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Experimentally Calibrated COMSOL Multiphysics Model for Glucose-Stimulated Insulin Release: Effect of Encapsulation and Device Geometry on First- and Second Phase Insulin Response

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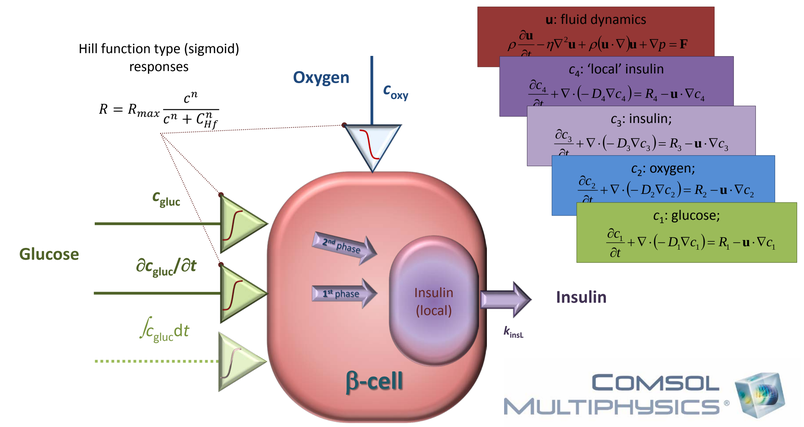
FEM-Based GSIR Model: Concept and Implementation

Computational modeling is done with our recently developed and calibrated COMSOL Multiphysics model of insulin secretion in avascular islets) [1-3]. Insulin-secreting β-cells are assumed to act as sensors of both the local glucose concentration and its change:

- c_{gluc} (local glucose concentration) → second-phase insulin response
- $\partial c_{gluc}/\partial t$ (change in local c_{gluc}) → first-phase insulin response

All nutrient consumption and hormone release rates are assumed to follow Hill-type sigmoid dependences on local concentrations. Parameterization has now been done with experimental GSIR perifusion data for both human [1, 2] and murine islets (including alginate-encapsulated ones) [3].

Present Model of Insulin Secretion (Avascular Islets)



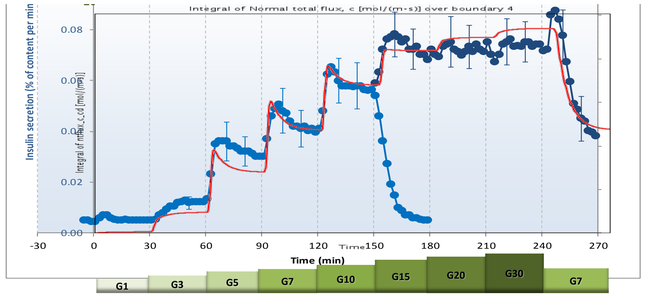
Schematic concept of the present model of glucose-stimulated insulin secretion in β-cells. It was conceived within the general framework of sigmoid proportional-integral-derivative (SPID) controllers. Response is determined by the local glucose concentration, c_{gluc}, and its rate of change, $\partial c_{gluc}/\partial t$, but it is also influenced by the local oxygen concentration, c_{oxy}, as the availability of oxygen can be a major limiting factor in avascular islets. A total of four concentrations are modeled for glucose (c_{gluc}), oxygen (c_{oxy}), and 'local' and released insulin (c_{insL}, c_{ins}), respectively. All hormone secretion and nutrient consumption kinetics are coupled with diffusive and convective transport via a fluid dynamics model. The model can account for both first- and second-phase insulin secretion, and can be used for arbitrary geometries and glucose stimulation sequences.

Model	Var.	C_{Hf}	n	R_{max}	Comments
R_{oxy}, oxygen consumption, base	c_{oxy}	1 μM	1	–0.034 mol/m³/s	Cut to 0 below critical value, $c_{oxy} < C_{cr,oxy}$.
R_{oxy}, oxygen consumption, $\varphi_{o,g}$ metabolic part	c_{gluc}	7 mM	2.5	N/A	Due to increasing metabolic demand; parallels second-phase insulin secretion rate.
R_{gluc}, glucose consumption	c_{gluc}	10 μM	1	–0.028 mol/m³/s	Contrary to oxygen, has no significant influence on model results.
$R_{ins,ph2}$, insulin secretion rate, second-phase	c_{gluc}	7 mM	2.5	3×10^{-5} mol/m³/s	Total secretion rate is modulated by local oxygen availability (last row).
$R_{ins,ph1}$, insulin secretion rate, first-phase	$\partial c_{gluc}/\partial t$	0.03 mM/s	2	21×10^{-5} mol/m³/s	Modulated via equation below to have maximum sensibility around c_{gluc} = 5 mM and be limited at very large or low c_{gluc}.
Insulin secretion rate, $\varphi_{o,g}$ oxygen depend.	c_{oxy}	3 μM	3	N/A	To abruptly limit insulin secretion if c_{oxy} becomes critically low.

