Presented at the COMSOL Conference 2010 Boston

COMSOL Multiphysics-Based Exploratory Insulin Secretion Model for Isolated Pancreatic Islets

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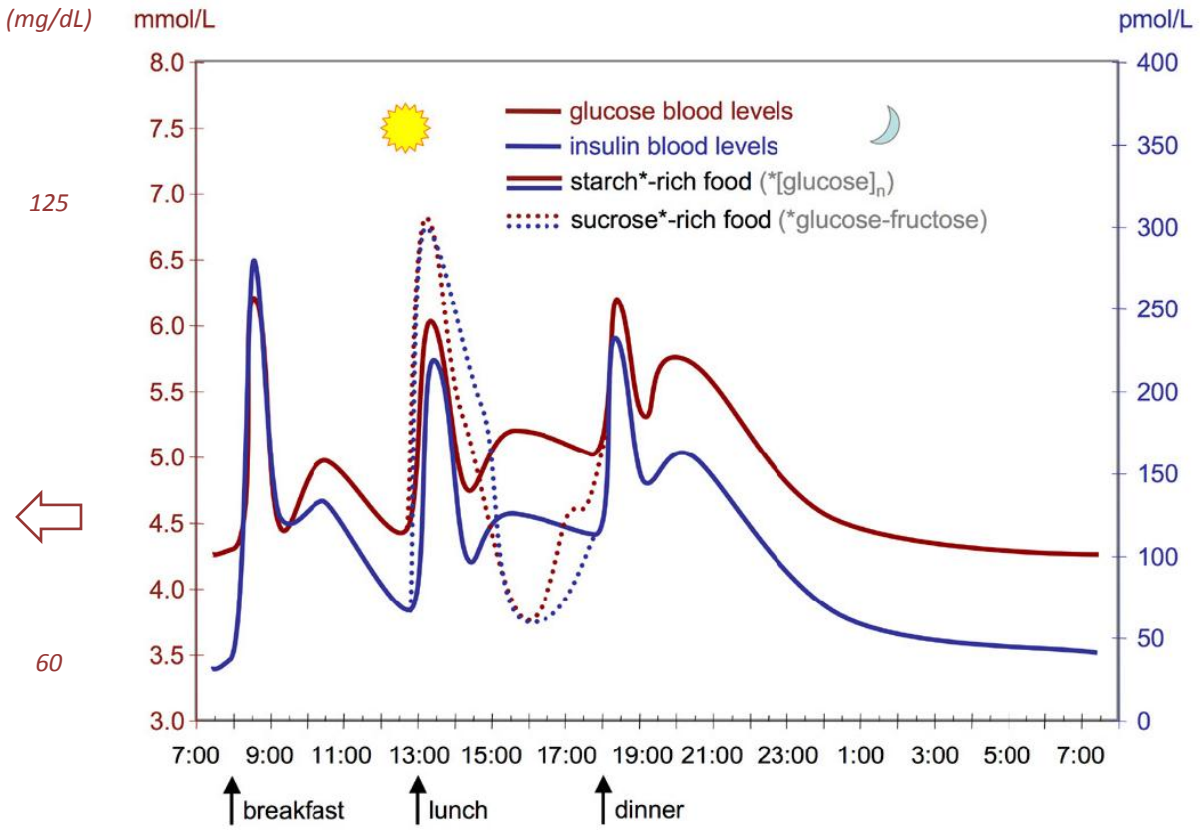
Normal Human Blood Glucose and Insulin Levels

- In healthy humans, blood glucose levels have to be maintained in a relatively narrow range (3.5–7.0 mM, 60–130 mg/dL in fasting subjects)
- Mainly achieved by adjusting insulin levels with the β cells of pancreatic islets acting as glucose sensors and releasing insulin

Total blood glucose (in 75 kg human) ≈ **5 g**



Suckale, J.; Solimena, M. *Front. Biosci.* **2008**, *13*, 7156.

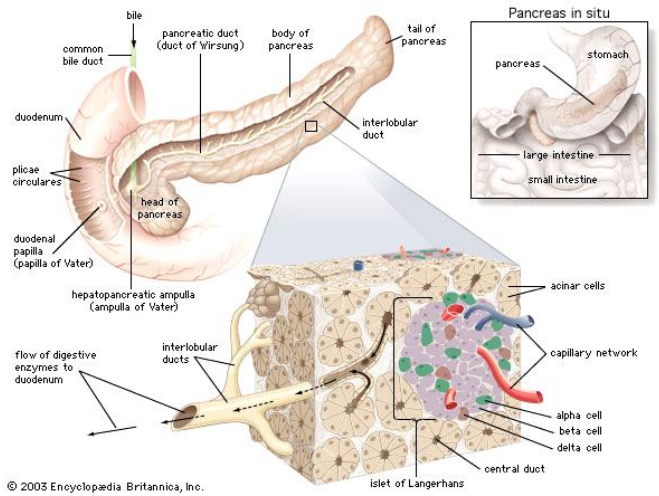
Islets of Langerhans

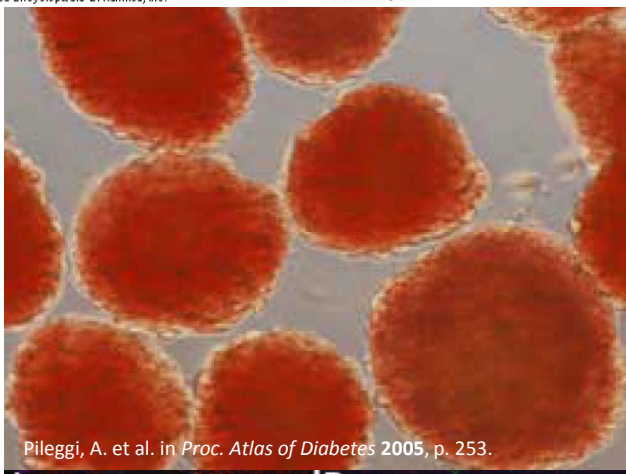
- Cellular aggregates of approx. 2,000 cells and diameters of about 150 μm (range: 50–500 μm) located in the pancreas and responsible for its endocrine (hormone releasing) function
- Represent only 1–2% of the pancreas
- Humans have approx. 1,000,000 islets (≈ 2 mL)
- Four major cell types secreting different hormones:

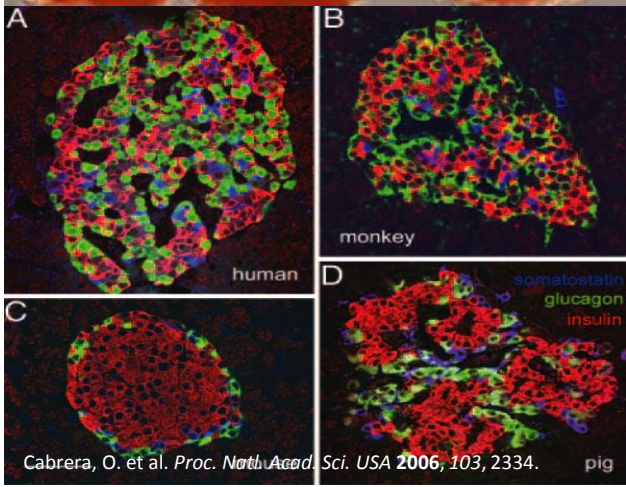
α cells (glucagon)	[~35%, human]
β cells (insulin)	[~60% , human]
δ (somatostatin), and	[~5%, human]
PP cells (pancreatic polypeptide)	

- There are considerable species differences

- Insulin causes cells to take up glucose (from the blood) and store it as glycogen (liver, muscle); it also stops the use of fat as energy source

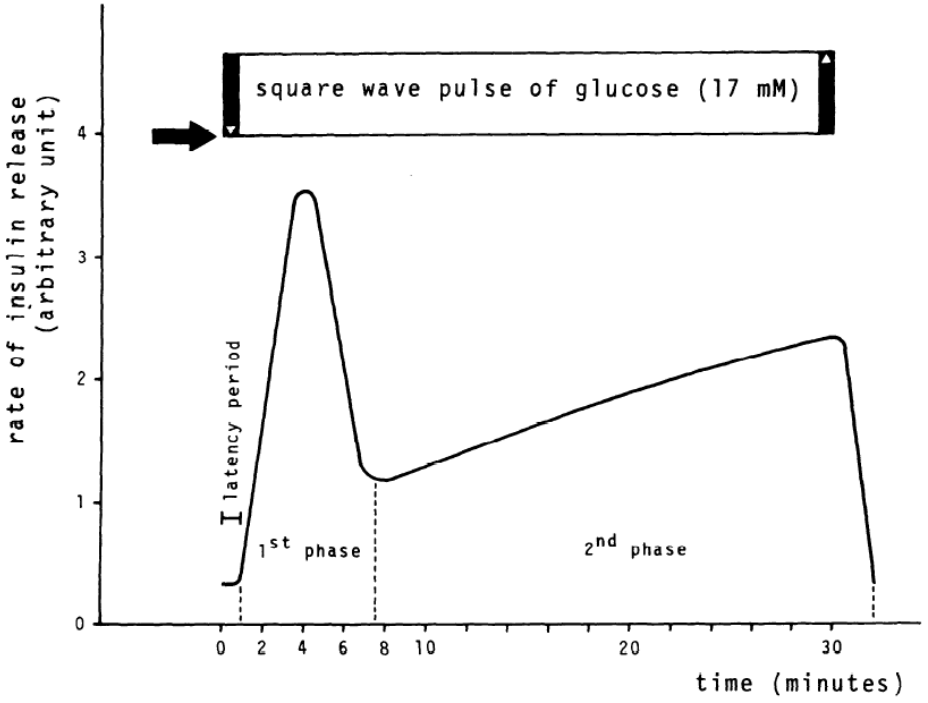



Pileggi, A. et al. in *Proc. Atlas of Diabetes* **2005**, p. 253.

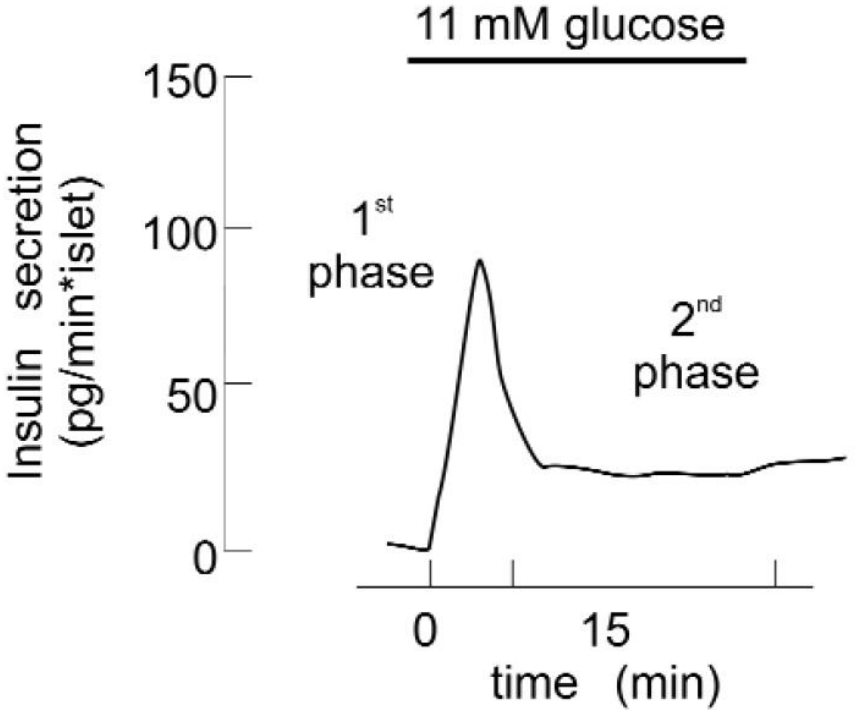


Cabrera, O. et al. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 2334.

Phases of Insulin Secretion



Hedeskov, C. J. *Physiol. Rev.* **1980**, *60*, 442.



