

Preface

The motivation for this book is two-fold. On one hand, the book seeks to promote the notion that mathematical and computational *modeling* is critically important in advancing the scientific understanding of the physiological processes underpinning the regulation of blood glucose and, therefore, can be valuable in medical/clinical efforts to manage diabetes mellitus. On the other hand, the book advocates the view that these modeling efforts must rely primarily on *data-based* approaches as the scientific and methodological pathway leading to our ultimate objective in a most efficient and expeditious manner. Although both aforementioned reasons for the publication of this book are widely accepted by the peer community as being valid and meritorious, they have not been given—in the view of the co-editors—the requisite attention in the vast literature on glycemic regulation and the clinical management of diabetes mellitus. Through the publication of this book, the co-editors and the distinguished contributing co-authors aspire to make a contribution in addressing this need for rigorous, reliable and effective methodological tools that can be useful in achieving the goal of quantitative data-based modeling of the physiological process of glycemic control in a practical context—thus providing a valuable vehicle for the improved clinical management of diabetes mellitus.

These modeling tools should take into account the intrinsic characteristics of the human metabolic system, particularly in diabetic patients, which render the problem of achieving reliable and robust automatic glucose regulation very difficult. These include, but are not limited to, the *patient-specific* and *time-varying* nature of glucose metabolism in diabetic patients, the presence of large, possibly unpredictable and/or unobservable *disturbances*, and the *incomplete information* that is available to the modeler due to the complex interplay between a large number of physiological and behavioral factors that cannot be accounted for in a practical setting. Due to the aforementioned characteristics, choosing the proper model type, the estimation methodology and the control strategy are crucial for achieving the desired result.

The contents of the book can be divided into two parts conceptually. The first half (Chapters “[Data-Driven and Minimal-Type Compartmental Insulin-Glucose Models: Theory and Applications](#)” to “[Pitfalls in Model Identification: Examples from Glucose-Insulin Modelling](#)”) focuses mostly on methodological considerations related to modeling approaches in diabetes, whereas the second half

(Chapters “Simulation Models for In-Silico Evaluation of Closed-Loop Insulin Delivery Systems in Type 1 Diabetes” to “Nonlinear Modeling of the Dynamic Effects of Free Fatty Acids on Insulin Sensitivity”) focuses on the applications aspect of such approaches. Specifically, the first chapter (Mitsis and Marmarelis) demonstrates the relation between widely used compartmental differential equation models of glucose metabolism and input–output nonlinear Volterra-type models in an analytical manner. It also illustrates the feasibility of obtaining Volterra models from simulated data generated by these compartmental models as well as from experimental animal data.

The second chapter (by Ståhl, Johansson and Renard) concerns the important issue of whether a single optimal model may be identified for glucose prediction, given the highly complex nature of metabolism outlined above. In this context, the authors discuss the use of the model merging/switching approach to achieve robust and reliable prediction.

The third chapter (by Bequette) considers the crucial, potentially life-threatening occurrence of hypoglycemic events, particularly those occurring during the night. Various predictive algorithms that may be used to detect such events and consequently schedule the function of the insulin pump, as well as challenges linked to their implementation, are discussed.

The fourth chapter (by Daskalaki, Diem and Mougiakakou) addresses ways to handle the time-varying nature of glucose metabolism, which is one of the most important challenges in designing reliable therapeutic schemes. These time-varying characteristics may arise from intrinsic nonstationarities and/or the effect of exogenous unobserved factors and the authors consider the use of adaptive algorithms to perform on-line glucose regulation and detection of hypo/hyperglycemic events.

The fifth chapter (by Panunzi and DeGaetano) discusses the possible pitfalls that may arise when constructing parametric models of glucose–insulin interactions, i.e., differential equation models that assume a specific structure for the underlying system. They discuss the importance of examining the qualitative behavior of a model (e.g., whether this behavior is physiologically plausible) and investigate the presence of undesired noise in the input signal used to obtain parameter estimates—an issue that is particularly important in closed-loop systems, such as the glucose metabolism system.

The second, applications-oriented, half of the book commences with the sixth chapter (by Wilinska and Hovorka), which reviews the use of realistic virtual patient models to assess the performance of automated closed-loop glucose regulation systems. These models are beginning to constitute a crucial part of the design process in the quest for an artificial pancreas, as they may accelerate the design process and the transition to clinical trials, as demonstrated by their recent approval as a substitute for pre-clinical trial test beds by regulatory bodies (e.g., the Food and Drug Administration of the USA).

The seventh chapter (by Tura and Pacini) presents applications of the oral glucose tolerance test, as well as recently proposed mathematical models for the analysis of such data, in order to quantify sex-related differences in glucose

metabolism as well as glucose absorption in pregnant women with gestational diabetes. The results demonstrate that rich information may be extracted when models that are well suited to the experimental data at hand are designed.

The eighth chapter (by DeGaetano et al.) takes a longer-term perspective on the effects of diabetes, presenting a model (Diabetes Progression Model) that aims to quantify the evolution of the glucose–insulin system and particularly its compensation to progressively worsening insulin resistance. This perspective is equally important in the design of therapeutic interventions, such as metabolic surgery or beta cell protection, as it provides a way to quantify the long-term effects of these (or other) therapies.

The ninth chapter (by Cescon and Johansson) considers the use of widely used systems identification techniques, such as autoregressive and state-space models, in order to perform individualized short-term (up to 2 h) prediction of future glucose values in a group of patients with Type 1 diabetes. While the overall performance of these approaches was deemed reasonable, the prerequisites to achieve this performance were partially met, suggesting room for improvement, such as the design of optimized experimental protocols to perform system identification.

Finally, the tenth chapter (by Marmarelis, Shin and Mitsis) considers the application of a multivariate, data-driven approach to quantifying the dynamic effects of spontaneous fluctuations of plasma insulin and free fatty acids on glucose concentration in a fasting dog. The obtained dynamic, nonlinear, data-driven models are then linked to more traditional measures of glucose metabolism, such as insulin sensitivity and its interactions with free fatty acid levels, illustrating the importance of obtaining models that are amenable to physiological interpretation.

Concluding, we wish to extend our warm thanks to all contributors for submitting high quality work to this research volume, which we hope will prove useful in promoting further research on this important topic.

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