

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

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Mojtaba Barzegari <[mojtaba.barzegari@kuleuven.be](mailto:mojtaba.barzegari@kuleuven.be)>

Hans Van Oosterwyck <[hans.vanoosterwyck@kuleuven.be](mailto:hans.vanoosterwyck@kuleuven.be)>



# 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

# 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 temperature 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

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


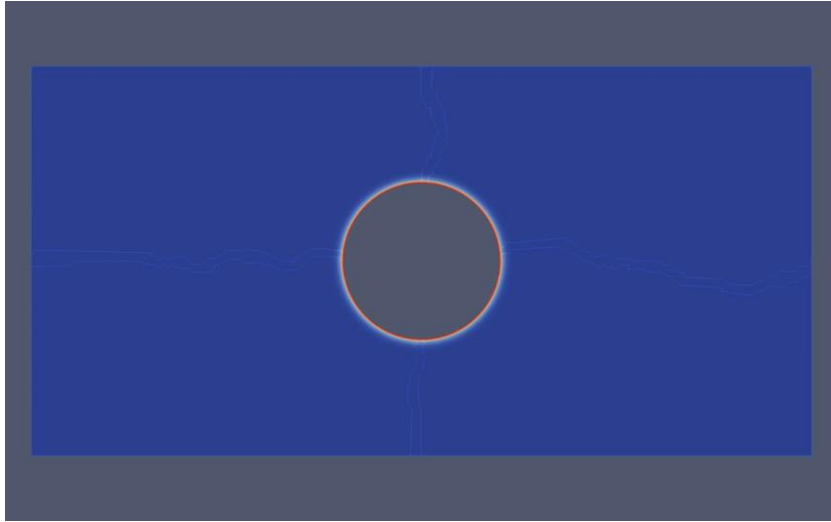
$$\nabla f = \left( \frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z} \right) f = \frac{\partial f}{\partial x} \mathbf{i} + \frac{\partial f}{\partial y} \mathbf{j} + \frac{\partial f}{\partial z} \mathbf{k}$$

