Quantitative Biology Colloquium, University of Arizona, March 1, 2011

Reductionist Paradox

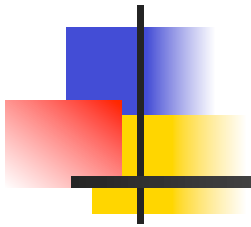
Are the laws of chemistry and physics sufficient for the discovery of new drugs?

Gerry Maggiora, Ph.D.

Adjunct Professor, College of Pharmacy
& BIO5 Institute,
University of Arizona
Translational Genomics Research Institute,
Phoenix, AZ

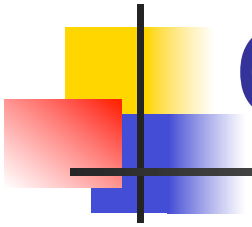
COMP Division Symposium – Challenges in Industrial Computational Methods

American Chemical Society Meeting, Boston, MA, August 22-26, 2011



"Are the laws of chemistry and physics sufficient for the discovery of new drugs?"

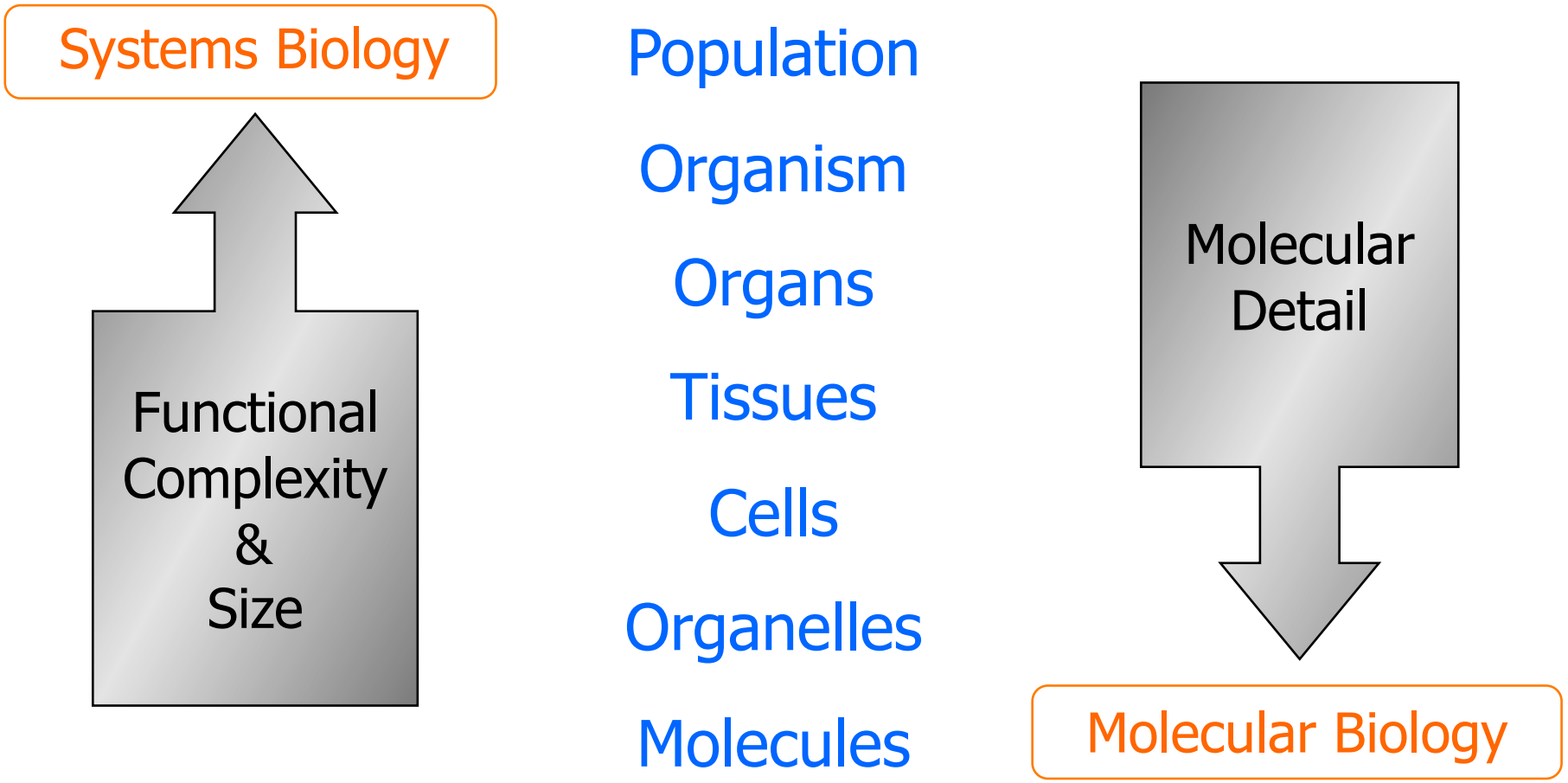
No!



