Symmetry and Bifurcation in Biology

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A brief background

Interest in the application of mathematical methods to biology has been growing rapidly, worldwide, in recent years. The great advances in molecular biology have opened up major new areas, but it is becoming recognised that DNA sequences and other molecular information are only one aspect of the understanding of biological systems. Organisms make use of DNA in highly dynamic contexts. For example DNA has a significant role in organising the development of an organism, but that very little information about the form of the organism and its developmental path can be 'read off' from its DNA sequence. Genetics acts in concert with dynamical physical and chemical processes. The more we learn about genes, the more evident becomes the need for a good understanding of dynamic effects in biology— in growth, in development, in the regulation of genetic networks, in ecosystems, and in evolution.

The mathematics of dynamical systems has undergone its own revolution, as the need to consider nonlinear effects has become clear. The theory of dynamical systems is one of the major growth areas of today's mathematical research, and one of its strengths is a strong conenction with applied science.

Pattern formation in physical systems is one of the major research frontiers of mathematics and one of the ways that patterns are studied is through symmetry-breaking bifurcations. Standard examples of pattern forming systems include the Taylor-Couette experiment, Benard convection, and combustion [11]. In these systems patterns may be spatial or a combination of spatial and temporal.

Only more recently have patterns been studied in biological systems using symmetry techniques. In physical systems symmetry often appears through homogeneity — the equations of fluid dynamics and reaction-diffusion systems are identical near every point in space. Biological systems are very good at producing (near) identical cells and this is often the source of symmetry in these systems. Examples of pattern forming biological systems appear through Turing bifurcations in the work of Murray, Maini and others (whose mathematical formulation is close to those in physical systems — mainly reaction-diffusion systems) and central pattern generators (that control rhythms in the nervous system). Moreover, in biological systems, finite symmetry groups seem to be as important as continuous ones.

Mathematically, the symmetries of a system can be used to work out a 'catalogue' of typical forms of behavior and bifurcation theory can be used to decide which of these forms are likely to be seen first. This catalogue is to a great extent model-independent. By this we do not mean that the specific model involved is irrelevant, but that a much can be deduced by knowing only the

symmetries of that model. In a sense, all models with a given symmetry explore the same range of pattern-forming behaviors, and that range of behaviors can be studied in its own right without reference to many details of the model. This workshop addressed both the relevant theory and its application to a variety of biological systems.

Here is a short list of biological systems where pattern formation research has been active.

- Pattern Formation: Turing [22], Murray and Maini [16, 17, 15], Gierer and Meinhardt [10].

  Patterns appear in a variety of biological contexts — most notably in the skin of many animals. Attempts to explain these patterns using reaction-diffusion equations and symmetry-breaking bifurcations began with Turing's seminal work.

- Locomotor central pattern generators: Ermentrout and Kopell [13, 14], Buono, Collins, Golubitsky, and Stewart [12, 6].

  Many biologists believe that there is a cluster of neurons (called central pattern generators) somewhere in the nervous system that generate the rhythms seen in animal locomotion. Models for CPGs often involve symmetry and the rhythms themselves are described by spatio-temporal symmetries of persiodic states.

- Visual cortex: Ermentrout and Cowan [7]; Bressloff, Cowan, Golubitsky, and Thomas [4, 3].

  Ermentrout and Cowan showed that geometric visual hallucinations could be viewed as pattern formation in an 'activity variable' representing the voltage of neurons in the visual cortex. These pattern formation arguments were based on symmetry arguments just as in Turing bifurcations. However, the story is more complicated as neurons in the primary visual are sentitive to the direction of contours in the visual field. This physiological fact changes the way that symmetry arguments are used in pattern formation arguments leading to new forms of bifurcation and new applications.

- Genetic code: Forger and Hornos [9, 1].

  Can the 'genetic code' (the ways that codons represent amino acids) be a product of symmetry breaking. Hornos and Forger argue yes. It is a speculative but interesting idea based on representation theory (in analogy to the way that elementary particles are viewed as irreducible representations.

- Speciation: Elmhirst, Cohen, and Stewart [18, 19, 20].

