BIO304: Systems biology

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- Office hour: Thursday
- 10:20-11:50AM

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Week 1: 2/19/2018

What is systems biology?

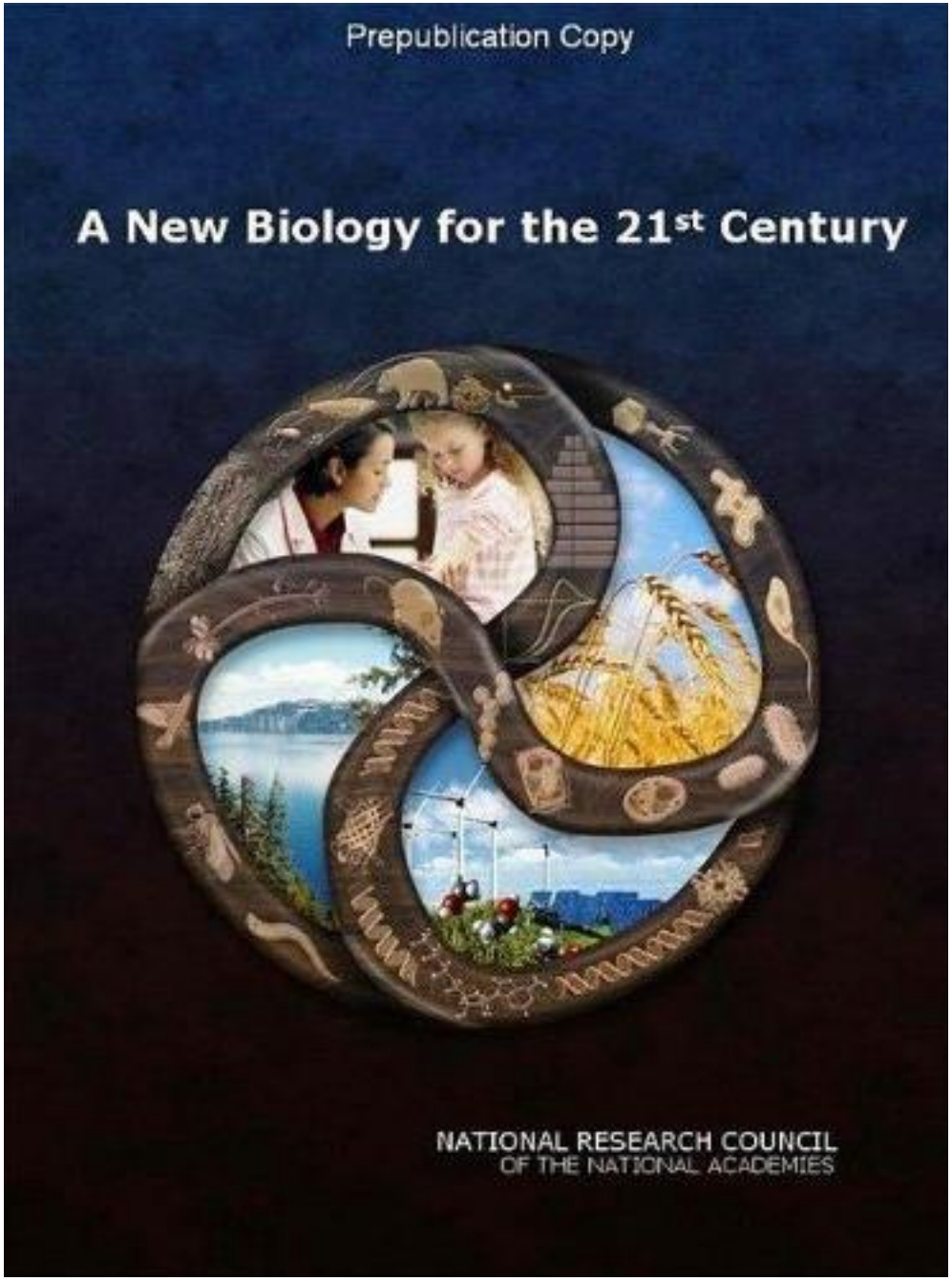
Welcome to the “New Biology”

A brief historical overview and necessity for systems biology

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.



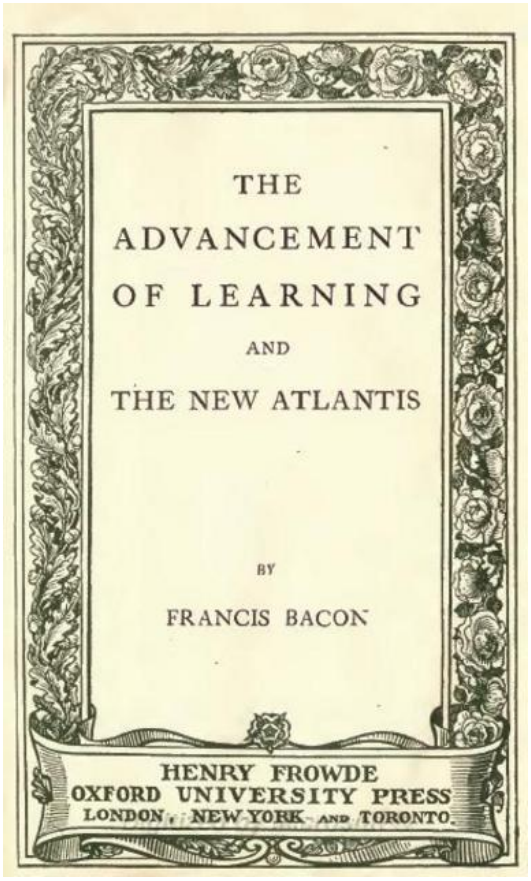
The essence of the New Biology, as defined by the committee, is integration—re-integration of the many sub-disciplines of biology, and the integration into biology of physicists, chemists, computer scientists, engineers, and mathematicians to create a research community with the capacity to tackle a 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

