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

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Department of Computation Sciences

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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

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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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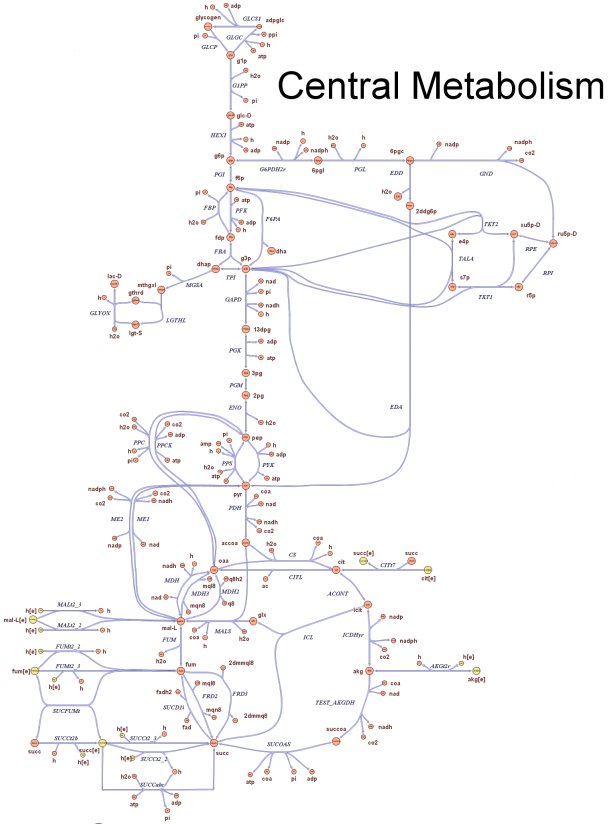
Biological Circuits



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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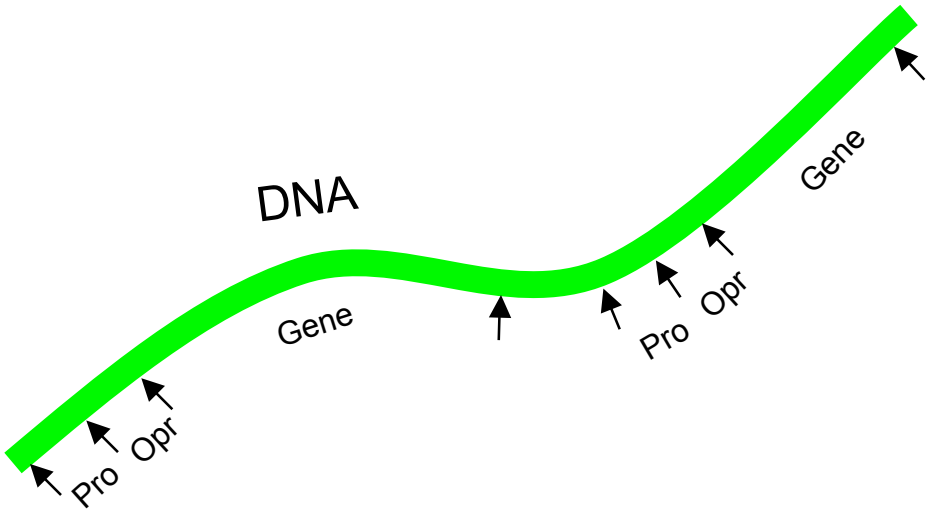
Biological Circuits



Simplified Genetic Switch

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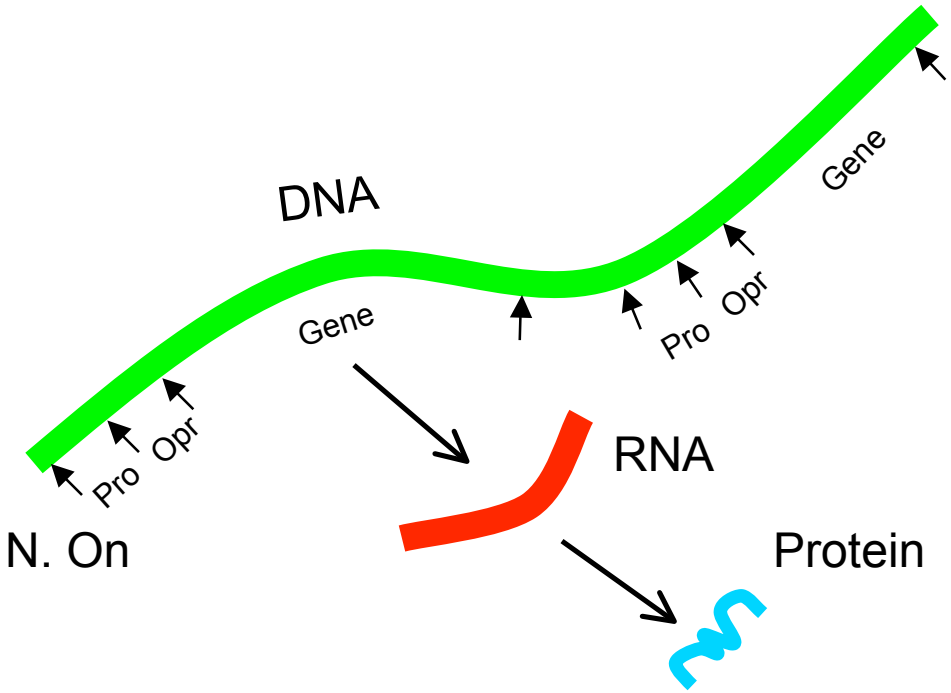
Biological Circuits



