Hands-on session on computer methods for mass transport in tissue engineering

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Outline

- Transport equation

- Diffusion, convection, and reaction

- Manually solving diffusion problems

- Computer methods: Introducing Python and Jupyter

- Solving diffusion problems using symbolic computing

- Solving transient problems using numerical computing

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Transport Equation

- How a scalar quantity is transported in space

- Commonly used in transport phenomena studies

- From a mathematical point of view:

  a (partial) differential equation to describe the conservation

Transport Equation

- Reaction-Diffusion-Advection equation

- $c = c(x, y, z, t)$, variable of interest
  (e.g. species concentration in mass transfer or temperate in heat transfer)

$$\frac{\partial c}{\partial t} = \underbrace{\nabla \cdot (D\nabla c) +}_{\text{Diffusion}} \underbrace{\nabla \cdot (\mathbf{v}c) +}_{\text{Advection}} \underbrace{f(c)}_{\text{Reaction}}$$

$$\left(A + 2B \xrightarrow{k} C \Rightarrow \frac{\partial [C]}{\partial t} = k[A][B]^2 \right)$$
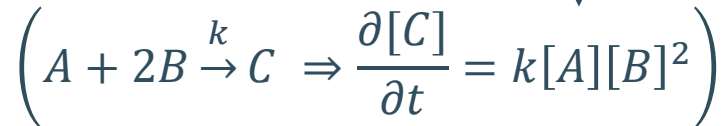
Reaction-Diffusion-Advection PDE

- A short introductory video on the equation:
  https://www.youtube.com/watch?v=YiIT3p507S0

Reaction-Diffusion-Advection PDE

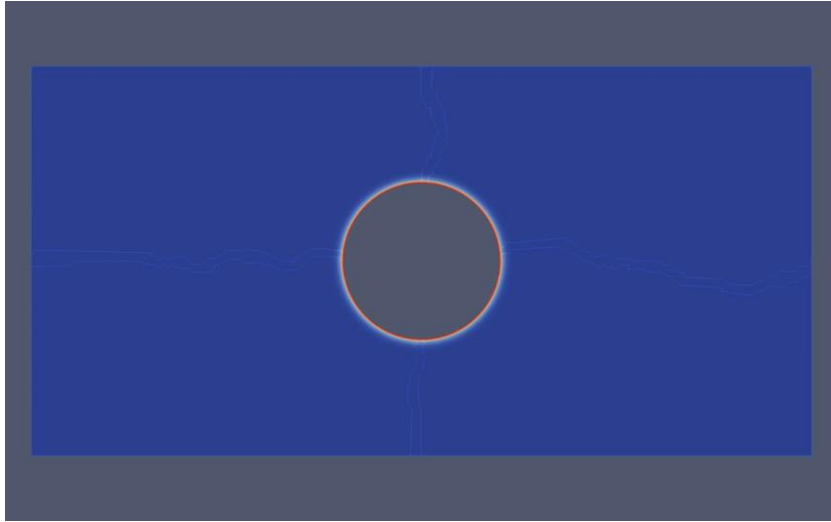$$\frac{\partial u}{\partial t} = \nabla \cdot [D\nabla u] - \nabla \cdot (\mathbf{v}u) + f(u)$$

$$\nabla f = \left(\frac{\partial}{\partial x},\ \frac{\partial}{\partial y},\ \frac{\partial}{\partial z}\right)f = \frac{\partial f}{\partial x}\mathbf{i} + \frac{\partial f}{\partial y}\mathbf{j} + \frac{\partial f}{\partial z}\mathbf{k}$$

$$\nabla \cdot \mathbf{F} = \left(\frac{\partial}{\partial x},\ \frac{\partial}{\partial y},\ \frac{\partial}{\partial z}\right) \cdot (F_x,\ F_y,\ F_z) = \frac{\partial F_x}{\partial x} + \frac{\partial F_y}{\partial y} + \frac{\partial F_z}{\partial z}$$

$$\Delta f = \nabla^2 f = (\nabla \cdot \nabla)f = \frac{\partial^2 f}{\partial x^2} + \frac{\partial^2 f}{\partial y^2} + \frac{\partial^2 f}{\partial z^2}$$
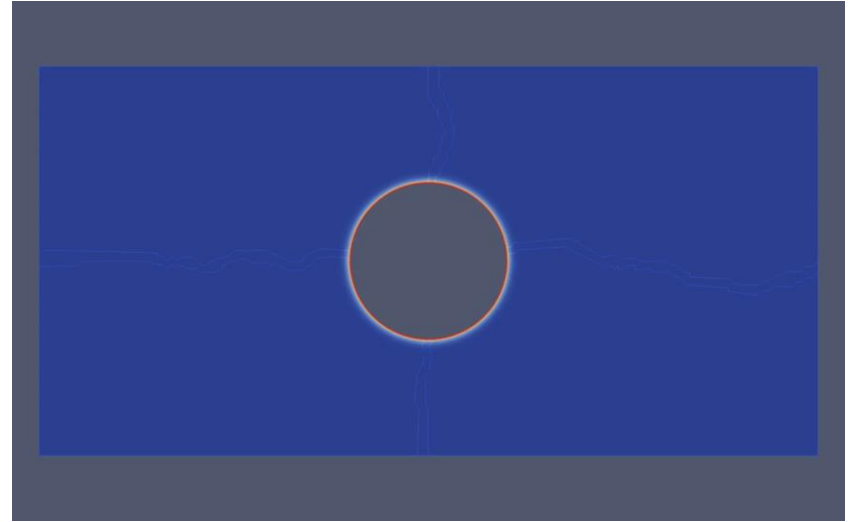
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Convection Effect