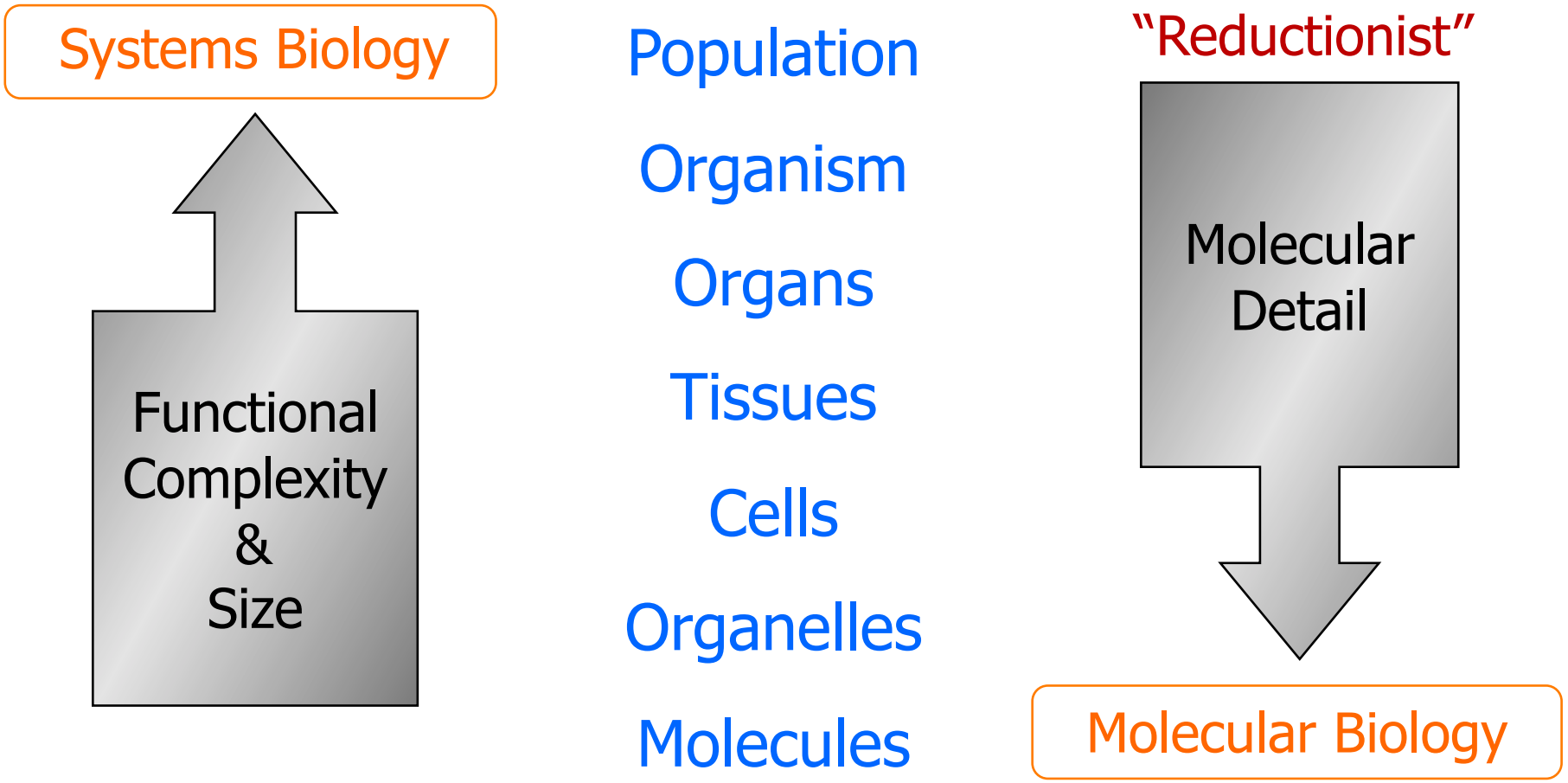
Overview

- What the talk is not about –
  - Challenges posed by the development and application of chemical and physical methods for the study of biological systems.
- What the talk is about –
  - Issues associated with the nature of biological systems and why the traditional approach to pharmacological research has resulted in a diminishing number of new pharmaceuticals.
  - What is computational chemistry's role?

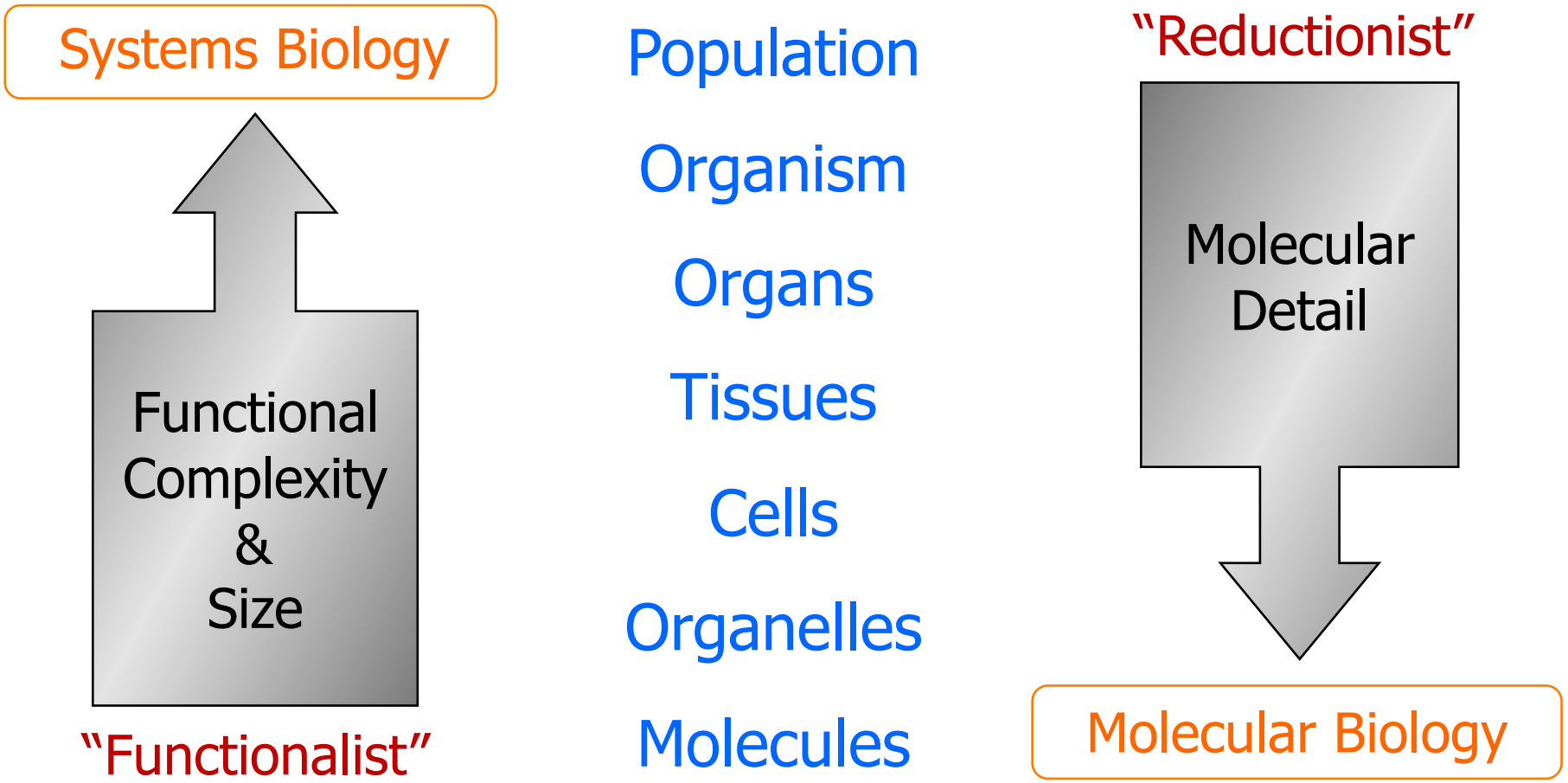
Hierarchical nature of biological systems