  Sympatric speciation (the dividing of co-mingling species into new species) can be viewed as a symmetry-breaking bifurcation. The traditional view that most speciation was due to allopatric speciation (new species forming from two identical but geographically separated species evolving differently) was based in part on the traditional misconception that a symmetric system must have symmetric solutions. Once it is realized that most solutions to a symmetric equation are asymmetric, spontaneous symmetry-breaking can show broadly why sympatric speciation is a reasonable alternative.

- Spiral waves: Barkley [2], Winfree [24], Glass [5], Wulff [8]

  Spiral waves are known to occur in various biological systems including the heart (eg [5]) and to be asociated with unwanted dynamics. Thus the description and control of spiral waves could in principle have inportant applications. Spiral waves are rotating waves (time evolution is the same as spatial rotation) and symmetry is a good way to describe these states [11]. Winfree [24] explored various quasiperiodic meandering spiral wave states. Much about these states were understood phenomenologically using Euclidean symmetry by Barkley and then more rigously by Wulff *et al*.

- Slime mold: Takamatsu and Tanaka [21], Weijer [23].

  In an unexpected way the growth of slime molds leads to periodic states exhibiting spatiotemporal symmetries.

Objectives of the workshop

There are two distinct ways to encourage interaction between mathematics and biology. 'Horizontal' programs select specific problems in biology (such as protein-folding) and bring many different mathematical methods to bear. Our workshop was the other kind of meeting: a 'vertical' program organized around a package of general methods that apply to many different biological problems. In this case, the package is the exploitation of symmetries in nonlinear dynamial systems, and the strong relation between symmetry and pattern formation.

Over the past 15 years, we and other authors have explored a far more active role for symmetry, in the context of nonlinear dynamical systems. It has become apparent that the symmetries of a system of nonlinear ordinary or partial differential equations can be used, in a systematic and unified way, to analyze, predict, and understand many general mechanisms of pattern-formation.

It is important to understand that 'pattern' here is not restricted to visual patterns such as shape or pigmentation. The structure and function of the visual cortex involves patterns, and can be modelled by a symemtric network of neurons. The formation of new species is a pattern: oen group of organisms, a highly symmetric situation, splits into two groups— a less symmetric one. Synchronous firing of neurons, which seems to be an important feature of brain function, is a pattern. Phase relations in biological oscillators are patterns.

In physics, patterns can often be understood by writing down very specific and accurate mathematical models — equations. Few areas of biology are yet equipped with equations of comparable accuracy. It is here the the symmetry approach has major advantages: it is a general method that applies to a variety of models. It can lead to general conclusions even when specific models are unknown, or controversial, or of limited accuracy.

The point here is not the literal symmetry of a biological system, or an organism, or a process. Hardly anything in biology is exactly symmetric. But a huge range of biological systems possess approximate symmetries (for example all organisms in a species are approximately identical), and the best way to model such systems is to exploit the symmetry of an idealised model, and then consider what changes might occur to the conclusions if the symmetry is close, but not exact.

Activities and Developments

Our workshop on *Symmetry and Bifurcation in Biology* brought together mathematicians studying the role of symmetry in pattern formation and more generally equivariant dynamics, with mathematical biologists and neuroscientists studying interesting biological systems, in an attempt to crossfertilize. Participants benefited from the inspirational beauty of the natural setting as much as as from the efficiently run infrastructure of BIRS, that freed them from everyday distractions. Discussions continued out of the lecture room and into the lounge and beyond, to the hiking trails and the excursion to the top of Sulfur Mountain.

In the course of the Workshop several important sub themes emerged, which can be described as follows.

Synchronization and spatio-temporal patterns in coupled oscillator systems

As mentioned above, many biological systems involve networks of symmetrically connected identical "cells", each of which can oscillate. Speakers described many variations on this theme of coupled cells. Peter Ashwin and Mike Field presented new results on coupled cell networks with invariant sets, linked by many heteroclinic connections of which only a small number are selected by the dynamics. Igor Belykh studied models of networks of neurons, oscillating chaotically but capable of synchronization, even when the cells are not identical so that the perfect symmetries are broken. Luciano Buono presented a model of the CPG for locomotion of quadrupeds. The spatio-temporal symmetries of his model correspond to all the observed "gaits" of quadrupeds, and lead to a natural distinction between primary and secondary gaits. Rod Edwards studied gene regulation networks, in the mathematically tractable "hard switching" limit. His theory predicts a rich variety of stable dynamics and allows a natural classification of bifurcations of limit cycles. Marty Golubitsky and Jeroen Lamb presented a potpourri of theory and examples of coupled cell systems and addressed the