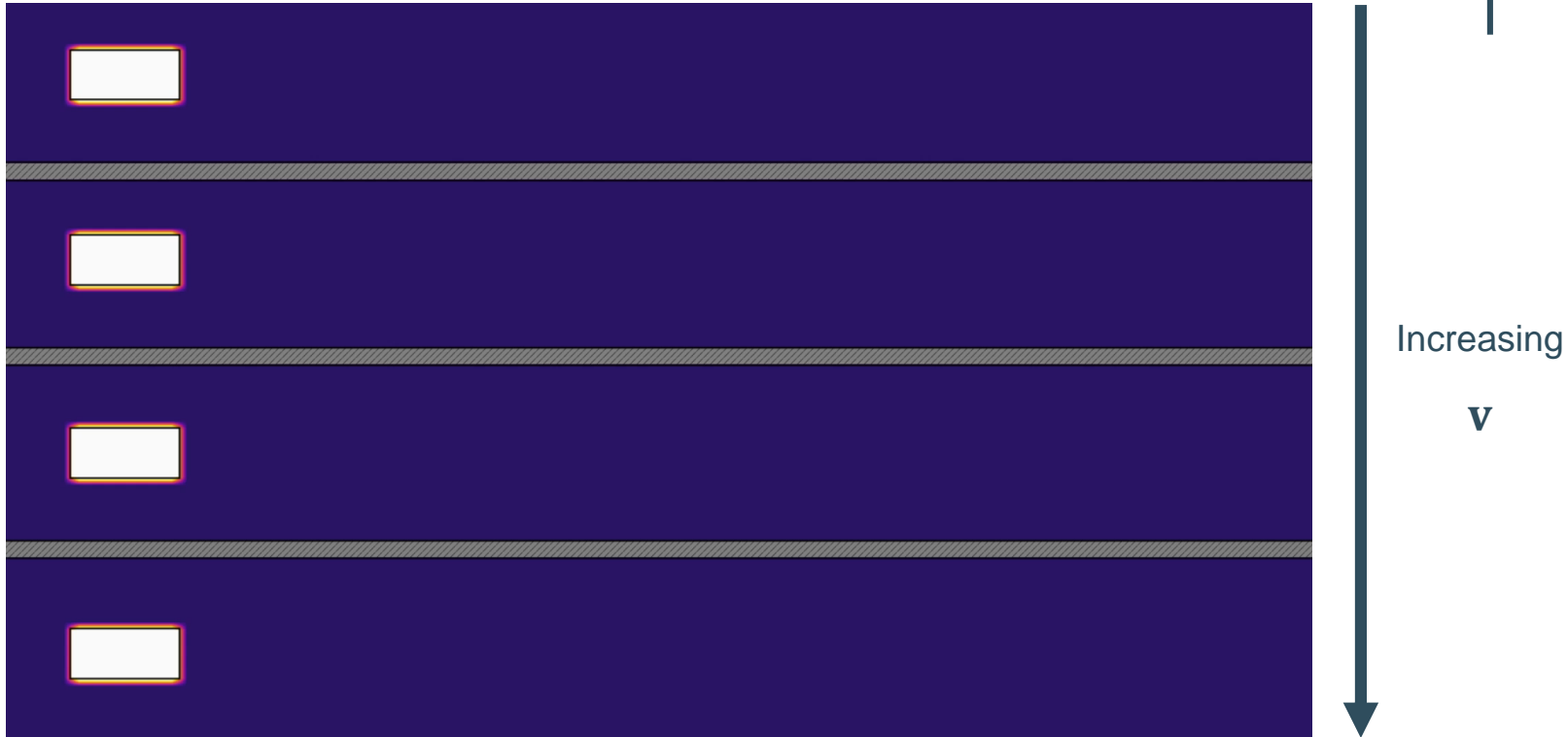$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c)$$

$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + \nabla \cdot (\mathbf{v} c)$$

Diffusion

Diffusion-Advection

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Convection Effect - Velocity

$$\frac{\partial c}{\partial t} = \nabla . (D \nabla c) + \nabla . (\mathbf{v} c)$$

Increasing

$\mathbf{v}$

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Solving Problems Manually

- Integrating the conservative form of equations

- Applying appropriate boundary conditions to obtain integration coefficients

- In case of transient (not steady state) problems: apply initial conditions

- Calculate quantities of desire (e.g. maximum diffusion depth)

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Steady State Examples

- Some examples were already on the mass transport slides

- Let's solve the equations for case 3 (slide 18): 1d diffusion in cellular construct

Simple case 3: 1D-diffusion in cellular construct (Cartesian coordinates)

- Passive transport in cellular construct:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - V_{max,cell} \underbrace{\rho_{cell}}_{\text{cell density (\#cells/m}^3)}$$
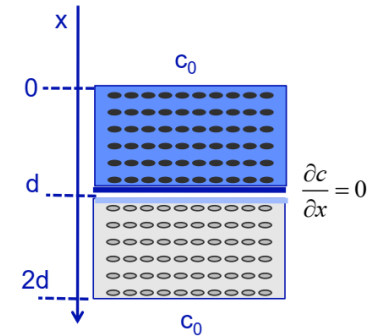
- Steady state solution:
  - At x=0: c(x=0) = c_0
  - At x=d: Γ=0 (impermeable or symmetric)

$$c(x) = \frac{V_{max,cell} \rho_{cell}}{D}(\frac{x^2}{2} - dx) + c_0$$

- Maximum diffusion depth (for c(x=d) = 0):

$$d_{max} = \sqrt{2c_0 \frac{D}{V_{max,cell}\rho_{cell}}}$$

x

c_0

0

d $\frac{\partial c}{\partial x} = 0$

2d

c_0

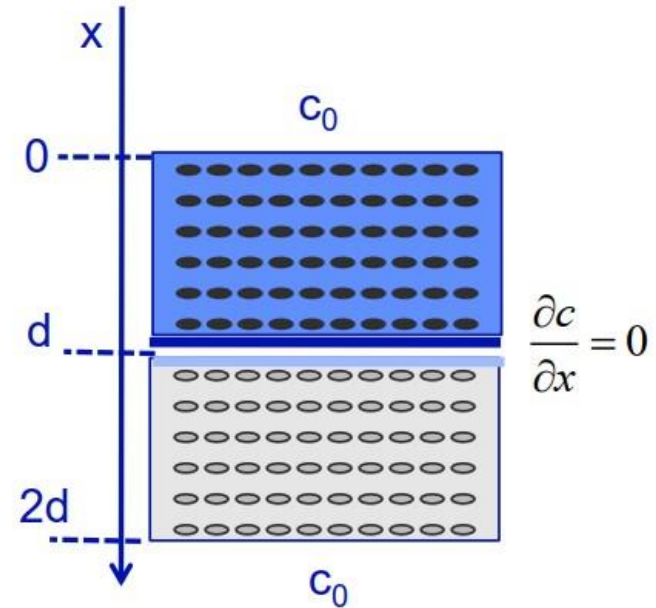Mass transport in tissue engineering

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1D Diffusion in Cellular Construct

