SAND2006-7275C

# Examining Tissue Differentiation Stability through Large Scale, Multi-Cellular Pathway Modeling

**November 13, 2006**

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**Department of Computation Sciences**

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# Outline

- Pathway Modeling / Biological Circuits
  What are they?
- Implementation and Modeling Approach
- Tissue Differentiation Systems
- Conclusions

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# Pathway Modeling & 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**

**J. Edwards & B. Palsson, Proc. Nat. Acad. Sci., 97 (2000)**

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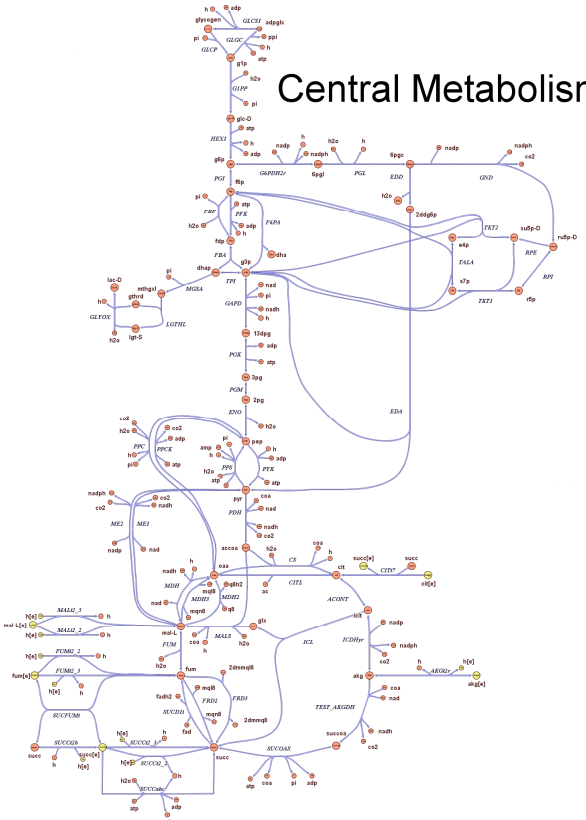
# Pathway Modeling & Biological Circuits




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

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

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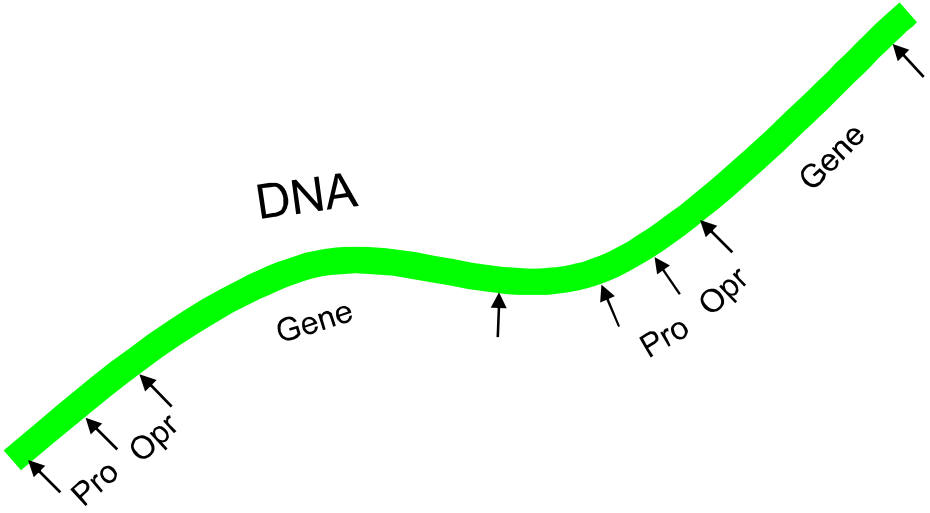
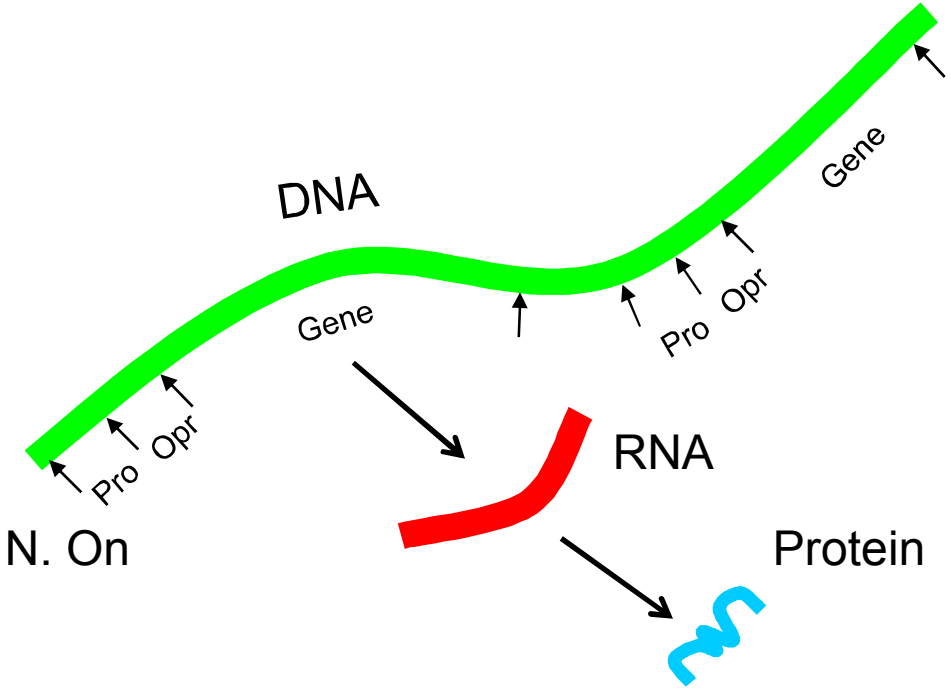
# Biological Circuits