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

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

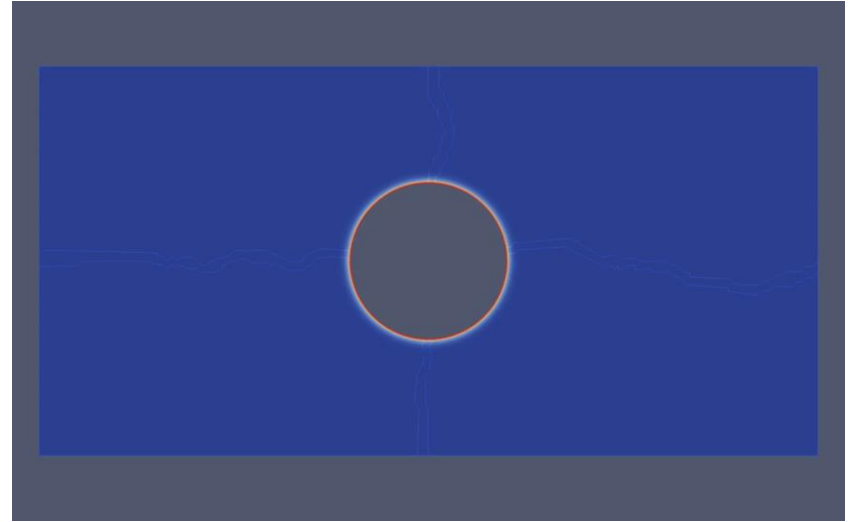
# Convection Effect

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



Diffusion

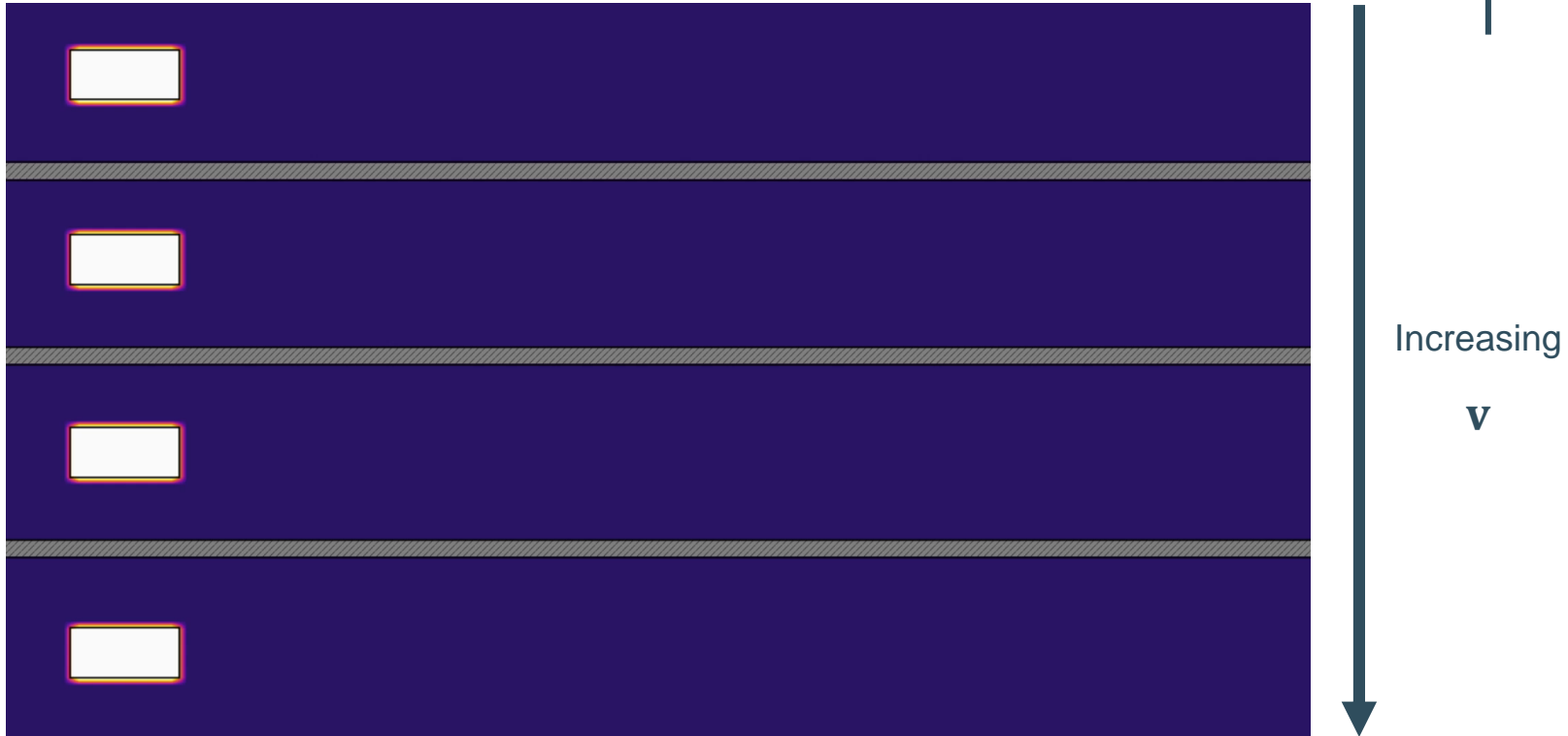
$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + \nabla \cdot (\mathbf{v}c)$$



Diffusion-Advection

# Convection Effect - Velocity

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



# 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)



# 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:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - V_{\max, \text{cell}} \underbrace{\rho_{\text{cell}}}_{\text{cell density (\#cells/m}^3\text{)}}$$

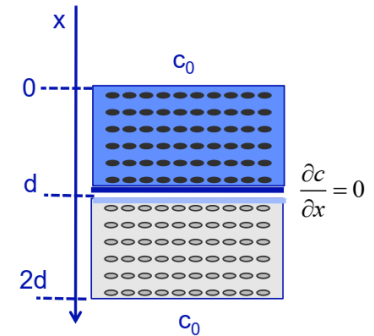
- Steady state solution:

- At  $x=0$ :  $c(x=0) = c_0$
- At  $x=d$ :  $\Gamma=0$  (impermeable or symmetric)

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

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

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



# 1D Diffusion in Cellular Construct

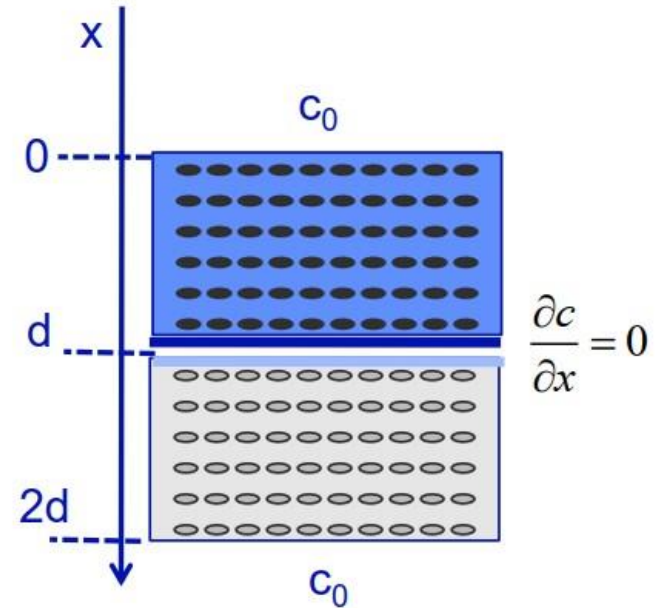
- The problem is to solve the following equation

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

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

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

- Maximum depth of oxygen penetration?