- The problem is to solve the following equation

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - V_{max,cell}\rho_{cell}$$

- For a steady state solution, we can neglect the left hand side term

$$D\frac{\partial^2 c}{\partial x^2} - V_{max,cell}\rho_{cell} = 0$$

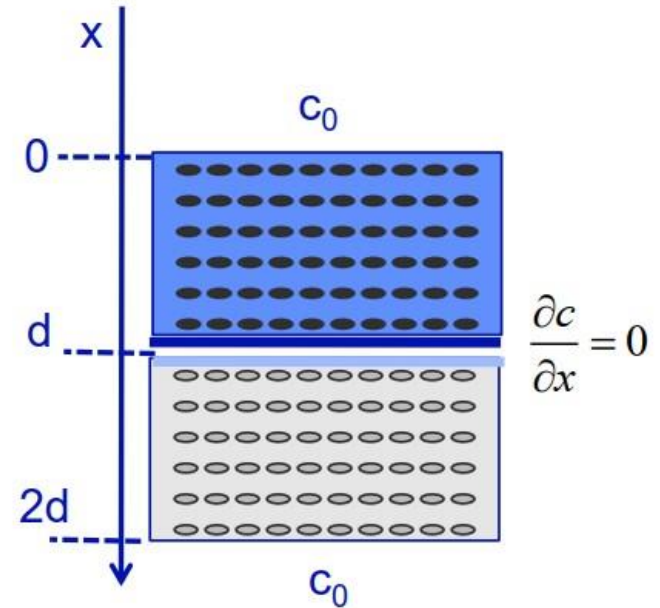- Maximum depth of oxygen penetration?

1D Diffusion in Cellular Construct

- It is a 1-D problem, so let's say c = c(x)

$$D \frac{d^2 c}{dx^2} = V_m \rho \rightarrow \frac{d^2 c}{dx^2} = \frac{V_m \rho}{D}$$

- Integrating both sides of the equation yields

$$\int \frac{d^2 c}{dx^2} dx = \int \frac{V_m \rho}{D} dx$$

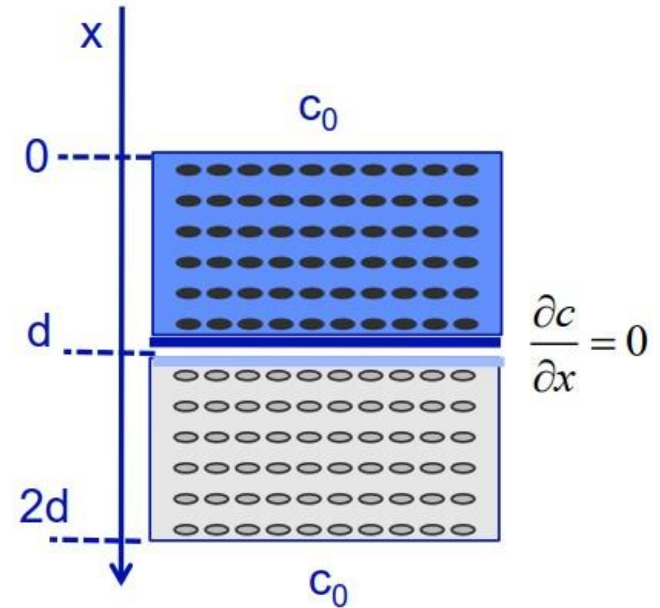$$\rightarrow \frac{dc}{dx} = \frac{V_m \rho}{D} x + C_1$$

