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Exploratory FEM-Based Multiphysics Oxygen Transport and Cell Viability Models for Isolated Pancreatic Islets

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Pancreas and Islets of Langerhans

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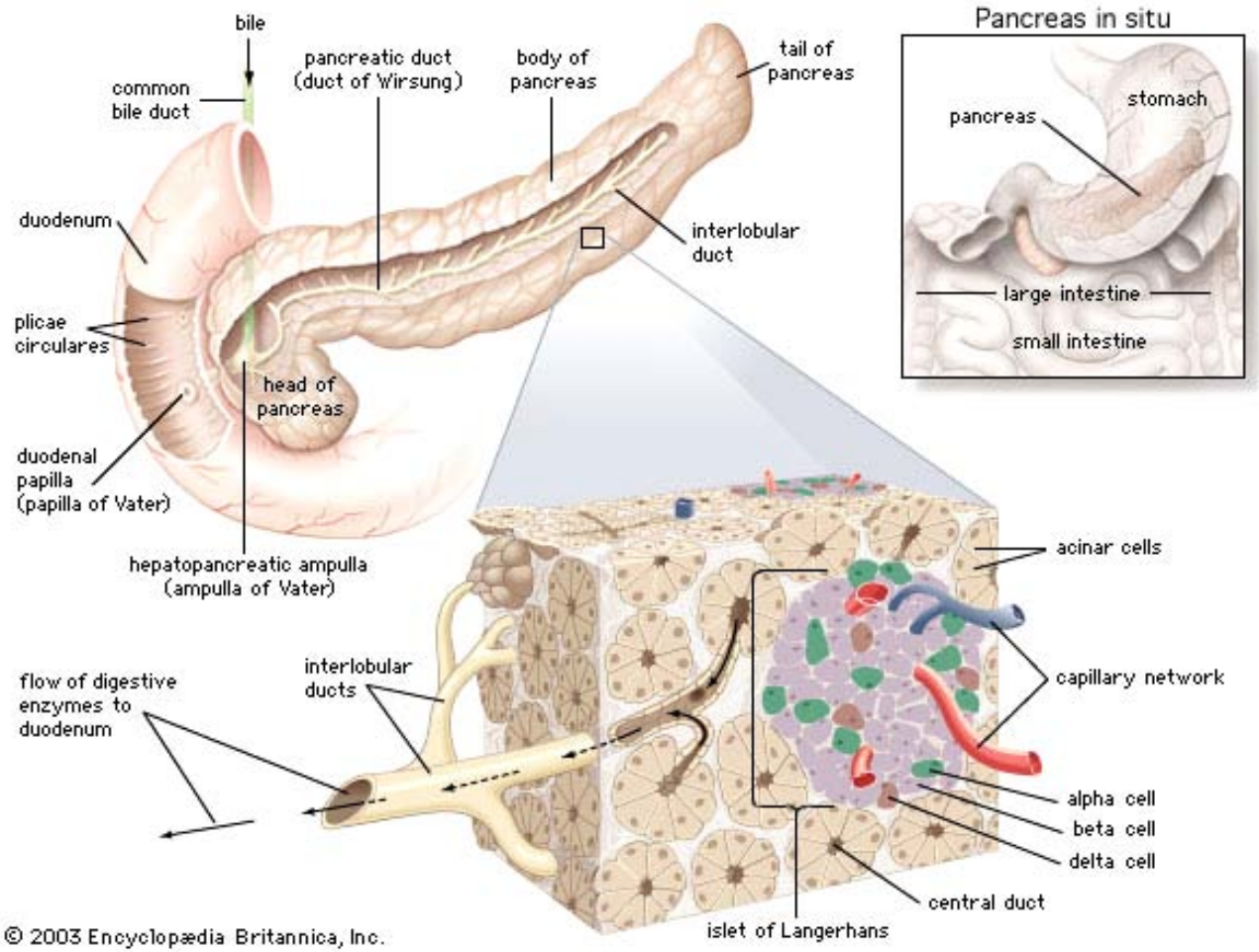
Pancreas (human ~80 g) has dual function:

- exocrine (secrets digestive enzymes)
- endocrine (produces hormones such as insulin, glucagon, and somatostatin)

Islets of Langerhans:

- responsible for the endocrine function
- four major cell types secreting different hormones:
  α cells (glucagon),
  β cells (insulin),
  δ (somatostatin), and
  PP cells (pancreatic polypeptide)



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

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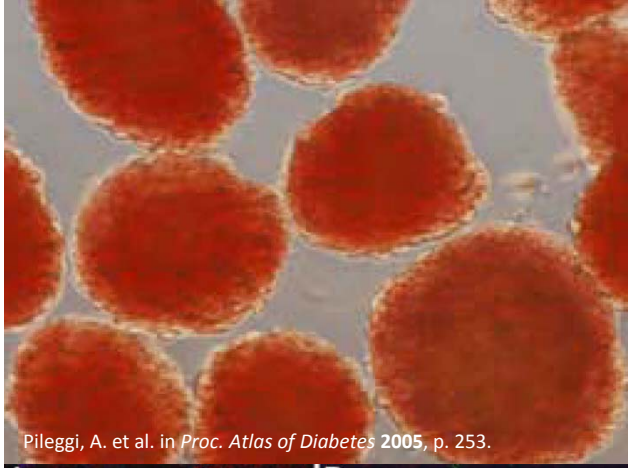
Islets of Langerhans

- Cellular aggregates of ~2,000 cells and diameters of about 150 μm (range: 50–500 μm)
- Represent only 1–2% of the pancreas
- Humans have approx. 1,000,000 islets
- Four major cell types secreting different hormones:

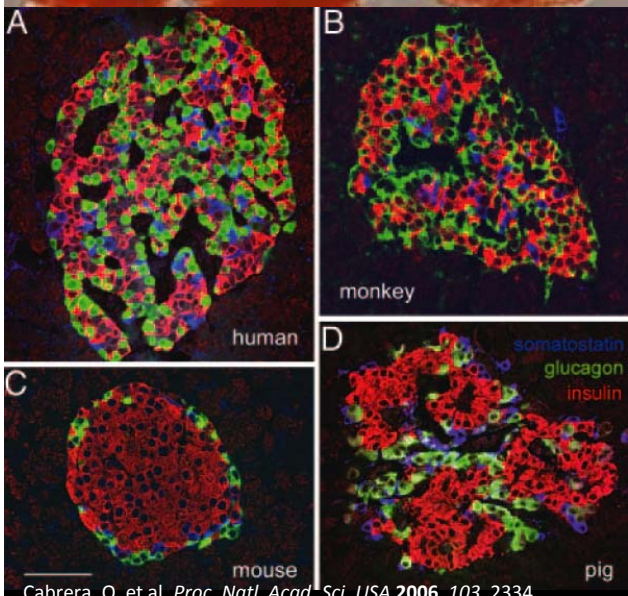
α cells (glucagon)	[~35%, human]
β cells (insulin)	[~60% , human]
δ (somatostatin), and	[~5%, human]
PP cells (pancreatic polypeptide)	

- There are considerable species differences

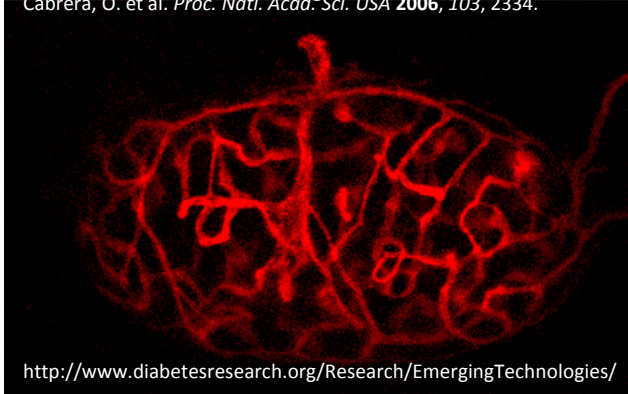
- Highly vascularized, highly perfused; receiving 10–20% of the blood flow of the pancreas



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



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



http://www.diabetesresearch.org/Research/EmergingTechnologies/

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Transplantation of Islet Cells

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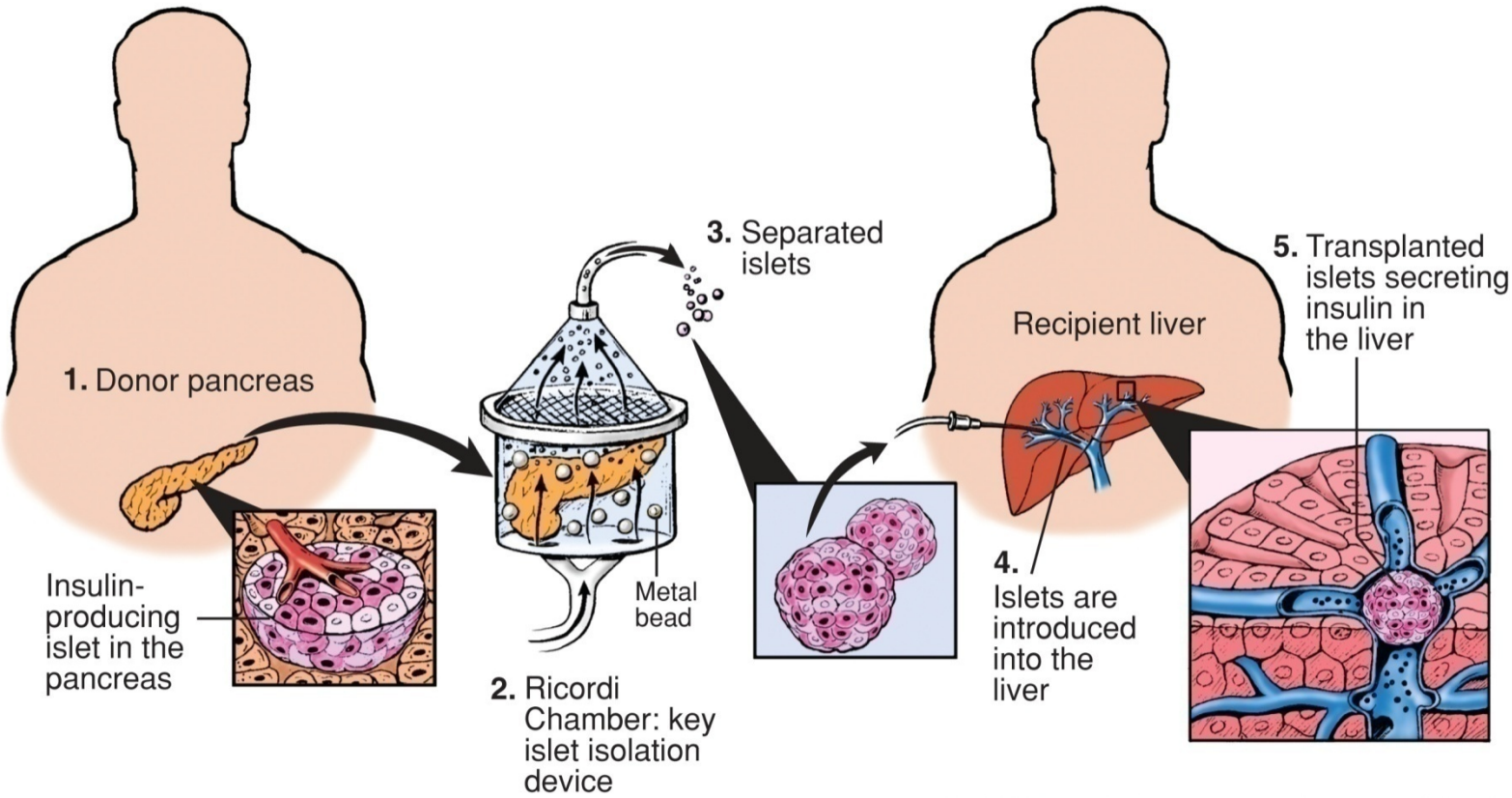

Artist: Robert Margulies

- Can normalize metabolic control much better than exogenous insulin
- Explored as an experimental therapy for a selected patients (in US, conducted under IND)
- Requires life-long immunosuppression; limited to the most severe forms of diabetes
- Results are continuously improving (e.g., Edmonton protocol)

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Islet Culture

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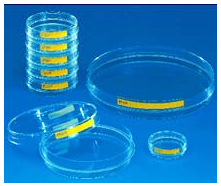
- Islets are cultured for up to two days as a standard practice before being transplanted
  - to recover from the isolation-induced damage
  - to assess their quality and safety
  - to make possible the recipient's travel to the transplantation site
  - to start immunosuppression before transplantation



- Typically, they are cultured at 37°C in humidified mixed 95% air, 5% CO_2 in non-tissue treated, 175 cm^2 flasks at a density of ~20,000 IEQ in 30 mL of media containing 0.5% human serum albumin [corresponding to only 100–200 IEQ/cm^2 and a flask surface utilization of 2–3%, hence, up to 30 or more flasks are needed per human pancreas]

Ichii, H. et al. *Am. J. Transplant.* **2007**, *7*, 1010.
Khan, A. et al. In *The Bioartificial Pancreas and other Biohybrid Therapies*, **2008**, in press.
Sander S.; Eizirik D. L. In *Human Cell Culture Protocols* , **1996**, 391.

