Computational models of stem cell fates

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Part 1:

• Stem cell systems
• Computational challenges
• Modeling transcriptional dynamics

Part 2:

• The embryonic stem cell switch
• Hematopoietic switches
• Bistability, irreversibility, priming
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- Stem cell systems
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Part 2:

- The embryonic stem cell switch
- Hematopoietic switches
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Important issues not covered:

- Interactions between cells
- Signaling pathways
- Cell population models
Stem cells – development and maintenance

Development

Embryonic stem cell

Maintenance

blood  liver  intestinal  skin  brain  ........

Mature stem cells – organ specific

Self-renewal  Differentiation
Stem cells – development and maintenance

Development

Embryonic stem cell

Maintenance

Self-renewal

Differentiation

Mature stem cells – organ specific

blood liver intestinal skin brain ........
The cancer stem cell connection

100 cancer stem cells → 100,000 cancer cells
Stem cell fates

Self-renewal, pluripotency
Differentiation
Apoptosis

What is the program determining this fate

- Genetic network architecture
- Dynamics

External signals triggers the transcriptional machinery
Provides switch behaviour
Transcriptional regulation

Example:

Transcription factors (TF) A and B causes gene g1 to transcribe

With proper interactions e.g. AND logics is obtained

For mammals in general more than 2 TFs

Model small modules of genes:

Verify functionality

Infer additional components/interactions
Modeling transcriptional regulation

• Boolean models

  High level description; crude approach; does not relate to underlying physics/chemistry

• Michaelis-Menten

  Useful phenomenological parametrizations

• Shea-Ackers thermodynamical formalism

  Transparent with regard to different interaction components; gateway to stochastic methods

• Stochastic methods

  Both Michaelis-Menten and Shea-Ackers assume a “large” number of molecules – one works with concentrations. When this is not the case, one has to treat each molecule stochastically (e.g. Gillespie algorithm).

  Computationally tedious.
The Shea-Ackers statistical mechanics approach

Method originally developed for the lysis/lysogeny switch in Lambda phage

Two time scales:

- Slow:

  Transcription/Translation/Degradation

- Fast:

  Binding/unbinding of TFs to gene – thermal equilibrium makes sense

Possible cases: TF, TF+RNAP, RNAP - probability associated with each

Enumerate all cases, compute probability of bound RNAP

Transcription rate is proportional to promoter occupancy
The Shea-Ackers approach

Example: Two transcription factors A and B

Enumerate all possibilities - binding/unbinding of A, B and RNAP

The “partition function” $Z$ contains $2^3 = 8$ terms

$$Z = \sum_{i,j,k} A^i B^j R^k e^{-\delta G_{ijk}/T}$$

Free energies (parameters)

Low free energy – strong binding and vice versa

$i,j,k = [1, 0]$ (binding/unbinding)

$[A]$ and $[B]$: TF concentrations

$[R]$: RNAP concentration

$T$: temperature
The Shea-Ackers approach

Example: Two transcription factors A and B

Enumerate all possibilities - binding/unbinding of A, B and RNAP

The “partition function” $Z$ contain $2^3 = 8$ terms

$$Z = \sum_{ijk} [A]^i [B]^j [R]^k e^{-\frac{\delta G_{ijk}}{T}}$$

One can write down a “truth table”

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>R</th>
<th>weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0</td>
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<td>1</td>
<td></td>
</tr>
</tbody>
</table>
The Shea-Ackers approach

Example: Two transcription factors A and B

Enumerate all possibilities - binding/unbinding of A, B and RNAP

The “partition function” Z contain $2^3 = 8$ terms

$$Z = \sum_{ijk} [A]^i [B]^j [R]^k e^{-\delta G_{ijk}/T}$$

$$= Z_{\text{on}} + Z_{\text{off}}$$

bound not bound

The transcription rate is proportional to

$$P = \frac{Z_{\text{on}}}{Z_{\text{on}} + Z_{\text{off}}}$$
Relation to equilibrium calculations

Equilibrium calculations, commonly used in enzymatic reactions, yields the same transcription rates as the Shea-Ackers approach (as it should).