1D Diffusion in Cellular Construct

$$\frac{dc}{dx} = \frac{V_m \rho}{D} x + C_1$$

- We know $\frac{dc}{dx} = 0$ at $x = d$

$$0 = \frac{V_m \rho}{D} d + C_1 \rightarrow C_1 = -\frac{V_m \rho d}{D}$$

c_0

x

0

d

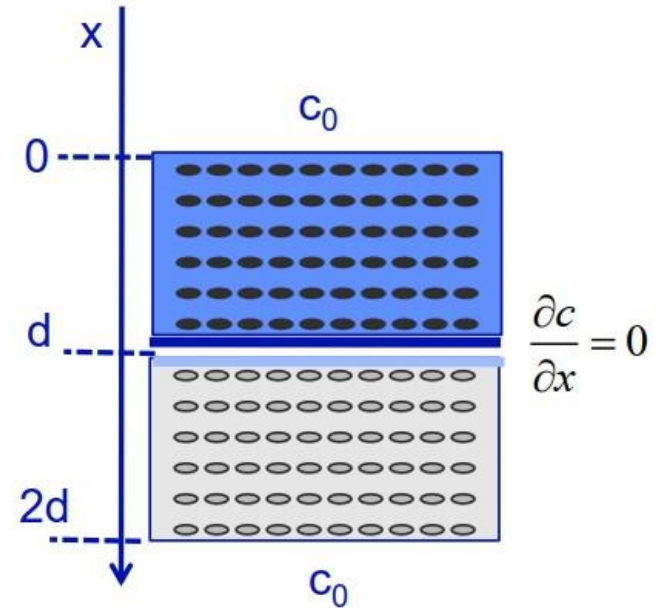$\frac{\partial c}{\partial x} = 0$

2d

c_0

1D Diffusion in Cellular Construct

- Still have a derivative term, so we eliminate it

$$\int \frac{dc}{dx} dx = \int (\frac{V_m \rho}{D} x + C_1) dx$$

$$\rightarrow c(x) = \frac{V_m \rho}{D} \frac{x^2}{2} + C_1 x + C_2$$

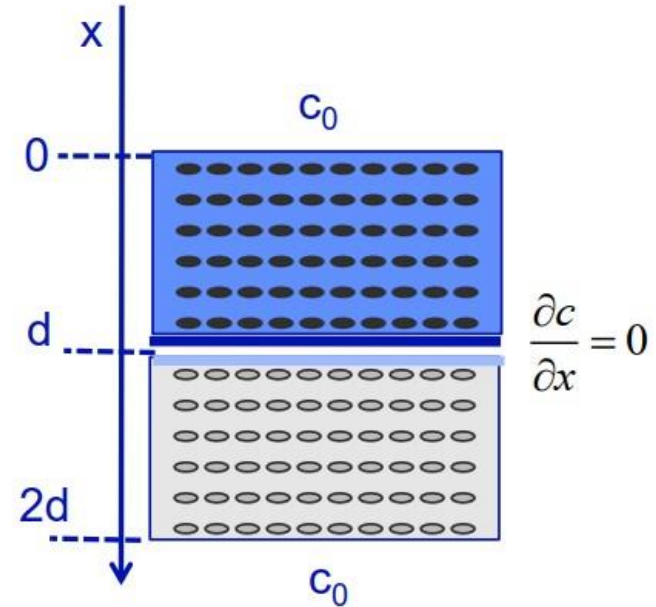- We know $c = c_0$ at x = d

$$C_2 = c_0$$

1D Diffusion in Cellular Construct

- So, by knowing C_1 and C_2, we can write the equation of the change of concentration of oxygen throughout the construct:

$$c(x) = \frac{V_m \rho}{D}\frac{x^2}{2} - \frac{V_m \rho d}{D}x + c_0$$

$$\rightarrow c(x) = \frac{V_m \rho}{D}\left(\frac{x^2}{2} - xd\right) + c_0$$

- How to find the maximum diffusion depth?
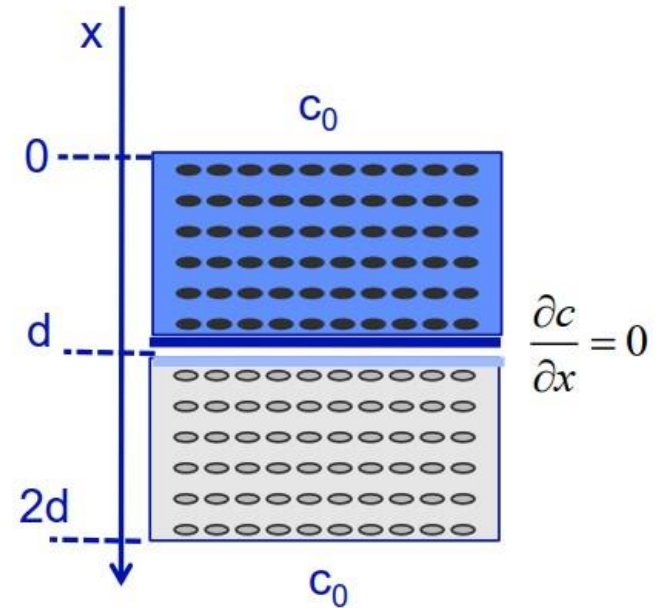
1D Diffusion in Cellular Construct

- We know $c(x) = 0$ at $x = d_{max}$, so

$$c(x) = \frac{V_m \rho}{D} \frac{x^2}{2} - \frac{V_m \rho d}{D} x + c_0$$

$$x = d_{max}, d = d_{max}, c(x) = 0$$

$$\rightarrow 0 = \frac{V_m \rho}{D} \left(\frac{d_{max}^2}{2} - d_{max}^2\right) + c_0$$

$$\rightarrow d_{max} = \sqrt{2 c_0 \frac{D}{V_m \rho}}$$

A Similar Problem, Solve It as Exercise

- Bone healing in large bone defects
- Derive the expression for the penetration depth $c(x = d) = c_{\min}$
- Bone segmental defect (a symmetry BC?)
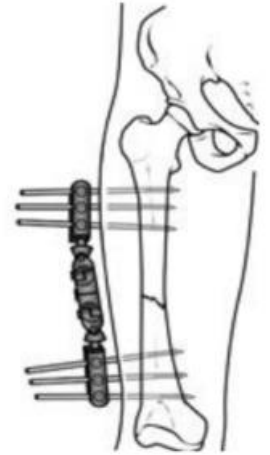- Use the following values:

$$D = 3 \times 10^{-9} \dots 10^{-10} \text{ m}^2/\text{s}$$
$$V_{\max} \approx 10^{-18} \dots 10^{-17} \text{ mole/cell.s}$$
$$\rho_{\text{cell}} = 10^6 \dots 10^8 \text{ cells/ml}$$
$$c_0 = 21 \ \dots 10\%$$
$$c_{\min} = 5 \ \dots 1\%$$

A Recap on Solubility

- A big difference between the bone healing problem and the cellular construct is the solubility of oxygen.

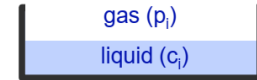- The solubility should be taken into account (slide 59)

Oxygen solubility

- Partial pressure p_i for molar fraction x_i in gas mixture:

$$p_i = x_i p$$

- Henry's law: steady state concentration c_i of dissolved gas (for ideally dilute solution):

$$c_i = \sigma_i p_i$$

gas (p_i)

liquid (c_i)

- Solubility σ_i of respiratory gases in blood plasma:

gas	σ (Molar/mmHg)
O_2	1.4×10^{-6}
CO_2	3.3×10^{-5}
CO	1.2×10^{-6}
N_2	7×10^{-7}
He	4.8×10^{-7}

(Molar = M = mole/l)

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Another Example

- Krogh cylinder model of tissue oxygenation (slide 22)

- Radial diffusion in cylindrical coordinate

Krogh cylinder model of tissue oxygenation

$$\frac{D_{O_2}}{r}\frac{d}{dr}\left(r\frac{dC_{O_2}}{dr}\right) = R_{O_2}$$

$$r = R_c \qquad C_{O_2} = C_{R_c} \qquad (C_{R_c}\text{ dissolved oxygen in blood plasma})$$

$$\text{At } r = R_0, \qquad -D_{O_2}\frac{dC_{O_2}}{dr} = 0 \quad \text{(symmetry)}$$

with R_{O2} = oxygen consumption rate (in mole x m^{-3} x s^{-1})