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Oxygen Transport in Isolated Islets

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- After isolation, islets are avascular and have to rely on passive diffusion for nutrient and metabolite transport
- Lack of oxygen (hypoxia) is a major problem limiting the viability and functionality of cultured, transplanted, and/or encapsulated islets
- Oxygen solubility in aqueous media is relatively low, around 0.2 mM under atmospheric conditions
- Oxygen availability is usually far more sever than glucose availability because glucose has a considerably higher solubility (~20 mM) more than compensating for its lower diffusivity
- Pancreatic islets are particularly susceptible due to their relatively large size, large metabolic demand, and increased sensitivity to hypoxia

Diffusion governed by the generic diffusion equation (nonconservative formulation; incompressible fluid)

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

c the concentration [mol·m^{-3}] and D the diffusion coefficient [m^2·s^{-1}] of the species of interest (oxygen), R the reaction rate [mol·m^{-3}·s^{-1}], $\mathbf{u}$ the velocity field [m·s^{-1}], and ∇ the standard *del* (*nabla*) operator $\nabla \equiv \mathbf{i}\frac{\partial}{\partial x} + \mathbf{j}\frac{\partial}{\partial y} + \mathbf{k}\frac{\partial}{\partial z}$

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Oxygen Consumption
Michaelis-Menten–Type Dependence on c_{O2}

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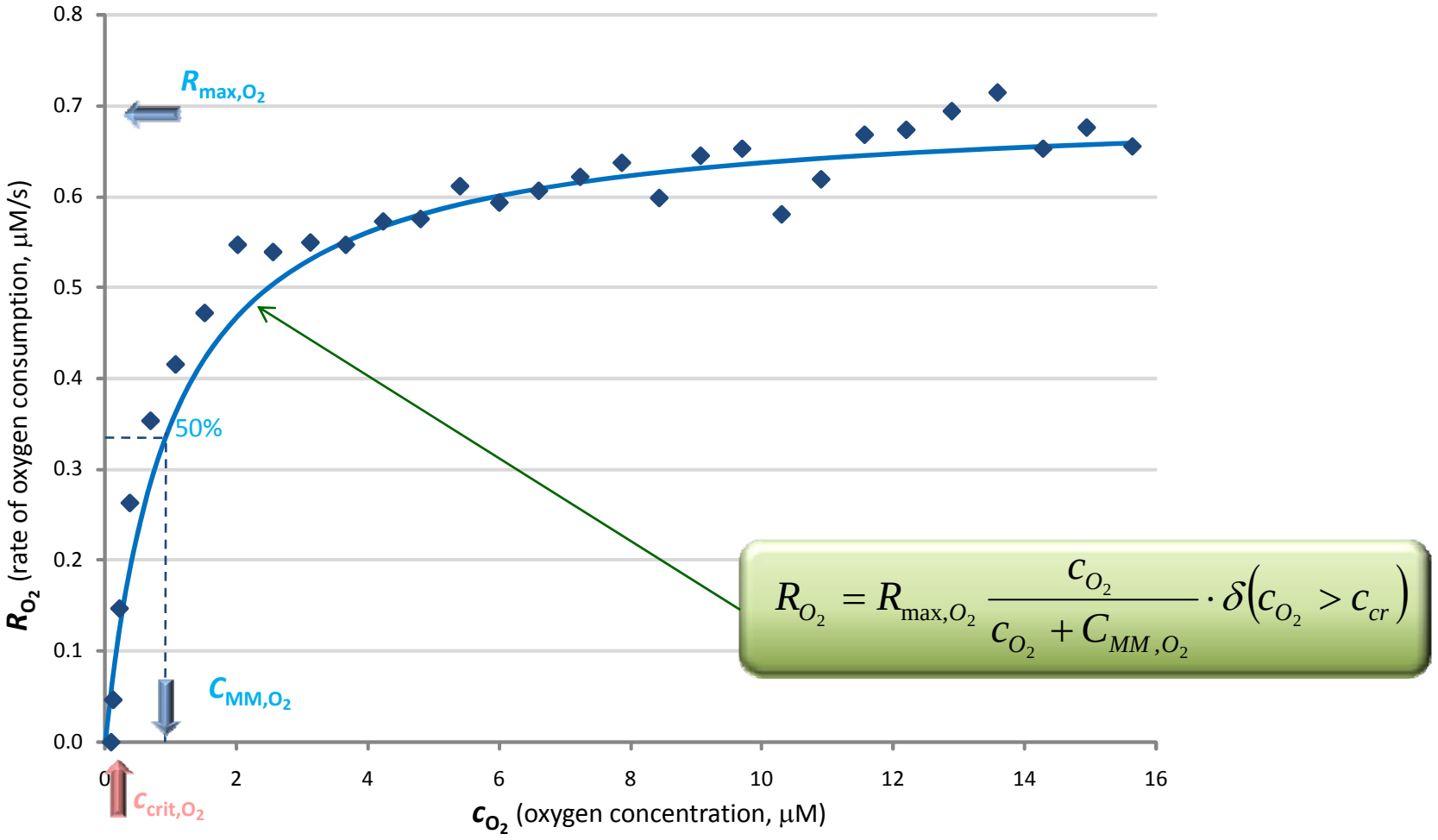

Oxygen consumption of well coupled mitochondria measured at low oxygen concentrations (Wilson, D. F. *et al. J. Biol. Chem*. **1988**, *263*, 2712) is shown fitted with the Michaelis-Menten–type (rectangular hyperbola-shaped) consumption rate used in the present model ($C_{MM,O2}$ = 1 μM = 1×10^{-3} mol/m^3).

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Multiphysics Models

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Convection and diffusion:

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

Fluid dynamics (incompressible Navier-Stokes):

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

Heat transfer (convection and conduction):

$$\rho c_p\frac{\partial T}{\partial t}+\nabla\cdot\left(-k\nabla T\right)=Q-\rho c_p\mathbf{u}\cdot\nabla T$$

Parameter settings

Oxygen concentrations and diffusion:

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

$D_w = 3.0\times10^{-9}$ m^2/s (O_2 in water); $D_t = 2.0\times10^{-9}$ m^2/s (O_2 in tissue)

Oxygen consumption rate (homogeneous in islets, none in media)

$R = R_{max}\, c/(c+C_{MM})\cdot\delta(c>c_{cr})$

R_{max} = 0.034 mol/s/m^3

[with $V_{IEQ} = 1.77\times10^{-12}$ m^3 standard islet volume for ϕ = 150 μm ⇨ $R_{max} = 0.06\times10^{-12}$ mol/s/IEQ]

$C_{MM} = 1.0\times10^{-3}$ mol/m^3 (Michaelis-Menten constant; 1.0 μM; ≈0.7 mmHg)

$c_{crit} = 1.0\times10^{-4}$ mol/m^3 (critical for survival; 0.1 μM; ≈0.07 mmHg)

$\delta(c>c_{cr})$ = `flc1hs`(c–0.0001, 0.00005)

Flow (aqueous media at room temperature):

T_0 = 310.15 K, ρ = 993 kg/m^3, $\eta = 0.7\times10^{-3}$ Pa·s, c_p = 4200 J/kg/K, k_c = 0.634 J/s/m/K, $\alpha = 2.1\times10^{-4}$ K^{-1}

parabolic inflow profile on inlet $4v_{in}(y/y_{max})(1-y/y_{max})$

- 2D cross-section models with realistic geometries (islets with diameters of ϕ = 100, 150, and 200 μm)
- Default 'extra fine' mesh size used (mesh sizes of 5000-9000 elements)
- Solved as time-dependent problem for sufficiently long to reach steady state with the UMFPACK direct solver

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Islet Culture 2D Model

Mesh and Boundary Conditions for FEM Calculations

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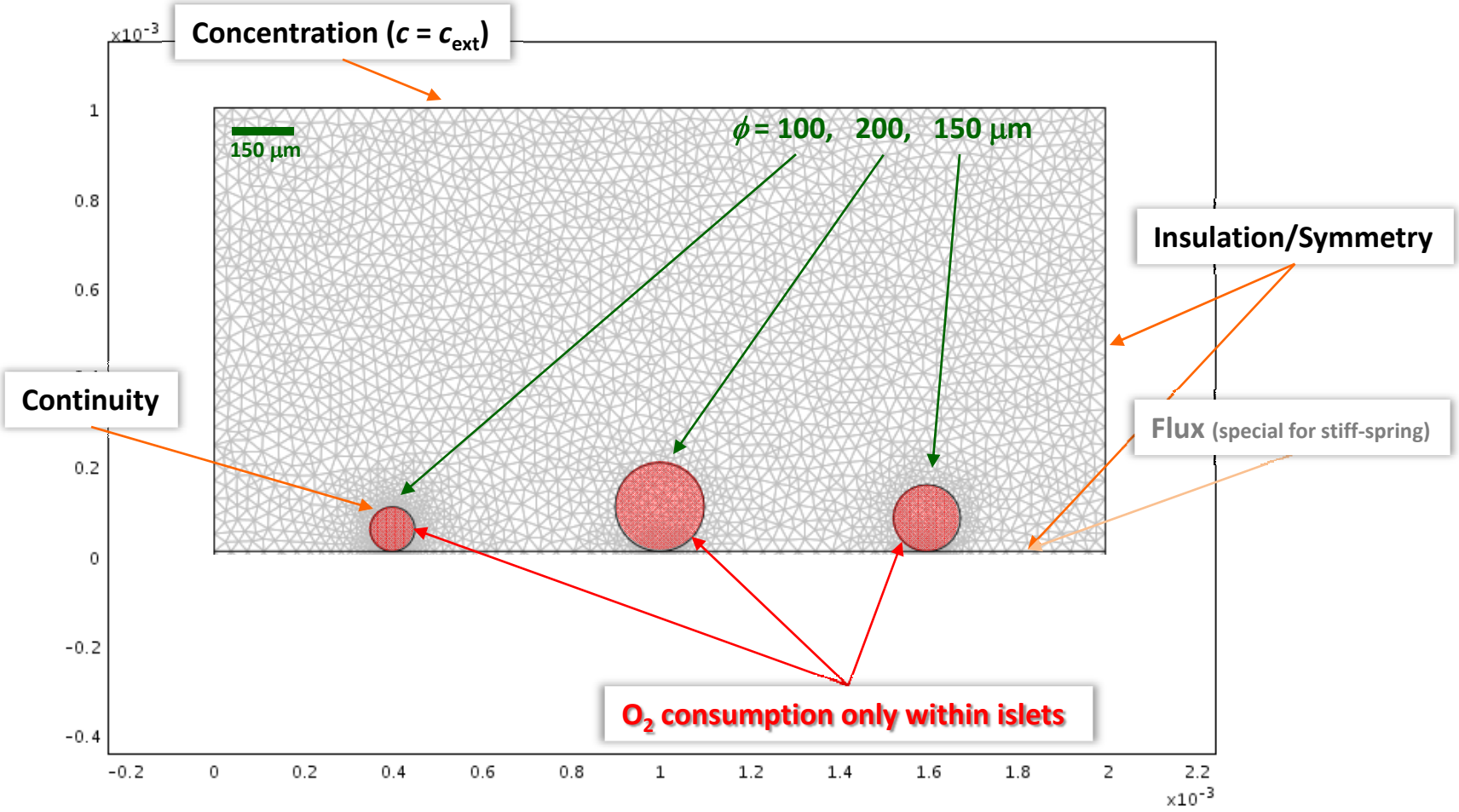

Mesh structure used for finite element method (FEM) calculations in Comsol Multiphysics obtained using the default "Extra fine mesh" setting. A realistic 2D cross section model of three islets (with diameters ϕ = 100, 150, and 200 µm) in culture conditions with a media height of 1-2 mm is used (here, a bottom membrane is also included). Oxygen gradient-driven passive diffusion is assumed in all subdomains; oxygen consumption only takes place within the islets.

