

Goal of the course:

Study spatiotemporal models in biology (model depending on both the time and the location) and related mathematics

Motivation of Math Biology

Most technology innovations in 20th century were based on physics, and it is expected that most technology innovations in 21th century will be based on biology

A branch of sciences is considered mature and reliable if a mathematical theory of this branch is established and matches with experiments (physics is, and biology is not)

What role does mathematics play in biology?

What are central questions in biology (or science)?

At what level is mathematics involved in biological sciences?

Answer from a distinguished “panel”:

James Murray (Oxford University, University of Washington)

Ian Stewart (Univ. Warwick, famous writer and mathematician)

a panel of National Science Foundation

Donald Knuth (Stanford University)

Robert May (Oxford Univ., President of Royal Society)

Mathematical models in biology (from Murray's Preface)

Why use mathematics to study something as intrinsically complicated and ill understood as development, angiogenesis, wound healing, interacting population dynamics, regulatory networks, marital interaction and so on? We suggest that mathematics, rather theoretical modelling, must be used if we ever hope to genuinely and realistically convert an understanding of the underlying mechanisms into a predictive science. Mathematics is required to bridge the gap between the level on which most of our knowledge is accumulating (in development biology it is cellular and below) and the macroscopic levels of patterns we see.

The aim in all these applications is not to derive a mathematical model that takes into account every single process because, even

if this were possible, the resulting model would yield little or no insight on the crucial interactions within the system. Rather the goal is to develop models which capture the essence of various interactions allowing their outcome to be more fully understood. As more data emerge from the biological system, the models become more sophisticated and the mathematics increasingly challenging.

In development (by way of example) it is true that we are a long way from being able to reliably simulate actual biological development, in spite of the plethora of models and theory that abound. Key processes are generally still poorly understood. Despite these limitations, I feel that exploring the logic of pattern formation is worthwhile, or rather essential, even in our present

state of knowledge. It allows us to take a hypothetical mechanism and examine its consequences in the form of a mathematical model, make predictions and suggest experiments that would verify or invalidate the model; even the latter casts light on the biology. The very process of constructing a mathematical model can be useful in its own right. Not only must we commit to a particular mechanism, but we are also forced to consider what is truly essential to the process, the central players (variables) and mechanisms by which they evolve. We are thus involved in constructing frameworks on which we can hang our understanding. The model equations, the mathematical analysis and the numerical simulations that follow serve to reveal quantitatively as well as qualitatively the consequences of that logical structure.

Mathematical models in biology

(from Murray's Preface)

Models can provide biological insight and be very useful in summarizing, interpreting and interpolating data.

There is no “right” model: producing similar temporal or spatial patterns to those experimentally observed is only a first step and does not imply the model mechanism is the one which applies.

Mathematical descriptions are *not* explanations. Mathematics can never provide the complete solution to a biological problem on its own.

Modern biology is certainly not at the stage where it is appropriate for mathematicians to try to construct comprehensive theories.

Life's other secret (from Stewart's Preface)

Until the middle of the twentieth century, it was totally unclear whether life had any kind of inorganic basis. The discovery of the first secret of life, the molecular structure of DNA (deoxyribonucleic acid), solved that particular riddle. Life is a form of chemistry, but chemistry unlike any that ever graced a test tube, chemistry is so complex that it makes an industrial city look like a village. Inside every living creature on Earth—and we know of none off it—a complex molecular code, a Book of Life, prescribes the creature's form, growth, development, and behavior. Our fate is written in our genes.

Without any question, this discovery was one of the most significant ever made. It irrevocably changed our views about the living world: it opened up entirely new ways to unravel many of life's secrets but not all of them.

