dynamic processes in cells
(a systems approach to biology)

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example

reversible Michaelis-Menten scheme

\[ E + S \xrightleftharpoons[k_2]{k_1} ES \xrightleftharpoons[k_4]{k_3} E + P \]

**nonlinear dynamics**

\[
\frac{d[E]}{dt} = (k_2 + k_3)[ES] - k_1[E][S] - k_4[E][P]
\]

\[
\frac{d[ES]}{dt} = -(k_2 + k_3)[ES] + k_1[E][S] + k_4[E][P]
\]

**linear Laplacian dynamics**

\[
\frac{d}{dt} \begin{pmatrix}
[E] \\
[ES]
\end{pmatrix} = \begin{pmatrix}
-(k_1[S] + k_4[P]) & (k_2 + k_3) \\
(k_1[S] + k_4[P]) & -(k_2 + k_3)
\end{pmatrix} \begin{pmatrix}
[E] \\
[ES]
\end{pmatrix}
\]

**uncoupling condition**: a concentration appearing in a label cannot be that of a vertex in the graph (but it can be that of a slow variable or a fast variable that is not a vertex in the graph). this can be dispensed with in some contexts
elimination of internal complexity

when $G$ is strongly connected, so that $\ker \mathcal{L}(G) = \langle \rho \rangle$

if there is a steady state $x^* \in \ker \mathcal{L}(G)$

$$x^* = \lambda \rho \begin{pmatrix} x_1^* \\ \vdots \\ x_n^* \end{pmatrix} = \lambda \begin{pmatrix} \rho_1 \\ \vdots \\ \rho_n \end{pmatrix}$$

then each of the $x_i^*$ can be **eliminated**

$$x_i^* = \left( \frac{\rho_i}{\rho_1 + \cdots + \rho_n} \right) x_{tot}$$

$$x_i^* = \frac{\rho_i}{\rho_1} x_1^*$$

**rational expressions**
**calculating \( \rho \)**

1. for any strongly connected graph, \( \rho \) can be calculated in terms of the labels, without having to know their numerical values, by the **Matrix-Tree Theorem**.

2. if the steady state of the system is one of thermodynamic equilibrium, then **detailed balance** holds and \( \rho \) can be calculated more simply, using a single path in the graph, without having to enumerate all the spanning trees.

3. this gives the same answer as **equilibrium statistical mechanics**.

\[
x_i^* = \left( \frac{\rho_i}{\rho_1 + \cdots + \rho_n} \right) x_{tot} \text{ partition function}
\]

4. the linear framework offers a way to also do **non-equilibrium statistical mechanics**.
calculating $\rho$ using the MTT

**Matrix-Tree Theorem:** whenever $G$ is strongly connected

$$
\ker \mathcal{L}(G) = \langle \rho \rangle \quad \rho_i = \sum_{T \in \Theta_i(G)} \left( \prod_{j \rightarrow k \in T} a \right) \quad \text{positive}
$$

$\Theta_i(G)$ = set of spanning trees rooted at $i$

rooted spanning tree – a sub-graph $T$ of $G$ which

- **SPANS** $G$ – every node of $G$ is also a node of $T$
- is a **TREE** – $T$ has no cycles, ignoring edge directions
- is **ROOTED** at $i$ – $i$ is the only node of $T$ with no outgoing edges


spanning trees and the MTT

\[
\begin{align*}
\begin{pmatrix}
-(a_2 + a_3) & a_1 & 0 \\
 a_2 & -a_1 & a_4 \\
 a_3 & 0 & -a_4 \\
\end{pmatrix}
\begin{pmatrix}
 a_1 a_4 \\
(a_2 + a_3) a_4 \\
 a_1 a_3 \\
\end{pmatrix}
&= 0
\end{align*}
\]

Laplacian \( \rho \)

for a proof, see the Appendix in Mirzaev & Gunawardena, Bull Math Biol 75:2118-49 2013
**reversible michaelis-menten**

