

Mathematical Biology: What Have You Done for Me Lately?

J. P. Keener

Department of Mathematics

University of Utah



The Dilemma of Modern Biology

- The amount of data being collected is staggering. Knowing what to do with the data is in its infancy.
- The parts list is nearly complete. How the parts work together to determine function is essentially unknown.

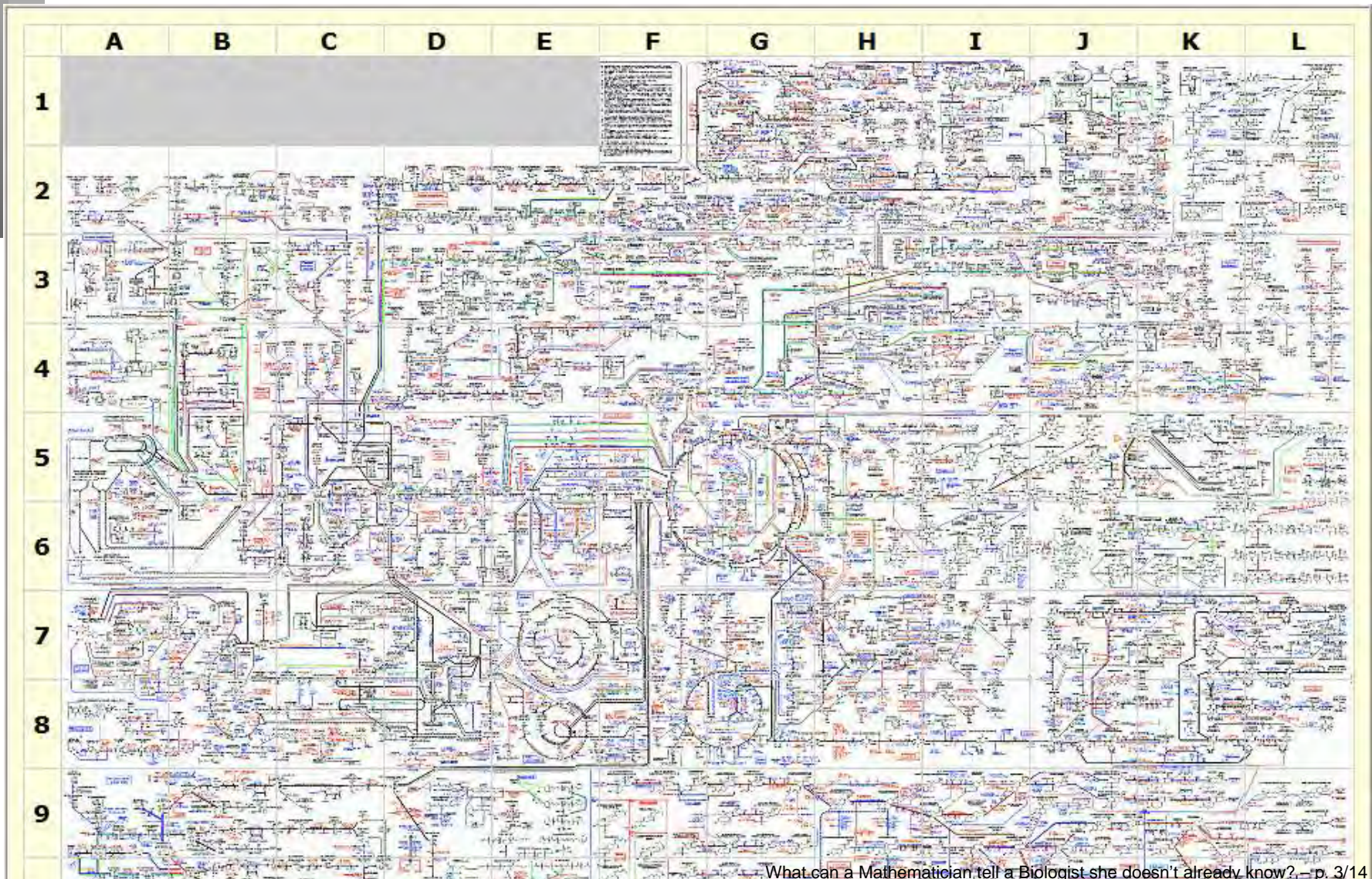
The Dilemma of Modern Biology

- The amount of data being collected is staggering. Knowing what to do with the data is in its infancy.
- The parts list is nearly complete. How the parts work together to determine function is essentially unknown.

