



# Mathematical Modeling and Simulations of Organ-on-Chip (OOC)

Internship Presentation

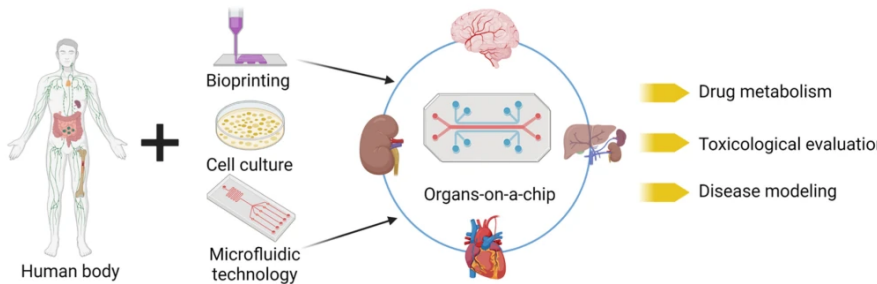
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# Organ-on-Chip: Context and Motivation

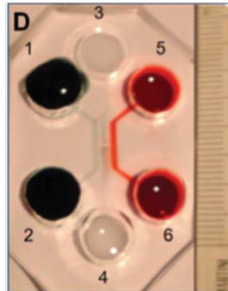
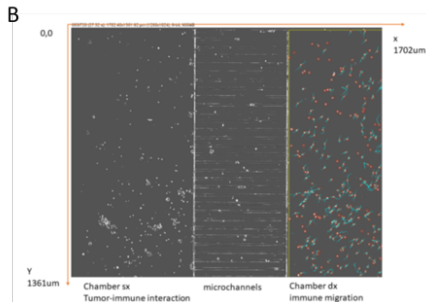
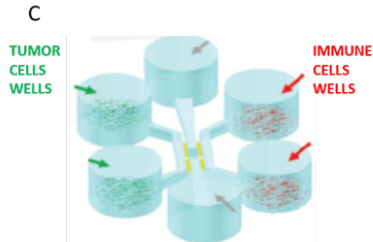
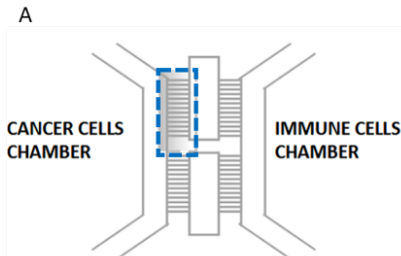
- **What is OOC?** A 3D microfluidic platform that mimics human tissue microenvironments to simulate cellular dynamics and interactions.



- **Motivation:**

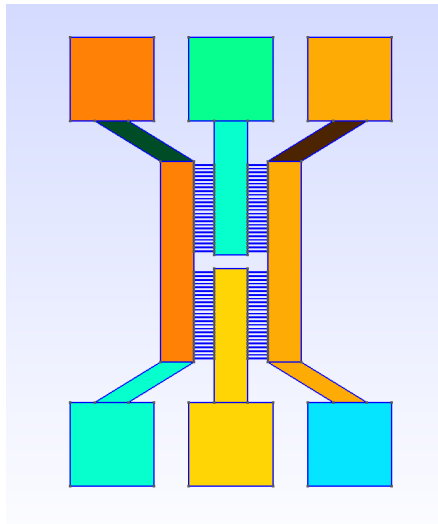
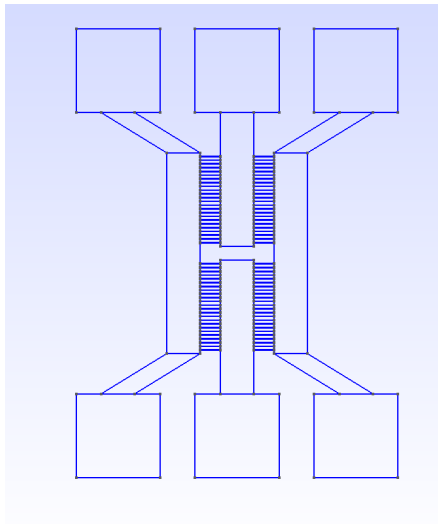
- Understand the mechanisms governing cell dynamics in microfluidic systems.
- Investigate interactions between immune and tumor cells.