Simplified Genetic Switch

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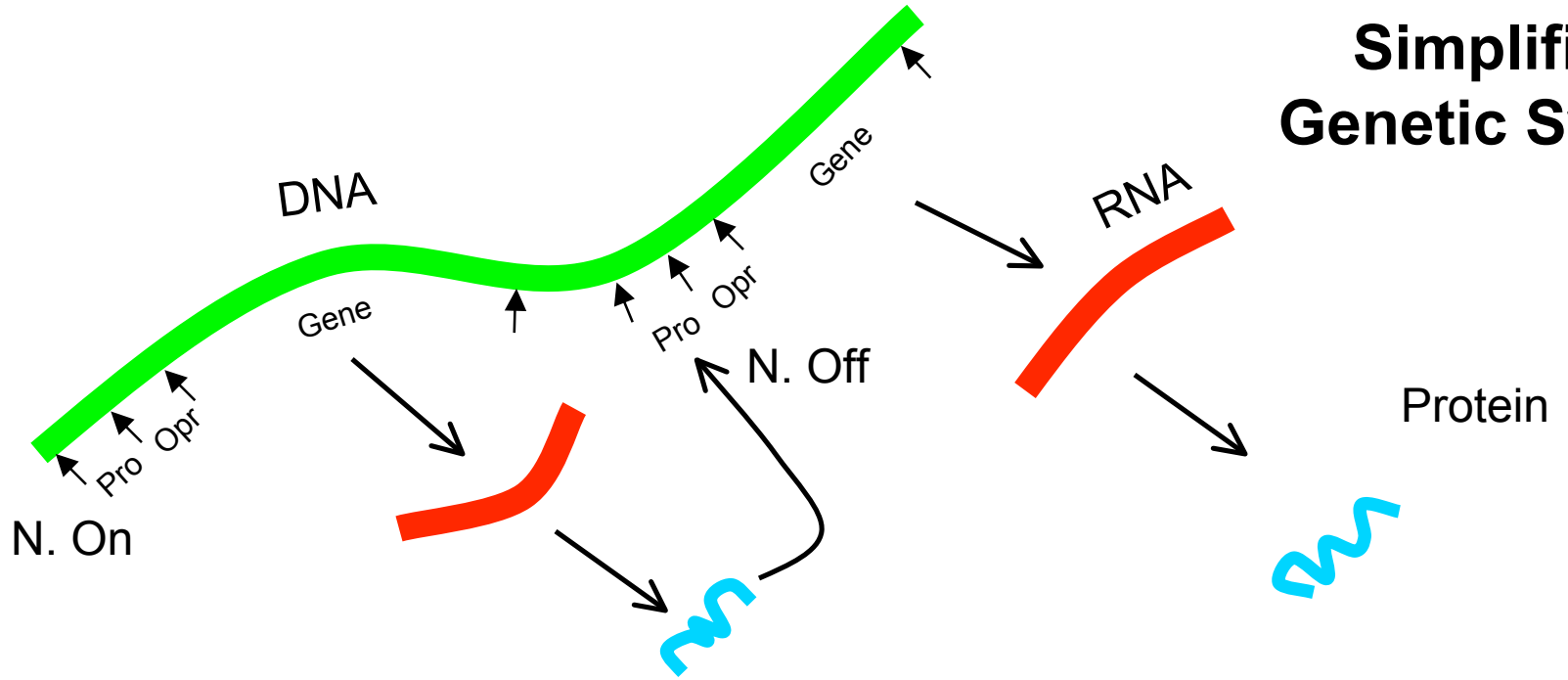
Biological Circuits

Simplified Genetic Switch



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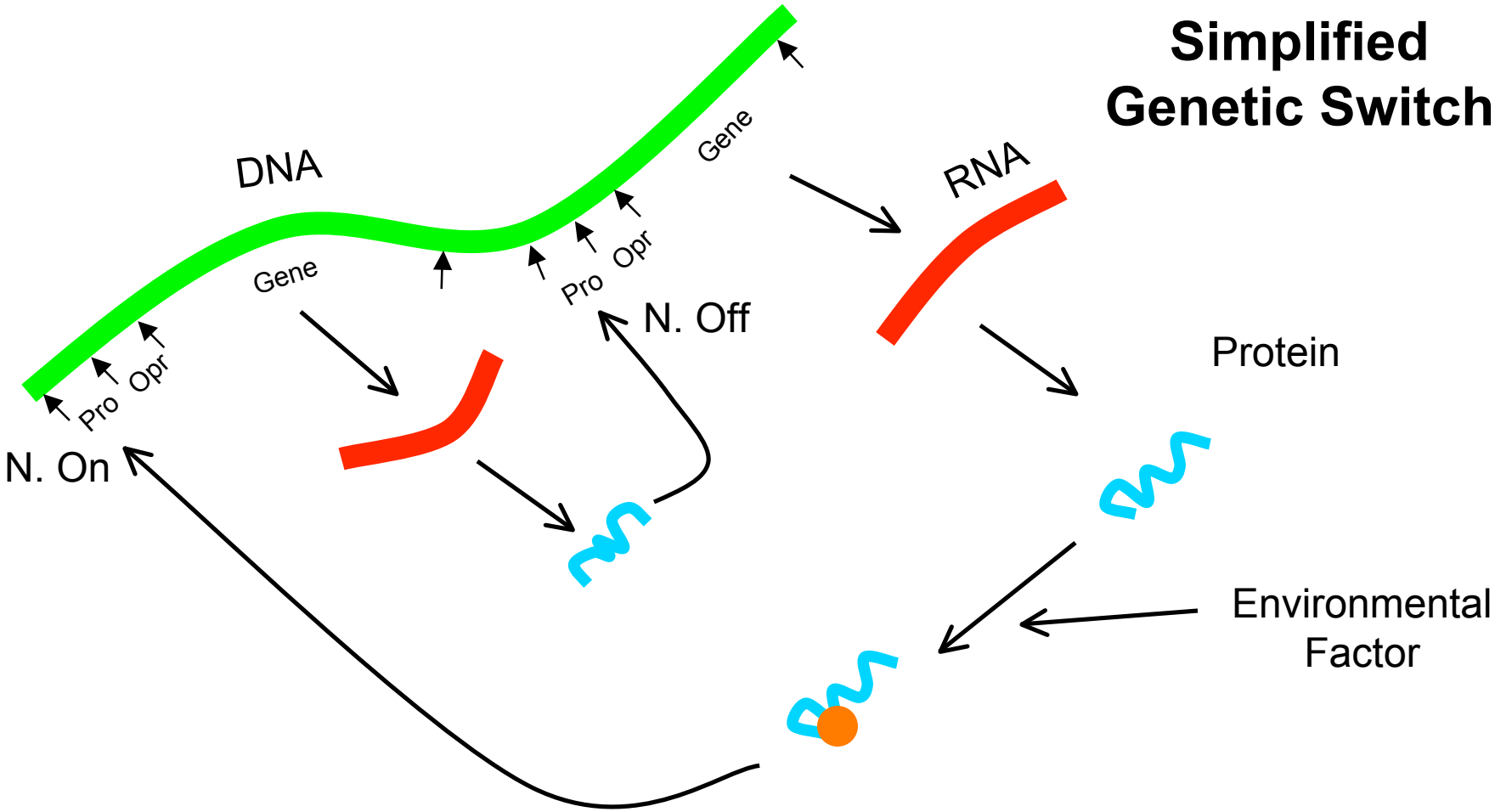
Biological Circuits