# 1D Diffusion in Cellular Construct

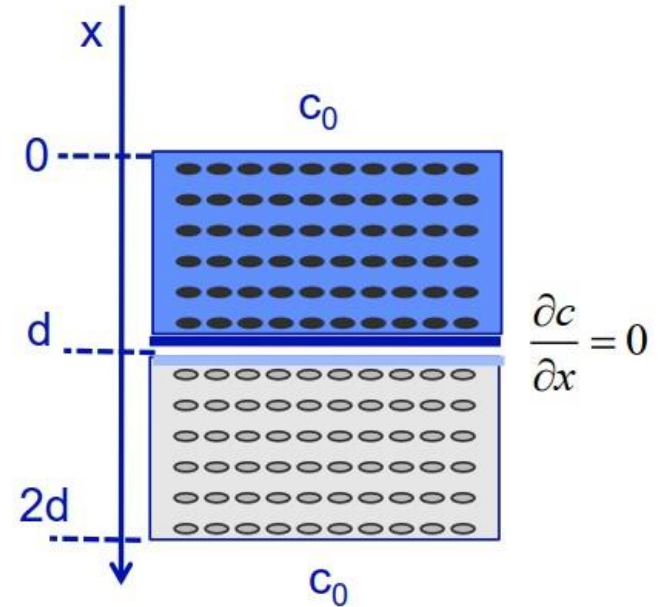
- It is a 1-D problem, so let's say  $c = c(x)$

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

- Integrating both sides of the equation yields

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

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

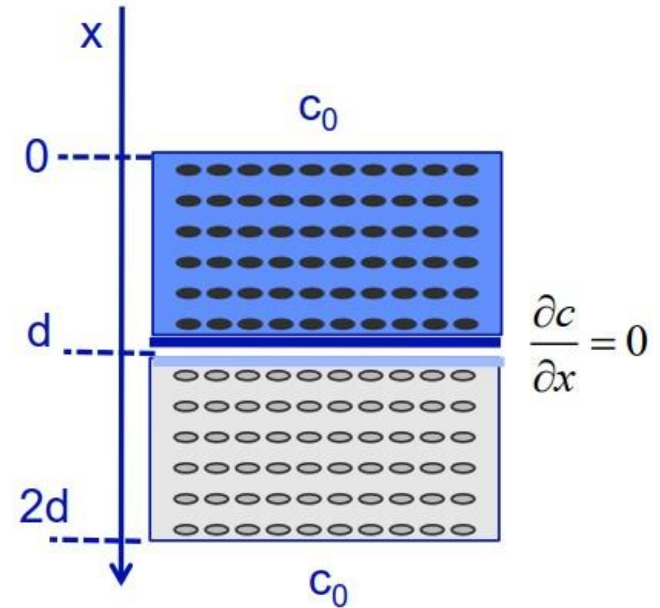


# 1D Diffusion in Cellular Construct

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

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

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



# 1D Diffusion in Cellular Construct

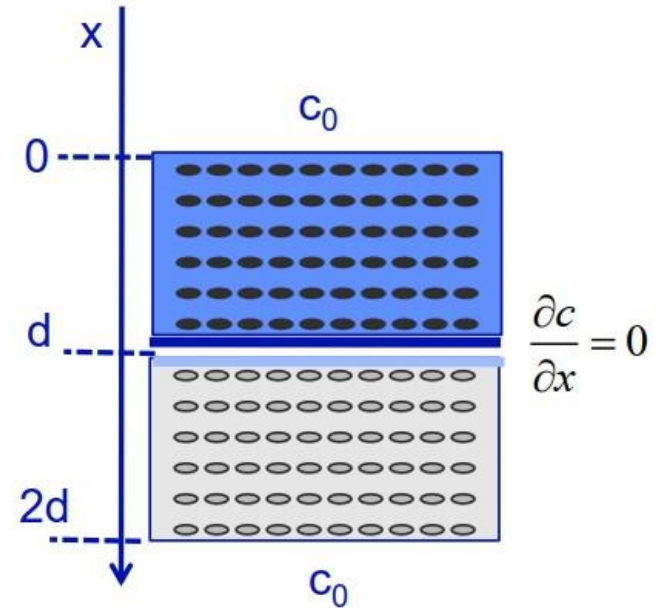
- Still have a derivative term, so we eliminate it