Biology is both a young and old discipline

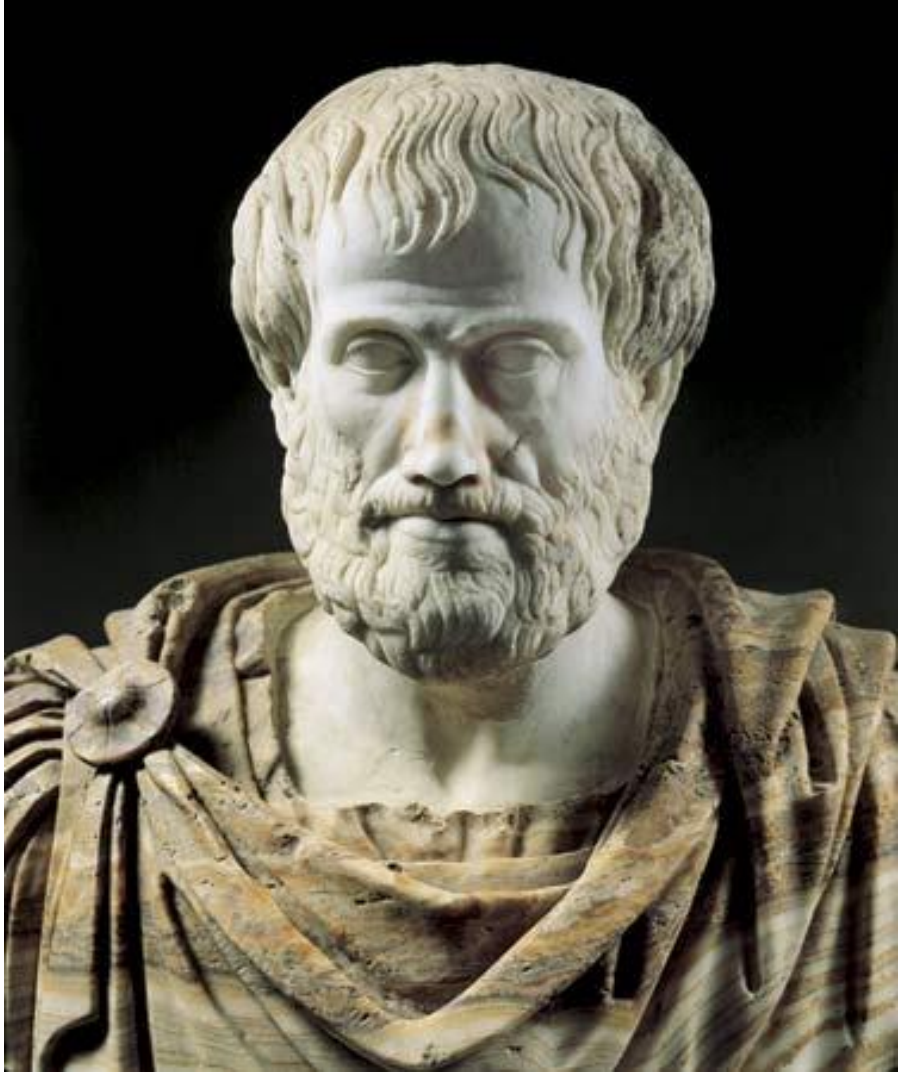
- Much of the “natural philosophy”, going back to the Greeks and before, dealt with the living world
- But biology wasn’t really a *separate* discipline until the late 18th Century; and the name “biology” didn’t come into use until the early 19th.

Physical sciences separated from biology as it settled upon a particular intellectual program.

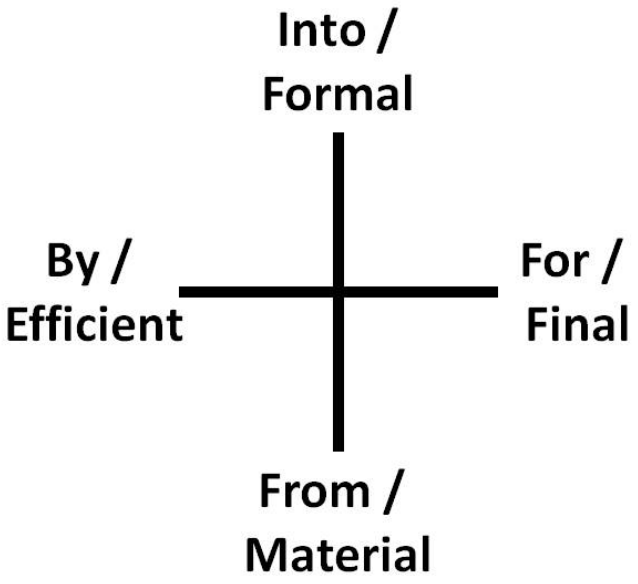


1605

…natural science "doth make inquiry, and take consideration of the same natures : but how? Only as to the material and efficient causes of them, and not as to the forms."



Aristotle's four "causes" 四因论



Bacon: Science was for mechanistic explanation: what are the materials and how do they cause the phenomenon. The scientist formulates mechanistic hypotheses, and then tests them.

Abandonment of *function* (for) cause in biology

- Physiology

  Explicitly focused on linking mechanism to function

- Developmental Biology

  Always about the function, goal-directness of embryogenesis

- Ecology

  Tinbergen's "four categories of explanation"

Molecular Biology

Milestones in Molecular Biology

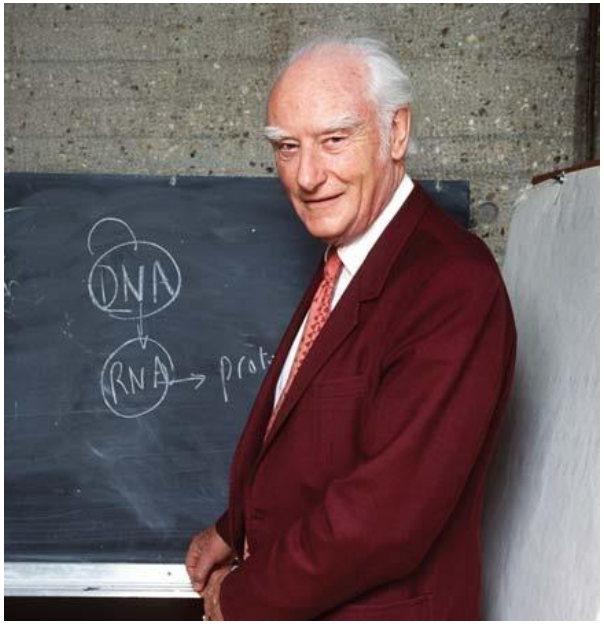
Genes are DNA (Avery et al., 1944)

