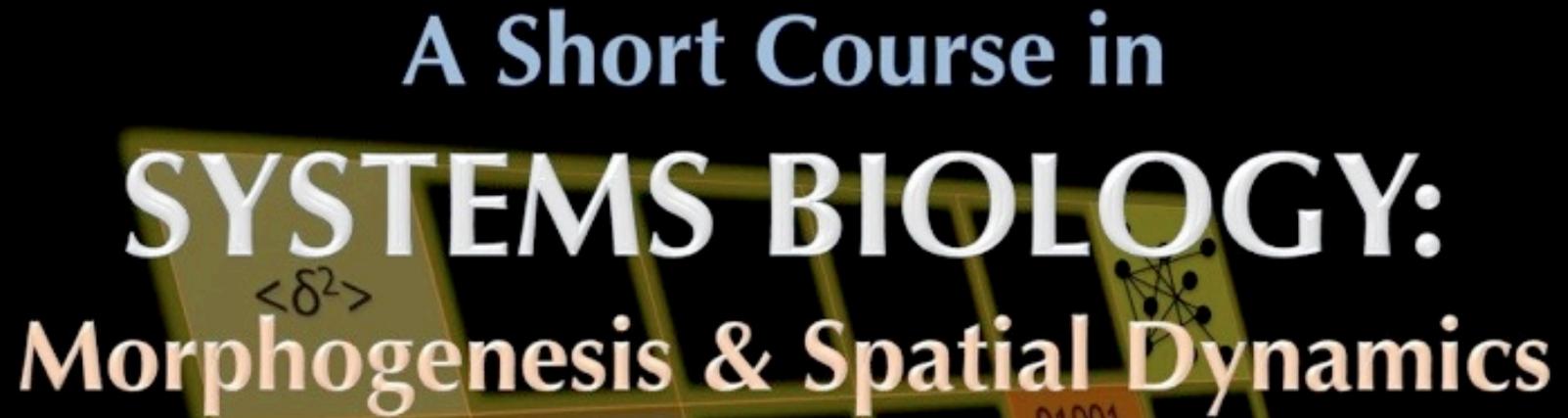


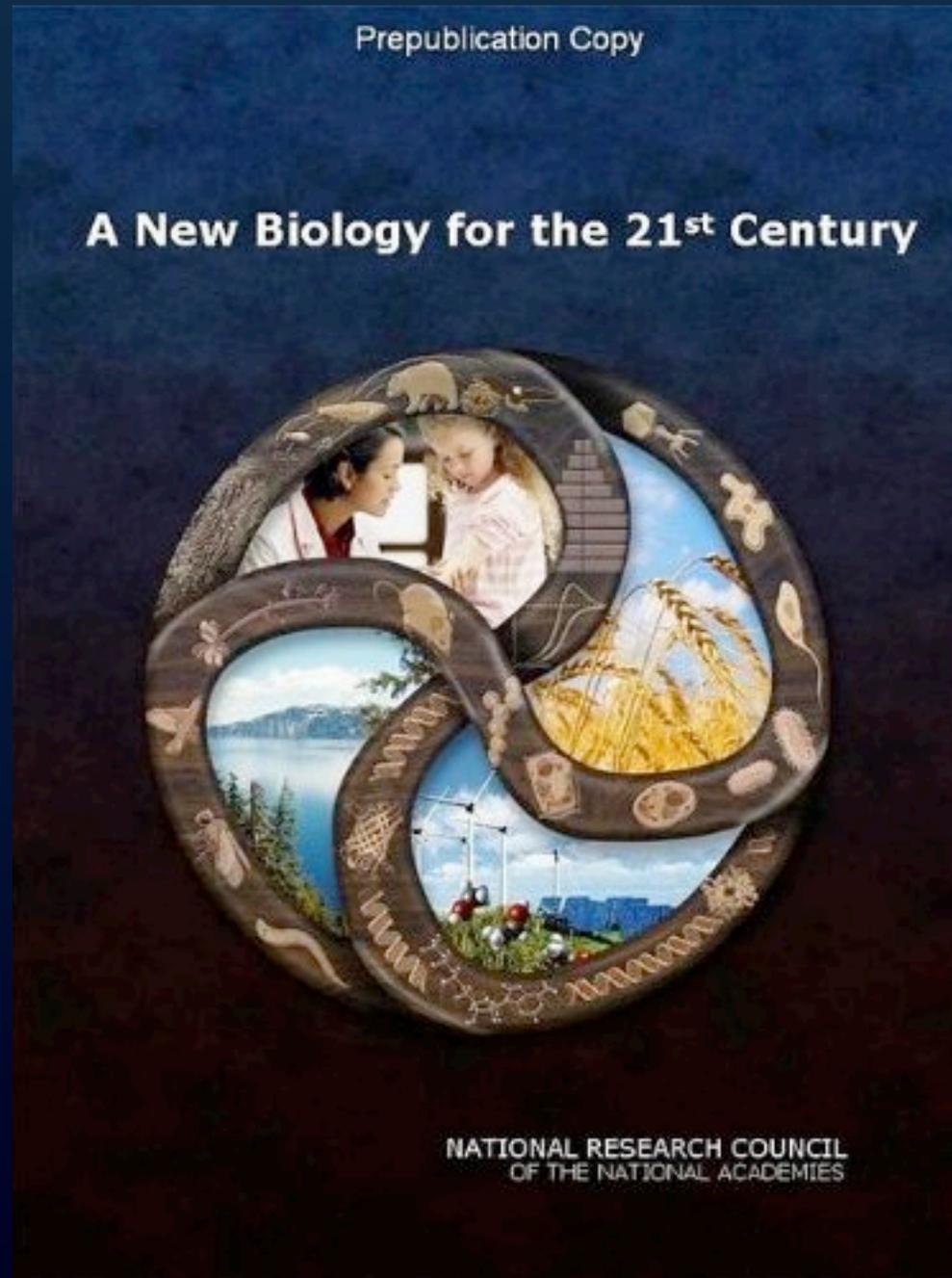
A Short Course in  
**SYSTEMS BIOLOGY:**  
Morphogenesis & Spatial Dynamics



Introduction to the Course

The 2009 report of the  
**Committee on a New  
Biology for the 21st  
Century:  
Ensuring the United  
States Leads the Coming  
Biology Revolution**

NATIONAL RESEARCH  
COUNCIL OF THE  
NATIONAL ACADEMIES  
THE NATIONAL  
ACADEMIES PRESS  
Washington, D.C.



The essence of the New Biology, as defined by the committee, is integration—re-integration of the many sub-disciplines of biology, and the integration into biology of physicists, chemists, computer scientists, engineers, and mathematicians to create a research community with the capacity to tackle a broad range of scientific and societal problems. Integrating knowledge from many disciplines will permit deeper understanding of biological systems, which will both lead to biology-based solutions to societal problems and also feed back to enrich the individual scientific disciplines that contribute new insights.

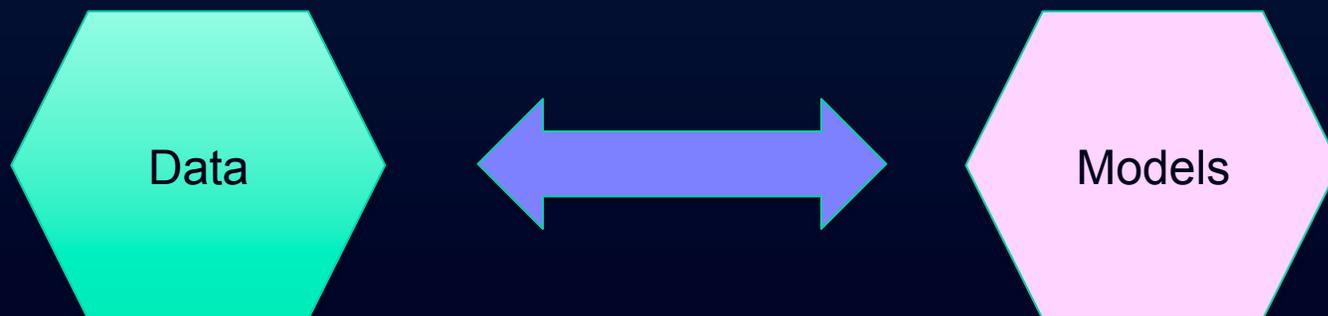
- Re-integration
- Interdisciplinary synthesis

# What is actually going on in Systems Biology?

- Themes and Approaches
- Cultural Change

# Major Themes in Systems Biology

1. Understanding biological regulation
2. Inferring the details of complex processes
3. Probing the constraints on, and limits of, biological performance



# Four points about models

- Models are incomplete representations of the world that are useful because they are simpler and more abstract than reality.
- Models may be explicit (mechanistic) or phenomenological.
- The usefulness of a model may or may not have to do with its predictive power
- Explicit models do not necessarily make explicit predictions

# Major Themes in Systems Biology

- 1. Understanding biological regulation

- Metabolic control
- Signaling networks
- Gene regulatory networks
- Growth control
- Transport processes
- Pattern formation
- Morphogenesis

*Often approximated as  
“well-stirred”*

*Explicitly spatial*



# Signaling Networks

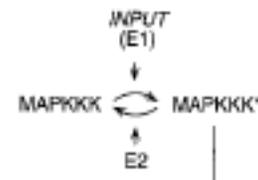
## Ultrasensitivity in the mitogen-activated protein kinase cascade