How can mathematics help?

- The search for general principles; organizing and describing the data in more comprehensible ways.
- Develop quantitative, predictive, mechanistic theories to replace qualitative, correlative, verbal explanations.

Biological Systems are Complex!!



Quick Overview of Biology

- The study of biological processes is over many space and time scales (roughly 10^{16}):

Quick Overview of Biology

- The study of biological processes is over many space and time scales (roughly 10^{16}):
- Space scales: Genes → proteins → networks → cells → tissues and organs → organism → communities → ecosystems

Quick Overview of Biology

- The study of biological processes is over many space and time scales (roughly 10^{16}):
- Space scales: Genes → proteins → networks → cells → tissues and organs → organism → communities → ecosystems
- Time scales: protein conformational changes → protein folding → action potentials → hormone secretion → protein translation → cell cycle → circadian rhythms → human disease processes → population changes → evolutionary scale adaptations

Some Biological Challenges

- DNA -information content and information processing;

Some Biological Challenges

- DNA -information content and information processing;
- Proteins - folding, enzyme function;

Some Biological Challenges

- DNA -information content and information processing;
- Proteins - folding, enzyme function;
- Cell - How do cells move, contract, secrete, reproduce, signal, make decisions, regulate energy consumption, differentiate, etc.?

Some Biological Challenges

- DNA -information content and information processing;
- Proteins - folding, enzyme function;
- Cell - How do cells move, contract, secrete, reproduce, signal, make decisions, regulate energy consumption, differentiate, etc.?
- Multicellularity - organs, tissues, organisms, development, coordinating cellular activities and behaviors.

Some Biological Challenges

- DNA -information content and information processing;
- Proteins - folding, enzyme function;
- Cell - How do cells move, contract, secrete, reproduce, signal, make decisions, regulate energy consumption, differentiate, etc.?
- Multicellularity - organs, tissues, organisms, development, coordinating cellular activities and behaviors.
- Human physiology - health and medicine, drugs, physiological systems (circulation, immunology, neural systems), disease processes, epidemics.

Some Biological Challenges

- DNA -information content and information processing;
- Proteins - folding, enzyme function;
- Cell - How do cells move, contract, secrete, reproduce, signal, make decisions, regulate energy consumption, differentiate, etc.?
- Multicellularity - organs, tissues, organisms, development, coordinating cellular activities and behaviors.
- Human physiology - health and medicine, drugs, physiological systems (circulation, immunology, neural systems), disease processes, epidemics.
- Populations and ecosystems - biodiversity, extinction, invasions.

Report from the Advisory Committee to the NIH Director on the Biomedical Workforce - 2012

"The NIH Biomedical Workforce report concluded that we probably have a serious oversupply in the pipeline of basic science PhD level investigators. BUT there is a serious shortage in one area, namely quantitative scientists..."

"The report challenged the NIH to initiate a serious and substantial training effort to close this gap. Thus, the two independent task forces came to one common conclusion that there is a serious shortage of trained quantitative scientists and the gap is widening."

Places Math is Needed

- To provide quantitative and predictive theories for how biological processes work.

Places Math is Needed

- To provide quantitative and predictive theories for how biological processes work.
- Moving across spatial and temporal scales - What details to include or ignore, understanding emergent behaviors.

Places Math is Needed

- To provide quantitative and predictive theories for how biological processes work.
- Moving across spatial and temporal scales - What details to include or ignore, understanding emergent behaviors.
- Understanding stochasticity - Is it noise or is it real?

Places Math is Needed

- To provide quantitative and predictive theories for how biological processes work.
- Moving across spatial and temporal scales - What details to include or ignore, understanding emergent behaviors.
- Understanding stochasticity - Is it noise or is it real?
- The challenge of complex systems (e.g., the nature of robustness), to discover general principles underlying biological complexity. The science of putting the parts together to understand how the system works.

Places Math is Needed

- To provide quantitative and predictive theories for how biological processes work.
- Moving across spatial and temporal scales - What details to include or ignore, understanding emergent behaviors.
- Understanding stochasticity - Is it noise or is it real?
- The challenge of complex systems (e.g., the nature of robustness), to discover general principles underlying biological complexity. The science of putting the parts together to understand how the system works.
- Data handling and data mining - Extracting information and finding patterns when you don't know what to look for, to organize and describe the data in more comprehensible ways.