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Islet Culture 2D Model

Oxygen Concentrations in Nonvascularized Islets in Traditional Culture

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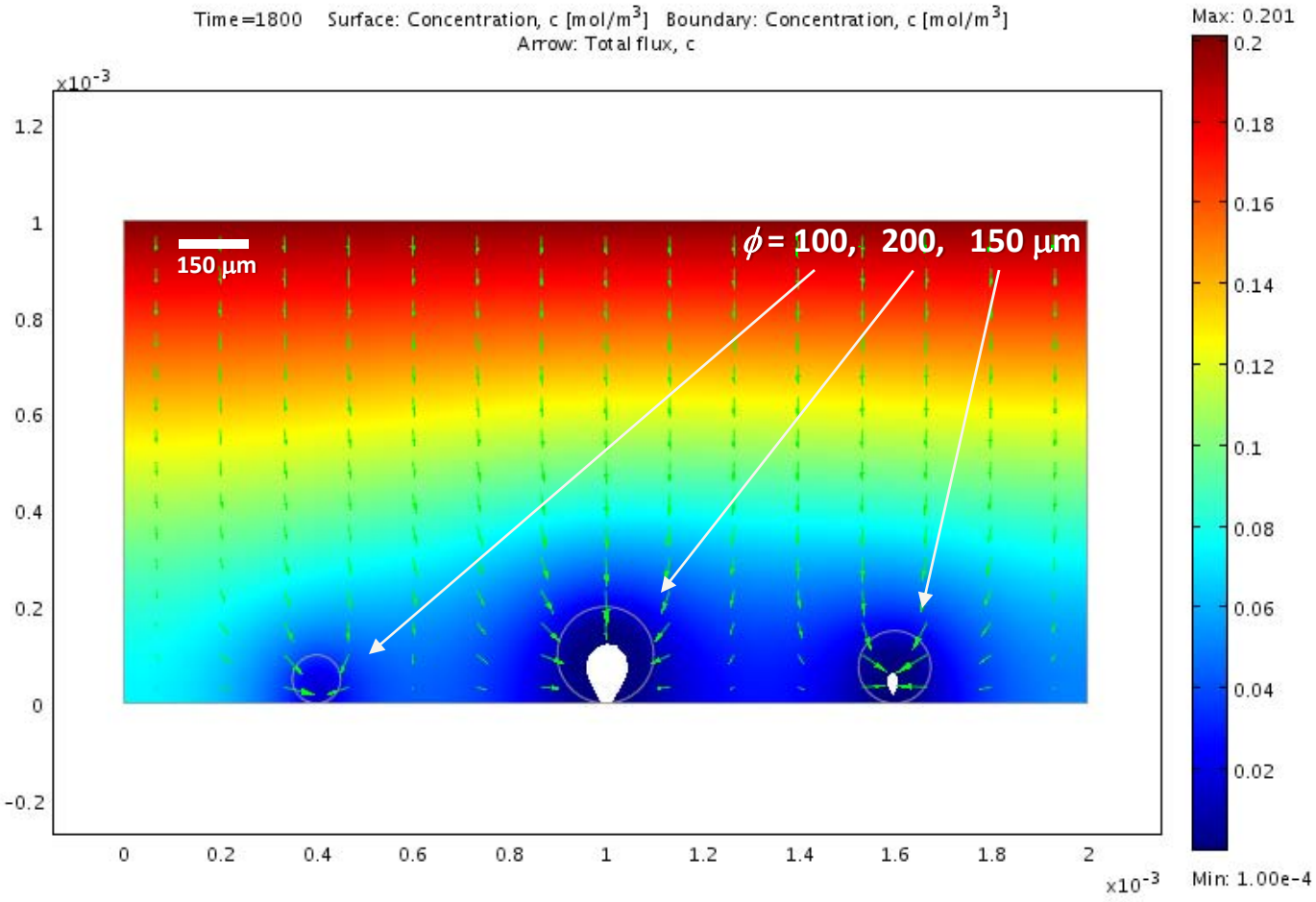

Calculated oxygen concentration for three islets (with diameters ϕ = 100, 150, and 200 µm) in standard culture conditions after stationary conditions have been reached (h = 1 mm assumed). The color-coded surface represents the oxygen concentration (red corresponding to higher and blue to lower values), whereas green arrows represent oxygen flux. 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.

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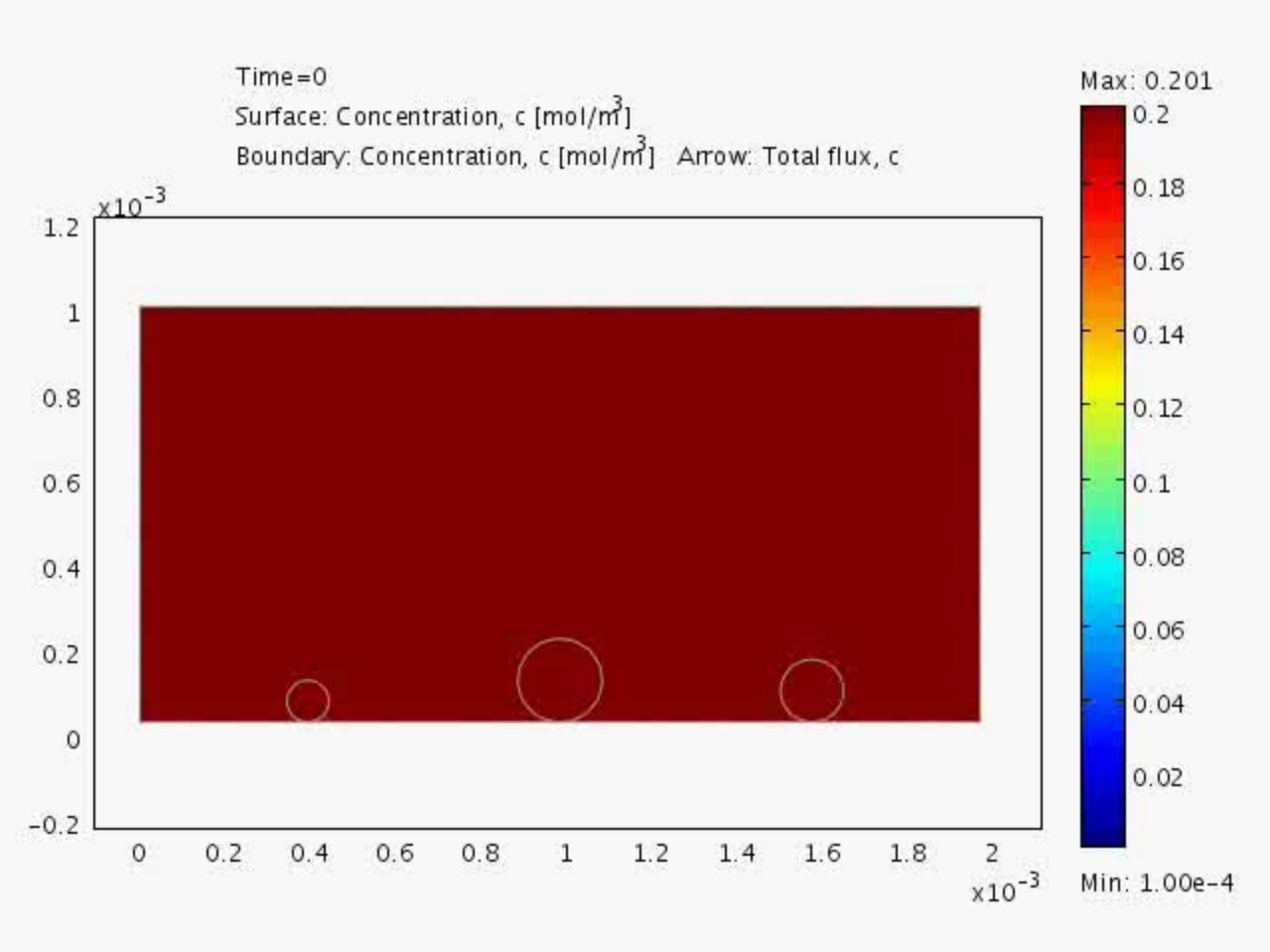

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Viability of Isolated Rat Islets

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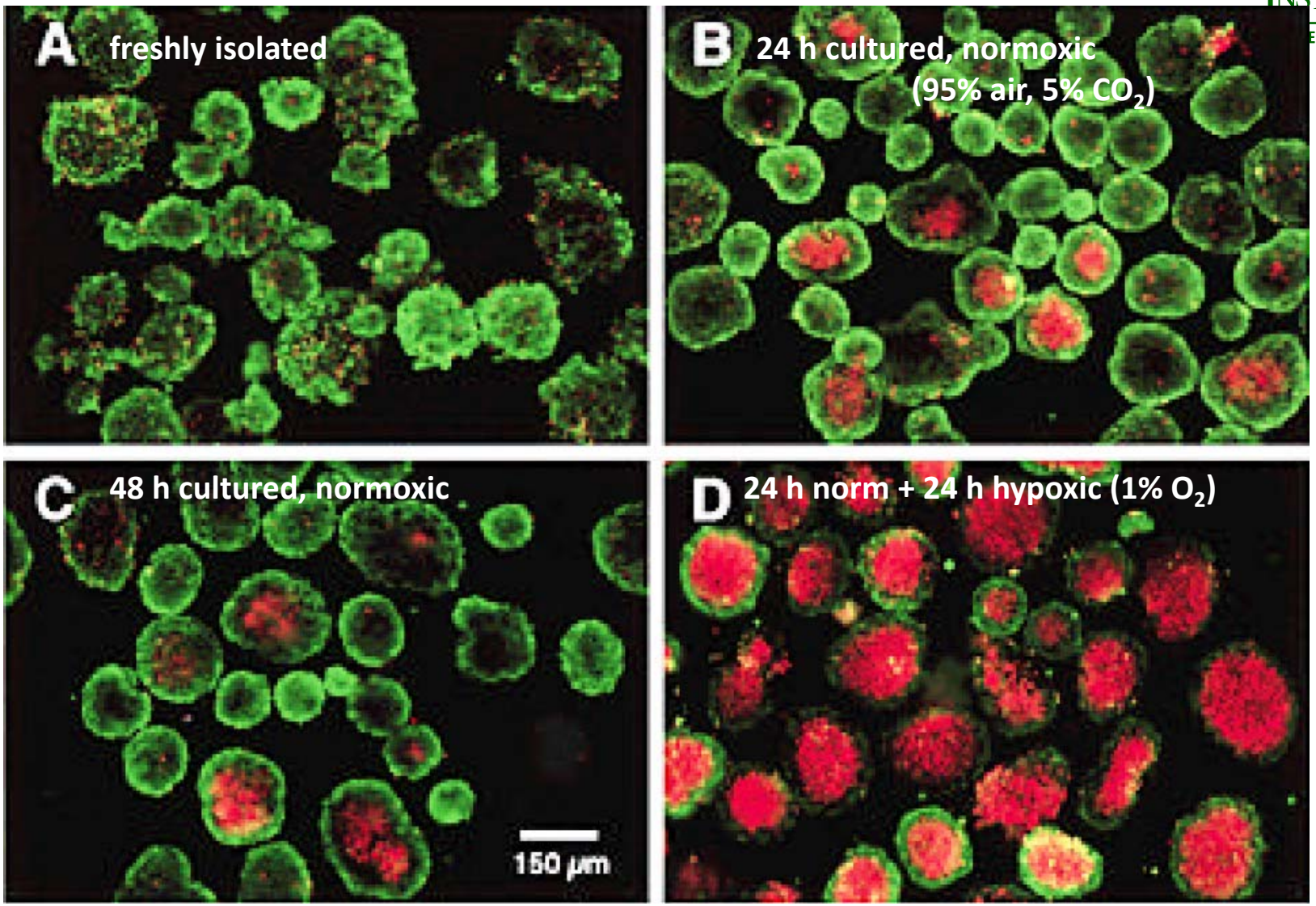

Viability of isolated rat islets with green fluorescence corresponding to live and red to dead cells (determined using Calcein-AM and propidium iodide viability stains and visualized at the same time using specific filters for fluorescein and Texas red).

Vasir, B. et al. *Diabetes* **1998**, *47*, 1894.

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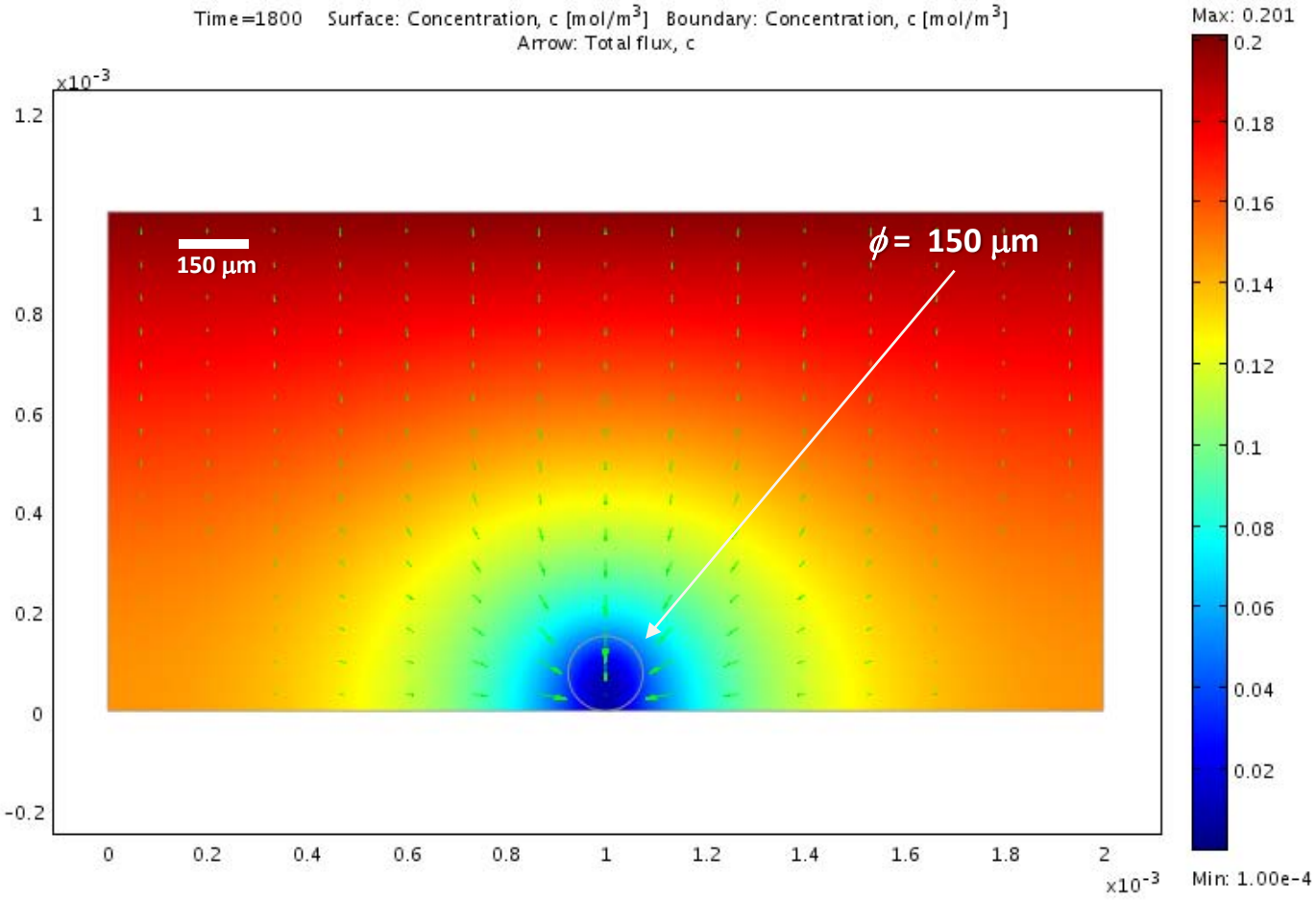