CHI-YING F. HUANG AND JAMES E. FERRELL, JR.†

Department of Molecular Pharmacology, Stanford University School of Medicine, Stanford, CA 94305-5332

Communicated by Daniel E. Koshland, Jr., University of California, Berkeley, CA, May 16, 1996 (received for review January 22, 1996)

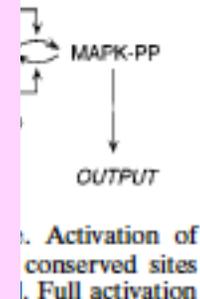
**ABSTRACT** The mitogen-activated protein kinase (MAPK) cascade is a highly conserved series of three protein kinases implicated in diverse biological processes. Here we demonstrate that the cascade arrangement has unexpected consequences for the dynamics of MAPK signaling. We solved the rate equations for the cascade numerically and found that MAPK is predicted to behave like a high-gain switch, even though it was not assumed that it



Commonly makes use of a reverse-engineering approach

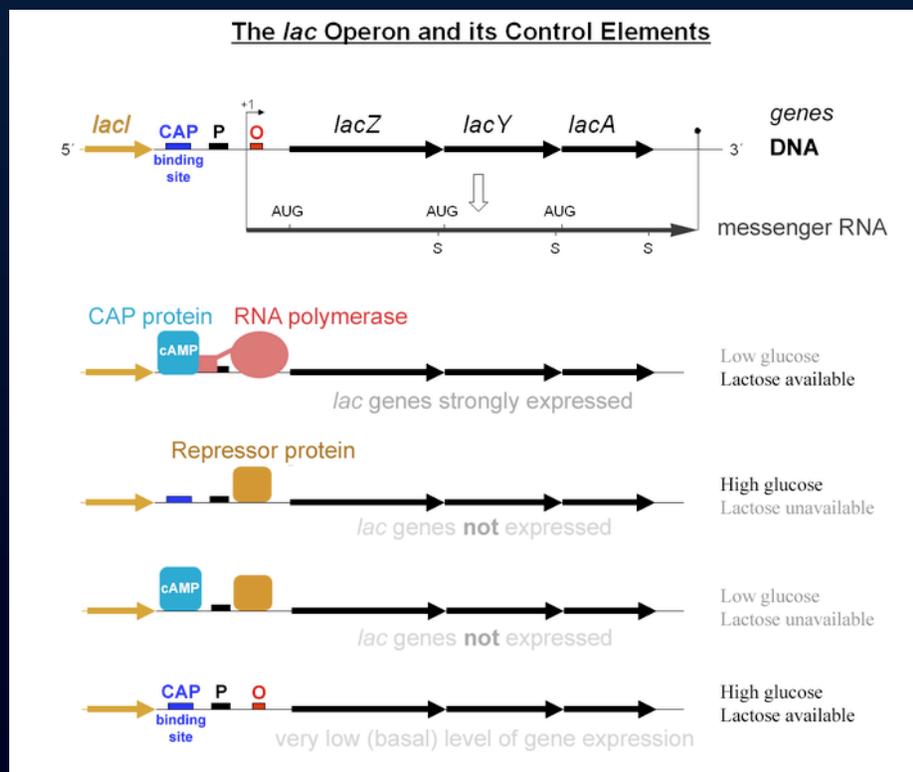
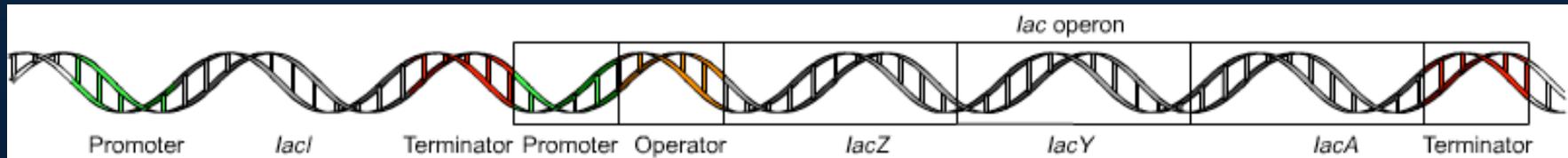
Emphasizes design principles

“Spiraling complexity” due to multiple modification states is driving development of new methodologies



James Ferrell

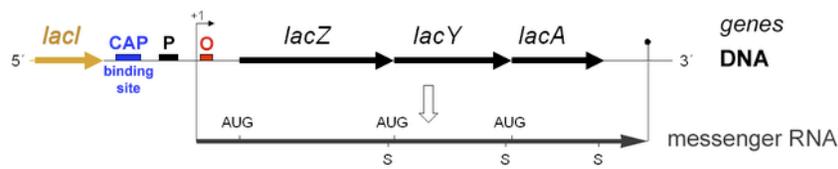
# Gene Regulatory Networks



Francois Jacob (1920-) and Jacques Monod (1910-1976)

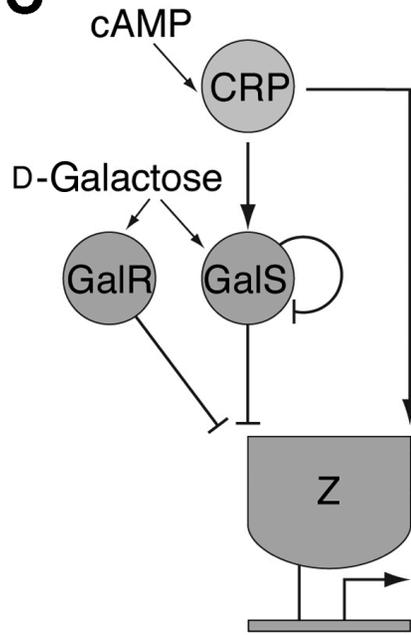
# Gene Regulatory Networks

The *lac* Operon and its Control Elements

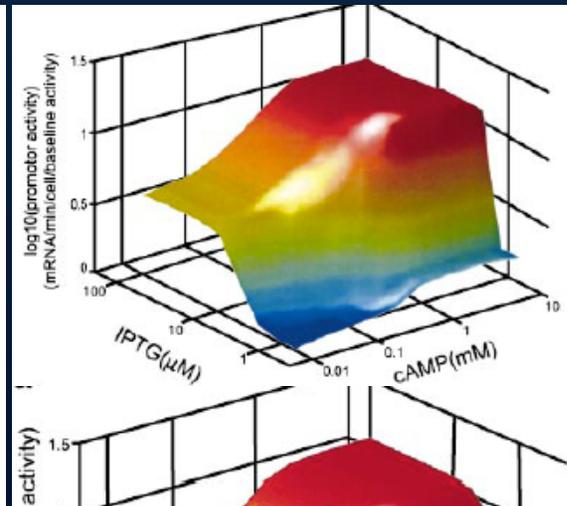


CAP protein RNA polymerase

C



Low glucose  
Lactose available  
High glucose  
Lactose unavailable



Emphasizes explicit, quantitative modeling of gene regulation

Uses the concept of “network motif” as a design unit (approach borrowed from electrical engineering)



Uri Alon

# Gene Regulatory Networks

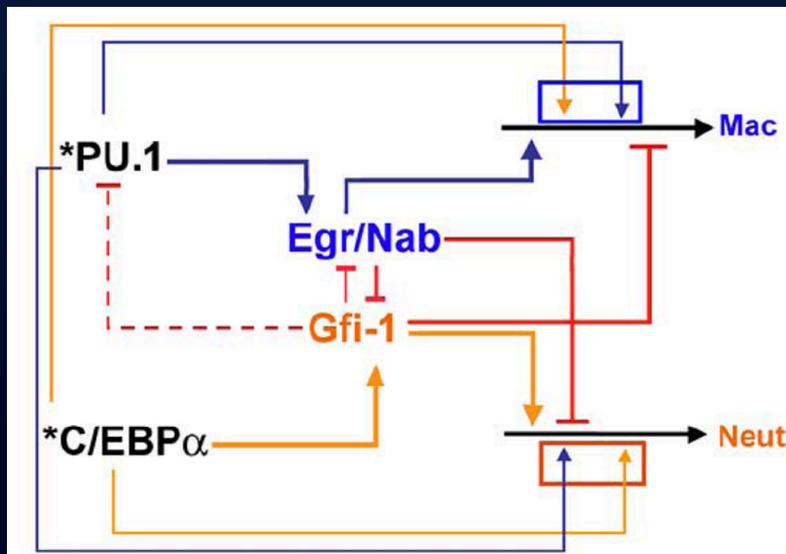
## Construction of a genetic toggle switch in *Escherichia coli*

