Computation in Cellular and Molecular Biological Systems

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COMPUTATION IN CELLULAR AND MOLECULAR BIOLOGICAL SYSTEMS
Selected Papers from IPCAT 95

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Computation in Cellular and Molecular Biological Systems

This book is dedicated to the memory of

Roy Cuthbertson

(1954–1996)

PREFACE

The First International Workshop on Information Processing in Cells and Tissues (IPCAT) was held in Liverpool between 6th - 8th September 1995. The purpose as advertised to the scientific community was

> "to bring together a multidisciplinary group of scientists working in the general area of modelling cells and tissues".

In the end it attracted 85 delegates from 19 different countries. The discipline specialists attending included: mathematicians, biochemists, cell biologists, neuroscientists, physiologists,computer scientists, biophysicists, immunologists, medics and electronic engineers. This book represents a selection from over forty papers which were presented at IPCAT 95. The first chapter provides an introductory overview to the book which is then divided into three general areas:

- Information processing and signalling processes
- Information processing and cellular systems
- Dynamical models of cellular systems and information processing

It is important to note however that because the material is interrelated in many ways it could have been organised differently. The reader is encouraged to view the text as a whole and find many meaningful links outside of the three sections.

There is often a great deal of discussion these days about multi-disciplinary research and the value of exchanging ideas and methods across traditional discipline boundaries. Indeed, it could be justifiably argued that many of the advances in science and engineering take place because the ideas, methods and the tools of thought from one discipline become re-applied in others. Sadly, it is also the case that many subject areas develop specialised vocabularies and concepts and indeed may also approach more general problems in fairly narrow subject-specific ways. As a result barriers develop between disciplines that prevent the free flow of ideas and the collaborations that could often bring success. This is particularly true in biology and computing where recent rapid developments in research create a danger that many of the advances made do not get exploited in the other subject. As one participant commented:

> "I would say that IPCAT has opened a forum of a unique nature: both experimentalists and theoreticians from the biosciences and computer science badly needed to join their forces in order to make sense of the contemporary glut of new bio-molecular-informational data. It is a timely and rewarding enterprise."

Now is an excellent time to try to bring the two communities together to evaluate progress, educate and inspire each other in the expectation that significant rewards will follow.

A central theme for IPCAT 95 was to explore the nature of biological information and the ways it is processed in cells and tissues. The workshop sought to provide a forum to report research, discuss emerging topics and gain new insights into biological and computational information processing systems. Comments from one participant reflect this view:

> "I was surprised to encounter such a strong interest in models on a subcellular level. Considering the state of cellular and network models, which have seen an enormous development recently, it may be hoped that the subcellular level will equally well develop. However, this level also holds particular difficulties e.g. the limited spatial and temporal resolution of techniques that could provide data on local concentrations of reactants in vivo. Thus, both better modeling and experimental approaches to subcellular information processing are required."

The multidisciplinary and international nature of IPCAT meant that a variety of viewpoints were exposed and discussed. One participant commented:

> "I found the conference very stimulating in many respects. Especially, what I like are as follows.
>
> (1) The conference covered many different topics relevant to biology.
>
> (2) Most of the scientists who participated seem very knowledgeable in a wide variety of topics. Experimentalists had interests in theory and were quite knowledgeable in theory. Theoreticians dealt with biologically relevant problems, not just mathematically oriented problems.
>
> I learned a lot from the talks given by the speakers and also through the discussions during the breaks."

This view was widely shared and most participants felt that the conference was a uniquely stimulating experience. We hope to repeat the event in 1997.

One of the key motivations underlying the first IPCAT Workshop and this book was to attempt to provide a common ground for dialogue and reporting research without emphasising one particular research constituency or way of modelling or singular issue in this area. This is quite a challenging agenda when one considers the great variety of techniques and perspectives involved and the great variety of biological phenomena being studied. There are many exciting and novel avenues that are worth exploring but the understanding of biological phenomena should always be a primary aim.

The IPCAT idea did not take very long to evolve. It started about one year prior to the event when initial discussions between the editors got underway on running a workshop in this area. It soon became clear to us that such an event was timely and this was to some degree endorsed when many of the people we approached happily agreed to become members of the programme committee. However, it was still a risky business and so we are grateful to a number of sponsors (listed below) who provided a much-needed buffer should the event have been unsuccessful.