## Simplified Genetic Switch

# Biological Circuits




## Simplified Genetic Switch

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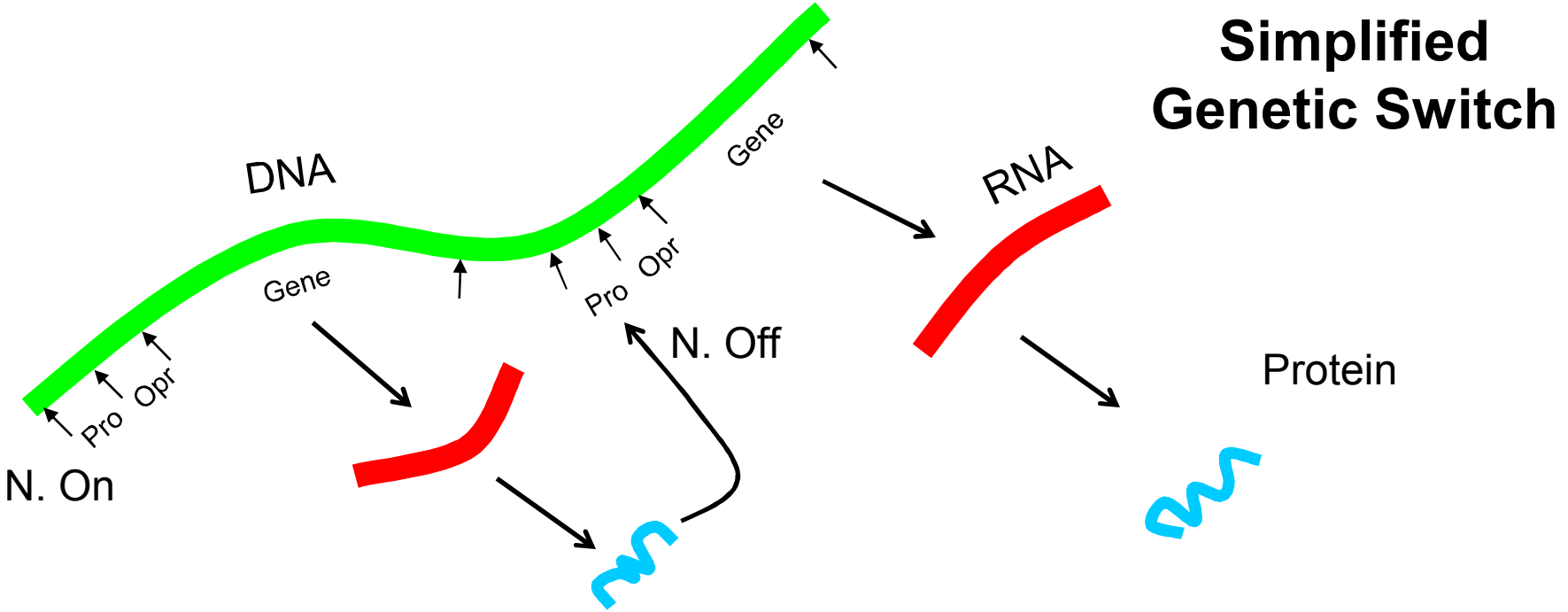
# Biological Circuits

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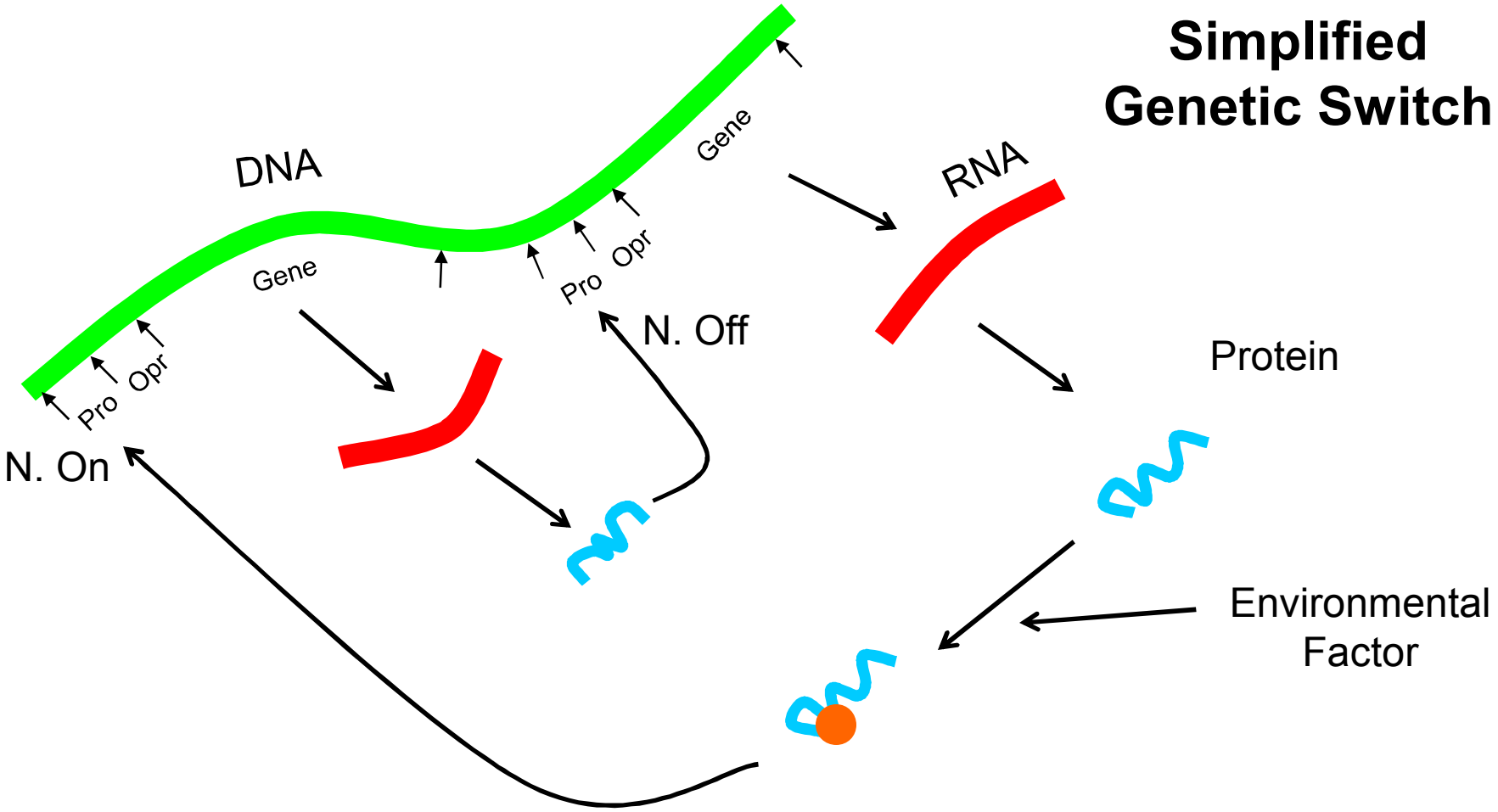
# Biological Circuits