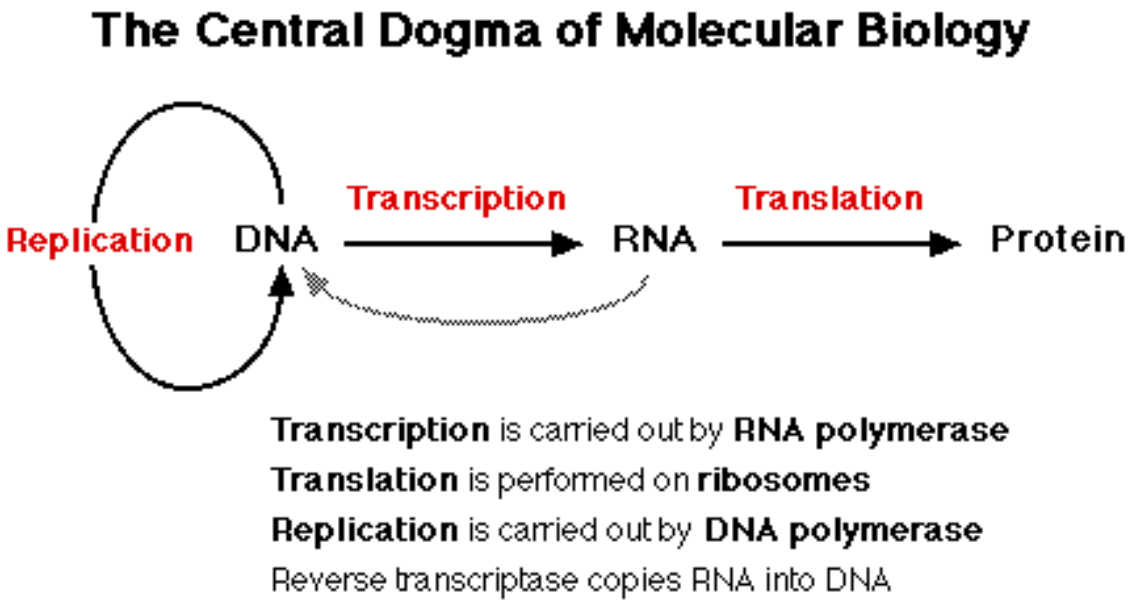
Genes encode enzymes (proteins) (Beadle and Tatum, 1941)

Cloning and sequencing

DNA is a 4-letter code (Crick and Watson, 1953)

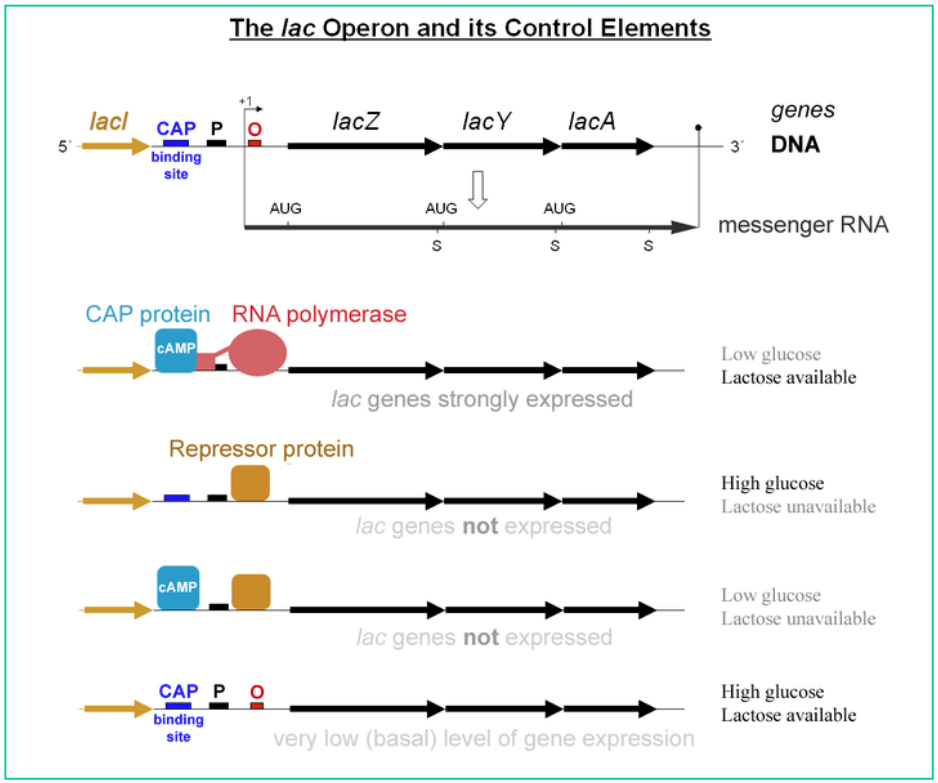
DNA code dictates the structures of proteins (Nirenberg, Khorana, Holley, 1961-1965)