Part of the challenge of IPCAT and this book is to re-appraise the types of models used to describe and explain the systems of interest and explore complementary viewpoints. Hence, some participants commented:

> "After IPCAT 95 we became more conscious that there is still a lot of work to do concerning the modelling of biological systems. This work concerns not only the sort of models we are working with to represent and quantitate biological systems, but to a real questioning of the implicit built-in assumptions of our models. Many of these implicit assumptions are contained in the experimental evidence we choose as a source of the piece of reality we intend to model ... IPCAT 95 provided us the following question: is information always associated with organization? and if so, how ?"

We hope this issue will be addressed further in future IPCAT events.

It was with sadness that during the production of this book Roy Cuthbertson died. His work on calcium oscillators and positive feedback attracted international recognition and his ideas and enthusiasm contributed greatly to the workshop. As a small token of our appreciation and in recognition of his work we dedicate this book to his memory.

Our thanks to Richard Lim of World Scientific for his interest in IPCAT 95 and encouragement and advice during the production of this book. The editors also acknowledge the help and support of a number of organisations who made the first IPCAT workshop possible: GPT, Unilever, Zeneca, SmithKline Beecham, Merseytravel, The University of Liverpool and The Royal Society.

Finally our thanks to the programme review committee:

Georg Brabant	-	Endocrinology (Hanover)
Michael Conrad	-	Computer Science (Detroit)
Roy Cuthbertson	-	Cell Biology (Liverpool)
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Ray Paton and Mike Holcombe
June, 1996

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Introduction

INFORMATION PROCESSING IN CELLS AND TISSUES

RAY PATON AND MIKE HOLCOMBE

This chapter contains a summary of selected contributions from the proceedings of IPCAT 95. As noted in the preface, the book is collected around three organising themes:

- Information processing and signalling processes
- Information processing and cellular systems
- Dynamical models of cellular systems and information processing

It is important to remember that the material is interrelated in many ways it could have been organised differently. The reader is encouraged to view the text as a whole and find many meaningful links between the many contributions.

The first section of the book looks at information processing and signalling processes in cellular systems. It begins with a study by Thomas Hoeffer and Philip Maini of the interplay of cell-cell signalling and multicellular morphogenesis during *Dictyostelium* aggregation. The development of multicellularity in the life cycle of this microorganism provides a paradigm model system for the study of biological pattern formation. Following starvation, periodic waves of cyclic AMP initiate the aggregation of *Dictyostelium* amoebae. Subsequently, a pattern of branching cell streams is formed which coalesce into an aggregation centre. Thomas and Philip derive a model of the aggregation process which is based on the interplay of the dynamics of the cell distribution, governed by chemotactic movement towards cAMP, with the previously much-studied intercellular cAMP signalling. The model shows how signal relay, chemotactic movement and adaptation orchestrate the collective modes of cell communication and migration in the aggregating cell layer. The chemically mediated cell-cell interaction causes the break-up of the initially uniform cell layer via a chemotaxis-driven instability, leading to the formation of the cell stream morphology which marks the onset of multicellularity in situ. The model provides a unifying framework within which a variety of experimental observations on this unusually complex excitable medium can be explained.

The next few papers report on work concerned with investigations of intracellular signalling. Firstly, Rolf Koetter, Dirk Schirok and K Zilles present a kinetic approach to modelling the concerted regulation of cAMP by calcium,

calmodulin and dopamine. They investigated the variation of intracellular cyclic adenosine monophosphate (cAMP) concentrations in response to brief dopamine and calcium stimuli in a kinetic model of adenylate cyclase (AC) and phospodiesterase (PDE) regulation: The model included stimulation of AC by calmodulin/calcium complex ($CaMCa_4$) and dopamine, inhibition of AC by intracellular free calcium, and stimulation of PDE by $CaMCa_4$. The equilibrium concentration of cAMP was in the nanomolar range. Both dopamine and small calcium pulses increased cAMP levels. In contrast, large calcium pulses produced a stimulation of cAMP levels that was initially suppressed by calcium-mediated inhibition. Temporal shifts of large calcium and dopamine pulses in respect to each other revealed an asymmetric interaction: Coincidence of the two pulses abolished the effect of dopamine while a large calcium pulse preceding dopamine by more than 0.5 s produced synergistic increases of cAMP levels. The validity of these findings and their possible significance is discussed.