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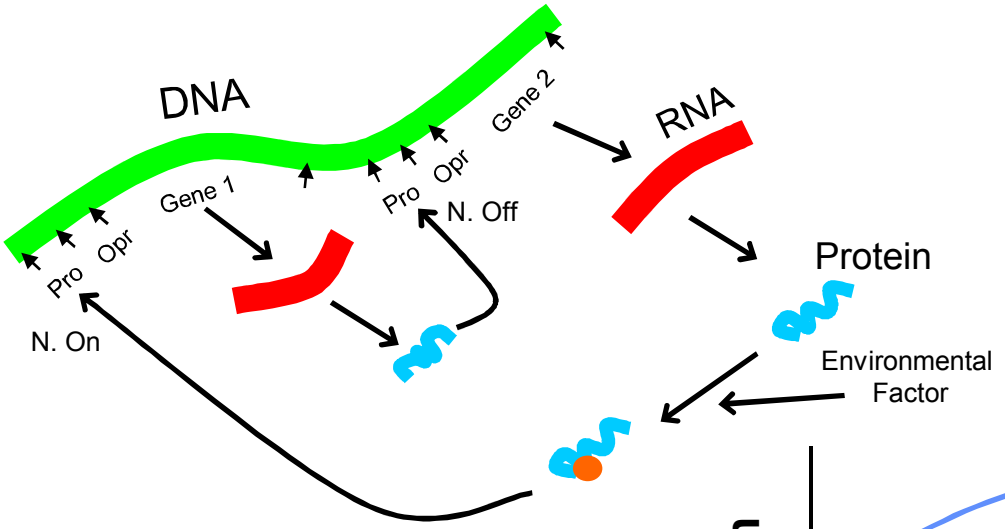


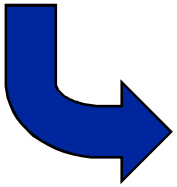

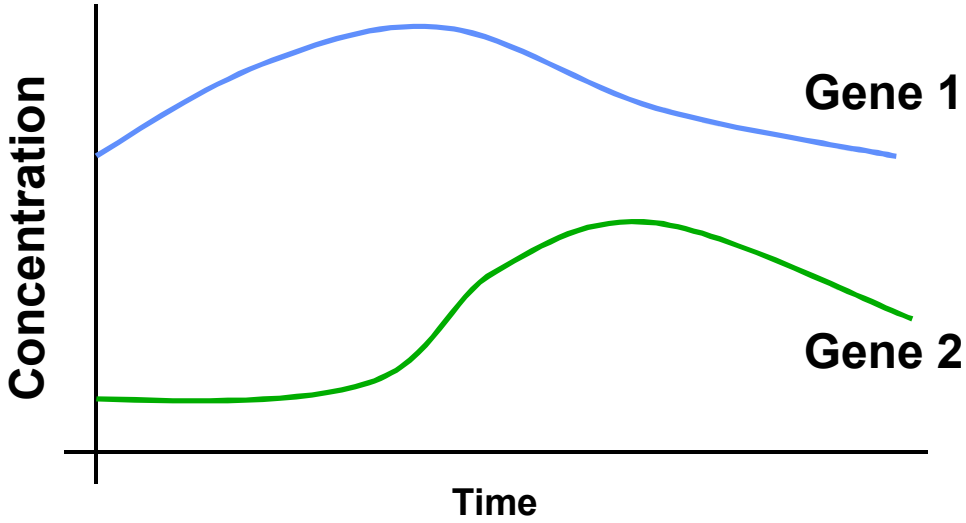


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# Implementation and Modeling Approach

**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.**


McAdams, H. & Shapiro, L., *Science*, 269 (1995)

McAdams, H. & Arkin, *Annu. Rev. Biophysics* (1998)

von Dassow *et. al.*, *Nature*, 406 (2000)

A. Arkin, *IEEE Bioinformatics Conf.* August (2003)

BioSpice Community.


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.**

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# Implementation and Modeling Approach

| Electrical Domain | Biochemical Domain |
|---|---|
| **Charge** | **Mass** |
| **Current** | **Rate of mass change** |
| **Voltage** | **Concentration** |
| **Kirchoff's Voltage Law** | **Stoichiometry** |
| **Kirchoff's Current Law** | **Conservation of Mass** |

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

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$2\ H_2 + O_2 \rightarrow 2\ H_2O$

