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# The Emergence of Systems Biology

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# Systems Biology

**Goal: To help the biologist model, simulate, analyze, design and diagnose biological systems.**

- Develop system-level understanding of biological systems
  - Genomic DNA, Messenger RNA, proteins, information pathways, signaling networks
  - Intra-cellular systems, Inter-cell regulation...
  - Cells, Organs, Organisms
    - ~12 orders of magnitude in space and time!
- Key question: Function from Structure
  - How do various components of a biological system interact in order to produce complex biological functions?
  - How do you design systems with specific properties (e.g. organs from cells)?
- Share Formal Theories, Code, Models ...

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*Promises profound advances in Biology and Computer Science*

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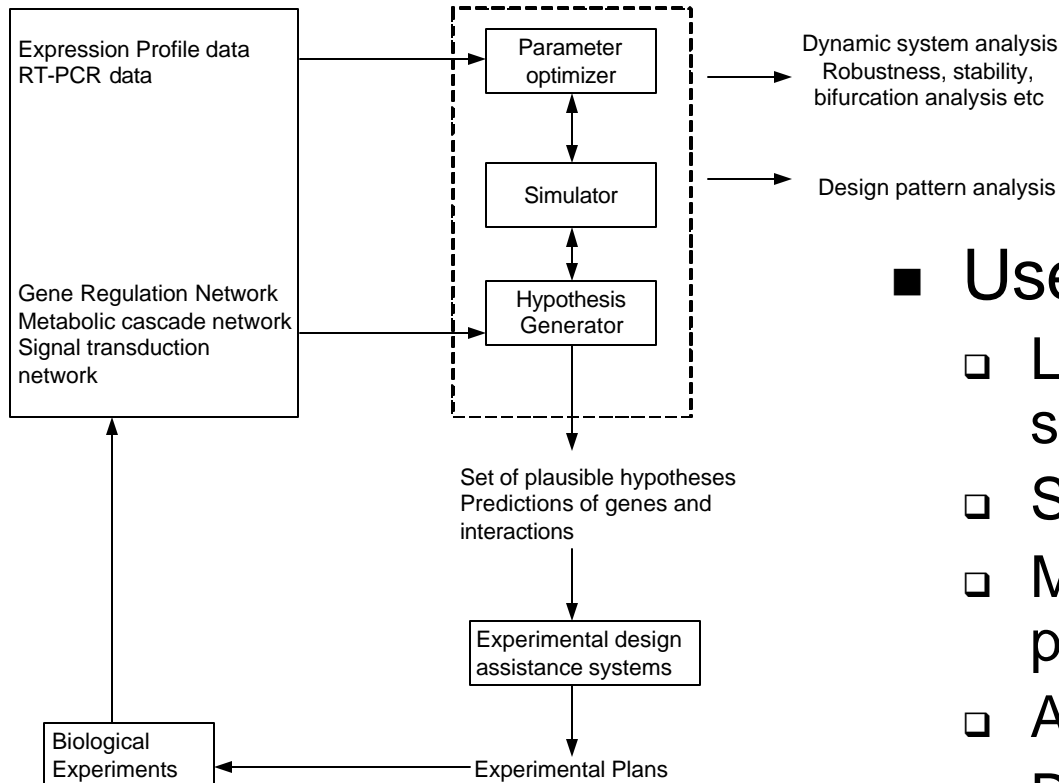
# Systems Biology

- Work subsumes past work on mathematical modeling in biology:
  - Hodgkin-Huxley model for neural firing
  - Michaelis-Menten equation for Enzyme Kinetics
  - Gillespie algorithm for Monte-Carlo simulation of stochastic systems.
  - Bifurcation analysis for *Xenopus* cell cycle
  - Flux balance analysis, metabolic control analysis...
- Why Now?
  - Exploiting genomic data
  - Scale
    - Across the internet, across space and time.
  - Integration of computational tools
  - Integration of new analysis techniques
  - Collaboration using markup-based interlingua
  - Moore's Law!

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*This is not the first time...*

# Integrating Computation into experimentation



**An integrated approach to biological experimentation  
(From Kitano [Sys-Bio])**

## ■ Use *all* of Comp Sci

- Logic and Hybrid systems
- Symbolic Analysis Tools
- Machine learning and pattern recognition
- Algorithms
- Databases
- Modeling languages

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# Area is Exploding in interest...

