

Stochastic Modelling  
in Biology



Workshop on

# STOCHASTIC MODELLING IN BIOLOGY

Relevant Mathematical Concepts and  
Recent Applications

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**STOCHASTIC MODELLING IN BIOLOGY**

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## Introduction

The present volume contains 20 papers presented at the workshop "Stochastic Modelling in Biology: Relevant Mathematical Concepts and Recent Applications", held in Heidelberg, August 8-12, 1988, under the sponsorship of the German Research Society (Deutsche Forschungsgemeinschaft, DFG) and with the assistance of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ). Two papers written by young collaborators in the Department of Mathematical Models at the DKFZ, which were partially presented in the workshop, are now included as self-contained papers.

This workshop was the third meeting on stochastic models in biology organized in Heidelberg: the first one, "Biological Growth and Spread" [BGS], took place in July 1979, and the second one, "Stochastic Spatial Processes" [SSP], in September 1984. I make use of this opportunity to emphasize that the organization of all three meetings would not have been possible without the financial support of the DFG - as well as of the DKFZ. Both institutions have encouraged the existence and the activity of a small research group working on stochastic modelling in biology at the DKFZ (Department of Mathematical Models) and since 1978 in the Research Project "Stochastic Mathematical Models" (SFB 123) of the DFG.

In retrospect, one can determine that the main aim of the first meeting [BGS] was the comparison between stochastic and deterministic models, whereas the second one [SSP] concentrated on different stochastic approaches which could be used to investigate the spatial behaviour of different biological systems. The aim of the present workshop appears quite ambitious in its attempt to examine the progress realized in the last years in the field of interest. According to this interpretation, a flavour of continuity and concentration is apparent.

Obviously, a choice of topics both from the mathematical side as well as from the biological side was characteristic of all three meetings. The areas of biological applications were especially those of cell biology - i.e., cell cycle and growth, morphogenesis and carcinogenesis - and in a certain measure genetics, neurophysiology and epidemiology. It goes without saying that the presence of distinguished biologists in all these meetings was evident: in the first, large meeting [BGS], the contributions of R. Baserga (cell cycle genetics), G.I. Bell (cell adhesion), H.C. Berg (chemotaxis), B.I. Lord (stem cells), C.S. Potten (epithelial structures) and A. Robertson (embryogenesis through cellular interaction) have been highly

appreciated; in [SSP], D.A. Ede surveyed his own research (since 1969) dealing with the computer modelling in embryogenesis. I should stress that in the same year (1984), the British Society for Developmental Biology organized a symposium on "Programmes for Development".

In the present volume, important biological problems have been treated by R.A. Clayton (transdifferentiation) and by Z. Darzynkiewicz and his colleagues (cell cycle and its metabolically distinct compartments). If we could put together all these papers (after making them up-to-date), we would have a good piece of *theoretical biology* – maybe in the sense suggested by C.H. Waddington (1968):

*"it should be pointed out that the analogy between theoretical biology and theoretical physics involves a comparison of two bodies of theory which are at very different stages of historical development. The theory of the physical world already contains very well worked out accounts of the connections between highly complex systems . . . and underlying units which are tolerably elementary . . . In contrast, general theories relating the more complex biological phenomena to elementary units are not very satisfactory . . . Biology is in fact still in the process of creating its theories 'from the elementary units to the complex' at the same time as it is making such rapid advances in the analysis of the units. But the analysis by itself is not sufficient until the intellectual apparatus for building upwards towards the complex is better developed."*

The development of the required intellectual apparatus might be the contribution of mathematical modelling; we must build a stable bridge between mathematical biology and theoretical biology.

Actually, for all three meetings the choice of mathematical models and theories was governed by the biological problems mentioned above – with the distinction that they have been recently developed, I would say still *in status nascendi*. This particular choice explains to some extent the existence of many mathematical papers, in spite of a formidable barrier of language and difference of objectives. However, the mutual professional respect has been without fail. Intuitively or not, the advice of S. Ulam to biologists "ask not what mathematics can do for you, ask what you can do for mathematics" was followed.

✧

The material of the proceedings is divided into five sections but, again, in retrospect, a similar classification could be applied to the material of the previous meetings [BGS] and [SSP].

