Quasi-thermodynamic Push-Pull Models

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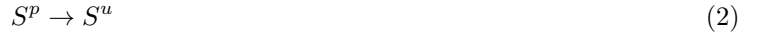
I. ONE-WAY PUSH MODEL

In this model, we have a substrate S^u and a writer (kinase) W. The writer is able to phosporylate the substrate from S^u to S^p. In this model, we do not explicitly include an eraser (phosphatase), but there is a dephosphoralation background rate (and a phosphoralation background rate).

Reactions:

$$W + S^u \leftrightarrows WS^u \to WS^p \leftrightarrows W + S^p \tag{1}$$

Background:

$$S^p \to S^u \tag{2}$$
$$S^u \to S^p \tag{3}$$
$$WS^p \to WS^u \tag{4}$$
$$WS^u \to WS^p \tag{5}$$

Total Concentrations: We define total concentrations for each species and also separately for unphosporylated and phosporylated states.

- Total writer: $[W_T] = [W] + [WS^u] + [WS^p]$

- Total substrate: $[S_T] = [S_T^u] + [S_T^p]$

- Total unphosporylated substrate: $[S_T^u] = [S^u] + [WS^u]$

- Total phosporylated substrate: $[S_T^p] = [S^p] + [WS^p]$

If we know the

Binding Energies: We assume the binding energies are the same for the unphosporylated and phosporylated states.

- Writer + substrate: $\Delta\epsilon_{WS}$

One-way Reaction Rates: These are the reaction rates that cannot be described by binding energies.

- Phosphorylation of substrate by writer: k_{WS}^p

- Background phosphorylation of substrate (independent of binding state): k_S^p

- Background dephosphorylation of substrate (independent of binding state): k_S^u

Partition Functions and Probabilities: We write down partition functions for each species based on the states listed in the total concentrations above. Partition function cannot mix unphosporylated and phosporylated states for the same species, so we do not write down a partition function for the total S. We assume the unbound state of each species is zero energy (although this choice doesn't matter).

- Writer: $Z_W = 1 + e^{-\beta(\Delta\epsilon_{WS} - k_B T \log[S^u])} + e^{-\beta(\Delta\epsilon_{WS} - k_B T \log[S^p])}$

- Unphosphorylated substrate: $Z_{S^u} = 1 + e^{-\beta(\Delta\epsilon_{WS} - k_B T \log[W])}$

- Phosphorylated substrate: $Z_{S^p} = 1 + e^{-\beta(\Delta\epsilon_{WS} - k_B T \log[W])}$

We definee the reaction velocity

$$v_{WS} = e^{-\beta\Delta\epsilon_{WS}} \tag{6}$$

The associated conditional probabilities are then

$$p(W|S^u, S^p) = \frac{[W]}{[W_T]} = \frac{1}{Z_W} = \frac{1}{1 + v_{WS}([S^u] + [S^p])} \tag{7}$$

$$p(WS^u|S^u, S^p) = \frac{[WS^u]}{[W_T]} = \frac{e^{-\beta(\Delta \epsilon_{WS} - k_B T \log[S^u])}}{Z_W} = \frac{v_{WS}[S^u]}{1 + v_{WS}([S^u] + [S^p])} \tag{8}$$

$$p(WS^p|S^u, S^p) = \frac{[WS^p]}{[W_T]} = \frac{e^{-\beta(\Delta \epsilon_{WS} - k_B T \log[S^p])}}{Z_W} = \frac{v_{WS}[S^p]}{1 + v_{WS}([S^u] + [S^p])} \tag{9}$$

$$p(S^u|W) = \frac{[S^u]}{[S_T^u]} = \frac{1}{Z_{S^u}} = \frac{1}{1 + v_{WS}[W]} \tag{10}$$

$$p(WS^u|W) = \frac{[WS^u]}{[S_T^u]} = \frac{e^{-\beta(\Delta \epsilon_{WS} - k_B T \log[W])}}{Z_{S^u}} = \frac{v_{WS}[W]}{1 + v_{WS}[W]} \tag{11}$$

$$p(S^p|W) = \frac{[S^p]}{[S_T^p]} = \frac{1}{Z_{S^p}} = \frac{1}{1 + v_{WS}[W]} \tag{12}$$

$$p(WS^p|W) = \frac{[WS^p]}{[S_T^p]} = \frac{e^{-\beta(\Delta \epsilon_{WS} - k_B T \log[W])}}{Z_{S^p}} = \frac{v_{WS}[W]}{1 + v_{WS}[W]} \tag{13}$$