(Truskey et al, Transport Phenomena in Biological Systems, 2004)
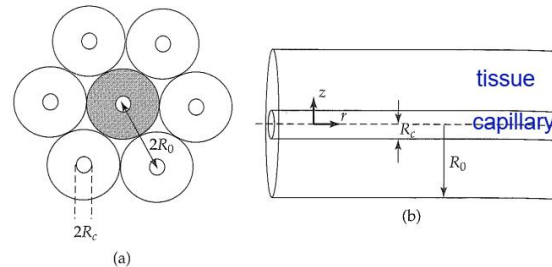
August Krogh
(1874-1949)
Nobel prize in medicine (1920)

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Krogh Cylinder Model

- The problem is solving the following equation

$$\frac{D_{O_2}}{r}\frac{d}{dr}\left(r\frac{dC_{O_2}}{dr}\right) = R_{O_2}$$

- Simplifying the notations:

$$c = C_{O_2}, D = D_{O_2}, R = R_{O_2}$$

$$\frac{D}{r}\frac{d}{dr}\left(r\frac{dc}{dr}\right) = R$$
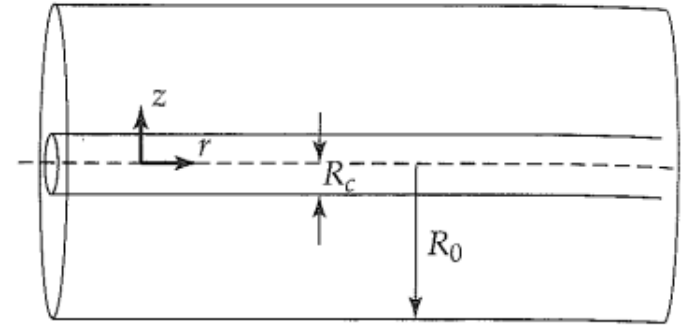
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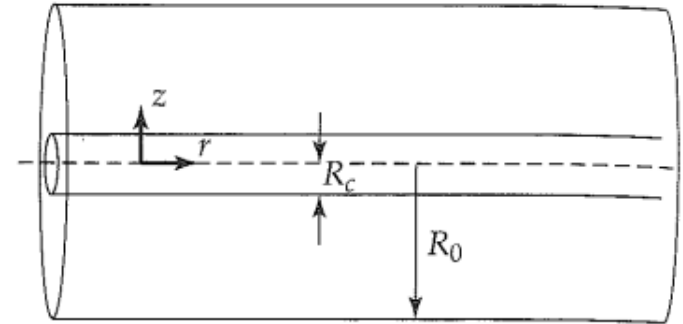
Krogh Cylinder Model

- The procedure is exactly the same as before

$$\int \frac{d}{dr}\left(r\frac{dc}{dr}\right)dr = \int \frac{Rr}{D}\,dr$$

$$\rightarrow r\frac{dc}{dr} = \frac{Rr^2}{2D} + C_1$$

$$r = R_0, \frac{dc}{dr} = 0$$

$$0 = \frac{RR_0^2}{2D} + C_1 \rightarrow C_1 = \frac{-RR_0^2}{2D}$$

Krogh Cylinder Model

- Let's continue to integrate

$$\int \frac{dc}{dr}dr = \int \frac{Rr}{2D}dr + \int \frac{C_1}{r}dr$$

$$\rightarrow c(r) = \frac{Rr^2}{4D} + C_1\ln(r) + C_2$$

$$r = R_c, c = C_{R_c}$$

$$C_{R_c} = \frac{RR_c^2}{4D} - \frac{RR_0^2}{2D}\ln R_c + C_2$$

$$\rightarrow C_2 = \frac{R}{4D}(2R_0^2\ln R_c - R_c^2) + C_{R_c}$$
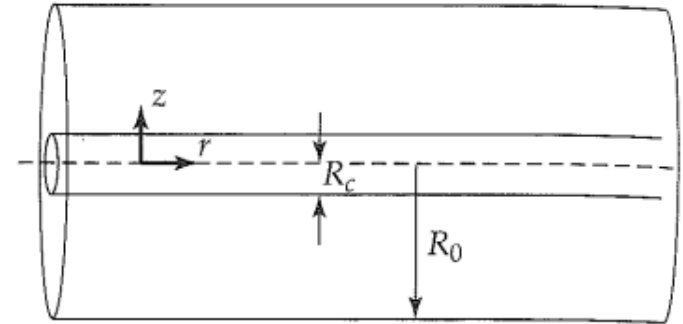
Krogh Cylinder Model

- And now, assembling everything together yields

$$C = \frac{Rr^2}{4D} - \frac{RR_0^2}{2D}\ln(r) + \frac{R}{4D}\left(2R_0^2\ln R_c - R_c^2\right) + C_{R_c}$$
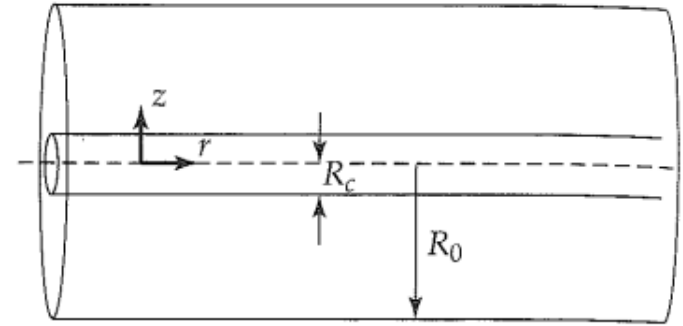
Handling the Complexity with Computers

- Solving problems with symbolic computing

- MATLAB, Maple, and Python are the common options

- Python is becoming dominant computing language

- Jupyter is a great tool to facilitate working with Python

Introduction to Python and Jupyter

- Learning Python is super easy

- Go through the provided materials

- Getting started

  - Installing Jupyter locally

  - Running the examples on free online services

Running the Examples Locally

- Go to https://github.com/mbarzegary/mass-transport-tissue-engineering-spring2021

- Download the code by clicking "Code" and then "Download ZIP"

- Open the downloaded code and follow the installation guide (PDF file)