$2\ H_2O \rightarrow 2\ H_2 + O_2$

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

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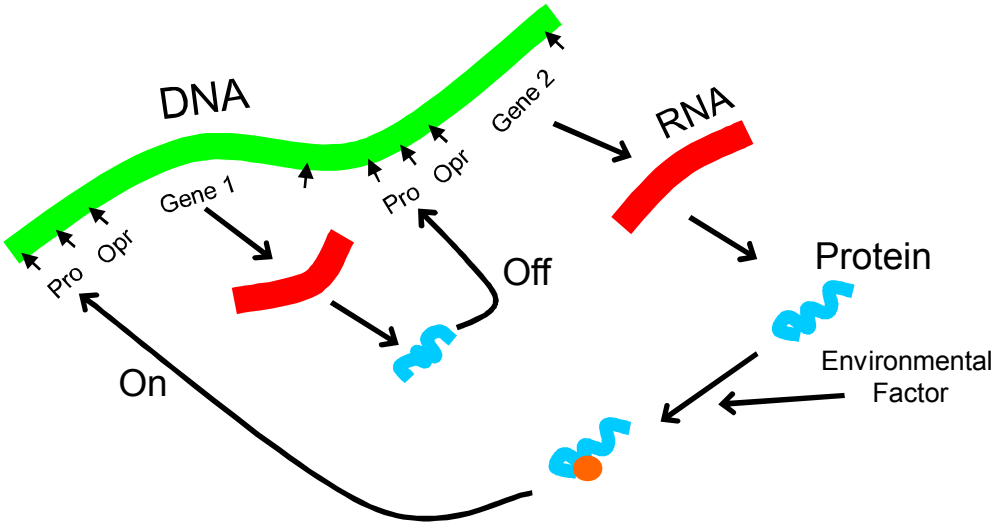
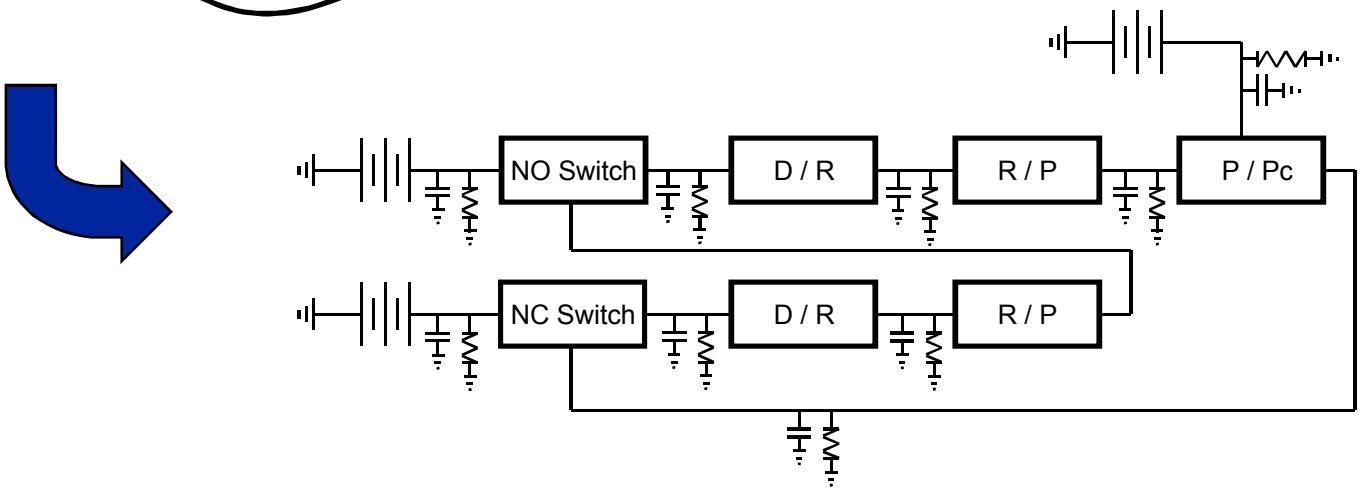
# Implementation and Modeling Approach




**Biological circuits are typically modeled as RC-circuits where voltage on a given circuit line is proportional to a chemical concentration.**

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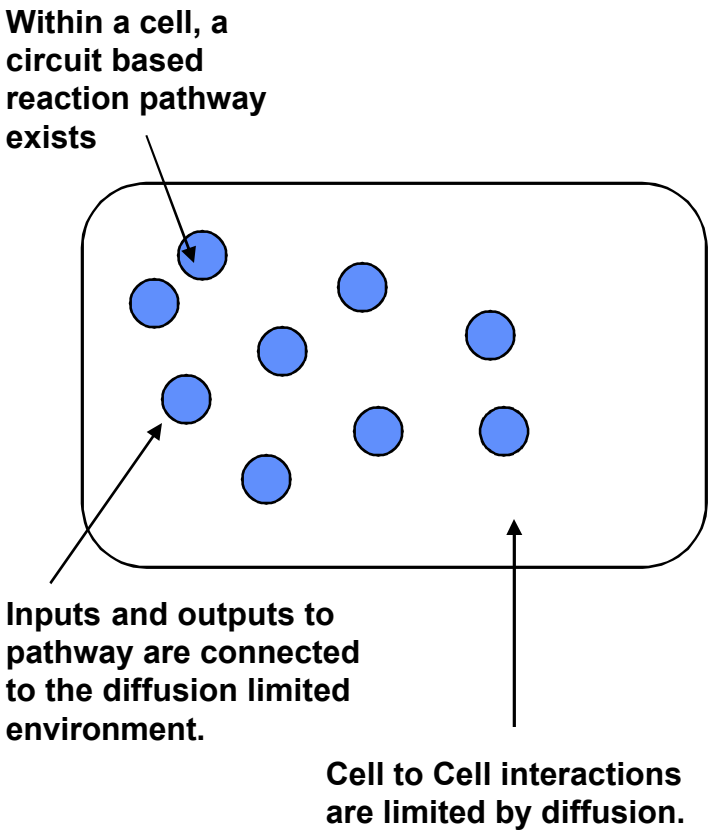
# Tissue Differentiation Systems

- To simulate and understand how groups of cells interact, one should simulate many cells connected by a diffusive environment.
- Implemented a Diffusion PDE device in Xyce to couple many cells in one common environment.
- Target application is cellular differentiation.

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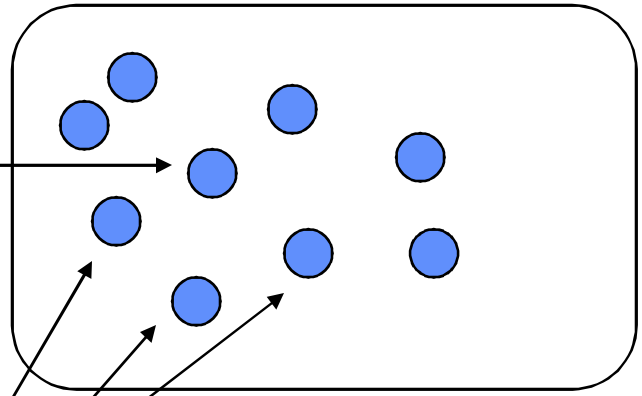
# Tissue Differentiation Systems