**1. Interacting random systems.** Since the pioneering work of F. Spitzer (1970), this new branch of probability theory has been intensely developed; numerous lecture notes, large surveys and books have been written and the list of



published papers is impressive. At the first meeting in 1979, F. Spitzer and T. Liggett gave profound exposés of the models in progress as well as new development perspectives; the paper of F. Spitzer was published in *Annals of Probability* as the 1979 Wald Memorial Lecture. Furthermore, H. Föllmer introduced a voter model with a global signal, and K. Schürger presented a generalization of Eden models. M. Bramson and D. Griffeath reported their first results in the analysis of the Williams-Bjerknes model of the spread of a malignant clone as an interacting particle system, and P. Tautu commented on the stochastic model for carcinogenesis developed at the DKFZ. In [SSP], R. Durrett and L. Gray introduced particle systems with sexual reproduction, and T. Liggett gave an overview of the theory of nearest particle systems. Also, J.T. Cox and D. Griffeath investigated the qualitative behaviour (critical clustering) of the voter model on a two-dimensional lattice. Obviously, the dual processes of the interacting systems were not ignored: in [BGS] K. Schürger studied branching processes with interactions, and in [SSP] P. Donnelly considered some death processes as duals in genetics.

The continuity of the earlier meetings is preserved in this volume: L. Gray presented comparison theorems for some interacting systems as growth models; it should be noted that one of them is the re-statement of a conjecture of T. Liggett given in [SSP]. B. Röthinger and P. Tautu traced the genealogy of the malignant cells produced by developing the stochastic configuration model for carcinogenesis mentioned above. The proceedings also include problems of particle interaction and dispersal on  $\mathbb{R}^d$ : interacting diffusion processes and the associated propagation of chaos (S. Méléard), particle systems with gradient interaction (K. Oelschläger) and the spatial segregation effects of repulsive interactions (M. Nagasawa), a subject first introduced by the author in [BGS].

It is often pointed out that the stochastic theory of interacting particle systems is motivated by some distinct problems of statistical mechanics. Generally speaking, the primary objective of statistical mechanics is to determine the relationships – both in equilibrium and non-equilibrium – between the microscopic properties of ensembles of interacting particles and the macroscopic variables and laws observed in these ensembles. The way in which statistical mechanics bridges the gap between the microscopic and macroscopic description of a large particle system is by identification of macroscopic states with probability measures on the phase space of the system and by identification of the values of macroscopic variables with expected values of appropriate functions with respect to such measures. This short description provides an understanding of the interest many theoretical biologists have in statistical mechanics; for instance, M.A. Garstens (1970) suggested that "the central problem of theoretical biology is to supply the missing links between purely descriptive approach to the field and the powerful mathematical techniques present in modern physics". However, this is not exactly what

C.H. Waddington meant in the long quotation above. The "statistical mechanics analogy" suggests to biologists the quest of those properties of microscopic objects, e.g., cells or genes, which can be precisely related with the properties of macroscopic biological systems, e.g., cell populations. Yet, we still do not know the laws of interaction between the microscopic parts, and we cannot explain how, for example, macroscopic biological systems "in equilibrium" have no apparent macroscopic changes even though microscopic objects are changing wildly. The intellectual apparatus "for building upwards towards the complex" is only anticipated. Waddington's comparisons are but a different view of Garstens' aim: it appears that "a description that is adequate to the facts will seldom have the right mathematical structure" (Cartwright, 1983).

In all three meetings some theoretical physicists were also present: W.A. Little (the Ising model of a neural network) in 1979, and H.N.V. Temperley (Potts models) and J.W. Halley (polychromatic percolation) in 1984. At the present workshop, D. Stauffer reported his results of large-scale simulations of the Eden cluster model, and A. Hansen discussed the chaotic behaviour of Kauffman's genetic model. (The last four papers were not included in the respective proceedings. Moreover, H.E. Stanley who announced his talk on fractal growth models and neuron growth patterns was unable to participate.) It is quite easy to emphasize the essential differences between mathematics and mathematical physics, but I should like to repeat D.J. Gross (1988) concluding "vive la difference!". Biologists may be stimulated to take advantage of both the power of abstraction of mathematicians as well as of the inventive capacity of theoretical physicists, but they must keep in mind that the abstractions are the most significant and the most useful facts we have about real phenomena.