- View the notebooks 0 to 5
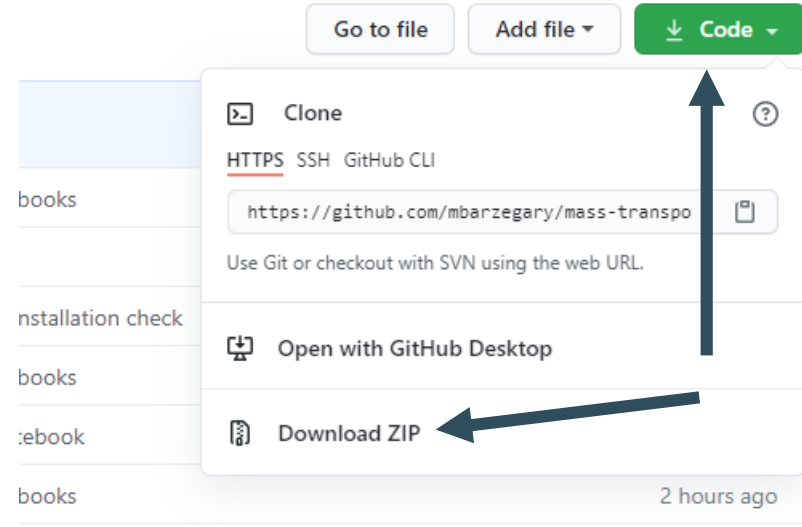
Running the Examples Online

- Go to https://github.com/mbarzegary/mass-transport-tissue-engineering-spring2021

- Click on the "launch binder" badge

- Wait until the server starts, and then, click
  on the notebooks 0 to 5 to view them

README.md

Mass Transport in Tissue

🟠 launch | binder ⬅

This repository contains the teaching materials for
spring 2021.

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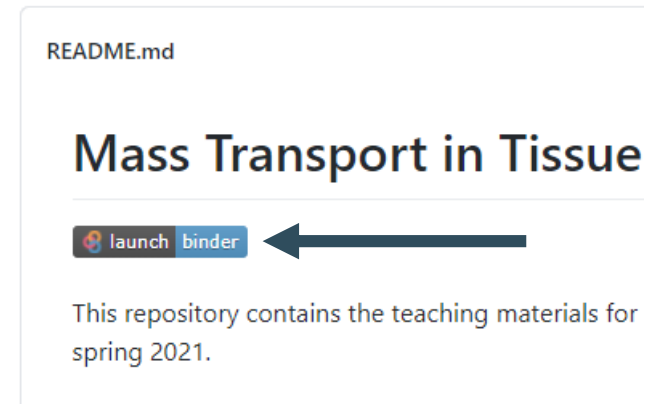
Solving Transient Problems

- How to solve more complex models?

- Real application models usually cannot be solved analytically (symbolically)

- A simple example of a transient case:

$$\frac{\partial c}{\partial t} = \nabla.(D\nabla c) \rightarrow \frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2}\right)$$
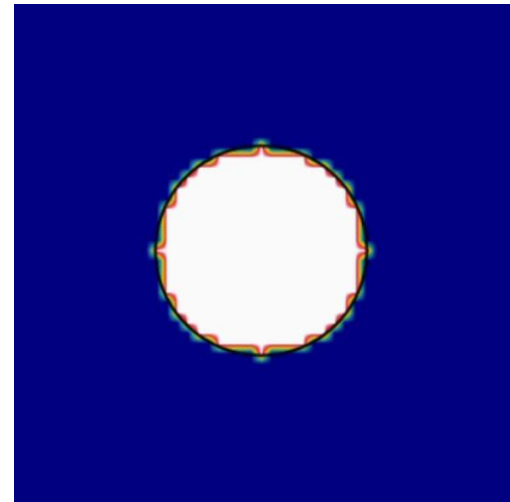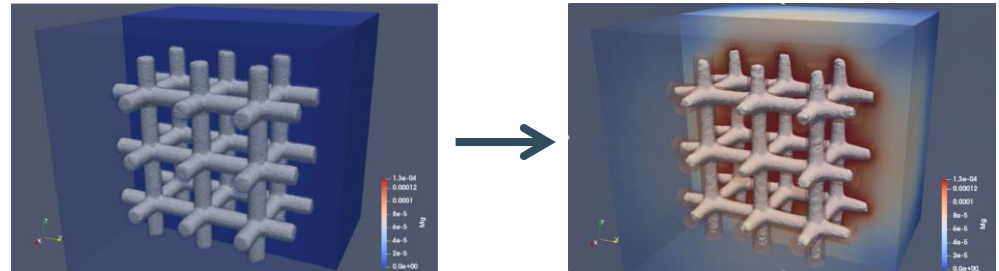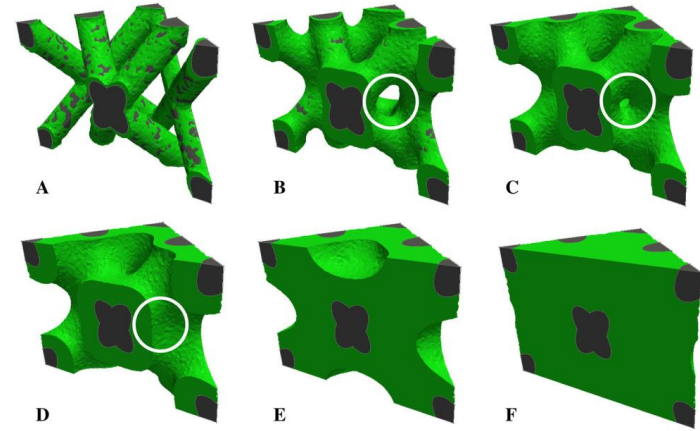
Numerical Computing

