Example 1: Modeling signal transduction in bacterial chemotaxis

**First:** System is biologically defined; known motile behavior  
**Input:** concentration of proteins in the signal transduction network  
**Hypotheses:** receptor state determines the transmitter’s efficiency  
**Validation:** reproduces known output  
**Explored:** changes in reaction rates  

**Insight:** overall behavior is robust to changes in individual rates .


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E. coli live in the gut and feed on amino-acids

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Bacteria change the direction of their motion in response to chemical signals

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The signal transduction network is an example of a two-component pathway
Bacteria respond to concentration changes but adapt to a constant stimulus

Attractor/repellent concentration

Motor input

Adaptation is based on changes in the methylation levels.

The steady state concentrations are determined by the equilibrium between activation and inhibition.

Modeling the signal transduction network

Idea: The cell contains a large set of receptors and other proteins
Input: ligand concentration
Variables: concentrations of
- the different (ligand bound, methylated) states of the receptor complex
- CheR, CheB, CheBp, CheY, CheZ
Output: the concentration of CheYp
Method: differential equations describing the reaction kinetics.
Three types of reaction: ligand binding, phosphorylation, methylation.


The Spiro-Parkinson-Othmer model takes into account all reactions

The key to adapting perfectly is to return the level of phosphorylated receptor to its pre-stimulus level, and this occurs because CheA autophosphorylates more rapidly the more highly methylated the receptor.

Barkai-Leibler model suggests a robust mechanism for adaptation
- the receptor complex has two functional states, active or inactive (rough correlation with phosphorylation state).
- only the active complex can autophosphorylate.
- the fraction of complexes in the active state depends only on the ligand occupancy and methylation state of the complex.
- only active complexes are demethylated.
- the output is the activity $A = \sum a_i T_{ak} + \alpha M T_{ak}$

$\frac{d T_{ak}}{dt} = -k_L T_{ak} + k_i LT - k_i T_{ak} + k_i T_{ak} - \gamma V_{out} + \frac{V_i}{K + V} + \frac{B_i h_i T_i}{1 + h_i T_i}$

Ligand binding/release  phosphorylation  methylation  demethylation

Reaction rates close to the experimentally known values lead to perfect adaptation.


The steady state concentrations are determined by the occupancy of the active and inactive states.
The Barkai-Leibler model exhibits perfect adaptation

Reference system

\[ \alpha = \alpha^d = \alpha^i = 0 \]
\[ \alpha = 0.5, \quad \alpha = 0.5 \]

plausible values for rate constants

The system activity is independent of the constant ligand concentration.

Adaptation is robust to factor of two changes in the biochemical parameters

Step-like addition of a saturating amount (mM) of attractant

Total parameter variation

The adaptation time does depend on the biochemical parameters.

Example 2: Modeling the segment polarity gene network

First: System is biologically defined; known expression patterns
Input: segment polarity genes
Hypotheses: transcription factors act as enzymes
Validation: reproduces known gene expression patterns.
Explored: changes in reaction rates

Insight: topology is a main source of robustness.


Segmentation of the fruit fly embryo

Syncytial blastoderm, 1h

End of gastrulation, 7h

- Cell differentiation is based on differential gene expression.
- The segment polarity genes determine and maintain the parasegment borders.
Segmentation is governed by a cascade of genes

Transient gene products, initiate the next step then disappear.

The role of the segment polarity genes

- The segment polarity genes are initiated by the pair-rule genes.
- Several segment polarity genes are expressed (active) in stripes that are repeated in every fourth cell.
- These genes interact via a complex regulatory network.
- The expression pattern of the segment polarity genes is maintained for 3 hours.
- The parasegment borders appear between the cells expressing the two most important segment polarity genes, engrailed and wingless.

Segment polarity genes

<table>
<thead>
<tr>
<th>Genes</th>
<th>Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>wingless (wg)</td>
<td>Wingless protein (WG) - secreted</td>
</tr>
<tr>
<td>hedgehog (hh)</td>
<td>Hedgehog protein (HH) - secreted</td>
</tr>
<tr>
<td>engrailed (en)</td>
<td>Engrailed protein (EN) - transcription factor</td>
</tr>
<tr>
<td>patched (ptc)</td>
<td>Patched protein (PTC) - receptor</td>
</tr>
<tr>
<td>cubitus interruptus (cid)</td>
<td>Cubitus activator (CID) - transcription factor</td>
</tr>
<tr>
<td></td>
<td>Cubitus repressor (CN) - transcription factor</td>
</tr>
</tbody>
</table>

Gene products form a network that maintains a gene expression pattern initiated in an earlier stage.

Evolution of gene expression patterns

- early stages: 2.50 h
- pre-pattern: 3:00-3:30 h
- stable pattern: 4:20-7:20 h
- 3:30 h
Wild type, stable gene patterns

- **en** is expressed in the anterior part of the parasegment.
- **wg** is expressed in the posterior part of the parasegment.
- Parasegmental grooves form between the **wg** and **en** stripes.

- Two ptc stripes in each parasegment.
- A pattern is complementary to that of en.

**Gene interaction network in the von Dassow model**

Gene interaction network diagram showing interactions between different genes and proteins, with symbols for mRNA, protein, and protein complex, and indicating inhibition, transport, and biological processes.

**Dose-response curves for regulated processes**

Dose-response curves illustrating the relationship between mRNA or protein concentration and transcriptional activator activity, with parameters for maximum rate, half-maximal activity, and Hill coefficient.

Assumption: combinatorial regulation of synthesis can be approximated with similar sigmoidal curves.
Gene expression patterns
The 2D pattern is reduced to 1D, assume cells are hexagonal
The gene expression is essentially binary (ON in some cells, OFF in others)

Simulations
• Start from the wild type initial condition for en and wg
• Generate a set of kinetic parameters from the biologically relevant range (48 unknown parameters)
• Run the simulation until steady state is reached.
• Use threshold (>6% of maximal concentration) to decide whether node is ON or OFF.
• Compare with wild type pattern, if the same accept as a solution

Gene expression patterns

Simulations

Robustness to parameter changes
The von Dassow model has 13 equations and 48 unknown parameters.

Systematic search shows that 1 in every 46 parameter combinations lead to wild type final patterns. The others are not good.

The parameter combinations leading to wild type steady states are distributed homogeneously in the biologically relevant parameter space.

It is not the fine-tuning of the kinetic rates but the overall network topology what matters.