2. Stochastic processes with branching mechanisms. Perhaps the most adequate and interesting biological applications of the theory of branching processes are those where the parameters, e.g., splitting time or intensities, are dependent on some factors or are themselves stochastic processes. There is no book dealing specifically with these types of processes, but in their famous book (1972), K.B. Athreya and P.E. Ney selected a few such models under the heading "Special Processes" and remarked that these models "point the direction to some promising problems for the future". A summary classification would consider (I) the dependence on external conditions, ranging from different types of environment to violent catastrophes, (II) the dependence on "demographic" parameters such as population size, density, or generation, and (III) the spatial motion with or without interaction. The analysis of these models requires new, complicated techniques (as Athreya and Ney already pointed out) and strongly suggests the application of approximation methods. In [BGS], H. Kesten examined basic problems concerning

many random processes in a random environment (e.g., random walk, diffusion), including branching processes (BPs). At the same meeting W. Rittgen introduced multivariate, population size-dependent continuous time BPs, and Carla Wofsy described the behaviour of limiting diffusions for density-dependent BPs, which revealed some basic problems in the investigation of these processes, particularly the difficulties in the correct approximation of Markov population processes. Also in [BGS] J. Biggins represented the spatial spread in BPs and K. Schürger introduced new BPs with interactions on the lattice [models of type III]. Although the 1984 meeting was devoted to stochastic spatial processes, BPs of type III were investigated only by Gail Ivanoff (limit theorems for multitype branching random walks) and L.G. Gorostiza (branching random fields with immigration, branching transport processes, etc.). In his overview on qualitative behaviour and stochastic geometry of measure-valued processes, D.A. Dawson presented a model of population of branching random walkers. As a branching model of type II, T. Götz introduced generation-dependent BPs with immigration.

Obviously, all types of BPs are considered in the present volume. H.-P. Altenburg introduced a multitype BP with disasters and suggested its application for the study of the dynamics of malignant cells which are susceptible or resistant to chemotherapy. Iris Reinhard investigated the quantitative behaviour of some slowly growing population-dependent Markov BPs, and W. Rittgen studied the weak convergence to diffusion limits of sequences of "approximately critical" multivariate population-dependent Markov BPs. In "Variants of the simple branching process", J.D. Biggins scrutinizes three generalizations of the Bienaymé-Galton-Watson process, allowing more general reproduction processes, generation dependence, and spatial structure. A general (Crump-Mode-Jagers) BP counted by random characteristics is introduced by Z. Taib in population genetics, by assuming that the individuals can undergo neutral mutations according to the infinite alleles model. Coalescing branching random walks are briefly discussed in the paper by B. Röthinger and P. Tăutu.

**3. Stochastic analysis and growth models.** Stochastic analysis is a branch of the general theory of random processes that is essentially concerned with the analytical properties of random functions. The study of stochastic equations has been all along the most active field of probabilistic analysis, so that in [BGS] Section V, "Stochastic versus Deterministic Approaches" contains the contributions of H. Doss, T.G. Kurtz and G.C. Papanicolaou on this topic. As a result, some population models benefited from this analytical research: M. Turelli (joint effects of interspecific competition, demographic and environmental stochasticities) and H.C. Tuckwell (random processes with jump discontinuities, logistic growth with random disasters, etc.) gave in this sense an exemplary treatment in [BGS].

In the present book, G. Kersting summarizes his results on the asymptotic properties of stochastic difference equations (law of large numbers, central limit theorem, asymptotic distribution); C. van der Mee proves the existence of stationary solutions of a linear transport equation and gives the conditions for the convergence of the time-dependent solution to the steady-state profile, and a similar equation is also introduced by L. Pilz. In her paper, Mirjam Kretzschmar analyzes an (infinite) system of partial differential equations by using generating functions and derives a fixed point problem. Though these investigations are of abstract nature, their aim is the modelling of important biological processes like population growth (G. Kersting), cell proliferation (L. Pilz, C. van der Mee) and the dynamics of a structured population infected by different species of parasites (M. Kretzschmar).

Stochastic analysis today applies and extends not only concepts and results from functional analysis but also from other branches of mathematics, e.g., measure theory and operator theory – just to mention some of the most important ones. Certainly, modern mathematics becomes an enormous, powerful instrument of inquiry, largely beyond the intuition of nonspecialists. Measure-valued random processes represent an example of this particular rigour: they arise in a great variety of real situations (e.g., infinitely many neutral alleles diffusion models) as well as in some other mathematical constructions (e.g., marked point processes, measure-valued martingales, predictable accumulation processes, etc.). In [SSP], three papers dealt with such models: D.A. Dawson provided an excellent review of recent developments and applications, followed by A. Bose ("Age distributions in birth and death processes"), and G. Rosenkranz ("Stochastic measure diffusions as models of growth and spread"). A particular application is the spectral approach used by W.G. Sullivan in [SSP] to study the convergence of simple random walks; one of the interesting conclusions is that the diffusion limiting operators are Schrödinger operators.

