Multiscale modeling of insulin secretion

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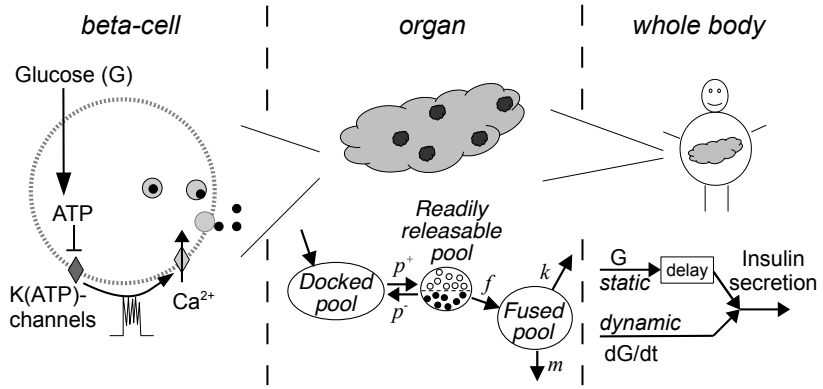
Abstract:

Diabetes results from insufficient insulin secretion either as a result of autoimmune destruction of the pancreatic beta-cells (type 1 diabetes), or due to impaired beta-cell function typically in addition to insulin resistance (type 2 diabetes) [1]. We will here concentrate on multiscale modeling of insulin secretion.



Modeling has been used on several levels of insulin secretion to support or interpret experimental data, from the study of molecular events in the signaling cascade underlying glucose-stimulated insulin secretion [2, 3, 4], over organ models of the entire pancreatic islet population [5], and all the way to whole-body and population descriptions of insulin secretion and action [6]. A large-scale simulation model have been also recently accepted by FDA as an in silico substitute for pre-clinical (animal) studies for certain insulin treatments, including artificial pancreas [7].

Linking between these different levels of insulin secretion has mainly been done using ad-hoc simplifications. For example, complex bursting electrical activity can be replaced by square-pulses [3], or all cellular processes from glucose uptake via electrical activity to exocytosis of insulin-containing granules can be reduced to a direct effect of glucose on secretion [5]. More rigorous coupling between organ-scale and whole-body minimal models of secretion was recently performed using mathematical simplifications [8], which explained how derivative control of insulin secretion can appear from the assumption that single beta-cells become active at different glucose concentrations [5]. On the molecular level, the control of such a glucose threshold for electrical activity by different ion-channels in human beta-cells has recently been investigated using a mathematical model [2]. We have also shown [9] that the multiscale approach can be used to justify our recent model of GLP-1 amplification on insulin secretion [10].

At the level of the pancreas, new models should capture characteristic insulin secretion profiles such as biphasic secretion. This pattern has been suggested to be caused by the release of distinct pools of granules or to be due to the observed biphasic calcium

pattern. Likely both granule pools and calcium dynamics contribute to the secretion pattern. We now extend our previous granule pool model [5] by including calcium dynamics.

The organ-level model is then analyzed in order to understand the mechanistic meaning of the terms and parameters in the parsimonious secretion model used to extract information from clinical data on the whole-body level, following the ideas in our previous work [8]. In particular, we show that the inclusion of calcium in the organ-level model yields new clinical insight.

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