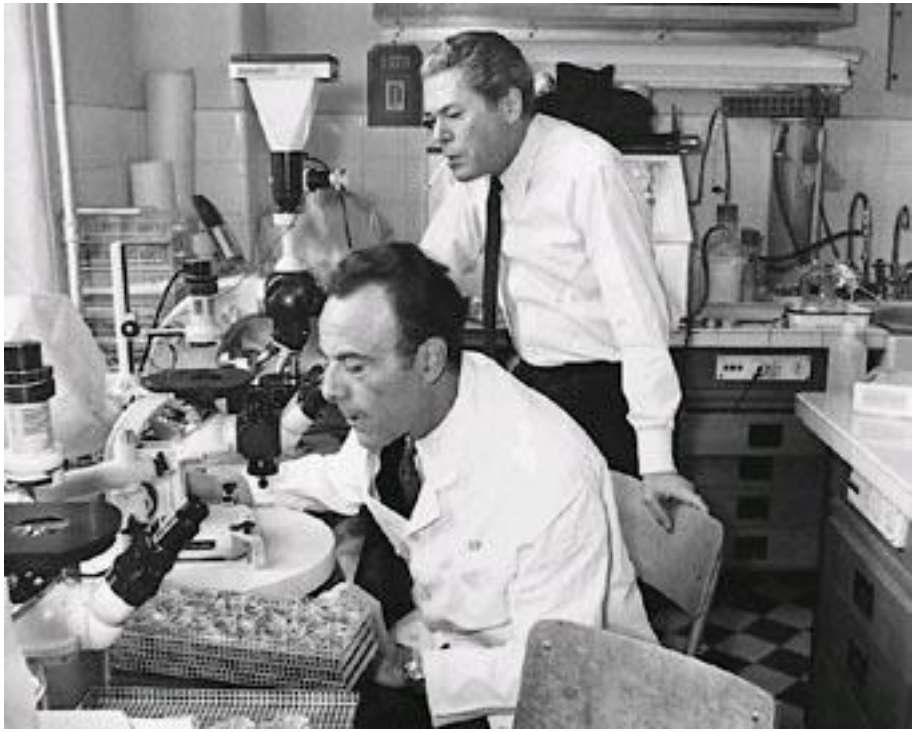




The Lac Operon

one of the high points of Molecular Biology



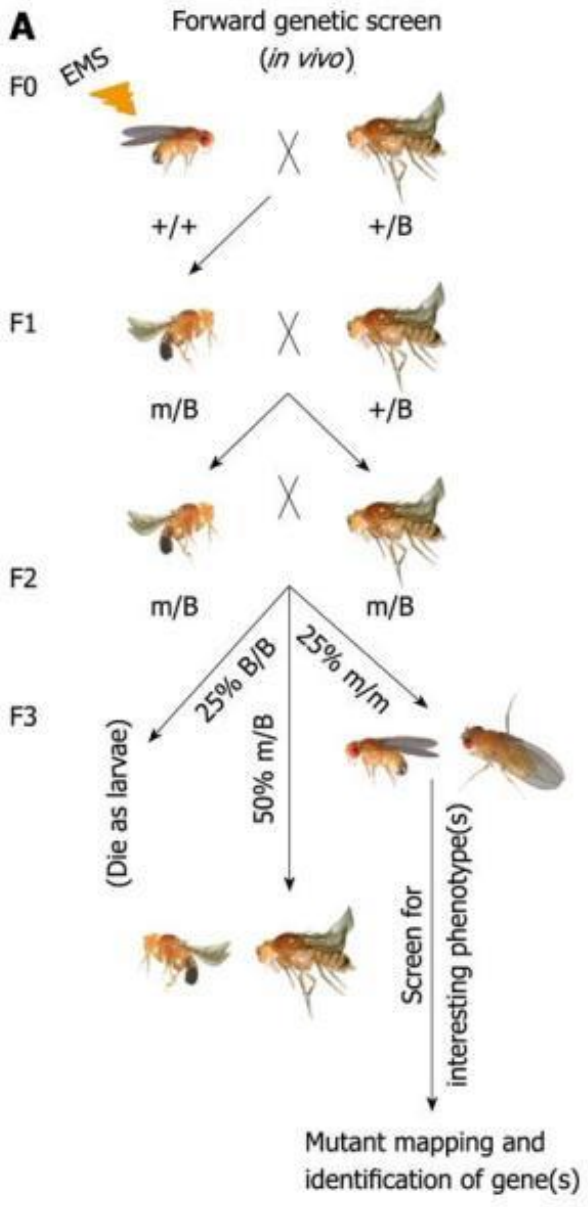


Francois Jacob (1920-) and Jacques Monod (1910-1976)

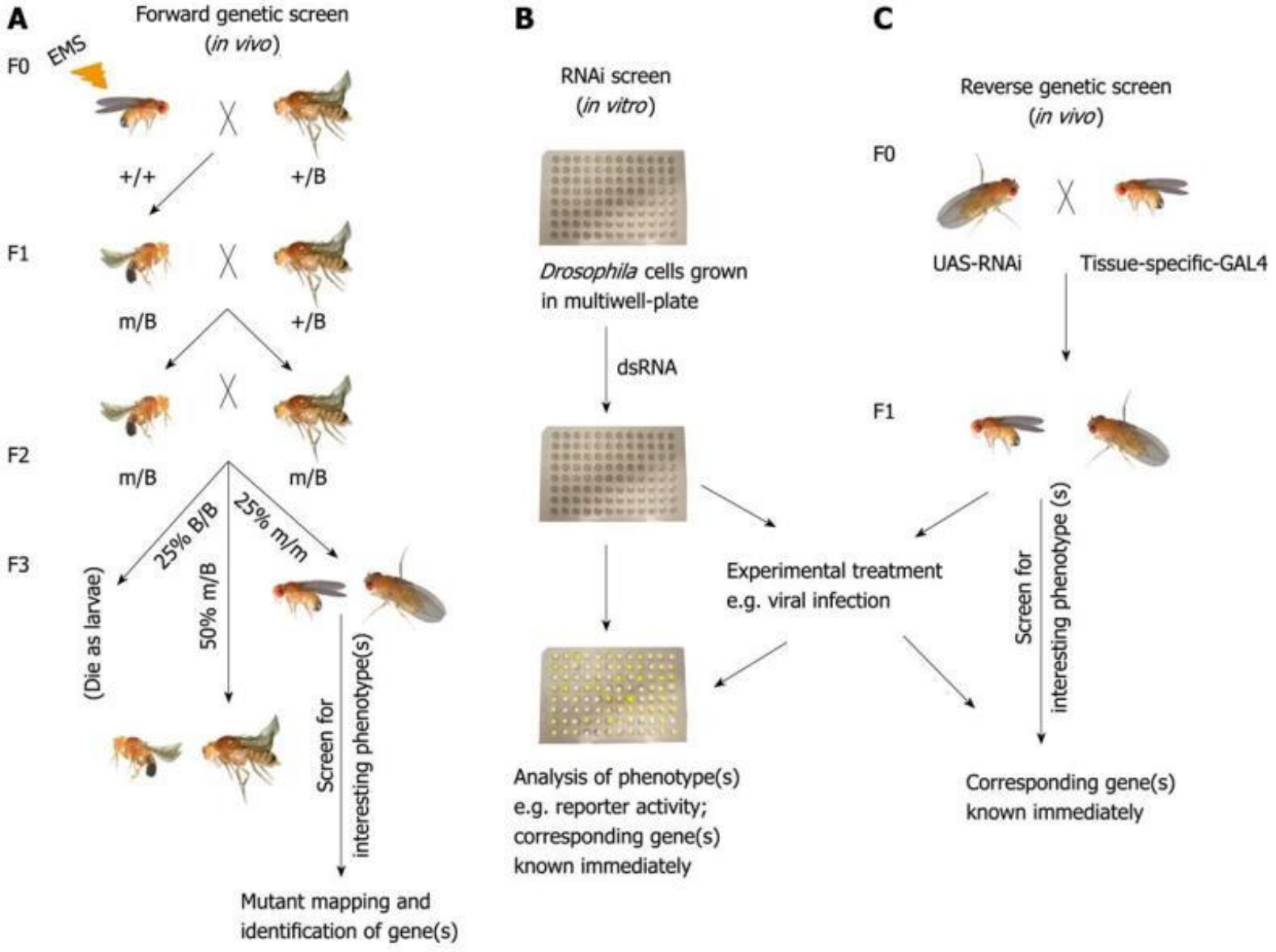
The goal of molecular biologists was to show how all of biology could be explained without out any reference to the “for” cause.

A key feature that enabled molecular biologists to conduct such studies was a method for linking genes to functions prior to knowing anything about how those genes mediate the functions.