In this volume the deterministic notion of attractor meets its stochastic analogue, the confiner. The authors, J. Demongeot and Christine Jacob, show that the confiner can be used to describe the equilibrium states of a stochastic process and also serve as a mathematical framework for theorems of convergence of stochastic processes to deterministic ones.

**4. Special stochastic and statistical approaches.** This is a mixed section but is dominated by some important topics. The first one is percolation because of the strong connections with the theory of interacting particle systems. As R. Zallen (1983) noted "the intellectual appeal of the percolation model resides in its almost gamelike mathematical aspects and the fact that it provides a well-defined, transparent, and intuitively satisfying model for spatially random processes . . . (it) is a

fine pedagogic instrument for illustrating concepts central to the physics of phase transitions and critical phenomena". Indeed, in 1976, A. Coniglio and his colleagues demonstrated the intimate connection between percolation and phase transition in the Ising model and recently R. Durrett (1988) constructed his book "Lecture Notes on Particle Systems and Percolation" on the idea that "everything we do is percolation". It can truthfully be said today that in the mathematical characterization of "disorder" the key words are random walk, percolation, fractals and chaos.

In the first two meetings, important problems arising in percolation theory were discussed by J. Hammersley ("Percolation") and R.T. Smythe ("Percolation models in two or three dimensions") in [BGS], and by G. Grimmett ("Percolation processes and dimensionality") and D.J.A. Welsh ("Correlated percolation and repulsive particle systems") in [SSP]. (The contribution of H.-O. Georgii, "Disordered Markov fields and percolation", was not included in [SSP].)

However, in the present book another interesting topic is involved, namely cell automata. These mathematical objects are generally used to characterize discrete models for homogeneous systems with local interactions: time and space are assumed to be discrete and the value of each lattice site evolves according to the same deterministic rules. Analogously, discrete interacting particle systems are often referred as stochastic cellular automata. As in many other cases, the mathematical concept of a cellular automaton introduced by S. Ulam and J. von Neumann around 1950 has a biological motivation: it was intended to "abstract the logical structure of life" concerning the properties of self-replication and survival. As it is well-known, "LIFE" is also the name of a two-dimensional cellular automaton invented in 1970 by J.H. Conway; it is able of creating "order out of chaos" (the "primeval soup" is a disordered initial condition) and thus circumventing the Second Law of Thermodynamics (Vichniac, 1986). The theory of cellular automata developed rapidly in the last two decades and strongly enlarged its range of applications to many different problems, from Ising models, metastability/instability transitions and fluid dynamics to pattern recognition, genetic or immunological networks, and morphogenesis. In the present volume, D. Stauffer tackles an important medical problem: the autoimmune and immune-deficient diseases.

As a matter of fact, the main subject here is the description of the behaviour of (biological) dynamic systems by different mathematical approaches. It then appears that cellular automata are single examples of dynamic systems: under certain conditions they can exhibit ordered and at the same time very complex behaviour, and the emergence of complexity is a result of different choices of their local transition rules. In the infinite case, the possible configurations of a cellular automaton may be considered to form a Cantor set, and its temporal evolution is an

iterated continuous mapping of this Cantor set to itself. This is similar to the iterated mappings of intervals of the real line as it is studied in the theory of dynamic systems. The paper "Periodic orbits for interval maps" by G. Keller included in this volume marks our interest in such mathematical investigations; the author proves the relation between Lebesgue-continuous invariant measures for interval maps and uniform distributions on periodic orbits. Unfortunately, another paper presented at the workshop, "Some problems in random mapping theory" by S. Berg, will be published elsewhere.