Rorsman, P. et al. *News Physiol. Sci.* **2000**, *15*, 72
(after Ma, Y. H., …, Grodsky, G.M. et al. *Eur. J. Endocrinol*. **1995**, *132*, 370)

Schematic illustration of latency period and the two phases of insulin release. Depending on experimental conditions, second phase of secretion may be of much longer duration than shown here.

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Quantitative Glucose-Insulin Models

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Am. J. Physiol., 236(6): E667–E677, 1979

Quantitative estimation of insulin sensitivity

RICHARD N. BERGMAN, Y. ZIYA IDER, CHARLES R. BOWDEN, AND CLAUDIO COBELLI

Computer Methods and Programs in Biomedicine, 32 (1990) 277–285

Kinetic modelling as a tool for the design of a vascular bioartificial pancreas: feedback between modelling and experimental validation

Gérard Reach [1] and Michel Y. Jaffrin [2]

DIABETES CARE, VOLUME 27, NUMBER 6, JUNE 2004

Use and Abuse of HOMA Modeling

TARA M. WALLACE, MD
JONATHAN C. LEVY, MD
DAVID R. MATTHEWS, MD

COMPUTERS AND BIOMEDICAL RESEARCH 17, 570–579 (1984)

A Mathematical Insulin-Secretion Model and Its Validation in Isolated Rat Pancreatic Islets Perifusion

MAKOTO NOMURA, MOTOAKI SHICHIRI, RYUZO KAWAMORI, YOSHIMITSU YAMASAKI, NORIMICHI IWAMA, AND HIROSHI ABE

Journal of Biomechanical Engineering
1990, Vol. 112 / 221

Theoretical Analysis of the Effect of Convective Flow on Solute Transport and Insulin Release in a Hollow Fiber Bioartificial Pancreas

M. R. Pillarella*
A. L. Zydney

BioMedical Engineering OnLine 2006, **5**:43

A critical review of mathematical models and data used in diabetology

A Boutayeb*† and A Chetouani†

Biotechnol. Prog. **1995**, *11*, 115–126

Tissue Engineering of a Bioartificial Pancreas: Modeling the Cell Environment and Device Function

Evangelos Tziampazis and Athanassios Sambanis*

Applied Numerical Mathematics 56 (2006) 559–573

Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview

Athena Makroglou [a,*], Jiaxu Li [b], Yang Kuang [b,1]

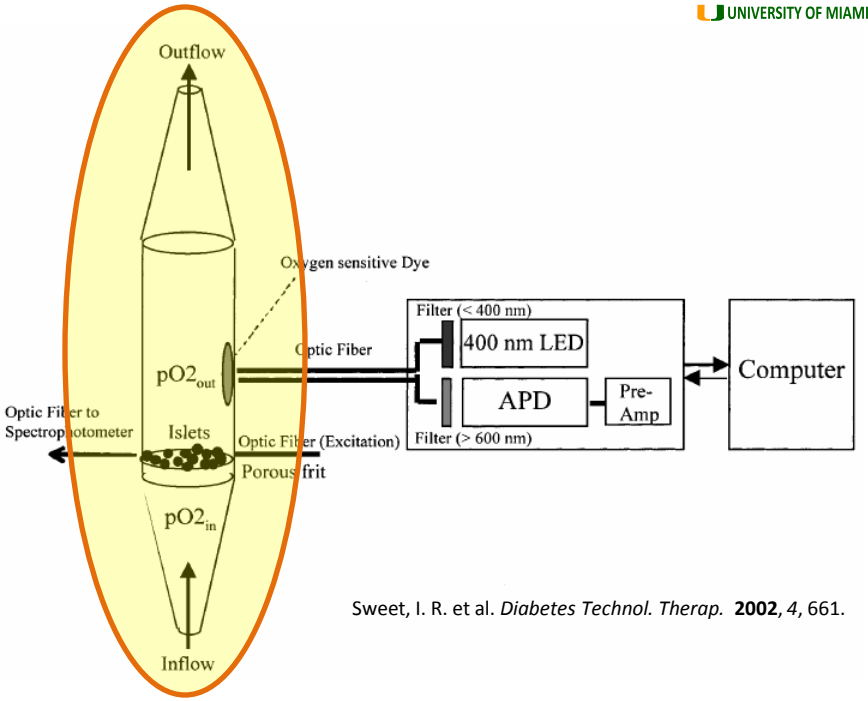
Journal of Biomechanical Engineering
2005, Vol. 127 / 1054

What are the Relevant Parameters for the Geometrical Optimization of an Implantable Bioartificial Pancreas?

Jean-Luc Dulong
Cécile Legallais[1]

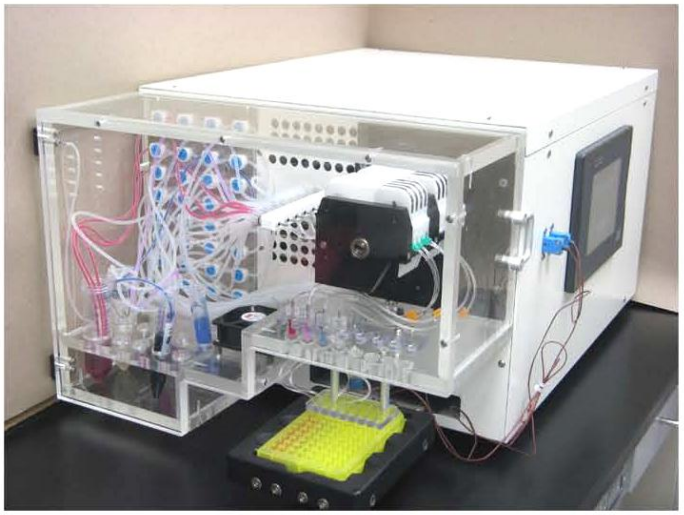
Perifusion Device with Flowing Media

- Routinely used to assess islet quality and function
- Allows the dynamic measurement of the glucose-stimulated insulin release (GSIR) (and/or other metabolic products)



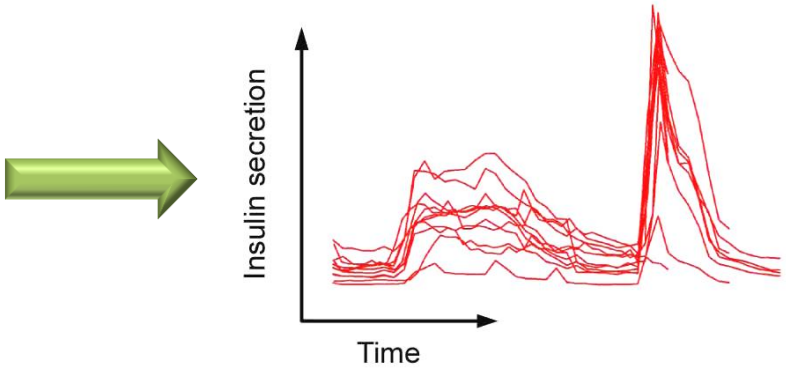
Sweet, I. R. et al. *Diabetes Technol. Therap.* **2002**, *4*, 661.

Automated Perifusion



Cabrera, O. et al. *Cell Transplant.* **2008**, *16*, 1039.

Secretion profiles



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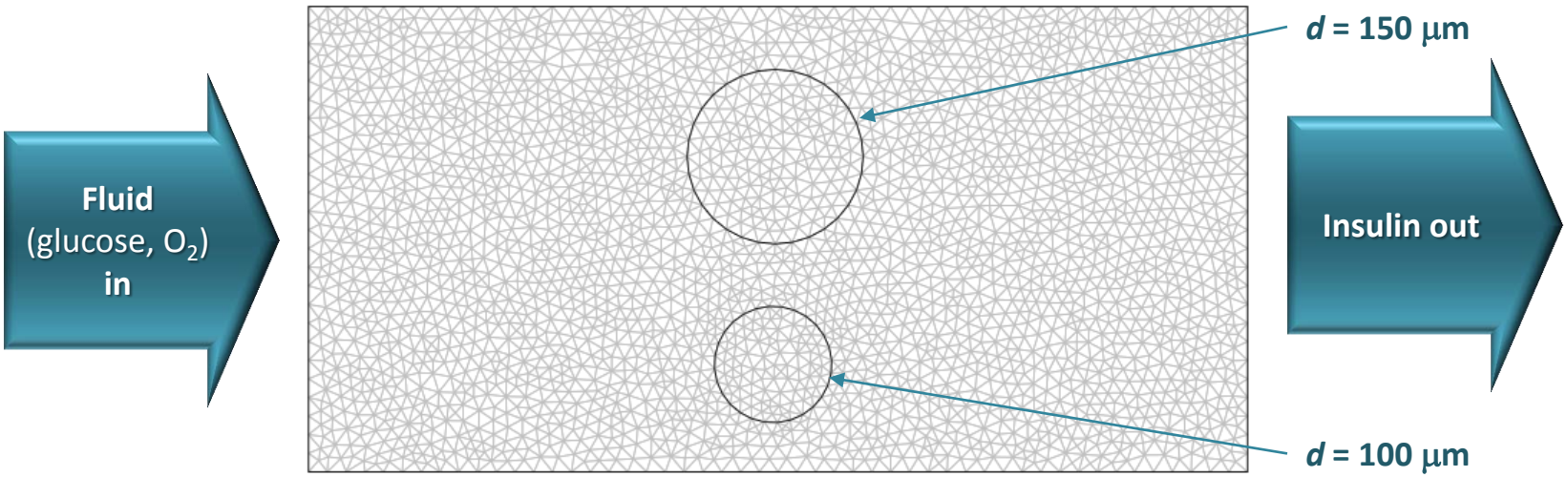
Insulin Release in Dynamic Perifusion Model: Geometry and Mesh



Considering the size distribution of human islets (Buchwald, P. et al. *Cell Transplant.* **2009**, *18*, 1223), islets with diameters *d* = 100 and 150 µm are most representative.

Multiphysics Model

Convection and diffusion (3×)

$$\frac{\partial c}{\partial t}+\nabla\cdot\left(-D\nabla c\right)=R-\mathbf{u}\cdot\nabla c$$

Fluid dynamics (incompressible Navier-Stokes(convection and conduction):

$$\rho\frac{\partial \mathbf{u}}{\partial t}-\eta\nabla^2\mathbf{u}+\rho\left(\mathbf{u}\cdot\nabla\right)\mathbf{u}+\nabla p=\mathbf{F};\quad \nabla\cdot\mathbf{u}=0$$

c_1: insulin; c_2: glucose; c_3: oxygen

Hormone secretion and nutrient consumption kinetics, which form the essence of the model, are built into *R*s

Parameter settings

Flow (aqueous media at room temperature):

T_0 = 310.15 K, ρ = 993 kg/m^3, η = 0.7×10^{-3} Pa·s, c_p = 4200 J/kg/K, k_c = 0.634 J/s/m/K, α = 2.1×10^{-4} K^{-1}

parabolic inflow profile on inlet $4v_{in}(y/y_{max})(1–y/y_{max})$; v_{in} = 10^{-4} m/s

Incoming oxygen:

c_{atm} = 0.200 mol/m^3 (0.2 mM; pO_2 ≈140 mmHg; normal culture 95% air, 5% CO_2; 37°C)

hypoxia: c_{in} = 0.036 mol/m^3 (0.036 mM; pO_2 ≈25 mmHg), etc.

