Modelling Diabetes

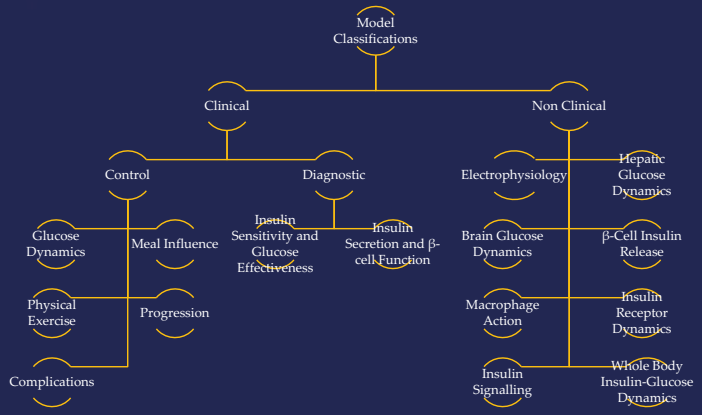
AUCKLAND BIOENGINEERING INSTITUTE
THE UNIVERSITY OF AUCKLAND NEW ZEALAND
Te Whare Wānanga o Tāmaki Makaurau

Background

The aim of this project was to create an extensive repository of carefully curated CellML models which would act as a framework for further research. The anticipated outputs were:

- Curated CellML-encoded models, dealing with a number of aspects of diabetes, available both individually and as a composite model.
- Develop, apply, and document methods for adding biological descriptions to the curated mathematical models, and encoding the simulation experiments in a standard format.

Using the CellML framework, various models have been curated describing the whole-body implications of diabetes and its progression. The central aspects of the diabetes models are shown in the figure below.



Semantic Enrichment of the Physiome Repository

In addition to models already in the physiome repository, new models created in COR were saved in the .cellml format based on the XML markup language. This format allowed the models to be annotated using the program OpenCOR, in which users can link individual model components (representing biological entities) by associating these components with the appropriate gene ontology terms. These annotations can then be used for enrichment of the semantic repository of models present in the physiome library, once they have been RDF indexed by their respective authors. Over the 100+ models annotated, the most common ontology terms included voltage-gated channel activities, such as "voltage-gated calcium channel activity" or "voltage-gated sodium channel complex".

The result is a network of similar models with relevant components linked by the appropriate annotations, allowing for international collaboration between scientists working on similar models. There are hundreds of models which still require annotation so there is plenty of work left to do in this area of research.

Further Research

This project will complement an MWC funded ABI project on developing medical device technologies for servo needle-assisted blood sampling and diagnostic (glucose and insulin) and needle-free drug delivery.

At a later stage, the curated models will be validated with patient-specific data in conjunction with the instrumentation developed for the diabetes project.

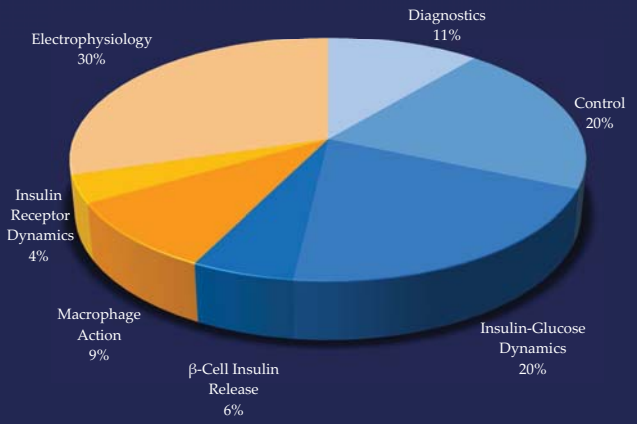


Figure 1. Pie-Chart of the distribution of models within the Diabetes categories

Insulin and Glucose Dynamics

Plasma glucose can be regarded as the summation of several processes such as hepatic glucose production, absorption of exogenous glucose, and glucose utilisation by various tissues. The presence of insulin causes the uptake and utilization of glucose by the insulin-dependent tissues. The study of insulin-glucose dynamics aims to fully understand these processes, to improve the effectiveness of clinical responses to the failure of these mechanisms.

