Preface

Aside from the obvious statement that it should be a theory capable of unifying all our knowledge about insulin secretion, in both health and disease, not much is known about a *systems biology* of regulated exocytosis in pancreatic β-cells.

Let us recall common knowledge: Patients with diabetes suffer from an absolute or relative lack of the hormone insulin. Insulin is produced by pancreatic β-cells and secreted by *regulated exocytosis*. In type 1 diabetes (juvenile diabetes) β-cells are destroyed by autoimmune mechanisms. In type 2 diabetes, and pre-diabetic states, we observe a decline in β-cell function.

There has been a great deal of experimental work over the last 50 years, and a fair amount of mathematical modelling since the 1980s, but the systems biology approach is new and not fully developed. Genome-wide scans for diabetes genes have pointed to promising candidates involved in β-cell function, raising the importance of systems issues to a new level.

This book gives a snapshot of the field at the threshold of a possible explosion in knowledge. We introduce recent advances in observational techniques, ranging from genetic epidemiology via proteomics to multi-parameter cell sensoring, MRI, ET and nanoparticle-based cell imaging. We summarize what these techniques have revealed regarding β-cell function: the generation of huge new data sets, dealing with ions, DNA, proteins, electrical phenomena, cell membranes, cell organelles and tissue, in extreme spatial and temporal scales from Ångström to micrometres and from picoseconds to minutes and hours.

Because it is an exciting area of research, there are many new ideas about the systems biology of insulin secretion, but they often diverge to such an incredible degree that it seems impossible to decide which of the many possible directions one should pursue.

The division of the text into five overlapping parts reflects the duality between the medical pull and the technological push originating from model-based measurements and mathematical modelling, estimation, control and simulation: The *clinical and pharmaceutical need* of a systems biology approach is to go beyond umbrella diagnosis and solely symptomatic non-individualized treatment – by distinguishing different levels and different traits of functioning within a comprehensive picture of the disease(s). The technological push towards systems biology is based on the

design and use of the so-called *mathematical microscope*. By that term we denote general and/or specific mathematical methods to:

1. interconnect local and global, small and asymptotic phenomena;
2. specify bio-medical ideas and processes;
3. expand heuristically the imagination by theorems and simulations;
4. guide new experiments and exploit traditional experiments more efficiently, and,
5. identify mechanisms and parameters.

In Part I, the medical scene is presented. Systems biology of β-cells is introduced; established facts and open questions of the focused systems analysis are summarized; tutorial reviews on mitochondria and metabolic signals, on β-cell ontogenesis and on the role of the cytoskeleton in transport and release of insulin-containing granules are given. We close this part describing the ideal (up to now mostly a hope) of the aforementioned mathematical microscope, i.e. the replacement of lengthy, expensive, and ethically worrying, in vivo experiments by in vitro-tuned computer simulations.

In Part II, we give five tutorial reviews on new developments in imaging and sensors, emphasizing magnetic resonance imaging, electron tomography, in vivo applications of inorganic nanoparticles, sensor-based assays and bioimpedance spectroscopy.

In Part III, four tutorial reviews are devoted to DNA variations, genetically programmed defects, proteomic analysis and the role of islet amyloid polypeptide in the pathogenesis of type 2 diabetes.

In Part IV, physiological, pharmaceutical and clinical applications are addressed by three tutorial reviews: one on the present state of islet transplantation; one on predictive protein networks and the identifications of drug targets; and one on nanotoxicity.

In Part V, different examples of well-established and developing applications of mathematical modelling and numerical simulation in β-cell analysis are demonstrated. We begin this part with a discussion of the silicon cell paradigm of making experiment-based computer replicas of parts of a biological system, and a presentation of a novel class of mesoscopic simulations probing cellular dynamics. We show how rigorous harmonic analysis raises doubt about metabolic oscillations, and present two mathematical models of minimal complexity able to assess β-cell function in an individual. In the closing chapter on geometric and electromagnetic aspects, we wish to show the heuristic use of mathematical modelling and the recourse to first principles, namely to generate radically new hypotheses for future verification – or falsification.

Beyond our interest in presenting systems biology approaches to understanding and curing diabetes mellitus, our specific "story" is intended to provide a worked case of a systematic teaching of the basics of systems biology, namely how to overcome the three basic challenges, met wherever systems biology is demanded:

1. Interconnect the multiple levels: diabetes syndromes, β-cell function, membrane processes, intracellular dynamics, proteomics and genome mapping.

2. Bridge multiple scales: DNA, plasma membrane, insulin granules, cells and islets.
3. Learn to collaborate in a multi-disciplinary environment.

The chapters of this book were written as tutorial reviews for a broad audience of students of human biology, informatics, mathematical biology and medicine. The level was chosen for teaching graduate classes, studying in Ph.D. programmes and postdoctoral training. For two chapters, namely Chapters 8 and 20, additional material is provided on the Internet for the convenience of students, and in order to compensate at least to some extent for the 2D display limit of print media when used to illustrate 3D image information. The major caveat is, of course, that the extremely fast progress of the field makes one run the risk of presenting already obsolete viewpoints at the time of use of the textbook. Therefore, when we describe the state of the art, we emphasize the principles involved. In such a way the book shall serve as a companion also for work going forward.

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