Hierarchical nature of biological systems



Hierarchical nature of biological systems



Biological reductionism

- The reductionist method of dissecting biological systems into the constituent parts has been effective in explaining the chemical basis of many living processes.
- Many biologists now, however, realize this approach has reached its limit.
- Biological systems are extremely complex and have emergent properties that cannot be explained, or even predicted, by studying their individual parts.

M.H.V. Van Regenmortel, "Reductionism and complexity in molecular biology", *EMBO Report* **5(11)**, 1016-1020 (2004).

Emergent properties

Functionalism

Reductionism

LEGO Babbage difference engine

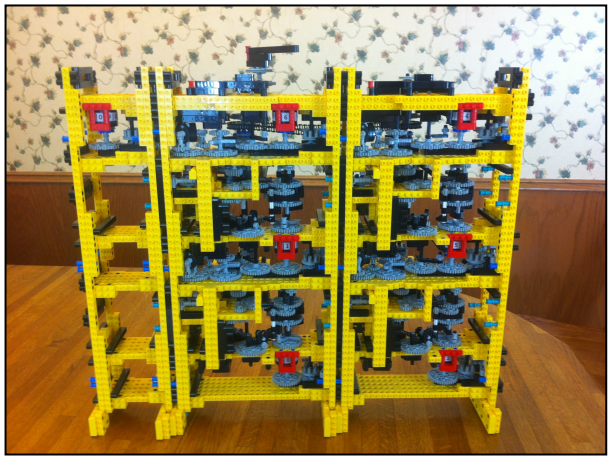


Photo courtesy of Andy Carol

Evaluates

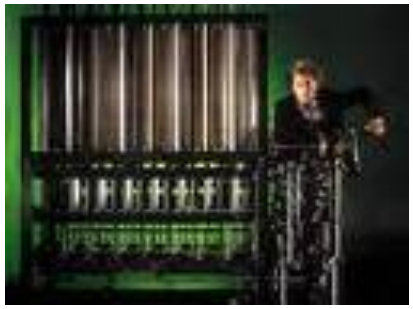
$$f(x) = a x^2 + b x + c$$

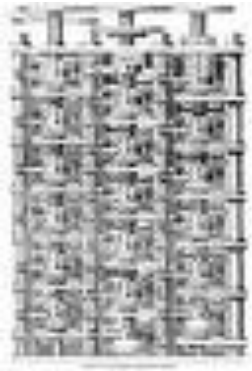
for $x = 0, 1, 2, 3, \ldots, n$

(3 - digit accuracy)

acarol.woz.org/difference_engine.html

Other realizations of Babbage's computing engine





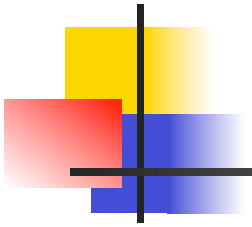
A mathematical example

$$\overbrace{\{\vartheta\},\{\varphi\},\ldots,\{\psi\}}^{\textit{Basis Sets}}$$

$$\Downarrow$$

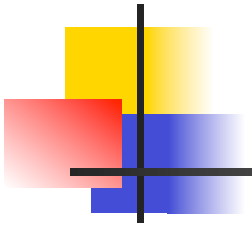
$$\underbrace{f \approx \sum_{\ell} a_{\ell}\vartheta_{\ell} \approx \sum_{\ell} b_{\ell}\varphi_{\ell} \approx \cdots \approx \sum_{\ell} w_{\ell}\psi_{\ell}}_{\textit{Function Estimates}}$$

Many different basis sets can be used to approximate a given function



Recapitulation

- There are many ways to realize or represent the same functionality.
- A given functionality may be deconstructed (“reduced”) at some level into its constituent parts.
- The reverse process is not, in general, possible.



