Mathematical and Computational Modeling of Diabetes: a Brief Overview

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Systemic regulation of blood glucose

• Modeling the mechanisms used by the body to regulate its function
• Specific focus: systemic regulation of blood glucose
• Innovative technology based upon the “top-down cognitive approach,” which incorporates a unique mathematical model of both the physiological systems and autonomic nervous system
• The 'top-down' approach considers the neural regulation of the physiological systems and the neurological, cognitive and biochemical consequences of systemic dysfunction, i.e., the consequences of sensory input upon the neural regulation of the body's systems, organs, and its cellular and molecular biochemistry
• (Most systems biology adopts a reductionist bottom-up approach seeking systemic justification for biochemical and biophysical research findings)
• Results: the onset and progression of Diabetes Mellitus cannot be accurately assessed by individual biomedical indices but instead the regulation of blood glucose is one of a number of inter-related physiological systems which act in a coordinated manner in order to maintain the body's physiological stability
Hierarchical model of whole-body glucose homeostasis

• (Type 2 diabetes is one of the most widespread and rapidly spreading diseases world-wide)

• However, understanding the molecular basis of the disease is increasing piecemeal and a consensus regarding the overall picture of normal metabolic regulation and malfunction in diabetes has not emerged

• Systems biology approach: combining mathematical modelling with simultaneous high-throughput measurements

• (Large-scale) pharmacokinetic and pharmacodynamic models: whole-body level → more physiologically realistic organ-based

• (Small-scale) detailed models for crucial cellular processes → complete modules that potentially can be “fitted” into whole-body organ-based models

• Result: a multi-level hierarchical model → complete picture of diabetes mellitus
Type 2 diabetes is a **systems disorder**, i.e., it cannot be explained or understood by a single mutation or interaction. Instead, glucose homeostasis – the ability to regulate the blood glucose level – is the result of a complex interplay between a number of organs, hormones, metabolic sub-systems, and neuronal control mechanisms. Also *within each cell*, the contribution and response to the whole-body regulation is the result of a complex interplay of protein–protein interactions, transcriptional and translational processes, etc. Classical biochemical and medical reductionist approaches, which tend to study and analyze single components, lead to piecemeal increases in knowledge and not to a complete and consistent picture.
A sketch of the **minimal model**. This is one of the most cited PKPD models, and has been treated as a benchmark in subsequent modeling, because it is identifiable with respect to data where insulin is used as input signal, because it best describes a given set of such data, and because the insulin sensitivity index may be calculated analytically from the parameters in the model. Even though it often can be given a physiological interpretation, such interpretations are usually hampered by problems with unrealistic estimated parameter values.
Modelling is probably the most powerful tool for data analysis available today. It has the ability to take a given set of data and explanations and evaluate their relationship in a systematic and objective manner, way beyond what is possible using classical reasoning and intuition.

Two important phases of modeling of diabetes: identification of acceptable models and model structures, and analysis of acceptable models. The first step is the **hypothesis testing** step, which checks whether a given model may serve as an acceptable explanation to the given data. The strongest and most informative statement in this step is a rejection. A model that has not been rejected, on the other hand, cannot be thought of as true or permanently acceptable, since it might be unable to describe future data. It is, nevertheless, only the accepted model structures that pass on to the second step: **model analysis**.
Pharmaco-kinetic/-dynamic modeling in diabetes mellitus

• Numerous mathematical models have been developed to: (i) describe the glucose-insulin system, (ii) analyze data from diagnostic tests, and (iii) quantify drug effects for the diverse therapeutic agents (since 1960)
• Limited to diagnostic purposes: the “minimal model” has remained the most popular choice for several decades, and numerous extensions have been developed
• Mechanistic models include glucose-insulin feedback in both directions: (i) “bio-phase distribution models” → “indirect response models” of the effects of various anti-diabetic agents on glucose-insulin homeostasis
• (Also used to describe secondary drug effects on glucose and insulin, and effects on ancillary biomarkers)
• Modeling of diabetes progression can utilize indirect response models as a disturbance of homeostasis
• Future needs: consider dual drug effects on complementary subsystems, and incorporate elements of disease progression
References