Places Math is Needed

- To provide quantitative and predictive theories for how biological processes work.
- Moving across spatial and temporal scales - What details to include or ignore, understanding emergent behaviors.
- Understanding stochasticity - Is it noise or is it real?
- The challenge of complex systems (e.g., the nature of robustness), to discover general principles underlying biological complexity. The science of putting the parts together to understand how the system works.
- Data handling and data mining - Extracting information and finding patterns when you don't know what to look for, to organize and describe the data in more comprehensible ways.

Recent Successes of Quantitative Approaches

- BioFire Diagnostics
- Merrimack Pharmaceuticals
- Tylenol overdose

BioFire Diagnostics

- A young biotech company developing PCR (Polymerase Chain Reaction) technology for rapid testing for viral and bacterial infection.

BioFire Diagnostics

- A young biotech company developing PCR (Polymerase Chain Reaction) technology for rapid testing for viral and bacterial infection.
- Mathematical Problems
 - reliable algorithms for melting curve analysis and qPCR (quantitative PCR)
 - primer design - high reliability and specificity
 - production efficiency, quality control issues

BioFire Diagnostics

- A young biotech company developing PCR (Polymerase Chain Reaction) technology for rapid testing for viral and bacterial infection.
- Mathematical Problems
 - reliable algorithms for melting curve analysis and qPCR (quantitative PCR)
 - primer design - high reliability and specificity
 - production efficiency, quality control issues
- Math Analysis effort spearheaded by 3 of our UofU PhD students/postdocs

BioFire Diagnostics

- A young biotech company developing PCR (Polymerase Chain Reaction) technology for rapid testing for viral and bacterial infection.
- Mathematical Problems
 - reliable algorithms for melting curve analysis and qPCR (quantitative PCR)
 - primer design - high reliability and specificity
 - production efficiency, quality control issues
- Math Analysis effort spearheaded by 3 of our UofU PhD students/postdocs
- Last month, BFD sold for \$450M cash!

Merrimack Pharmaceuticals

- A young cancer/Systems Biology company

Merrimack Pharmaceuticals

- A young cancer/Systems Biology company
- Developed a large DE simulator of biochemical network associated with several cancers. Used massive amounts of high-throughput data of mRNA and protein reactivities to fit the model.

Merrimack Pharmaceuticals

- A young cancer/Systems Biology company
- Developed a large DE simulator of biochemical network associated with several cancers. Used massive amounts of high-throughput data of mRNA and protein reactivities to fit the model.
- Discovered new drug targets

Merrimack Pharmaceuticals

- A young cancer/Systems Biology company
- Developed a large DE simulator of biochemical network associated with several cancers. Used massive amounts of high-throughput data of mRNA and protein reactivities to fit the model.
- Discovered new drug targets
- 6 compounds discovered this way are currently in stages of FDA approval.

