

# Mathematical Biology

## Research Trends

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**Lachlan B. Wilson**  
Editor

# MATHEMATICAL BIOLOGY

## RESEARCH TRENDS

LACHLAN B. WILSON

EDITOR



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## PREFACE

Applying mathematics to biology has a long history, but only recently has there been an explosion of interest in the field. Some reasons for this include: the explosion of data-rich information sets, due to the genomics revolution, which are difficult to understand without the use of analytical tools, recent development of mathematical tools such as chaos theory to help understand complex, nonlinear mechanisms in biology, an increase in computing power which enables calculations and simulations to be performed that were not previously possible, and an increasing interest in *in silico* experimentation due to the complications involved in human and animal research. Applying mathematics to biology has a long history, but only recently has there been an explosion of interest in the field. Some reasons for this include: the explosion of data-rich information sets, due to the genomics revolution, which are difficult to understand without the use of analytical tools, recent development of mathematical tools such as chaos theory to help understand complex, nonlinear mechanisms in biology, an increase in computing power which enables calculations and simulations to be performed that were not previously possible, and an increasing interest in *in silico* experimentation due to the complications involved in human and animal research.

Chapter 1 presents mathematical models of infectious disease transmission, which add a new dimension of information to assist in public health policy for disease control. They are useful for understanding complex nonlinear systems of transmission and to predict future epidemic trajectories based on different intervention or resource allocation strategies. The science of mathematical and computational population biology that advances this understanding uses various forms of models that vary from deterministic compartmental models, to stochastic models, to dynamically evolving contact networks between individuals. All models require realistic detail and realistic parameter values. For practitioners in this field to make a real-world difference and influence public health policy, policy-makers and/or medical experts must be consulted or heavily involved to ensure realism of model structure and most importantly appropriate parameter estimates. Detailed mathematical analyses are generally of very little real-world importance but uncertainty and sensitivity analyses are a highly under-developed component of current models and must be utilized to a much greater extent (such methodology is clearly presented here in a manner for implementation by any quantitative practitioner). Instead of bringing specific quantitative tools to the research arena, one should determine the important research questions in need of investigation and then use (or obtain) the necessary tools to address the specific key research issues. Additionally, the incorporation of data analysis tools within mechanistic causal models is also important for

future innovative modeling in this field. Above all, the clear and powerful presentation of results in various forms, including effective communication to disseminate results to key authorities, is essential if modeling is to be used insightfully and influentially in designing (or changing) policy decisions.

The theory of metabolism can be subdivided in two main fields: dynamic theory and structural theory. Dynamic theory attempts to produce a description of the systemic dynamic behavior from as little experimental information as possible. Structural theory provides ways of decomposing complex networks in ways that reveal inherent functional relationships between the parts of the system. Since metabolic systems function out of equilibrium, due to the permanent input of material and energetic fluxes, dynamic theory has to deal with non-linearities. On the other hand, structural theory analyses the null-space of a matrix of relationships (usually, the stoichiometric matrix, giving rise to stoichiometric analysis) and therefore it belongs to either linear or convex analysis. Chapter 2 provides a new dynamic theory that generalizes some others, such as Metabolic Control Analysis (MCA) and Biochemical Systems Theory (BST), to time-varying external fluxes of any form, and provides a straightforward way of connecting the non-linear dynamics of metabolic systems to their stoichiometric structure, by means of a set of new properties. In particular, the non-linear response is described in terms of a generalized perturbation theory whose main coefficients are the susceptibilities (much in the same way as in non-linear optics). These coefficients are time-dependent (on one or more perturbation times) and become translationally invariant in time as the system approaches a steady state (the main realistic state of metabolic networks, apart from oscillatory behavior). Hence they can be integrated into constant coefficients, the responsivities, that provide a set of constraints connecting the dynamics and the stoichiometry of the network. As a consequence, the number of stoichiometric degrees of freedom can be reduced because of the dynamics of a specific system. This result, is illustrated by means of examples. The theory presented herein falls in the field of functional analysis, since the susceptibilities are functional derivatives of the response with respect to complete time-courses of the input fluxes, which work as the excitations of the metabolic network and can be manipulated in experiments. Hence, the constraints provided by the theory should help simplify highthroughput experiments.