Experimental Genetics



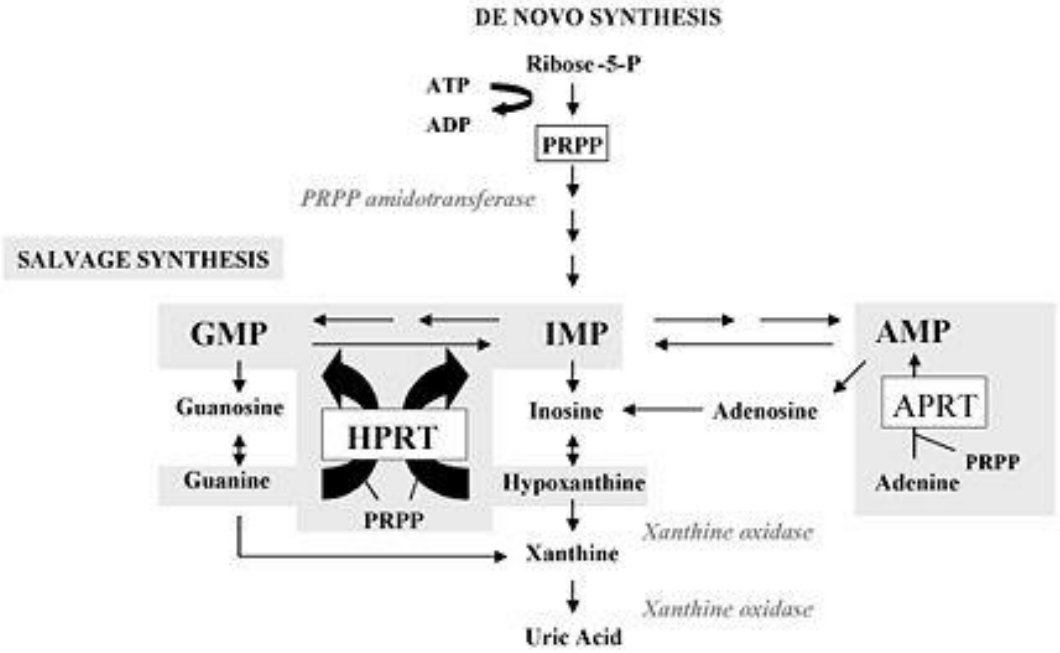
Molecular genetics: exploration of genotype-phenotype relationship



By 1990s, molecular genetics became the single most powerful tool by which molecular biologists linked gene-level mechanisms to organismal function.

It is the technology that made the sequencing of whole genomes a truly worthwhile enterprise, since with it there was an accepted method by which the functional role of a new gene could be ascertained.

Phenotype vs. Function



The phenotype of Null mutation in a nucleotide salvage pathway is mental retardation. HPRT is a gene for mental function. However such information is of little practical value.

- Despite such caveats, Molecular Genetics has largely embraced the concept of equivalence between phenotype and function.
- In the 1960's molecular biologists are eager to identify the molecular mechanisms responsible for specific organismal behaviors.
- In the 1990's they are mostly to identify the molecular mechanisms responsible for causing a particular phenotype, where that phenotype may be just a change in the level of an enzyme, or the size of the organism, or a predisposition to cancer.
- One consequence of this is an explosion of literature of the form "X regulates Y".

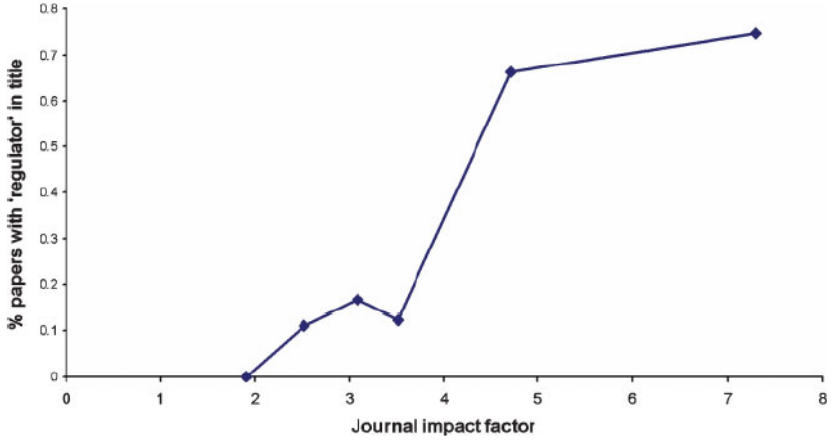


Figure 2. Articles with 'regulator' in their titles represent a higher proportion of articles in high-impact journals than in lower-impact journals. PubMed was used to search for all articles published from 1/1/2000 to 31/1/2009 in six developmental journals (*Development, Developmental Biology, Mechanisms of Development, Developmental Dynamics, Genesis,* and *Development, Growth and Differentiation*)

The underline assumption: that with the elucidation of sufficient causal connections between genes and their products, all of biological function should become clear.