Simplified Genetic Switch



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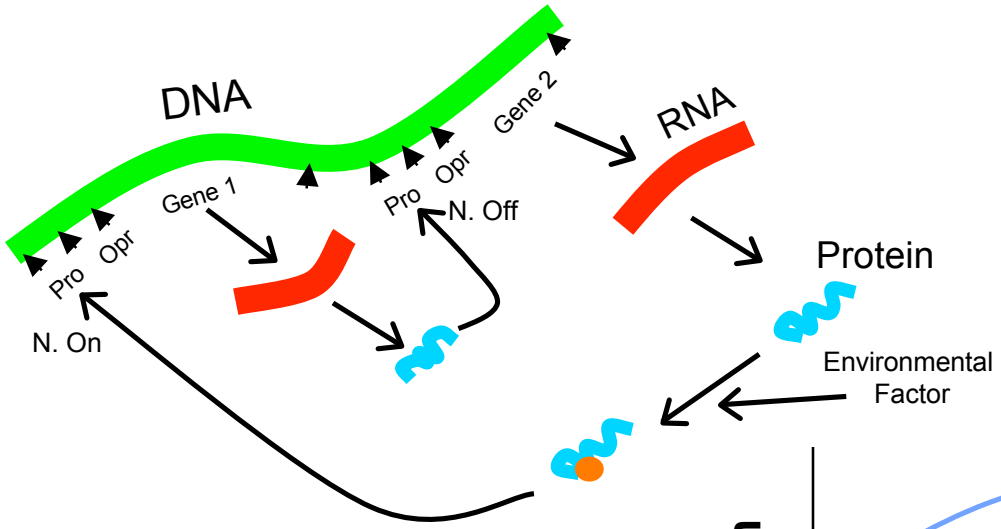
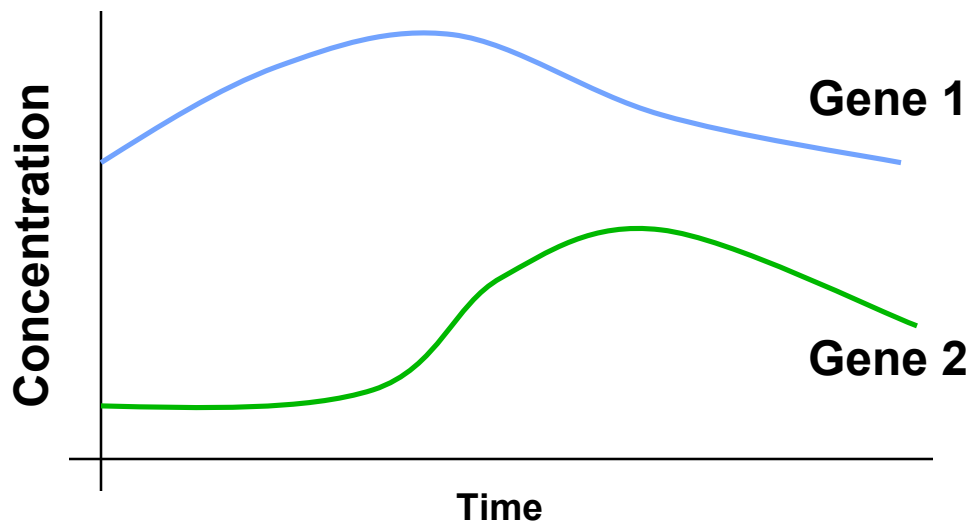
Biological Circuits





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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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Implementation and Modeling Approach

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

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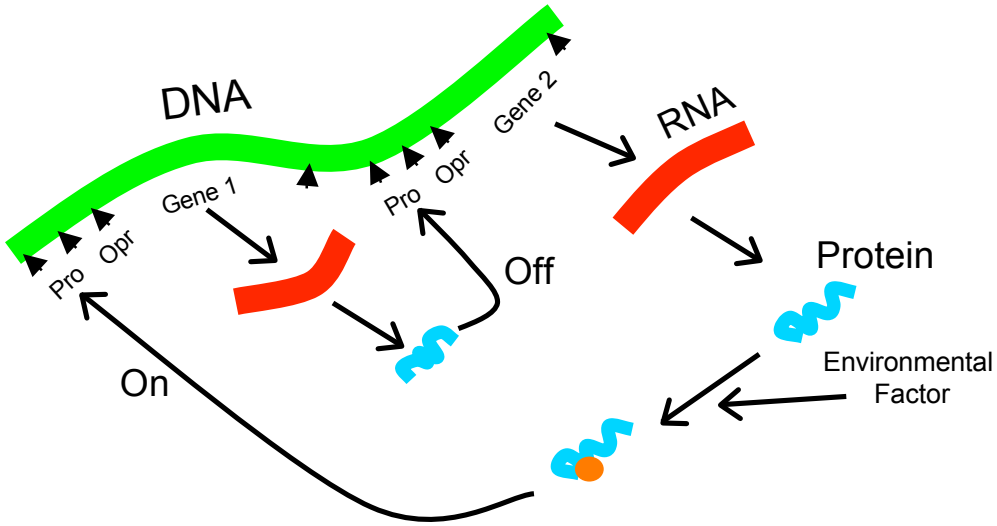
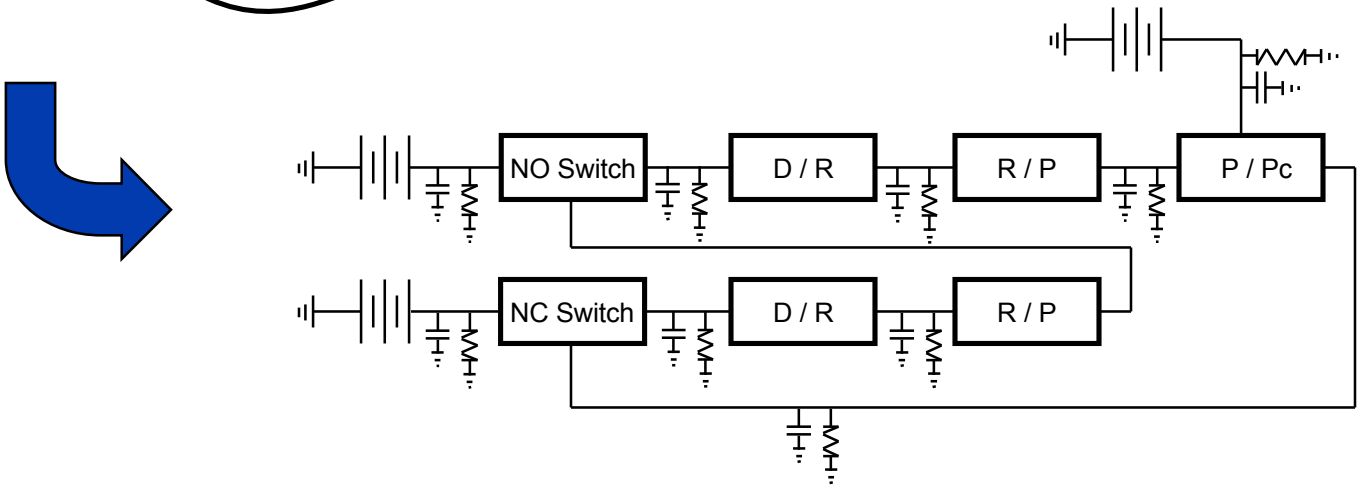
Implementation and Modeling Approach



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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Implementation and Modeling Approach

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, …)