**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)**

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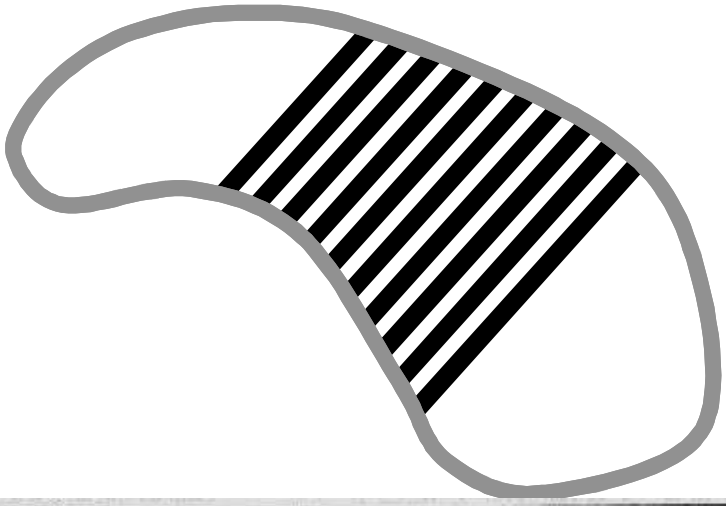
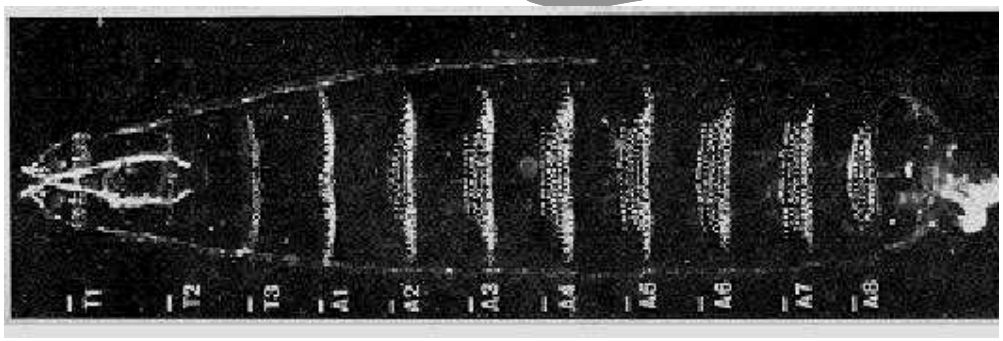
# Cellular Differentiation in *Drosophila sp.*






**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.**

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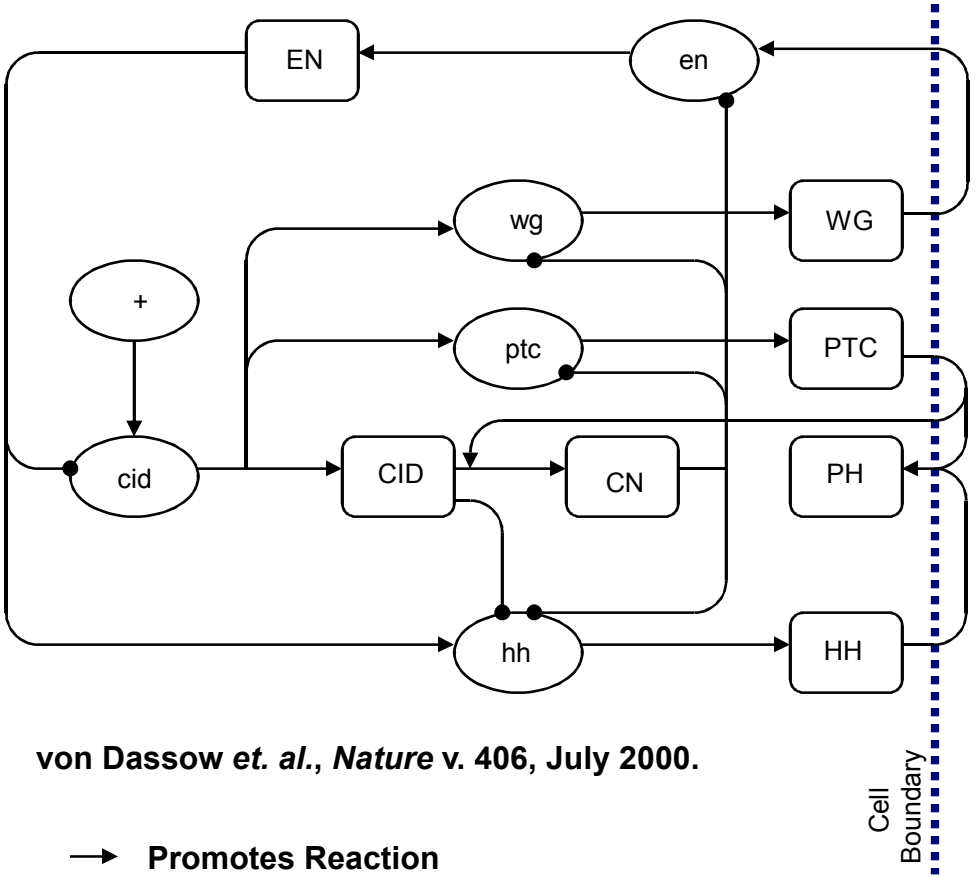
# Cellular Differentiation in *Drosophila sp.*




**Cells develop into two types**

- **wg expressing and**
- **hh expressing**

**von Dassow *et. al.*, *Nature* v. 406, July 2000.**

→ **Promotes Reaction**

⊸ **Inhibits Reaction**

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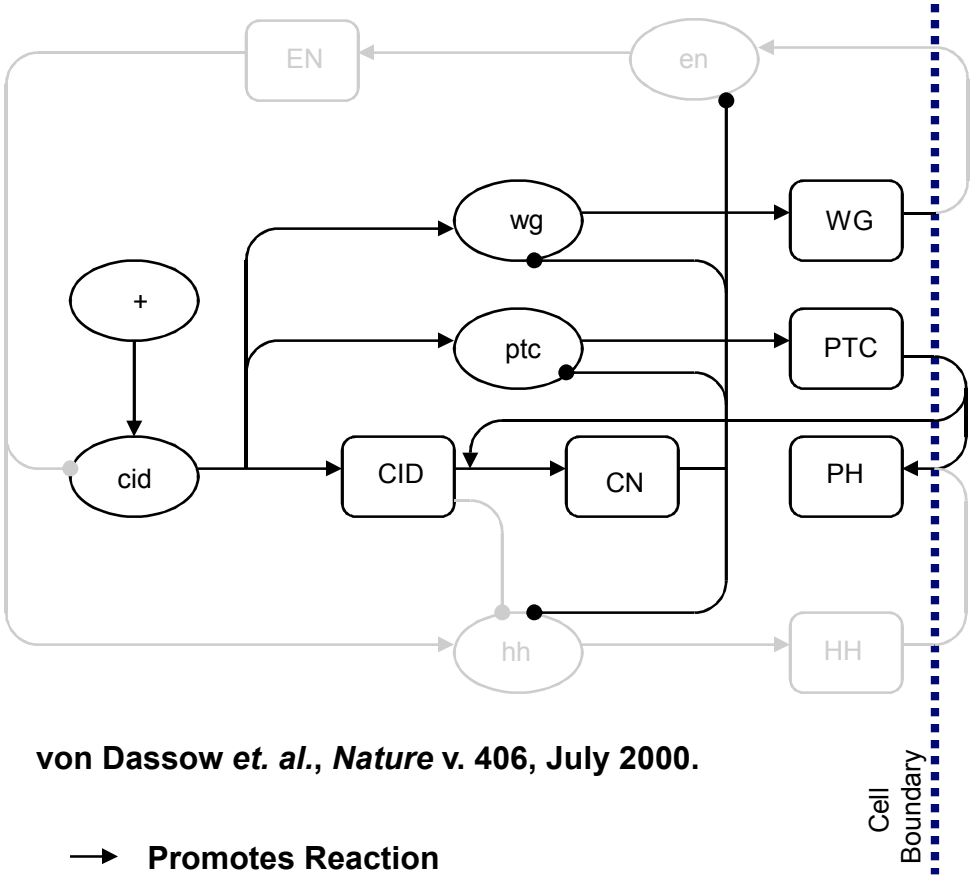