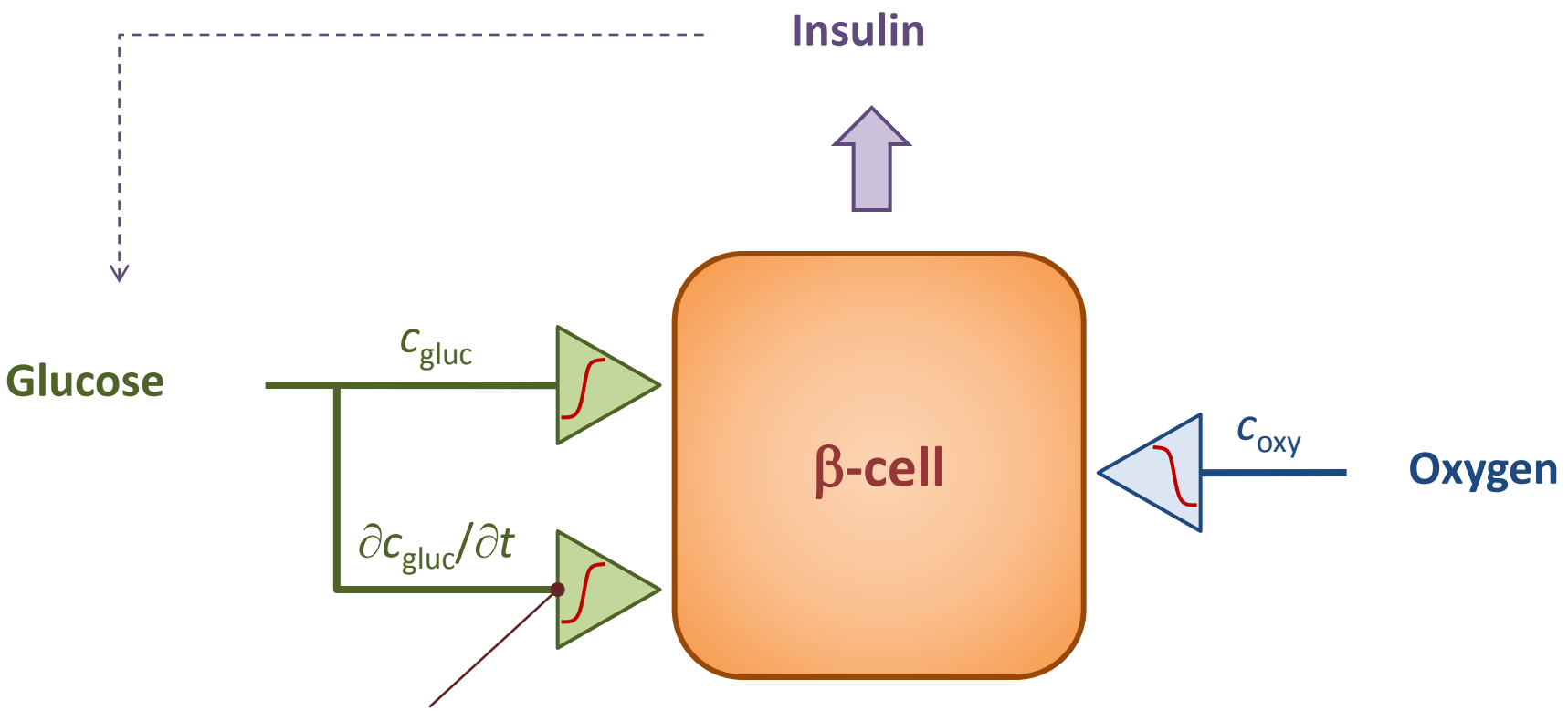
Incoming glucose:

incoming c_{gluc} increased stepwise from 1 mM to 10–19 mM using sum of Heaviside functions

2D cross-section models with realistic geometries (islets with diameters of *d* = 100 and 150 μm)

- Default ‘extra fine’ mesh size used (mesh sizes of 5,000-9,000 elements)
- Solved as time-dependent (transient) problem with the Pardiso direct solver

Present Glucose-Insulin(-Oxygen) Model

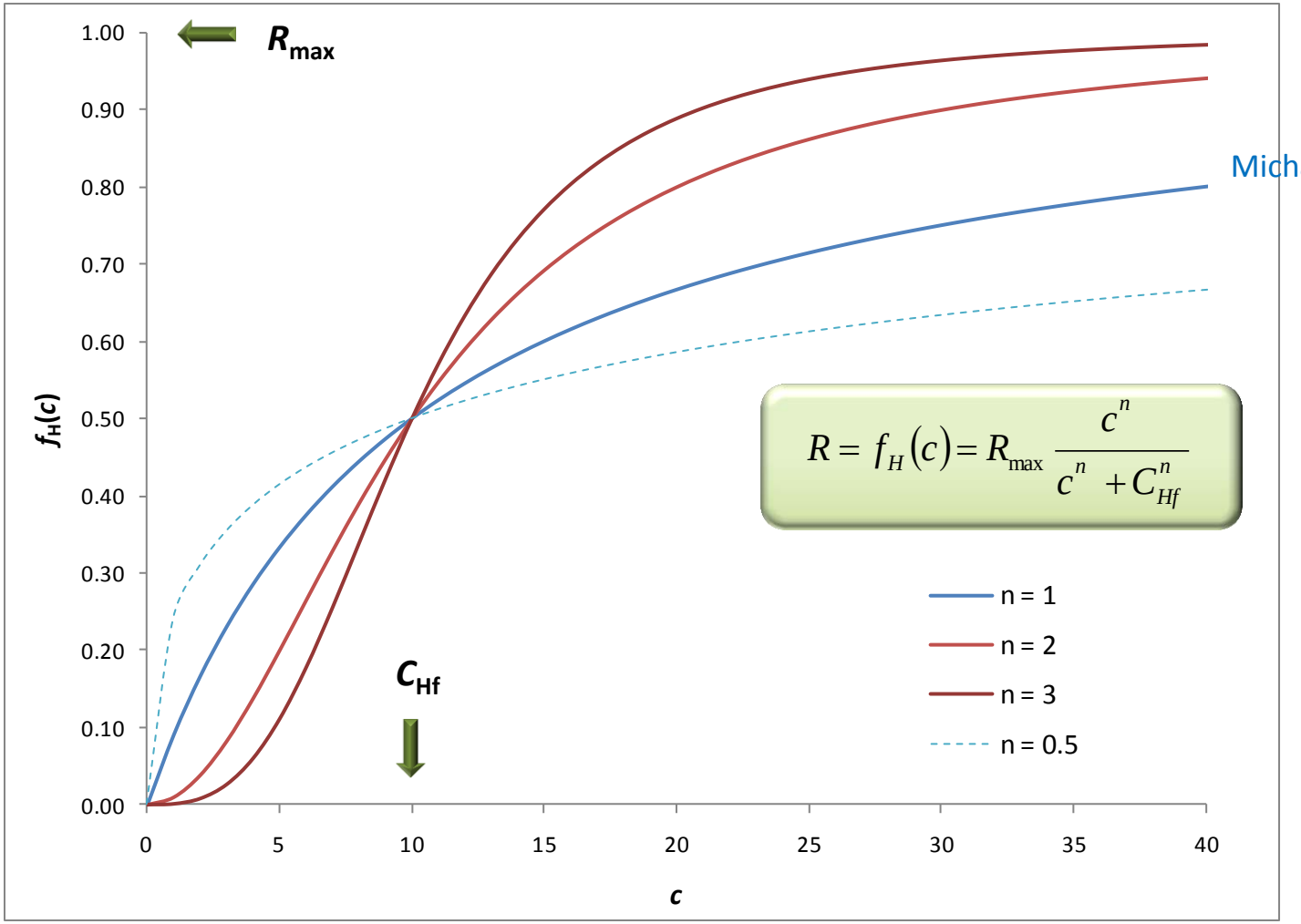


Sigmoid, Hill function type responses

$$R = R_{max} \frac{c^n}{c^n + C_{Hf}^n}$$

Buchwald, P. *COMSOL Conf. Boston* **2010**.

Hill Function / Hill Equation
(Generalized Michaelis-Menten Kinetics)



Michaelis-Menten
$n = 1$

Oxygen Dynamics

Main assumptions – Oxygen

Oxygen concentrations:

$c_{in} = c_{atm} = 0.200$ mol/m^3 [140 mmHg; atmospheric, 21%]

$c_{tissue} = 0.050$ mol/m^3 [35 mmHg; tissue & venous ≈ 40 mmHg]

$c_{art} = 0.130$ mol/m^3 [90 mmHg; arterial]

$c_{in,low} = 0.036$ mol/m^3 [25 mmHg; hypoxia for perifusion]

Diffusion:

$D_{oxy,w} = 3.0\times10^{-9}$ m^2/s (O_2 in water)

$D_{oxy,t} = 2.0\times10^{-9}$ m^2/s (O_2 in islet tissue)

$D_{oxy,Si} = 2.0\times10^{-9}$ m^2/s (O_2 in silicone rubber)

Oxygen consumption and cell viability:

$$R_{oxy} = R_{\max,oxy}\frac{c_{oxy}}{c_{oxy}+C_{Hf,oxy}}\cdot\varphi_{o,g}\left(c_{gluc}\right)\cdot\delta\left(c_{oxy}>C_{cr,oxy}\right)$$

$R_{max,oxy} = 0.034$ mol/m^3/s {i.e., 0.6×10^{-13} mol/s/IEQ} (averaged best estimate)

$C_{Hf,oxy} = 1.0\times10^{-3}$ mol/m^3 (Michaelis-Menten constant) [0.7 mmHg]

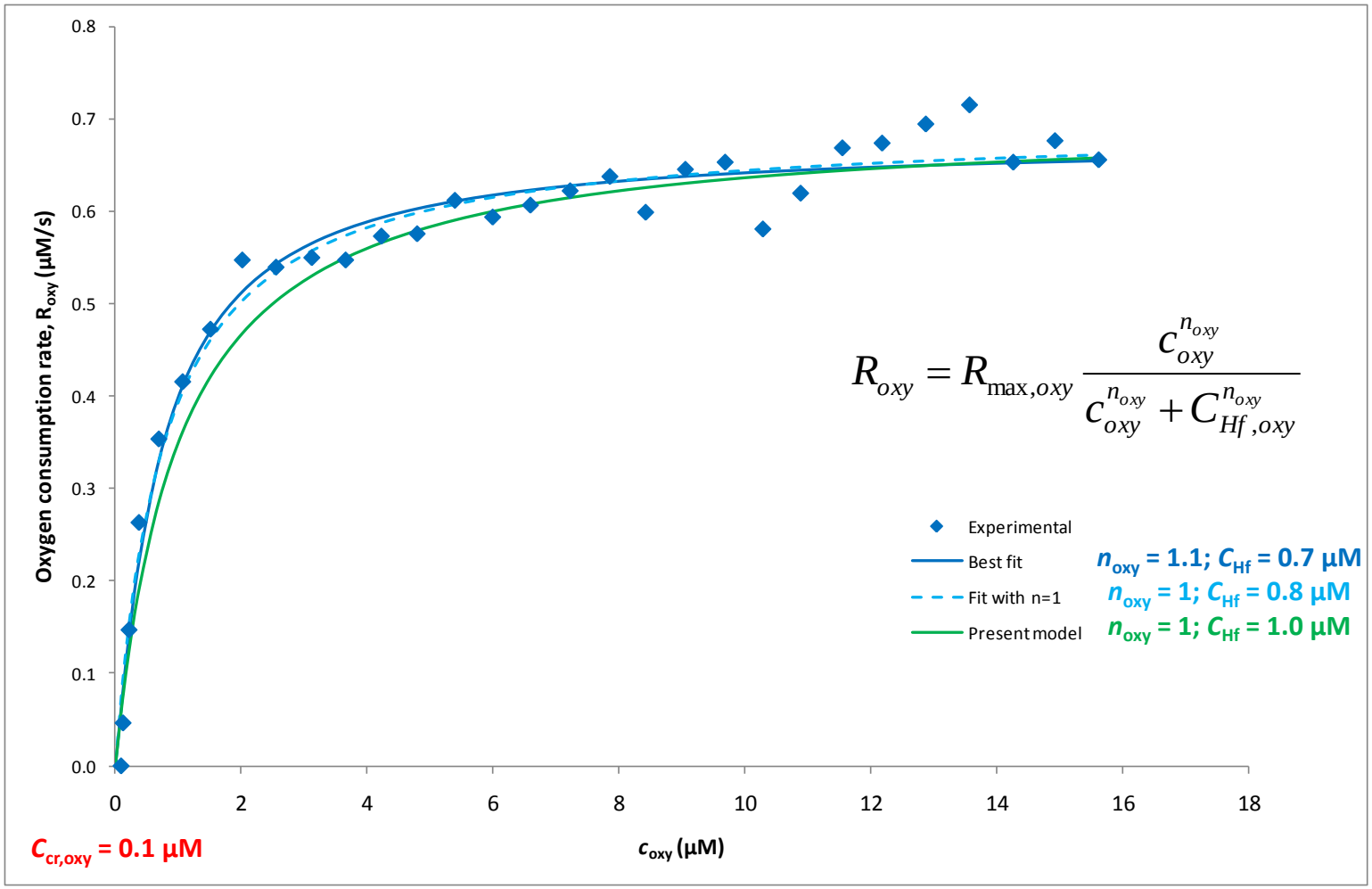
$C_{cr,oxy} = 1.0\times10^{-4}$ mol/m^3 (critical for survival) [0.07 mmHg]

$\delta(c)$ = `flc1hs`($c_{oxy} - 1.0\cdot10^{-4}$, $0.5\cdot10^{-4}$) – COMSOL's smooth Heaviside function (step-down)

$\varphi_{o,g}(c_{gluc})$ modulating factor to account for increased oxygen consumption at high glucose due to increased metabolic demand – here, assumed to have a base component (50%) and a metabolic component that increases in parallel with increasing insulin secretion

Buchwald, P. *Theor. Biol. Med. Model.* **2009**, *6*: 5.