Timothy S. Gardner\*†, Charles R. Cantor\* & James J. Collins\*†

\* Department of Biomedical Engineering, † Center for BioDynamics and ‡ Center for Advanced Biotechnology, Boston University, 44 Cummington Street, Boston, Massachusetts 02215, USA

$$\frac{du}{dt} = \frac{\alpha_1}{1 + v^\beta} - u$$

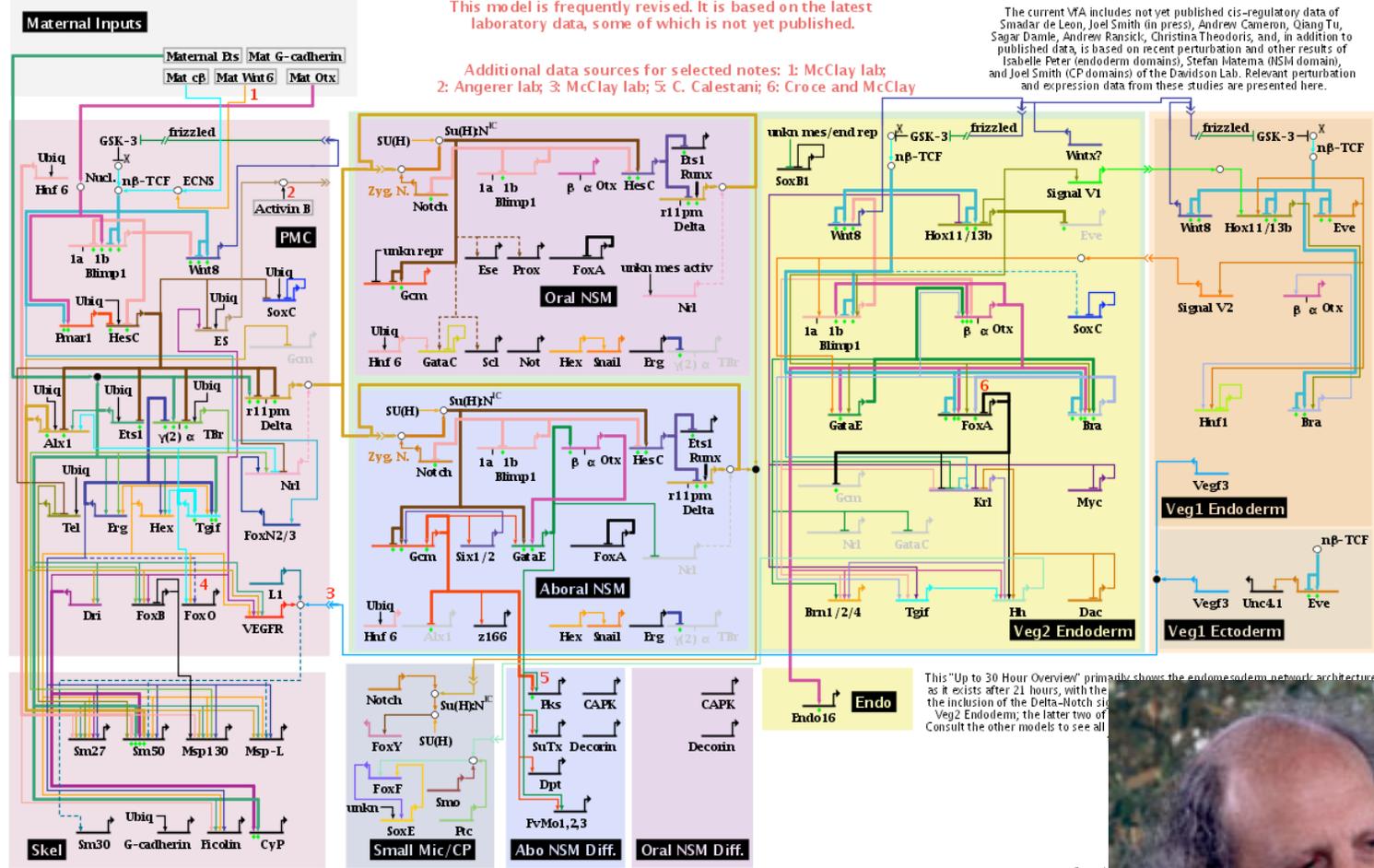
$$\frac{dv}{dt} = \frac{\alpha_2}{1 + u^\gamma} - v$$



Re-acquaints biology with the engineering concept of bi-stability (Max Delbrück introduced it first)

Endomesoderm Specification up to 30 Hours

August 12, 2010



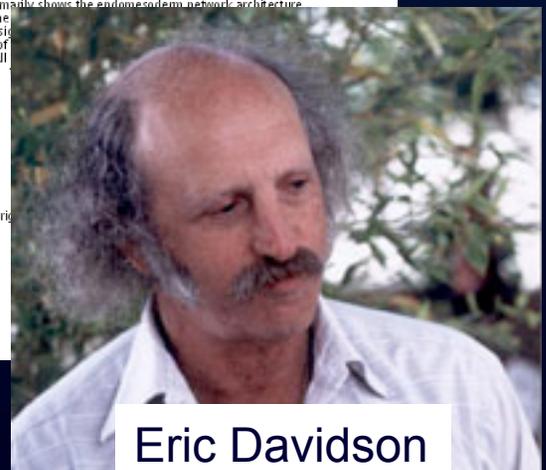
This model is frequently revised. It is based on the latest laboratory data, some of which is not yet published.

Additional data sources for selected notes: 1: McClay lab; 2: Angerer lab; 3: McClay lab; 5: C. Calestani; 6: Croce and McClay

The current MFA includes not yet published cis-regulatory data of Smadar de Leon, Joel Smith (in press), Andrew Cameron, Qiang Tu, Sagar Damle, Andrew Ransick, Christina Theodoris, and, in addition to published data, is based on recent perturbation and other results of Isabelle Peter (endoderm domains), Stefan Hiltens (NSM domain), and Joel Smith (CP domains) of the Davidson Lab. Relevant perturbation and expression data from these studies are presented here.

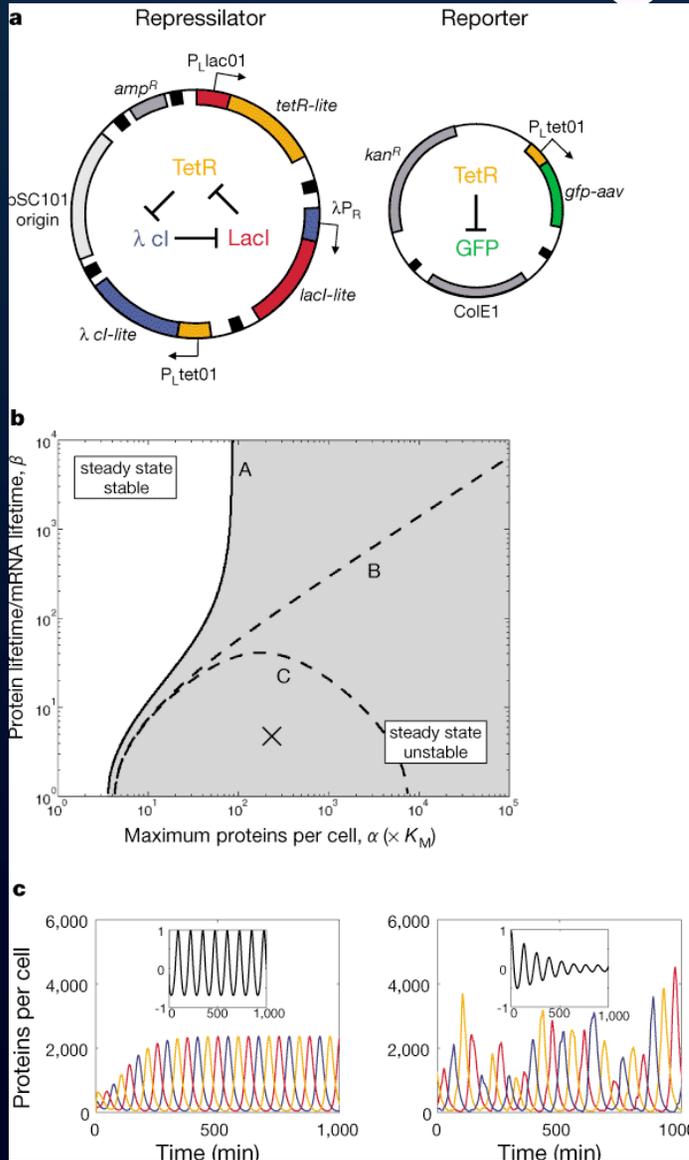
This 'Up to 30 Hour Overview' primarily shows the endomesoderm network architecture as it exists after 21 hours, with the inclusion of the Delta-Notch signaling pathway in the Veg2 Endoderm; the latter two of Consult the other models to see all