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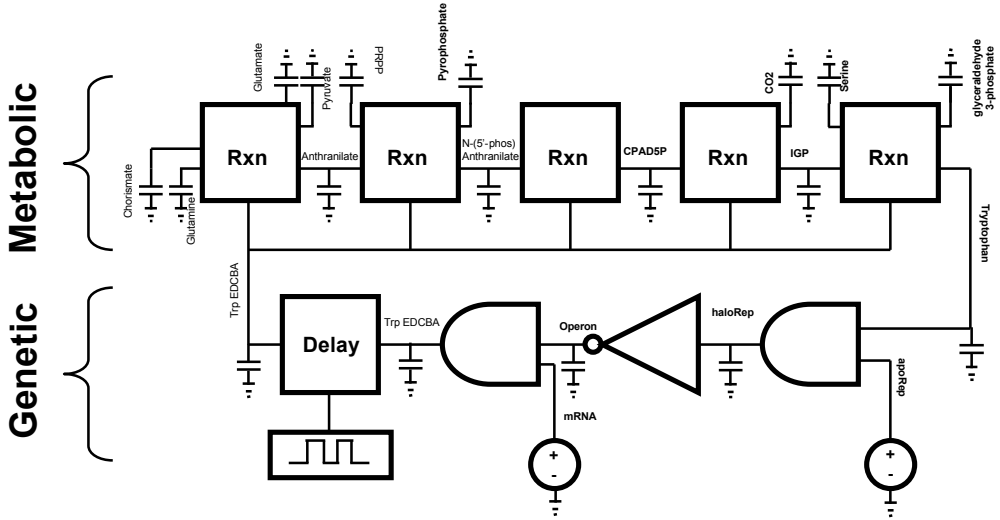
Metabolic and Genetic Coupling

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.



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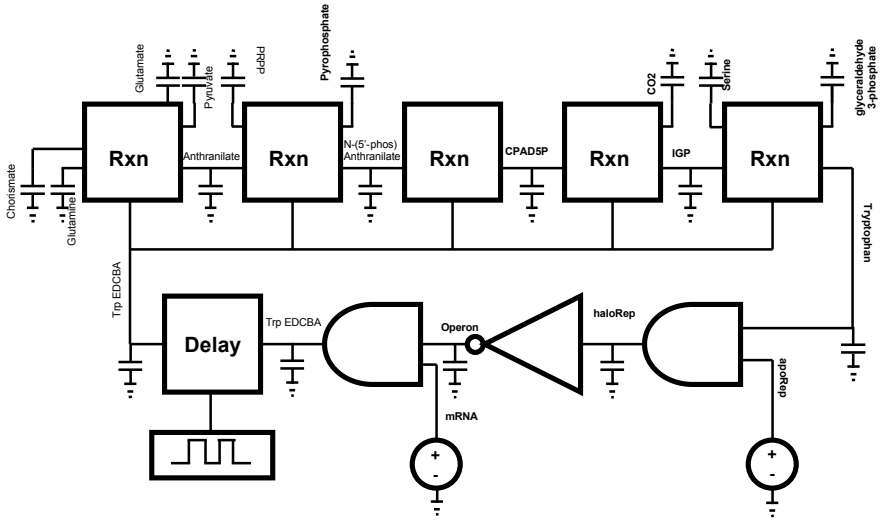
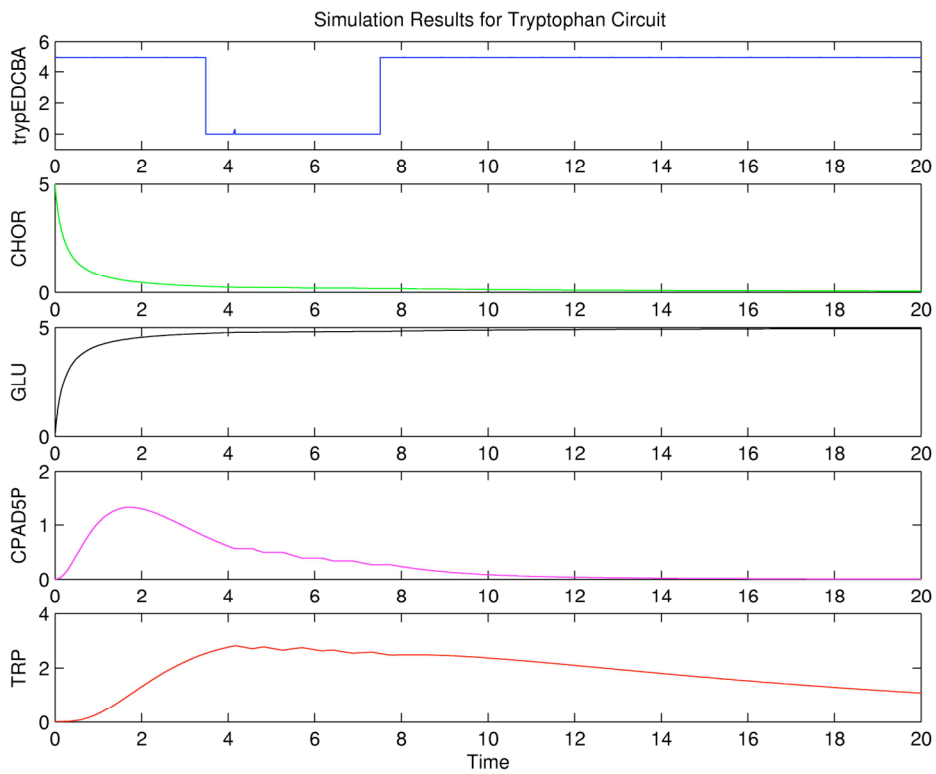
Metabolic and Genetic Coupling





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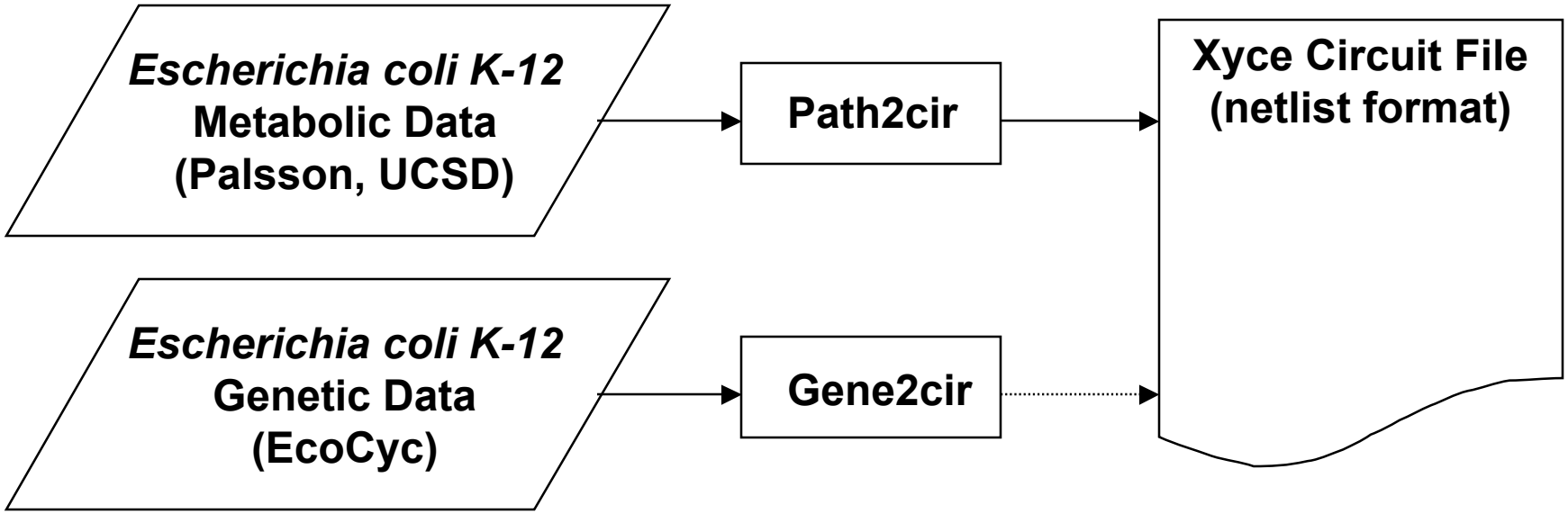
Bacterial Systems

To simulate entire cell systems an automated method was created to convert public databases into circuits.



