Computational modeling in biology

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About

- goal: develop quantitative models, with focus on stem cell differentiation
- founded in 2007
- now: 4 postdocs & 11 PhDs

http://cmb.helmholtz-muenchen.de
Our approach

prior knowledge

inference

data

model

experimental design

Table 2:

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No degradation of A but production of B</td>
</tr>
<tr>
<td>II</td>
<td>No degradation of A and back production of B</td>
</tr>
<tr>
<td>III</td>
<td>No degradation of A, and back production of B, no change in B</td>
</tr>
<tr>
<td>IV</td>
<td>Combination of degradation of A and back production of B</td>
</tr>
<tr>
<td>V</td>
<td>Combination of degradation of A and back production of B</td>
</tr>
<tr>
<td>VI</td>
<td>Combination of degradation of A and back production of B</td>
</tr>
</tbody>
</table>

As examples seven different model structures on the amplitude of activation and the time-to-peak response.

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\[
\begin{align*}
A(t) &= \frac{k_1 S}{k_2 + S} \\
B(t) &= \frac{k_1 S}{k_2 + S} \\
C(t) &= \frac{k_1 S}{k_2 + S}
\end{align*}
\]
Modeling challenges

- scale
  - multi
  - single

- accuracy
  - qualitative
  - quantitative
Biological focus: stem cell differentiation

Diagram showing stages of development from zygote to blastocyst.
Blood stem cell differentiation

collab T. Schroeder, ISF, HMGU
The Odefy toolbox is platform-independent due to the Octave ODE script files, the Systems Biology (SB) Toolbox and thus provides a versatile interchange format. The advanced analysis functions for dynamical systems like one Boolean steady state.

It consists of two mutual inhibitory factors (here with auto-activation). Intuitively, only one of the two factors can be fully active at any given time, leading to a switch-like behavior of this circuit.

Figure 5: Mutual inhibitory switch
- Mutually inhibitory switch (Figure 5A) is a well-known circuit.
- Regulatory network known to take a prominent role in stem cell differentiation processes (see e.g. [22]).

Results and Discussion

Despite its simplicity the circuit displays remarkable dynamic characteristics leading to the fate decision between opposing differentiation lineages. Various theoretical studies have been published recently investigating different aspects and molecular assumptions for this.

In the following we demonstrate the use of Odefy for the analysis of a simple regulatory motif. The mutual inhibitory switch model consists of two mutual inhibitory factors (here with auto-activation). Intuitively, only one of the two factors can be fully active at any given time, leading to a switch-like behavior of this circuit.

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Neural stem cell differentiation

Question: changes on regulatory level?

collab J. Ninkovic & M. Götz, ISF, HMGU
Define prior edges

- Database search
- Promoter Analysis

**Known activation**

**Known inhibition**

**Predicted interaction**
Large-scale analysis

significantly regulated miRNAs

CA4d  CA6d  CA8d  P14h  N7d

mmu-miR-92b
mmu-miR-219
mmu-miR-...

ESCs

differentiation

neurons

determine 'special' principal components
Principal components of $R^G_\tau$

[Image: Graph showing eigenvectors and contribution over time.

- Red line for Source 3.
- Blue line for Source 1.
- Green line for Source 2.

Contribution over time:
- CA4d
- CA6d
- CA8d
- P14h

Eigenvectors:

- Neurod1
- Id2
- Sp1
- Egr1
- Pax6
- Bhlhe22

Neurod1 & miR-495 anticorrelated

Reference:

[Kowarsch et al, BMC Bioinformatics, 2010]
Consensus model in neighbourhood of Pax6

method:
Bayesian model inference

\[ P(\theta|x) \sim P(x|\theta)P(\theta) \]

posterior likelihood prior
Predicted time series

- Bhlhe22
- Egr1
- Id2
- Lhx1
- Neurod1
- Neurog2
- Otx2
- Patz1
- Pax6
- Sp1
- mmu-miR-129-5p
- mmu-miR-300
- mmu-miR-495

Red line: mean of simulated data
Shaded area: standard deviation of simulated data
Blue crosses: experimental data

Standard deviation of simulated data
Outlook: latent causes in stem cell specification

→ predict & analyze off-target effects of drugs

collab H. Lickert, ISF, HMGU
Projects at CMB

- **2008**
  - control of regulatory networks

- **2009**
  - microRNA array analysis
  - metabolomics modeling

- **2010**
  - omics biostatistics
  - modeling (‘virtual liver‘)

- **2011**
  - classification

- **2012**
  - stoch. ESC model
  - model extension

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**MedSys**
- microRNA array analysis

**MedSys**
- metabolomics modeling

**GerontoSys**
- omics biostatistics

**HepatoSys**
- modeling (‘virtual liver‘)

**InKomBio**
- classification

**SPP pluripotency**
- stoch. ESC model

**model extension**

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**CoReNe**
- LungSys

**SysMBo**
- Systems Biology of Metatypes

**Stromal Aging**
- virtual liver network

**Latent Causes**
- SPP 1356
WANTED!

If systems modeling is your thing (any level), please apply!

http://cmb.helmholtz-muenchen.de