Some Reflections on the Emergence of Molecular Systems Biology

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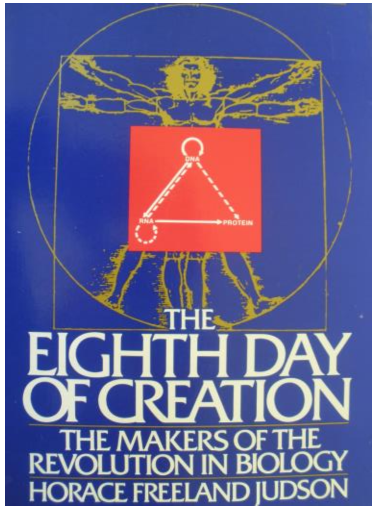


1952-1979

The Ninth Day (1980—2000): the triumphs of molecular genetics and genomics

Watershed: Millennial Issue of *Cell* (vol 100, 07 Jan 2000)

Paul Nurse, 'A long twentieth century of the cell cycle and beyond'

One of the major objectives in the next century should be a complete description and understanding of the eukaryotic cell cycle [*insert here your favorite aspect of cell biology*]. ... The aim should be to develop a full description of the molecular machines that make up the modules responsible for the different steps of cell cycle progression, to determine how these modules are linked together, and to demonstrate how their operation brings about the reproduction of the cell. … An important starting point for this program will be the whole genome sequences of simple [eukaryotes like yeasts]. … The next objective will be the description of the molecular machines required to execute cell cycle steps. … These machines then need to be linked and integrated together to define the modules and overall regulatory networks required to bring about the reproduction of the cell. This task will require system analyses that emphasize the logical relationships between elements of the networks, information flow between the modules, how the networks operate dynamically and spatially within the cell, and how more global cellular characteristics such as increase in cell mass or elapse of time interface with the cell cycle. … These **experimental analyses** will need to be complemented by new **data handling methodologies** and **fresh conceptual approaches**, both to deal with the high level of information generated, and to gain insight into how the regulatory networks and molecular machines actually operate. … We imagine molecular mechanisms and cellular functions in terms of mind pictures of objects interacting with each other like tiny billiard balls organized together in linear causal pathways. This common sense view has difficulty dealing both with regulatory networks in which linear causality might not be the dominating feature, and with phenomena that exhibit complex changes in space and time. Dealing with these system properties, which ultimately must underlie our understanding of all cellular behavior, will require more abstract conceptualization than biologists have been used to in the past. … Perhaps a proper understanding of the complex regulatory networks making up cellular systems like the cell cycle will require a similar shift from common sense thinking. We might need to move into a strange more abstract world, more readily analyzable in terms of mathematics than our present imaginings of cells operating as a microcosm of our everyday world.

The Tenth Day (2000—20xx): the ascent of molecular systems biology

- 'experimental analyses' – quantitative biology
- 'data handling methodologies' – bioinformatics
- 'fresh conceptual approaches' – mathematical modeling

1. Some of the earliest successful applications of mathematical modeling in cell biology

A. Biochemistry: glycolytic oscillations (Chance, Hess)

Joseph Higgins (1967) The theory of oscillating reactions, Ind Eng Chem

B. Molecular genetics: lac operon (Jacob & Monod)

J.S. Griffith (1968) Mathematics of cellular control processes, J Theor Boil

2. Some early applications of math modeling not based on a knowledge of the underlying mechanism

A. Alan Turing (1952) The chemical basis of morphogenesis. Phil Trans R Soc Lond B

B. Art Winfree's topological studies of the circadian rhythm in fruit fly eclosion (1970s)

C. René Thom: bifurcation theory of Waddington's epigenetic landscape

3. Some early modeling of dynamically complex chemical reaction systems

A. The 'Brusselator': Prigogine & Lefever (1968)

B. The Belousov-Zhabotinsky reaction:

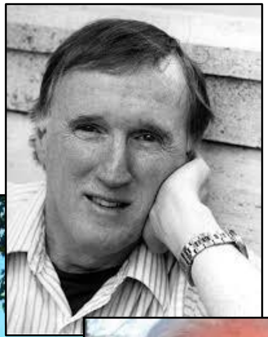
Oscill, bistability and traveling waves

C. Chemical computers?

Otto Rössler (1972) Z Naturforsch

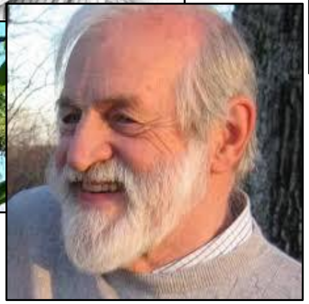
> "the class of chemical switches will provide promising candidates for a possible new technology of chemical reaction systems"

4. Theoretical and Mathematical Biology in 1980s



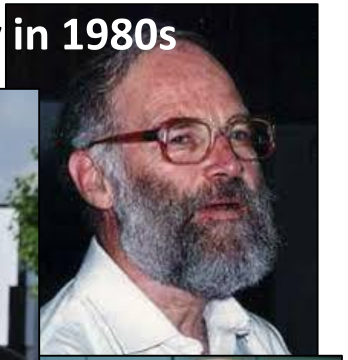
George Oster

Garry Odell



Jim Murray

Albert Goldbeter

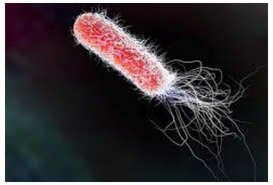


Lee Segel

Joel Keizer

The molecular biology revolution of the 1980s revealed molecular mechanisms ripe for modeling

Bacterial chemotaxis



Bray, Bourret & Simon (1993) Computer simul of phosph'n cascade…, Mol Biol Cell

21 biochemical reactions among 7 proteins

Rate constant values estimated from experimental data

Simulated chemotactic behavior of wt and mutant bacteria (46 strains; del & op)

Circadian rhythms

Goldbeter (1995) Model for circadian oscil in Drosophila PER protein, Proc R Soc Lond B

Leloup, Gonze & Goldbeter (1999) Models for circadian rhythms based on transcriptional regul …, J Biol Rhythms

Kim & Forger (2012) Robust circadian timekeeping via stoichiometric balance, Mol Syst Biol

Frog egg mitotic cycles

Novak & Tyson (1993) Numerical analysis of a comprehensive model…, J Cell Sci

10 nonlinear ODEs, 26 kinetic constants estimated to fit observations of Kirschner, Dunphy, Solomon, …

Predictions:

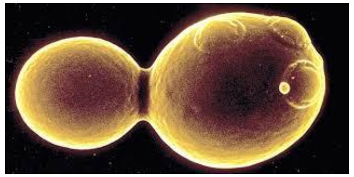
1) Bistability in extracts with a fixed concen of cyclin B

2) Unreplicated DNA raises the cyclin B threshold

3) Travel waves of MPF activation, speed ~50 μm/min

Confirmations: Jill Sible's group and Jim Ferrell's group

Growth-controlled cell cycles in budding yeast



Chen et al. (2000) Kinetic analysis of a model of yeast cell cycle, Mol Biol Cell

- 11 nonlinear ODEs, ~65 parameters
- Model fitted to quantitative phenotypes of wt and 50 mutant strains (~150 data values)

Kraikivski et al. (2015) Computational analysis of cell cycle control in budding yeast, NPJ Syst Biol Appl

- ~60 species and ~260 mutant strains

Gordon Research Conference on Theoretical Biology and Biomathematics, 1982