The figure below follows the dynamics of insulin receptor binding. The binding of insulin to these receptors, found on many body cells, allow the glucose uptake and utilisation which leads to homeostasis of blood glucose levels in a healthy subject.

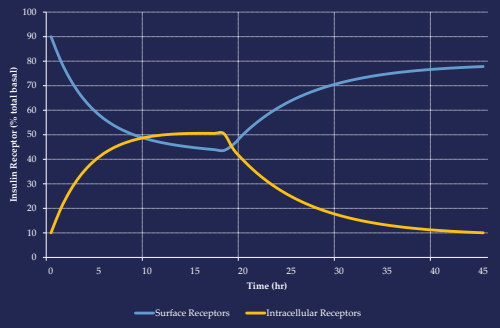


Figure 2. Insulin Receptor Dynamics simulated using OpenCOR

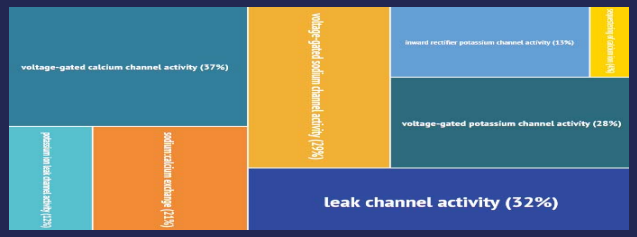


Figure 3. Tree-map of Common Biological Entities Used in Annotations

Electrophysiology

One important characteristic of beta cells is the electrical bursting displayed. Many models have been developed to explain these periodic active and silent phases in which the cell undergoes electrical spiking and subsequent depolarisations. The following models are built on the theories put forth by Hodgkin and Huxley (1952).

Hodgkin & Huxley Model (1952)
- Provided insights into the electrical activity occurring in the cell by modelling the primary currents flow through the activation gates.

Minimal Model (Chay & Keizer,1983)
- Formulated a mathematical model explaining the bursting phenomenon using voltage gated potassium calcium and potassium gates as well as a calcium-gated potassium channel.

Further Research (1983 – Present)
- The minimal model along with Hodgkin and Huxley formed the basis for many others. The following models differ primarily on the channels and the method of negative feedback used.

The release of insulin by β-cells in the pancreatic islets plays a key role in glucose homeostasis. One of the main characteristics associated with this release is the electrical bursting exhibited by these cells, as seen in the figure below. The mechanisms behind these oscillations are yet to be fully understood, and thus was one of the primary focuses in this project in order to aid further research.

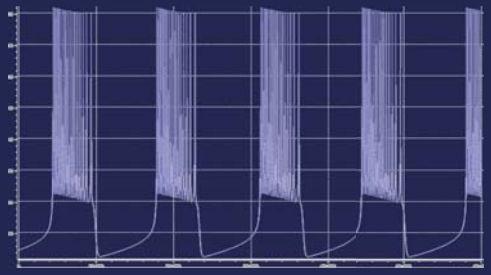


Figure 4. Electrical Bursting in the Pancreatic Beta Cell simulated using OpenCOR

References

Chay, T. R., & Keizer, J. (1983). Minimal model for membrane oscillations in the pancreatic beta-cell. *Biophysical Journal*. doi:10.1016/S0006-3495(83)84384-7

Hodgkin, A. L., & Huxley, A. F. (1952). A Quantitative Description Of Membrane Current and its Application to Conduction and Excitation in Nerve. *The Journal of Physiology*, *117*(4), 500-544.

QUON, M., & CAMPFIELD, L. (1991). A mathematical model and computer simulation study of insulin receptor regulation. Journal of Theoretical Biology. doi:10.1016/S0022-5193(05)80475-8

Vries, G. D. (2000). Channel Sharing in Pancreatic β Cells Revisited: Enhancement of Emergent Bursting by Noise. *Journal of Theoretical Biology*. doi:10.1006/jtbi.2000.2193

Acknowledgements

We would like to thank our supervisors, Dist Prof. Peter Hunter and Dr. David Nickerson, for their support and the opportunity to work on this project.

Abinaya Rajasekar, Dhanya Herath, Ray Cai, Nathan Henry