- This is where numerical computing comes into play

- Solving the equations numerically on a mesh

- Widely used in a broad range of engineering fields
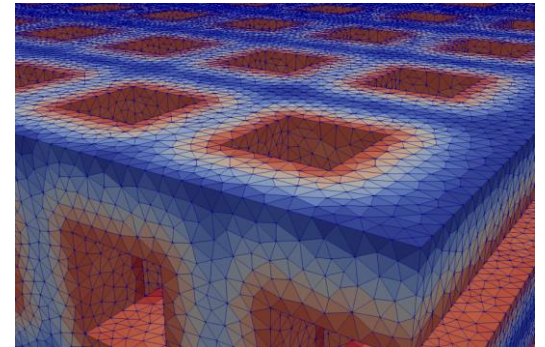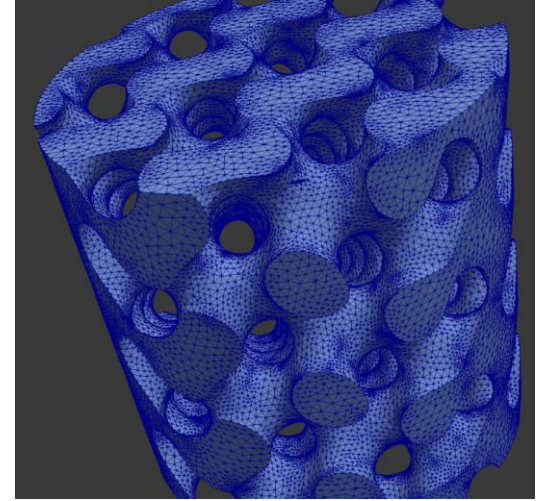
Examples in Tissue Engineering

- Tissue remodeling

- Oxygenation

- Scaffold degradation

- Cell proliferation / tissue growth

- Cell viability

- …

Example: Cell Viability for Pancreatic Islets

- Islet transplantation to treat type 1 diabetes

- Will the implanted islets survive?

- The mathematical model consists of a
  (nonlinear) reaction-diffusion-advection equation

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

$$R_{O_2} = R_{\max,O_2} \cdot \varphi \, \frac{c_{gluc}}{c_{gluc} + C_{MM,gluc}} \cdot \frac{c_{O_2}}{c_{O_2} + C_{MM,O_2}} \cdot \delta(c_{O_2} > C_{cr})$$

Well

Islet

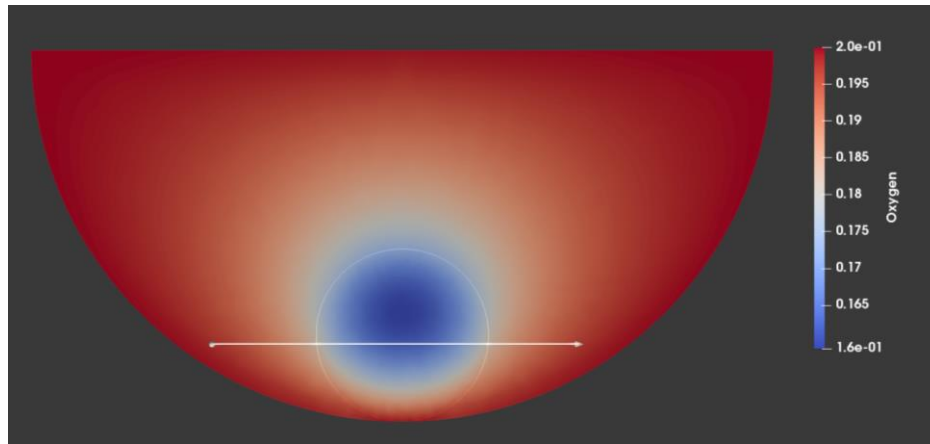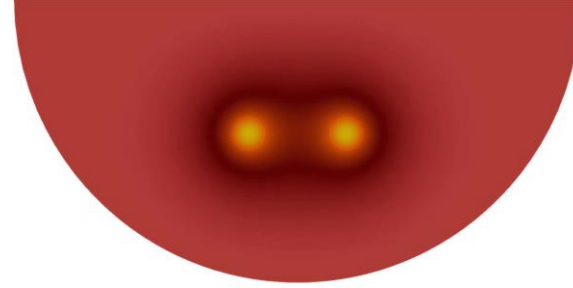# Example: Cell Viability for Pancreatic Islets

- One islet
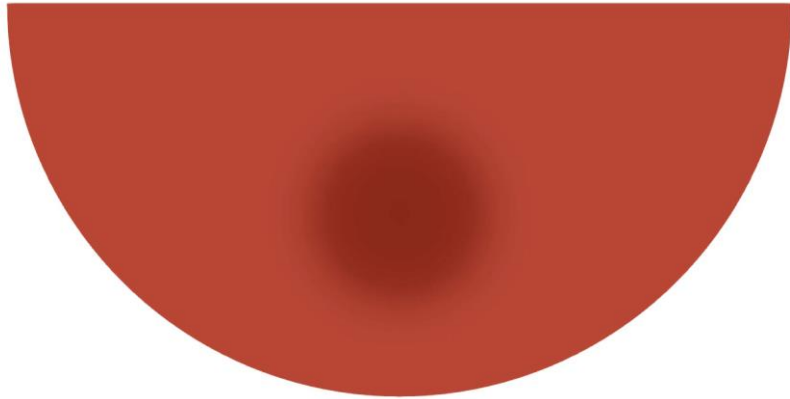
- Two islets
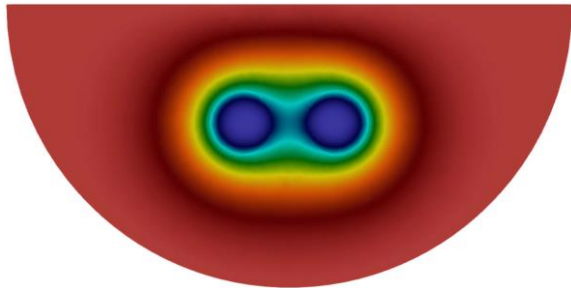
Example: Cell Viability for Pancreatic Islets

- Checking viability (hypoxia)