**enumeration of spanning trees**

\[ \begin{align*}
    k_1[S] + k_4[P] \\
    k_2 + k_3 \\
    k_2 + k_3 \\
    k_2 + k_3 \\
    k_1[S] + k_4[P]
\end{align*} \]

\[ \rho = \begin{pmatrix}
    k_2 + k_3 \\
    k_1[S] + k_4[P]
\end{pmatrix} \]

**elimination**

\[ [ES] = \left( \frac{k_1[S] + k_4[P]}{k_2 + k_3 + k_1[S] + k_4[P]} \right) E_{tot} \]

\[ [E] = \left( \frac{k_2 + k_3}{k_2 + k_3 + k_1[S] + k_4[P]} \right) E_{tot} \]
reversible michaelis-menten

\[
\begin{align*}
E & \xrightleftharpoons[k_2]{k_1} ES & \xrightleftharpoons[k_4]{k_3} E & \xrightleftharpoons[k_4]{k_3} E & \xrightleftharpoons[k_1]{k_2} P \\
\frac{d[P]}{dt} &= k_3[ES] - k_4[E][P]
\end{align*}
\]

\[
\frac{d[P]}{dt} = \left( \frac{V_f[S]/K_f - V_r[P]/K_r}{1 + [S]/K_f + [P]/K_r} \right)
\]

\[
V_f = k_3E_{tot} \quad V_r = k_2E_{tot} \quad K_f = \frac{k_2 + k_3}{k_1} \quad K_r = \frac{k_2 + k_3}{k_4}
\]

forward & reverse maximal rates \quad forward & reverse Michaelis-Menten constants

In summary

The examples discussed previously can all be treated in this way:

There is an underlying graph whose Laplacian dynamics describes the fast sub-system.

The graph is strongly connected and satisfies the uncoupling condition.

4. cellular identity & gene regulatory networks
human embryonic development

stage 1, day 1
totipotent zygote or fertilised oocyte

stage 3, day 4-5
pre-implantation blastocyst

stage 7, day 15-17
gastrulation, notochord

stage 9, day 19-21
neural folds, somites 1-3

stage 11, day 23-26
13 somites

stage 13, day 28-32
leg buds, pharyngeal arches, lens placode

stage 17, day 42-44
fingers emerging

stage 19, day 48-51
fingers emerged, bone has started to form

UNSW Carnegie Stages

Kyoto Human Embryo Visualization Project http://bird.cac.med.kyoto-u.ac.jp/index_e.html
hierarchical construction of cellular identity

in the blood ("hematopoietic") system, which undergoes continuous renewal

"myeloid" = from the bone marrow

"lymphoid" = from the lymphatic system

progenitor and stem cells

specialised ("terminally differentiated") cells
cellular identity is both stable and plastic

EMT – epithelial-mesenchymal transition
MET – mesenchymal-epithelial transition

cellular identity can be re-programmed - I

<table>
<thead>
<tr>
<th>Four strategies to induce reprogramming of somatic cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear transfer</td>
</tr>
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</table>

- **Reproductive cloning**
  - Reproductive cloning
  - Chances: abnormal

- **Customized ES cells**
  - Customized ES cells
  - Inefficiency: ethics, human eggs

- **Reprogramming in the test tube**
  - Reprogramming in the test tube
  - Fused cells: 4n

- **Infection with virus**
  - Infection with virus
  - Limited to germ cells?
  - Retroviral vectors: mutations, tumors

Jaenisch, Young, “Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming”, Cell, 132:567-82, 2008; Lensch, Mummery, “From stealing fire to cellular reprogramming: a scientific history leading to the 2012 Nobel Prize”, Stem Cell Reports 1:5-17, 2013

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John Gurdon (1933-)
Shinya Yamanaka (1962-)

in frogs

in mammals

John Gurdon (1933-)
Shinya Yamanaka (1962-)

in frogs

in mammals

Keith Campbell (1954-2012)
Dolly the Sheep (1996-2002)
Fay Weldon
Ian Wilmut (1944-)
cellular identity can be re-programmed - II

“The results also furnish an unequivocal example in animals of a non-mutational basis for transformation to malignancy and of reversal to normalcy.”

cellular behaviour can also be re-programmed