We illustrate this with a single autoregulatory gene $X$ that binds to itself.

The transition rate is given by

$$T \propto \frac{(\delta_1 + \delta_2 [X])[R]}{1 + \delta_1 [R] + (\delta_3 + \delta_2 [R])[X]}$$

There are four possible states subject to the normalization

$$G_0 + G_X + G_R + G_{XR} = 1$$
Relation to equilibrium calculations

Reaction scheme defining the network

\[ X + G_0 \rightleftharpoons G_X \quad (k_{1f}, k_{1b}) \]
\[ R + G_0 \rightleftharpoons G_R \quad (k_{2f}, k_{2b}) \]
\[ R + G_X \rightleftharpoons G_{RX} \quad (k_{3f}, k_{3b}) \]

At thermodynamic equilibrium one has

\[ K_i = \frac{k_{if}}{k_{ib}} \]

\[ K_1 = \frac{[G_X]}{[G_0][X]} \quad K_2 = \frac{[G_R]}{[G_0][R]} \quad K_3 = \frac{[G_{XR}]}{[G_X][R]} \]

In this lingo the fractional probability of the gene being bound by RNAP is

\[ P \propto [G_R] + [G_{XR}] = \frac{K_2[R] + K_1K_3[R][X]}{1 + K_2[R] + K_1[X] + K_1K_3[X][R]} \]
Relation to equilibrium calculations

\[ P \propto \frac{K_2[R] + K_1 K_3[R][X]}{1 + K_2[R] + K_1[X] + K_1 K_3[X][R]} \]

Equilibrium approach

\[ T \propto \frac{(\delta_1 + \delta_2[X])[R]}{1 + \delta_1[R] + (\delta_3 + \delta_2[R])[X]} \]

Shea-Ackers

• The statistical mechanics (Shea-Ackers) approach is more intuitive

• However:
  The equilibrium approach allows us to define a reaction scheme in terms of measured kinetic constants

Platform for stochastic simulations (Gillespie)
The Michaelis-Menten approach

Yet another way of doing it (deterministically)

In general: An enzyme $E$ binds to a substrate $S$
and turns it into a product $P$

$$S + E \rightleftharpoons SE \rightarrow P + E$$

Rate equations for the concentrations:

$$\frac{d[S]}{dt} = -k_{1f}[S][E] + k_{1b}[SE]$$

$$\frac{d[E]}{dt} = -k_{1f}[S][E] + k_{1b}[SE] + k_2[SE]$$

$$\frac{d[SE]}{dt} = k_{1f}[S][E] - k_{1b}[SE] - k_2[SE]$$

$$\frac{d[P]}{dt} = k_2[SE]$$
The Michaelis-Menten approach

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Fast - equilibrium

$$\frac{d[E]}{dt} = -k_{1f}[S][E] + k_{1b}[SE] + k_2[SE]$$

$$\frac{d[SE]}{dt} = k_{1f}[S][E] - k_{1b}[SE] - k_2[SE]$$

Approximate to zeroe

$$\frac{d[P]}{dt} = k_2[SE]$$

Solving the fixed point equation
The Michaelis-Menten approach

\[ K = \frac{k_{1f}}{k_{1b} + k_2} = \frac{[SE]}{[S][E]} \]

Assume a constant amount of enzyme

\[ [E] + [SE] = E_0 \]

One gets

\[ [SE] = K[S][E] = K[S](E_0 - [SE]) \]
\[ [SE](1 + K[S]) = KE_0[S] \]
\[ [SE] = \frac{KE_0[S]}{1 + K[S]} = \frac{E_0[S]}{(1/K + [S])} \]