# Illustration of the Organ-on-Chip Device and Geometries



Typical

# Illustration of the Organ-on-Chip device and geometries



Typical Organ-on-Chip geometry: microchannels and chambers(made with GMSH tool)

# Goal and Applications

- **Goal:**

- Develop numerical tools to simulate cellular dynamics (e.g., chemotaxis) in Organ-on-Chip systems.
- Build a mathematical model based on chemotaxis, adapted to complex OOC geometries (2D chambers and 1D channels);
- Use Hybrid Discontinuous Galerkin (HDG) method or feelpp toolboxes for solving the models, focusing on stability and accuracy;
- Test and validate the method on simple analytical cases and realistic OOC configurations;
- Explore improvements such as adaptive meshes and integration of experimental data for model calibration;

- **Applications:**

- Test biological hypotheses.
- Optimize experimental conditions.
- Predict cellular behaviors.

# Why Use the HDG Method?

- **Context:** Discontinuous Galerkin (DG) methods are powerful for solving nonlinear hyperbolic systems, offering:
  - High-order accuracy for convection and diffusion.
  - Flexibility on arbitrary meshes.
  - Simple boundary condition handling.
  - Good parallelization and adaptivity.
- **Limitation:** DG methods are often computationally expensive due to many globally coupled unknowns.
- **HDG Solution:**
  - Reduces global degrees of freedom compared to DG.
  - Provides optimal approximation for both primal and flux variables.
  - Enables local postprocessing for improved accuracy and conservation.

# HDG Method: Overview and Stabilization

- **Hybridizable Discontinuous Galerkin (HDG):**

- Solves PDEs on polyhedral meshes, reduces global unknowns to numerical trace  $\hat{p}_h \in M_h$ .
- Local spaces:  $\mathbf{V}(K) = [P_k(K)]^n$ ,  $W(K) = P_k(K)$ ,  $M_h = P_k(\mathcal{E}_h)$ .

- **Formulation:**

$$\begin{aligned}(\Lambda \mathbf{u}_h, \mathbf{v})_{\mathcal{T}_h} - (p_h, \nabla \cdot \mathbf{v})_{\mathcal{T}_h} + \langle \hat{p}_h, \mathbf{v} \cdot \mathbf{n} \rangle_{\partial \mathcal{T}_h} &= 0, \\ \langle \hat{\mathbf{u}}_h \cdot \mathbf{n}, \mu \rangle_{\partial \mathcal{T}_h \setminus \Gamma} &= 0, \\ \hat{\mathbf{u}}_h &= \mathbf{u}_h + \tau(p_h - \hat{p}_h)\mathbf{n}.\end{aligned}$$

- **Stabilization:**

- Stabilization parameter  $\tau$  affects convergence:
- Table of convergence rates:

$\tau$	$\mathbf{u}_h$	$p_h$	$\bar{p}_h$	$k$
$O(h)$	$k+1$	$k$	$k+2$	$\geq 1$
$O(1)$	$k+1$	$k+1$	$k+2$	$\geq 1$
$O(1/h)$	$k$	$k+1$	$k+1$	$\geq 1$

# HDG Methods for Convection-Diffusion Problems

- **Problem Setup:**

- Second-order elliptic problem on polyhedral domain  $\Omega \subset \mathbb{R}^n$ :

$$\begin{cases} \Lambda \mathbf{u} + \nabla p - \Lambda \alpha p = \mathbf{0}, & \text{in } \Omega, \\ \nabla \cdot \mathbf{u} + dp = f, & \text{in } \Omega, \end{cases}$$

- Boundary conditions:  $p = h_D$  on  $\Gamma_D$ ,  $\mathbf{u} \cdot \mathbf{n} = h_N$  on  $\Gamma_N$ .