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

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

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

$$C_2 = c_0$$



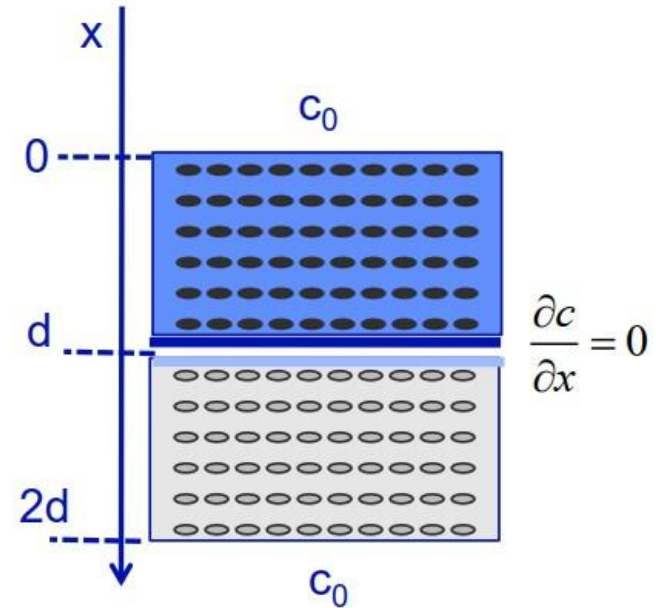
# 1D Diffusion in Cellular Construct

- 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

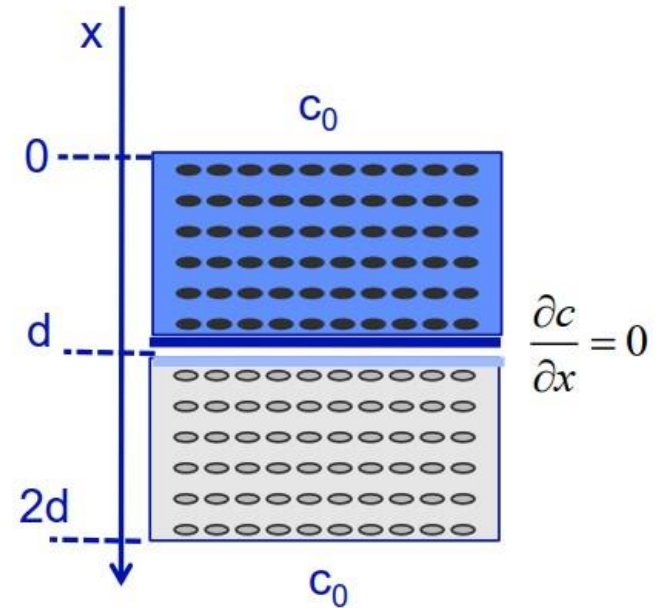
- We know  $c(x) = 0$  at  $x = d_{\max}$ , so

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

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

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

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



# 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:

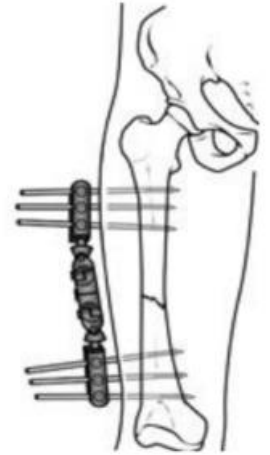
$$D = 3 \times 10^{-9} \dots 10^{-10} \text{ m}^2/\text{s}$$

$$V_{\max} \approx 10^{-18} \dots 10^{-17} \text{ mole/cell.s}$$

$$\rho_{\text{cell}} = 10^6 \dots 10^8 \text{ cells/ml}$$

$$c_0 = 21 \dots 10\%$$

$$c_{\min} = 5 \dots 1\%$$





# 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)

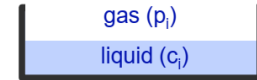
## Oxygen solubility

- 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):

$$c_i = \sigma_i p_i$$



- Solubility  $\sigma_i$  of respiratory gases in blood plasma:

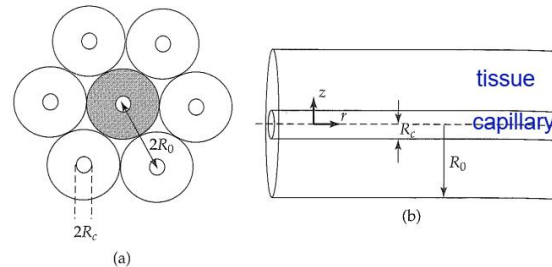
gas	$\sigma$ (Molar/mmHg)
$O_2$	$1.4 \times 10^{-6}$
$CO_2$	$3.3 \times 10^{-5}$
CO	$1.2 \times 10^{-6}$
$N_2$	$7 \times 10^{-7}$
He	$4.8 \times 10^{-7}$

(Molar = M = mole/l)

# Another Example

- Krogh cylinder model of tissue oxygenation (slide 22)
- Radial diffusion in cylindrical coordinate

## Krogh cylinder model of tissue oxygenation



August Krogh  
(1874-1949)

Nobel prize in medicine (1920)

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

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

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

with  $R_{O_2}$  = oxygen consumption rate (in mole  $\times$  m $^{-3}$   $\times$  s $^{-1}$ )

(Truskey et al, Transport Phenomena in Biological Systems, 2004)

Mass transport in tissue engineering

# Krogh Cylinder Model

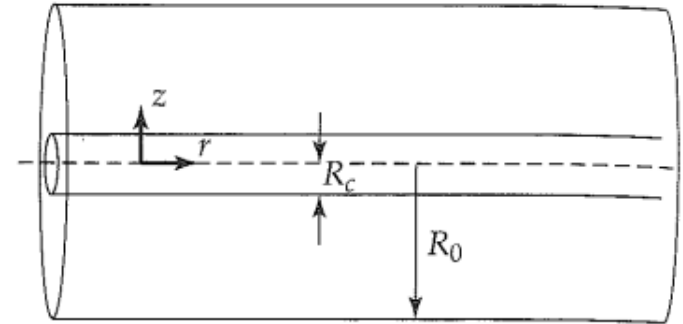
- The problem is solving the following equation