Scaling up to more complicated, spatiotemporal performance objectives



Eric Davidson

# Gene Regulatory Networks

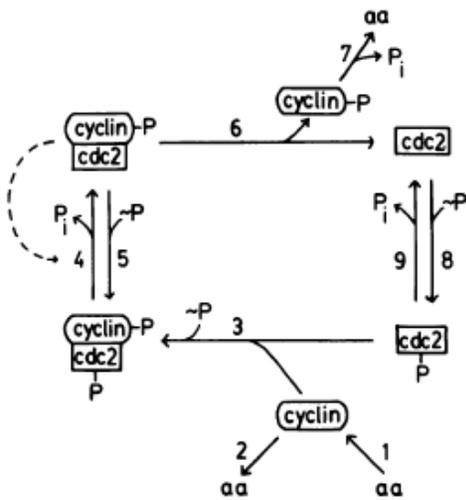


Synthetic biology; learning by building



Michael Elowitz

# Grow



$$du/dt = k_4(v - u)(\alpha + u^2) - k_6u$$

$$dv/dt = (k_1[aa]/[CT]) - k_6u.$$



John Tyson

$$\frac{dactCycA}{dt} = (k_{1ap} + k_{1app} \cdot TF_B) \cdot mass + (V_{da} + k_{daa}) \cdot Tri_A - (V_{da} + k_{dae} \cdot freeCKI) \cdot actCycA$$

$$\frac{dactCycE}{dt} = V_{1b} \cdot mass + V_{25} \cdot (CycB - Tri_B - actCycB) + (k_{dbb} + V_{da}) \cdot (CycB - preMPPF - actCycB) - (V_{db} + V_{wee} + k_{dab} \cdot freeCKI) \cdot actCycE$$

$$\frac{dactCycB}{dt} = (k_{1ep} + k_{1epp} \cdot TF_B) \cdot mass + (V_{da} + k_{dae}) \cdot Tri_B - (V_{da} + k_{dae} \cdot freeCKI) \cdot actCycB$$

$$\frac{dCycA}{dt} = (k_{1ap} + k_{1app} \cdot TF_B) \cdot mass - V_{da} \cdot CycA$$

$$\frac{dCycE}{dt} = V_{1b} \cdot mass - V_{db} \cdot CycE$$

$$\frac{dCycB}{dt} = (k_{1ep} + k_{1epp} \cdot TF_B) \cdot mass - V_{da} \cdot CycB$$

$$\frac{dCdh1}{dt} = \frac{(k_{ahp} + k_{ahpp} \cdot Cdc14) \cdot (1 - Cdh1) \cdot (k_{1ap} + k_{1app} \cdot actCycA + k_{1ebp} \cdot actCycB + k_{1ebpp} \cdot actCycE + k_{1ebpppp} \cdot CycD) \cdot Cdh1}{J_{ah1} + 1 - Cdh1}$$

$$\frac{dCKI}{dt} = V_{s} - V_{a} \cdot CKI$$

$$\frac{dTri_B}{dt} = k_{ab} \cdot (CycB - Tri_B) \cdot freeCKI - (k_{dbb} + V_{db} + V_{da}) \cdot Tri_B$$

$$\frac{dpreMPPF}{dt} = V_{wee} \cdot (CycB - preMPPF) - (V_{25} + V_{db}) \cdot preMPPF$$

$$\frac{dAPCP}{dt} = \frac{k_{apc} \cdot actCycB \cdot (1 - APCP)}{J_{apc} + 1 - APCP} - \frac{k_{apc} \cdot APCP}{J_{apc} + APCP}$$

$$\frac{dCdc20_A}{dt} = \frac{k_{a20} \cdot APCP \cdot (Cdc20_T - Cdc20_A)}{J_{a20} + Cdc20_T - Cdc20_A} \cdot \left( \frac{k_{120}}{J_{120} + Cdc20_A} + k_{a20} \right) \cdot Cdc20_A$$

$$\frac{dCdc20_T}{dt} = \frac{k_{120} + k_{120pp} \cdot actCycB^n}{J_{20}^n + actCycB^n} - k_{a20} \cdot Cdc20_T$$

$$CycD = CycD^0 \cdot mass$$

$$V_{af} = k_{afp} + k_{afpp} \cdot actCycA + k_{afpppp} \cdot actCycE + k_{afppppp} \cdot CycD$$

$$TF_B = GK(V_{af}, k_{1ep} + k_{1epp} \cdot actCycB + k_{1epppp} \cdot actCycE, J_{af}, J_{ep}, J_{ep})$$

$$V_{da} = k_{dap} + k_{dapp} \cdot actCycE + k_{dapppp} \cdot actCycA + k_{dappppp} \cdot actCycB$$

$$V_{db} = k_{dbp} + k_{dbpp} \cdot Cdc20_A + k_{dbpppp} \cdot Cdc20_T$$

$$Cdc14 = Cdc20_A$$

$$TF_i = GK(k_{af}, Cdc14, k_{1ep} + k_{1epp} \cdot actCycB, J_{af}, J_{ep})$$

$$V_{si} = k_{1ep} + k_{1epp} \cdot TF_i$$

$$V_{da} = \frac{k_{dap} + k_{dapp} \cdot actCycA + k_{dapppp} \cdot actCycB + k_{dappppp} \cdot actCycE + k_{dapppppp} \cdot CycD}{1 + k_{14a} \cdot Cdc14}$$

$$Tri_A = CycA - actCycA$$

$$Tri_B = CycB - actCycE$$

$$freeCKI = CKI - Tri_B - Tri_A - Tri_B$$

$$TF_B = GK(k_{af}, actCycB, k_{1ep}, J_{af}, J_{ep})$$

$$V_{1b} = k_{1bp} + k_{1bpp} \cdot TF_B$$

$$V_{db} = k_{dbp} + k_{dbpp} \cdot Cdh1 + k_{dbpppp} \cdot Cdc14$$

$$Weel = GK(k_{aweep} + k_{awepp} \cdot Cdc14, V_{wee}, k_{weep} + k_{wepp} \cdot Weel)$$

$$Cdc25 = GK(k_{a25} \cdot actCycB, k_{125p} + k_{125pp} \cdot actCycB, J_{a25})$$

$$V_{25} = k_{25p} + k_{25pp} \cdot Cdc25$$

$$BB(A1, A2, A3, A4) = A2 - A1 + A3 - A2 + A4 - A3$$

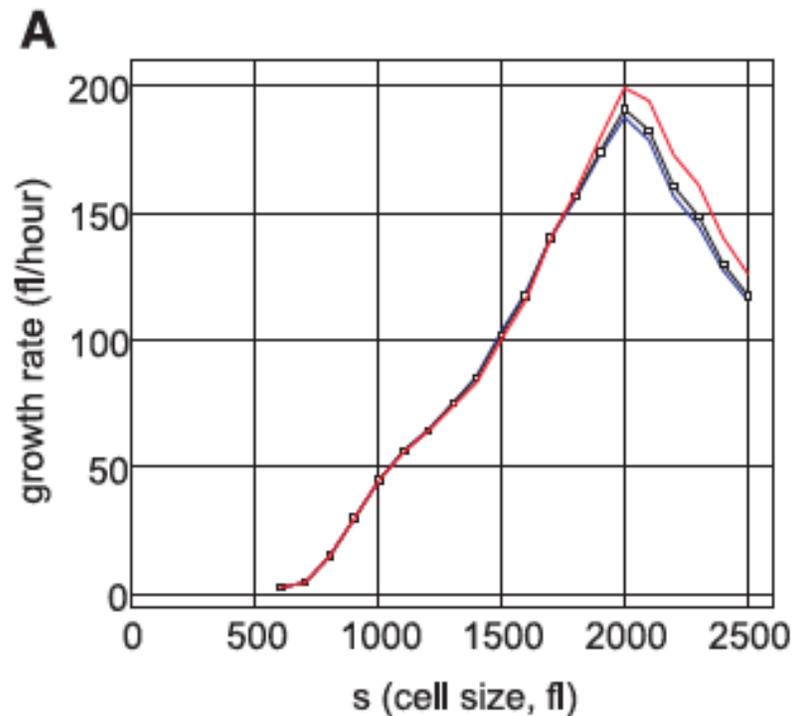
$$GK(A1, A2, A3, A4) = \frac{2 \cdot A4 \cdot A1}{BB(A1, A2, A3, A4) + \sqrt{BB(A1, A2, A3, A4)^2 - 4 \cdot (A2 - A1) \cdot A4 \cdot A1}}$$