Laws of Nature

- Laws of the physical sciences are basically simple:
  - Mechanics: $F \sim ma$
  - Electrostatics: $F \sim q\, q' / r^2$
  - Relativity: $E = m\, c^2$
- There are no equivalently simple laws in the biological sciences.
- "Laws of Biology," if they exist, are inherently complex.
- For example the Central Dogma that

  DNA ➔ RNA ➔ Protein

  does not accord with "biological reality".

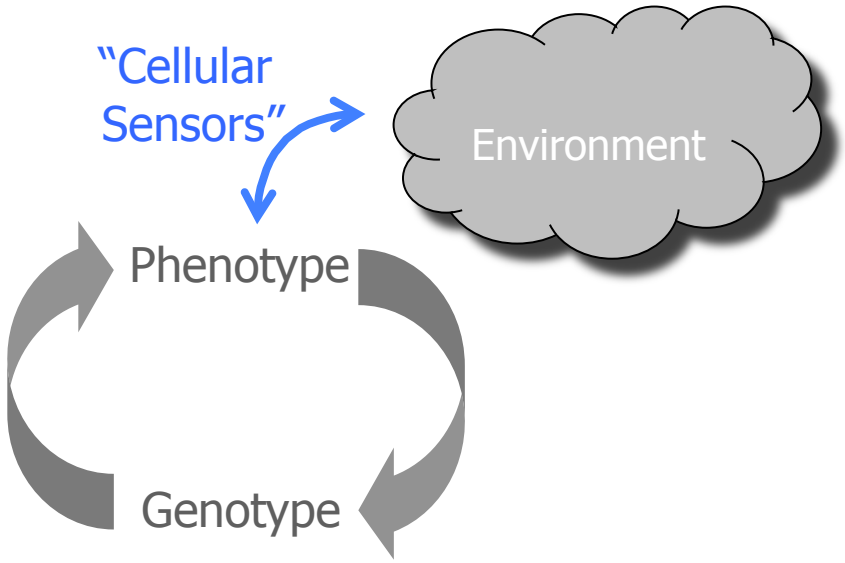
The "Central Dogma" & beyond

"Central Dogma"
linear relationship

"Flow of genetic information"

DNA → { "RNA" } → Protein

More complex
non-linear
relationship
with feedback

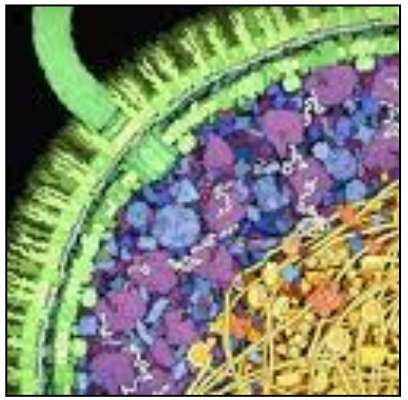


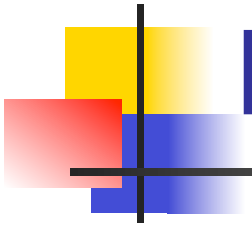
"Toward a New Theoretical Framework for Biology," T. Otter (http://ivan.research.ucf.edu/SOE/SOE002.pdf)

Why are biological systems so difficult to study?

- Complex
  - Number, variety, and connectivity of components
  - Hierarchical structure
  - Strength & types of interactions
- Possess emergent properties
- Exhibit redundancy & degeneracy
- Exhibit modularity (functional subsystems)
- Open, stable, heterogeneously-distributed non-equilibrium systems
- Exhibit significant non-linear behavior

Cartoon of cell



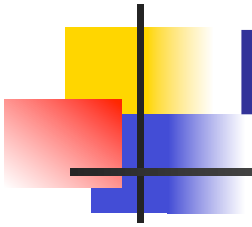


Mega-scale biology

"To really understand [complex] systems, you have to collect global datasets from each of these levels [of the hierarchy] and then integrate them together if you're to get a coherent understanding of the system"

Leroy Hood, *C&E News,* May 19, 2003

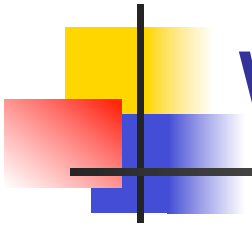
This suggests a "high-throughput" approach to biology.



High-throughput biology

- High-throughput biology
  - High initial and on-going cost
  - Highly data driven, moderately hypothesis driven
  - "There must be a pony somewhere in all that manure" assumption
- Pitfalls of high-throughput biology
  - "Industrialization" of biology, "assembly line" science
  - Noisy data can confound data-driven analyses
- High-throughput science generally depends on "smooth" behavior in the systems studied

Can we understand biology with mega-experiments?



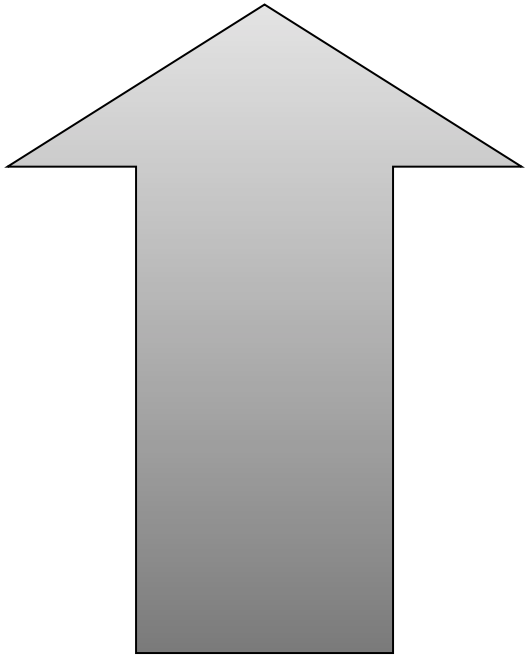
- Large amount of data needed: Is too much data a good thing or bad thing?
- Many weak 'signals'.
- Can we find patterns in very large, noisy, and possibly sparse datasets?
- The problem of chance correlations.
- Cellular concentrations are generally quite low.
- Are time-dependent factors important?
  - Multiple timescales, event sequences, and threshold effects.

