

## Contributions of Mathematical Modeling of Beta Cells to the Understanding of Beta-Cell Oscillations and Insulin Secretion

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### Abstract

Mathematical modeling of pancreatic beta cells has contributed significantly to the understanding of the mechanisms involved in glucose-stimulated insulin secretion (GSIS). Early models of insulin secretion built in the 1970s were phenomenological with little biological foundation for the proposed mechanisms. In the 1980s, models focused on identifying the regulation of bursting electrical activity known to be important for insulin secretion. The main result was to reject proposed mechanisms as new data emerged, but important results of the role of cell-to-cell coupling were also established. New models have been proposed that provide possible explanations for the occurrence of various patterns of bursting and calcium oscillations. In addition, modeling has played an important role in comparing competing effects of calcium on both NADH and adenosine 3'-5'-cyclic monophosphate levels. Models including modern cell biological results of the regulation of insulin containing granules and cell heterogeneity have appeared, providing updated versions of the early models proposed in the 1970s. These models, when coupled to electrophysiological- and calcium-based ones, have the prospect to aid in understanding the overall picture of GSIS. In addition, they might be useful for estimating *in vivo* beta-cell functioning. Beta-cell modeling will likely move closer to clinical applications, where it can be expected to play an important role, as it has and will, in understanding the complex oscillatory phenomena observed in beta cells and islets.

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**Abbreviations:** (AC) adenylyl cyclase, (ADP) adenosine diphosphate, (ATP) adenosine-5'-triphosphate, (cAMP) adenosine 3'-5'-cyclic monophosphate, (ER) endoplasmic reticulum, (GLP-1) glucagon-like peptide-1, (GSIS) glucose-stimulated insulin secretion,  $[I_{K(Ca)}]$  calcium-sensitive potassium current,  $[K(ATP)]$  adenosine-triphosphate-sensitive potassium channels,  $[NAD(P)H]$  nicotinamide adenine dinucleotide (phosphate), (PDE) phosphodiesterase, (PFK) phosphofructokinase

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