Focus on precision and robustness; predictive modeling; stochastic effects

# Growth Control

## Cell Growth and Size Homeostasis in Proliferating Animal Cells

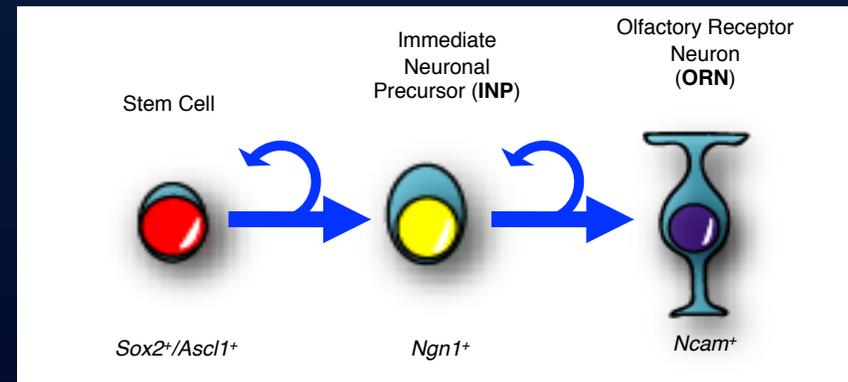
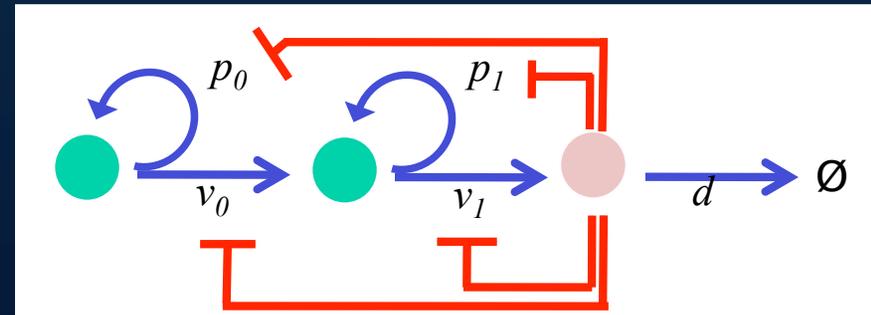
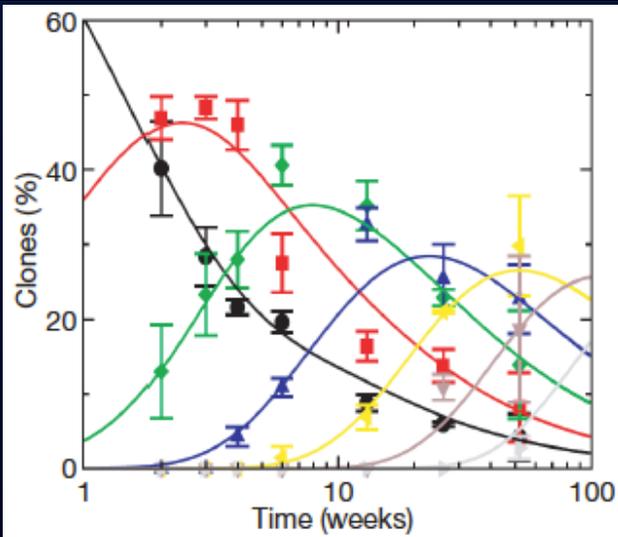
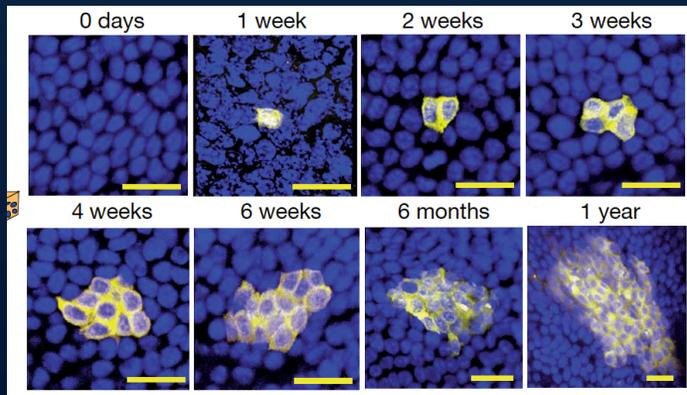
Amit Tzur,<sup>1\*</sup> Ran Kafri,<sup>1\*</sup> Valerie S. LeBleu,<sup>2</sup> Galit Lahav,<sup>1</sup> Marc W. Kirschner<sup>1†</sup>



Marc Kirschner

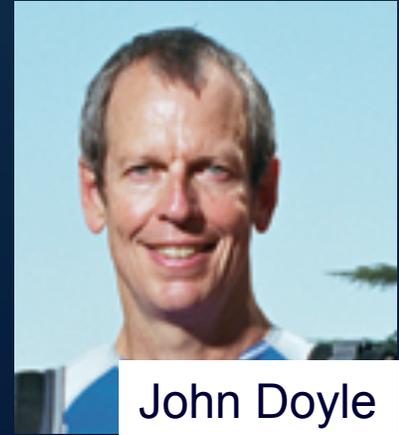
Emphasis on careful measurement; extracting parameters; testing models; stochastic effects

# Growth Control



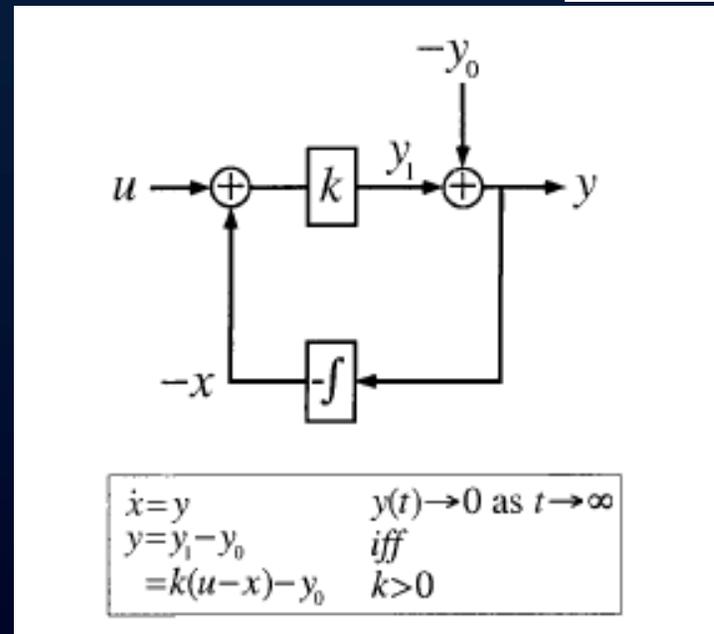
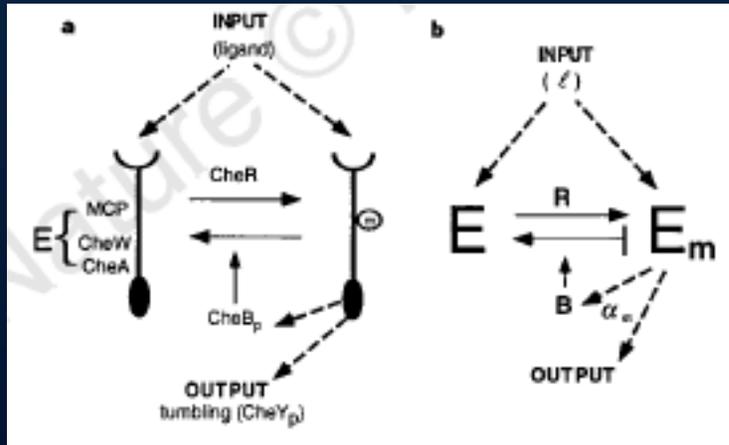
Focus on lineage progression;  
feedback control; robustness;  
stochastic events

# Transport Processes



John Doyle

## *E. Coli* chemotaxis



$$\begin{aligned} \dot{x} &= y & y(t) &\rightarrow 0 \text{ as } t \rightarrow \infty \\ y &= y_1 - y_0 & \text{iff} & \\ &= k(u - x) - y_0 & k > 0 & \end{aligned}$$



Stan Leibler

Robustness, integral feedback control, noise filtering, optimal strategies

# Transport Processes

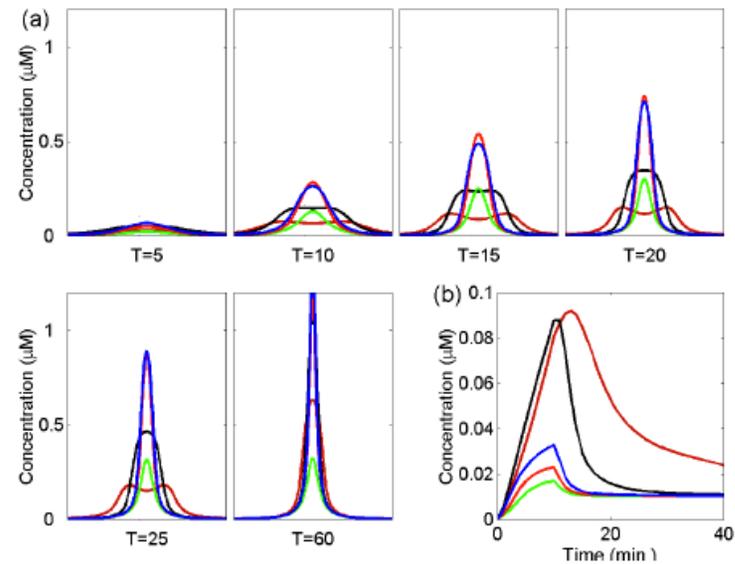
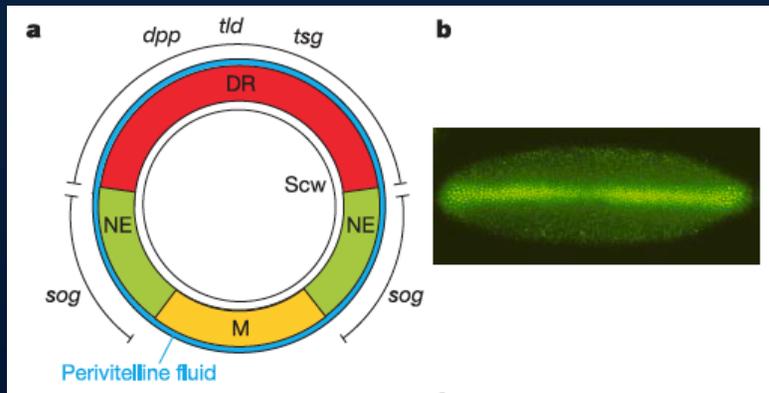


