Preface to the Special Issue of *Acta Applicandae Mathematicae* on Mathematics in Biology

GIORGIO KOCH
Department of Mathematics, University of Rome, Istituto Matematico Guido Castelnuovo, Città Universitaria, I 00100, Rome, Italy

and

MICHIEL HAZEWINKEL
Centre for Mathematics and Computer Science, P.O. Box 4079, 1009 AB Amsterdam, The Netherlands

One service mathematics has rendered the human race: it has put common sense back where it belongs, on the top shelf next to the dusty cannister labelled 'discarded nonsense' – Eric T. Bell, 1951.

Practically every mathematical procedure that is useful in physics, engineering, and economics has also found an important application in the life sciences – E. Batschelet, 1971.

The more traditional fields of the application of mathematics are physics and engineering. This came about, at least partly, because (to quote just a few instances) Newtonian mechanics, elasticity, and fluid dynamics were already sufficiently developed theories to allow for abstract formalization and, consequently, for mathematical modelling and investigation.

For some years now, biology has reached a similar stage. Indeed, more or less recent progress in genetics, molecular biology, cellular biology, neurology, general population dynamics, and ecology have established sound bases and frameworks which deserve and call for mathematical description and analysis.

Mathematics is a tool for thought, to use C. H. Waddington's felicitous phrase. It is also a highly-necessary tool. As stressed by the same Waddington (and Eric T. Bell in the introductory quotation above), our unaided brains simply did not evolve to deal with complex systems with nonnegligible feedback effects. They are geared towards simple, linearly-ordered cause and effect chains and ill-equipped to deal with the often surprising consequences – and not rarely condradictions – which result from, at first sight, quite reasonable assumptions. Thus, in connection with research in plant and animal breeding and control of diseases, W. J. Ewens notes in his book *Mathematical Population Genetics*:

While increased research in these areas naturally leads to a greater understanding of them, it also shows, particularly with the mathematical theory of population genetics, that previous arguments have sometimes been misleading, important points have been glossed over, and our knowledge of the genetic behavior of populations is not as firm as might previously have been thought.

In biology, of course, highly interconnected dynamical systems, full of feedback loops, are omnipresent. And from this point of view, it is mildly surprising that mathematics in biology did not take hold much earlier. It seems, as in several other cases, that the tool had to be honed first, which also 'explains' perhaps why the early inspired efforts of Lotka, Volterra and Kostizin temporarily faded away. Now, however, some mathematical tools at least seem to be ready, and as J. D. Murray remarked some years ago in a book review, mathematical biology is now probably the fastest growing branch of applied mathematics.

And, as always with a new vigorous field in which mathematics is nontrivially used, changes result for the mathematician, and not only because of the obvious scientifically and socially relevant implications that the solutions of mathematical problems in biology carry along. Indeed, quite often these problems require new development of mathematical theories, and their solutions involve new sophisticated mathematical techniques.

These considerations suggested that we should put together a special issue of *Acta Applicandae Mathematicae* on the Mathematics of Biology. We think that such an issue falls within the purposes of this journal in that it provides evidence of the interest that biologists should attach to mathematics and of the wide variety of branches of mathematics (some of which are in an active state of development), which provide formalization and analysis tools for biological problems.

At the same time, it should stimulate further research work in these areas, by a process similar to that which mathematics once underwent because of the needs of physics and engineering. After a somewhat quiescent period, this is again happening, of course, but with the additional major stimuli coming from chemistry and geology.

The issue opens with a paper by Kanehisa and De Lisi on the problem of matching two given sequences of nucleotides (DNA and RNA strings) or of aminoacids (proteins). This, of course, is directly related to the basic question of how and where is the relevant information coded in the sequences.

After a very detailed discussion of the relevant biological concepts and structures, the authors discuss the matching problem as an optimization one (local or global) and develop dynamic programming algorithms to solve it.

Markov chains provide the tool to incorporate stochasticity into the model and Monte Carlo simulation is used to test the algorithm.

In the following three papers, the focus of attention is switched from the intracellular level and molecular biology to phenomena occurring on the cell membrane and cell-to-cell interaction.

Gandolfi, Gerardi and Marchetti survey existing models for lateral diffusion. The fluctuation of antibodies or other proteins and complexes in the membrane is described in terms of partial (possibly nonself-adjoint) operators with suitable boundary conditions. When the spectrum is discrete, reaction and diffusion rates may be interpreted as the first eigenvalue of the operator. Estimates are then given for the rates, and the effect of membrane curvature on the model is discussed.

Macken and Perelson use probabilistic models to get notable insights in the rapidly developing field of immunology. Specifically, they examine the cell mediated immune

response in two experimental settings and model the various stages of the process (lethal hit analysis) by point processes, and birth and death processes.

The aim of the paper is to know how possible biological assumptions are described by different models, and how probabilistic analysis of these leads to conclusions which may be proved or disproved by experimental data, thus providing grounds of discrimination for the assumptions themselves.

The paper by Johannesma and Van den Boogaard deals with investigations of information processing in a neuron. Neural interactions are modeled by linear deterministic equations for generator potentials and by nonlinear stochastic processes for action potentials.

The model supplies the theoretical foundations for experimental data, and includes basic physiological assumptions and evidence about synaptic connectivity and neural interaction, with a preliminary careful and detailed discussion of the most convenient and proper mathematical setting (deterministic/stochastic, discrete time/continuous time, etc.). Thus, it clearly appears that a single problem may well call for a variety of mathematical tools.

With the paper by Falcone and Israel we enter the field of population dynamics. They introduce the reader to an interesting prey-pedator problem suggested in a letter by the biologist U. d'Ancona to V. Volterra: its feature is a special type of competition between predators.

The interest of the problem also stems from the possibility of implementing biological control of one species by means of the others, as opposed, for instance, to pesticide control. Two dimensional and three dimensional cases are discussed by qualitative analysis (and in particular number, location and type of equilibrium points), as well as numerical analysis for the less tractable situations.

Finally, at the system level, Shikata and Watanabe give a formalization to the problem of classifying oscillators from a topological point of view. They also present a theory to determine the topological type of the potential from qualitative data (harmonic analysis for black boxes) and apply it to α-rhythm in EEG. The research work is still in progress so that the paper appears rather unusual for a journal mainly devoted to survey of state-of-the-art papers. Indeed, it is not so much a paper in the usual mathematical sense, as a description of a program and a challenge. It is also but the tip of an iceberg. However, we believe this note to be stimulating and likely to generate some new thinking about mathematical tools and results for the qualitative analysis of oscillators.

Two reviews of recent books on biomathematics, by J. Grasman and R. M. May, complete the issue.