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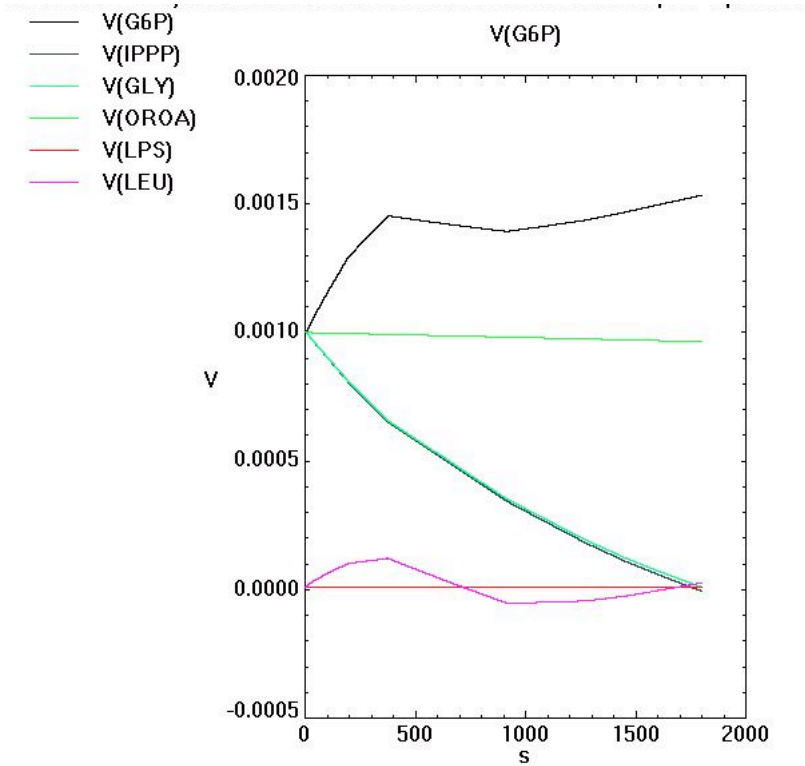
Bacterial Systems

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



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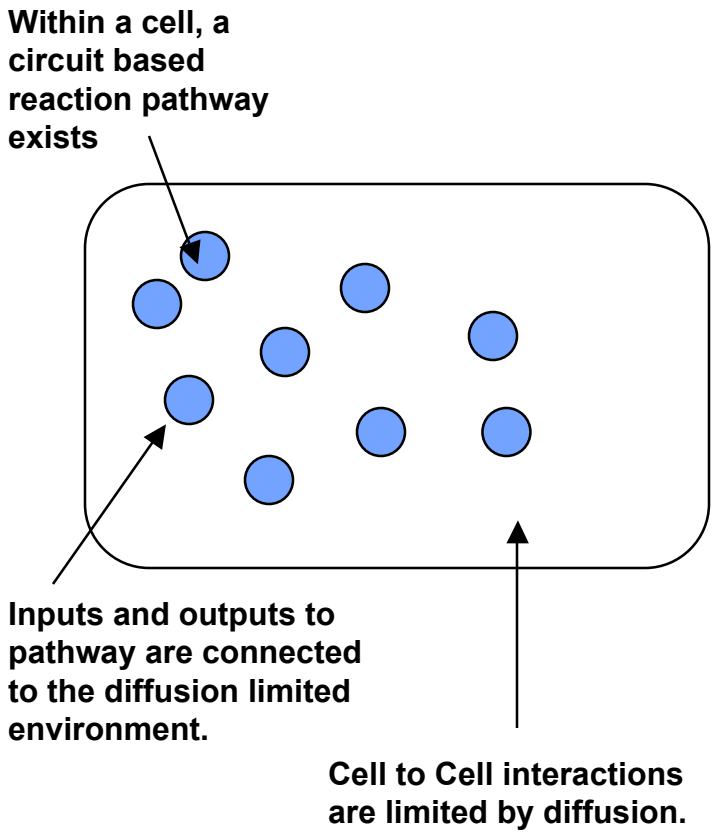
Tissue Differentiation Systems

- 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.



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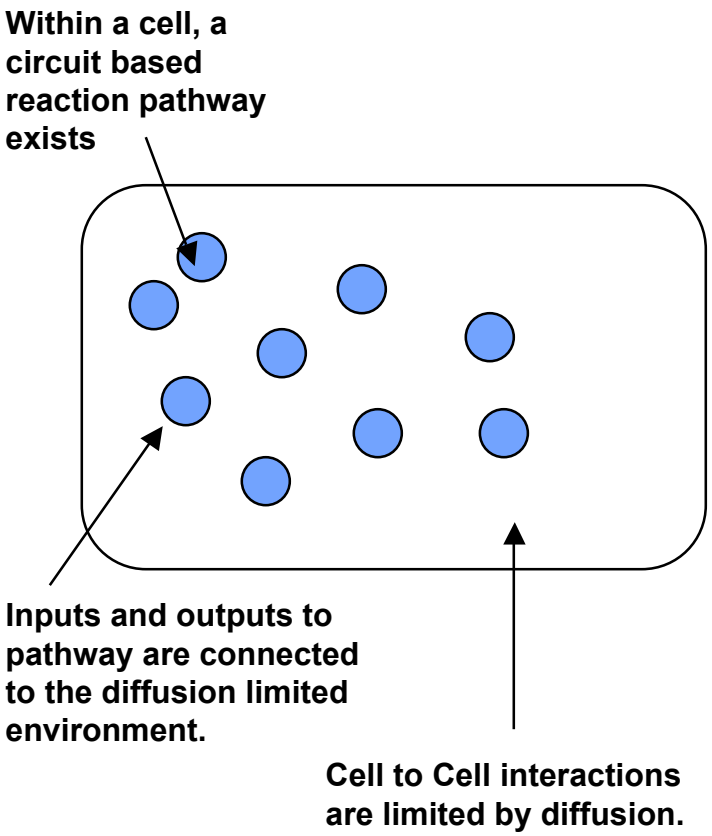
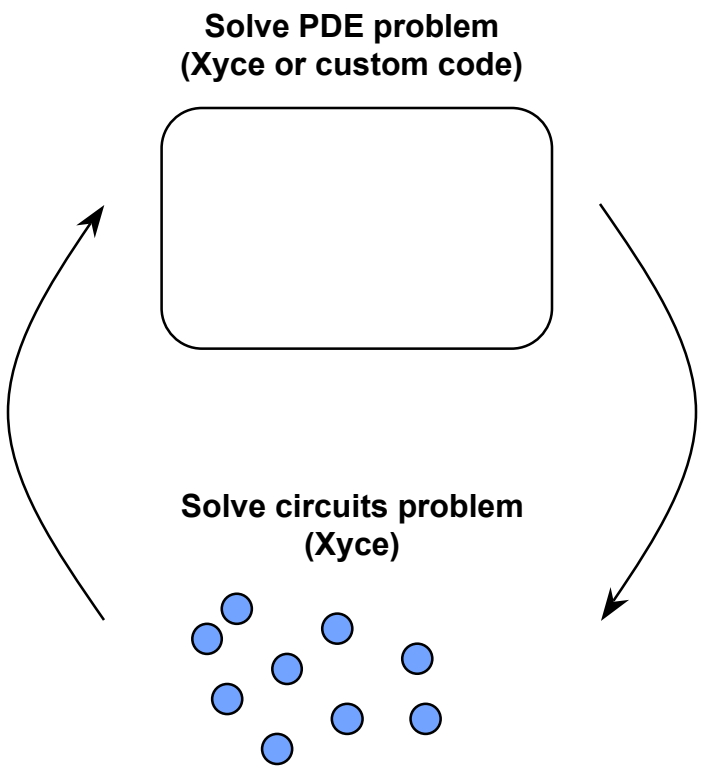
Tissue Differentiation Systems