In Chapter 3, the authors develop a mathematical model describing the haptotactic migration of cells in a pre necrotic avascular tumour. Initially, the model which involves a moving boundary is developed for general three dimensional geometry and then modified for the specific multicell tumour spheroid geometry. A full nondimensionalisation is performed and the model is mapped to a fixed domain to facilitate numerical simulation. Numerically calculated solution profiles are then presented to provide predictions of the behaviour of cells in pre necrotic multicell tumour spheroids. Attention is paid to both passively migrating cells, and cells that respond to gradients in a simultaneously constructed extracellular matrix that is, cells that migrate haptotactically. The model solutions are used to propose biologically relevant hypotheses about the behaviour of cells in pre necrotic avascular tumours and the extracellular matrix in which they reside.

Cholera is a gastrointestinal disease caused by a gram negative comma shaped bacterium of the genus *Vibrio cholerae*. It is often associated with poor hygiene of drinking water, food preparations and waste disposal particularly faeces. It rapidly causes diarrhea, vomiting and dehydration which could be fatal if not medically attended to timeously. The

diarrhea is caused by a toxin produced by the bacterium. This toxin causes the efflux of salts and water into the gastrointestinal tract. Cholera as a disease is a serious public health problem in the developing world, and since the first recorded cases, it has spread rapidly across continents, resulting in numerous deaths. The aim of Chapter 4 is to use mathematical modeling to analyze the dynamics of this disease with and without treatment. Thus, the authors present a single-season deterministic model for cholera transmission dynamics with carriers in a human population and a pool of pathogens. The mathematical features such as the epidemic threshold, equilibria and stabilities are determined. A Lyapunov functional approach is used to analyse the stabilities of equilibria. The authors qualitatively analyse positivity and boundedness of solutions. In the absence of treatment, the trivial equilibrium is shown to be a saddle, while the two biologically meaningful equilibria, namely the disease-free is globally asymptotically stable provided certain conditions are met, and the endemic equilibrium state is only locally stable. The epidemic threshold is used to assess the effectiveness of treatment in controlling cholera in a community. Conditions for cholera containment and persistence are derived using comprehensive analytical and numerical techniques. It is shown from the study that treatment of cholera sufferers reduces the burden of the disease in the community. Further, it is also shown that as long as the pathogen is present in the environment, it will be difficult to eradicate cholera and the existence of carriers may remain a challenge in the control of the epidemic in settings with treatment of cholera sufferers.

The functioning of the immune system involves tightly regulated proliferation, differentiation and death processes of heterogeneous cell populations, including T lymphocytes, B lymphocytes, antigen presenting cells, etc. To quantify the turnover kinetics of specific subsets of immune cells under normal conditions and during infections, labeling techniques (e.g., with fluorescent markers CFSE or BrdU) in conjunction with flow cytometry analysis (FACS) are used in experimental and clinical immunology. To obtain information about the kinetic structure of the cellular responses of heterogeneous cell populations from data that in addition to experimental fluctuations (noise) exhibit considerable variation between different study animals, careful computational analysis is needed. The primary objectives of Chapter 5 are: (i) to introduce mathematical models in the form of hyperbolic partial differential equations (PDEs) which allow direct reference to single or double label histograms of cell distributions, (ii) to illustrate the potential of the modeling and parameter identification technology by representative examples from CFSE and BrdU labeled T cell proliferation studies, and (iii) to compare the proposed PDE models with alternative modeling approaches which are based upon the use of ordinary differential equations.

In Chapter 6 the authors review a number of immunological models of HIV as well as the contribution of mathematical immune modeling of HIV to understanding of HIV. The authors also review a number of epidemiological models, particularly those of HIV. The focus of this review is the development of novel immuno-epidemiological models which link immunological and epidemiological models. The authors first review a simple immunoepidemiological model of transient disease (a disease where infected individuals necessarily recover), and then they introduce an immuno-epidemiological model of HIV. The authors discuss the drawbacks of this simple immuno-epidemiological model as well as methods to address them. They introduce and discuss several other models and their advantages and disadvantages. In the discussion the authors focus on the types of questions

that can be addressed with immuno-epidemiological models and how those can contribute for the development of mathematical biology.