## ■ Conferences...

- BioConcur '03
- Pacific Sym BioComputing '04
- International Workshop on Systems Biology
- Comp Methods in Sys Bio, 2004
- Systematics 2004

## ■ Websites

- [www.sbml.org](http://www.sbml.org)
- [www.cellml.org](http://www.cellml.org)
- [www.systemsbiology.org](http://www.systemsbiology.org)

## ■ Projects

- BioSpice (DARPA)
- CellML (U Auckland)
- SBML
  - CalTech, U Hertfordshire, Argonne, Virginia, U Conn...
- Post-genomic institutes
  - Harvard/MIT, Princeton

## ■ Systems

- BioSpice, Charon, Cellerator, COPASI, DBSolve, E-Cell, Gepasi, Jarnac, JDesigner, JigCell, NetBuilder, StochSim, Virtual Cell...

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# Hybrid Systems

- Traditional Computer Science
  - Discrete state, discrete change (assignment)
  - E.g. Turing Machine
  - Brittleness:
    - Small error → major impact
    - Devastating with large code!
- Traditional Mathematics
  - Continuous variables (Reals)
  - Smooth state change
    - Mean-value theorem
    - E.g. computing rocket trajectories
  - Robustness in the face of change
  - Stochastic systems (e.g. Brownian motion)
- Hybrid Systems combine both
  - Discrete control
  - Continuous state evolution
  - Intuition: Run program at every real value.
    - Approximate by:
      - Discrete change at an instant
      - Continuous change in an interval
- Primary application areas
  - Engineering and Control systems
    - Paper transport
    - Autonomous vehicles...
  - And now.. *Biological Computation.*

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Emerged in early 90s in the work of Nerode, Kohn, Alur, Dill, Henzinger...

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# Hcc: Hybrid Concurrent Constraint Progg.

Very flexible programming and modeling language

Based on a general theory of concurrency and constraints

- Has a built-in notion of continuous time
- Supports smooth *and* discontinuous system evolution
- Supports stochastic modeling
- Provides powerful, extensible constraint solver
- Can handle variable-structure systems
- Supports qualitative and quantitative modeling.
- Built on a formal operational and denotational semantics
- Supports meta-programming (dynamic generation of programs)
- Completely integrated with Java

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# Hcc: A language for hybrid modeling

- Hcc is based on a very few primitives
  - **c**
    - Establish constraint c now
  - **if(c) {S}**
    - Run S when c holds (at this instant)
  - **unless(c) {S}**
    - Run S unless c holds (at this instant)
  - **S, S**
    - Run the two in parallel
  - **hence S**
    - Run S at every real after now
- Language can be used to express any pattern of evolution across time:
  - **always{S}**
    - run S at every time point
  - **every(c) {S}**
    - run S at every time point at which c holds.
  - **watching(c) {S}**
    - run S, aborting it as soon as c holds.



# Hcc for Systems Biology

<i>Systems Biology</i>	<i>jcc</i>
Reaching Threshold	Discrete change
Time, species conc	Continuous variables
Kinetics	Differential equations
Gene interaction	Concurrency, defaults
Stochastic behavior	Stochastic variables

Bockmayr, Courtois: "Using hccp to model dynamic biological systems", ICLP 02

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# Basic example

- Expression of gene x inhibits expression of gene y; above a certain threshold, gene y inhibits expression of gene x:

if ( $y < 0.8$ )  $\{x' = -0.02 * x + 0.01\}$ ,  
If ( $y \geq 0.8$ )  $\{x' = -0.02 * x, y' = 0.01 * x\}$



2geneinteraction.ps

# Bioluminescence in *E. Fischeri*

## ■ Bioluminescence in *V. fischeri*

- When density passes a certain threshold, (marine) bacteria suddenly become luminescent

## ■ Model:

- Variables  $x_7, x_9$  represents internal (ext) concentration of  $A_i$ .
- Variables  $x_1, \dots, x_6, x_8$  represent other species

## ■ Use generic balance eqn:

- $x' = v_s - v_d \pm v_r \pm v_t$ 
  - $v_s$ : synthesis rate
  - $v_d$ : degradation rate
  - $v_r$ : reaction rate
  - $v_t$ : transportation rate

□ E.g.

always{

if ( $x_7 < A_{i\_min}$ )  $x_1' = \mu_1 * ((0.5 * x) - x_1)$ ,

If ( $x_7 \geq A_{i\_plus}$ )  $x_1' = -\mu_1 * x_1, \dots$

}

The conditional ODEs governing 9 system variables can be directly transcribed into jcc.