General Hill-Type Concentration-Dependence of Oxygen Consumption in Mitochondria



Fit of Hill type (generalized Michaelis-Menten) type dose response for oxygen consumption at low oxygen concentrations by allowing a variable Hill slope. Data from Wilson, D. L et al. *J. Biol. Chem.* **1988**, *263*, 2712.

There seems to be no need for *n* > 1.

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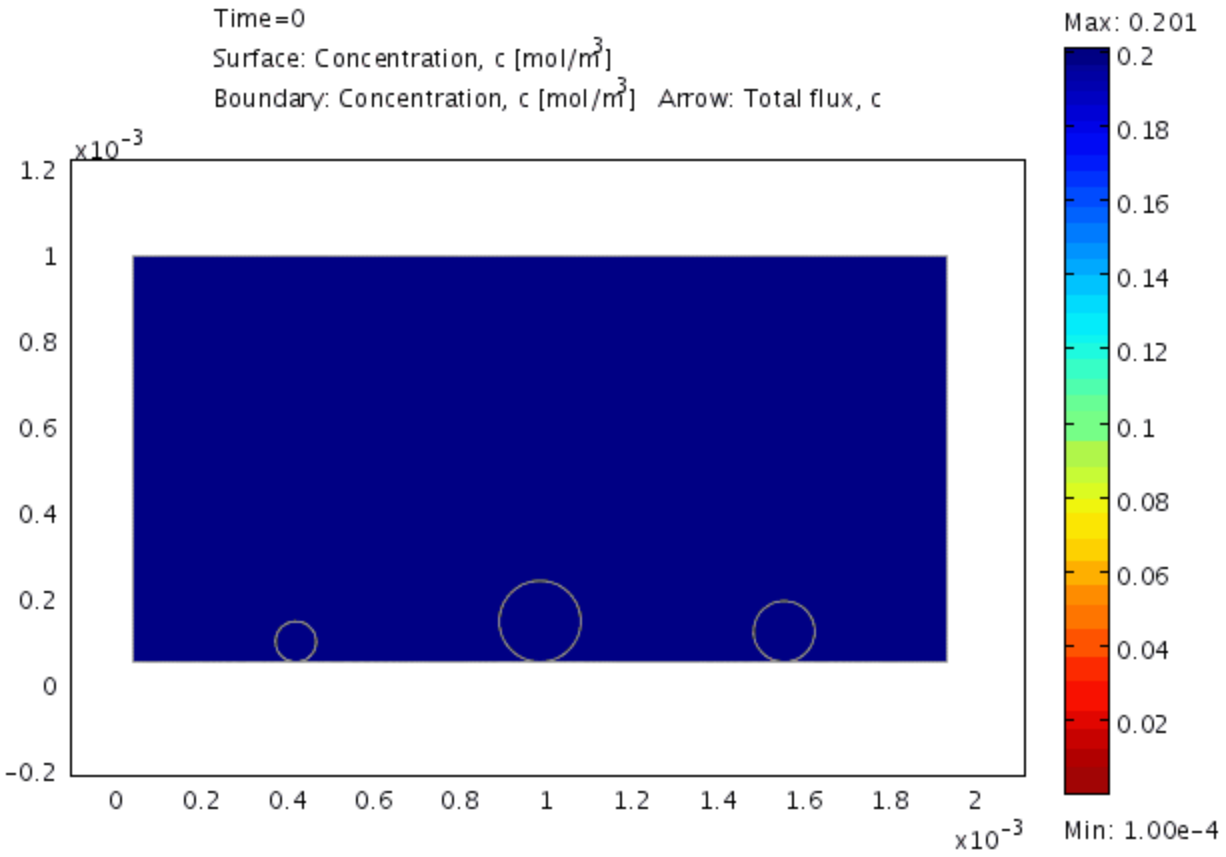
Islet Culture 2D Model

Oxygen Concentrations in Nonvascularized Islets in Traditional Culture



Calculated oxygen concentration for three islets (with diameters ϕ = 100, 150, and 200 μm) in standard culture conditions as stationary conditions are being reached (h = 1 mm assumed). The color-coded surface represents the oxygen concentration (blue corresponding to higher and red to lower values). Areas with values below a critical value (<10^{-4} mol·m^{-3}), where the lack of oxygen (hypoxia) is predicted to cause cell death (necrosis) are left uncolored (white). Because this is a 2D cross-section, it roughly corresponds to a 3D culture density of about 1,600 IEQ/cm^2.

Buchwald, P. *Theor. Biol. Med. Model.* **2009**, *5*:6.

Glucose-Insulin(-Oxygen) Dynamics

Main assumptions – Glucose & Insulin

Diffusion:

$D_{ins,w}$ = 1.5×10^{-10} m^2/s (insulin in blood)

$D_{ins,t}$ = 0.5×10^{-10} m^2/s (insulin in islet tissue) */somewhat lowered to account for cellular release/*

$D_{gluc,w}$ = 9.0×10^{-10} m^2/s (glucose in blood)

$D_{gluc,t}$ = 3.0×10^{-10} m^2/s (glucose in islet tissue) */somewhat lowered to account for cellular uptake/*

Glucose consumption:

$$R_{gluc} = R_{\max,gluc}\frac{c_{gluc}}{c_{gluc}+C_{Hf,gluc}}\cdot\delta\left(c_{oxy} > C_{cr,oxy}\right)$$

$R_{max,gluc}$ = 0.028 mol/m^3/s

$C_{Hf,gluc}$ = 10.0×10^{-3} mol/m^3 [10 μM]

Insulin release:

second phase

$$PR_{ins,ph2} = PR_{\max,ins2}\frac{c_{gluc}^{n_{ins2,gluc}}}{c_{gluc}^{n_{ins2,gluc}}+C_{Hf,ins2,gluc}^{n_{ins2,gluc}}}$$

$PR_{max,ins2}$ = 3.0×10^{-5} mol/m^3/s [~20 pg/IEQ/min]

$n_{ins2,gluc}$ = 2; $C_{Hf,ins2,gluc}$ = 7.5 mM (glucose)

first phase

$$PR_{ins,ph1} = PR_{\max,ins1}\frac{\left(\frac{\partial c_{gluc}}{\partial t}\right)^{n_{ins1,gluc}}}{\left(\frac{\partial c_{gluc}}{\partial t}\right)^{n_{ins1,gluc}}+Ct_{Hf,ins1,gluc}^{n_{ins1,gluc}}}$$

$PR_{max,ins1}$ = 1.5×10^{-5} mol/m^3/s

$n_{ins1,gluc}$ = 2; $Ct_{Hf,ins1,gluc}$ = 0.01 mM/s (glucose change)

total with oxygen modulation

$$PR_{ins} = \left(PR_{ins,ph1}+PR_{ins,ph2}\right)\cdot\frac{c_{oxy}^{n_{ins,oxy}}}{c_{oxy}^{n_{ins,oxy}}+C_{Hf,ins,oxy}^{n_{ins,oxy}}}$$

$n_{ins,oxy}$ = 3; $C_{Hf,ins,oxy}$ = 3.0×10^{-3} mol/m^3 [2.1 mmHg]

Buchwald, P. *COMSOL Conf. Boston* **2010**.

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General Hill-Type Concentration-Dependence of Glucose-Induced Insulin Secretion in Perifused Human Islets

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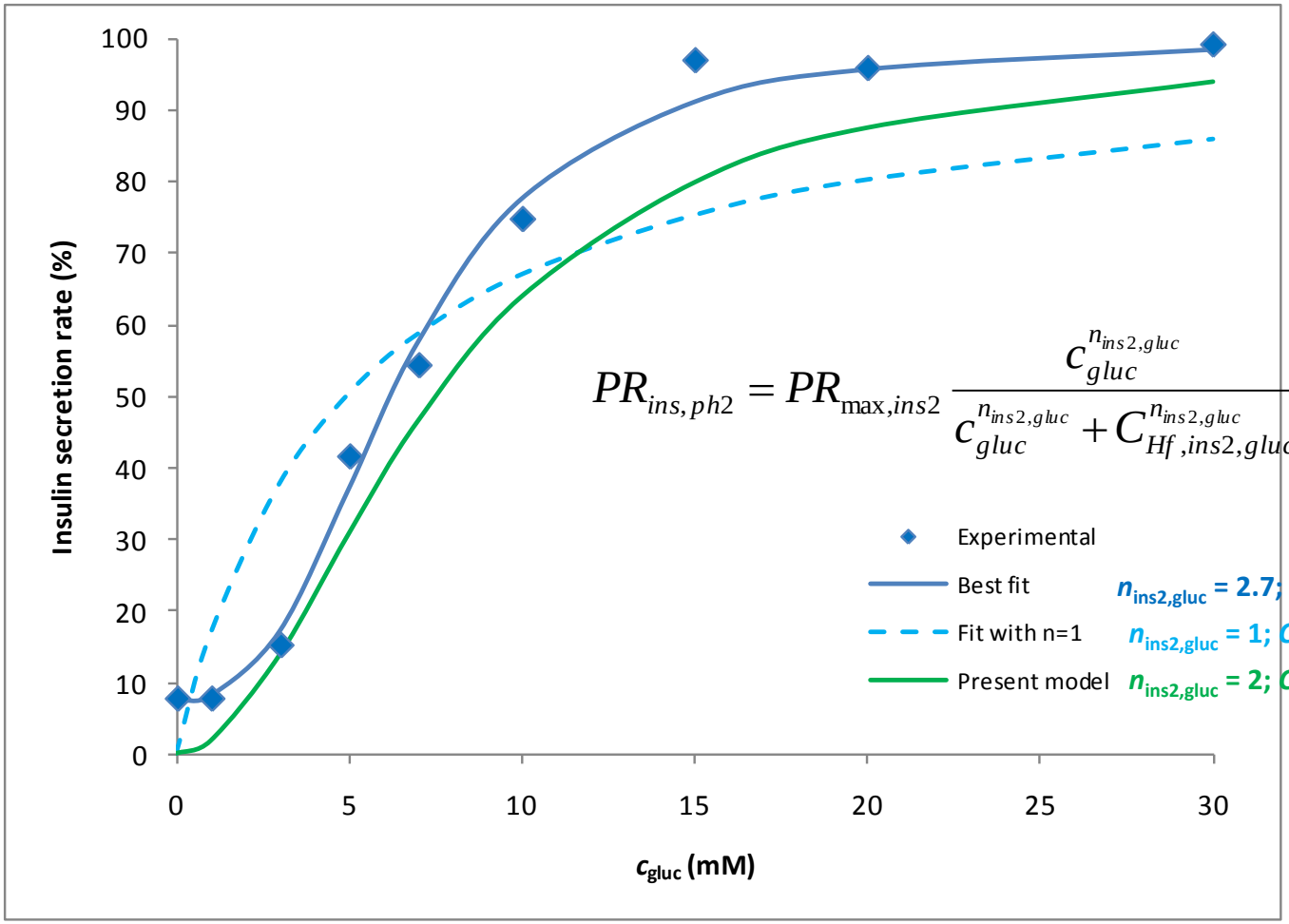

Fit of Hill type (generalized Michaelis-Menten) type dose response for insulin secretion rate allowing a variable Hill slope. Data from Henquin, J. C. et al. *Diabetologia* **2006**, *55*, 3470.