- **Notations:**

- Mesh  $\mathcal{T}_h$ , faces  $\mathcal{E}_h = \mathcal{E}_h^\circ \cup \mathcal{E}_h^\partial$ .
- Spaces:  $\mathbf{V}_h$ ,  $W_h$  for flux  $\mathbf{u}_h$  and scalar  $p_h$ ;  $M_h$  for numerical trace  $\hat{p}_h$ .

- **Weak Formulation on Elements:**

$$\begin{aligned} (\Lambda \mathbf{u}_h, \mathbf{v})_K - (p_h, \nabla \cdot \mathbf{v})_K - (\Lambda \alpha p_h, \mathbf{v})_K + \langle \hat{p}_h, \mathbf{v} \cdot \mathbf{n} \rangle_{\partial K} &= 0, \\ -(\mathbf{u}_h, \nabla w)_K + \langle \hat{\mathbf{u}}_h \cdot \mathbf{n} w \rangle_{\partial K} + (dp_h, w)_K &= (f, w)_K. \end{aligned}$$

- **Foundation for HDG:** Local solvers on each element, global coupling via  $\hat{p}_h$ .



# HDG Methods for Convection-Diffusion Problems

## Matrix Formulation and Static Condensation

- **Goal:** Reduce the HDG system to a linear system for the numerical trace  $\hat{p}_h$  (static condensation).
- **System with Numerical Flux:**

$$\begin{aligned}(\Lambda \mathbf{u}_h, \mathbf{v})_{\mathcal{T}_h} - (p_h, \nabla \cdot \mathbf{v})_{\mathcal{T}_h} - (\Lambda \alpha p_h, \mathbf{v})_{\mathcal{T}_h} + \langle \hat{p}_h, \mathbf{v} \cdot \mathbf{n} \rangle_{\partial \mathcal{T}_h} &= 0, \\ (\nabla \cdot \mathbf{u}_h, w)_{\mathcal{T}_h} + \langle \tau p_h, w \rangle_{\partial \mathcal{T}_h} + (dp_h, w)_{\mathcal{T}_h} - \langle \tau \hat{p}_h, w \rangle_{\partial \mathcal{T}_h} &= (f, w)_{\mathcal{T}_h}.\end{aligned}$$

- **Static Condensation Process:**
  - Eliminate  $\mathbf{u}_h$  and  $p_h$  locally on each element  $K$ .
  - Solve globally for  $\hat{p}_h$ .
  - Reconstruct  $\mathbf{u}_h$  and  $p_h$  element-wise using local equations.

# HDG: Boundary Conditions, Local and Global solvers

- **Dirichlet Boundary Conditions:**

- On  $\Gamma_D$ :  $\langle \hat{p}_h, \mu \rangle_{\Gamma_D} = \langle h_D, \mu \rangle_{\Gamma_D}$ .
- Compute  $L^2$ -projection of  $h_D$  onto  $M_h|_{\Gamma_D}$  to set  $\hat{p}_h$  values.

- **Neumann Boundary Conditions:**

- On  $\Gamma_N$ : Use numerical flux to contribute to the global system via  $\langle h_N, \mu \rangle_{\Gamma_N}$ .

- **Global System Assembly:**

- Enforce flux continuity across interior faces.
- Assemble global matrix  $\mathbb{M}$  and vector  $\mathbf{F}$  from local  $D^K, D_f^K$ .
- System:  $\mathbb{M}\hat{\mathbf{p}} = \mathbf{F} + \mathbf{G}_N$ .
- Solve for  $\hat{p}_h$ , then recover  $\mathbf{u}_h, p_h$  locally.

# Keller-Segel Model

- **Mathematical Model**

- Variables: Describes chemotaxis: cell density  $u$ , chemoattractant  $\varphi$ .
- Equations:

$$\begin{cases} \partial_t u - \nabla \cdot (\mu \nabla u - \chi u \nabla \varphi) = f_u, \\ \partial_t \varphi - \nabla \cdot (\nu \nabla \varphi) + a \varphi - b u = f_\varphi \end{cases} \quad \begin{cases} \nu \nabla \varphi \cdot n = 0, \\ \mu (\nabla u - \chi u \nabla \varphi) \cdot n = 0 \end{cases} \quad \text{on } \partial\Omega$$

- **Auxiliary Variables:**

$$\begin{cases} j = -\mu \nabla u + \chi u \nabla \varphi \\ \psi = -\nu \nabla \varphi \end{cases} \quad \begin{cases} j \cdot n = 0, \\ \psi \cdot n = 0 \end{cases} \quad \text{on } \partial\Omega$$

- **Expected:**

- Preserve non-negativity of  $u$ ,  $\varphi$ .
- Capture blow-up phenomenon in test cases.
- Mass conservation under zero-flux conditions.