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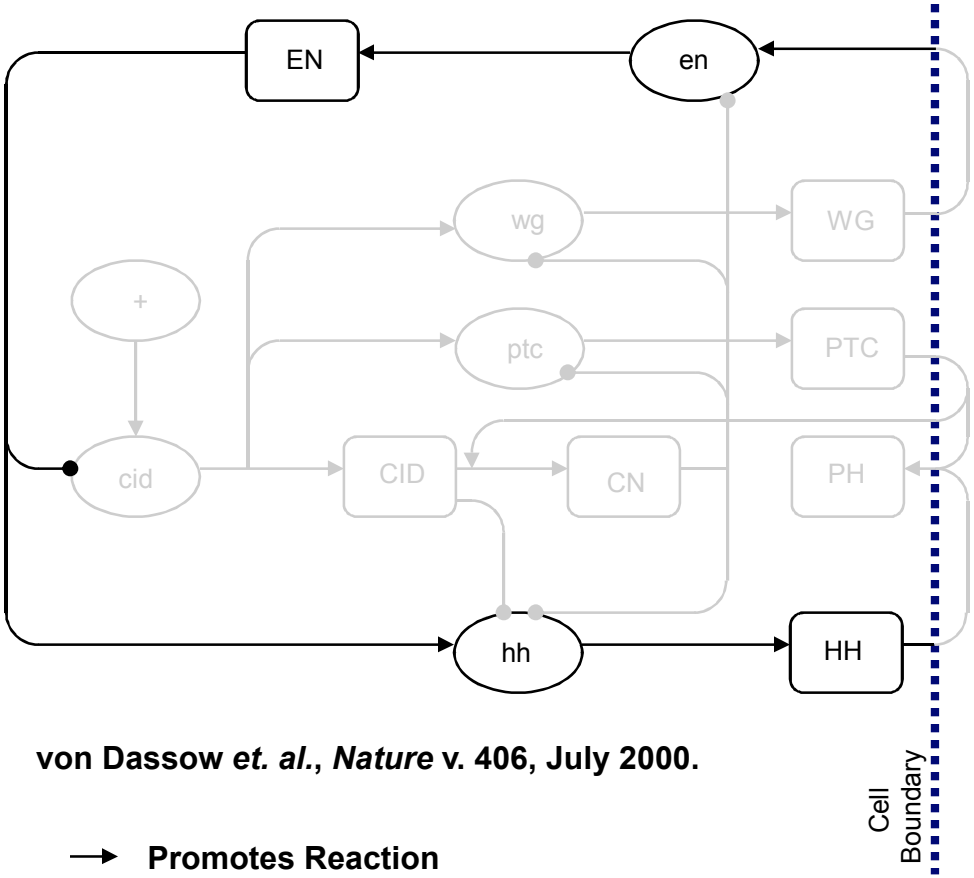


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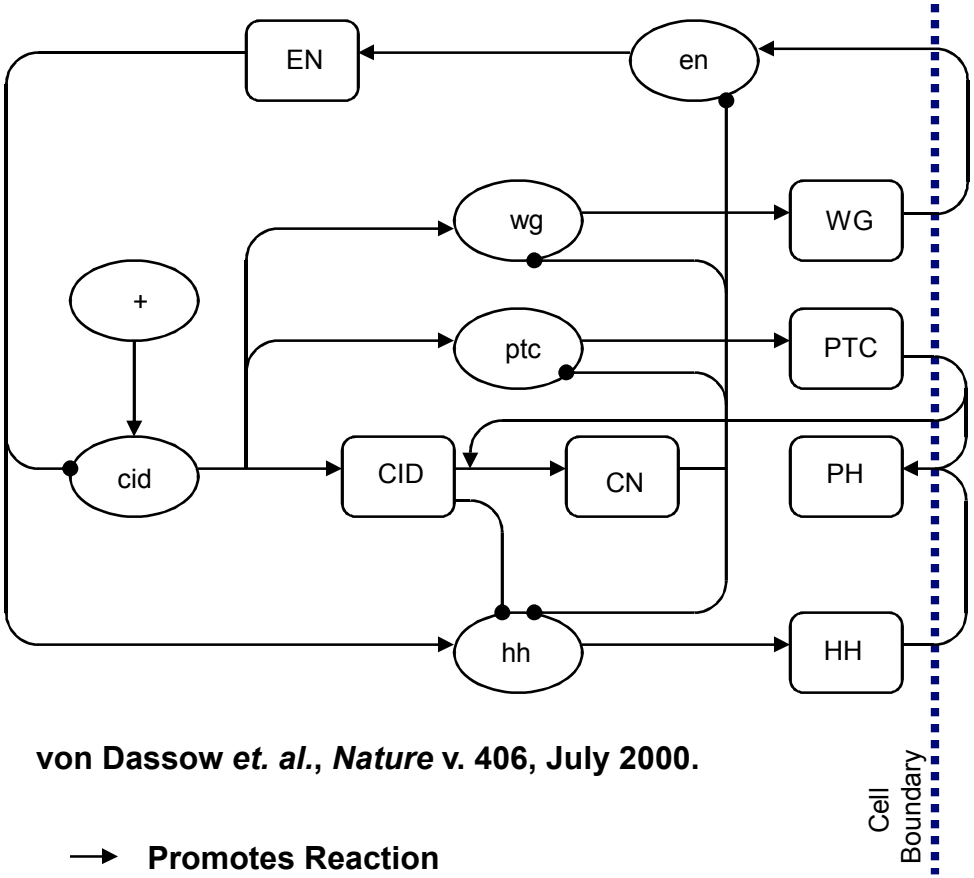


von Dassow *et. al.*, *Nature* v. 406, July 2000.

