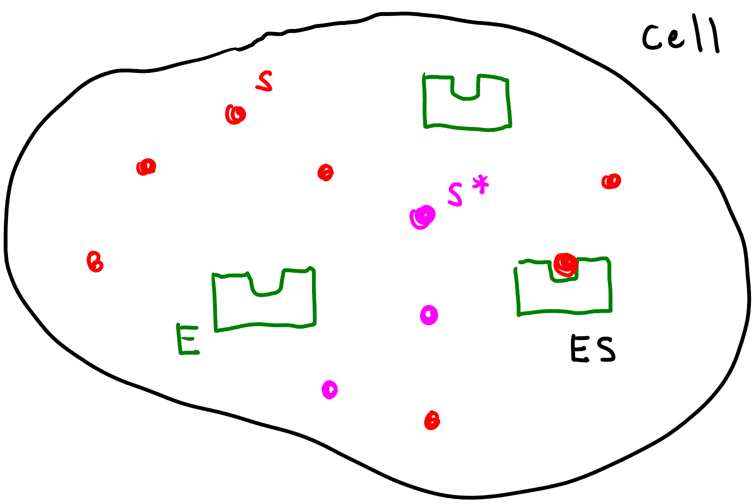
enzyme E (type of protein)

substrate S (another protein or small molecule)

reaction $S \to S^*$ (modified version of substrate)

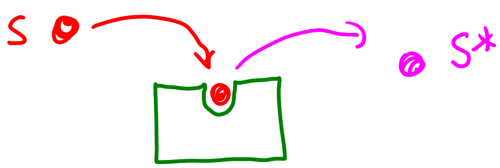


reaction scheme:

binding k_b / unbinding k_u / k_{cat} catalysis rate

$$E + S \underset{k_u}{\overset{k_b}{\rightleftharpoons}} ES \xrightarrow{k_{cat}} E + S^*$$

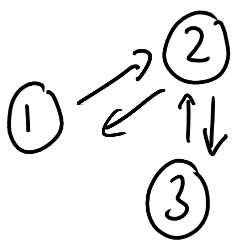
usually quite small & can be ignored



chemical state:

$\vec{n} = (n_S, n_E, n_{ES}, n_{S^*})$

n_α = # of type α in your system

states  $\Rightarrow \Omega_{nm}$ $m \to n$

generalize trans. matrix $\Omega_{\vec{n}\vec{m}}$ = trans. rate from $\vec{m}$ to $\vec{n}$ when $\vec{n} \neq \vec{m}$

probability $p_{\vec{n}}(t)$ = prob. to be in state $\vec{n}$ at time t

$$\sum_{\vec{n}} p_{\vec{n}}(t) = 1$$

$$\sum_{n_S=0}^{\infty} \sum_{n_E=0}^{\infty} \cdots \sum_{n_{S^*}=0}^{\infty}$$

columns of $\Omega_{\vec{n}\vec{m}}$ sum to zero: $\sum_{\vec{n}} \Omega_{\vec{n}\vec{m}} = 0$

$$\frac{d}{dt} p_{\vec{n}}(t) = \sum_{\vec{m}} \Omega_{\vec{n}\vec{m}} \, p_{\vec{n}}(t)$$

chemical master equ.

$(0,0) = 1$
$(0,1) = 2$
$(0,2) = 3$
$\vdots$
$(1,0) = 17$
$\vdots$

Conservation laws (stoichiometry)

$$n_E + n_{ES} = \text{const.} \equiv M_E$$

$$n_S + n_{ES} + n_{S^*} = \text{const} \equiv M_S$$

example: $M_S = 2$ $M_E = 2$

allowed states

$$\begin{array}{cc} & \begin{array}{cccc} n_S & n_E & n_{ES} & n_{S^*} \end{array} \\ \vec{n} = & (2, \; 2, \; 0, \; 0) \\ & \big\downarrow \text{binding} \\ & (1, \; 1, \; 1, \; 0) \\ & \big\downarrow \text{binding} \\ & (0, \; 0, \; 2, \; 0) \\ & \big\downarrow \text{catalysis} \\ & (0, \; 1, \; 1, \; 1) \end{array}$$

How to characterize all possible non-zero trans.