Calculated oxygen concentration for a single standard islet (with diameter ϕ = 150 µm) in standard culture conditions after stationary conditions have been reached (h = 1 mm assumed). The color-coded surface represents the oxygen concentration (red corresponding to higher and blue to lower values), whereas green arrows represent oxygen flux. 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).

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Islet Culture 2D Model

Oxygen Concentrations in Nonvascularized Islets in Traditional Culture

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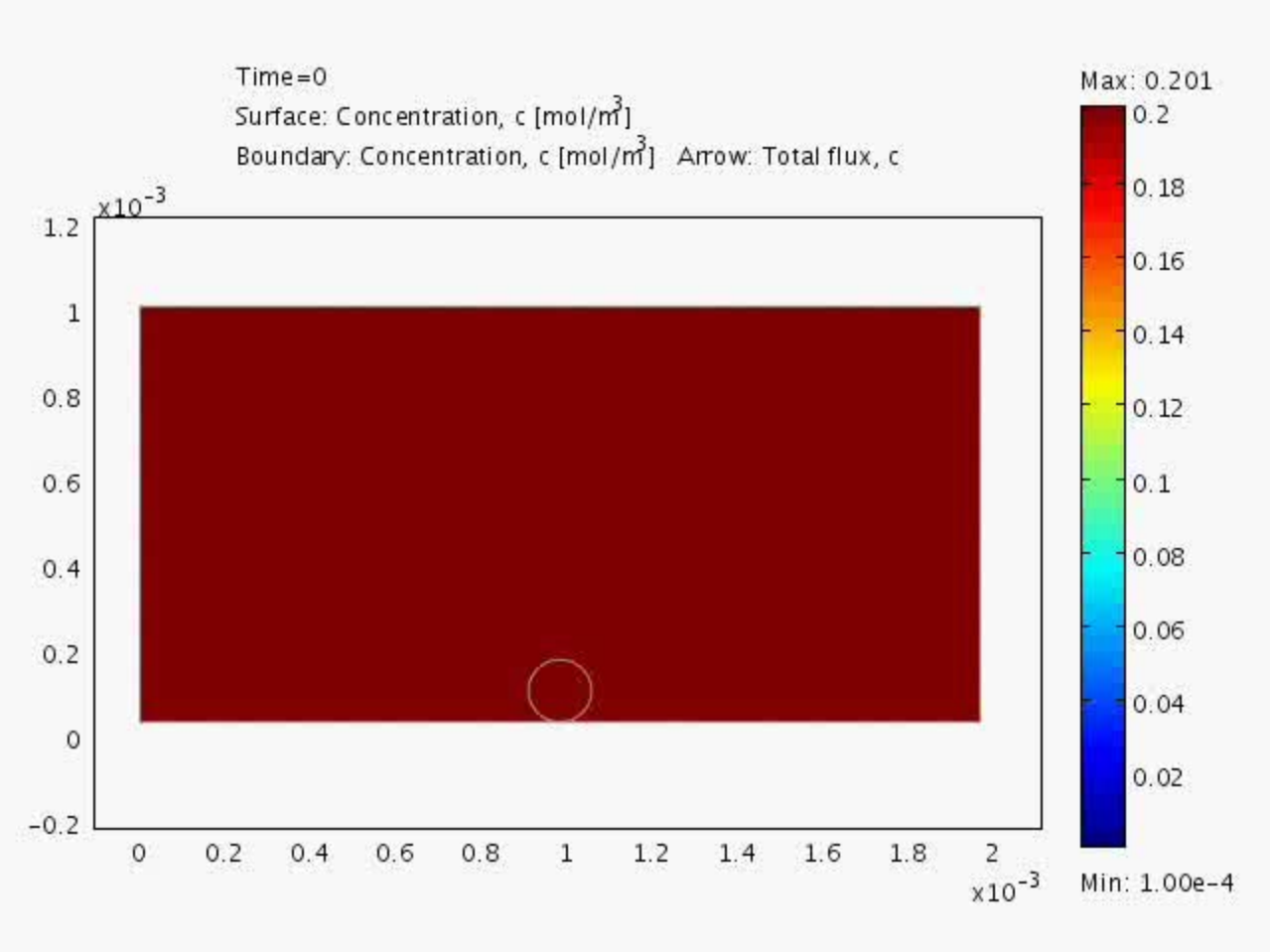

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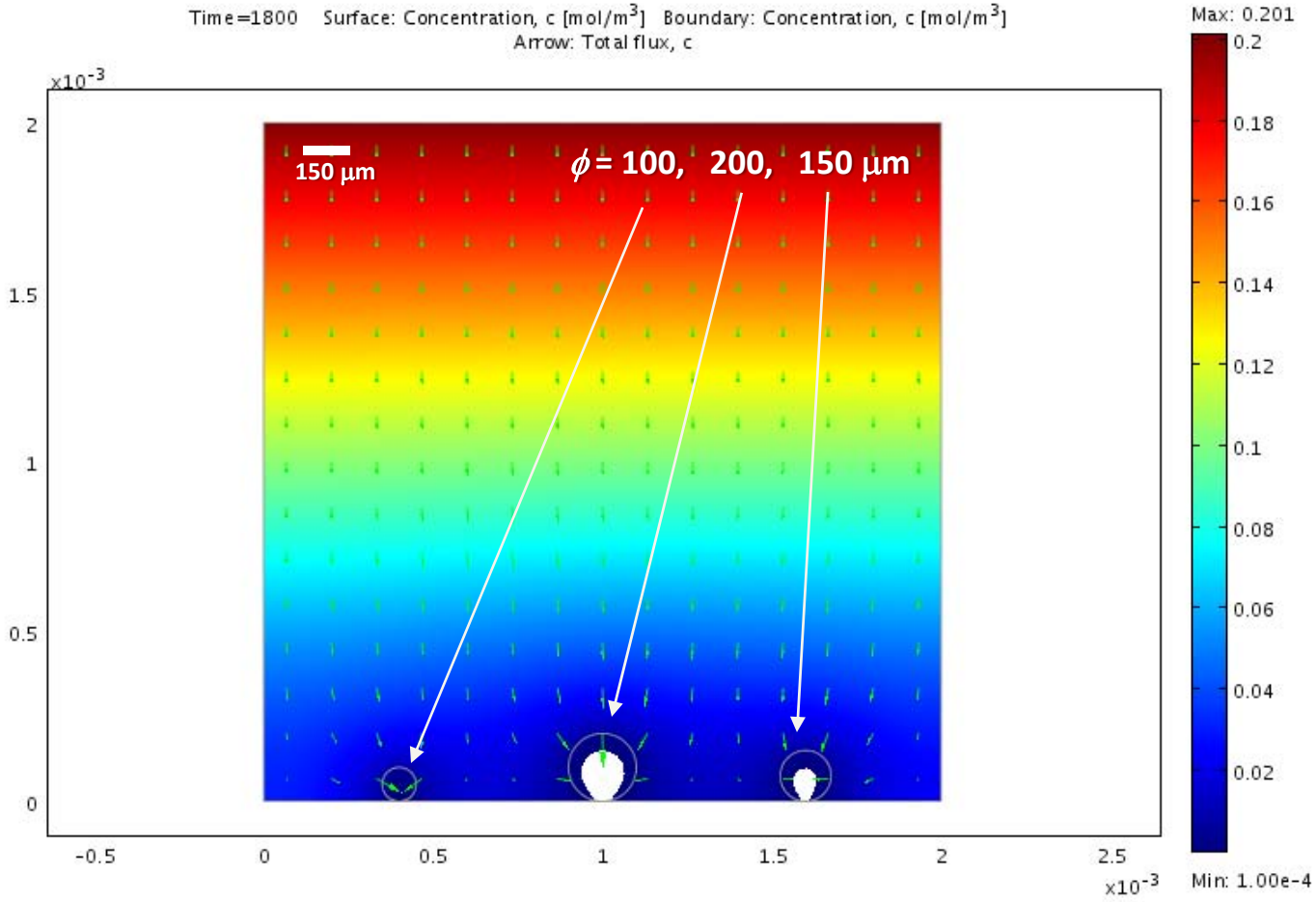

Calculated oxygen concentration for three islets (with diameters ϕ = 100, 150, and 200 µm) in standard culture conditions after stationary conditions have been reached (h = 2 mm assumed). The color-coded surface represents the oxygen concentration (red corresponding to higher and blue to lower values), whereas green arrows represent oxygen flux. 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.

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Culture Methods with Enhanced Oxygenation: Oxygen Permeable Membranes

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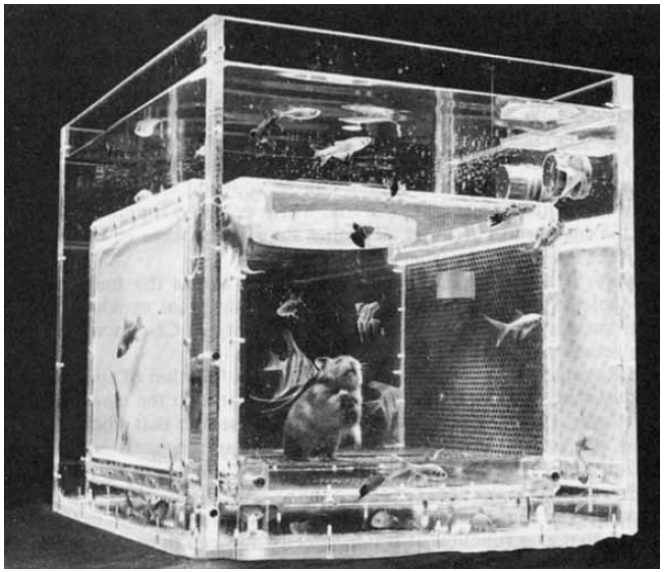
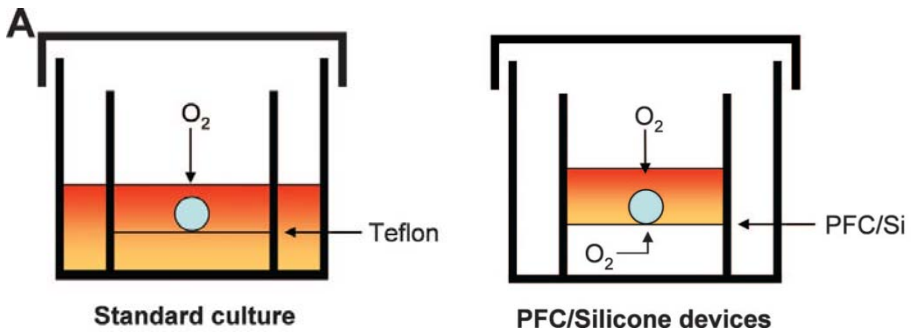
- Silicone rubber membranes have excellent oxygen permeability and have been suggested as possible solutions to provide enhanced oxygenation

(e.g., Fleischaker, R. J.; Sinskey, A. J. *Eur. J. Appl. Microbiol. Biotechnol*. **1981**, *12*, 193).

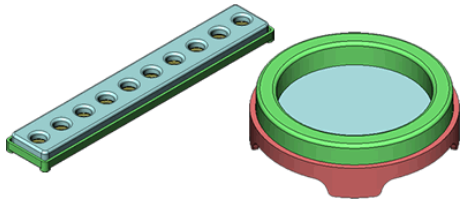


Hamster in submerged cage with silicone membrane sides.
Robb, W.L. *Ann. NY Acad. Sci.* **1968**, *146*, 119.