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**Model Characteristics**

- 12 Species.
- Reactions treated as:
  - Simple kinetics (power law)
  - Michaelis-Mention (enzyme kinetics)
- 47 Unknown parameters

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# Cellular Differentiation in *Drosophila sp.*

**Want to know:**

**Can a collection of cells successfully differentiate with noise?**

**Approach:**

- **Simulated a culture of 676 and 100 interacting cells (26 x 26 and 10x10 grid)**
- **Two dimensional, full diffusion model joins cells (adds 4 more unknown parameters)**
- **Apply patterned WC initial conditions with and without noise.**
- **Entire System is almost 11,000 unknown variables!**


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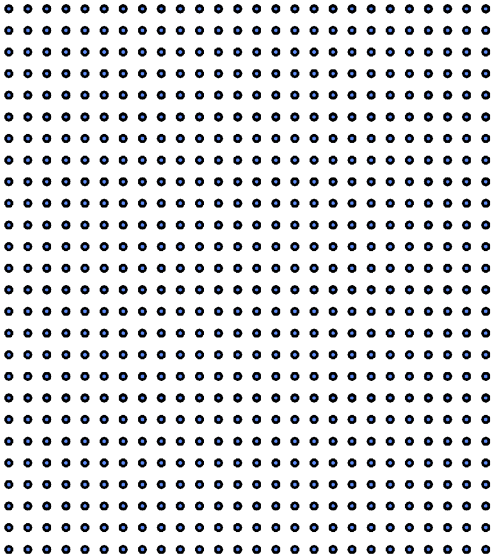
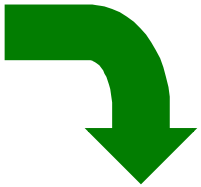
# Simulating a Cell Culture





Xyce™
Parallel Electronic Simulator

**Simulate circuit in Xyce.**

- **Handles very large circuits (1M+ elements)**
- **Serial & Parallel versions**
- **Good at stiff problems.**

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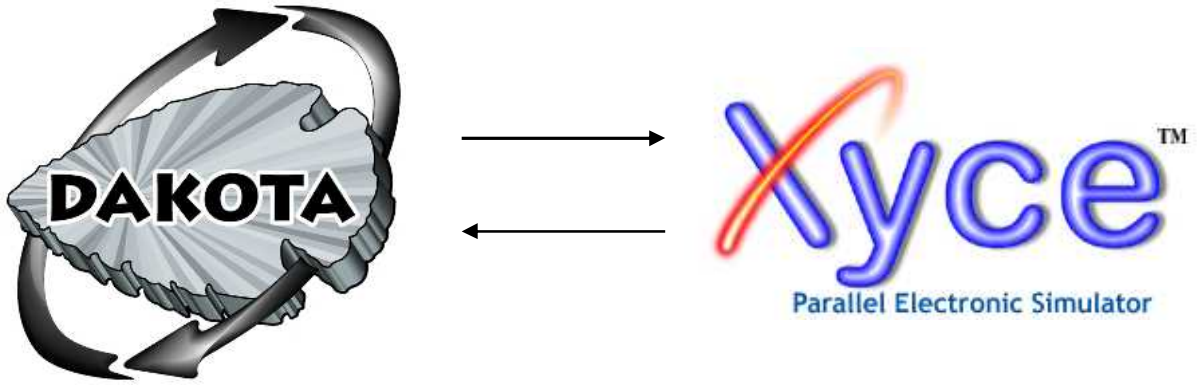
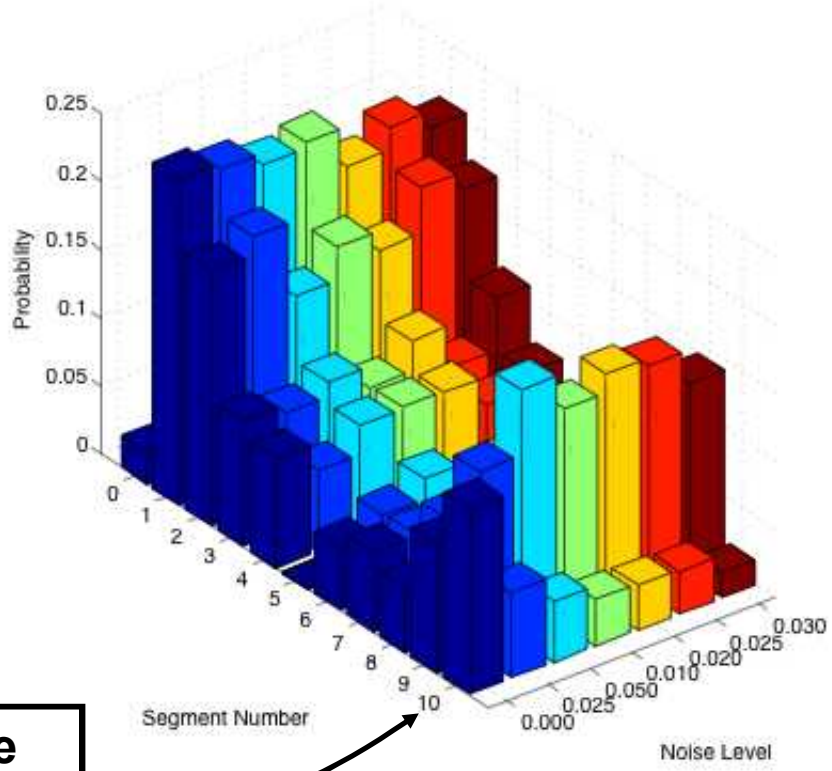
# Understanding System Parameters




- Focus on 25 parameters directly involved in cell type switching (expression levels, reaction rates)
- Use Dakota:
  - Select system parameters
    - Design of experiments parameter blocking.
    - Latin hyper cube system sampling.
    - Logarithmic range sampling.
  - Organize and instantiate Xyce runs
  - Collect run data.

# Differentiation with noise

- Over 115,000 simulations conducted.
- Even a small amount of noise dramatically reduces the system's stability.