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

- Simplifying the notations:

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

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



# Krogh Cylinder Model

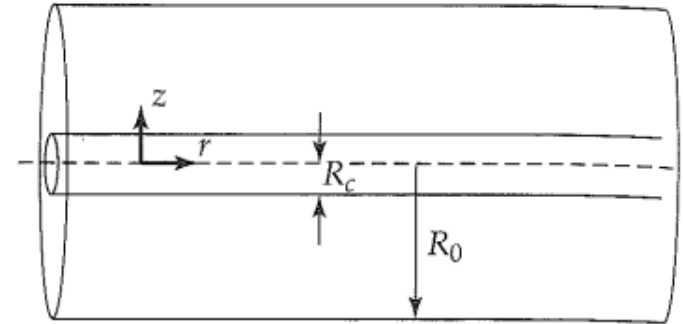
- The procedure is exactly the same as before

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

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

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

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



# Krogh Cylinder Model

- Let's continue to integrate

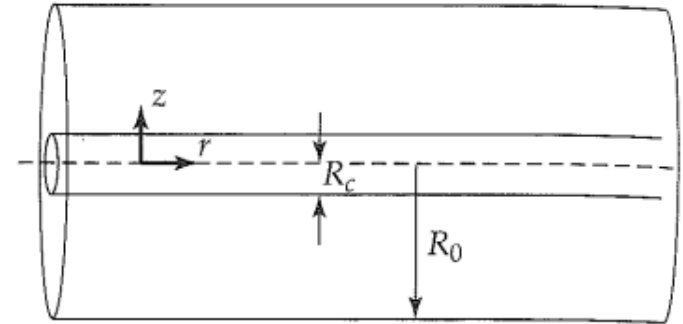
$$\int \frac{dc}{dr} dr = \int \frac{Rr}{2D} dr + \int \frac{C_1}{r} dr$$

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

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

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

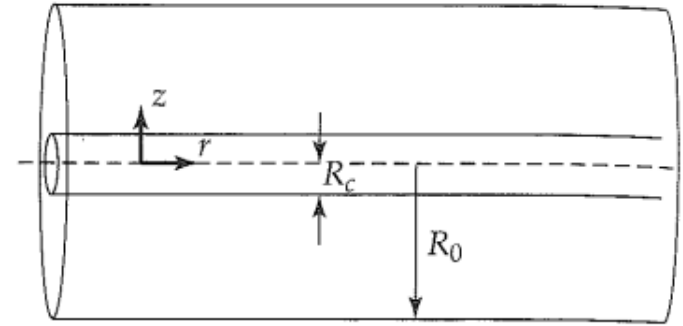
$$\rightarrow C_2 = \frac{R}{4D} (2R_0^2 \ln R_c - R_c^2) + C_{R_c}$$



# Krogh Cylinder Model

- And now, assembling everything together yields

$$C = \frac{Rr^2}{4D} - \frac{RR_0^2}{2D} \ln(r) + \frac{R}{4D} (2R_0^2 \ln R_c - R_c^2) + C_{R_c}$$



# 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

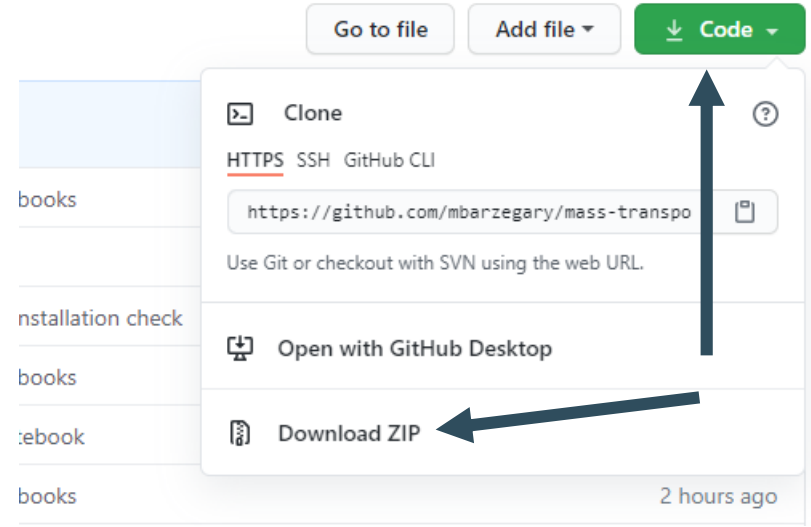
# Introduction to Python and Jupyter

- Learning Python is super easy
- Go through the provided materials
- Getting started
  - Installing Jupyter locally
  - Running the examples on free online services