Enhanced oxygenation in PFC/Si devices. Schematic representation of the oxygen sandwich principle. In standard culture vessels, atmospheric oxygen can reach the tissue only after diffusion through the culture medium. In PFC/Si devices, the sample rests atop a perfluorocarbon-enriched, air-permeable silicone membrane, which provides additional oxygenation.

Fraker, C. A. et al. *Stem Cells* **2007**, *25*, 3155.



http://www.biorep.com/customequipment.asp

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Islet Culture 2D Model

Oxygen Concentrations in Nonvascularized Islets with Oxygen Permeable Membrane Bottom Culture

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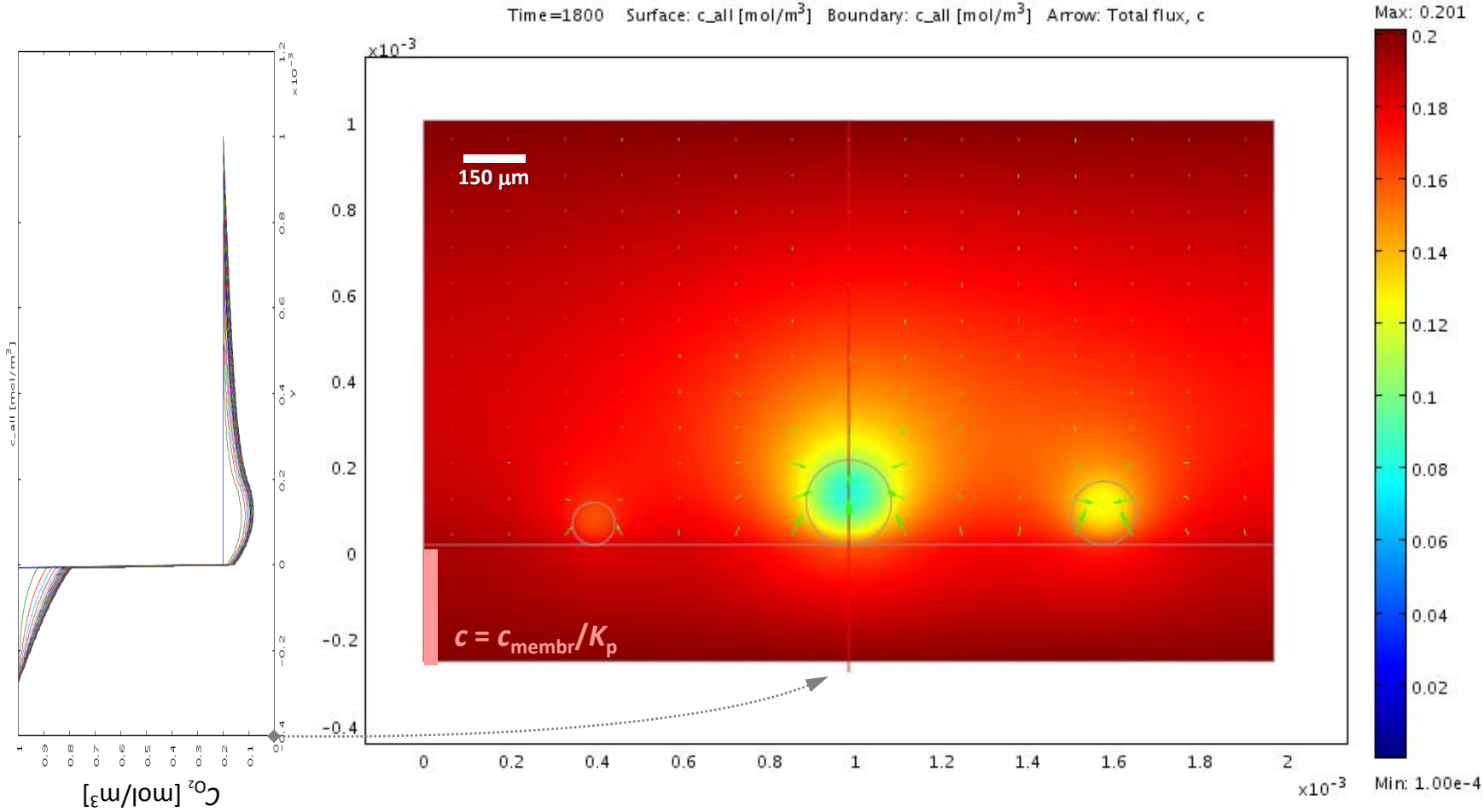

Calculated oxygen concentration for three islets (with diameters ϕ = 100, 150, and 200 µm) in a culture device with oxygen permeable (e.g., silicone rubber membrane) bottom after stationary conditions have been reached (h = 1 mm assumed). Concentrations in the membrane are higher than in the media as shown on the rotated figure on the left, which illustrates c_{O2} along the middle cross section together with its progression in time, but were rescaled using the partition coefficient $K_p = c_{membr}/c$ for the color-coded surface plot. Here, a membrane/media partition coefficient $K_p = c_{membr}/c$ was built into the model for oxygen through a **special boundary condition using the stiff-spring method**. A separate c_2 was added for the membrane (with a corresponding application mode), and to maintain continuous flux at the interface, an inward flux boundary condition was imposed along the membrane-fluid boundary with $\upsilon(c_2 - K_p c)$ and υ = 10,000 m·s^{-1}.

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Islet Culture 2D Model

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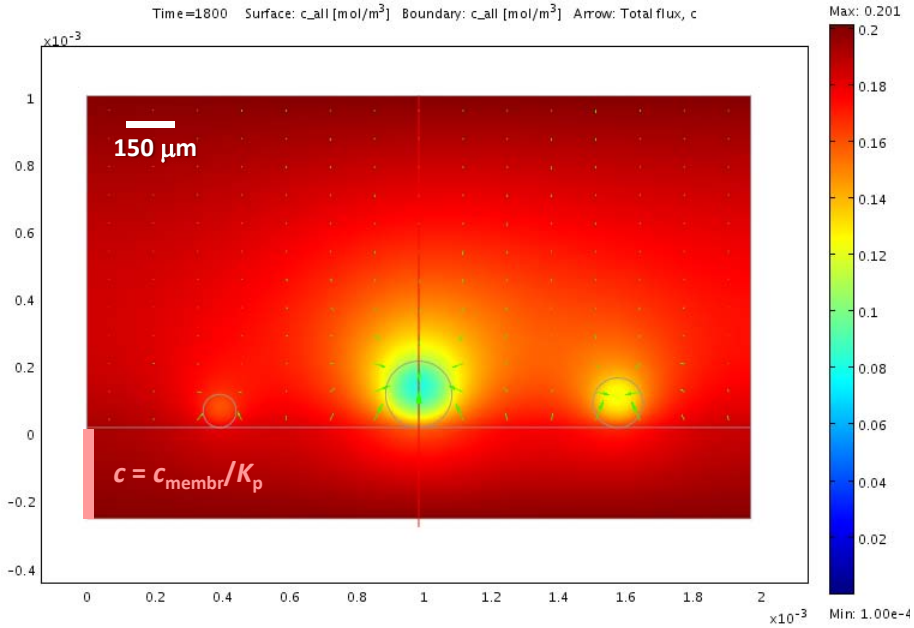
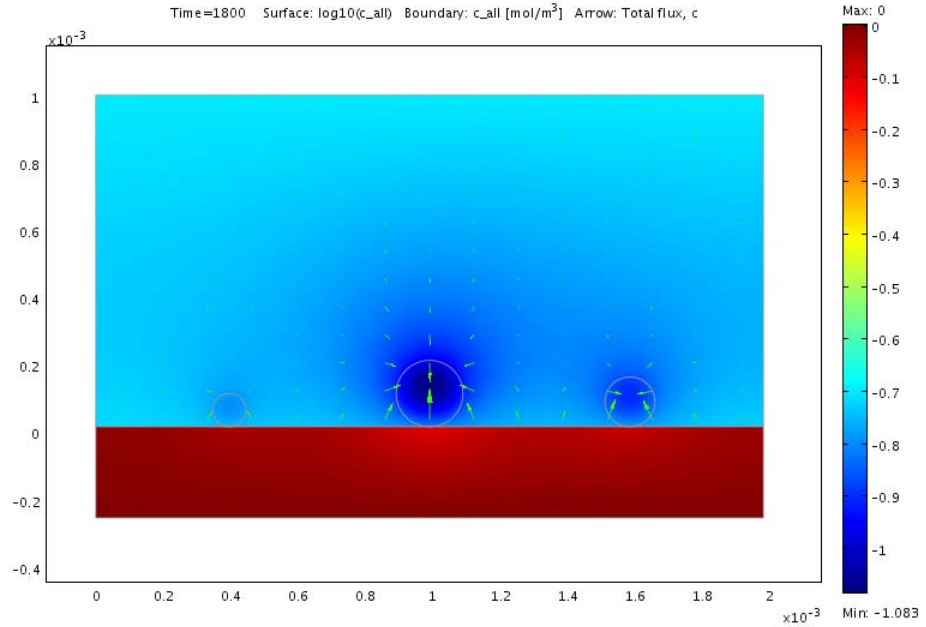
Rescaled oxygen concentration



Non-rescaled oxygen concentration (log scale)



Calculated oxygen concentration for three islets (with diameters ϕ = 100, 150, and 200 μm) in a culture device with oxygen permeable (e.g., silicone rubber membrane) bottom after stationary conditions have been reached (h = 1 mm assumed). Concentrations in the membrane are higher than in the media as shown in the figure on the right, which shows log(c_{O2}) without the rescaling used in the left figure (by usinging the partition coefficient $K_p = c_{membr}/c$). Here, a membrane/media partition coefficient $K_p = c_{membr}/c$ was built into the model for oxygen through a **special boundary condition using the stiff-spring method**. A separate c_2 was added for the membrane (with a corresponding application mode), and to maintain continuous flux at the interface, an inward flux boundary condition was imposed along the membrane-fluid boundary with $\upsilon(c_2 - K_p c)$ and υ = 10,000 m·s^{-1}.

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Oxygen Concentrations in Nonvascularized Islets with Oxygen Permeable Membrane Bottom Culture

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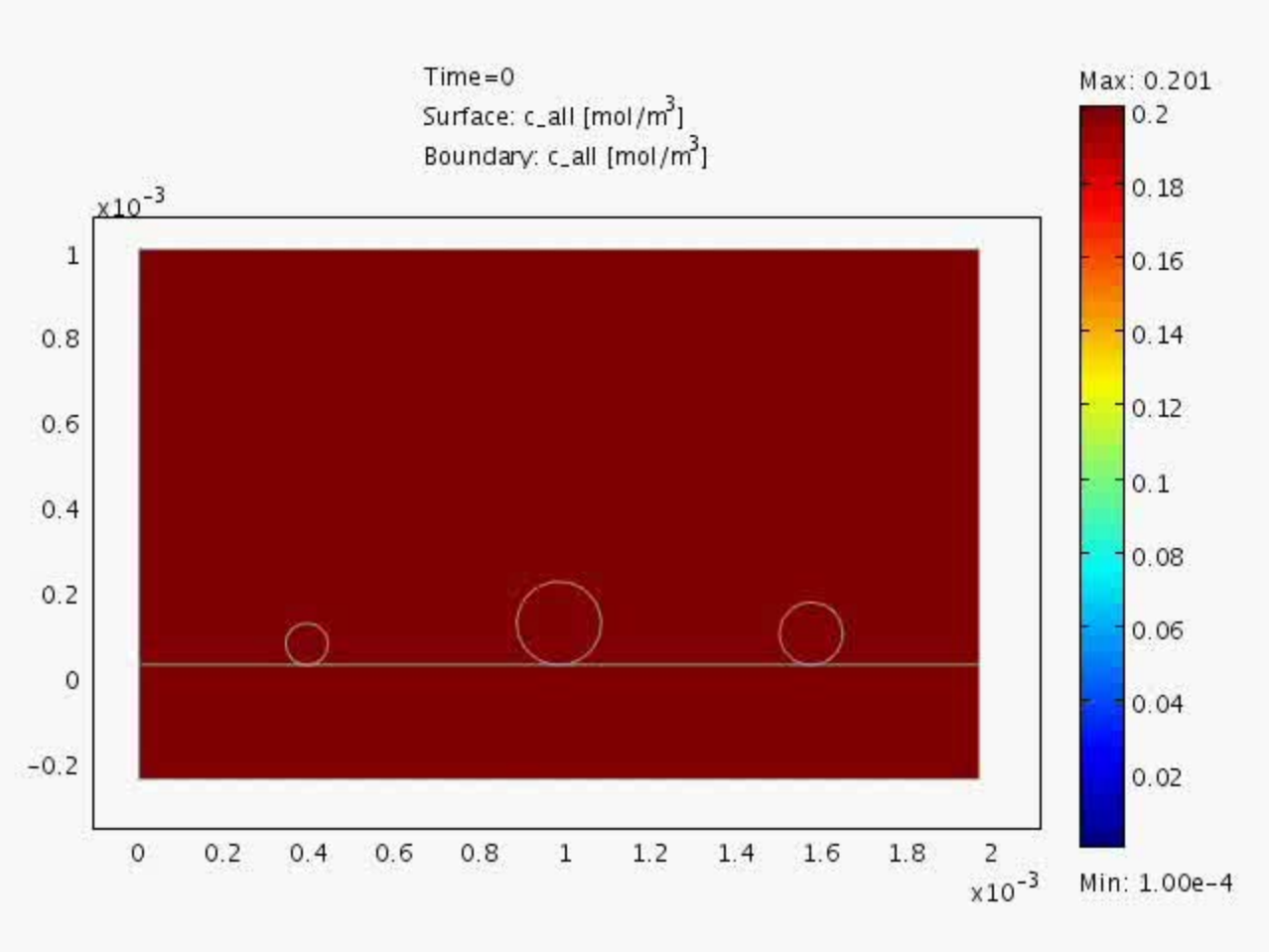