Oxygen concentrations used: c_{atm} = 0.200 mol/m³ (0.2 mM; pO_2 ≈140 mmHg, 18% O_2; normal culture 95% air, 5% CO_2; 37°C); 'tissue' (slight hypoxia: c_{in} = 0.06 mol/m³ (0.06 mM; pO_2 ≈45 mmHg, 5% O_2).
Human islets: k_{insL} = 0.003 s^{-1} → **Mouse islet**: k_{insL} = 0.006 s^{-1}.

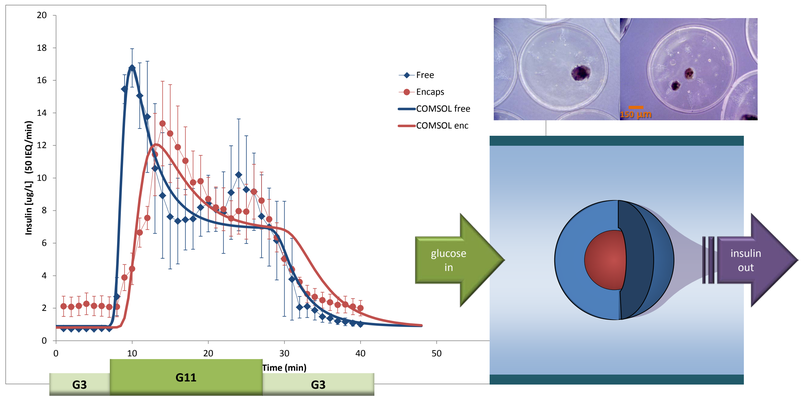
Results – Fit of Human and Murine Islet Data

Human Islets – Dynamic Perifusion, Staircase Experiment

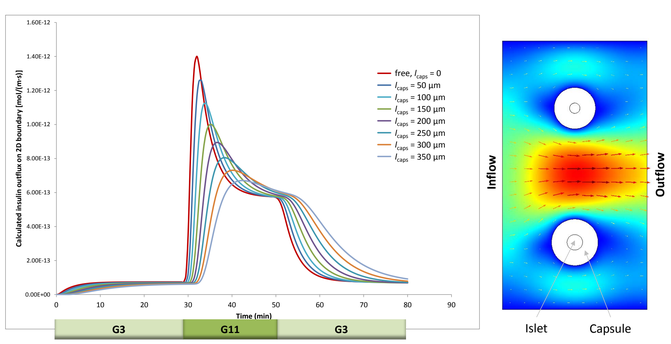


GSIR (perifusion) data (human islets) used for model parametrization [1]. Experimental data (blue disks, ●) are for human islets (Henquin et al. *Diabetes* **2006**, *55*, 3470) and values calculated with the present model (red line, —) after final calibration are shown superimposed on the same time-scale [1].

Murine Islets – Parallel Perifusion of Free and Encapsulated Islets

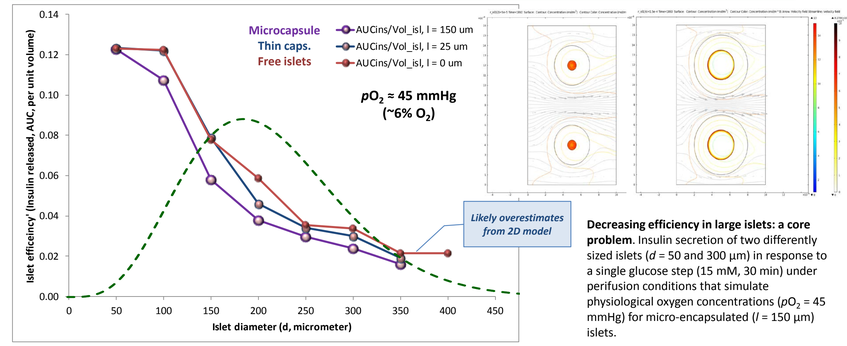


GSIR (perifusion) data for un-encapsulated (naked or free) and encapsulated islets perifused in parallel and their fit with the present computational model [3]. Experimental data (symbols) were determined in dynamic perifusion with frequent sampling (every minute) using free and alginate-encapsulated (d ≈ 800 μm) islets (~50 IEQ, average of three experiments in duplicates) in response to a single glucose step as show. Corresponding model-calculated insulin outflow is shown for capsule thicknesses of 0 (free islets) and l_{caps} = 150 μm assuming islet sizes as shown in figure with geometry and following a 2D to 3D conversion with a total islet volume scaled to 50 IEQ (see text).