# Keller-Segel Model: HDG Discretization

- Numerical fluxes:

$$\begin{cases} \widehat{j}^K \cdot n^K = j^K \cdot n^K + \gamma_u(u^K - \widehat{u}^K) \\ \widehat{\psi}^K \cdot n^K = \psi^K \cdot n^K + \gamma_\varphi(\varphi^K - \widehat{\varphi}^K) \end{cases}$$

- Stabilization parameters:

$$\boxed{\gamma_u = \frac{\tau_D}{h} + \tau_C}, \quad \tau_C = \max(\psi \cdot n, 0), \quad \tau_D \text{ constant} = 1 \text{ or } 10$$

**Problem:** Find  $U_h = (u_h, \widehat{u}_h, j_h) \in V_h$  and  $\Phi_h = (\varphi_h, \widehat{\varphi}_h, \psi_h) \in S_h$  such that,  $\forall W = (w, \widehat{w}, q) \in V_h$  and  $\Theta = (\tau, \widehat{\tau}, \theta) \in S_h$ , it holds:

$$\begin{aligned} & \left( \frac{\partial u_h}{\partial t}, w \right)_\Omega + (\widehat{j}_h \cdot n, w)_{\mathcal{E}_h} - (j_h, \nabla w)_{\mathcal{T}_h} = (f_u, w)_\Omega, \\ & \left( \frac{\partial \varphi_h}{\partial t}, \tau \right)_\Omega + (\widehat{\psi}_h \cdot n, \tau)_{\mathcal{E}_h} - (\psi_h, \nabla \tau)_{\mathcal{T}_h} + (a \varphi_h, \tau)_\Omega - (b u_h, \tau)_\Omega = (f_\varphi, \tau)_\Omega, \\ & (\beta \psi_h, \theta)_\Omega - (\varphi_h, \nabla \cdot \theta)_{\mathcal{T}_h} + (\widehat{\varphi}_h, \theta \cdot n)_{\mathcal{E}_h} = 0, \\ & (\alpha j_h + \beta \chi u_h \psi_h, q)_\Omega - (u_h, \nabla \cdot q)_{\mathcal{T}_h} + (\widehat{u}_h, q \cdot n)_{\mathcal{E}_h} = 0, \end{aligned}$$

# OOc model: One chamber model Description

- Domain:  $\Omega = [0, 500] \times [0, 1000] \text{ (}\mu\text{m)}.$
- Variables:
  - $u(x, y, t)$ : Density of immune cells.
  - $v(x, y, t)$ : Density of tumor cells.
  - $\varphi(x, y, t)$ : Chemotactic factor secreted by immune cells.
  - $\psi(x, y, t)$ : Chemotactic factor secreted by tumor cells.
- Main equations:

$$\begin{aligned}\partial_t v - \nabla \cdot (D_v \nabla v) + \lambda(\varphi)v &= 0, \\ \partial_t u - \nabla \cdot (D_u \nabla u - \chi u \nabla \psi) &= 0, \\ \partial_t \varphi - \nabla \cdot (D_\varphi \nabla \varphi) + \beta \varphi - \alpha u &= 0, \\ \partial_t \psi - \nabla \cdot (D_\psi \nabla \psi) + a_\psi \psi - b_\psi v &= 0,\end{aligned}$$

- $\lambda(\varphi) = \frac{k_1 \varphi}{k_2 + \varphi}$ : Tumor destruction by immune cells.