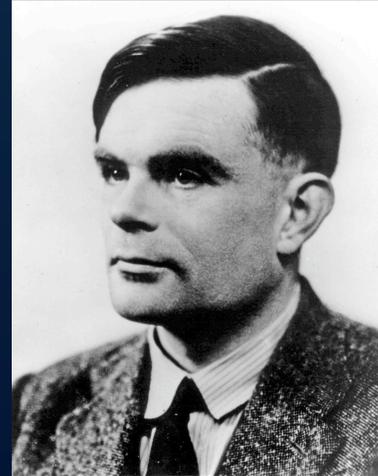
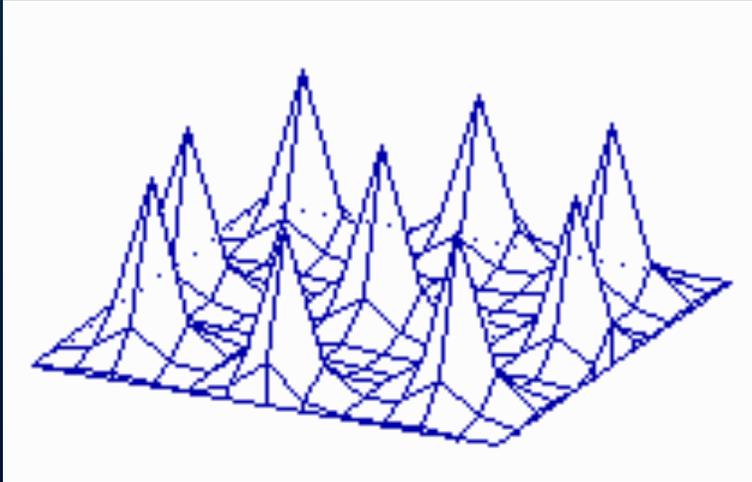
Figure 3: (a) Sew profiles at different times for the reference system (blue), Tld overexpression (dark red) and Sog (black), Sew (green) and Tld (red) heterozygous systems.



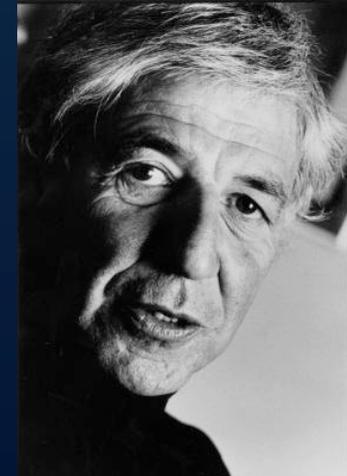
Naama Barkai

Diffusion, robustness, precision,  
timing

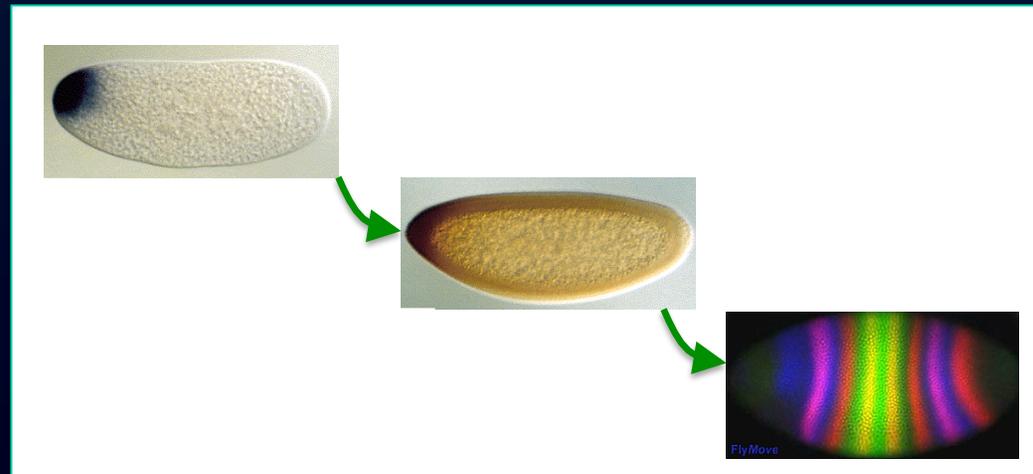
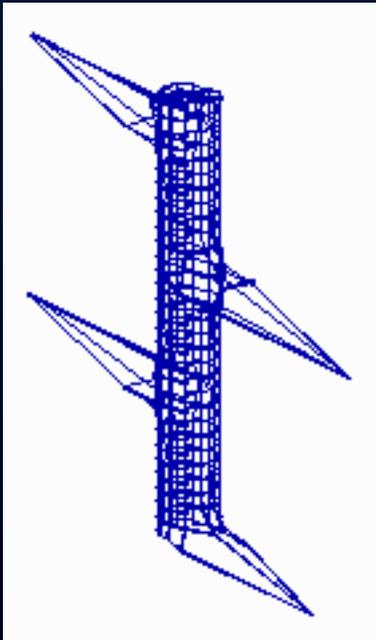
# Pattern Formation



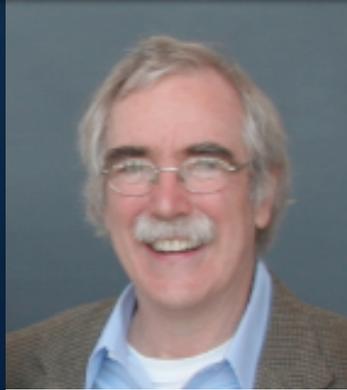
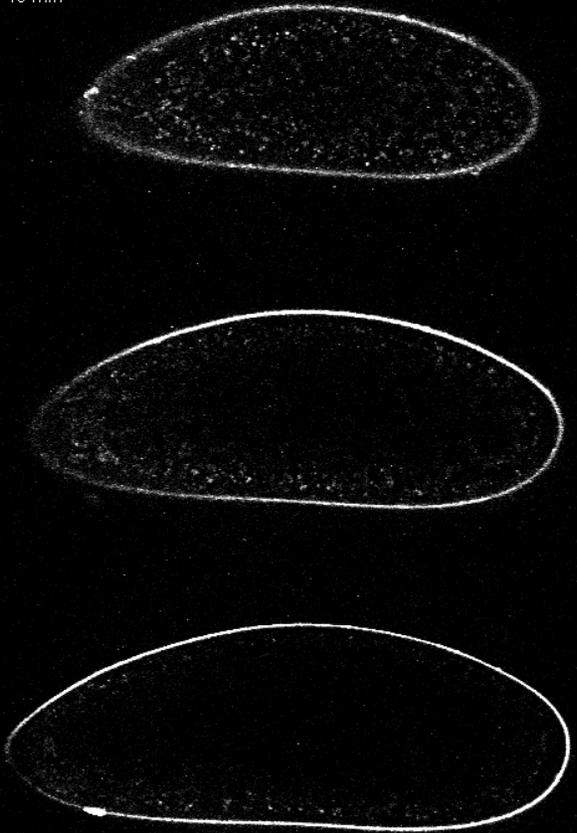
Alan Turing



Lewis Wolpert



40 min



Eric Wieschaus

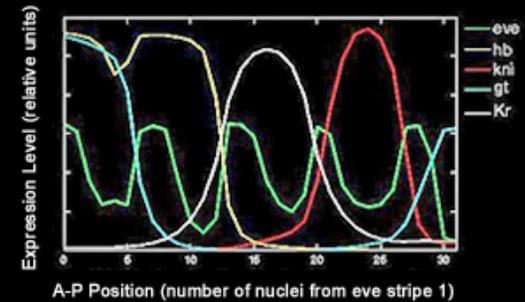
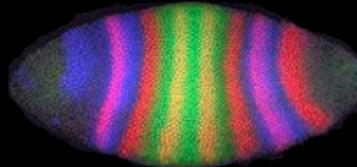
# Pattern Formation

Spatial dynamics; diffusion; scaling; precision;



John Reinitz

$$\frac{dv_i^a}{dt} = R_a g_a \left( \sum_{b=1}^N T^{ab} v_i^b + m^a v_i^{bcd} + h^a \right) + D(n) [(v_{i-1}^a - v_i^a) + (v_{i+1}^a - v_i^a)] - \lambda_a v_i^a$$

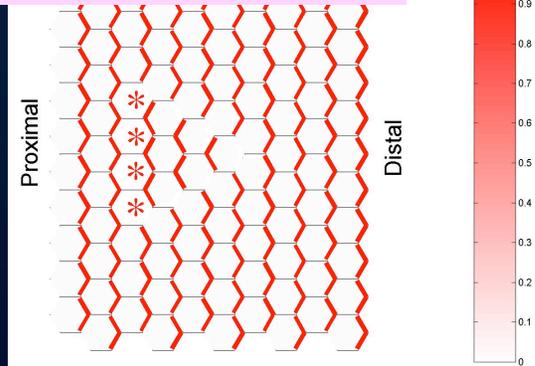
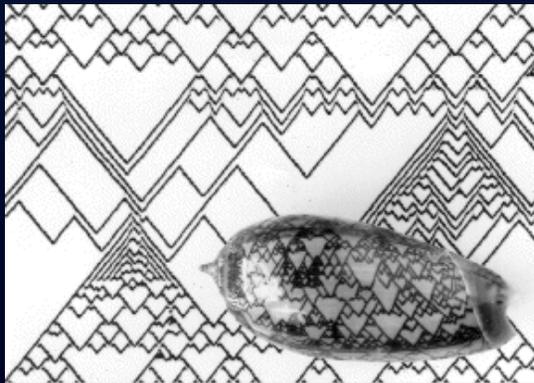