Has technology helped?

- Enabling technologies have helped "deconstruct" much of biology into its molecular components.
- However, many of these technologies have reinforced the reductionist paradigm.
- Industrial influence has lead to
  - Over reliance on large numbers: *e.g.* compound collections.
  - Over reliance on sophisticated, high-throughput methodologies.
- The "Myth of novel targets."

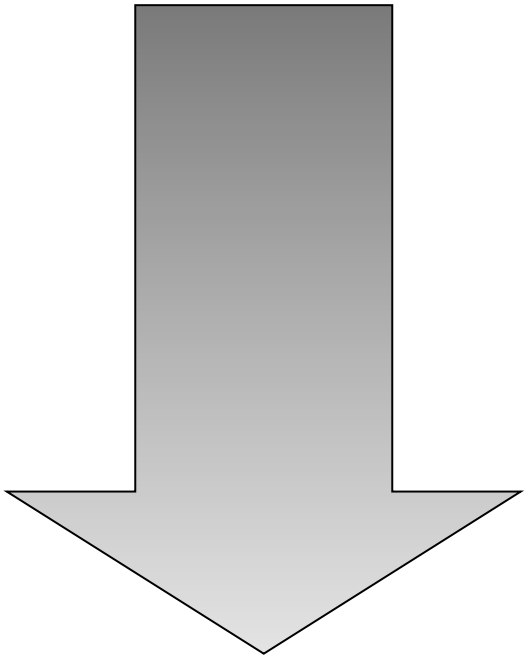
Where are the new drugs?

ca. US$38 billion
(2006)



Expenditures for
drug research

New drugs



< 20 in 2006
> 50 in 1992

What's the problem?

Population

Organism

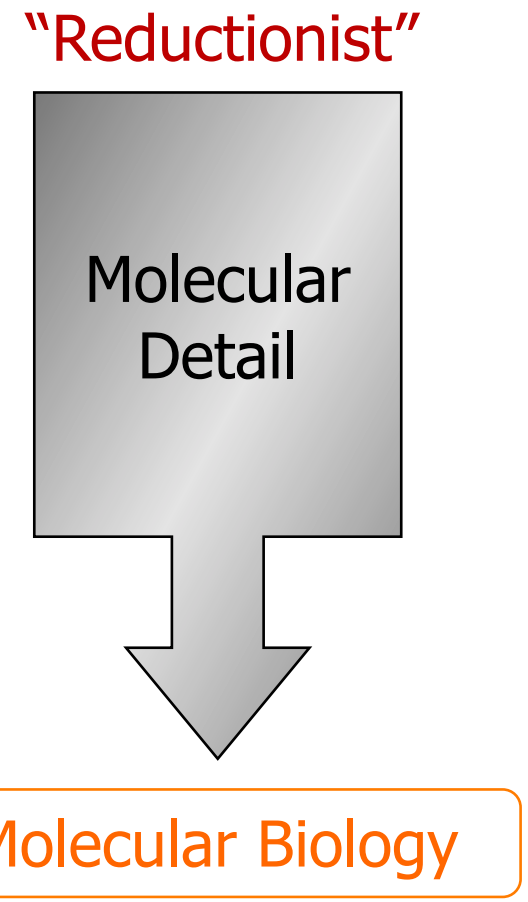
Organs

Tissues

Cells

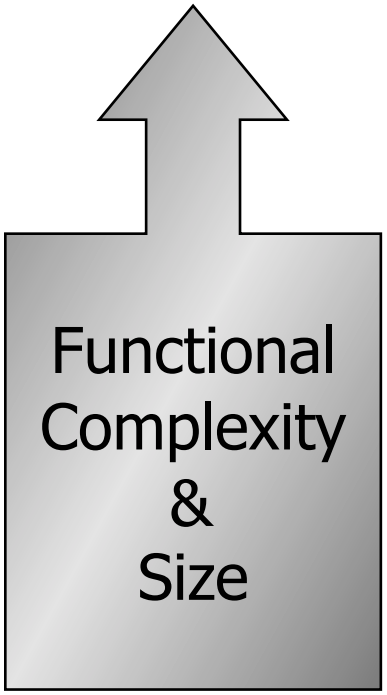
Organelles

Molecules



What should be done about it?

Systems Biology



"Functionalist"

