Scalable Multi-core Model Checking: Technology & Applications of Brute Force
Part IV: Biology

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1. Modeling Signaling Networks in Cell Biology
2. ANIMO: Interactive Modeling and Analysis
3. In Silico Experiment: Osteoarthritis
Kinase pathways: spreading the Phosphor token

- Biochemical equilibrium reactions:
  - $E + S + ATP \iff ES + ATP \rightarrow ESP + ADP \iff E + SP + ADP$
- Simplify to one interaction (here activation): $E \rightarrow S$
Complex network dynamics

- Node interactions:
  - activation
  - inhibition

- Crosstalk and Feedback

- Ultimate questions:
  - understand & control
  - key to finding a cure of “system” diseases
  - cancer, diabetes, arthritis
How to model signaling networks?

Mathematical models (ODE) [Gillespie '77]

\[
\frac{dA}{dt} = k_1 \cdot B - k_2 \cdot C - k_3 \cdot A
\]

- $A, B, C$ are molecule concentrations
- $k_1, k_2, k_3$ are kinetic parameters
- Precise, strong tools (simulation, stability)
- Difficult, too many parameters are unknown

Boolean networks [Kauffman'69]

\[ B \land \neg C \implies A \]

- Easy to handle, biologically relevant
- No timing, no concentrations at all
- So how to execute this?
Simplified version of Timed Automata

Basic modeling ideas

- Discretized activity levels
- Clocks constrained by upperbound and lowerbound
- Activation/Deactivation is communicated over channels
Using Networks of Timed Automata

Modeling Assumptions

- Every reactant is modeled by a Timed Automaton.
- It maintains a discrete activation level: \( \frac{active}{active + inactive} \).
- Clocks trigger when the activation level goes up or down.
- Activation/Inhibition: broadcast communication between automata.

Time \( T \) depends on activation levels: \( L[r_1][r_2] \) and \( U[r_1][r_2] \).
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ANIMO is a Cytoscape plugin, running UPPAAL in the background.
ANIMO workflow

Draw topology, initial conditions, and investigate the behaviour.
Node colors/edges show activation level; view as graphs, heatmap.
Model Validation by Wet-Lab Experiments

Phosphorylation of proteins in human chondrocytes: Time series under three experimental conditions.
Validation by Wet-Lab Experiments

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<th>IL-1β</th>
<th>Wnt 3a</th>
<th>IL-1β + Wnt 3a</th>
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**Cytoscape Desktop**

- **Network 0**
  - **Results Panel**
    - **ANIMO Results**
      - **Change title**
      - **Reset to here**
      - **Difference with...**
      - **Save simulation data...**
      - **Close**

**Legend**

- **Activity**
  - Max
  - Min

- **Protein category**
  - Cytokine
  - Receptor
  - Kinase
  - Phosphatase
  - Transcription factor
  - Other

**Graph**

- **IL-1β**
- **Wnt**
- **FZD**
- **Inh IL-1β sig**
- **Inh Wnt sig**
- **IL-1β R**

**Axes**

- **Protein activity (a. u.)**
- **Time (min)**

**Colors**

- **ERK**
- **ERK data**
- **JNK1**
- **JNK1 data**
- **p38**
- **p38 data**
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Osteoarthritis

- Mesenchymal stem cells can differentiate to
  - either Osteoblasts (bone)
  - or Chondrocytes (cartilage)

- Osteoarthritis: articular cartilage dries, wears out, forms bone

- Pain in “bone-to-bone” joints

- 60% of the population (> 65 years) will show symptoms

- Characterized by transcription factors: SOX9 or RUNX2
Development of Chondrocyte (cell fate)

- Mesenchymal Stem Cell
- Condensed Mesenchymal Stem Cell
- Chondrocyte
- Proliferating chondrocyte
- Hypertrophic chondrocyte
- RUNX2 activation?
- RUNX2 active: DKK1, FRZB, GREM1
- SOX9 active:
- Articular cartilage
ECHO: the Executable Chondrocyte
Put ECHO in ANIMO

Starting point: Boolean Network

Size

- 7 inputs
- 123 nodes
- 354 links
- Sox9, Runx2 as output
Validation by simulating results from literature

Basic validation by simulation

- Exhaustive / Monte Carlo simulation with $3^7$ input conditions
- Knock-out or overexpress individual nodes in the network

- There are only two stable states (SOX9 and RUNX2)
- WNT protein pushes SOX9 stable states to RUNX2
- DKK, FRZB and GREM stabilize healthy cartilage
In search for new knowledge: parameter sweeps
Multi-core Model Checking for Biological Applications?

Key questions (biological relevant answers)

- Which input combination/series causes a switch RUNX2 → SOX9
- Which interactions should be inhibited to prevent SOX9 → RUNX2
The Empirical Research Cycle/Spiral

produce

Experiments

update

Observations

build

Knowledge Theory

derive

Hypotheses

drive

Model
Literature on ANIMO

- Signalling ANIMO In Silico
- Literature on ANIMO

**Signaling Networks in Biology**

- Stefano Schivo, Jetse Scholma, B. Wanders, R. Urquidi, P. van der Vet, M. Karperien, R. Langerak, J. van de Pol, J.N. Post, *(BIBE’12, J-BHI’14)*
  
  Modelling biological pathway dynamics with Timed Automata

- Jetse Scholma, Stefano Schivo, R. Urquidi, J. van de Pol, M. Karperien, J. Post, *(GENE 533 (2013))*
  
  Biological networks 101: computational modeling for molecular biologists

- Stefano Schivo, Jetse Scholma, Marcel Karperien, Janine N. Post, Jaco van de Pol, Rom Langerak, *(SynCoP 2014)*
  
  Setting Parameters for Biological Models With ANIMO