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Predicted Oxygen Partial Pressures in Gas-Permeable Cell Culture Bags

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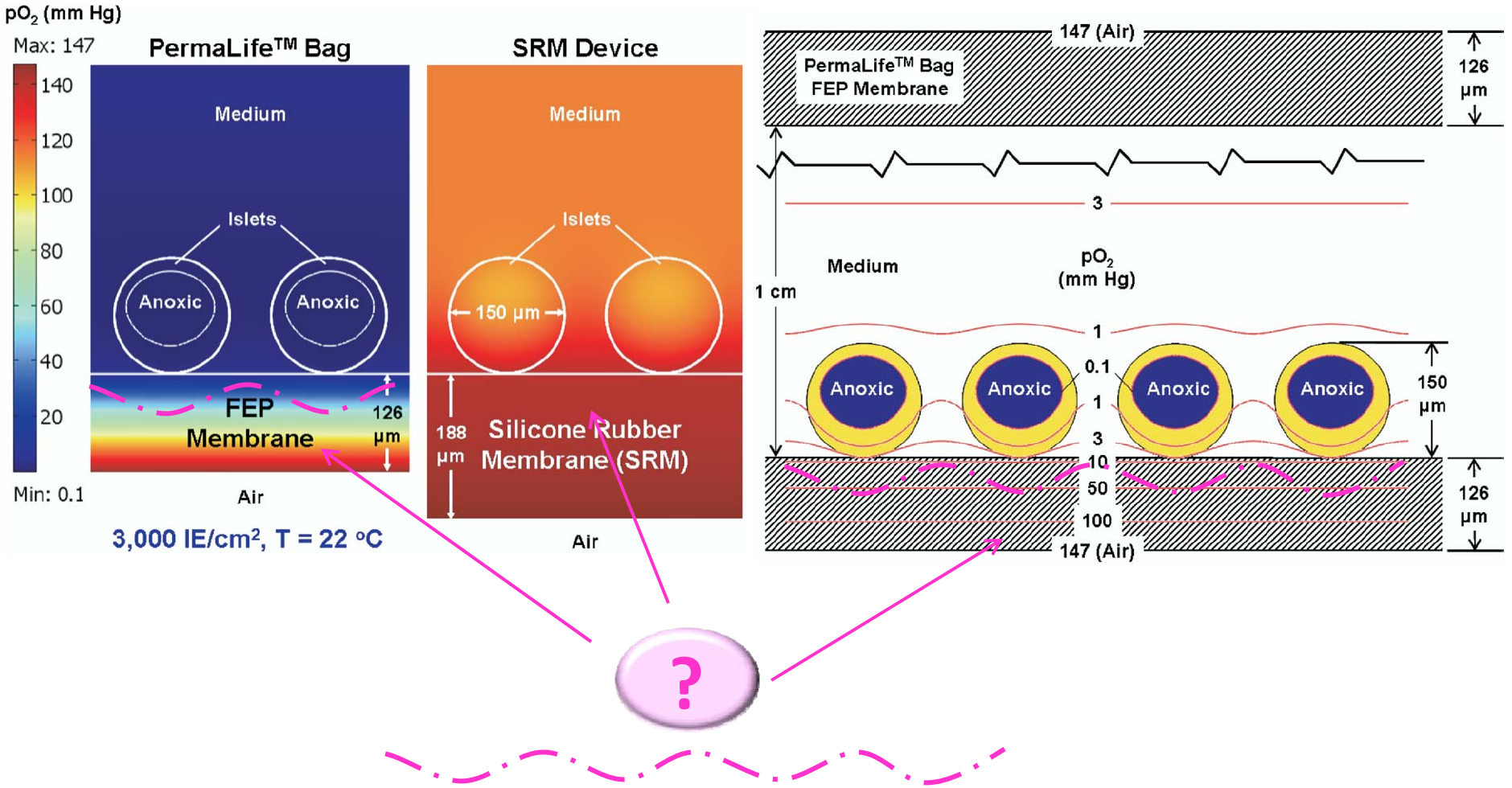

Avgoustiniatos, E. S.; Hering, B. J.;… Papas, K.K. et al. *Transpl. Proc*. **2008**, *40*, 395.

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Perifusion Device with Flowing Media

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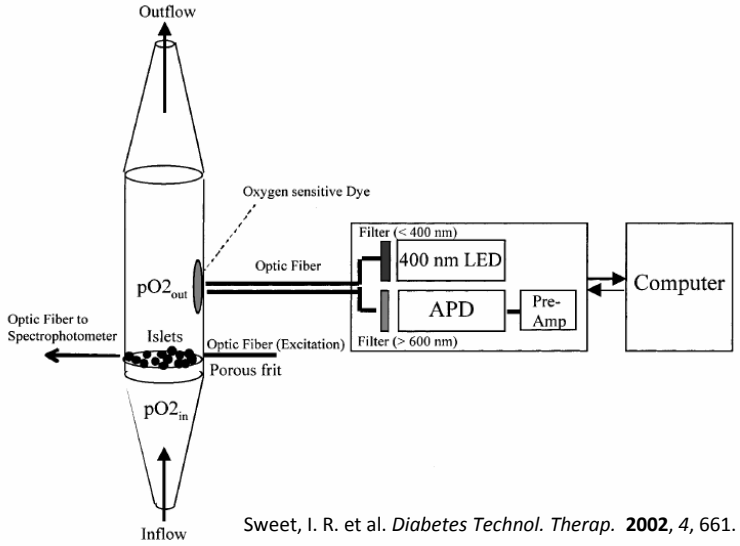
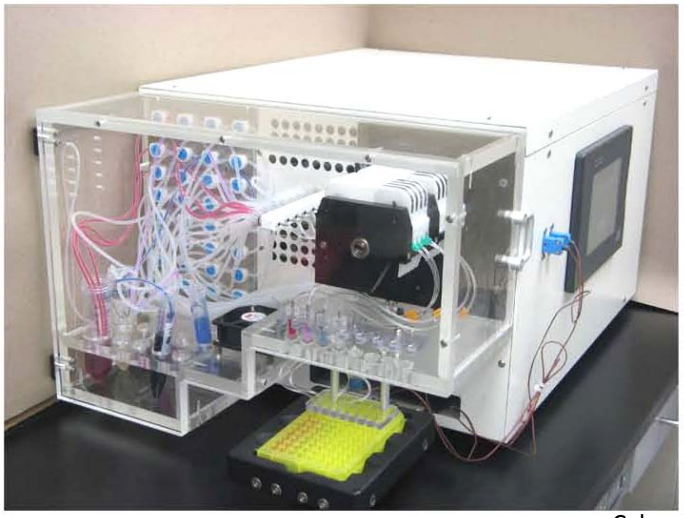
- Routinely used to assess islet quality and function
- Allow the dynamic measurement of the glucose-stimulated insulin release (GSIR) (and/or other metabolic products)

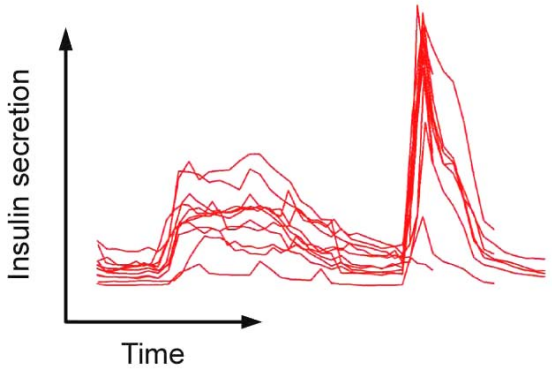


Sweet, I. R. et al. *Diabetes Technol. Therap.* **2002**, *4*, 661.

Automated Perifusion



Secretion profiles



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

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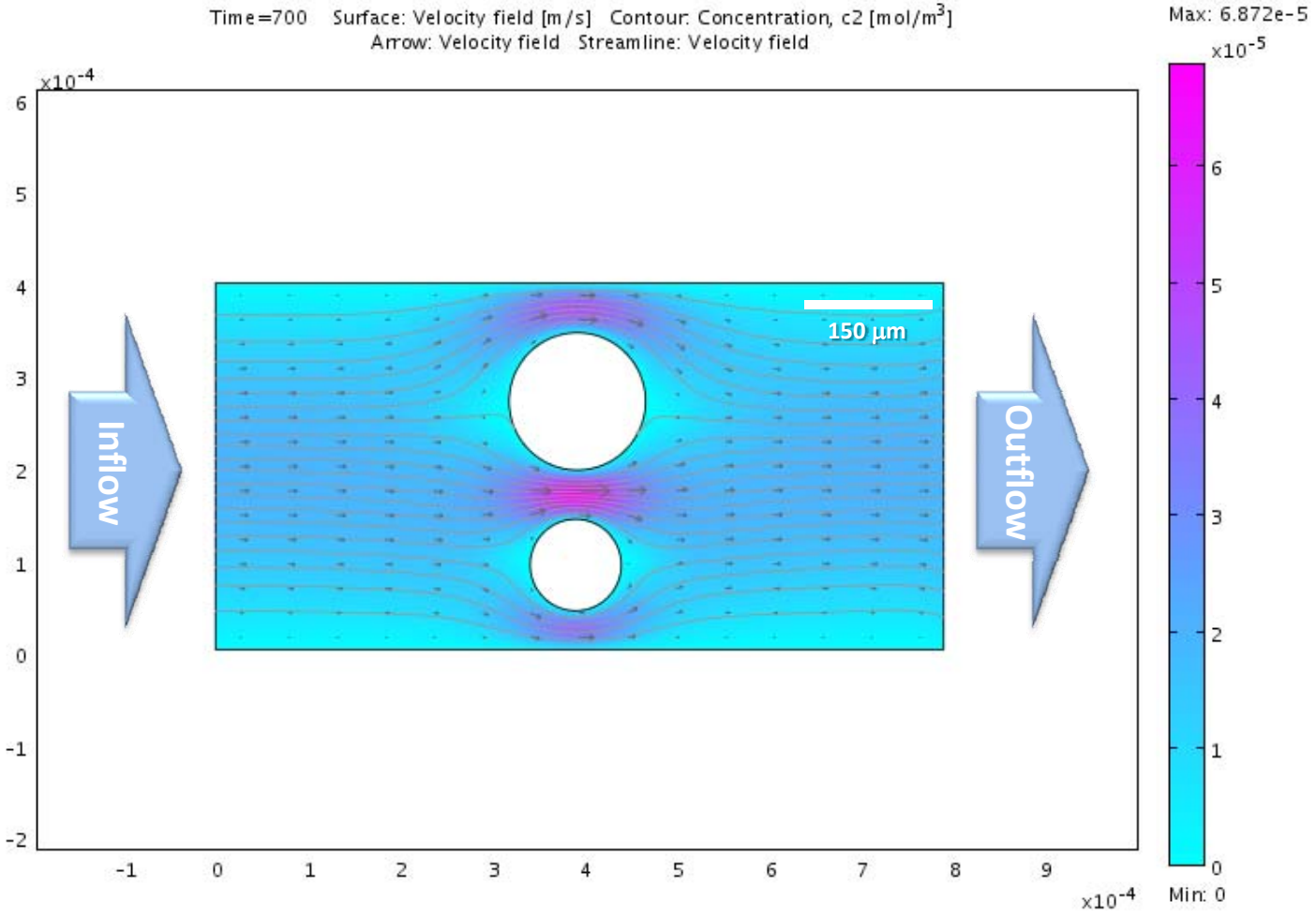
Islets in Perifusion Device

Velocity Field



Calculated velocity field for two islets (with diameters ϕ = 100 and 150 µm) in a perifusion device model. Aqueous media flows from left to right at constant flux (v_{in} = 0.2 mm/s). The velocity field (color coded with purple corresponding to higher and light blue to lower velocities; also, proportional gray arrows for direction) and the streamlines corresponding to the flow of the perifusion media are shown. A **parabolic inflow profile** with $4v_{in}(y/y_{max})(1–y/y_{max})$ was used on the inlet and pressure, no viscous stress with p_0 = 0 on the outlet.