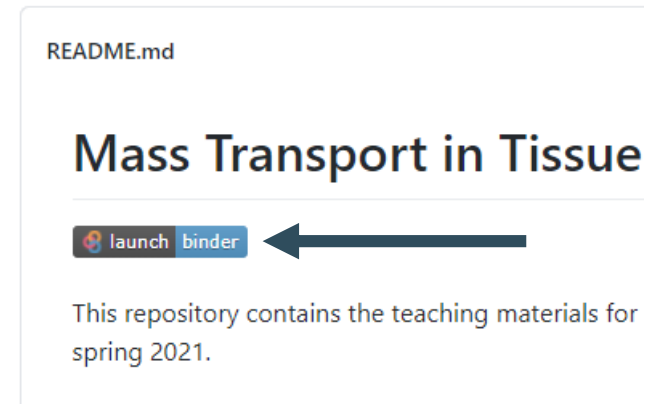
# Running the Examples Locally

- Go to <https://github.com/mbarzegary/mass-transport-tissue-engineering-fall2021>
- 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

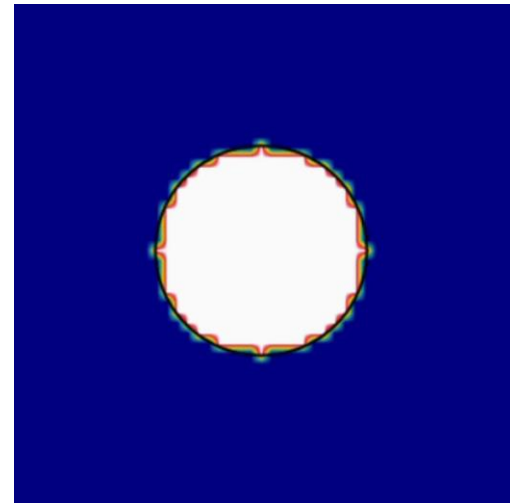
- Go to <https://github.com/mbarzegary/mass-transport-tissue-engineering-fall2021>
- Click on the “launch binder” badge
- Wait until the server starts, and then, click on the notebooks 0 to 5 to view them



# Solving Transient Problems

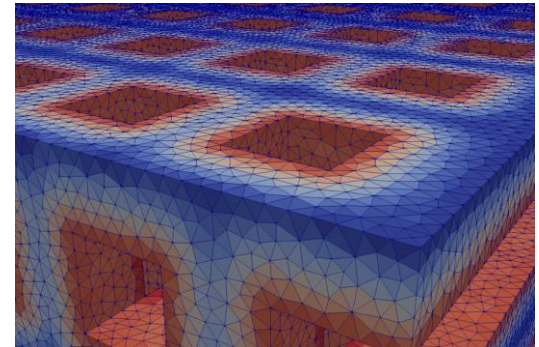
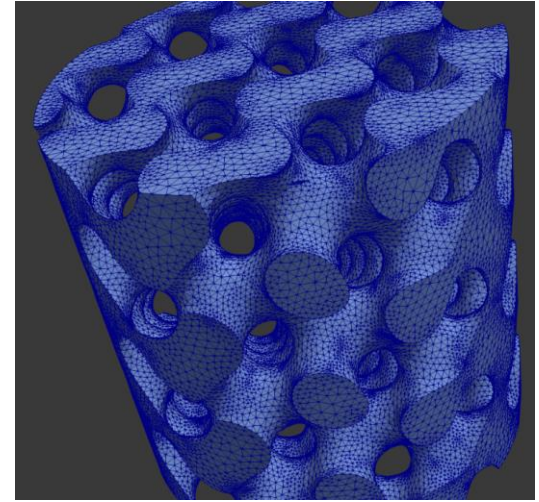
- How to solve more complex models?
- Real application models usually cannot be solved analytically (symbolically)
- A simple example of a transient case:

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



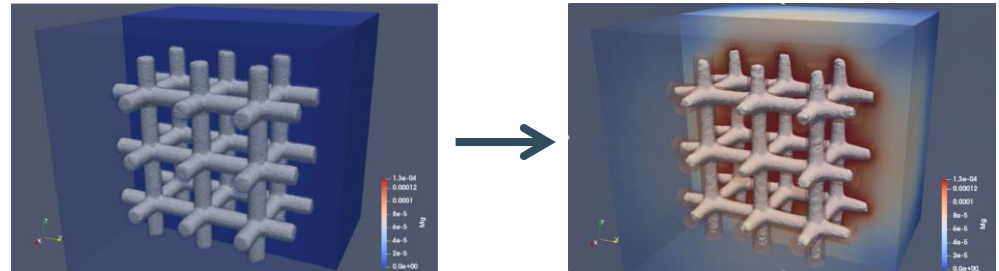
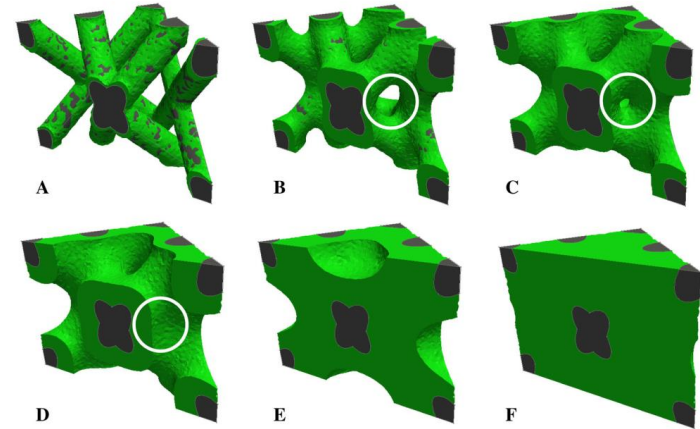
# Numerical Computing