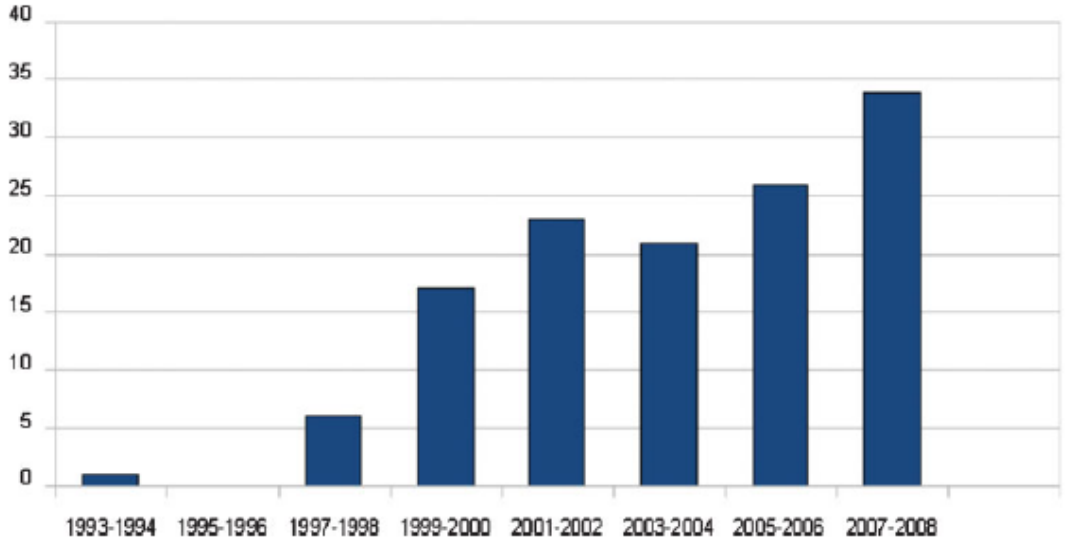
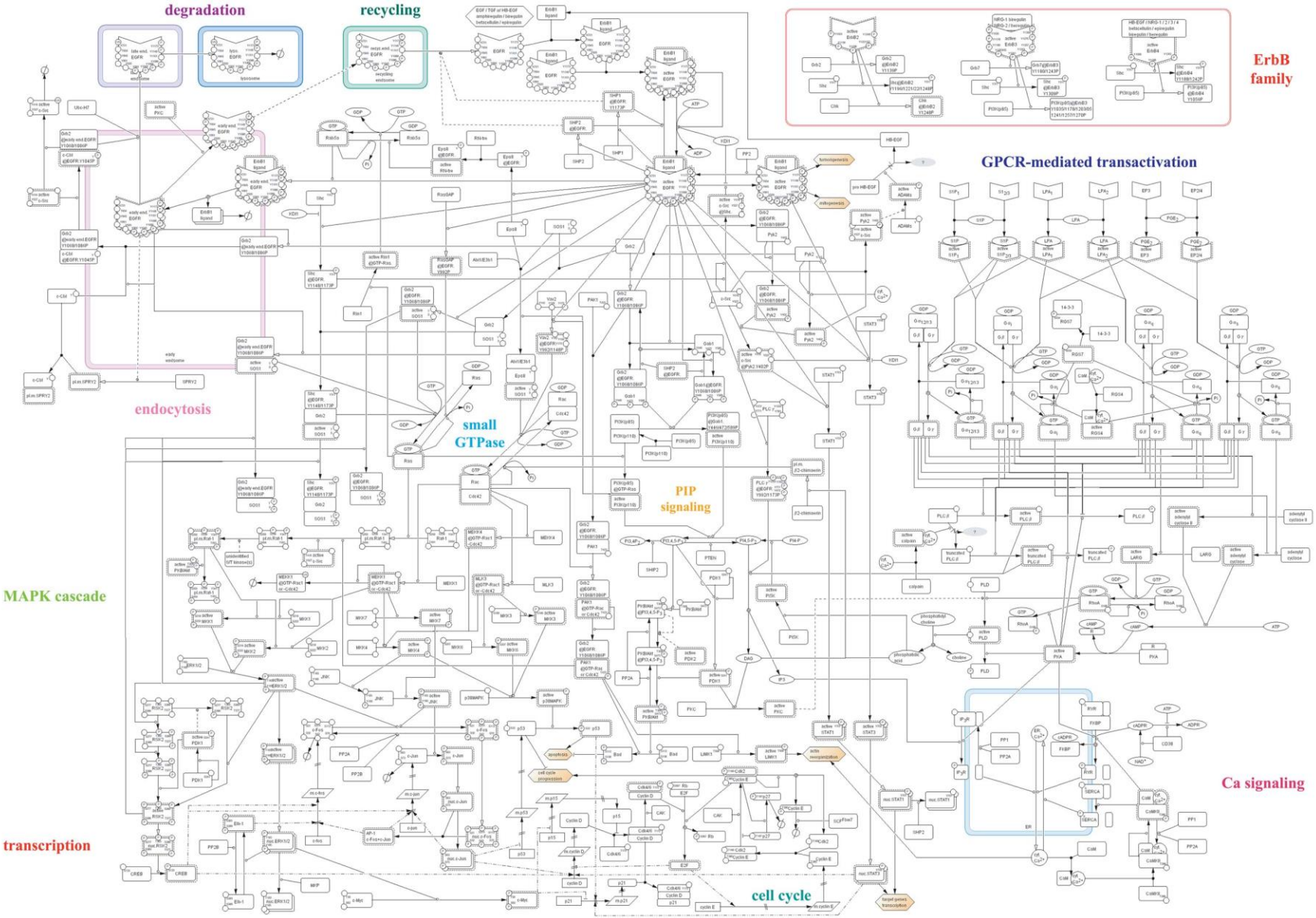


Figure 3. The year-by-year increase in the number of articles claiming to have identified a regulator only on the evidence of a knockout.

Davies, J. (2009) Bioessays 31:826-830

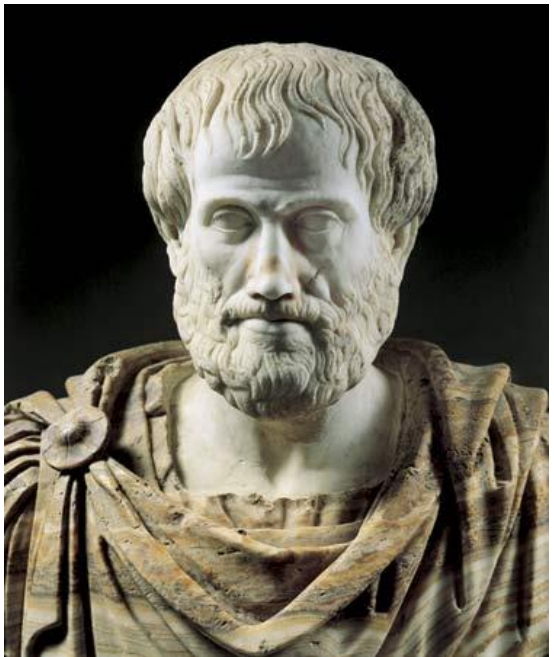
Epidermal Growth Factor Pathway (ca. 2008)

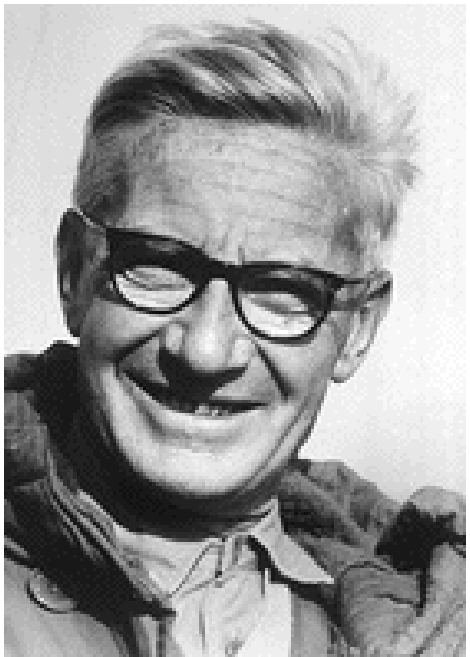


The Martians and the microwave

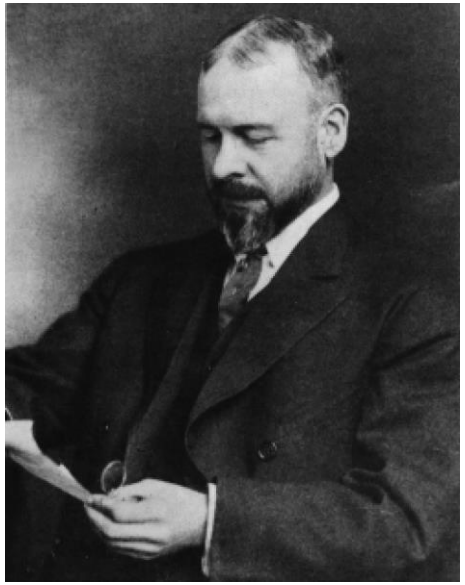
Functions are not merely phenomena

- It is not a statement about the way the world is.
- It is about what we have to do to achieve understanding.
- A mechanistic account of everything lacks explanatory power because even though it tells us what everything does, it doesn't, by itself, tell us what anything is for.
- For that we need to use other tools.