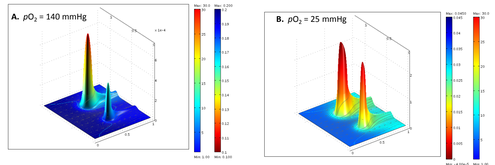
Model-predicted effect of capsule thickness on insulin secretion profile [3]. Calculated insulin outflow is shown in response to a stepwise glucose stimulation with the current computational model for two encapsulated islets (d = 100 & 150 μm) as a function of increasing capsule thickness (l_{caps}) from 0 (free islets) and 50 to 350 μm. Inset (right) shows an illustration of the main geometric setup used for the current model with fluid flow from left to right, and 100 (top) and 150 (bottom) μm islets.

Estimated Islet Efficiency (Free and Encapsulated Avascular Islets)



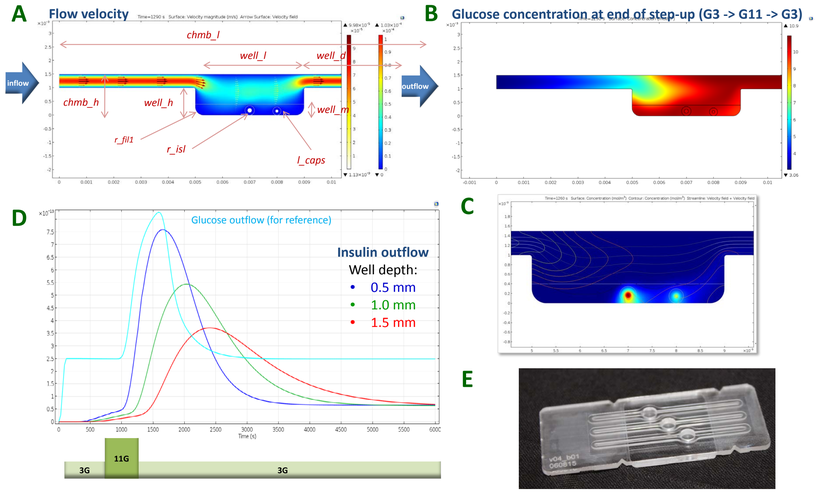
Decreasing efficiency in large islets: a core problem. Insulin secretion of two differently sized islets (d = 50 and 300 μm) in response to a single glucose step (15 mM, 30 min) under perifusion conditions that simulate physiological oxygen concentrations (pO_2 = 45 mmHg) for micro-encapsulated (l = 150 μm) islets.

Insulin secreting efficiency of differently sized islets. Data shown are *islet efficiency* [calculated as the total insulin release per islet volume (area for 2D)] overlapped with the size distribution of human islets (dashed green line). Insulin release is total insulin release (AUC) of differently sized islets, d = 50 to 350 μm, in response to a single glucose step (15 mM, 30 min) under perifusion conditions that simulate physiological oxygen concentrations (pO_2 = 45 mmHg) for free islets (l = 0) as well as thin- (l = 25 μm) and micro-encapsulated (l = 150 μm) islets.



Calculated insulin concentrations as 3D height data. Surfaces are color-coded for oxygen concentration (blue high, red low) for free islets in normoxic (p_{O2} = 140 mmHg) (**A**) and hypoxic conditions (p_{O2} = 25 mmHg) (**B**). The insulin secreting ability of the large islet is more severely affected by hypoxia as clearly indicated by the changes in relative height between **A** and **B** (note different scales).

First Model Calculations for Islet Microsystem Device



Results of the first simulations for a possible microfluidic device. Representative model calculations are shown for a fully parameterizable geometry (A) of a microfluidic device design that can be microfabricated (E). Calculated fluid flow (velocity field) (A), glucose (B), and insulin concentrations (C) as well as insulin outflux (D) in response to a glucose step-up at various well depths (0.5 to 1.5 mm) for two islets perifused at atmospheric oxygen (E).

References

1. Buchwald, P. A local glucose-and oxygen concentration-based insulin secretion model for pancreatic islets. *Theor. Biol. Med. Model*. **2011**, *8*, 20.
2. Buchwald, P. and Cechin, S. R. Glucose-stimulated insulin secretion in isolated pancreatic islets: multiphysics FEM model calculations compared to results of perifusion experiments with human islets. *J. Biomed. Sci. Eng*. **2013**, *6*, 26-35.
3. Buchwald, P.; Cechin, S. R.; Weaver, J. D.; Stabler, C. L. Experimental evaluation and computational modeling of the effects of encapsulation on the time-profile of glucose-stimulated insulin release of pancreatic islets. *Biomed. Eng. Online* **2015**, *14*, 28.

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