c_{ATP} r_2 e^{\Delta \epsilon_r} \alpha \quad (39)$$

$$g = r_1 e^{-\Delta \epsilon_r + \epsilon_t} + c_{ADP} r_2 e^{-\Delta \epsilon_r + \epsilon_t} \alpha \quad (40)$$

$$h = r_3 e^{-\Delta \epsilon_r + \epsilon_t} \quad (41)$$

$$b = c_{ATP} r_2 + c_P r_1 \quad (42)$$

$$e = r_1 e^{\epsilon_t} + c_{ADP} r_2 e^{\epsilon_t} \quad (43)$$

$$c = r_3 e^{\Delta \epsilon_r} \quad (44)$$

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 equation

$$\partial_t p_i = \sum_j (R_{ij} p_j - R_{ji} p_i) \quad \text{into the convenient form of} \quad \partial_t p_i = \sum_j W_{ij} p_j \quad (45)$$

using substitutions from before we get

$$\underline{\underline{W}} \leftrightarrow \begin{pmatrix} -a-b & c & e & 0 \\ a & -c-d & 0 & g \\ b & 0 & -e-f & h \\ 0 & d & f & -g-h \end{pmatrix} \quad (46)$$