There seems to be a clear need for $n > 1$.

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Hill Type Concentration-Dependence of Insulin Secretion on Oxygen Concentration vs. Bilinear Version of Johnson, Colton *et al*. (MIT)

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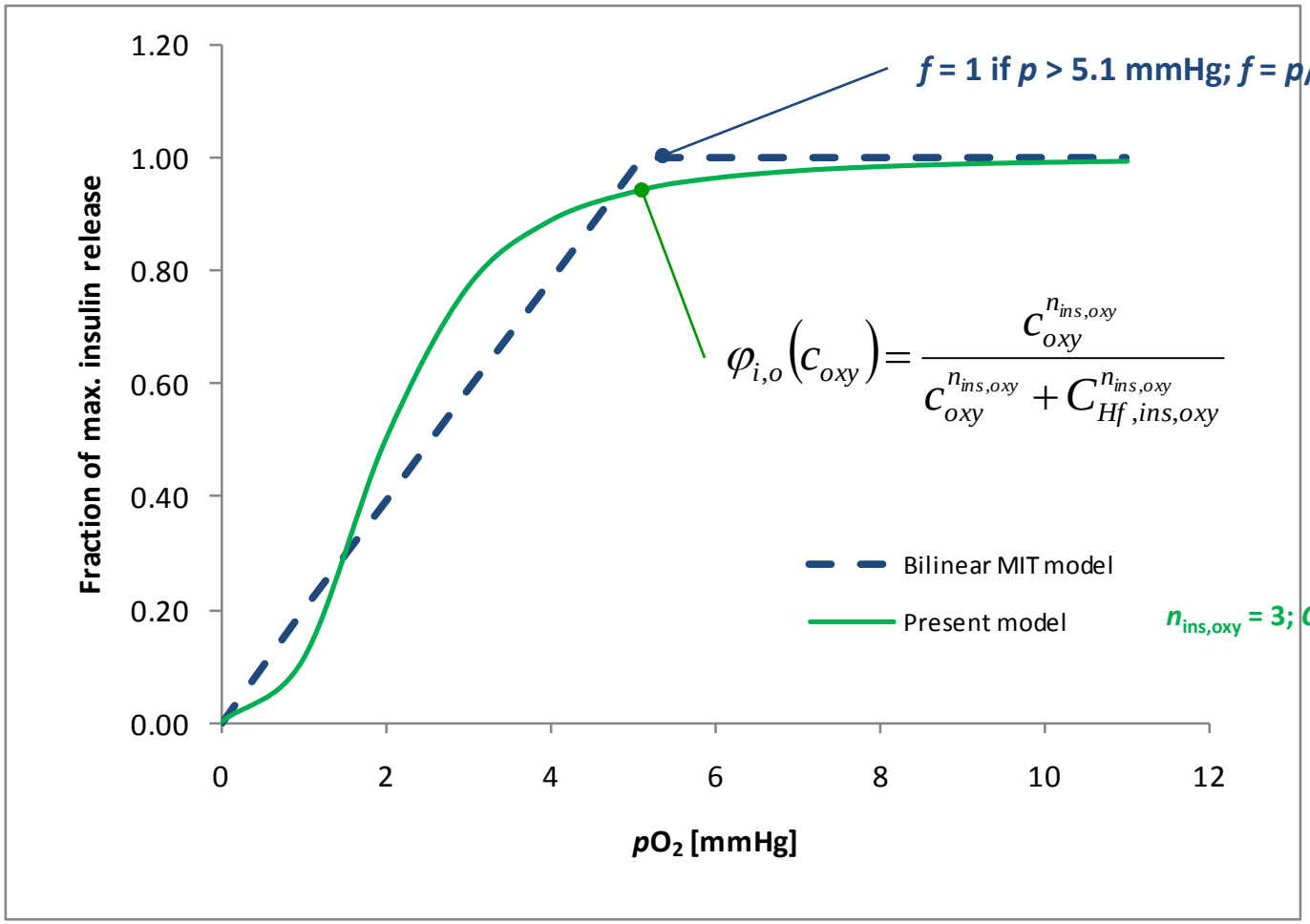

Local oxygen-dependent limiting function for insulin release used in the present model compared to the simple bilinear function used by Colton and co-workers at MIT (Johnson, A. S. et al. *Chem. Eng. Sci*. **2009**, *64*,4470).

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Insulin Release in Dynamic Perifusion Model

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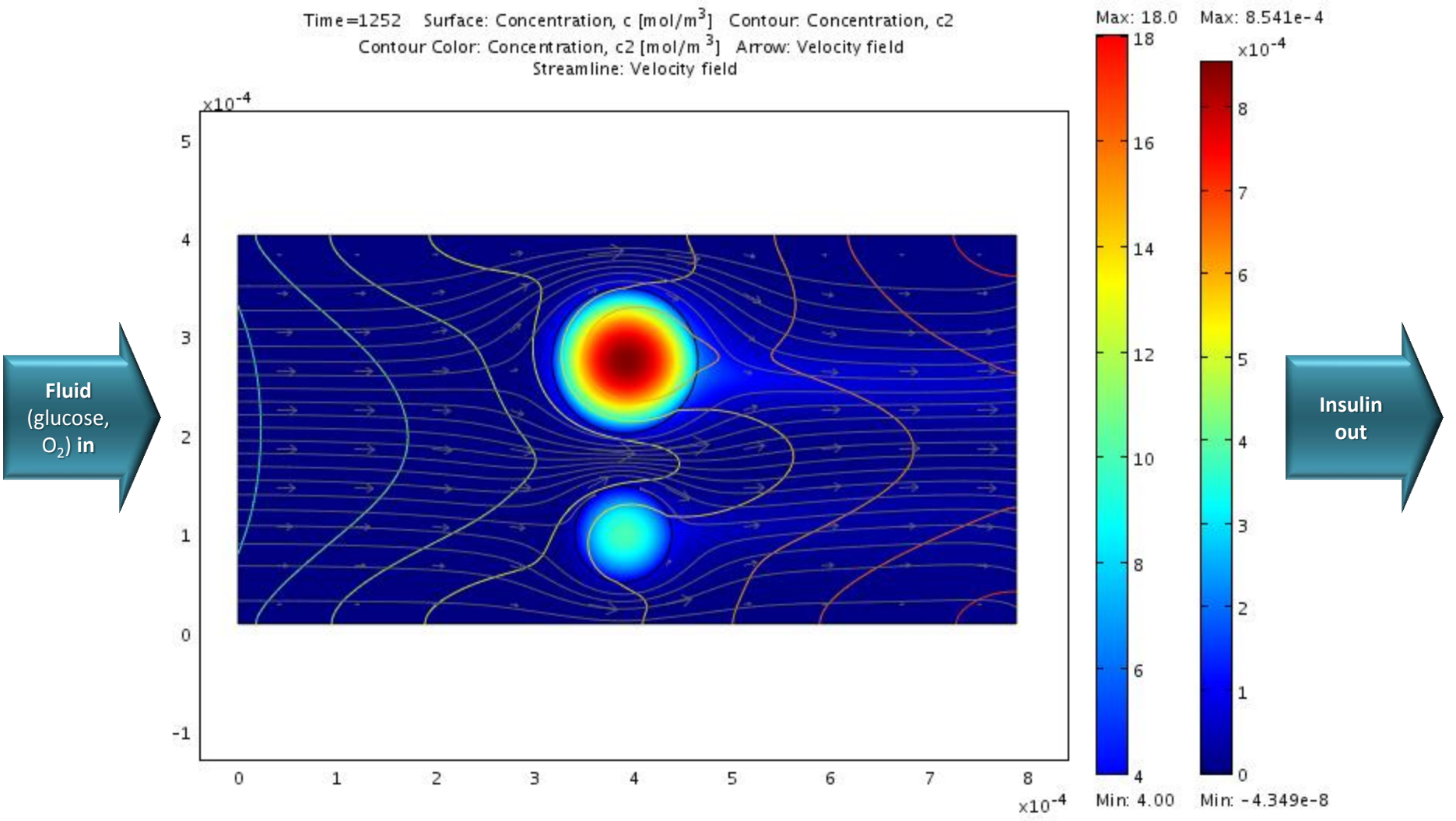
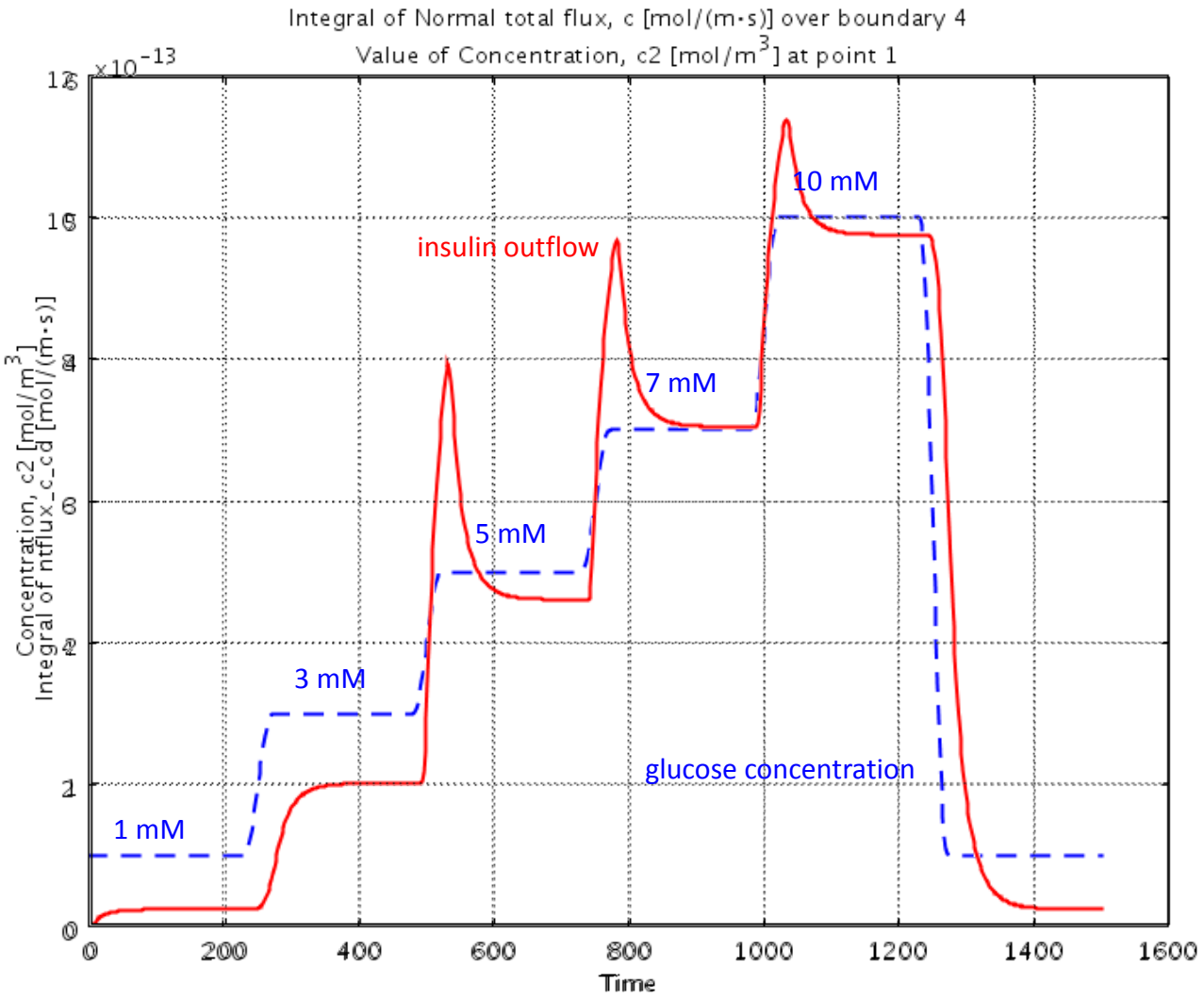


Calculated insulin concentration shown as color-coded from low (blue) to high (red) in two perifused islets shown at a time-point when the glucose concentration is decreasing abruptly (from 19 mM to 3 mM, colored contour lines). Gray streamlines and arrows illustrate the velocity field of the flowing perifusion fluid.

