PS5 q3

Sunday, May 2, 2021 8:30 AM

- Consider only two methylation states (m = 0, 1).
- Allow only the m = 1 state to be activated (i.e., set $\alpha_0^+ = 0$).
- Allow methylation to be zeroth order.
- Include the deactivation paths mediated by B and B_p (B acting as an "inhibitor").

Then the mass action kinetics are given by:

$E_0 \rightarrow E_1$	V_{max}^R	(1)
$E_1^* \leftrightarrow E_1$	α_1^-, α_1^+	(2)
$E_1^* + B_p \leftrightarrow \{E_1^* B_p\} \rightarrow E_0 + B_p$	a_{bp}, d_{bp}, k_{bp}	(3)
$E_1^* + B \leftrightarrow \{E_1^* B\} \rightarrow E_0 + B$	a_b, d_b, k_b	(4)
$\{E_1^* B_p\} \rightarrow E_1 + B_p$	β_1	(5)
$\{E_1^* B\} \rightarrow E_1 + B$	β_1	(6)
$B \leftrightarrow B_p$	$k_{1+} \times A, k_{1-}$	(7)

a) Express the balances in (a) as a series of ODEs for the seven species: E_0, E_1, E_1^*, B, B_p, $\{E_1^* B\}$, $\{E_1^* B_p\}$.
b) Using the parameter values (p. 877 of Barkai et al., 2001), justify the zeroth order approximation for methylation, give an expression for this rate, and find its numerical value for this rate.

The simulated reference system (*figure 3*) had $M = 2$ methylation sites ($m = 0, 1, 2$) and the following parameters: $a_r = 0.2\ s^{-1} \cdot \mu M^{-1}$, $d_r = 0.1\ s^{-1}$ and $k_r = 0.1\ s^{-1}$, $a_b = 1\ s^{-1} \cdot nM^{-1}$, $d_b = 1\ s^{-1}$, $k_b = 0$, $a_{bp} = 0.1\ s^{-1} \cdot nM^{-1}$, $d_{bp} = 0.01\ s^{-1}$, $k_{bp} = 1\ s^{-1}$, $k_+ = 1\ s^{-1} \cdot \mu M^{-1}$, $k_- = 1\ s^{-1}$, $\alpha_0^+ = 10\ s^{-1}$, $\alpha_1^+ = 1/(1+\ell)\ s^{-1}$, $\alpha_2^+ = 0$, $\alpha_0^- = 0$, $\alpha_1^- = \ell/(1+\ell)\ s^{-1}$, $\alpha_2^- = 10\ s^{-1}$, $\beta_0 = 0$, $\beta_1 = 2.5\ell/(1+\ell)\ s^{-1}$, and $\beta_2 = 25\ s^{-1}$. The concentration of receptors, CheR and CheB are 10 μM, 0.2 μM and 2 μM,

Balances

$$E_0: \quad \frac{dE_0}{dt} = -V_{max}^R + [E_1^* B_p] k_{bp} + [E_1^* B] k_b$$

$$E_1: \quad \frac{dE_1}{dt} = V_{max}^R + E_1^* \alpha_1^- - E_1 \alpha_1^+ + [E_1^* B_p] \beta_1 + [E_1^* B] \beta_1$$

$$E_1^*: \quad \frac{dE_1^*}{dt} = E_1 \alpha_1^+ - E_1^* \alpha_1^- - (E_1^*)(B_p) a_{bp} + [E_1^* B_p] d_{bp} - (E_1^*)(B) a_b + [E_1^* B] d_b$$

$$B: \quad \frac{dB}{dt} = -(E_1^*)(B) a_b + [E_1^* B] d_b + [E_1^* B] k_b + [E_1^* B] \beta_1 - B \cdot k_1^+ \cdot E_1^* + B_p k_1^-$$

$$B_p: \quad \frac{dB_p}{dt} = -(E_1^*)(B_p) a_{bp} + [E_1^* B_p] d_{bp} + [E_1^* B_p] k_{bp} + [E_1^* B_p] \beta_1 + B \cdot k_1^+ \cdot E_1^* - B_p k_1^-$$

$$[E_1^* B]: \quad \frac{d[E_1^* B]}{dt} = (E_1^*)(B) a_b - [E_1^* B] d_b - [E_1^* B] k_b - [E_1^* B] \beta_1$$

$$[E_1^* B_p]: \quad \frac{d[E_1^* B_p]}{dt} = (E_1^*)(B_p) a_{bp} - [E_1^* B_p] d_{bp} - [E_1^* B_p] k_{bp} - [E_1^* B_p] \beta_1$$

Methylation

methylation is most accurately described with M-M kinetics:

$$\frac{dE_{mtl}}{dt} = \frac{k_r [R] [E_m]}{\frac{k_r + d_r}{a_r} + [E_m]}$$

This expression can be simplified to the V_{max} equation, based on the observation that $a_r >> (k_r + \delta_r)$, so $\frac{k_r + \delta_r}{a_r} + E_n \approx E_n$

$\rightarrow$

$$\frac{\delta E_{n+1}}{\delta t} \approx \frac{k_r(R)(E_n)}{(E_n)} = k_r(R)$$

therefore $V_{max}^R = k_r(R) = (0.1\,s^{-1})(0.2\,\mu M) = 20\,nM \cdot s^{-1}$