Population

Organism

Organs

Tissues

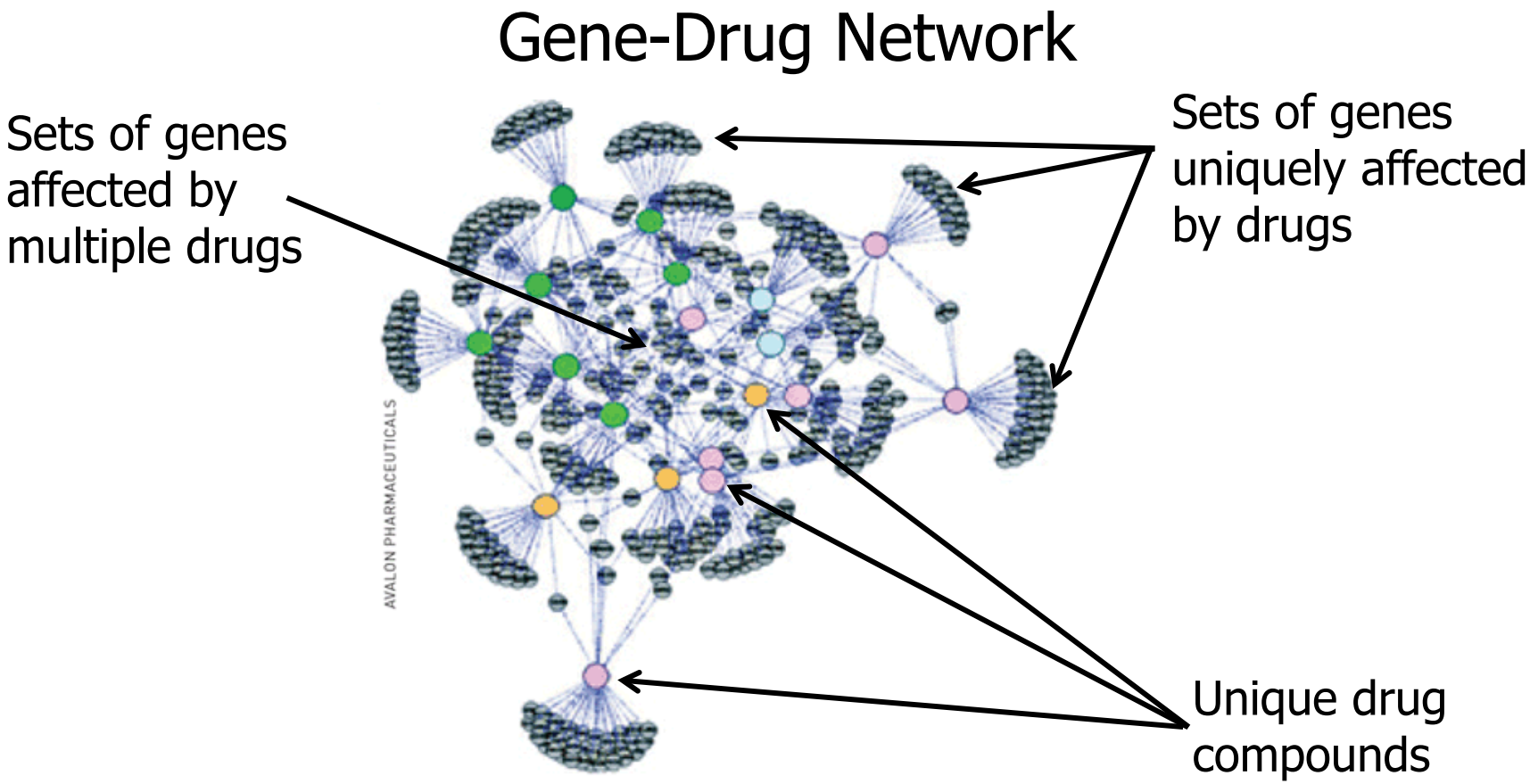
Cells

Organelles

Molecules

Putting biology back into pharmaceutical research

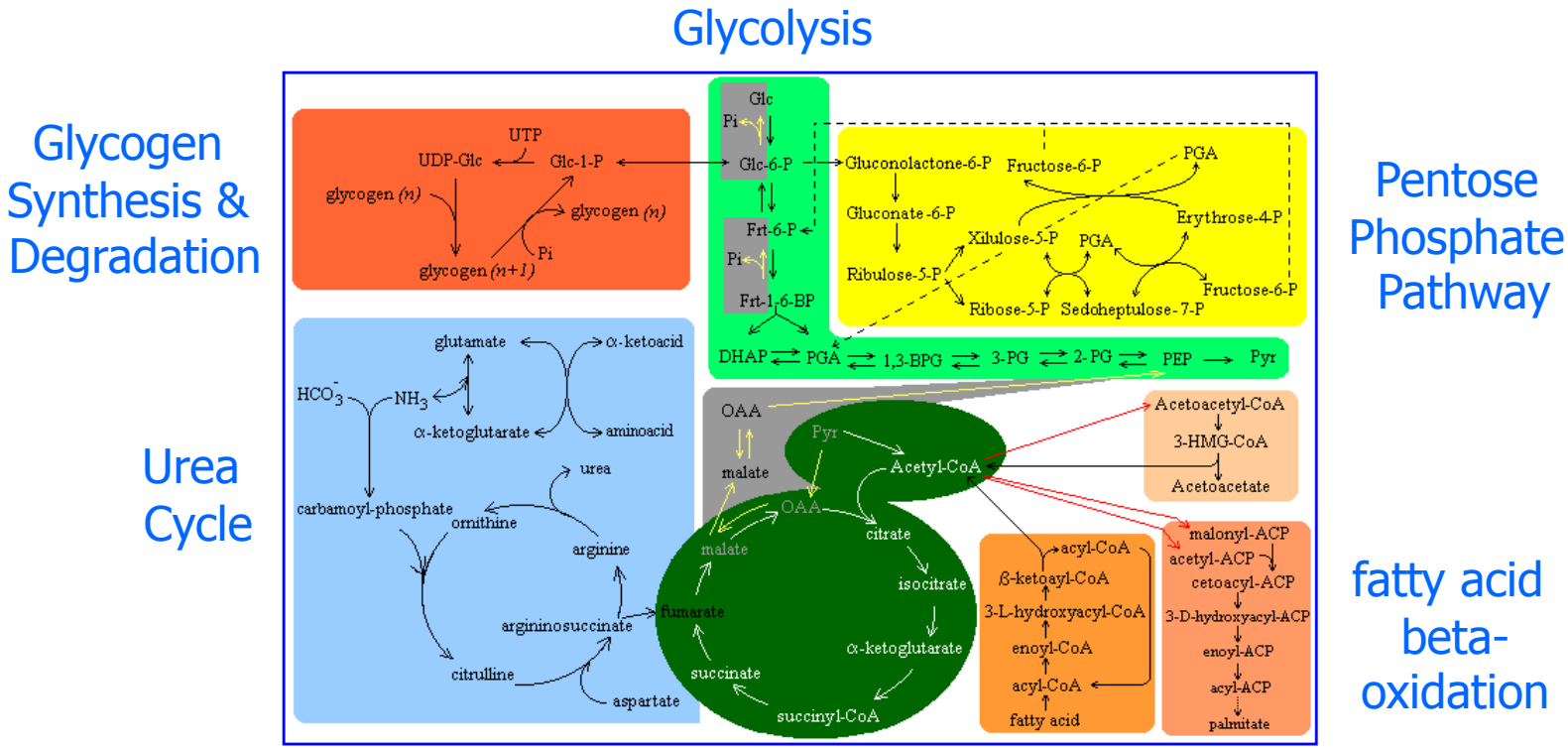
Network biology – relational models



C&ENews, Vol. 84, pp. 17-26 (2006)

Systems biology – dynamic models

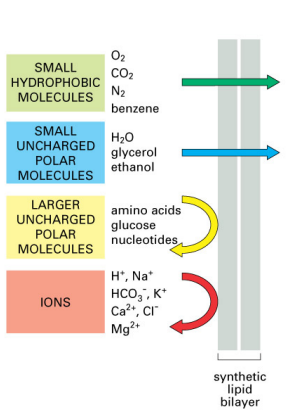
Metabolic Pathways

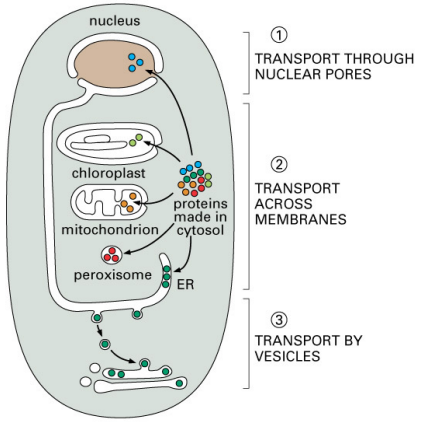


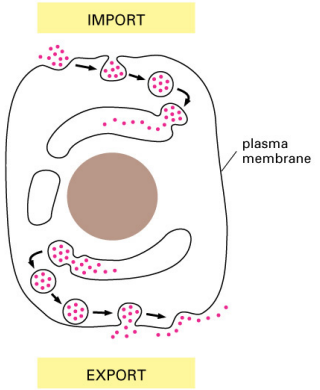
Courtesy of Professor Pedro Silva, Universidade Fernando Pessoa, Portugal

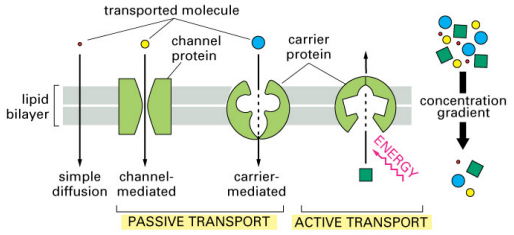
Biological transport mechanisms

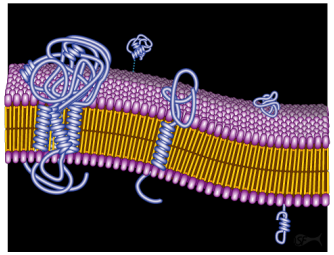
Biopharmaceutics, drug delivery & targeting











Essential Cell Biology, by Alberts, Bray, Johnson, Lewis, Raff, Roberts, and Walter, Garland Science, 2nd Edition, 2004.

Back to the future?

- Re-emergence of “classical” pharmacology.
- Development of more reliable animal models.
- Development of more effective biomarkers
- Growing importance of clinical research

An emerging paradigm shift

Single-drug, single-target model