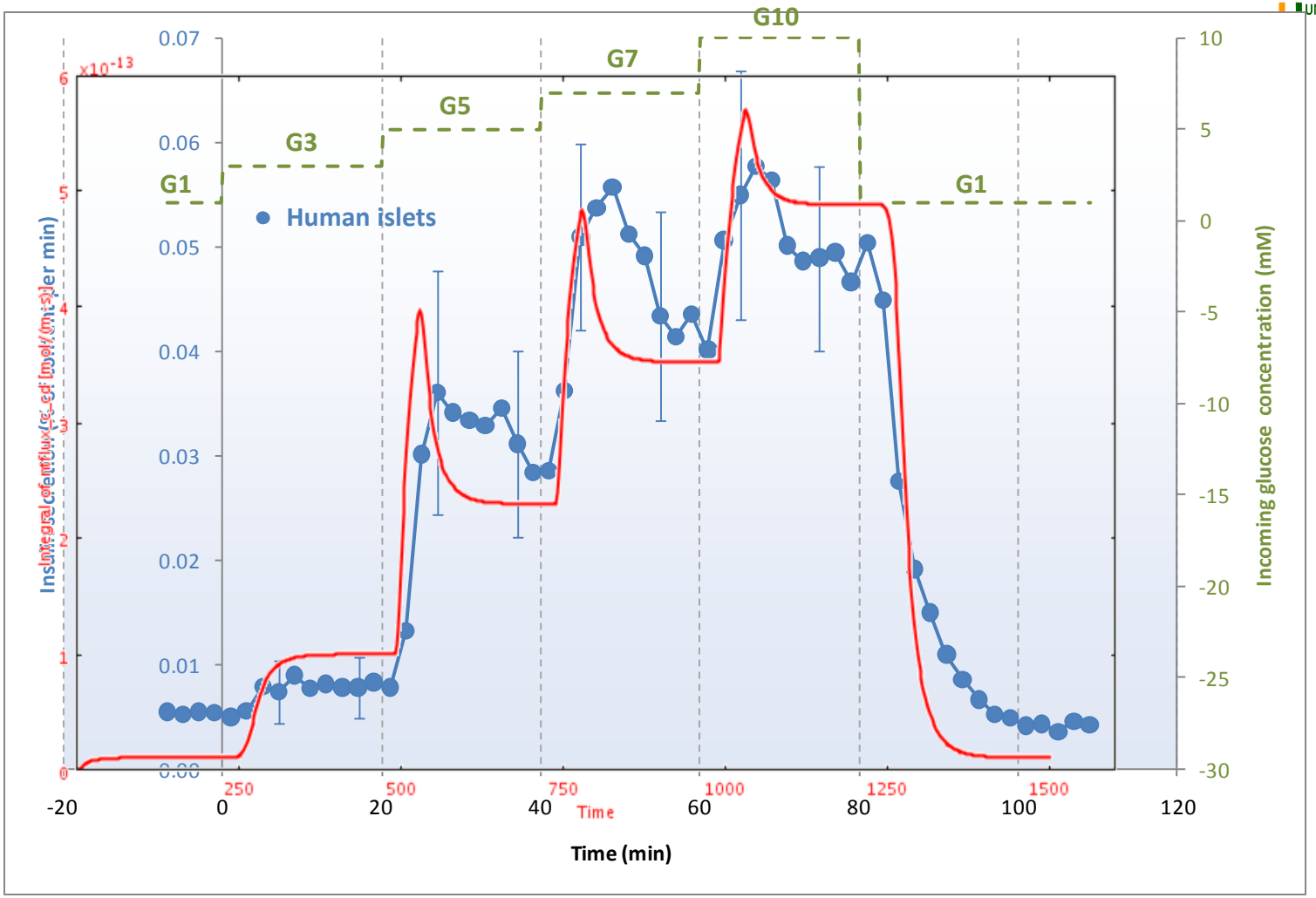
Model-Calculated Insulin Release



Boundary surface integral of total insulin flux out on outlet surface as a function of time.

Fully scaled 2D cross-section of islets in a hypothetical perifusion chamber. Finite element method (COMSOL Multiphysics 3.5) used for diffusion modeling with glucose-dependent insulin release and oxygen consumption rate. Aqueous media for flow; oxygen concentration: normal c_{atm} = 0.200 mol/m^3 (140 mmHg); fluid flow: v_{in} = 1.0×10^{-4} m/s; extra fine mesh, Pardiso direct solver, transient solution.

Calculated vs. Experimental Insulin Release



Boundary surface integral of total insulin flux out on outlet surface as a function of time.

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Experimental data from Dufrane, D. et al. *Diabetes Metabol.* **2007**, *33*, 430.

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Insulin Release in Dynamic Perifusion Model

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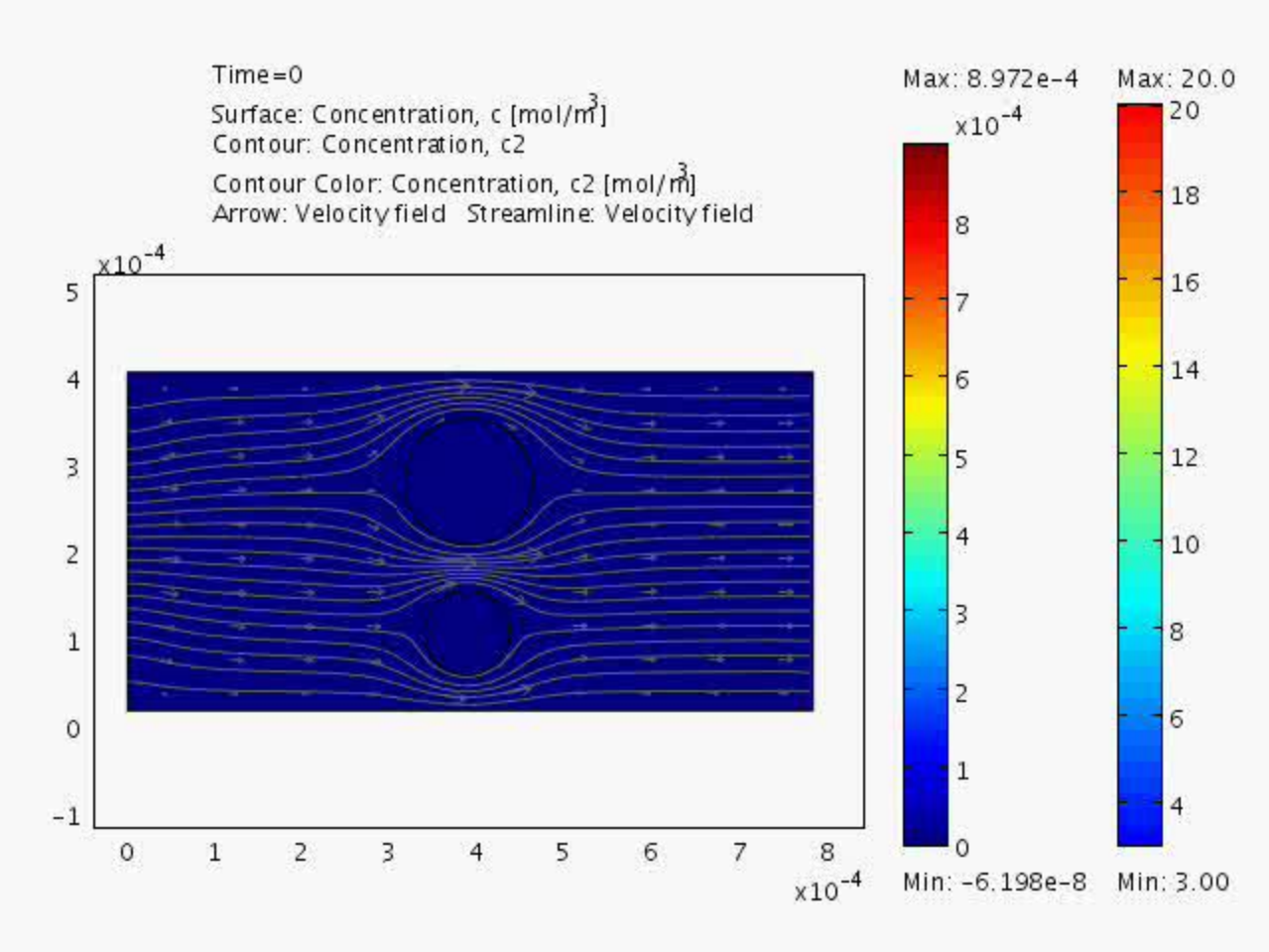

Calculated insulin concentration shown as color-coded from low (blue) to high (red) in two perifused islets shown at changing glucose concentrations (increasing stepwise from 3 mM to 19 mM than decreasing back to 3 mM, colored contour lines). Gray streamlines and arrows illustrate the velocity field of the flowing perifusion fluid.

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Glucose-Insulin(-Oxygen) Perifusion Model

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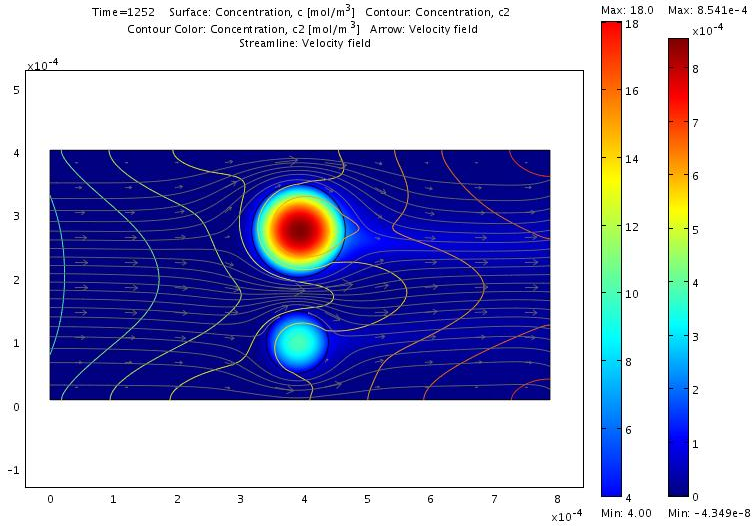
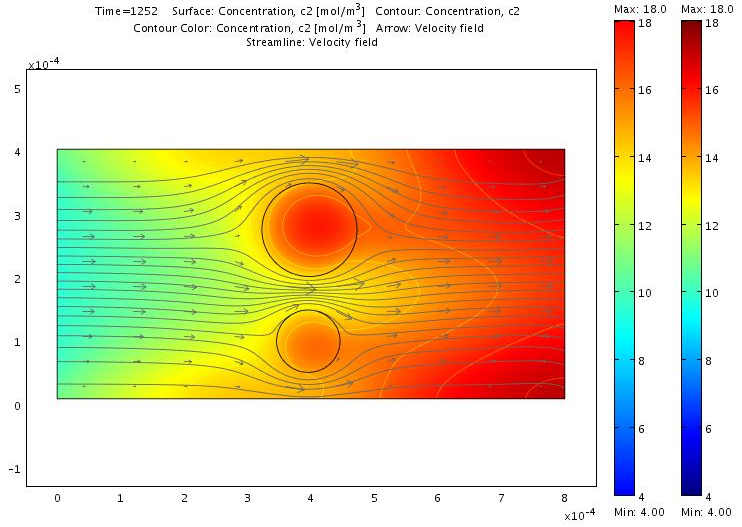
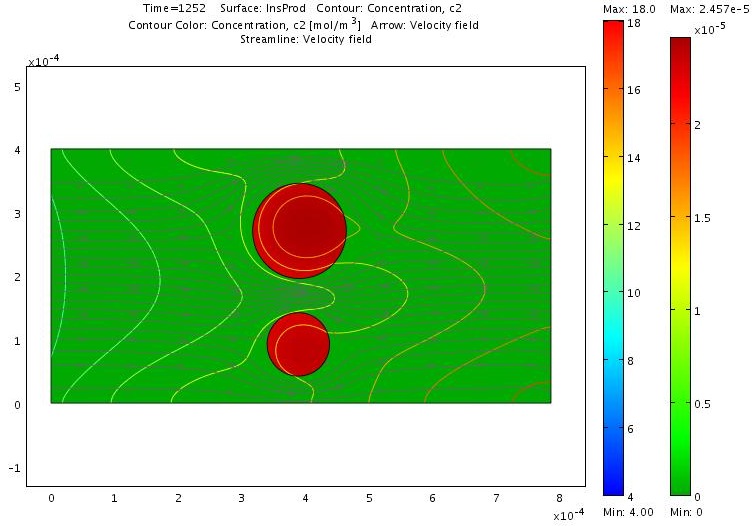
Insulin Concentration