Oxygen concentration over a line

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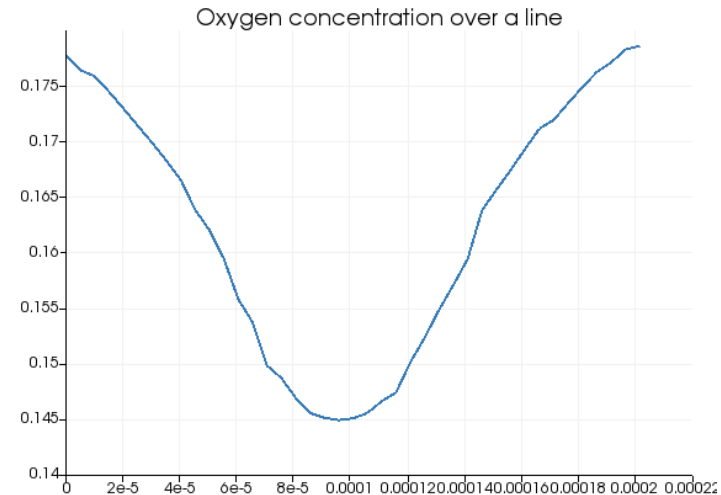
Example: Cell Viability for Pancreatic Islets
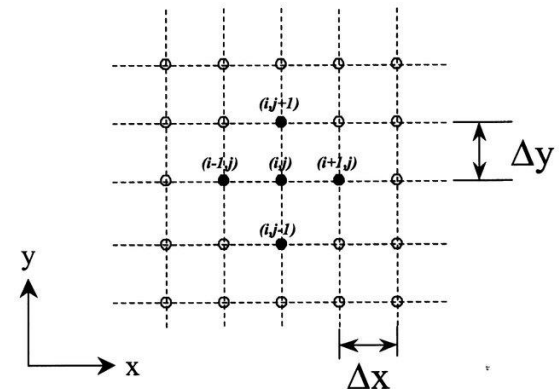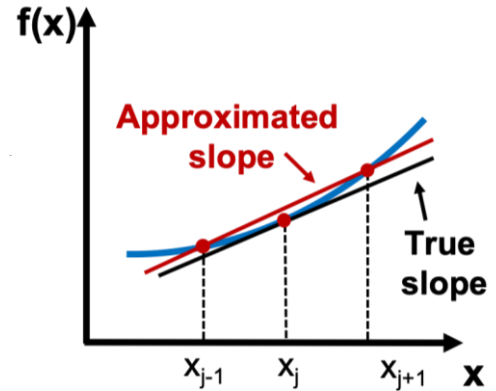
- Changing the size and distance of islets
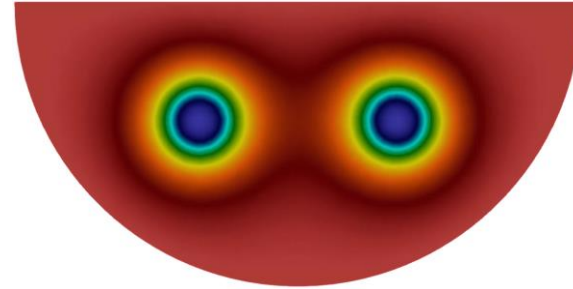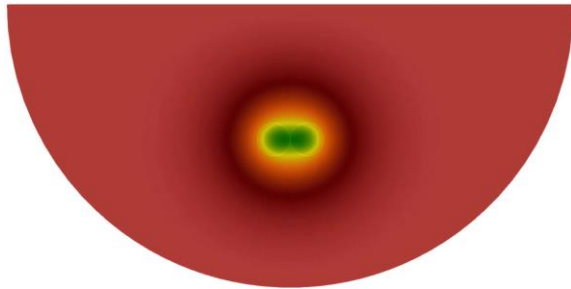
So, How It Works?

- The core idea is to approximate the derivation terms on a discrete space and time

$$\frac{\partial U}{\partial t} = D\left(\frac{\partial^2 U}{\partial x^2} + \frac{\partial^2 U}{\partial y^2}\right)$$
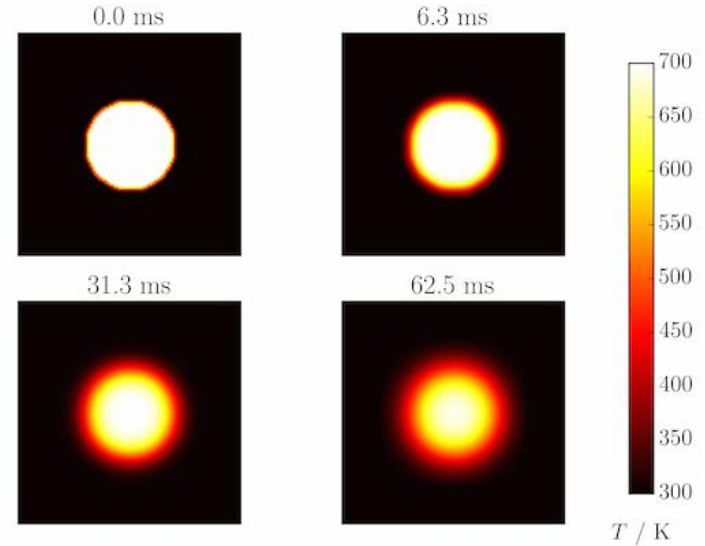
$$\frac{u_{i,j}^{(n+1)} - u_{i,j}^{(n)}}{\Delta t} = D\left[\frac{u_{i+1,j}^{(n)} - 2u_{i,j}^{(n)} + u_{i-1,j}^{(n)}}{\Delta x^2} + \frac{u_{i,j+1}^{(n)} - 2u_{i,j}^{(n)} + u_{i,j-1}^{(n)}}{\Delta y^2}\right]$$

$$u_{i,j}^{(n+1)} = u_{i,j}^{(n)} + D\Delta t\left[\frac{u_{i+1,j}^{(n)} - 2u_{i,j}^{(n)} + u_{i-1,j}^{(n)}}{\Delta x^2} + \frac{u_{i,j+1}^{(n)} - 2u_{i,j}^{(n)} + u_{i,j-1}^{(n)}}{\Delta y^2}\right]$$

A Simple Implementation

- The discretized form can be simply implemented in Python

- Check out the full implementation in the Jupyter notebooks

References

- GA Truskey, F Yuan, DF Katz, Transport Phenomena in Biological Systems, Pearson Education, 2004

- Peter Buchwald, FEM-based oxygen consumption and cell viability models for avascular pancreatic islets, Theoretical Biology and Medical Modelling, 6, 2009

- Christian Hill, Learning Scientific Programming with Python, Cambridge University Press, 2020

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