Life's other secret (from Stewart's Preface)

Some secrets lie deeper than the genetic code. Genes are fundamental to earthly life, but their role in determining form and behavior tends to be overstated—especially in the media. Genes are not like engineering blueprints; they are more like recipes in a cookbook. They tell us what ingredients to use, in what quantities, and in what order—but they do not provide a complete, accurate plan of the final result. Every cook knows that a recipe is not the same as a meal: Between the cook and the dining table lie the intricacies of ovens, grills, pots and-pans, seasoning to taste. and the maddeningly obtuse behavior of ingredients. Last week, the recipe for bread worked perfectly, but this week's bread is as flat as a pancake. You won't find out why by studying the recipe, or the oven, or even both; you must also take

account of the physical and chemical laws that govern water, bicarbonate of soda, hot air, and sticky dough—and a thousand other things.

In trying to understand life, however, it is so tempting just to look at life's recipe book—its DNA code sequences. DNA is neat and tidy; organisms are messy. DNA can be captured by little more than a list of symbols; the laws of physics require sophisticated mathematics even to state them. Also, the amazing growth in our understanding of genetics has opened up so many fruitful lines of research that it will take decades to follow up the most obvious ones, let alone the more elusive ones.

Life's other secret (from Stewart's Preface)

As a consequence, we are in danger of losing sight of an important fact: There is more to life than genes. That is, life operates within the rich structure of the physical universe and its deep laws, patterns, forms, structures, processes, and systems. Genes do their work within the context of physical laws, and if unaided physics or chemistry can accomplish a task then the genes can safely leave them to it. Genes nudge the physical universe in specific directions, to choose this chemical, this pattern this process, rather than that one, but the mathematical laws of physics; and chemistry control the growing organism's response to its genetic instructions.

The mathematical control of the growing organism is the other secret—the second secret, if you will—of life. Without it, we will

novel solve the deeper mysteries of the living world—for life is a partnership between genes and mathematics, and we must take proper account of the role of both partners. This cognizance of both secrets has run like a shining thread through the history of the biological sciences—but it has attracted the mavericks, not the mainstream scientists. Instead of thinking the way most biologists think, these mavericks have been taking a much different approach to biology by thinking the way that most physical scientists and mathematicians think. This difference in working philosophy is the main reason why understanding of the deeper aspects of life has been left to the mavericks.

Models to study in this class:

population biology (animal group(s) or humans)

biochemical model (bacteria, microorganism)

epidemiology (influenza, malaria, AIDS, Ebola, SARS, bird flu)

environmental science model (pollution)

natural resource management (fishery, forestry)

chemical reaction model (autocatalytic reactions)

self-organized pattern formation (sand dune, wetland, coral reef, Prigogine)

morphogenesis (stripe, spots of leopard and giraffe, pattern of seashell, Turing pattern)

neural conduction (Hodgkin-Huxley, FitzHugh-Nagumo equation)

finance (Black-Scholes's model)

Biological Systems of current interests

A Workshop at the National Science Foundation March 14 and 15, 1996

<http://www.nsf.gov/bio/pubs/mobs/mobs.htm>

I. MOLECULAR AND CELLULAR BIOLOGY

1. GENOME

2. PROTEIN STRUCTURE AND FUNCTION

3. SIMULATIONS

4. BIO-INSPIRED MATERIALS

II. ORGANISMAL BIOLOGY

1. CELL SIGNALING

2. MECHANICS AND EMBRYOLOGY

3. BIOFLUID DYNAMICS

4. IMMUNOLOGY AND VIROLOGY

5. NEUROSCIENCES

III. ECOLOGY AND EVOLUTIONARY BIOLOGY

- 1. Conservation biology, the preservation of biodiversity**
- 2. Global change**
- 3. Emerging disease**
- 4. Resource management**

Other areas

A. POPULATION GENETICS

B. CONSERVATION BIOLOGY

C. MANAGEMENT OF NATURAL SYSTEMS

D. GLOBAL CHANGE AND BIODIVERSITY

E. THE DYNAMICS OF INFECTIOUS DISEASES

Professor Donald Knuth on Biomathematics

<http://tex.loria.fr/historique/interviews/knuth-clb1993.html>

Professor Donald Knuth, of the Stanford Computer Science Department was once interviewed and had some comments on issues related to Biomathematics:

CLB: If you were a soon-to-graduate college senior or Ph.D. and you didn't have any "baggage", what kind of research would you want to do? Or would you even choose research again?