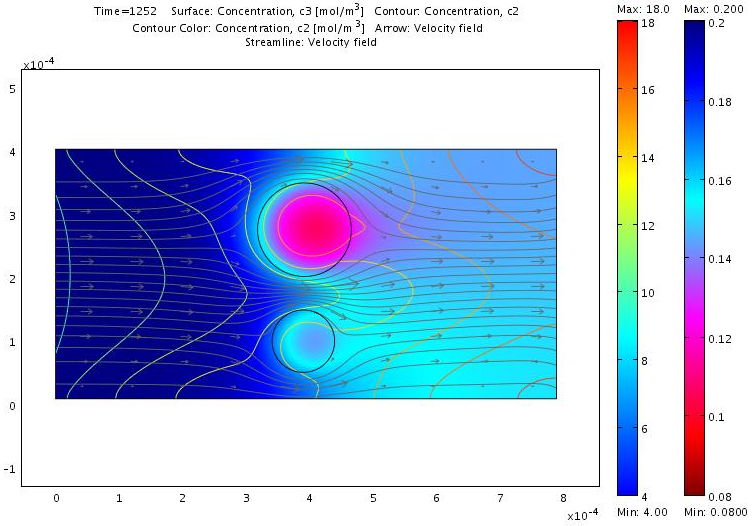
Glucose Concentration



Insulin Production



Oxygen Concentration



Calculated concentrations shown color-coded in two perifused islets at a time-point when the glucose concentration is decreasing abruptly (from 19 mM to 3 mM, colored contour lines).

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Calculated Insulin Release at Hypoxia

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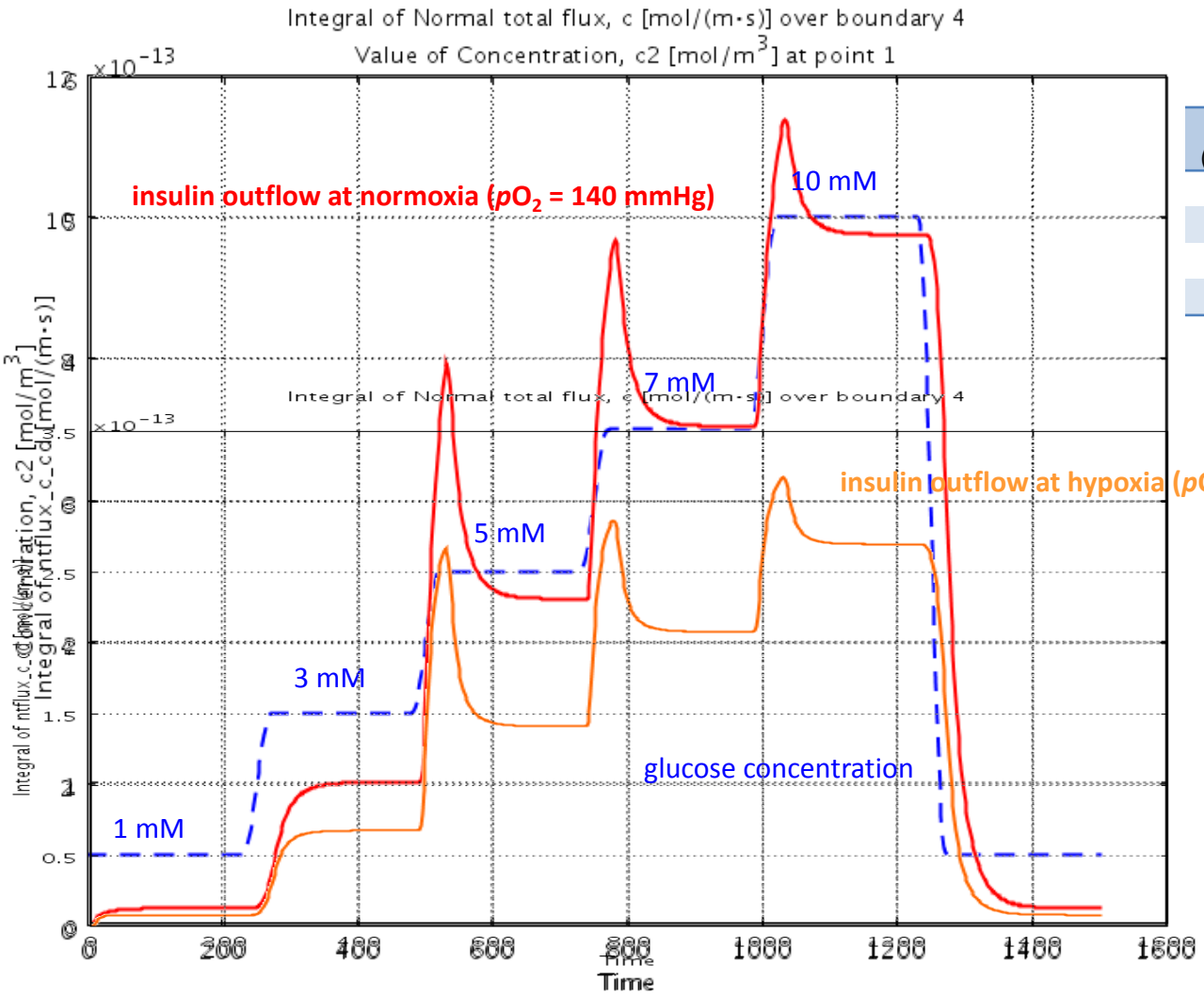

p_{O2} (mmHg)	$c_{oxy,in}$ (mM)	$F_{ins,exp}$	$F_{ins,pred}$
142	0.206	1.00	1.00
60	0.087	0.99	0.98
25	0.036	0.48	0.46
15	0.022	0.17	0.15

Experimental vs. predicted fraction of insulin secretion rate (F_{ins}) at hypoxic conditions.

Boundary surface integral of total insulin flux out on outlet surface as a function of time.

Fully scaled 2D cross-section of islets in a hypothetical perifusion chamber. Finite element method (COMSOL Multiphysics 3.5) used for diffusion modeling with glucose-dependent insulin release and oxygen consumption rate. Aqueous media for flow; oxygen concentration: normal c_{atm} = 0.200 mol/m^3 (140 mmHg); fluid flow: v_{in} = 1.0×10^{-4} m/s; extra fine mesh, Pardiso direct solver, transient solution.

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Glucose-Insulin(-Oxygen) Perifusion Model at Hypoxia

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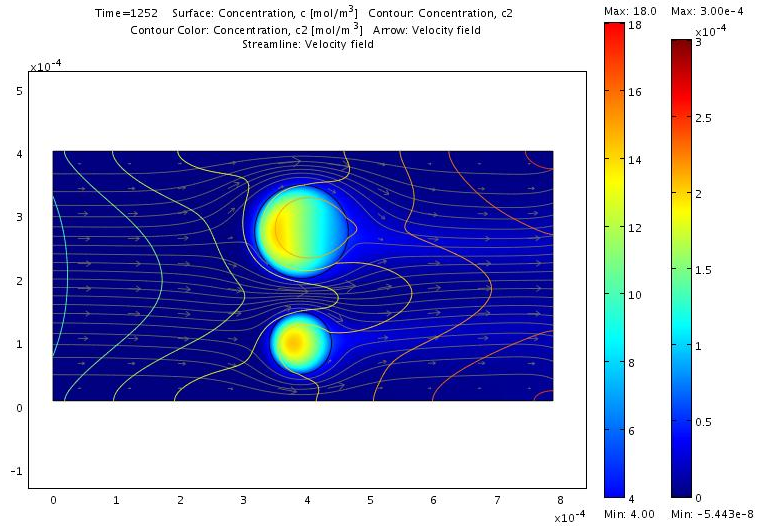
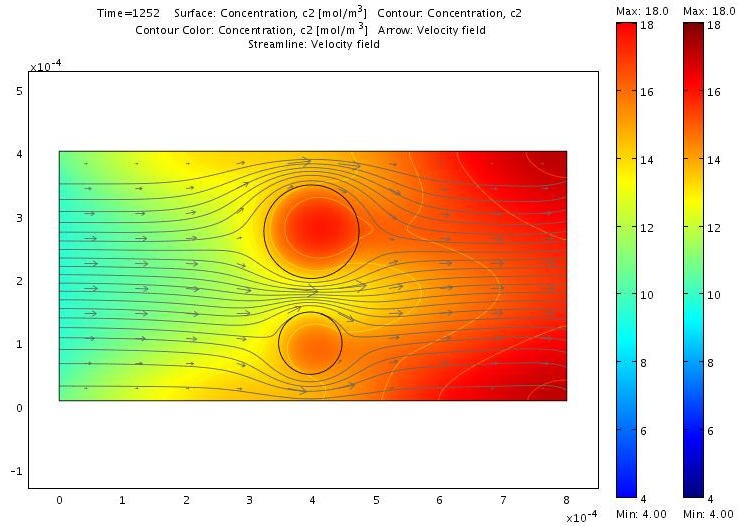
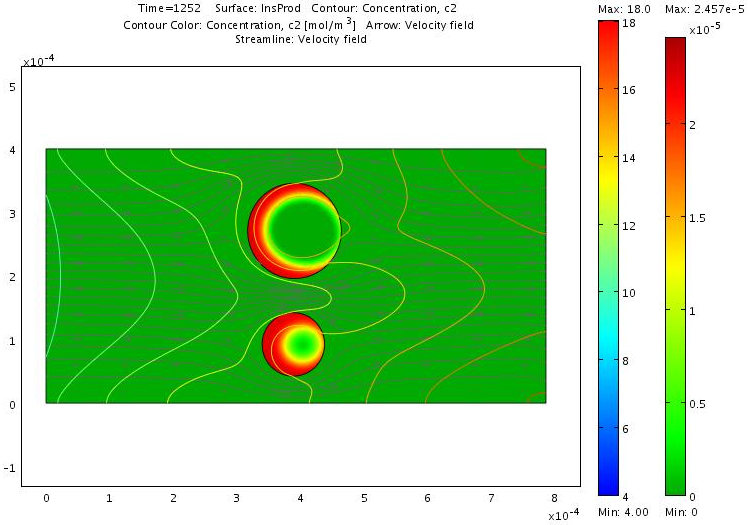
Insulin Concentration



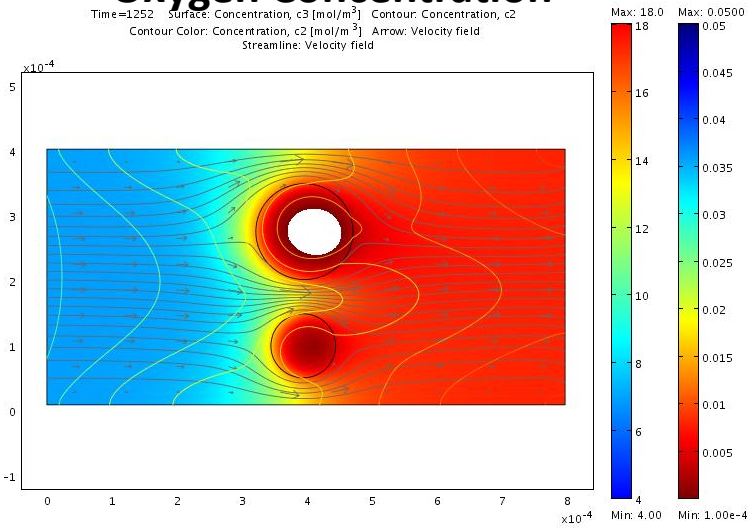
Glucose Concentration



Insulin Production



Oxygen Concentration



Calculated concentrations shown color-coded in two perifused islets at a time-point when the glucose concentration is decreasing abruptly (from 19 mM to 3 mM, colored contour lines).