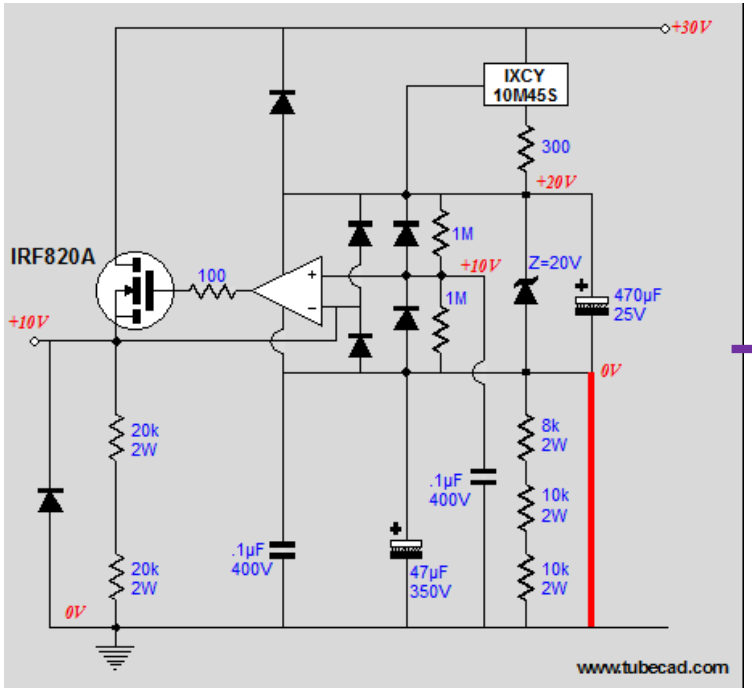
Sullivan's rule



"…form ever follows function"

In systems *designed* to do things, system architecture is dictated by the *performance objectives* of the system.

- Features of good design
  - Accuracy
  - Efficiency
  - Robustness
  - Interoperability
  - Flexibility



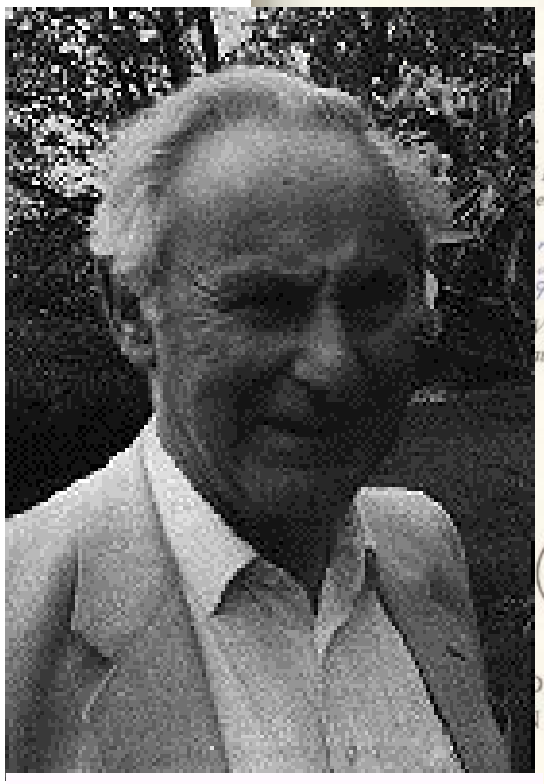
→ Voltage regulator

Conditions for Reverse Engineering

- 1. The system must display design principles
- 2. We must have comprehensive knowledge of what's in the system
- 3. We must have a way to recognize design
- 4. We must ultimately be able to test conjectures about function.

Systems biology is to find the design principle by reverse engineering

An earlier “systems biologist”



Henrik Kacser, 1918-1995

Biological Organization
at the Cellular and
Supercellular Level

Edited by
C. HARRIS
Experimental Biology and Virology
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and supra-cellular
962.]
Varenna, 24–27 September, 1962
uspices of UNESCO

1963
DEMIC PRESS
and NEW YORK

CONTENTS

INTRODUCTION

It is well known that organisms consist of molecules. It should, therefore, be possible to account for biological behaviour in terms of molecular behaviour. Yet it is evident that the complete enumeration, even were it possible, of all the molecules within an organism would not account for any but its most trivial aspects. The reason for this is, of course, that an organism is not simply a mixture but a system of interacting molecules. It is therefore to these interactions that we must look for an elucidation of biological behaviour.

It will be the thesis of this paper that molecular interactions impose on the organism a "structure" which is *sui generis*, that is, that properties necessarily arise due to the presence of many different reactions coupled within the same space. The useful experimental device of isolating single steps may lead us to view the organism logically as a sum of single consequences. The widespread phenomena of dominance, pleiotropy and epistasis in genetics and of regulation and differentiation in embryology have shown the inadequacy of such a view. There is, however, as yet no comprehensive scheme which links the evidence for the unitary genetic determination of protein structure with the bewildering array of epigenetic and metabolic consequences. To establish such a scheme it is necessary to uncover, both experimentally and logically, the causal connections of a system without isolating the steps of which it is composed. The language in which such a system is described must of necessity be the language of molecular interactions, namely kinetics. Our conventional logical apparatus, which is essentially a linear one and lacks quantitative rigour, cannot handle most of the situations which are of the essence of interacting systems. Some of the conclusions of the treatment which follows may therefore appear intuitively strange—but so much the worse for intuition.