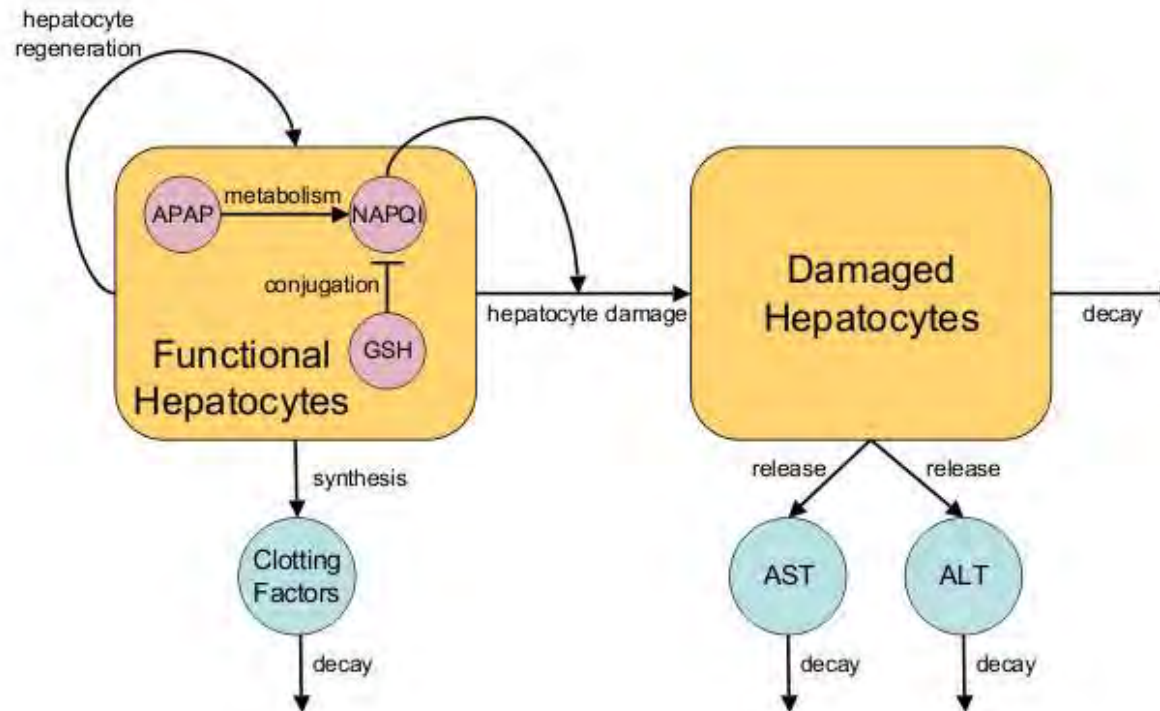
Tylenol Overdose

- The problem: Make a reliable prognosis for people with acetaminophen overdose

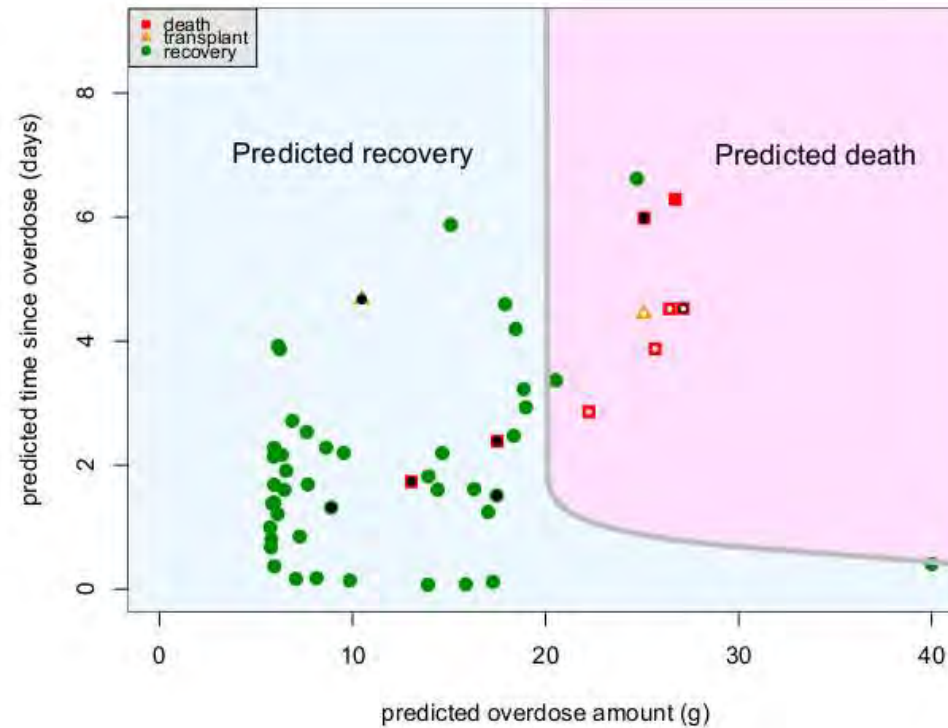
Tylenol Overdose

- The problem: Make a reliable prognosis for people with acetaminophen overdose
- Chris Remien and Fred Adler (UofU) built a (relatively simple) model (system of 7 differential equations) describing the dynamics of liver damage, glutathione and NAPQI concentrations, etc. that accurately predicts the outcome of antidote therapy.

Tylenol Overdose



Tylenol Overdose



New treatment protocols are currently under investigation ...

The use of math in modern (i.e. post-genomic, data-driven) biology is relatively new. However, the complexity of biology demands that mathematical/quantitative approaches be encouraged.