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Insulin Release and Oxygen Normoxic vs. Hypoxic Conditions

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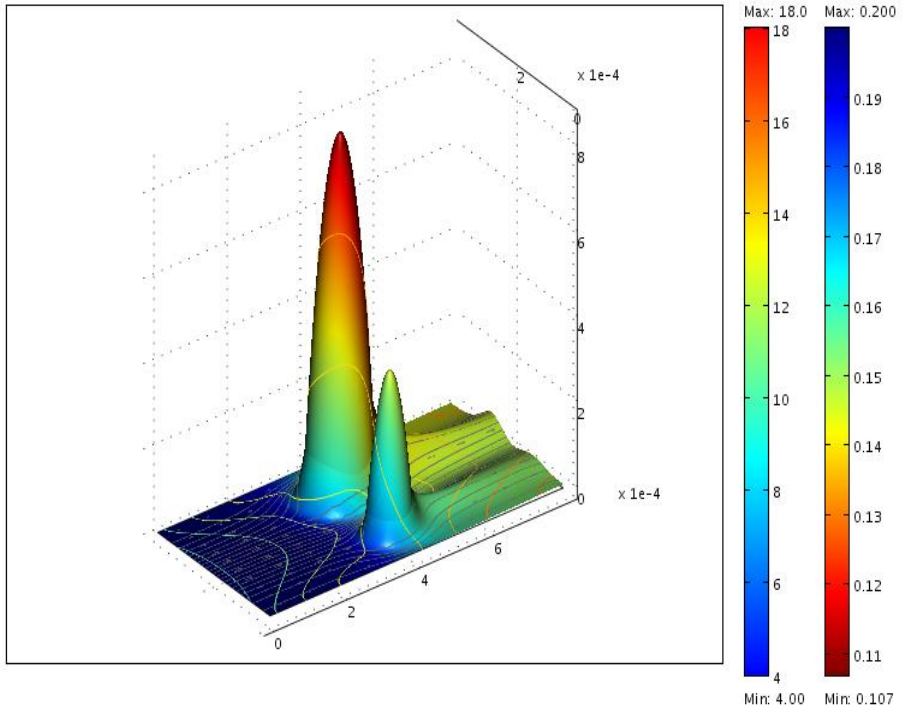
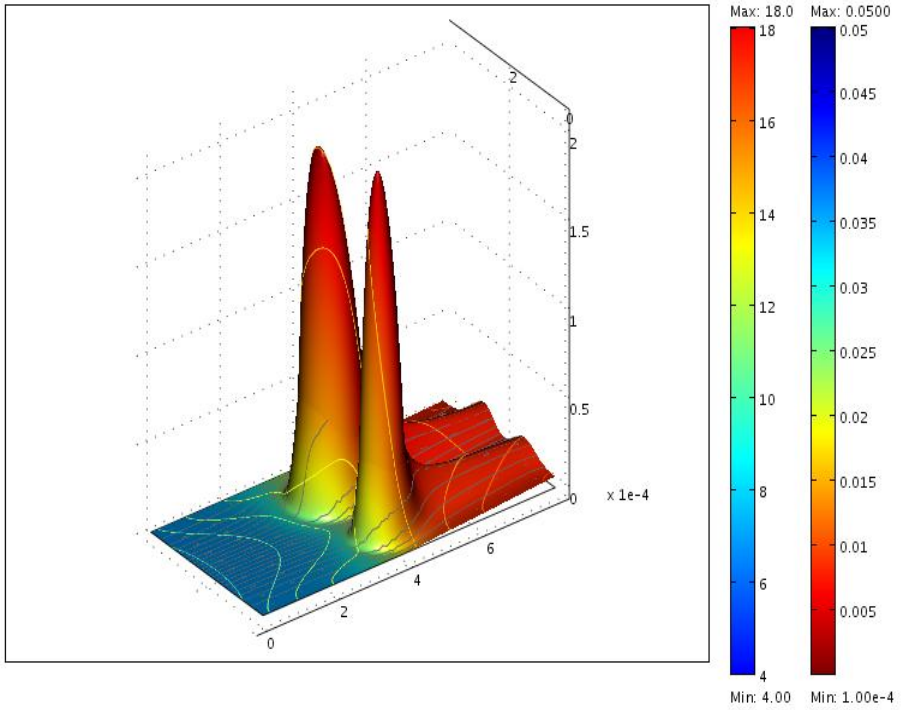
A. pO_2 = 140 mmHg



B. pO_2 = 25 mmHg



Local insulin concentration (as height data) colored by local oxygen concentration during a change in the perifusing glucose concentration (contour plot).

Fully scaled 2D cross-section of islets in a hypothetical perifusion chamber. Normal oxygen concentration $c_{in} = c_{atm}$ =0.200 mol/m^3 (140 mmHg) (A), hypoxic oxygen concentration c_{in} = 0.036 mol/m^3 (25 mmHg) (B); fluid flow: $v_{in} = 1.0 \times 10^{-4}$ m/s (0.1 mL/min).

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Insulin Release and Oxygen

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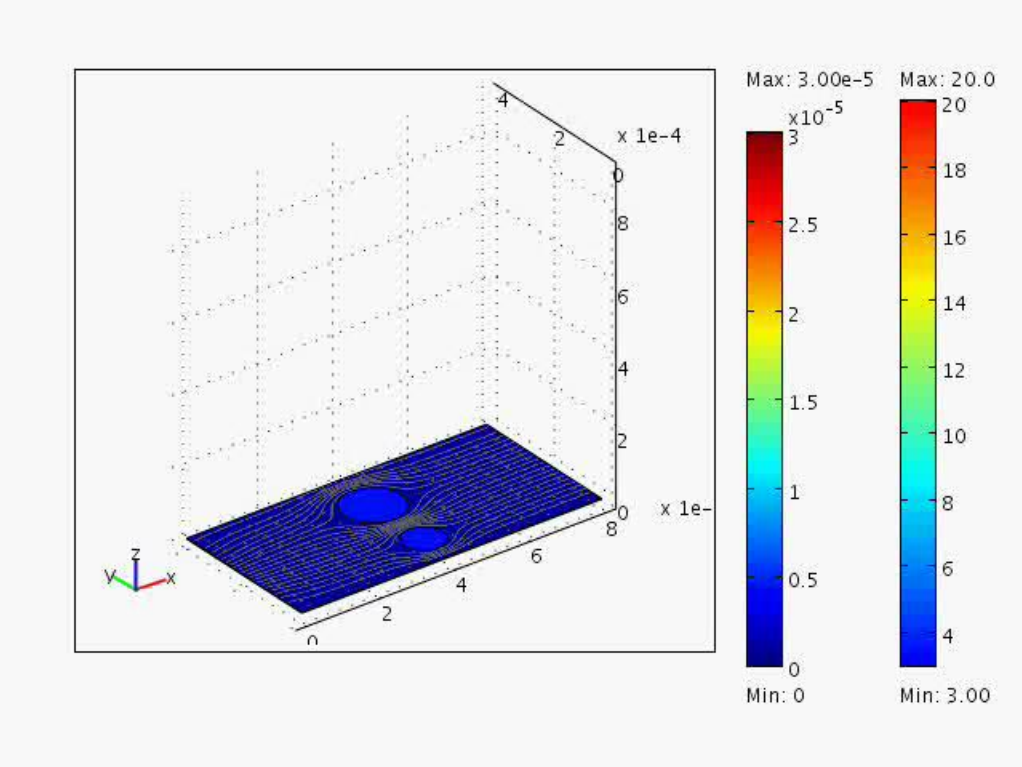
A. pO_2 = 140 mmHg

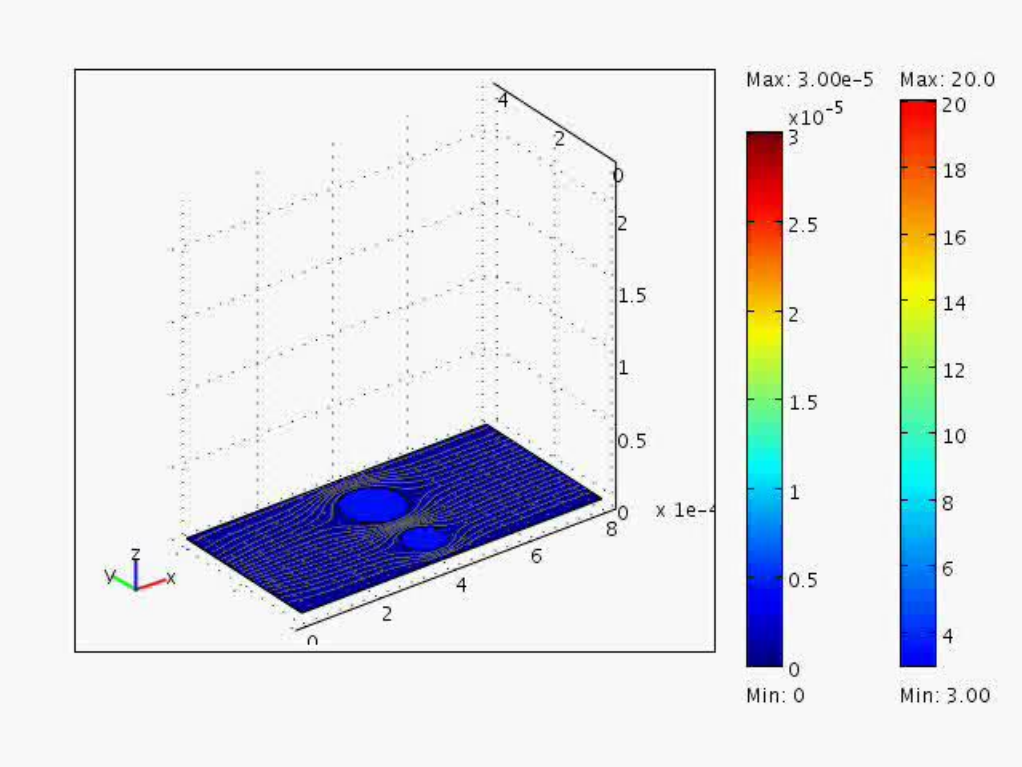


Local insulin concentration (as height data) colored by local insulin production during changing perifusing glucose concentrations (contour plot).

Fully scaled 2D cross-section of islets in a hypothetical perifusion chamber. Normal oxygen concentration c_{atm} = 0.200 mol/m^3 (140 mmHg); fluid flow: $v_{in} = 1.0 \times 10^{-4}$ m/s.

Insulin Release and Oxygen (Hypoxia)

B. pO_2 = 25 mmHg



Local insulin concentration (as height data) colored by local insulin production during changing perifusing glucose concentrations (contour plot).

Fully scaled 2D cross-section of islets in a hypothetical perifusion chamber. Normal oxygen concentration c_{atm} = 0.036 mol/m^3 (25 mmHg); fluid flow: $v_{in} = 1.0 \times 10^{-4}$ m/s.

Conclusions

- Exploratory insulin secretion model for avascular pancreatic islets has been implemented using **Hill-type sigmoid response functions**
- Model was parameterized to fit experimental data and **good fit could be obtained both for glucose- and for oxygen-dependence** (except time-scale of first-phase release)
- With COMSOL Multiphysics it is relatively straightforward
  - to couple **arbitrarily complex hormone secretion** and nutrient consumption kinetics with diffusive and even convective transport and
  - run simulations with **realistic geometries without symmetry or other restrictions**

  problems that seriously limited previous glucose–insulin modeling attempts

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