# Coefficient descriptions and modelling Choices

Symbol	Description	Value	Units
$D_v$	Tumor-cell diffusivity	$5.6 \times 10^1$	$\mu\text{m}^2/\text{s}$
$D_u$	Immune-cell diffusivity	$2.0 \times 10^2$	$\mu\text{m}^2/\text{s}$
$D_\varphi$	Diffusivity of $\varphi$	$9.0 \times 10^2$	$\mu\text{m}^2/\text{s}$
$D_\psi$	Diffusivity of $\psi$	$9.0 \times 10^2$	$\mu\text{m}^2/\text{s}$
$\chi$	Chemotactic sensitivity	$10^6$ - $10^{10}$	$M\mu\text{m}^2/(\text{s} \cdot \text{cell})$
$\alpha$	Production rate of $\varphi$ per immune cell	$1.0 \times 10^{-1}$	$\text{s}^{-1} \cdot \text{cell}^{-1}$
$\beta$	Decay rate of $\varphi$	$1.0 \times 10^{-4}$	$\text{s}^{-1}$
$a_\psi$	Decay rate of $\psi$	$1.0 \times 10^{-4}$	$\text{s}^{-1}$
$b_\psi$	Production rate of $\psi$ per tumor cell	$1.0 \times 10^{-1}$	$\text{s}^{-1} \cdot \text{cell}^{-1}$
$k_{\varphi_1}, k_{\varphi_2}$	Killing parameters	1.0, 1.0	—
$k_1$	cellular drift velocity	1.0	$M \cdot \mu\text{m}^2/\text{s}$
$k_2$	receptor dissociation constant	1.0	$M$
$k_3$	drift velocity	$1.56 \times 10^{10}$	$M \cdot \mu\text{m}^2/\text{s}$
$L_x, L_y$	chambers dimensions	500, 1000	$\mu\text{m}$
$c_L$	Channel length	600	$\mu\text{m}$
$c_w$	Channel width	12	$\mu\text{m}$
$c_d$	Width between channels	100	$\mu\text{m}$

# Initial and Boundary Conditions and Experimental Setup

- **Initial Conditions:**

- Gaussian distributions:

$$v(0, x, y) = 10^{-3} \exp\left(-\frac{x^2 + (y - 500)^2}{1000}\right) + 10^{-3} \exp\left(-\frac{x^2 + (y - 1000)^2}{1000}\right) \\ + 10^{-3} \exp\left(-\frac{x^2 + y^2}{1000}\right),$$

$$u(0, x, y) = 5 \cdot 10^{-3} \exp\left(-\frac{(x - 400)^2 + (y - 500)^2}{1000}\right) \\ + 4 \cdot 10^{-3} \exp\left(-\frac{(x - 400)^2 + (y - 900)^2}{1000}\right) + 2 \cdot 10^{-3} \exp\left(-\frac{(x - 400)^2}{1000}\right)$$

$$\phi(0, x, y) = 0, \quad \psi(0, x, y) = 0.$$

- **Boundary Conditions:** Homogeneous Neumann ( $\partial\Omega$ ):

$$\nabla v \cdot n = 0, \quad \nabla u \cdot n = 0, \quad \nabla \phi \cdot n = 0, \quad \nabla \psi \cdot n = 0.$$

- **Mesh:** Uniform triangulation of  $[0, 500] \times [0, 1000]$  with  $h = 5 \mu\text{m}$ .
- **Time Integration:**  $\Theta$ -scheme with  $\Delta t = 1 \text{ s}$ , up to  $T = 10\,000 \text{ s}$ .

# OOC model: Two chamber model Description

- **Domains:**  $\Omega^1, \Omega^2$ : chambers,
- **Governing equations in chambers** ( $\Omega^*, * = 1, 2$ ):

$$\partial_t \mathbf{v}^* - \nabla \cdot (D_v^* \nabla \mathbf{v}^*) + \lambda^* (\varphi^*) \mathbf{v}^* = 0,$$

$$\partial_t \mathbf{u}^* - \nabla \cdot (D_u^* \nabla \mathbf{u}^* - \chi \mathbf{u}^* \nabla \psi^*) = 0,$$

$$\partial_t \varphi^* - \nabla \cdot (D_\varphi^* \nabla \varphi^*) + \beta \varphi^* - \alpha \mathbf{u}^* = 0,$$

$$\partial_t \psi^* - \nabla \cdot (D_\psi^* \nabla \psi^*) + a_\psi^* \psi^* - b_\psi^* \mathbf{v}^* = 0,$$

