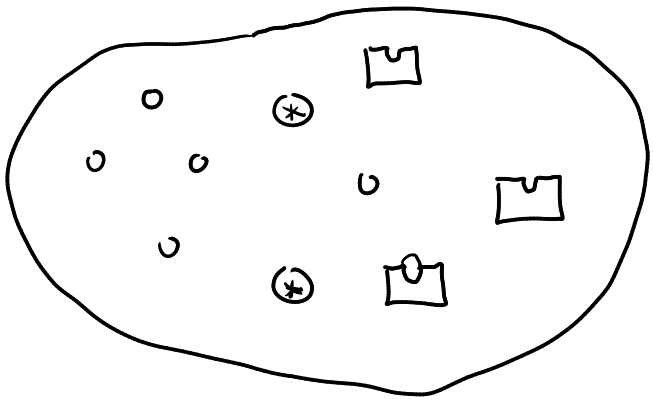
reaction:

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



= E = ES

o = S

⊛ = S^*

$\vec{n} = (5, 2, 1, 2)$

chemical state:

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

↑ # of S

n_α = # of type α in cell

before

$m \to n$ ⇝ generalize

Ω_{nm}

$\Omega_{\vec{n}\vec{m}}$ = trans. rate from state $\vec{m}$ to $\vec{n}$ (for $\vec{n} \neq \vec{m}$)

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

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

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

columns of $\Omega_{\vec{n}\vec{m}}$ sum to zero

$$\sum_{\vec{n}} \Omega_{\vec{n}\vec{m}} = 0$$

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

chemical master equation (accurate, but hard to solve)

Conservation laws (stoichiometry):

$$n_E + n_{ES} = \text{const.} \equiv M_E = 3$$

$$n_S + n_{ES} + n_{S^*} = \text{const.} \equiv M_S = 8$$

in our example

matrix can be restricted to just those states $\vec{n}$ allowed by cons. laws

another example: $M_S = 2, \quad M_E = 2$

$$\begin{matrix} & n_S & n_E & n_{ES} & n_{S^*} \\ \vec{n} = & (2 & 2 & 0 & 0) \\ \text{binding} \downarrow & (1 & 1 & 1 & 0) \\ \text{catalysis} \downarrow & (1 & 2 & 0 & 1) \end{matrix}$$

all possible non-zero off-diag. elements of $\Omega_{\vec{n}\vec{m}}$ for $\vec{n} \neq \vec{m}$

i) binding: $\vec{m} = (m_S, m_E, m_{ES}, m_{S^*})$ start

$\downarrow$

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

if $n_S = m_S - 1$, $n_E = m_E - 1$, $n_{ES} = m_{ES} + 1$, $n_{S^*} = m_{S^*}$

$$\Rightarrow \Omega_{\vec{n},\vec{m}} = \alpha_b K_S \frac{m_S}{V} m_E$$

(m_S: # of targets; V: cell vol.)

binding for single target $\sim \alpha_b K_S C$ (C: searcher conc.)

$$\Rightarrow \boxed{\Omega_{\vec{n},\vec{m}} = \tilde{k}_b n_S n_E} \qquad \tilde{k}_b = \frac{\alpha_b K_s}{V}$$

ii) unbinding

if $n_E = m_E + 1$, $n_S = m_S + 1$, $n_{ES} = m_{ES} - 1$, $n_S^* = m_S^*$ $\Rightarrow \boxed{\Omega_{\vec{n},\vec{m}} = k_u m_{ES}}$

iii) catalysis

if $n_E = m_E + 1$, $n_S = m_S$, $n_{ES} = m_{ES} - 1$, $n_S^* = m_S^* + 1$ $\Rightarrow \boxed{\Omega_{\vec{n},\vec{m}} = k_{cat} m_{ES}}$

portion of Ω:

end \ start	(2,2,0,0)	(1,1,1,0)	(1,2,0,1)	...
(2,2,0,0)	~	k_u		
(1,1,1,0)	$4\tilde{k}_b$	~		
(1,2,0,1)	0	k_{cat}	~	
⋮				

diag: sum of col's is zero

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

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

general version: $\langle n_s \rangle_t = \sum_{\vec{n}} n_s\, p_{\vec{n}}(t)$

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

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

⋮

plug in Ω : 1) $\frac{d\langle n_s \rangle_t}{dt} = \sum_{\vec{m}} \left[-\tilde{k}_b\, m_s m_E\, p_{\vec{m}}(t) + k_u\, m_{ES}\, p_{\vec{m}}(t) \right]$

⋮

4 eqn's:

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

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

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

5 unknowns: $\langle n_S \rangle_t$, $\langle n_E \rangle_t$, $\langle n_{ES} \rangle_t$, $\langle n_S^* \rangle_t$, $\langle n_S n_E \rangle_t$

but only 4 eqn's

"dirty trick": $\langle n_s n_E \rangle_t \approx \langle n_s \rangle_t \langle n_E \rangle_t$

$\Rightarrow$ this gives 4 eqn's for 4 unknowns

(simple example of moment closure approximation)

digression: imagine two var's X + Y describing system

joint prob. dist. $\mathcal{P}(X, Y)$

↳ frac. of pop. in ensemble w/ value (X, Y)

marg. prob. dist. $\mathcal{P}(X) = \sum_Y \mathcal{P}(X,Y)$

$\mathcal{P}(Y) = \sum_X \mathcal{P}(X,Y)$

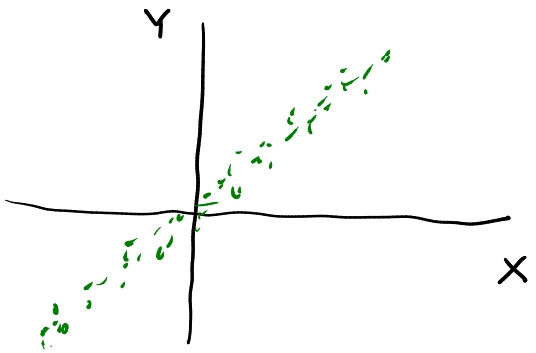
$\langle X \rangle = \sum_{X,Y} X\, \mathcal{P}(X,Y) = \sum_X X\, \mathcal{P}(X)$

$\langle Y \rangle = \sum_{X,Y} Y\, \mathcal{P}(X,Y) = \sum_Y Y\, \mathcal{P}(Y)$

$\langle XY \rangle = \sum_{X,Y} XY\, \mathcal{P}(X,Y)$

in general: $\langle XY \rangle \neq \langle X \rangle \langle Y \rangle$

when does $\langle XY \rangle \approx \langle X \rangle \langle Y \rangle$

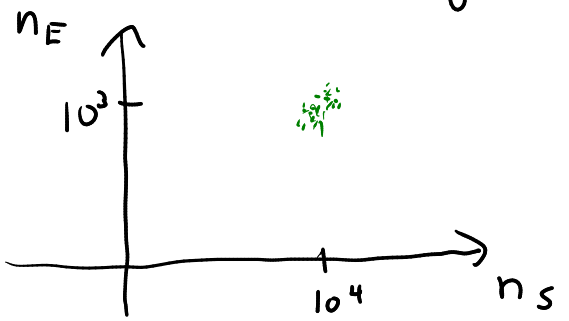


here

$\langle XY \rangle \neq \langle X \rangle \langle Y \rangle$

strongly correlated

in chemistry, when mean # of chemical types is high (10^2 - 10^5 mol/cell)



$\langle n_S n_E \rangle_t \approx \langle n_S \rangle_t \langle n_E \rangle_t$