The next paper could be placed as well in the first Section because the examined hierarchical model, proposed in 1971 by F.J. Dyson, is a one-dimensional particle system with long-range interactions, which exhibits a phase transition. Yet, the classification of the paper written by B. Prum in the group devoted to special processes is justified by the property of processes with strong dependence between the random variables to give rise to self-similar processes whose paths are fractals. Moreover, such processes are appropriate mathematical objects for investigating the influence of strong dependence on the limiting behaviour and also for closely examining the scaling theory of critical behaviour. For instance, random fields which are invariant with respect to the renormalization group are "self-similar" (called "automodal fields" by Ya.G. Sinai and R.L. Dobrushin). Lévy's Brownian motion is also interpreted as an isotropic self-similar random field.

Statistical inference for spatial stochastic processes has been presented in many other meetings abroad, so that in [SSP] only A.D. Barbour and G.K. Eagleson studied special aspects of statistical tests for space-time clustering. In the present volume, the paper of W.J. Braun and his colleagues could represent the beginning of a coherent investigation of lattice models in which data obtained by numerical experiments are used for statistical identification of the parameters of a simple two-dimensional spatial growth model.

Finally, I should like to mention three other papers which for authors' personal reasons are not included in this book: "Mathematical aspects of random fractals" (S. Graf), "Measure-valued branching processes and stochastic calculus: a generalized equation in a measure space" (S. Roelly-Coppoletta et al.), and "Semi-Markov processes for illness and death fed by Poisson processes: Applications to modelling prevalence and incidence" (N. Keiding).

\*

The comparison of the intentions in [BGS], [SSP] and this workshop suggests that the main common topics might represent a *research programme*, certainly not in the Lakatos' sense, that is, great achievements in physical sciences, but a modelling research programme, that is to say, a plan for understanding fundamental

biological processes by means of deep mathematical concepts and models. Relatively new and rather ignored mathematical approaches have been followed and investigated in their developments and ramifications in order to gain a clear view of their abilities of explaining some aspects of biological processes of interest. A powerful idea is always potentially applicable. Any scientist is aware of the fact that in such situations mathematics can dominate with respect to its applications because the basic precondition of the success of a new research programme is the continuous growth of the mathematical theory. As I. Lakatos pointed out, "mature" science consists of research programmes whereas "immature" science consists of a mere patched up pattern of "trial and error".

It is often claimed that if the use of a mathematical model stimulates experiments – *even it is wrong* – then this model has been successful. A variant of this opinion is illustrated by the following question posed in 1968 by H.H. Pattee: "Why is it necessary to use quantum mechanical description when it is known that in many cases, even in chemistry, a classical description is adequate for a good understanding of the process involved? In other words, why is it not possible to admit that a quantum mechanical description would indeed be more accurate, but that for all practical purposes a classical description is close enough?"

Let us translate these questions in terms of one of the problems in this book: Why is it necessary to introduce a sophisticated spatial growth model for carcinogenesis when it is known that the classical Gompertz function is satisfactory for fitting experimental and clinical data? First of all, the biological context is not the same; second, the first model has an explanatory function: it helps us to understand some aspects of tumour growth. As René Thom pointed out, "l'intérêt d'une recherche réside dans sa capacité à révéler une structure sous-jacente qui rend les phénomènes intelligibles". Third, a crucial distinction ought to be made between *cognitive problems* and *problems of actions*: knowledge is the main purpose in the fundamental scientific research. This is a point that even the men of letters were able to notice: in his superb dialogue "Eupalinos", Paul Valéry made up Socrates saying that "l'homme ne peut agir que parce qu'il peut ignorer" because "l'homme qui ne veut que vivre, n'a besoin ni du fer ni de l'airain 'en eux-mêmes'; mais seulement de telle dureté et de telle ductilité".

We are conscious that biology has become "the most exciting modern application of mathematics" (Murray, 1989). Recently, many meetings organized by mathematicians and theoretical physicists have dealt with interesting biological applications, and I should like to mention some proceedings which appeared in the interval between our last two workshops, [SSP] and the present one, containing similar (or close to our) problems: "On Growth and Form" (1986), "Disordered Systems and Biological Organization", "Science on Form" (1987), "Disordered

Systems and Biological Models" (1987), and "Chaos and Complexity" (1988). As this front of research will develop parallel with the progress in biology, the impact of mathematical axioms and notions will be greater. For theoretical physicists (states F.J. Dyson), as well as for theoretical biologists (my gloss), mathematics is not just a tool by means of which phenomena can be formally represented; it is the main source of concepts and principles by means of which new theories can be created.

Petre Tautu  
Heidelberg, November 1989

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