As presented in Chapter 7, the development of physical and mathematical models dealing with the deposition and bronchial clearance of aerosol particles in the human respiratory tract has its origin in the 1970s. Theoretical approaches of this time were usually based on an airway geometry being either approximated by a sequence of straight cylindrical tubes or by a single, variable cross-section channel resembling a trumpet shape. The branching network of lung airways was initially described by a fully symmetrical tree structure (e.g. Weibel's lung model A), within which tubes of the same airway generation were characterized by identical geometric parameters (i.e. diameters, lengths, branching and gravity angles). As a further consequence of this symmetry pathways leading from the trachea to the closing alveolar sacs consisted of the same number of tubes, representing a remarkable simplification for the simulation of deposition and clearance scenarios.

In reality, the human tracheobronchial tree is marked by a significant asymmetry due to the variation of airway geometry within a given generation. Since the end of the 1970s and the early 1980s increased attention was paid to this important fact by the construction of a five-lobe lung model, where intrasubject variation of bronchial geometry was still limited to the first three or four bifurcations. A better approach of the variability of airway properties took place by the formulation of a stochastic model of the human respiratory tract in the middle of the 1980s. With this model both asymmetry and randomness could be well approximated on the basis of available morphometric data. In addition, computation of deposition and bronchial clearance was improved due to a variation in the number of bifurcations leading from the proximal to the distal end of the bronchial pathway.

Currently, stochastic lung models represent the state of the art in simulating deposition and clearance of inhaled particles. In recent years, computation of particle deposition was successively refined by numerical approaches, enabling the determination of exact particle trajectories within single, double, and triple bifurcations. Bronchial clearance was improved by generation-specific variations of mucus thickness and mucus production, causing a remarkable variability of mucus velocity. Additionally, slow bronchial clearance mechanisms were defined, with the help of which particle residence times  $> 24$  hours could be explained.

Chapter 8 starts by introducing a brief review of the history of interdisciplinary research in biology, as well as some of basic concepts from molecular biology. Then, the authors present a survey of the philosophy and goals of a new area of interdisciplinary research: systems biology. Finally, the authors review their efforts of the past few years to understand, via mathematical modeling, the dynamic behavior of one of the most studied gene regulatory networks in bacteria: the tryptophan operon, and offer new results.

In Chapter 9 the authors consider the impacts of two factors, namely the form of the nonlinearity of the infectious disease transmission rate and the mortality associated with a disease, on the dynamics of this infectious disease in a population. The authors consider a very simple discrete-step compartment epidemiological models and a very general form of the nonlinear transmission assuming that the transmission is governed by an arbitrary function constrained by a few biologically feasible conditions. The authors show that when the population size can be considered constant, these models exhibit asymptotically stable steady states. Precisely, the authors demonstrate that the concavity of the disease transmission function with respect to the number of infective individuals is a sufficient condition for this

stability: in this case the models have either an unique and stable endemic equilibrium state, or no endemic equilibrium state at all; in the latter case the infection-free equilibrium state is stable.

The authors demonstrate that under some circumstances the mortality inflicted by the disease is able to destabilise endemic equilibrium state and can lead to a supercritical Hopf bifurcation in the system. However, it appears that for the majority of human infections the threshold for this bifurcation is too high to be realistic.

Human and animal locomotion represent a highly complex control problem. Internal and external disturbances increase these difficulties to maintain or achieve stability in static and dynamic situations. Two kinds of stability can be distinguished: on the one hand the stability is achieved by reflexes and control with neural feedback, and on the other hand stability is based on mechanical properties and the geometrical configuration of muscles and tendons within the musculoskeletal system. The present article is mainly interested in the latter one, which is called selfstability. Biological systems adapt the pure mechanical properties of muscles and passive structures to support stability and to cope with disturbances. In the following, the authors mainly restrict ourselves to one joint with a pair of antagonistic muscles; in particular, the authors will focus on the human elbow joint. The authors describe the most important mechanical properties of muscles and summarize them in a model of a general joint with antagonistic muscles. This model is a system of ordinary differential equations for the joint angle and its angular velocity.

If the antagonistic muscles are activated in a certain relation, then the joint is in an equilibrium state. The definition of stability in the mathematical sense is given using the framework of dynamical systems. The eigenvalues of the linearization at the equilibrium give a detailed characterization of solutions near the equilibrium: real and complex eigenvalues lead to qualitatively different behavior of solutions, and the absolute value of their real part tells us how fast the equilibrium state is approached after a small perturbation.

