Using Circuit Modeling to Simulate Large Scale, Multi-Cellular, Biological Pathways

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Outline

- Biological Circuits - What are they?
- Implementation and Modeling Approach
- Metabolic and Genetic Coupling
- Bacterial Systems
- Tissue Differentiation Systems
- Future Directions
Biological Circuits

At the biochemical level cells are characterized by:

- Many different chemical species (DNA, RNA, enzymes, proteins, ...)
- Many different reaction mechanisms (kinetic, enzymatic, promoters, repressors, ...)

Glucose metabolism in Escherichia coli:
- 436 chemical species
- 720 reactions

Biological Circuits

• Mechanism graphs were built to better understand the complexity.
• Network or circuit analysis approach is logical.

E. Coli Metabolism Map,
Systems Biology Research Group,
UCSD, http://gcrg.ucsd.edu
Biological Circuits

Simplified Genetic Switch
Biological Circuits

Simplified Genetic Switch

DNA ➔ Gene ➔ RNA ➔ Protein

N. On ➔ Pro Opr

Sandia National Laboratories
Biological Circuits

Simplified Genetic Switch

DNA → Gene → RNA → Protein
Biological Circuits

Simplified Genetic Switch

DNA → Gene → RNA → Protein

Environmental Factor → N. Off
Biological Circuits

DNA → RNA → Protein

Gene 1
Gene 2

Environmental Factor

Concentration

Time

Gene 1
Gene 2
Implementation and Modeling Approach

Two basic approaches:

1. Assume system is well mixed.
2. Describe reactions with differential equations.
3. Integrate species concentrations forward in time.

Neglects network information.

1. Assume nodes are well mixed.
2. Describe reactions with differential equations.
3. Propagate concentrations only along wires to the nodes.
4. Integrate species concentrations and fluxes forward in time.

Uses network information because hierarchy is useful.

BioSpice Community.
Cellular machinery can be modeled by charge sources/sinks and behavioral devices.
## Implementation and Modeling Approach

<table>
<thead>
<tr>
<th>Electrical Domain</th>
<th>Biochemical Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge</td>
<td>Mass</td>
</tr>
<tr>
<td>Current</td>
<td>Rate of mass change</td>
</tr>
<tr>
<td>Voltage</td>
<td>Concentration</td>
</tr>
<tr>
<td>Kirchoff’s Voltage Law</td>
<td>Stoichiometry</td>
</tr>
<tr>
<td>Kirchoff’s Current Law</td>
<td>Conservation of Mass</td>
</tr>
</tbody>
</table>

Cellular machinery can be modeled by charge sources/sinks and behavioral devices.

\[
2 \text{H}_2 + \text{O}_2 \rightarrow 2 \text{H}_2\text{O} \\
2 \text{H}_2\text{O} \rightarrow 2 \text{H}_2 + \text{O}_2
\]
Implementation and Modeling Approach

Biological circuits are typically modeled as RC-circuits where voltage on a given circuit line is proportional to a chemical concentration.
Goal: Large scale biological circuit simulation

Approach:

Use existing biological databases to develop whole cell circuits (metabolic, genetic, signal transduction …)

Couple cells in a comment environment to study multi-cell effects (culture growth, tissue development, synergistic functionality, …)
Metabolic and Genetic Coupling

Metabolic pathways translate directly into reaction networks.
Genetic control of the metabolic pathways is modeled as a binary network, or truth table.

Hybrid modeling of both the metabolic network and its associated genetic control is new and this is one of the first efforts in this field.
Metabolic and Genetic Coupling
To simulate entire cell systems an automated method was created to convert public databases into circuits.

Escherichia coli K-12 Metabolic Data (Palsson, UCSD) → Path2cir → Xyce Circuit File (netlist format)

Escherichia coli K-12 Genetic Data (EcoCyc) → Gene2cir
Bacterial Systems

- E. coli K-12 data.
- Approximately 8350 circuit unknowns.
- Serial and Parallel simulations.
- Model verification underway.
Tissue Differentiation Systems

- To simulate and understand how groups of cells interact, one should simulate many cell connected by a diffusive environment.
- Implemented a Diffusion PDE device in Xyce and with Trilinos/Entero to couple many cells in one common environment.
- Target application is cellular differentiation.
Within a cell, a circuit based reaction pathway exists. Inputs and outputs to pathway are connected to the diffusion limited environment. Cell to Cell interactions are limited by diffusion. 

Solve PDE problem (Xyce or custom code) 

Solve circuits problem (Xyce)
Cellular differentiation occurs when neighboring cells influence future development.

If this cell secretes a hormone, then...

these cells may develop into a different type of tissue (e.g. an artery wall or nerve cell)
Cellular Differentiation in *Drosophila sp.*

In a growing Drosophila larva, a series of bands develop which later develop into different tissue types.

Similar processes occur in humans as cells turn into skin, nerve, muscle tissue.
Cellular Differentiation in *Drosophila sp.*


Cells develop into two types
- wg expressing and
- hh expressing
Cellular Differentiation in *Drosophila* sp.


- ➔ Promotes Reaction
- ● Inhibits Reaction
Cellular Differentiation in *Drosophila sp.*


- ➡ Promotes Reaction
- ● Inhibits Reaction
Cellular Differentiation in *Drosophila sp.*

- Simulated a culture of 676 cells (26 x 26 grid)
- Applied a WG concentration gradient of 50%
- Two dimensional, full diffusion model joins cells
Cellular Differentiation in *Drosophila sp.*

Two layers of hh expressing cells surround a layer of wg expressing cells leading to tissue differentiation.
Future Directions

Unlike electrical circuits, biological circuits:
• Physical parameters are difficult to measure.
• Circuit connections may not be well understood.
• System architecture is not obvious.

Need to focus on:
• Parameter studies and parameter sensitivity analysis.
• Network stability studies.
• Fundamental block studies.