Most current drug research ('clean drugs')

An emerging paradigm shift

Single-drug, single-target model

'Omics'
Biological Networks
Systems Biology

Most Current Drug Research ('clean drugs')

Second 'Biological Revolution'

An emerging paradigm shift

Single-drug, single-target model

Most Current Drug Research ('clean drugs')

'Omics'
Biological Networks
Systems Biology

Second 'Biological Revolution'

Single-drug, multi-target &
multi-drug, multi-target models

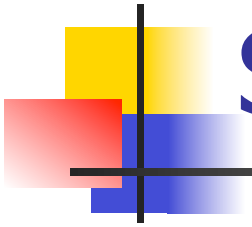
Polypharmacology ('dirty drugs')

What is computational chemistry's emerging role?

New" mathematics in addition to that traditionally used in physics and chemistry is needed if we are to fully understand biology.

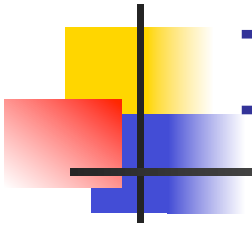
J. Casti, "Topological Methods for Social and Behavioral Systems," *Int. J. General Systems,* Vol. 8, pp. 187-210, 1982.

This is an opportunity for computational chemistry to expand its traditional role in drug research and pursue new directions to meet the needs of modern research in biology and pharmacology.