$\Omega_{\vec{n}\vec{m}}$, $\vec{n} \neq \vec{m}$ (all ways $\underset{\text{start}}{\vec{m}} \rightarrow \underset{\text{end}}{\vec{n}}$)

i) binding :

$$\vec{m} = (m_s, m_E, m_{ES}, m_{s*})$$
$$\downarrow$$
$$\vec{n} = (n_s, n_E, n_{ES}, n_{s*})$$

if

$$n_s = m_s - 1$$
$$n_E = m_E - 1$$
$$n_{ES} = m_{ES} + 1$$
$$n_{s*} = m_{s*}$$

is true $\Rightarrow$ $\Omega_{\vec{n},\vec{m}} = \alpha_b K_s \overbrace{\frac{m_s}{\underset{\text{cell volume}}{V}}}^{\text{conc. of searchers}} \underbrace{m_E}_{\#\text{ targets}}$

$$= \tilde{k}_b m_s m_E$$

$$\tilde{k}_b = \frac{\alpha_b K_s}{V}$$

ii) unbinding

if

$$n_E = m_E + 1$$
$$n_s = m_s + 1$$
$$n_{ES} = m_{ES} - 1$$
$$n_{s*} = m_{s*}$$

true $\Rightarrow$ $\Omega_{\vec{n},\vec{m}} = K_u m_{ES}$

iii) catalysis

if

$$n_E = m_E + 1$$
$$n_s = m_s$$
$$n_{ES} = m_{ES} - 1$$
$$n_{s*} = m_{s*} + 1$$

is true $\Rightarrow$ $\Omega_{\vec{n},\vec{m}} = K_{cat} m_{ES}$

portion of Ω:

	$(2,2,0,0)$	$(1,1,1,0)$	$(1,2,0,1)$	$\cdots$
$(2,2,0,0)$	$\sim$	k_u		
$(1,1,1,0)$	$4\tilde{k}_b$	$\sim$		
$(1,2,0,1)$	0	k_{cat}	$\sim$	
$\vdots$				

diag: make columns sum to zero

TRICK: recall $\langle i \rangle_t = \sum_i i \, p_i(t)$

derived $\frac{d\langle i \rangle_t}{dt} = \sum_{i,j} (j-i)\,\Omega_{ji}\, p_i(t)$

generalize: $\langle n_S \rangle_t = \sum_{\vec{n}} n_S \, p_{\vec{n}}(t)$

$\vdots$

$\langle n_E \rangle_t = \sum_{\vec{n}} n_E \, p_{\vec{n}}(t)$

1) $\frac{d\langle n_S \rangle_t}{dt} = \sum_{\vec{m},\vec{n}} (n_S - m_S)\,\Omega_{\vec{n},\vec{m}}\, p_{\vec{m}}(t)$

2) $\frac{d\langle n_E \rangle_t}{dt} = \sum_{\vec{m},\vec{n}} (n_E - m_E)\,\Omega_{\vec{n},\vec{m}}\, p_{\vec{m}}(t)$

$\vdots$

4)

$\Big\}$ 4 equ's

plug in Ω:

1) $$\frac{d\langle n_S\rangle_t}{dt} = \sum_{\vec{m}} \Big[-\tilde{k}_b m_S m_E \, p_{\vec{m}}(t) + k_u m_{ES} \, p_{\vec{m}}(t) \Big]$$

convert to averages

1) $$\frac{d\langle n_S\rangle_t}{dt} = -\tilde{k}_b \langle n_S n_E\rangle_t + k_u \langle n_{ES}\rangle_t$$

2) $$\frac{d\langle n_E\rangle_t}{dt} = -\tilde{k}_b \langle n_S n_E\rangle_t + (k_u + k_{cat}) \langle n_{ES}\rangle_t$$

3) $$\frac{d\langle n_{ES}\rangle_t}{dt} = \tilde{k}_b \langle n_S n_E\rangle_t - (k_u + k_{cat}) \langle n_{ES}\rangle_t$$

4) $$\frac{d\langle n_{S^*}\rangle_t}{dt} = k_{cat} \langle n_{ES}\rangle_t$$

These equations are exact.

4 equ's + $\langle n_S\rangle_t, \langle n_E\rangle_t, \langle n_{ES}\rangle_t, \langle n_{S^*}\rangle_t,$

$\langle n_S n_E\rangle_t$

5 unknowns

hack: $\langle n_S n_E\rangle_t \approx \langle n_S\rangle_t \langle n_E\rangle_t$

$\Rightarrow$ gives 4 eqn's + 4 unknowns

$\Rightarrow$ solve for all unknowns!

Why does this work?