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# Delta-Notch signaling in *X. Laevis*

- Consider cell differentiation in a population of epidermic cells.
  - Cells arranged in a hexagonal lattice.
  - Each cell interacts concurrently with its neighbors.
  - The concentration of Delta and Notch proteins in each cell varies continuously.
  - Cell can be in one of four states: Delta and Notch inhibited or expressed.
- Experimental Observations:
    - Delta (Notch) concentrations show typical spike at a threshold level.
    - At equilibrium, cells are in only two states (D or N expressed; other inhibited).

# Delta-Notch Signaling

## ■ Model:

- VD, VN: concentration of Delta and Notch protein in the cell.
- UD, UN: Delta (Notch) production capacity of cell.
- $UN = \sum_i VD_i$  (neighbors)
- $UD = -VN$
- Parameters:
  - Threshold values: HD, HN
  - Degradation rates: MD, MN
  - Production rates: RD, RN

## ■ Model:

- Cell in 1 of 4 states: {D,N} x {Expressed (above), Inhibited (below)}

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if (UN(i,j) < HN) {VN' = -MN*VN},  
if (UN(i,j) >= HN) {VN' = RN - MN*VN},  
if (UD(i,j) < HD) {VD' = -MD*VD},  
if (UD(i,j) >= HD) {VD' = RD - MD*VD},
```

- Stochastic variables used to set random initial state.
- Model can be expressed directly in hcc.

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Results: Simulation confirms observations. Tiwari/Lincoln prove that States 2 and 3 are stable.

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# Alternative splicing regulation

- Alternative splicing occurs in post transcriptional regulation of RNA
- Through selective elimination of introns, the same pre-messenger RNA can be used to generate many kinds of mature RNA
- The SR protein appears to control this process through activation and inhibition.
- Because of complexity, experimentation can focus on only one site at a time.
- Bockmayr et al use Hybrid CCP to model SR regulation at a single site.
  - Michaelis-Menten model using 7 kinetic reactions
- This is used to create an n-site model by abstracting the action at one site via a splice efficiency function.

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Results described in [Alt], uses default reasoning properties of HCC.

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# Programming Languages Issues

- Languages for large-scale modeling
  - Hi-perf num computation
  - Arrays
  - Stochastic methods
  - Large-scale parallelism (e.g SPMD)
- Efficient compilation issues
  - Identify patterns, integrate libraries of high-performance code
- Integration of reasoning techniques
  - Eg finite state analysis of hybrid systems
- Syntax/Semantics
- Integration of Spatial dimension
  - Moving to PDEs
- Developing models across the Internet
  - Semantic web...

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*Exciting time for the development of new languages!*

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# Acknowledgements

- [Sys-Bio]: Kitano “Systems Biology: Towards system-level understanding of Biological Systems”, in *Foundations of Systems Biology*, MIT Press, 2001
  - [Delta-Notch]: Tiwari, Lincoln “Automatic Techniques for stability analysis of Delta-Notch lateral inhibition mechanism”, *CSB 2002*.
  - [HCC-Bio]: Bockmayr, Courtois “Using hybrid concurrent constraint programming to model dynamic biological systems”, *ICLP 2002*
  - [Alt]: Eveillard, Ropers, de Jong, Branlant, Bockmayr “A multi-site constraint programming model of alternate splicing regulation”, *INRIA Tech Rep*, May 2003
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# HCC references

- Gupta, Jagadeesan, Saraswat “Computing with Continuous Change”, Science of Computer Programming, Jan 1998, 30 (1—2), pp 3--49
  - Saraswat, Jagadeesan, Gupta “Timed Default Concurrent Constraint Programming”, Journal of Symbolic Computation, Nov-Dec1996, 22 (5—6), pp 475-520.
  - Gupta, Jagadeesan, Saraswat “Programming in Hybrid Constraint Languages”, Nov 1995, Hybrid Systems II, LNCS 999.
  - Alenius, Gupta “Modeling an AERCam: A case study in modeling with concurrent constraint languages”, CP’98 Workshop on Modeling and Constraints, Oct 1998.
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# CFP: Wkshp Comp Methods in Sys Bio

Deadline : March 1, 2004

Call for Papers - International Workshop on Computational  
Methods in Systems Biology 2004 (CMSB'04)

Organized by Genoscope, Evry – Génopole, Evry – CNRS –  
University of Paris VII – BioPathways Consortium

Hotel Meridien Montparnasse, Paris, France 26-28 May, 2004

Deadline : March 1st, 2004

<http://www.genoscope.cns.fr/biopathways/CMSB04/>

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