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Islet Oxygenation in Perifusion Device

Increasing Glucose Gradient

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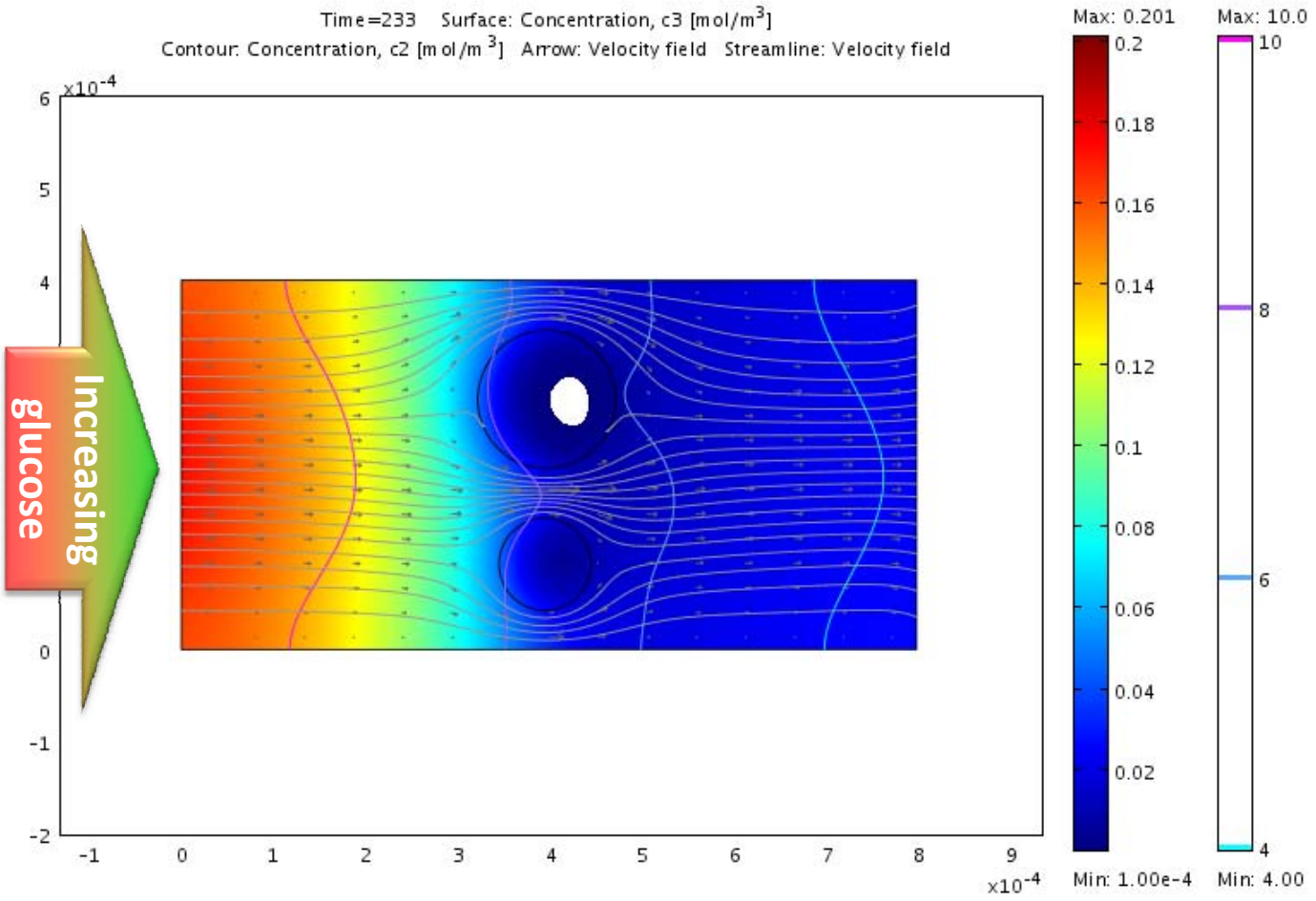

Calculated oxygen concentration for two islets in a perifusion device model. Media flows from left to right at constant flux (v_{in} = 0.2 mm/s). The color-coded surface represents the oxygen concentration (red corresponding to higher and blue to lower values). The velocity field (gray arrows) and the streamlines corresponding to the flow of the perifusion media are also shown. The image depicts a time-point during the transition from low (3 mM) to high (11 mM) incoming glucose as highlighted by the corresponding contour lines of the glucose gradient. Increasing glucose imposes increasing metabolic demand (to produce insulin) and, hence, an increased oxygen consumption.

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Islet Oxygenation in Perifusion Device

Low (t = 0 – 200, 500 – 700) and High (t = 200 – 500) Glucose

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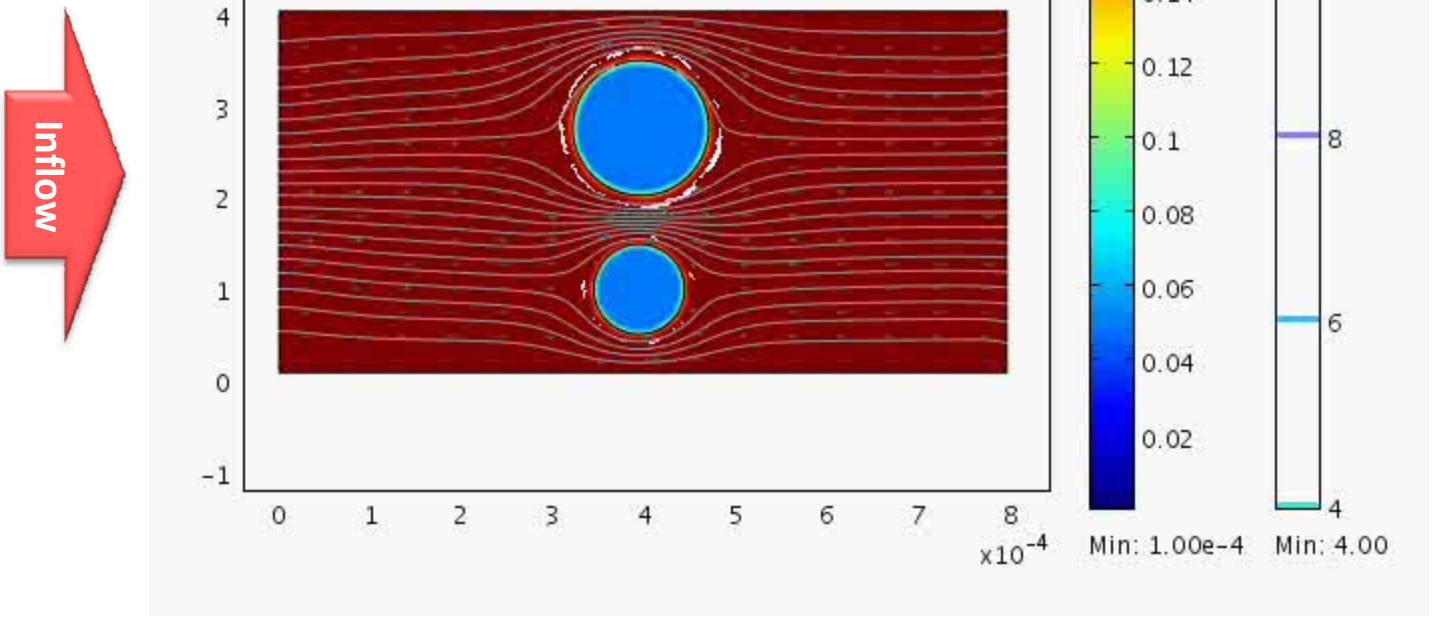
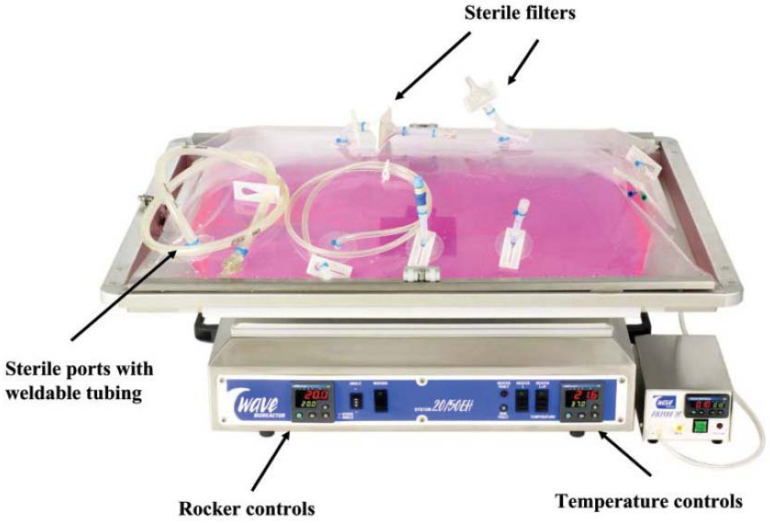


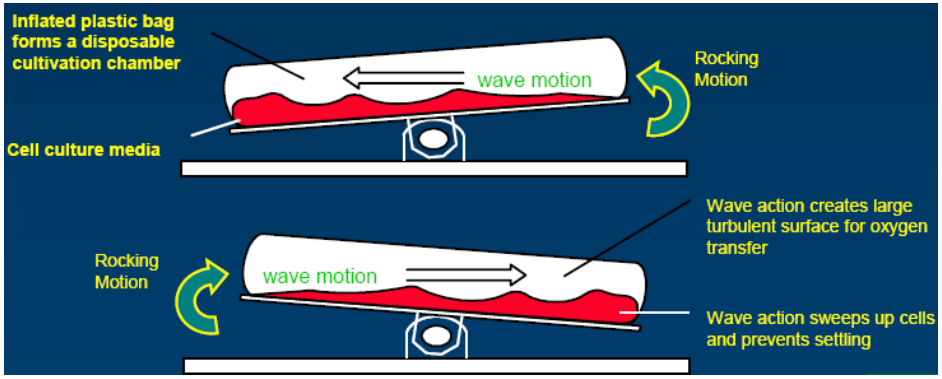
Calculated oxygen concentration for two islets in a perifusion device model. Media with fixed glucose concentration flows from left to right at constant flux (v_{in} = 0.2 mm/s). The color-coded surface represents the oxygen concentration (red corresponding to higher and blue to lower values). The velocity field (gray arrows) and the streamlines corresponding to the flow of the perifusion media are also shown. Initial low glucose (3 nM; 0 to 200 s) is increased to high glucose (11 nM, 200 to 500 s) and then back to low glucose (3 nM, 500 to 700 nM).

Culture Methods with Enhanced Oxygenation: WAVE Bioreactor System (GE Healthcare)

WAVE Bioreactor 2/10EH for use with working culture volumes between of 50 mL and 5 L. Designed for animal, insect, and plant cell culture with integral features such as aeration, heating, and temperature control.

- Adjustable rock rate 3 to 40 rocks/min
- Adjustable angle from 2 to 9°
- Integral airpump with mass flow meter
- 230 × 330 × 160 mm





http://www.wavebiotech.com/speed_train/

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Islets in Rocking Plate Device

Velocity Field

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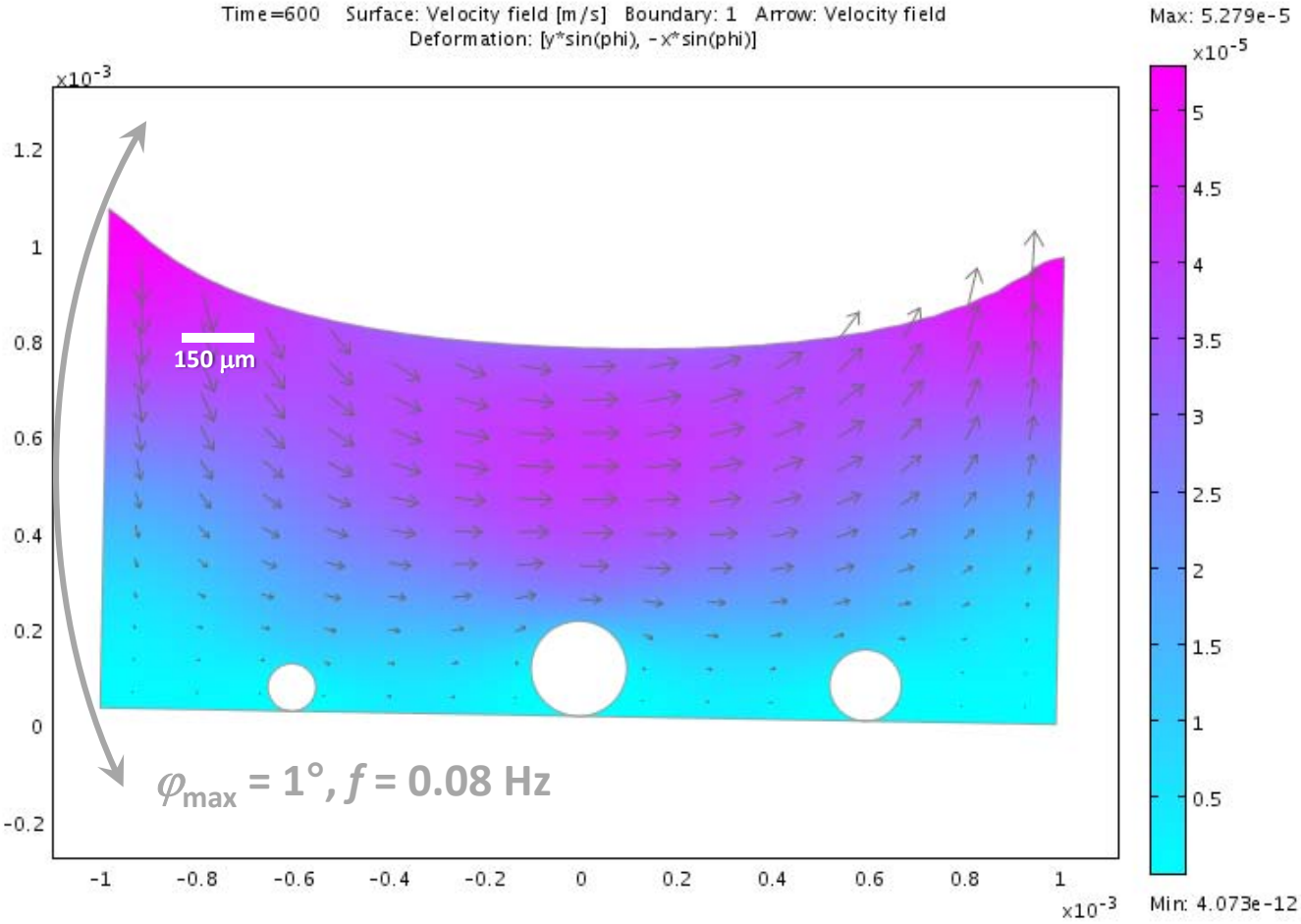