Some "new" mathematics

- Relational mathematics
  - Graphs & networks
  - Hypergraphs & simplicial complexes (multi-dimensional)
- Probablistic networks
- Pattern recognition (e.g. clustering, decision trees,…)
- Machine learning (e.g. support vector machines,…)
- Biological simulations
  - Continuous & discrete event
  - Stochastic
- Computational decision theory



Is new mathematics enough?

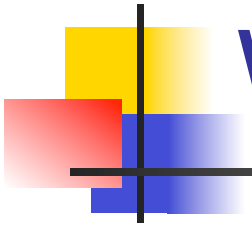
"As the amount of information grows, the level of detail at which it can be treated effectively must decrease".

Lofti Zadeh

The MD analogy.

Thus, the need arises to simplify and to deal with imprecise and uncertain data and information.

Soft computing methods provide a potential means for attaining this goal.



What is soft computing?

"Soft computing is an emerging approach to computing which parallels the remarkable ability of the human mind to reason and learn in an environment of uncertainty and imprecision."

Lofti Zadeh

- Fuzzy mathematics & logic
- Neural networks
- Genetic/evolutionary algorithms
- Belief networks
- Rough set theory
- Granular computing
- Chaos theory
- Etc…

We see what our minds are conditioned to see

Red

Blue

Orange

Yellow

Green

We see what our minds are conditioned to see

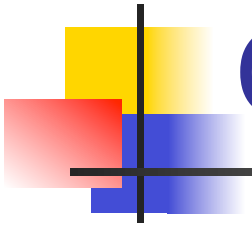
Yellow

Orange

Green

Blue

Red



Caveats

So far as the laws of mathematics refer to reality, they are not certain. And so far as they are certain, they do not refer to reality.

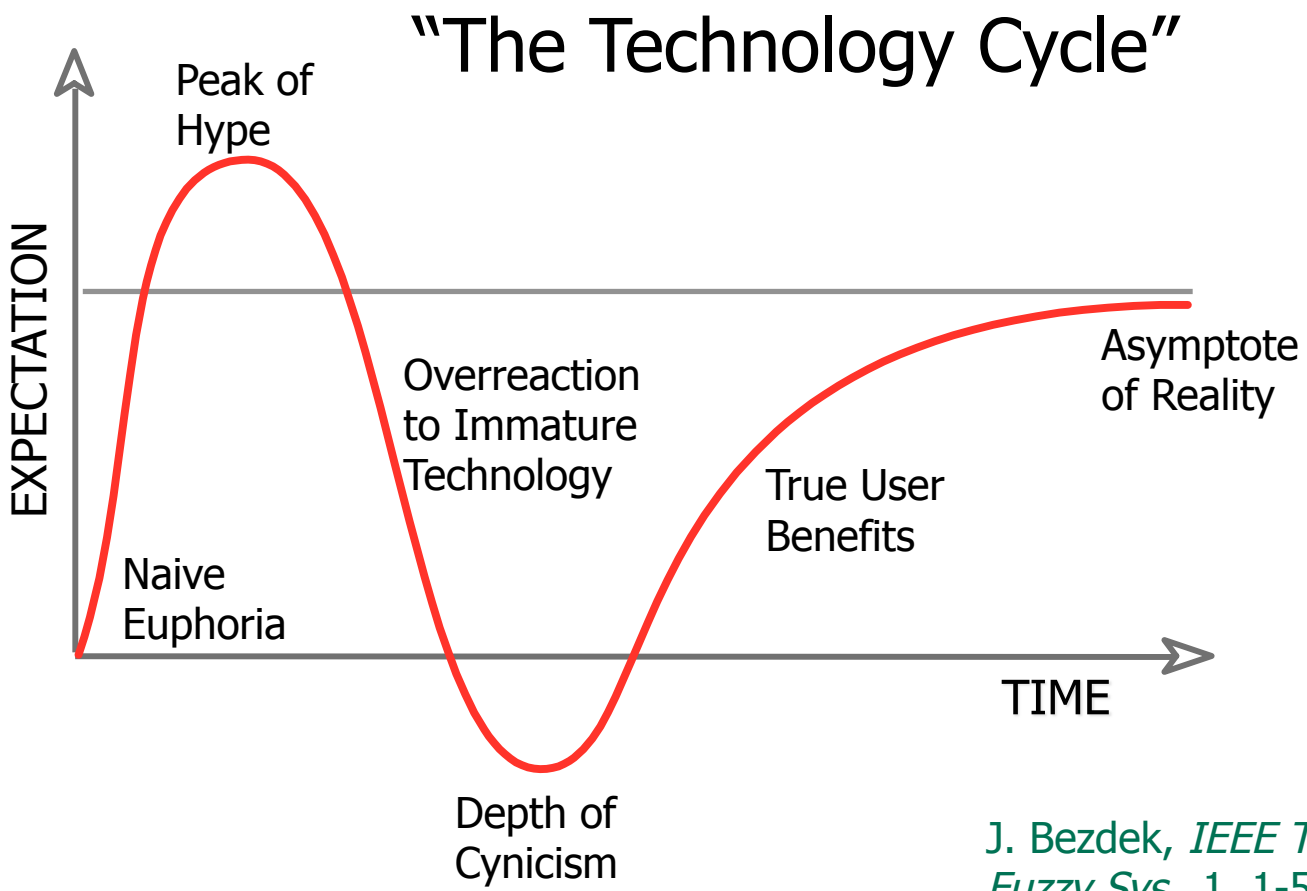
Albert Einstein, "Geometry and Experience"

Precision is not truth.

Henri Matisse, 1869-1954

Impressionist painter

An important perspective



J. Bezdek, *IEEE Trans. Fuzzy Sys.*, 1, 1-5 (1993)

A final thought

Drug research is not rocket science.
It is much more difficult!