For the production of \( P \) as function of \( S \) one has

\[ \frac{d[P]}{dt} = \frac{V_{max}[S]}{K_m + [S]} \]
The Michaelis-Menten and Hill equations

With $P$ being the transcribed gene, $TF$ the substrate and $DNA$ the enzyme one has

$$\frac{d[P]}{dt} = V_{max} \frac{[TF]}{K + [TF]}$$

Similarly for repression, one has

$$\frac{d[P]}{dt} = \frac{V_{max}K}{K + [TF]}$$

Problem: slow response with $[TF]$

Improvement: Hill exponents $n$

$$\frac{d[P]}{dt} = V_{max} \frac{[TF]^n}{K^n + [TF]^n}$$

Can be deduced from a model where the TFs have multiple binding sites
Biochemical reactions take place in noisy environments

Yet, we propose deterministic ordinary differential equations (ODEs)

Large number of molecules needed for justification. How large? Problem dependent (10-100)

Biochemical reactions take place in noisy environments

Langevin stochastic differential equation for genes $X$

\[
\frac{dX}{dt} = f(X) + \xi(t)
\]

If the noise is white (uncorrelated), we have

\[
\langle \xi(t) \rangle = 0 \quad \text{Mean}
\]

\[
\langle \xi(t)\xi(t') \rangle = D\delta(t - t') \quad \text{Variance}
\]
The Langevin equation

\[ \frac{dX}{dt} = v_m \frac{X}{K_M + X} - v_d X \]

**Deterministic approach**

**Gillespie approach**

1. \[ w_1 = v_m \frac{X}{K_M + X} \]
2. \[ w_2 = v_d X \]

**Langevin approach**

\[ \frac{dX}{dt} = v_m \frac{X}{K_M + X} - v_d X + \xi(t) \]
The Langevin equation

Gillespie

Langevin

From D. Gonze
Putting things together – bistability etc.

This is where the fun starts ..... 

So far transcription of single genes 

With a set of interacting genes (subnetwork) probe the dynamics e.g. stationary solutions

\[
\frac{dX_1}{dt} = F(X_1, X_2, ...) \\
\frac{dX_2}{dt} = F(X_1, X_2, ...) \\
\ldots 
\]
Bistability

In *Gardner et. al. (2000)* a genetic switch was constructed with two genes repressing each other by manipulation of DNA in *E.Coli*

Allows for direct comparisons with models

Hill-type equations plus degradation terms

\[
\frac{du}{dt} = \frac{\alpha_1}{1 + v^\beta} - u
\]

\[
\frac{dv}{dt} = \frac{\alpha_2}{1 + u^\gamma} - v
\]

Compute the nullclines

\[
\frac{du}{dt} = 0
\]

\[
\frac{dv}{dt} = 0
\]
Bistability - either $\beta$ or $\gamma$ needs to be larger than 1
Model summary

Boolean

Shea-Ackers

Reaction kinetics

$A + B \rightleftharpoons C$

Stochastic simulations (e.g. Gillespie)

Michaelis-Menten (Hill function)
Model summary

- Boolean
- Shea-Ackers
- Reaction kinetics: $A + B \rightleftharpoons C$
- Stochastic simulations (e.g. Gillespie)
- Michaelis-Menten (Hill function)

Deterministic

Stochastic
Model summary

Reaction kinetics

\[ A + B \rightleftharpoons C \]

Deterministic

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External signals triggers the transcriptional machinery

Provides switch behaviour
The embryonic stem cell switch

\[
\frac{dX_1}{dt} = F(X_1, X_2, \ldots) \\
\frac{dX_2}{dt} = F(X_1, X_2, \ldots)
\]

Indentify motifs, bistability, missing components etc.
The erythroid - myeloid switch

Identify motifs, bistability, missing components etc.

\[
\frac{dX_1}{dt} = F(X_1, X_2, \ldots)
\]

\[
\frac{dX_2}{dt} = F(X_1, X_2, \ldots)
\]

............

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