Can the authors quantify the stability of an equilibrium point? The authors would surely assume the equilibrium point to be the “more stable” the larger its basin of attraction is. The basin of attraction consists of all perturbations which are led back to the equilibrium. Is an equilibrium also the “more stable” the faster small perturbations are corrected? The mathematical analysis will show that the answer depends on the situation.

Besides an overview over the problems and results of mathematical stability analyses in biomechanics, in Chapter 10 the authors apply the theory to a specific situation. More precisely, the authors consider a waiter holding a glass of water. The task is not to spill the water in the glass under perturbations. The question is, whether less water is spilled by a high or a low co-activation of the elbow muscles. The mathematical analysis will show that the answer depends on the position of the upper arm.

There is a great interest for a mechanistic understanding of molecular transport across biological and reconstituted membranes due to its potential applications to the development of news methodologies in medical biotechnology, such as gene therapy and drug delivery. In the first part of Chapter 11, the authors present the behavior of the liposomes under osmotic stress. Because of the mechanical tension induced by osmotic flow, the liposomes expand, triggering transient lipidic pores that fluctuate at the nanoscopic level until their death. The authors report here that this is a periodic process. Such a liposome, also called a pulsatory liposome, is characterized by the number of successive pores, the time interval between two successive pores, and the amount of exchanged material through a single transmembrane



pore. The diffusion of water through the liposomal membrane is analyzed in detail. In the second part of this paper, the authors develop a theoretical model for analyzing experimental data, facilitating information about the diffusion and exchange through spherical interfaces. The effects of experimental parameters, including the bilayer stiffness and the viscosity of the internal fluid, are analyzed and discussed as well.

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## **SHORT COMMUNICATION**



# **BIOLOGICAL COMPLEXITY BY NATURAL SELECTION AND SELF-ORGANIZATION: A GAME OF SURVIVAL**

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Since the beginning of biology, a debate has existed between selectionists and neutralists. Fisher (1930) formalized Darwin's idea of natural selection and proved that the fitness of a species will be maximized in a pure-line population. This is equivalent to saying that if the natural selection really happens along billions of years of evolution, polymorphism in species will cause genetic load and therefore should be rare in nature. Counter-intuitively, this is not the case. Haldane (1930) and Wright (1930) at the same time criticized Fisher's arguments by the prevalence of polymorphism in species. According to the neutral theory (Kimura 1983), natural selection is almost futile at the molecular level as most genes are neutral in terms of the fitness of an organism. The result of this debate was the compromise on the unit of natural selection, i.e. at the individual level (although later a theory of group selection also emerged), and further put Darwin's evolution through natural selection into an awkward situation. However, allowed me to postulate: merging of functioning clusters of DNA sequences (gene) could be through the self-organization formed by the positive feedback between its products (protein) and the gene (or other genes) [proteins help genes to make proteins]. This co-evolved process (positive feedback) between particular DNA and protein could be interlinked with other similar processes and self-organized together forming a higher level of complexity, i.e. life itself.

At a larger scale, a similar story was retold. Clements (1916) asserted that under disturbance a community can converge onto a single, stable, mesophytic equilibrium (monoclimax), which determined by the regional climate (a superorganism). In other words, succession in an ecosystem is a universal, orderly process of progressive change. The real king will eventually return. Patten (1971) also regarded the ecosystem as an evolutionary entity. Gleason (1926) rejected this superorganism idea by an individualistic view. Egler (1954) rephrased this individualistic as this: succession is on a high level of sociologic integration, not a matter of individual species, i.e. a (instead of 'the') king will come. Drury

and Nisbet (1973) indicated that the first steps toward theories of succession should be based directly on properties of organisms, rather than emergent properties of ecosystems. My question is: (A) does a community (or an ecosystem) have its own identity or is it just a concoction of millions of individuals with thousands of species? (B) How can we test such an argument?