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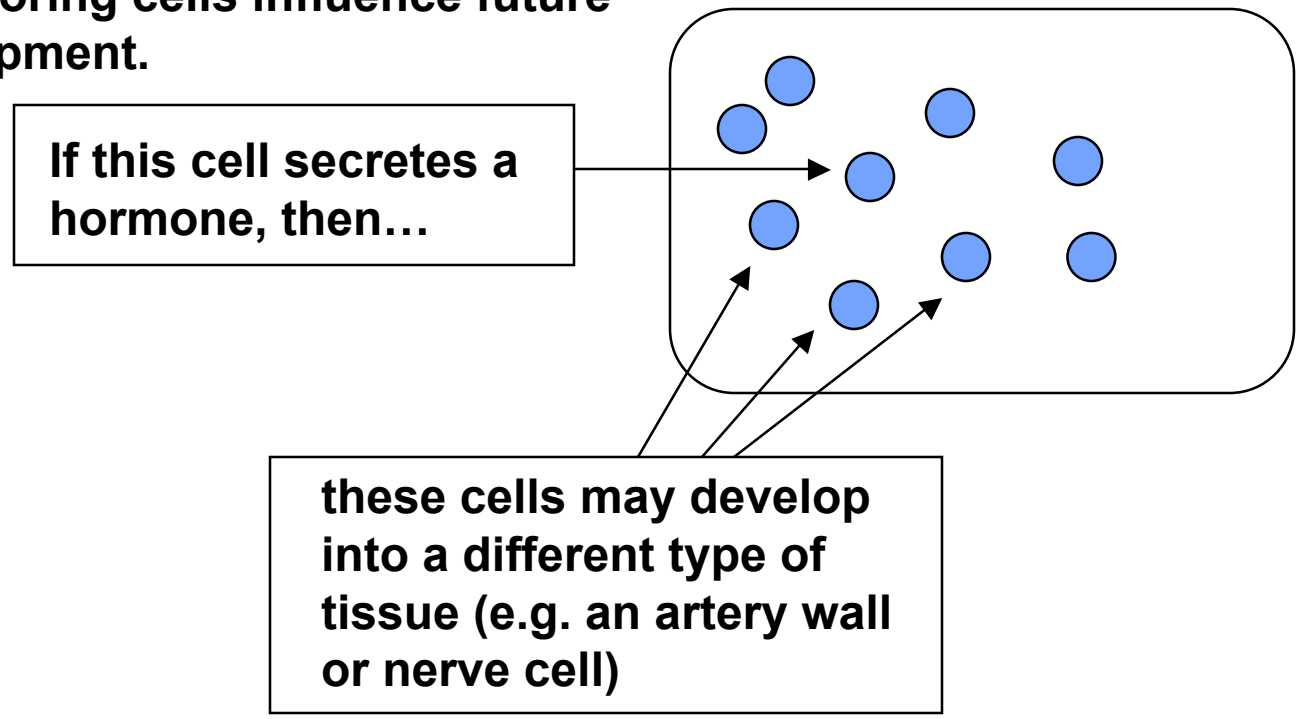
Tissue Differentiation Systems

Cellular differentiation occurs when neighboring cells influence future development.



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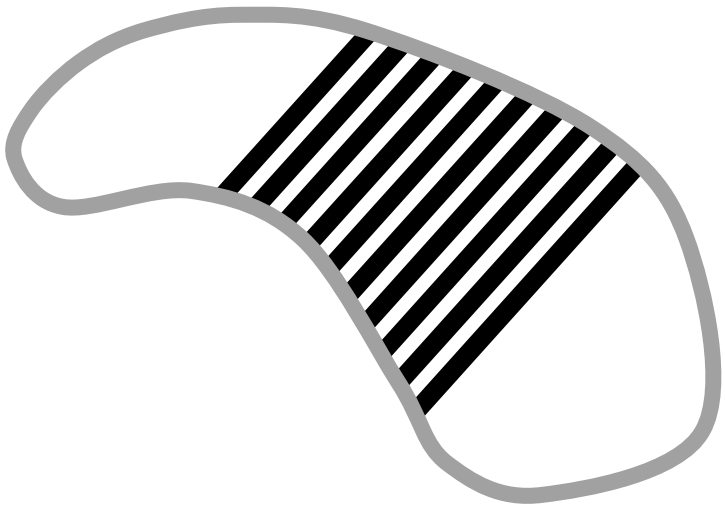
Cellular Differentiation in *Drosophila sp.*



