Dynamics and Synchrony of Pancreatic beta-cells and Islets

Pancreatic beta-cells secrete insulin in response to raised glucose levels. Malfunctioning of this system plays an important role in the metabolic disease diabetes. The biological steps from glucose stimulus to the final release of insulin are incompletely understood, and a more complete description of these processes and their interactions would provide important input in the search for a better treatment of the disease. The thesis describes several aspects of mathematical modeling of beta-cells relevant for the understanding of glucose stimulated insulin secretion. It consists of an introductory part with successive chapters tying together the ten original articles, which have been (co-)published, or submitted for publication, during the ph.d.-study. These papers consists the last and most substantial part of the thesis. Besides the results presented in the articles new preliminary results are included on stochastic events in beta-cells, on excitation wave propagation and on entrainment of insulin pulses to a periodic glucose stimulus. The thesis provides a study of dynamic aspects of beta-cell biology with attention to the difference between single cell behavior and the synchronized behavior of many coupled beta-cells as well as to the synchrony of islets. Rather than developing new biophysical models, the thesis investigates existing models, their integration and simplifications, and analyzed the corresponding dynamics, in order to use these models for investigating biological hypotheses. The subjects addressed are: Quasi-steady-state approximations of enzyme reactions, the effect of noise on bursting electrical behavior, excitation wave propagation in pancreatic islets, intra- and inter-islet synchronization and pulsatile insulin secretion, and mitochondrial dynamics.

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