To test whether a community is a functioning team or a mere conglomerate, two ways lie ahead. One is to judge by its consequences, i.e. the macroecological patterns generated. MacArthur and Wilson (1967) found that the species-area relationship on islands can be largely explained by a colonization-extinction process. Hubbell (2001) also showed the extreme closeness of the abundance rank curve in a neutral community to a real one. Range size distribution and many other patterns in macroecology have found their enlightenments in the neutral theory. However, Tilman (2004) argued that the niche theory (the beloved son of natural selection in ecology) can also perform realistic patterns in community. The debate has far from ended.

The other way to test the ‘meaning’ of a community has an obvious application in conservation, especially under the pressure of globalization. These early studies identified the characters of a ‘pioneer’ species as those with great seed production, high speed mobility, high light requirements (for plants) and ability to tolerate disturbed environments, high colonizing and dispersal ability, an opportunist, or a fugitive. All these characters fit the description of a perfect invader, i.e. for an alien species to establish and expand in an endemic community. According to Clements’ superorganism theory, an alien species that has the same trait (or function) as an endemic species will be difficult to invade due to the resilience (or competitive exclusion). Yet, Gleason’s and Hubbell’s neutral theory implies that an alien species with a similar niche as some endemic species will be easy to invade with the help of disturbance. We can only find out which one is true at the future synthesizing stage of invasion biology.

As far as I am concerned, two processes play an important role in the shaping and emerging of biological patterns (or complexity): natural selection and self-organization. Translated into ecology, these two processes become the niche and the neutral theory. Of course, to observe such a biological pattern, statistic artifacts and sampling prejudice come in and make a picture through our lenses. Like making a movie, the niche theory (natural selection) decides who will be the actors and what role (function) each actor will play. The neutral theory (self-organization) decides what kind of story they will tell and organizes species in a certain way to generate the community pattern. Statistic artifacts and sampling prejudice suggest that each one will have different feelings or responses to the movie. However, let’s forget those artifacts and prejudice for a while and only focus on the real patterns beneath.

There are five hierarchies of biological complexity. First, from biochemistry (physics) to life (self-organized replicating molecular system). Natural selection chooses which functioning clusters (of molecules) should interlink or compete with each other. Self-organization (such as crystal formation and reproduction) holds different functioning clusters together and generates the basic “self-replicating” character of life systems. Although the evolution of genetic code (DNA and RNA) and the emerging of advanced function in unicellular organisms could be far more complicated, the key process could be captured by natural selection and self-organization. Second, from simple life unit (cell) to organism. Will a self-organized cell clusters have a greater selection advantage than a single cell? Organism

development and metabolic allometry provide a possible start. Third, the population formation, its behavior and culture. Natural selection surely becomes an obvious process at this level. Behavior, such as altruism, and culture can be formed through ecological imprints and niche construction, accompanied by particular spatial patterns in time and in space. Fourth, speciation and the formation of a community. The species concept is crucial to the study of the evolution of complexity and biodiversity. The ecological interactions, such as resource competition, predation and migration (or dispersal) play an important role in the process of speciation. Meanwhile, evolutionary processes, such as mutation and gene drift, also affect this process. A community could be the necessary consequence of the speciation and ecological process (the evolutionary equilibrium might not be achieved in community). The boundary of a community could be just an artifact, as a community only generates patterns, without a clear function. Finally, the formation of ecosystem function and the self-containing of the whole biosphere. Individuals and species in the community are entangled with all kinds of biological interactions, which give rise to the new properties at the ecosystem and global level. Ecosystem service supports each species (including humans). The earth living system can self-sustain itself (Gaia theory). Energy and matter (such carbon cycle) flow in-and-out and interact with the abiotic sphere on earth. This is the final level of biological complexity.

I would like to end here by describing a game of survival. It simplifies the coevolved biological system by natural selection and self-organization. The game starts with twelve people who don't know each other. During one week of living together (on an isolated island), each one comes to know the others in terms of their personality, common interests, etc. Therefore, friendship begins to make clusters and divisions in these twelve people (a process of self-organization). At the end of each week, one person will be voted out (a process of natural selection), as each one plays double roles in the game, an actor and a judge. Guess who will win in the end. This game perfectly captures the essential characters of an adaptive (or a co-evolved) biological system. If it's a closed system, there will be only one who finally wins the game. Can we predict who will be? If it's an open system (i.e. each week we add a new person in the game), can you predict who will be there after many weeks? It is surely not a random game, but its direction (destiny) is an unfolding one.

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