Following this Hiroshi Okamoto and Kazuhisa Ichikawa present a role of Ca^{2+}/calmodulin-dependent protein kinase II in the induction of long-term potentiation. This work shows relations between the switching characteristics in Ca^{2+} signalling and digitalization of graded information into binary information. Long-term potentiation (LTP) has been extensively studied as an experimental model for usage-dependent change in synaptic efficiency that is thought to be a cellular mechanism underlying memory formation in the brain. A number of studies suggest that Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is crucially involved in LTP. However, the way CaMKII participates in LTP is far from elucidated. Hiroshi and Kazuhisa propose a theoretical model for biochemical-reaction networks comprising Ca^{2+}/calmodulin-dependent autophosphorylation of CaMKII and dephosphorylation of the kinase by phosphatase, and investigate a role of CaMKII in LTP by computer simulation of the model. A critical assumption of the model is based on recently reported biochemical evidence indicating that autophosphorylation of threonine 286 residue, the prerequisite process to the generation of Ca^{2+}/calmodulin independent (autonomous) activity of the kinase, is an intersubunit reaction. Results of our simulation show switching characteristics of the model: There is a threshold regarding Ca^{2+} signalling; if the intensity of the Ca^{2+} signal is above this threshold, autonomous activity of CaMKII is elevated maximum (i.e. switched on) if otherwise, it remains near zero (ie switched off). These results suggest a role of CaMKII in the induction phase of LTP: CaMKII digitizes graded information mediated by Ca^{2+} signalling to binary information which may determine whether LTP can subsequently be induced.

Jurgen Nauroschat and Uwe an der Heiden present a mathematical model

of transmembrane signalling via G-proteins. Guanine-nucleotide regulatory proteins (G-proteins) are important regulators of various cellular processes such as proliferation, differentiation and protein synthesis. In particular, they are imperative elements of the transmembrane signalling system, processing and conducting external messages from heptahelic receptors to the cytoplasmic domain. Since cellular behaviour crucially depends on such environmental influx, Jurgen and Uwe focus on the omnipresent receptor /G-protein/adenylate cyclase membrane pathway. They outline both its activation and its recently discovered negative feedback regulation by the G-proteins. A mathematical model comprising variables for distinct receptor states, the G-proteins, and the second messenger cAMP is then proposed. The model is based on reaction kinetics. Boundedness of solutions is mathematically shown by specifying a domain (prism) being invariant under the vector field of the model. Referring to the situation of sustained exposure of the membrane to a signal of fixed amplitude, the model exhibits a unique steady-state solution for any value of the amplitude and saturates with large amplitudes. All the steady-states are locally asymptotically stable. They also demonstrate dynamic features of the model such as hypersensitivity, adaption and saturation phenomena.

Roy Cuthberston's chapter is an edited version of some notes for a paper he was working on. Sadly, he died before the paper was completed but we include it here as a tribute. He provides some valuable insights into the nature of information flow in relation to signalling pheneomena. In particular the importance of positive feedback to biological systems. Roy looks at the relations between positive feedback, sigmoidal transfer functions and digital switches in a number of signalling contexts. There are some valuable insights into the role of positive feedback cycles in mouse oocyte fertilisation, CaM Kinase memory and heart disease.

Takako Igarashi, Yoko Nadaoka and Tsuguchika Kaminuma's paper reports on a data and knowledge base for cell signalling networks. They have developed a prototype of the data and knowledge base of the cell signalling networks that consists of interacting extracellular (xenobiotic) chemicals and biomolecules. The system contains structure and functional data and references of these molecules. The system will be useful for modelling cells and their information processing, and to explain important biological phenomena based on these models. The system may also be useful for designing new drugs and for the studies of the so called quantitative structure activity relation (QSAR). The prototype system was implemented on UNIX workstations using an object oriented database management system ACEDB. The system is also available on the Internet.

This first section of the book is concluded with three papers which apply