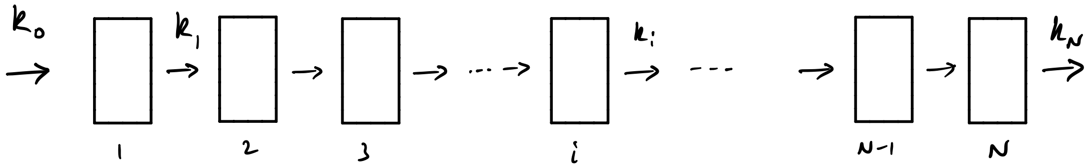
4.2.22

Deterministic Golgi model



N compartments, within each a reaction (eg. glycosylation) takes place $A_i \xrightarrow{m_i} B_i$

B_i is carried out of compartment i at rate k_i, providing source for A_{i+1}

Input flux k_0 given, output flux $k_N B_N$ to be determined.

$$\frac{dA_1}{dt} = k_0 - m_1 A_1 \quad \cdots \qquad \frac{dA_i}{dt} = k_{i-1} B_{i-1} - m_i A_i$$

$$\frac{dB_1}{dt} = m_1 A_1 - k_1 B_1 \quad \cdots \qquad \underbrace{\frac{dB_i}{dt} = m_i A_i - k_i B_i}_{i = 2, \dots, N}$$

In matrix form, writing $\underset{\sim}{v} = (A_1, B_1, A_2, B_2, \dots, A_N, B_N)^T$, $\quad \frac{d}{dt}\underset{\sim}{v} = \underline{\underline{C}}\, \underset{\sim}{v} + (k_0, 0, \dots 0)^T$

where

$$\underline{\underline{C}} = \begin{pmatrix} -m_1 & & & & & & & \\ m_1 & -k_1 & & & & & & \\ & & \ddots & & & & & \\ & & k_{i-1} & -m_i & & & & \\ & & & m_i & -k_i & & & \\ & & & & & \ddots & & \\ & & & & & k_{N-1} & -m_N & \\ & & & & & & m_N & -k_N \end{pmatrix}$$

$\underline{\underline{C}}$ has $2N$ eigenvalues $-m_1, -k_1, \dots, -m_N, -k_N$

$\Rightarrow$ exponential relaxation to steady state.

Steady state: $A_1 = \frac{k_0}{m_1}$, $B_1 = \frac{m_1 A_1}{k_1} = \frac{k_0}{k_1}$, $A_2 = \frac{k_1 B_1}{m_2} = \frac{k_0}{m_2}$, $B_2 = \frac{m_2 A_2}{k_2} = \frac{k_0}{k_2}$ ---

So $\underset{\sim}{v}_0 = k_0 (m_1^{-1}, k_1^{-1}, \dots, m_N^{-1}, k_N^{-1})$ is ultimate state.

Alternatively $\frac{d\underline{v}}{dt} = \underline{\underline{N}}\, \underline{k}$, where $\underline{\underline{N}}$ is the stoichiometric matrix

$\underline{v} \in \mathbb{R}^{2N}$ is vector of concentrations

$\underline{k} \in \mathbb{R}^{2N+1} = (k_0, m_1 A_1, k_1 B_1, \dots, m_i A_i, k_i B_i, \dots, m_N A_N, k_N B_N)$ is vector of reaction rates

and $\underline{\underline{N}}$ is $2N \times 2N+1$

$$
\frac{d}{dt}\begin{bmatrix} A_1 \\ B_1 \\ \vdots \\ A_i \\ B_i \\ \vdots \\ A_N \\ B_N \end{bmatrix} = \begin{array}{c} \\ 2N \end{array}
\underbrace{\begin{bmatrix}
1 & -1 & & & & & & & \\
& 1 & -1 & & & & & & \\
& & \cdots & & & & & & \\
& & & 1 & -1 & & & & \\
& & & & 1 & -1 & & & \\
& & & & & \cdots & & & \\
& & & & & & 1 & -1 & \\
& & & & & & & 1 & -1
\end{bmatrix}}_{2N+1}
\begin{bmatrix} k_0 \\ m_1 A_1 \\ n_1 B_1 \\ \vdots \\ m_i A_i \\ n_i B_i \\ \vdots \\ m_N A_N \\ n_N B_N \end{bmatrix}
$$

The flux vector $\underset{\sim}{k} = (1, 1, \ldots, 1)^T$ satisfies $\underline{\underline{N}}\,\underset{\sim}{k} = \underline{0}$

<u>Stochastic model</u> State vector is $(n_{A_1}, n_{B_1}, \ldots, n_{A_i}, n_{B_i}, \ldots, n_{A_N}, n_{B_N}) = \underset{\sim}{n}$

There are $2N+1$ possible transitions at any time, if we allow reactions to be reversible.
Set $k_0 = 0$ but assume $\underset{\sim}{n} = (1, 0, 0, \ldots, 0)$ at $t=0$. Then

$$
\underline{e}_1 \underset{m_1^-}{\overset{m_1^+}{\rightleftarrows}} \underline{e}_2 \underset{n_1^-}{\overset{n_1^+}{\rightleftarrows}} \underline{e}_3 \underset{m_2^-}{\overset{m_2^+}{\rightleftarrows}} \underline{e}_4 \rightleftarrows \cdots \underset{n_{i-1}^-}{\overset{n_{i-1}^+}{\rightleftarrows}} \underline{e}_{2i-1} \underset{m_i^-}{\overset{m_i^+}{\rightleftarrows}} \underline{e}_{2i} \underset{n_i^-}{\overset{n_i^+}{\rightleftarrows}} \cdots \underset{n_{N-1}^-}{\overset{n_{N-1}^+}{\rightleftarrows}} \underline{e}_{2N-1} \underset{m_N^-}{\overset{m_N^+}{\rightleftarrows}} \underline{e}_{2N} \xrightarrow{k^N} \underset{\sim}{0}
$$

Final irreversible step.