question of which of the observed dynamics is due to network architecture and which to the specifics of the cells. Yue Xian Li described a model-dependent approach to the modeling of animal gaits leading to a simplest possible network capable of producing the observed animal gaits. Jeff Moehlis presented new results on networks of identically coupled identical oscillators, obtained by reducing the original equations to phase variables that converge to fixed phase differences. The theory is applied to coupled Hodgkin-Huxley neurons. Reiko Tanaka found new hidden symmetric patterns in chains of slime mold oscillators and proposed a new model that can explain all the observed and hidden patterns.

Nonlinear wave patterns and PDE

Among the many nonlinear wave patterns known to occur in biology, those given the most intensive scrutiny in this Workshop were found in the brain and the heart. Paul Bressloff focussed on the effects of spatially periodic inhomogeneities in cortical patterns (brain waves) reflecting the underlying crystaline structure of the cortex, and showed how hallucinatory patterns may arise. Leon Glass studied the propagation of waves in the heart and their relatinship to abnormally fast cardiac arrhythmias that suddenly start and stop. Carlo Laing developed PDE methods for pattern fomation in a spatially extended domain in a plane. Victor LeBlanc presented new results on forced symmetry-breaking for spiral waves in excitable media modelled by reaction-diffusion PDE and Ian Melbourne explained the hypermeander of such spirals, in which the spiral tip undergoes Brownian-like motion. Wayne Nagata showed how the growing tips of plants may be modeled by reaction-diffusion equations, for which bifurcation theory predicts the branching of the growing tips. Peter Thomas and Andrew Torok discussed symmetry-induced coupling of cortical feature maps in the brain and showed how natural symmetry assumptions lead to patterns that are similar to hallucinations observed e.g. by drug users. Lindi Wahl investigated an evolutionary model of the division of labor, in which each individual carries a subset of all genes necessary for survival of the population, and predicts the evolution of the population into generalists, specialist and parasites.

Bursting patterns and neurons

Bursting behaviour of neurons is essential in brain functions such as motor control, information processing and memory formation. Gennady Cymbalyuk explained the interplay between experiments and dynamical systems analysis on the heartbeat motor pattern in leaches. Gerda DeVries presented a bifurcation analysis of the bursting behaviour of pancreatic beta cells, showing that a pair of two cells gives a better representation of a population of cells than a single cell. Brent Dorion studied sensory networks with time delays in the sensory feedback loop and applied this to electric fish. Tomas Gedeon investigated how sensory systems code information about the outside world in spike trains. Frank Hoppensteadt described bifurcation-based modeling of neural networks. Andrey Shilnikov argued that the Lukyanov-Shilnikov bifurcation of a saddle-node periodic orbit explains the bi-stability observed in a neuron model based on a Hodgkin-Huxley formalism.

Iterated function schemes and other variations

Modeling issues in areas such as sympatric speciation suggested some new variations on the existing coupled cell system approach of Cohen, Elmhirst, and Stewart, which employs a network with all-to-all coupling and full symmetric-group symmetry $\mathbf{S}_N$, where N is the number of coarse-grained samples from the population. The first is to form some kind of scaled limit of the ODE model as N tends to ∞. This presumably would be an integro-PDE modeling the time-evolution of the probability distribution of phenotypes, and it would therefore correspond directly and precisely to biological variables. The coupled cell system models would be discretizations of this continuum model. A second variation is to use a random interaction network at each iteration step, chosen (say) so that any given edge occurs with fixed probability p. The resulting model forms a nonlinear iterated function scheme in the sense of Barnsley, with the additional feature that the *set* of functions being iterated is invariant under the action of $\mathbf{S}_N$, even though most of the individual functions are

not invariant. Ths type of model deserves further investigation: it represents the biology more realistically, and it possesses new and interesting mathematical features.

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