- 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

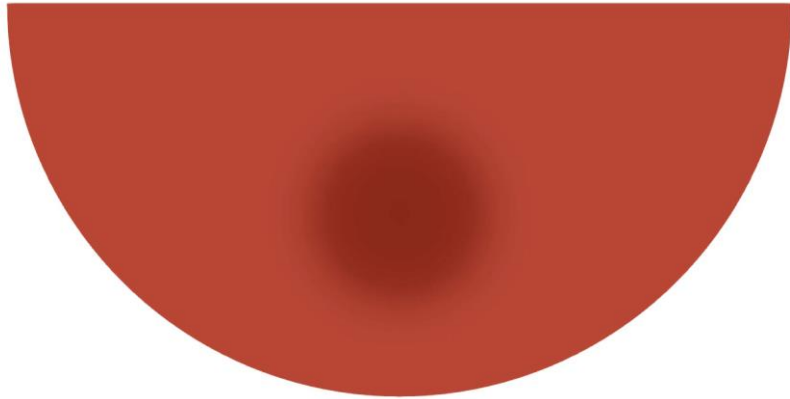
$$\frac{\partial c}{\partial t} + \nabla \cdot (-D \nabla c) = R - \mathbf{u} \cdot \nabla c$$

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



# Example: Cell Viability for Pancreatic Islets

- One islet

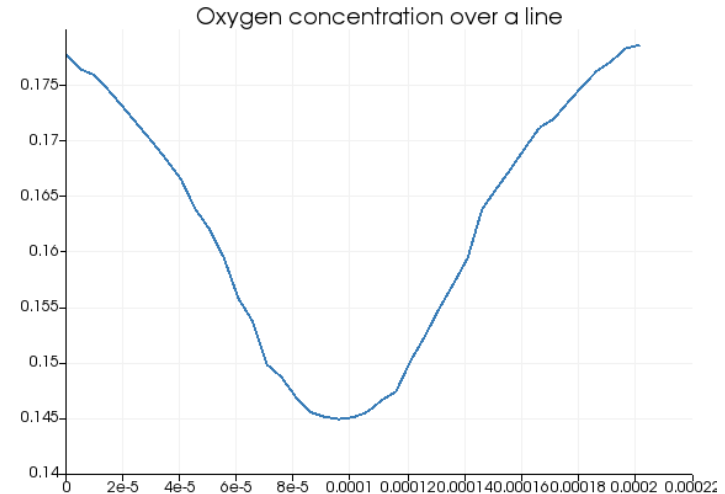
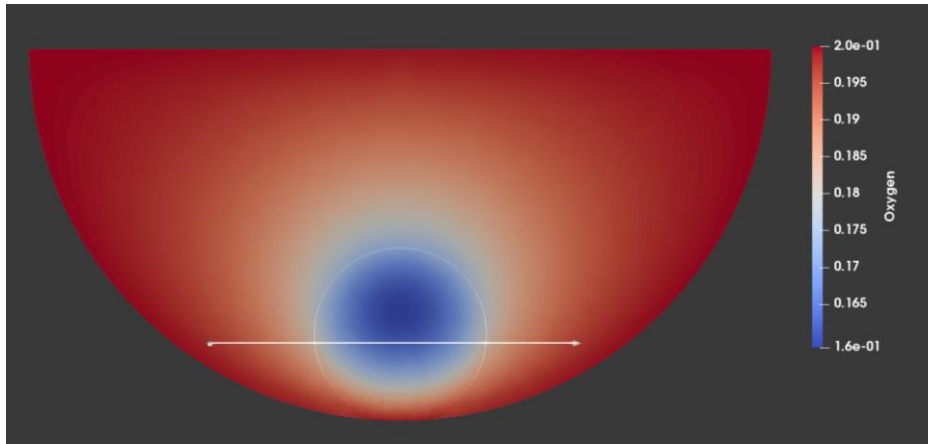