Knuth: I think the most exciting computer research now is partly in robotics, and partly in applications to biochemistry. Robotics, for example, that's terrific. Making devices that actually move around and communicate with each other. Stanford has a big robotics lab now, and our plan is for a new building that will have a hundred robots walking the corridors, to stimulate

the students. It'll be two or three years until we move in to the building. Just seeing robots there, you'll think of neat projects. These projects also suggest a lot of good mathematical and theoretical questions. And high level graphical tools, there's a tremendous amount of great stuff in that area too. Yeah, I'd love to do that... only one life, you know, but...

CLB: Why do you mention biochemistry?

Knuth: There's millions and millions of unsolved problems. Biology is so digital, and incredibly complicated, but incredibly useful. The trouble with biology is that, if you have to work as a biologist, it's boring. Your experiments take you three years and then, one night, the electricity goes off and all the things die! You start over. In computers we can create our own worlds. Biologists deserve a lot of credit for being able to slug it through.

It is hard for me to say confidently that, after fifty more years of explosive growth of computer science, there will still be a lot of fascinating unsolved

problems at peoples' fingertips, that it won't be pretty much working on refinements of well-explored things. Maybe all of the simple stuff and the really great stuff has been discovered. It may not be true, but I can't predict an unending growth. I can't be as confident about computer science as I can about biology. Biology easily has 500 years of exciting problems to work on, it's at that level.

An article by Robert May (Feb 6, 2004, Science):

A paradigmatic account of the uses of mathematics in the natural sciences comes, in deliberately oversimplified fashion, from the classic sequence of Brahe, Kepler, Newton: observed facts, patterns that give coherence to the observations, fundamental laws that explain the patterns.

Tycho Brahe (1546-1601) made the most precise instruments available before the invention of the telescope. The instruments of Brahe allowed him to determine the detailed motions of the planets. In particular, Brahe compiled extensive data on the planet Mars.

Johannes Kepler (1571-1630), Brahe's assistant. By using Brahe's data, he formulated the correct theory of the Solar System: Three Laws of Planetary Motion. But he was not able to prove them mathematically.

Isaac Newton (1642-1727) is the greatest scientist ever. He demonstrated that the motion of objects on the Earth could be described by three new Laws of motion, and then he went on to show that Kepler's three Laws of Planetary Motion were special cases of Newton's three Laws. In fact, Newton went even further: he showed that Kepler's Laws of planetary motion were only approximately correct, and supplied the quantitative corrections that with careful observations proved to be valid.

Consider the role played by applications of mathematics in sequencing the human and other genomes. This adventure began with the recognition of the doubly helical structure of DNA and its implications, an oft-told tale in which classical mathematical physics played a central role. Brilliant biochemical advances, allowing the 3 billion-letter-long human sequence to be cut up into manageable fragments, were a crucial next step. The actual reassembling of the sequence fragments, to obtain a final human genome sequence, drew on both huge computational power and complex software, itself involving new mathematics. The sequence information, however, represents only the Tycho Brahe stage. Current work on various genomes uses pattern-seeking programs to sort out coding sequences corresponding to individual genes from among the background that is thought to be noncoding. Again, elegant and sometimes novel mathematics is

involved in this Keplerian stage of the work in progress. We are only just beginning, if that, the Newtonian stage of addressing the deeper evolutionary questions posed by these patterns.

In this Newtonian quest, mathematical models will help in a different way than in earlier stages. Various conjectures about underlying mechanisms can be made explicit in mathematical terms, and the consequences can be explored and tested against the observed patterns.