- **Governing equations in the channel** ( $\omega$ ):

$$\partial_t \mathbf{v}^c - \partial_s (D_v^c \partial_s \mathbf{v}^c) + \lambda^c (\varphi^c) \mathbf{v}^c = 0,$$

$$\partial_t \mathbf{u}^c - \partial_s (D_u^c \partial_s \mathbf{u}^c - \chi \partial_s \psi^c \mathbf{u}^c) = 0,$$

$$\partial_t \varphi^c - \partial_s (D_\varphi^c \partial_s \varphi^c) + \beta \varphi^c - \alpha \mathbf{u}^c = 0,$$

$$\partial_t \psi^c - \partial_s (D_\psi^c \partial_s \psi^c) + a_\psi^c \psi^c - b_\psi^c \mathbf{v}^c = 0,$$

- **Boundary conditions:** Homogeneous Neumann on  $\partial\Omega^* \setminus \gamma^*$ :

$$\begin{cases} D_v^* \nabla \mathbf{v}^* \cdot \mathbf{n}^* = 0, \\ (D_u^* \nabla \mathbf{u}^* - \chi \mathbf{u}^* \nabla \psi^*) \cdot \mathbf{n}^* = 0, \end{cases} \quad \begin{cases} D_\varphi^* \nabla \varphi^* \cdot \mathbf{n}^* = 0, \\ D_\psi^* \nabla \psi^* \cdot \mathbf{n}^* = 0. \end{cases}$$



# Chemotactic Sensitivity and Killing Functions

- **Basic model:** directional movement up a spatial gradient of chemoattractant

$$\chi := k_3$$

with drift velocity  $k_3$  (see table 14).

- **Receptor saturation:** dependence on concentration of chemoattractant in a cell's local environment

$$\chi(\varphi) := k_1 \frac{1}{(k_2 + \varphi)^2}$$

where  $k_1$  is the cellular drift velocity and  $k_2$  the receptor dissociation constant (see table 14).

- **Overcrowding:** ability to move freely reduces at high densities

$$\chi(u, \varphi) := k_1 \frac{1}{(k_2 + \varphi)^2} \left( 1 - \frac{u}{u_{\max}} \right)$$

- **Killing function:** for the tumor cells, the killing function is defined as

$$\lambda(\varphi) := \frac{k_{\varphi_1} \varphi}{k_{\varphi_2} + \varphi}$$

# Initial and Boundary Conditions and Experimental Setup

- **Initial Conditions:**

- Gaussian distributions:

$$v(0, x, y) = 10^{-3} \exp\left(-\frac{x^2 + (y - 500)^2}{1000}\right) + 10^{-3} \exp\left(-\frac{x^2 + (y - 1000)^2}{1000}\right) \\ + 10^{-3} \exp\left(-\frac{x^2 + y^2}{1000}\right),$$

$$u(0, x, y) = 5 \cdot 10^{-3} \exp\left(-\frac{(x - 400)^2 + (y - 500)^2}{1000}\right) \\ + 4 \cdot 10^{-3} \exp\left(-\frac{(x - 400)^2 + (y - 900)^2}{1000}\right) + 2 \cdot 10^{-3} \exp\left(-\frac{(x - 400)^2}{1000}\right)$$

$$\phi(0, x, y) = 0, \quad \psi(0, x, y) = 0.$$

- **Boundary Conditions:** Homogeneous Neumann ( $\partial\Omega$ ):

$$\nabla v \cdot n = 0, \quad \nabla u \cdot n = 0, \quad \nabla \phi \cdot n = 0, \quad \nabla \psi \cdot n = 0.$$

- **Mesh:** Uniform triangulation of  $[0, 500] \times [0, 1000]$  with  $h = 5 \mu\text{m}$ .
- **Time Integration:**  $\Theta$ -scheme with  $\Delta t = 1 \text{ s}$ , up to  $T = 10\,000 \text{ s}$ .