- Two islets



# Example: Cell Viability for Pancreatic Islets

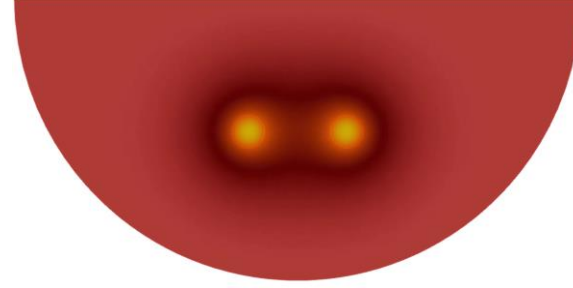
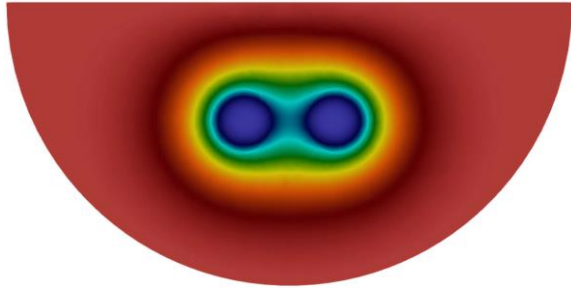
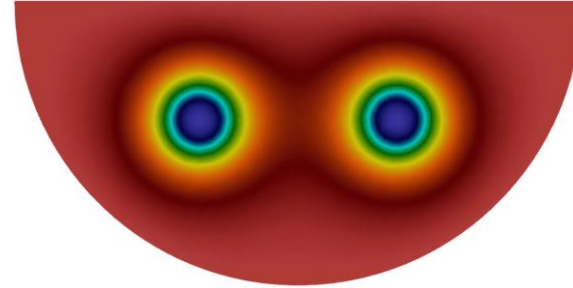
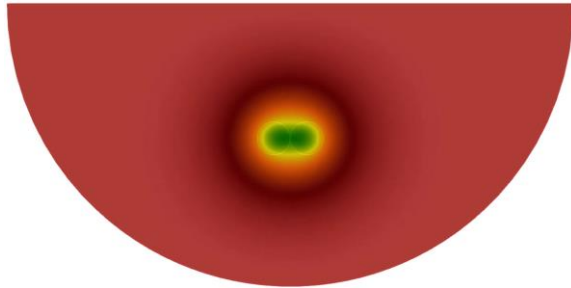
- Checking viability (hypoxia)





# Example: Cell Viability for Pancreatic Islets

- Changing the size and distance of islets



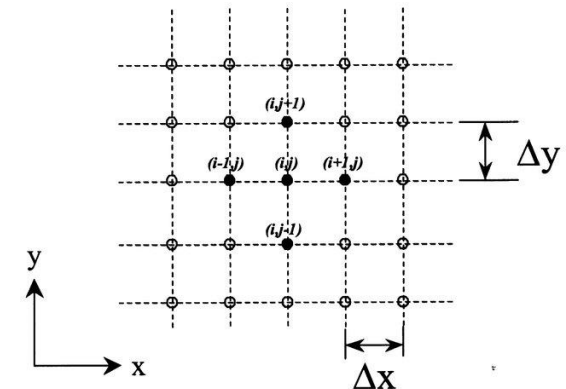
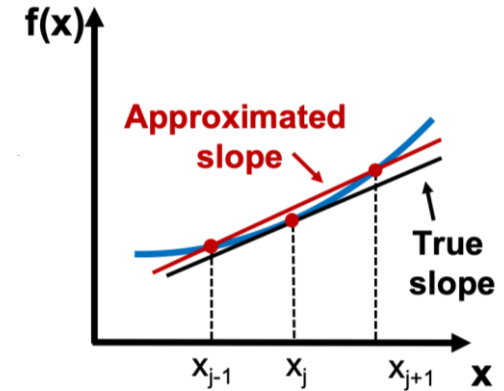
# So, How It Works?

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

$$\frac{\partial U}{\partial t} = D \left( \frac{\partial^2 U}{\partial x^2} + \frac{\partial^2 U}{\partial y^2} \right)$$

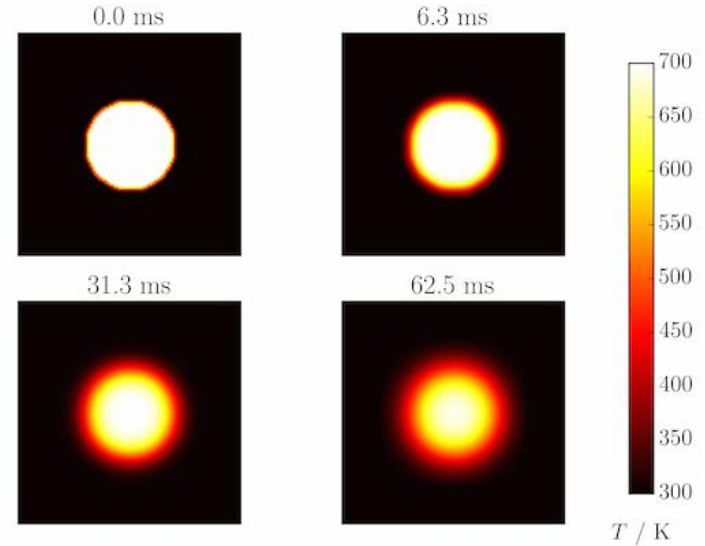
$$\frac{u_{i,j}^{(n+1)} - u_{i,j}^{(n)}}{\Delta t} = D \left[ \frac{u_{i+1,j}^{(n)} - 2u_{i,j}^{(n)} + u_{i-1,j}^{(n)}}{\Delta x^2} + \frac{u_{i,j+1}^{(n)} - 2u_{i,j}^{(n)} + u_{i,j-1}^{(n)}}{\Delta y^2} \right]$$

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



# 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