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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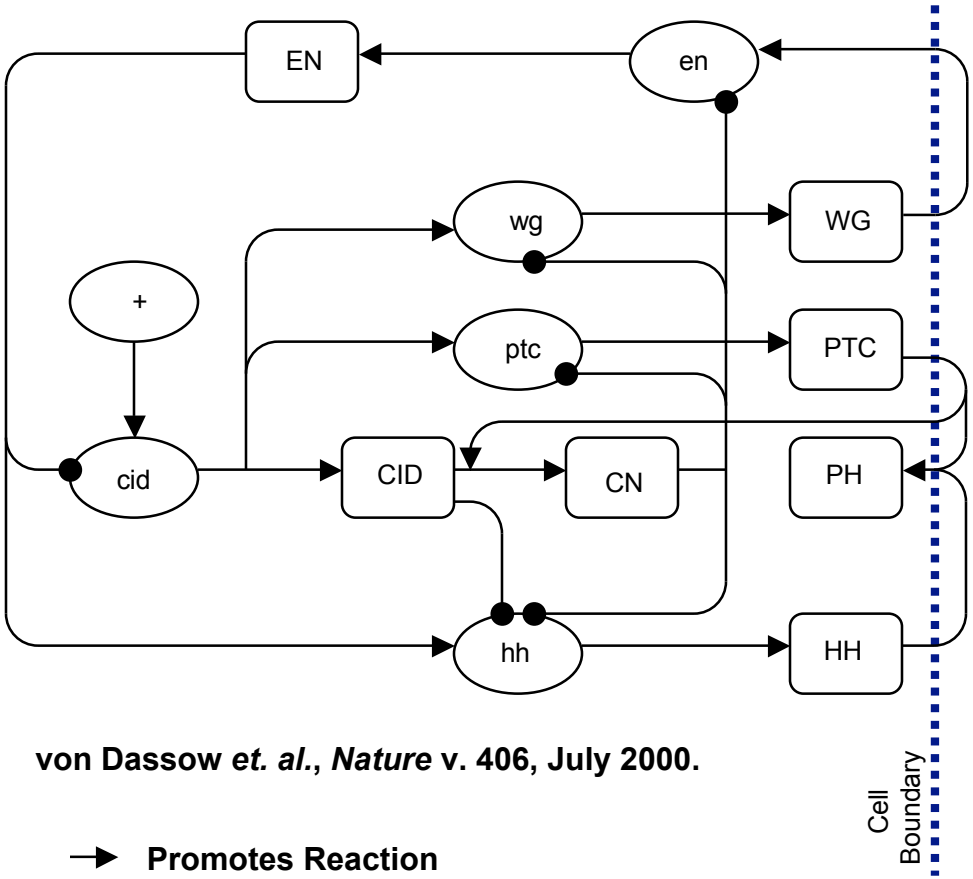
Cellular Differentiation in *Drosophila sp.*



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

→ Promotes Reaction

—● Inhibits Reaction

Cells develop into two types

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

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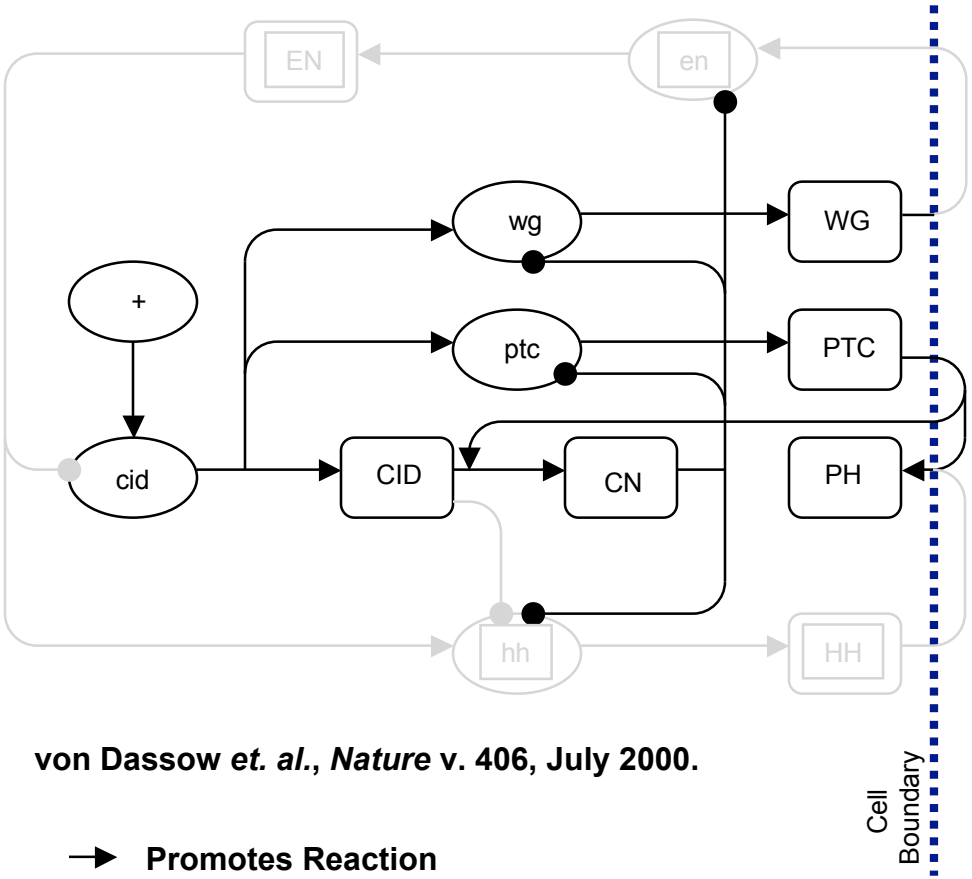
Cellular Differentiation in *Drosophila sp.*



wg expressing

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

→ **Promotes Reaction**

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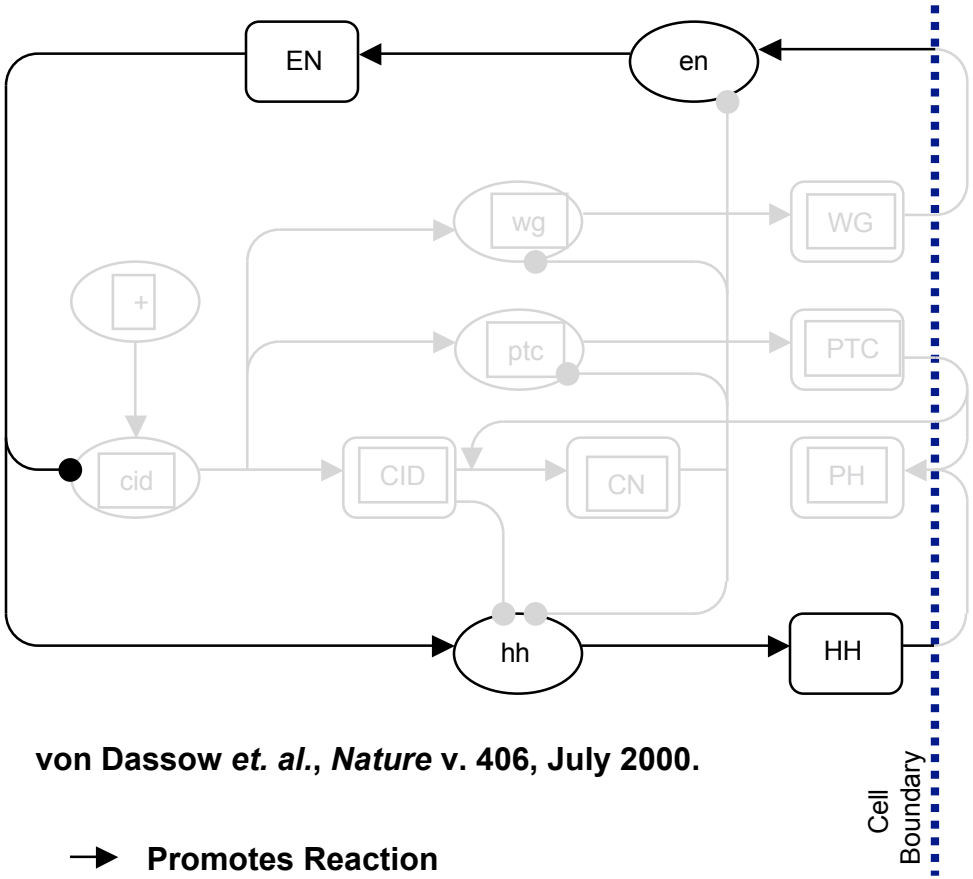
Cellular Differentiation in *Drosophila sp.*