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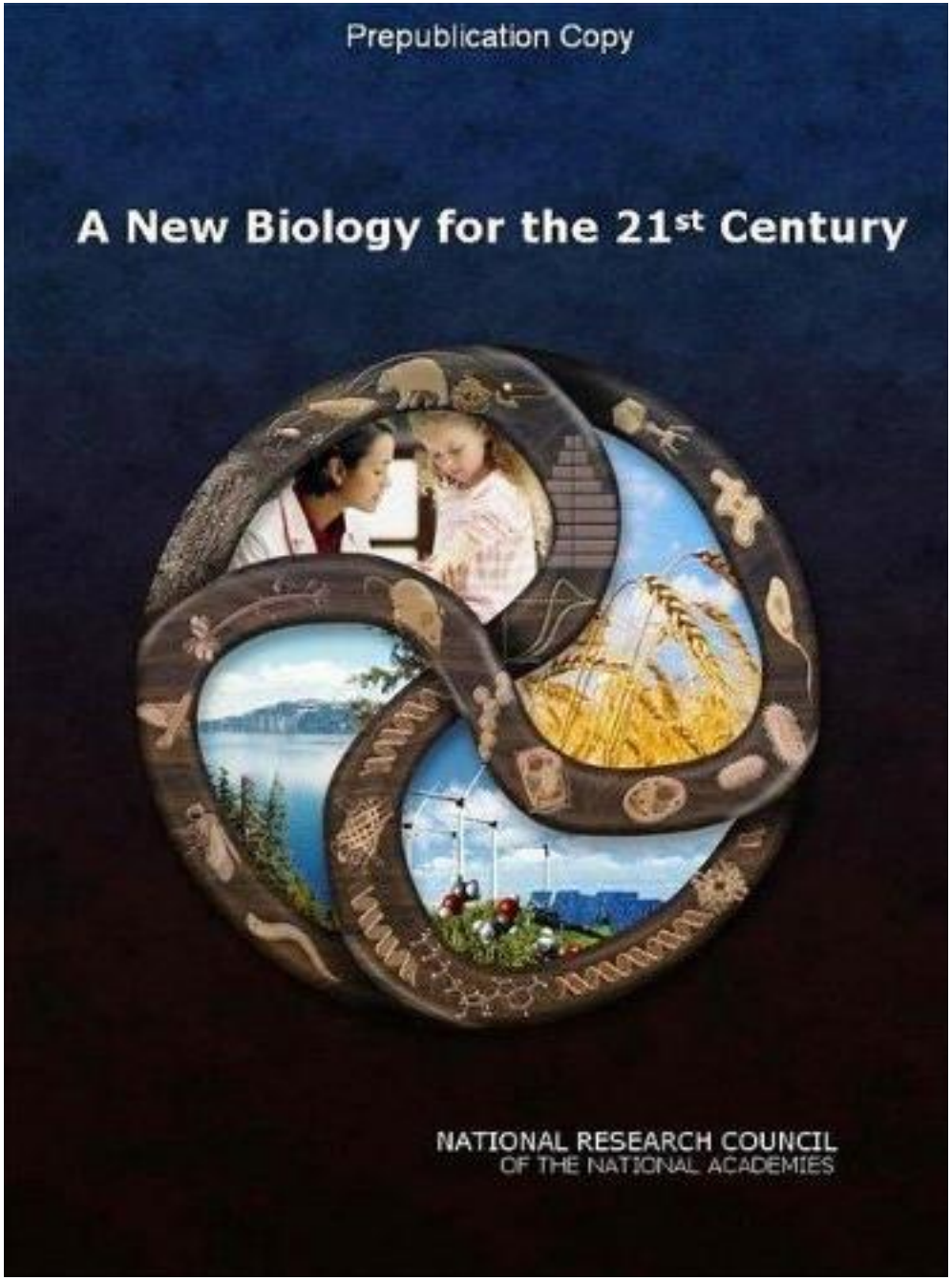


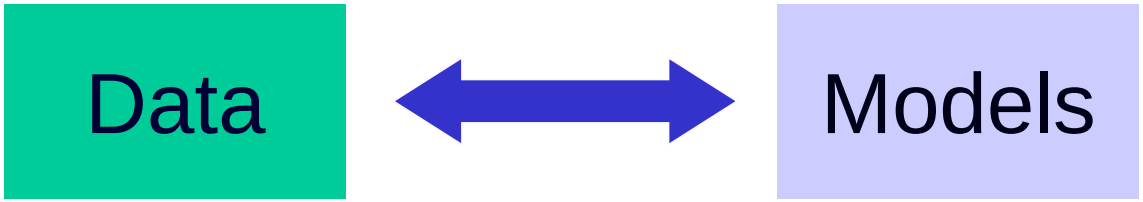
The two basic tenets of the report:
describe precisely what Systems Biology is doing.

1. By providing a level of explanation for biological phenomena that is explicitly functional—in effects, saying what things are "for" and "why they are there"—Systems Biology is re-uniting molecular biology with physiology, developmental biology, ecology and population genetics.

2. By committing to reverse engineering biological systems, Systems Biology becomes deeply dependent on numerous methodologies from math, physics, engineering and computer science.

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



Major themes in systems biology

- 1. Understanding biological regulation
  - Metabolic control
  - Signal networks
  - Gene regulatory networks
  - Growth control
  - Pattern formation
  - Morphogenesis

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

- Genomics, proteomics, other “omics”
- Chromosomal occupancy and structure: *ChiP*
- Epigenomics: *DNA and histone modification*
- RNAi and other screening
- Fluorescence activated cell sorting: *heterogeneity*
- Automated quantitative microscopy: *spatial-temporal dynamics*
- Literature mining
- etc

Statistical analysis of large scale data

Bioinformatics

Statistical inference

Frequentist's *vs* Bayesian approach

Major themes in systems biology

3. Probing the constraints and limits of biological performance
   - Exploring model behaviors:
     - *parameter sensitivity*
   - Elicidating physical and engineering constraints
     - *stochasticity, tolerance etc.*
   - Understanding the consequences of variation and selection
     - *Robustness vs evolvability, optical behaviors vs fluctuating environments etc,*

The goal of this course

- Expose you to the thinking and a few example of systems biology
- Prepare you for the decision of what questions you would pursue
- Having fun doing this

A few notions

- This is an introductory course, it only covers a small portion of systems biology
- “omics”, genomics, proteomics were covered in bioinformatics course
- Experimental methods are not covered explicitly and systematically

Syllabus

Part 1: Single reaction
Introduction, Michaelis-Menten kinetics
Matlab & Math tutorial
Equilibrium binding, cooperativity and ultrasensitivity

Part 2: Simple network, complex function
Positive feedback and multistability,
Stability analysis, **Matlab session**
HW for Part 1 due, Class discussion
Synthetic switches,
Synthetic genetic oscillator
Simulation of oscillator

Part 3: Small network, high performance
Bacteria chemotaxis, Howard Berg experiment, theory
Diffusion, Fick's law,
Project for Part 2 due, Class discussion

Part 4: larger network, less details
Gene regulation network: evidence-based vs large scale data-based network
Network modeling: differential equations.
Project for Part 3 due, Class discussion

Network inferring: whole gene regulatory network

Part 5: Spatial interactions and pattern models
Turing's model,
Recent experimental evidences of Turing's model
Morphogen gradient, theory and experiments

Part 6: Growth and differentiate, noise and robustness
Regulation of differentiation
Regulation of growth,

Grading

Components	weight(%)
HW & Projects, presentation	40
Attendance and class involvement	20
Final: literature review	40

1) Final Exam: please write a review on one particular research topic of systems biology, provide background, current research achievements, and future directions, please based your review based on multiple papers. You can come to me or other professors for consultations.

2) I will assign for study groups of 3 classmate each, for class projects and presentations