**Successful tissue differentiation only this row**

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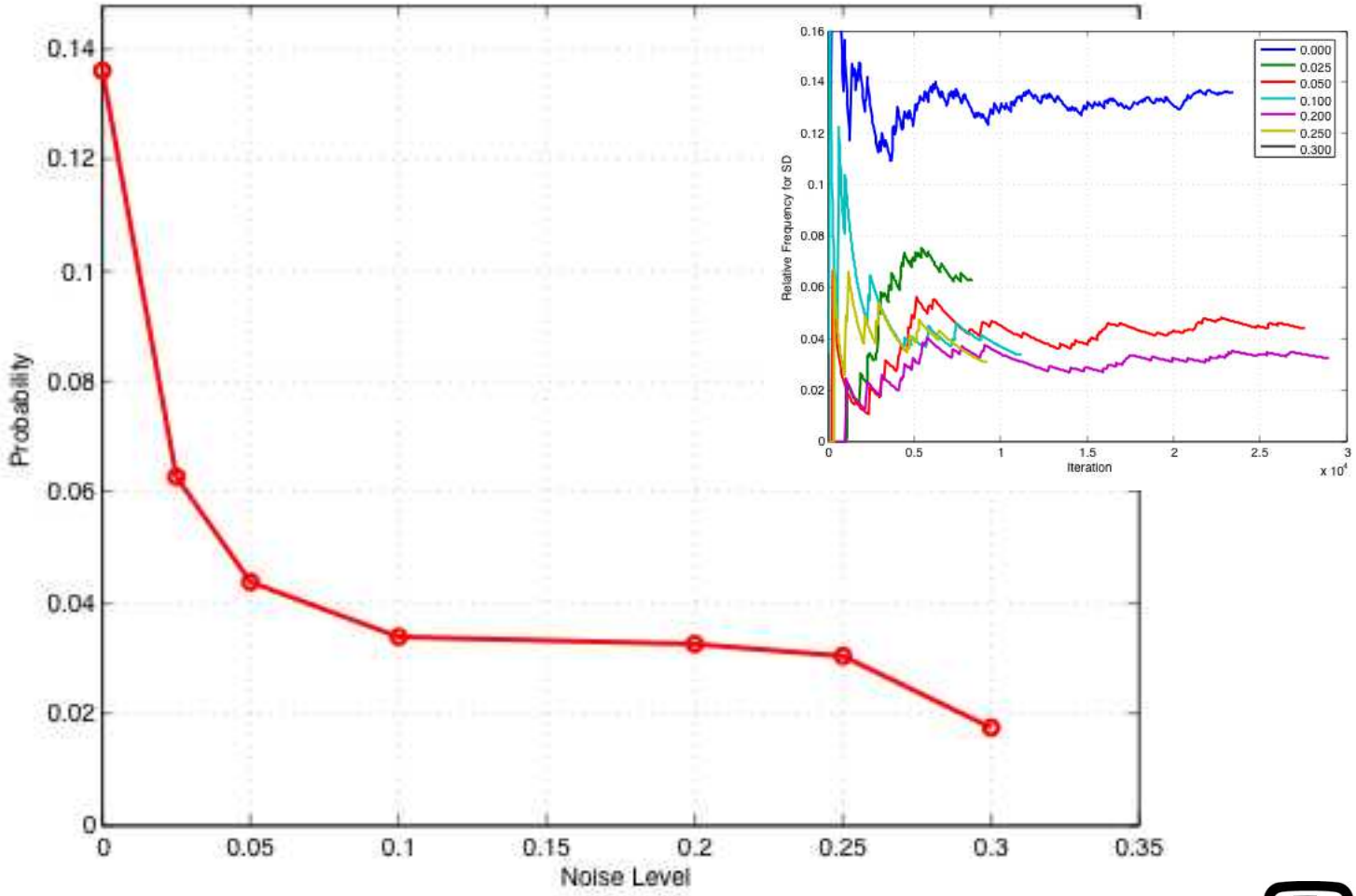
# Differentiation with noise

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# Conclusions

Circuit modeling frameworks offer significant advantages for pathway simulations:

- Scalability
- Numerical stability

Coupling to Optimization frameworks can answer dynamical questions for large, complex networks.

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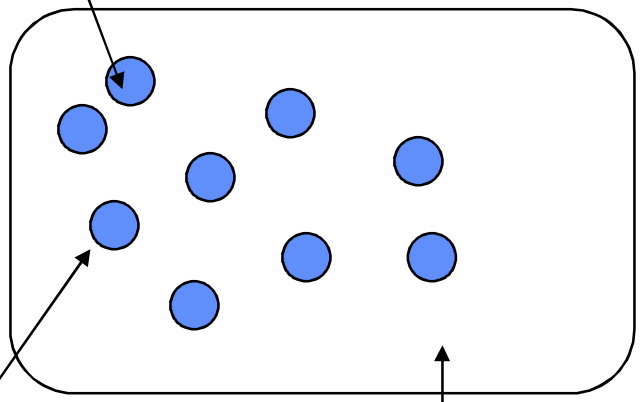
# Tissue Differentiation Systems

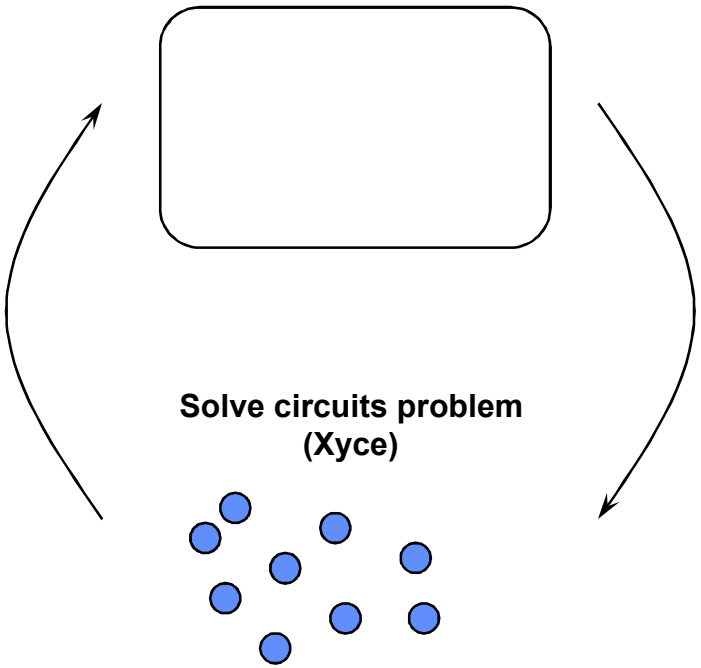
Within a cell, a circuit based reaction pathway exists



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)

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