hh expressing

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

→ **Promotes Reaction**

—● **Inhibits Reaction**

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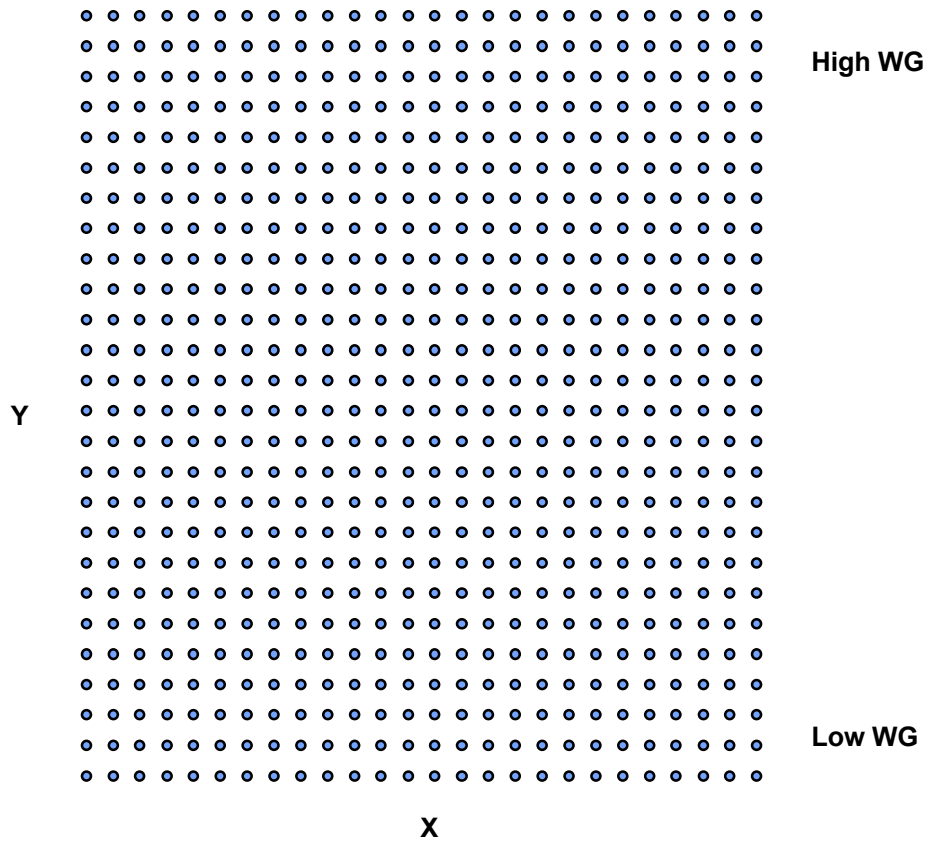
Cellular Differentiation in *Drosophila sp.*

- Simulated a culture of 676 cells (26 x 26 grid)
- Applied a WG concentration gradient of 50%
- Two dimensional, full diffusion model joins cells



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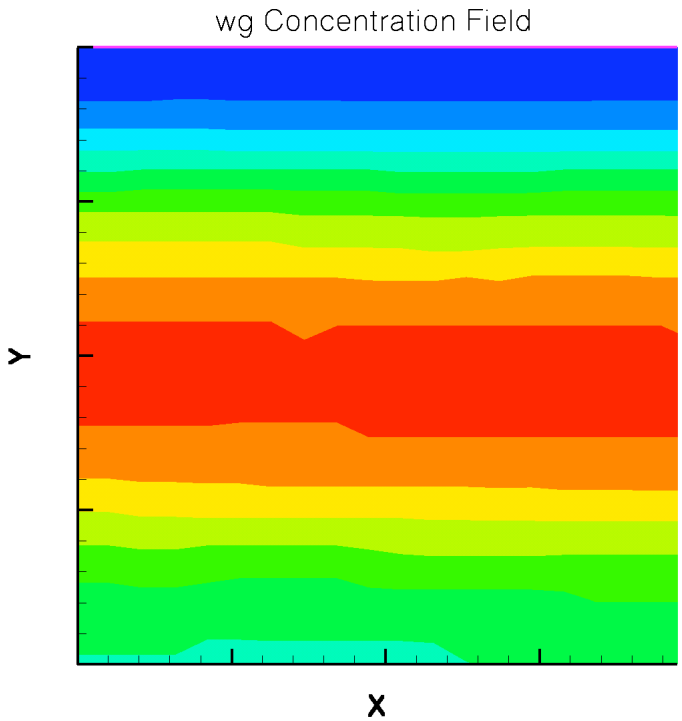
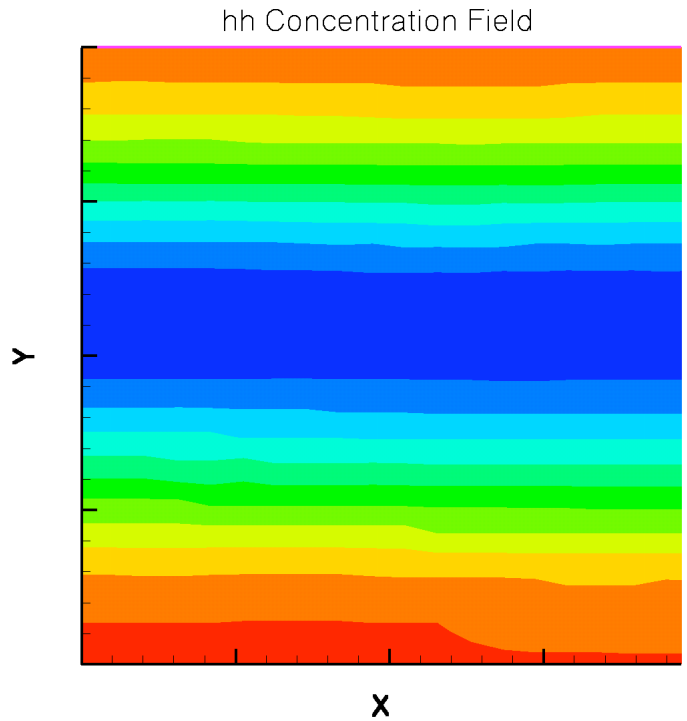
Cellular Differentiation in *Drosophila sp.*





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

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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.**

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