Calculated velocity field in a culture device with rocking plate–induced agitation after stationary conditions have been reached with three islets (with diameters ϕ = 100, 150, and 200 µm) (h = 1 mm assumed). Gray arrows represent the velocity field of the media movement due to the wave-generating rocking plate. Modeling of moving liquid surfaces, with some limitations, was achieved by addition of the **moving mesh (ALE, arbitrary Lagrangian–Eulerian) module** and use of an oscillating gravitational force that has horizontal ($F_x = \rho g \sin\varphi$) and vertical ($F_y = -\rho g \cos\varphi$) components defined by the inclination angle φ that follows a harmonic oscillation ($\varphi = \varphi_{max} \sin \omega t$). Inclination of the device was visualized by using the 'Deformed shape plot' function with X and Y components synchronized to the oscillation of the gravitational field. ***Draft, exploratory model only***: does not account for surface tension effects and unrealistically high viscosity had to be used.

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Islet Culture 2D Model

Oxygen Concentrations in Nonvascularized Islets in Culture with Rocking Plate-Induced Agitation

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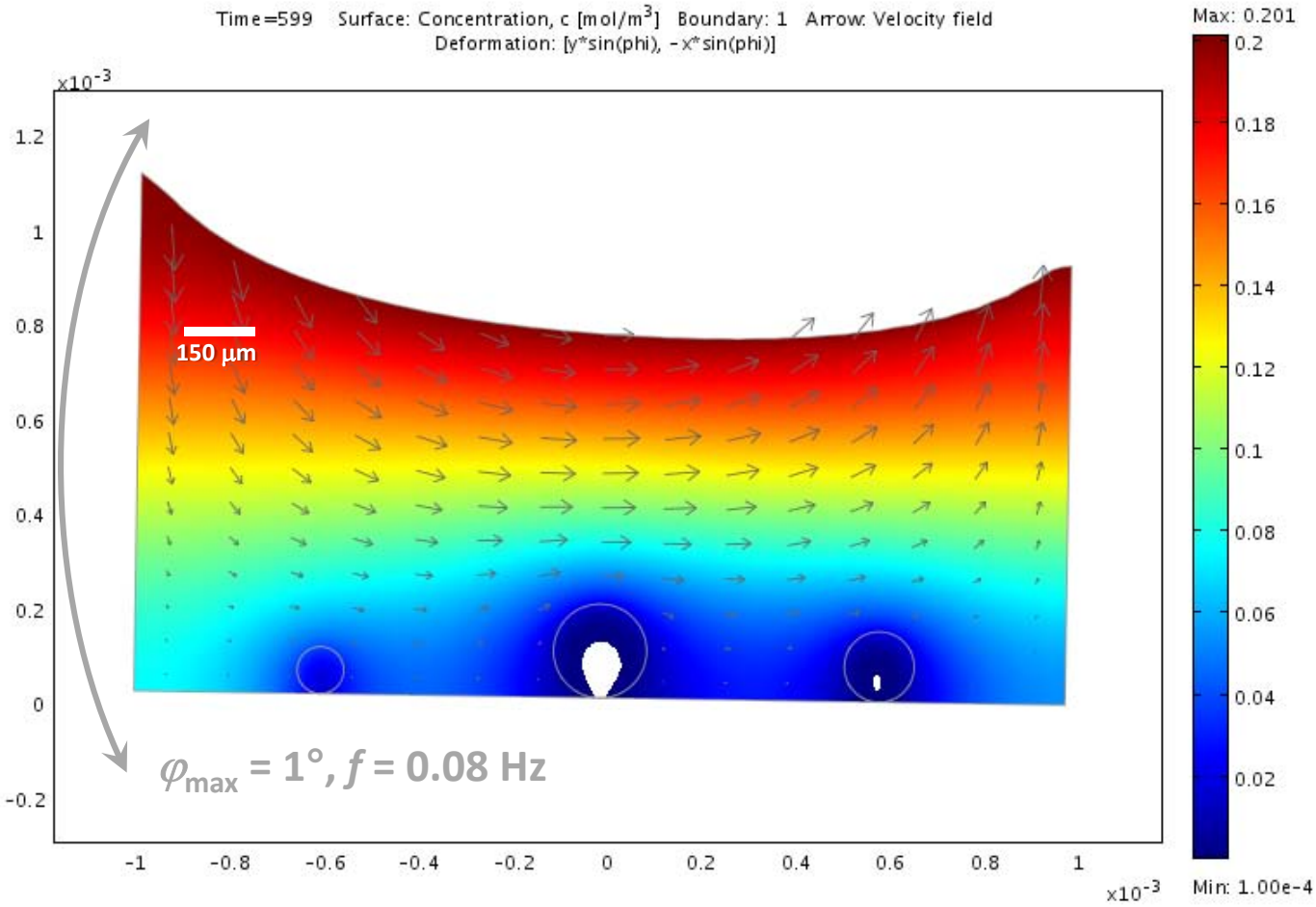

Calculated oxygen concentration for three islets (with diameters ϕ = 100, 150, and 200 µm) in a culture device with rocking plate–induced agitation after stationary conditions have been reached (h = 1 mm assumed). Gray arrows represent the velocity field of the media movement due to the wave-generating rocking plate. Modeling of moving liquid surfaces, with some limitations, was achieved by addition of the **moving mesh (ALE, arbitrary Lagrangian–Eulerian) module** and use of an oscillating gravitational force that has horizontal ($F_x = \rho g \sin\varphi$) and vertical ($F_y = -\rho g \cos\varphi$) components defined by the inclination angle φ that follows a harmonic oscillation ($\varphi = \varphi_{max} \sin\omega t$). Inclination of the device was visualized by using the 'Deformed shape plot' function with X and Y components synchronized to the oscillation of the gravitational field. ***Draft, exploratory model only***: does not account for surface tension effects and unrealistically high viscosity had to be used.

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Islet Culture 2D Model

Oxygen Concentrations in Nonvascularized Islets in Culture with Rocking Plate-Induced Agitation

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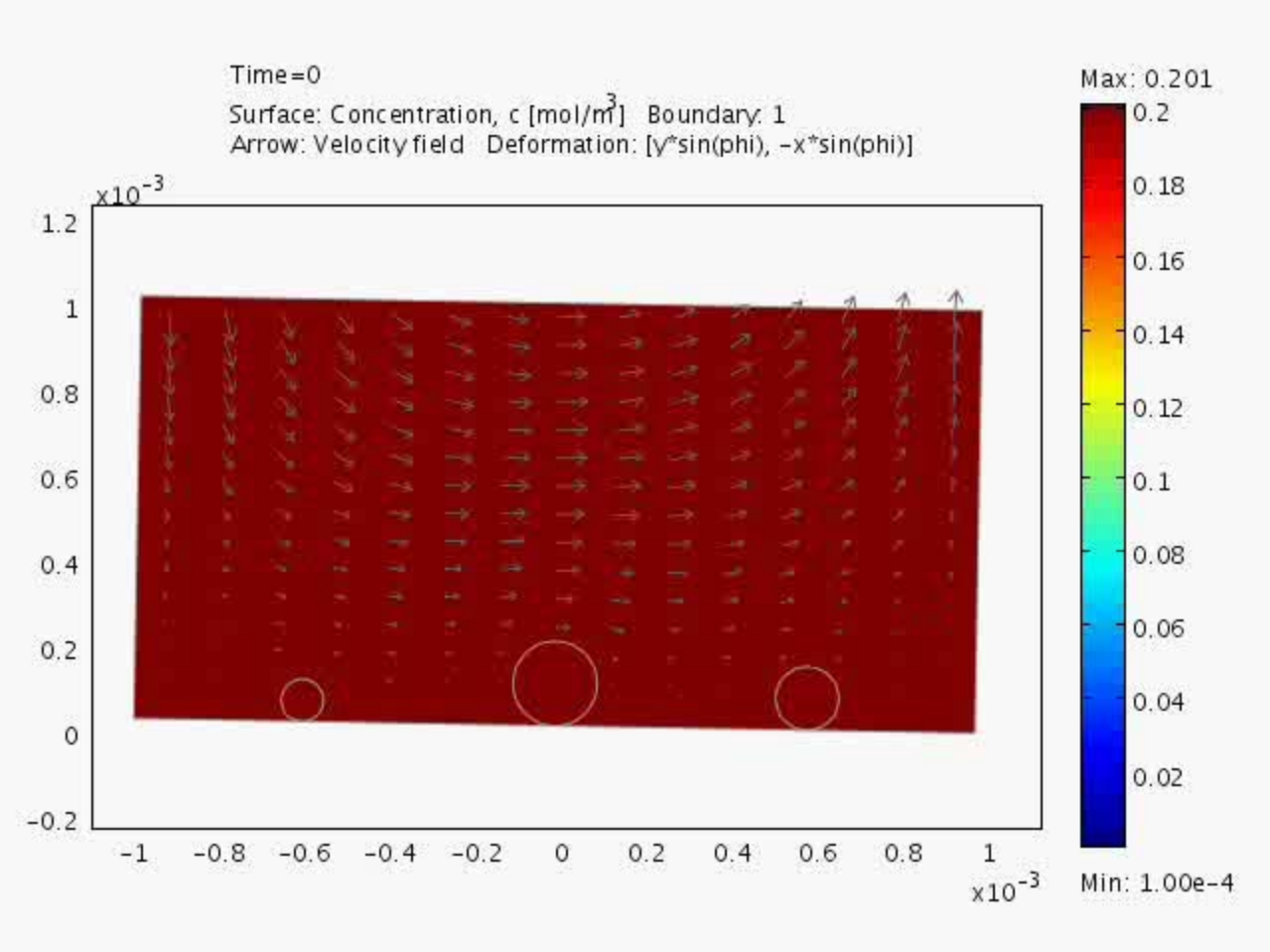

Calculated oxygen concentration for three islets (with diameters ϕ = 100, 150, and 200 μm) in a culture device with rocking plate–induced agitation after stationary conditions have been reached (h = 1 mm assumed). Gray arrows represent the velocity field of the media movement due to the wave-generating rocking plate. Modeling of moving liquid surfaces, with some limitations, was achieved by addition of the **moving mesh (ALE, arbitrary Lagrangian–Eulerian) module** and use of an oscillating gravitational force that has horizontal ($F_x = \rho g \sin\varphi$) and vertical ($F_y = -\rho g \cos\varphi$) components defined by the inclination angle φ that follows a harmonic oscillation ($\varphi = \varphi_{max} \sin\omega t$). Inclination of the device was visualized by using the 'Deformed shape plot' function with X and Y components synchronized to the oscillation of the gravitational field. ***Draft, exploratory model only***: does not account for surface tension effects and unrealistically high viscosity had to be used.

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Conclusions

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- Exploratory cellular-level oxygen consumption and cell viability models have been implemented in COMSOL Multiphysics for nonvascularized pancreatic islets using physiologically relevant geometries
- Results are in good agreement with existing experimental evidence
- Hypoxia is often a problem for nonvascularized islet and can lead to considerable cell death (necrosis), especially in the core region of large islets
- Such models are of considerable interest to improve the function and viability of cultured, transplanted, or encapsulated cells
- COMSOL Multiphysics allow convenient extension to true multiphysics applications, e.g., diffusion and consumption with flowing or moving media

Acknowledgments

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(www.diabetesresearch.org)