# Pattern Formation

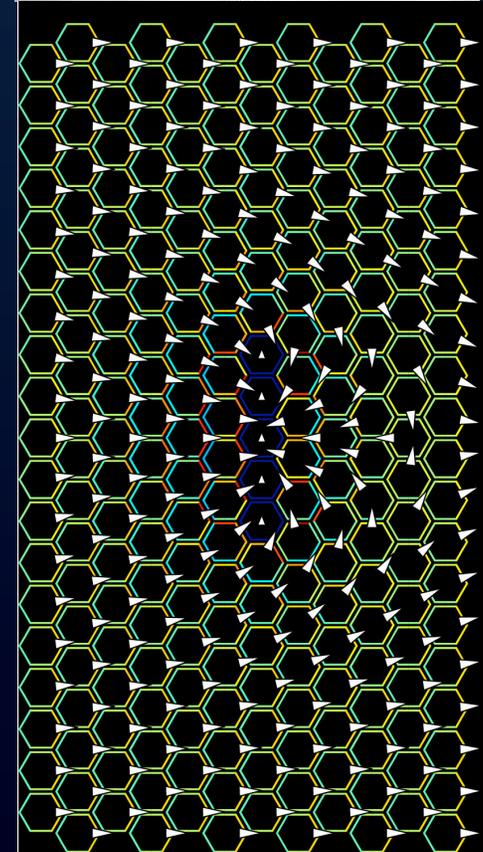
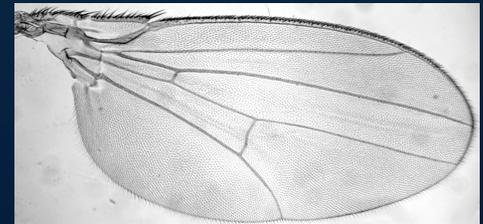
Reaction/diffusion mechanisms;  
Discrete vs. continuous modeling;  
phenomenological vs. explicit  
modeling



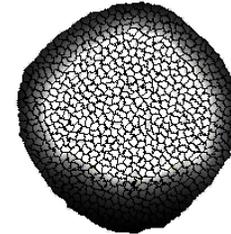
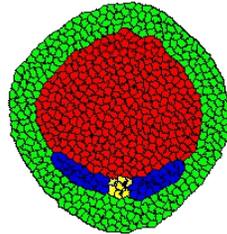
Hans Meinhardt



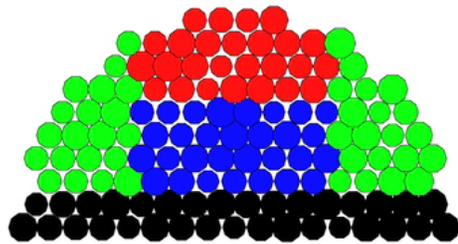
Clare Tomlin



# Morphogenesis



Agent based modeling; multiscale  
and hybrid modeling



Elliott Meyerowitz

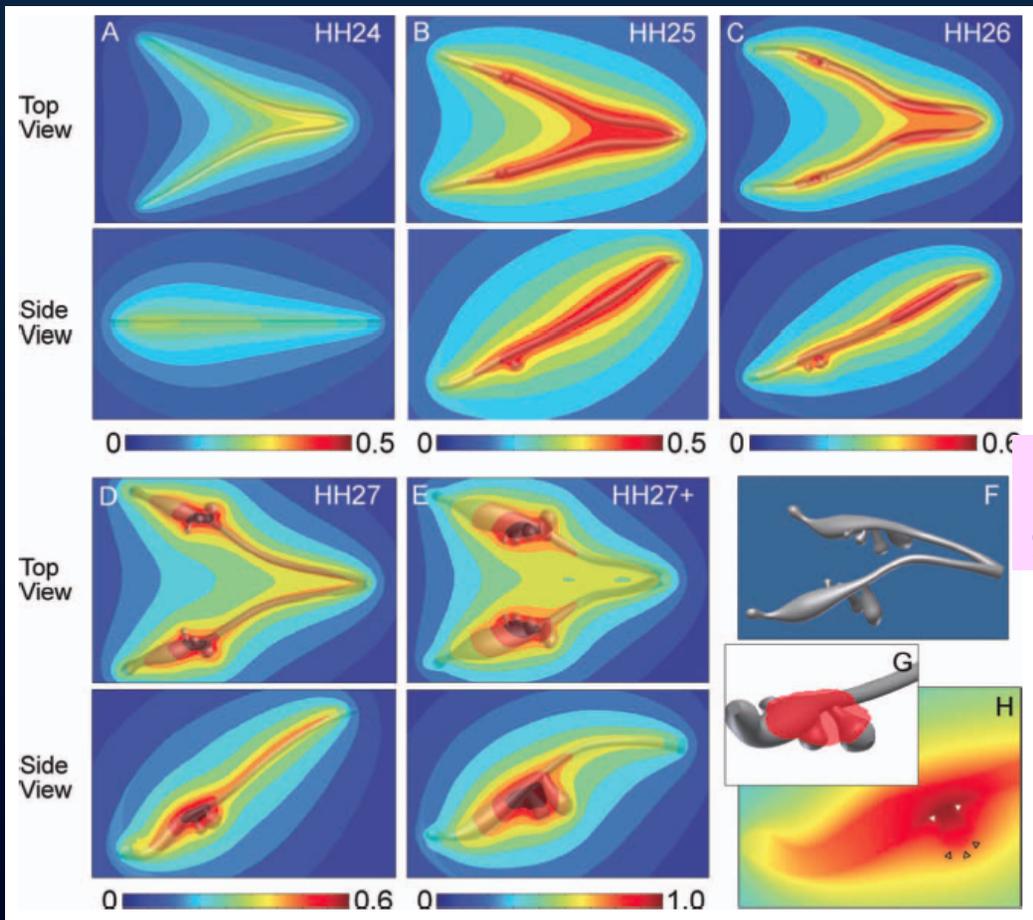


James Glazier

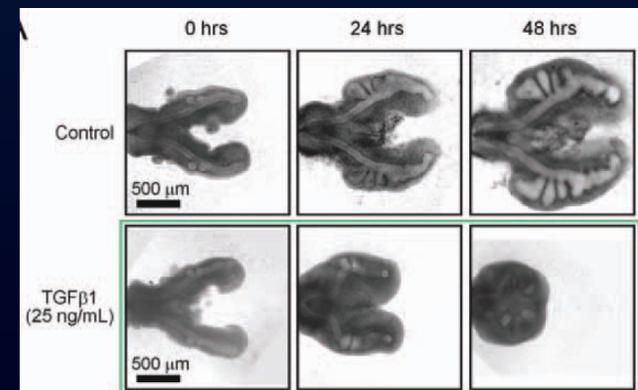
# Morphogenesis



Celeste Nelson



Interaction between mechanics, gradients and growth control



# Major Themes in Systems Biology

- 1. Understanding biological regulation

- Metabolic control
- Signaling networks
- Gene regulatory networks
- Growth control
- Transport processes
- Pattern formation
- Morphogenesis

*Often approximated as  
“well-stirred”*

*Explicitly spatial*

# Major Themes in Systems Biology

- 2. Inferring the details of complex processes
  - High throughput data acquisition
  - Statistical analysis of large-scale data
  - Statistical inference
  - Model fitting and predictive modeling

# High Throughput Data Acquisition

- DNA sequencing
  - Genomics, metagenomics
- Transcriptional profiling
  - Microarrays, RNAseq
- Proteomics, glycomics, lipidomics, metabolomics
- Chromosomal occupancy and structure (ChIP-chip, ChIP-seq, 3C, 4C, ChIA-PET, etc.)
- Epigenomics (DNA and histone modification)

# High Throughput Data Acquisition

- Fluorescence activated cell sorting
- Automated quantitative microscopy
- High throughput gene interaction screens
- High throughput RNAi screens
- Phenome projects
- Literature mining (classification, gene ontology, database integration)

# Challenges of analyzing high-throughput data

- Visualization: even simple relationships in large-scale data can't always be spotted by eye
- Potential complexity: “Hi-dimensional” data means a combinatorial explosion of possible relationships
- Classical statistical methods were mostly developed for dealing with simple relationships in low-dimensional data

# Statistical Analysis of Large Scale Data

- **Bioinformatics**

- Ways of finding correlations (structure) in the data: **Clustering, correlation of sequence data, expression data, gene interaction data, phenotypic data, time course data**
- Ways of testing significance: **Statistical hypothesis testing (e.g. microarray, RNA seq, and Chip-seq statistics, etc.)**
- Data visualization

# Examples of Statistical Inference

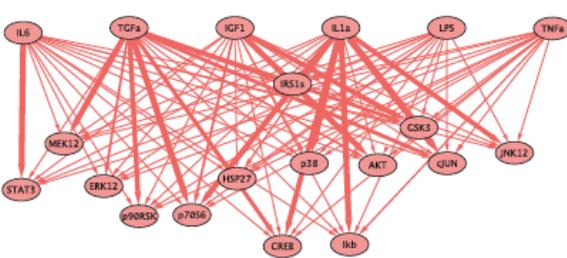
- Computational phylogenetics
- Identification of conserved, putative regulatory sequences
- Functional clustering: inferring gene-gene, and protein-protein interaction networks from various kinds of data sets
  - Frequentist vs. Bayesian approaches
  - Machine learning
- Genome wide association studies (GWAS)