Reactions in Detailed Balance: From the probabilities, we focus on the equations for the concentration of each species in its unbound state. These correspond to the kinetic equations for reactions not involving (de)phosphorylation.

$$\frac{[W]}{[W_T]} = \frac{1}{1 + v_{WS}([S^u] + [S^p])} \tag{14}$$

$$\frac{[S^u]}{[S_T^u]} = \frac{1}{1 + v_{WS}[W]} \tag{15}$$

$$\frac{[S^p]}{[S_T^p]} = \frac{1}{1 + v_{WS}[W]} \tag{16}$$

Reactions not in Detailed Balance: This is the kinetic equation for reactions involving (de)phosphorylation. It is possible for either S^u or WS^u to undergo this process, so we have two equations

$$\frac{\mathrm{d}[S^p]}{\mathrm{d}t} = k_{WS}^-[WS^p] - k_{WS}^+[W][S^p] + k_S^p[S^u] - k_S^u[S^p] \tag{17}$$

$$\frac{\mathrm{d}[WS^p]}{\mathrm{d}t} = k_{WS}^+[W][S^p] - k_{WS}^-[WS^p] + k_{WS}^p[WS^u] + k_S^p[WS^u] - k_S^u[WS^p] \tag{18}$$

where we have defined the forward and backward dissociation rates k_{WS}^+ and k_{WS}^- such that

$$v_{WS} = \frac{k_{WS}^+}{k_{WS}^-} \tag{19}$$

Adding these equations together, we eliminate these rates, giving us

$$\frac{\mathrm{d}[S_T^p]}{\mathrm{d}t} = k_{WS}^p[WS^u] + k_S^p[S_T^u] - k_S^u[S_T^p] \tag{20}$$

$$= k_{WS}^p[S_T^u]p(WS^u|W) + k_S^p[S_T^u] - k_S^u[S_T^p] \tag{21}$$

$$= k_{WS}^p([S_T] - [S_T^p])p(WS^u|W) + k_S^p([S_T] - [S_T^p]) - k_S^u[S_T^p] \tag{22}$$

Setting this to zero, we get

$$\frac{[S_T^p]}{[S_T]} = \frac{k_{WS}^p p(WS^u|W) + k_S^p}{k_{WS}^p p(WS^u|W) + k_S^p + k_S^u} \tag{23}$$

$$= \frac{1 + v_{WS}^p p(WS^u|W)}{1 + v_{WS}^p p(WS^u|W) + v_S^u} \tag{24}$$

where we have defined the reaction velocities relative to the background phosphorylation rate,

$$v_{WS}^p = \frac{k_{WS}^p}{k_S^p} \tag{25}$$

$$v_S^u = \frac{k_S^u}{k_S^p} \tag{26}$$

If the total concentrations $[W_T]$ and $[S_T]$ are known, this equation plus Eqs. (14)-(15) and the four equations for concentration comprise a system of 8 equations for the remaining 7 unknown concentrations. Since this system is over-determined, either one of the concentrations or one of Eqs. (14)-(15) maybe neglected.

II. GOLDBETER PUSH-PULL AMPLIFIER

Intermediate states missing WS^p and ES^u
Reactions:

$$W + S^u \leftrightarrows WS^u \to WS^p \to W + S^p \tag{27}$$
$$E + S^p \leftrightarrows ES^p \to ES^u \to E + S^u \tag{28}$$

III. COMPLETE PUSH-PULL AMPLIFIER

Reactions:

$$W + S^u \leftrightarrows WS^u \to WS^p \leftrightarrows W + S^p \tag{29}$$
$$E + S^p \leftrightarrows ES^p \to ES^u \leftrightarrows E + S^u \tag{30}$$

Background:

$$S^p \to S^u \tag{31}$$
$$S^u \to S^p \tag{32}$$
$$WS^p \to WS^u \tag{33}$$
$$WS^u \to WS^p \tag{34}$$
$$ES^p \to ES^u \tag{35}$$
$$ES^u \to ES^p \tag{36}$$