Here the $m_i^{\pm}, n_i^{\pm}$ can be treated as transition probabilities between states.
Let $\Pi_j(t)$ be the fraction of realisations in state j, $1 \le j \le 2N+1$

$$
\frac{d\Pi_j}{dt} = \sum_{k \ne j} \left(R_{j,k}\Pi_k - R_{k,j}\Pi_j \right) \quad \sim \quad \frac{d\underline{\Pi}}{dt} = \underline{\underline{R}}\,\underline{\Pi}
$$

$$
\frac{d}{dt}\begin{bmatrix} \Pi_1 \\ \Pi_2 \\ \Pi_3 \\ \Pi_4 \\ \vdots \\ \Pi_{2i-1} \\ \Pi_{2i} \\ \vdots \\ \Pi_{2N-1} \\ \Pi_{2N} \\ \Pi_{2N+1} \end{bmatrix} =
\underbrace{\begin{bmatrix}
-m_1^+ & m_1^- & & & & & & & & & \\
m_1^+ & -m_1^- - n_1^+ & n_1^- & & & & & & & & \\
& n_1^+ & -m_2^+ - n_1^- & m_2^- & & & & & & & \\
& & m_2^+ & -m_2^- - n_2^+ & n_2^- & & & & & & \\
& & & & \cdots & & & & & & \\
& & & & n_{i-1}^+ & -m_i^+ - n_{i-1}^- & m_i^- & & & & \\
& & & & & m_i^+ & -m_i^- - n_i^+ & n_i^- & & & \\
& & & & & & & \cdots & & & \\
& & & & & & & n_{N-1}^+ & -m_N^+ - n_{N-1}^- & m_N^{-1} & \\
& & & & & & & & m_N^+ & -m_N^- - n_N & \\
& & & & & & & & & n_N & 0
\end{bmatrix}}_{2N+1}
\begin{bmatrix} \Pi_1 \\ \Pi_2 \\ \Pi_3 \\ \Pi_4 \\ \vdots \\ \Pi_{2i-1} \\ \Pi_{2i} \\ \vdots \\ \Pi_{2N-1} \\ \Pi_{2N} \\ \Pi_{2N+1} \end{bmatrix}
$$

The stationary state is $\underset{\sim}{\pi}_s = (\underbrace{0, \dots, 0}_{2N}, 1)$

One can simulate the evolution to this state from the initial condition
$$\pi_0 = (1, 0, 0, \dots, 0)$$

Suppose the mean first passage time to the final state has probability density $f(t)$.

Then $\text{MFPT} = \int_0^\infty t\, f(t)\, dt$. The probability of not reaching the absorbing state at time t is $1 - \pi_{2N+1} = \sum_{i=1}^{2N} \pi_i$, so the probability of making a first passage to the absorbing state is $1 - \sum_{i=1}^{2N} \pi_i$, which has density $-\sum_{i=1}^{2N} \frac{d\pi_i}{dt} = f(t)$.

So $\text{MFPT} = \int_0^\infty -t \sum_{i=1}^{2N} \frac{d\pi_i}{dt}\, dt$ and $\frac{d\tilde{\underline{\pi}}}{dt} = \tilde{K}\tilde{\underline{\pi}}$ where $\tilde{K}$ is K minus its final column and final row, and $\tilde{\pi} = (\pi_1, \dots, \pi_{2N})$.

$\tilde{K}$ is invertible, so $\tilde{\underline{\pi}} = \tilde{K}^{-1} \frac{d\tilde{\pi}}{dt}$. Integrate by parts to give

$$\text{MFPT} = \left[-t \sum_{i=1}^{2N} \tilde{\pi}_i\right]_0^\infty + \int_0^\infty \sum_{i=1}^{2N} \tilde{\pi}_i\, dt \qquad (\tilde{\pi}_i \to 0 \text{ as } t \to \infty)$$

$$= \int_0^\infty \sum_{i=1}^{2N} \left\{\tilde{K}^{-1} \frac{d\tilde{\pi}}{dt}\right\}_i dt = \left[\sum_{i=1}^{2N} \left\{\tilde{K}^{-1}\tilde{\pi}\right\}_i\right]_0^\infty \qquad \tilde{\pi} = (1, 0, 0, \dots, 0) = \underline{e}_1 \text{ at } t = 0$$

$$= -\sum_{i=1}^{2N} \left\{\tilde{K}^{-1}\underline{e}_1\right\}_i$$

For a single unit: $\tilde{K} = \begin{bmatrix} -m_1^+ & m_1^- \\ m_1^+ & -m_1^- - k_1 \end{bmatrix}$, $\tilde{K}^{-1} = \frac{1}{m_1^+ k_1} \begin{pmatrix} -m_1^- - k_1 & -m_1^- \\ -m_1^+ & -m_1^+ \end{pmatrix}$

$\tilde{K}^{-1}\underline{e}_1 = \frac{1}{m_1^+ k_1} \begin{pmatrix} -m_1^- - k_1 \\ -m_1^+ \end{pmatrix}$ and $\text{MFPT} = \frac{m_1^+ + m_1^- + k_1}{m_1^+ k_1}$

So the MFPT $\approx k_1^{-1}$ if $m_1^+ \gg \{m_1^-, k_1\}$ (fast reaction, slow delivery)

but MFPT $\approx k_1^{-1}\left(\frac{m_1^+ + m_1^-}{m_1^+}\right)$ if $k_1 \ll \{m_1^+, m_1^-\}$ (slow reaction, fast delivery).