# Model fitting and predictive modeling

a. Primary Hepatocytes



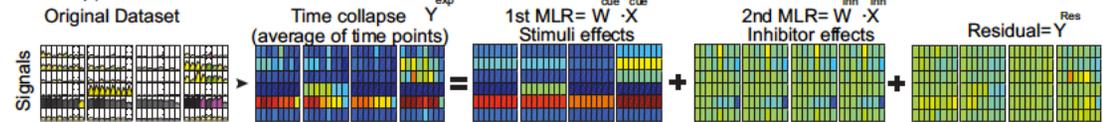
b. HepG2 cells



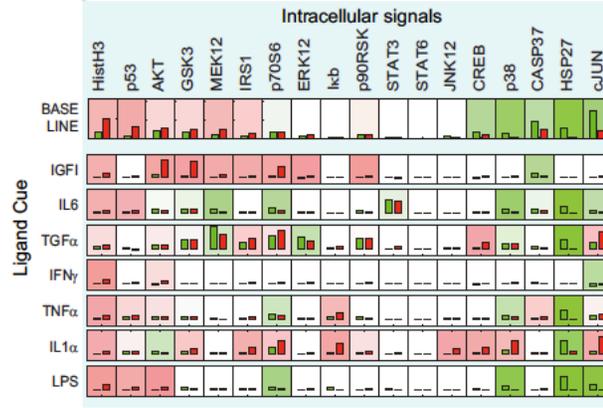
Networks Inferred from Biochemical Data Reveal Profound Differences in Toll-like Receptor and Inflammatory Signaling between Normal and Transformed Hepatocytes\*

Leonidas G. Alexopoulos<sup>1,2,3,4</sup>, Julio Saez-Rodriguez<sup>1,2,3,4</sup>, Benjamin D. Cosgrove<sup>5</sup>, Douglas A. Lauffenburger<sup>5</sup>, and Peter K. Sorger<sup>1,2,3,4</sup>

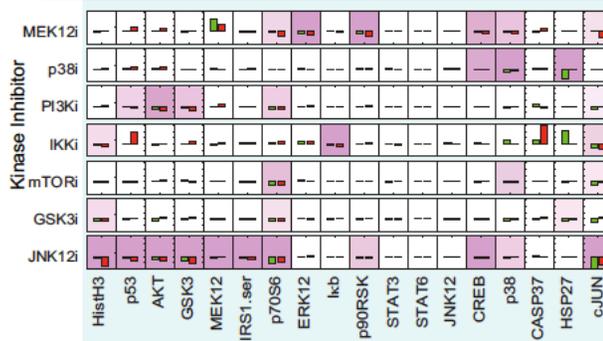
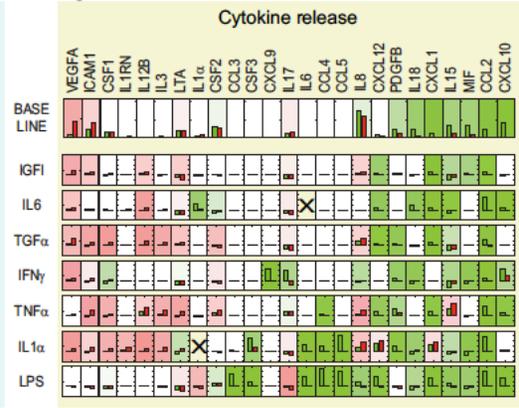
a. MLR Approach



b. Regression coefficients



c. Regression coefficients



HepG2 → Phenotype → Hepatocyte

Weak > Inhibition > Strong

# Major Themes in Systems Biology

- 3. Probing the constraints and limits of biological performance
  - Exploring model behaviors
  - Elucidating physical and engineering constraints
  - Understanding the consequences of variation and selection



# Elucidating physical and engineering constraints

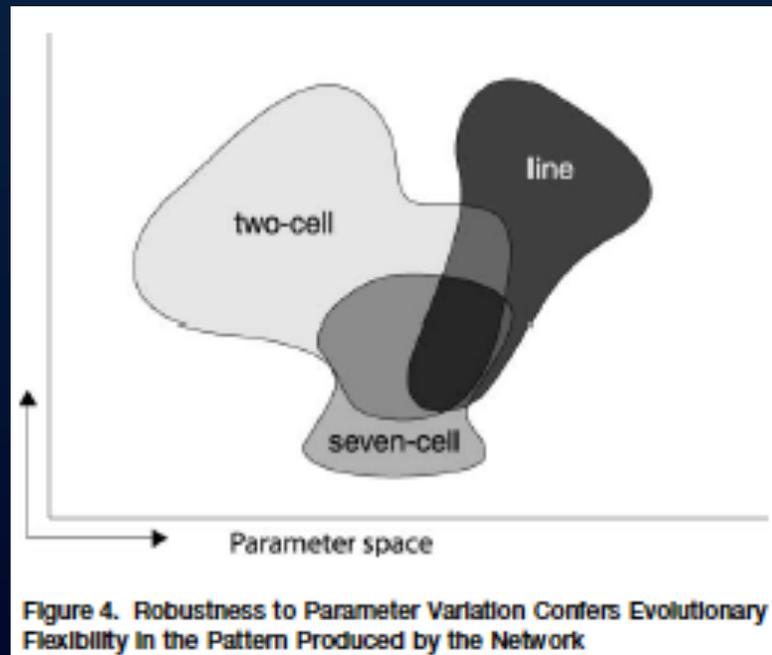
- **Physics**
  - Transport limits, timing limits, biochemical stochasticity, bursty gene expression
- **Engineering**
  - Interference among performance objectives
  - Conservation of fragility
  - Highly Optimized Tolerance

# Understanding the consequences of variation and selection

- Using optimality assumptions to simplify modeling
  - Flux Balance Analysis
  - Assuming that, if parameter space exploration finds a significantly large region in which a desirable behavior occurs, nature will likely find it, relieving the investigator of some of the need to measure parameters.

# Understanding the consequences of variation and selection

- **Evolvability**



## Robustness, Flexibility, and the Role of Lateral Inhibition in the Neurogenic Network

Eli Meir,<sup>1,2,3</sup> George von Dassow,<sup>1,2</sup> Edwin Munro,<sup>2</sup> and Garrett M. Odell<sup>1,2</sup>

Current Biology, Vol. 12, 778-786, May 14, 2002.

# Understanding the consequences of variation and selection

- Tradeoffs between robustness and evolvability
- Game theoretical approaches
- Optimal behaviors in fluctuating environments
  - Population diversification strategies
- Causes and consequences of genetic epistasis (combinatorialism)

# Cultural Change Associated with Systems Biology

- Molecular biologists are defining their work less and less by things (molecules, cells, tissues, organs) and more by processes.
- A richer variety of questions is being asked, including more teleological ones.
- Fields that once seemed irrelevant to molecular and cellular biology are newly important (physiology, evolution, ecology).
- More physicists, engineers and computer scientists are moving into biology

# Cultural Change Associated with Systems Biology

- Biologists are finding it much harder to avoid mathematics
- Biologists now have a strong incentive to engage in interdisciplinary collaboration
- Journals and funding agencies are struggling to fairly review Systems Biology proposals
  - Nevertheless, Systems Biology is doing extremely well in terms of publications, grant acquisition and job availability

# What is the future of Systems Biology?

- Potential breakthrough areas
  - “Personalized medicine”
  - Synthetic biology
  - Drug design
  - Therapeutics for complex, common diseases
  - Bio-inspired engineering

# What is the future of Systems Biology?

- Meaty research problems (selected)
  - Performance tradeoffs and their causes
  - Spatial dynamics (at all levels)
  - Are network motifs a useful “unit of design”?
  - Is biology really modular?
  - Better methods for network reconstruction
  - More efficient approaches for stochastic and multi-scale modeling.

A Short Course in  
**SYSTEMS BIOLOGY:**  
Morphogenesis & Spatial Dynamics



Organization of the Course

# Research Themes

Intracellular  
signaling  
(**Bardwell**)

Growth  
control  
(**Lander**)

Cellular  
decision-  
making  
(**Tyson,**  
**Cinquin**)

Morphogen  
gradients and  
patterning  
(**Lander**)

Morpho-  
genesis  
(**Nelson**)

Gene  
regulation  
(**Mortazavi**)

Cancer  
(**Waterman**)

# Analytical Methodologies

Dynamical  
Systems  
Methods  
(Enciso,  
Bardwell,  
Nie,  
Mjolsness)

Bio-  
informatics  
(Baldi,  
Mortazavi)

Discrete and  
Stochastic  
Modeling  
(Mjolsness,  
Encisco)

Reaction-  
diffusion  
modeling  
(Nie,  
Lowengrub)

Gene  
regulatory  
networks  
(Baldi, Nie)

# Data Gathering Methods

Fluorescence  
microscopy  
(Digman)

Fluorescence  
Dynamics  
(Gratton)

DNA and  
RNA  
Sequencing  
(Mortazavi)

Image  
Analysis  
(Fowlkes)

Organ  
culture,  
whole-mount  
microscopy  
(Edwards,  
Calof,  
Lander)

A Short Course in  
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Morphogenesis & Spatial Dynamics



Questions?