# Results for the one chamber model: Statistics and Visualization

Temporal evolution of immune cell concentrations for different chemotactic sensitivity values  $\chi$

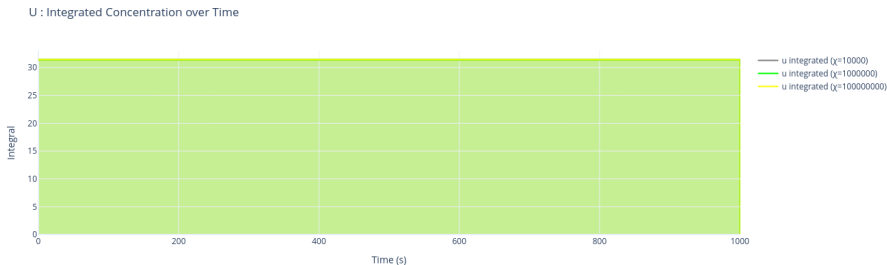


Figure: Immune cells

Explanation...

# Statistics and Visualization

## Evolution of tumor cell concentrations over time for different chemotactic sensitivity values $\chi$

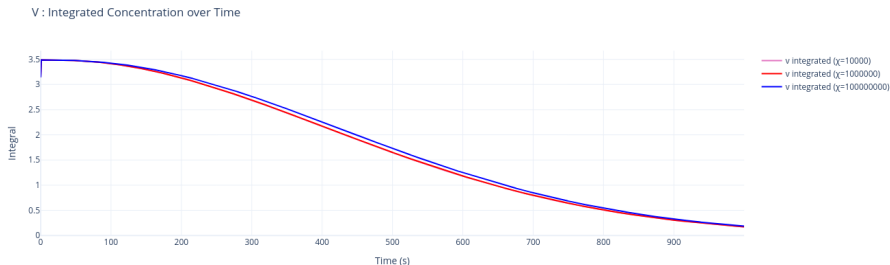


Figure: tumor cells

Explanation...

# Initial Distributions: Tumor and Immune Cells

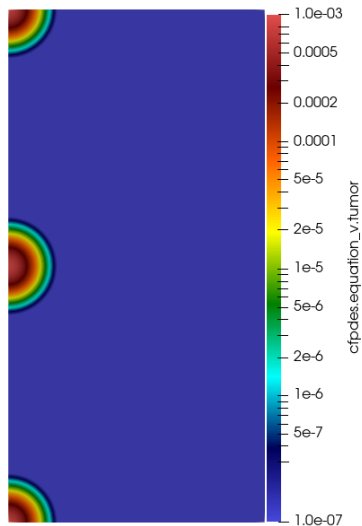


Figure: Tumor  $v$

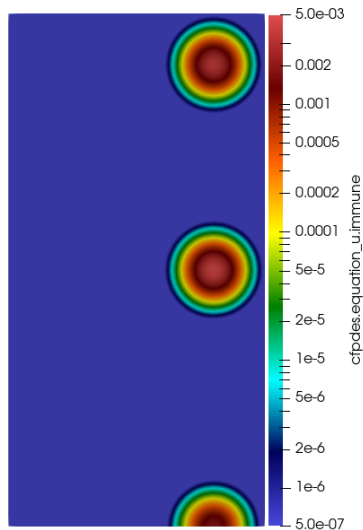


Figure: Immune  $u$

# Initial Distributions: Chemoattractants

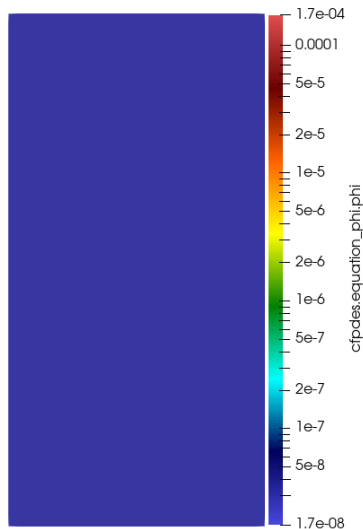


Figure: Chemoattractant  $\varphi$

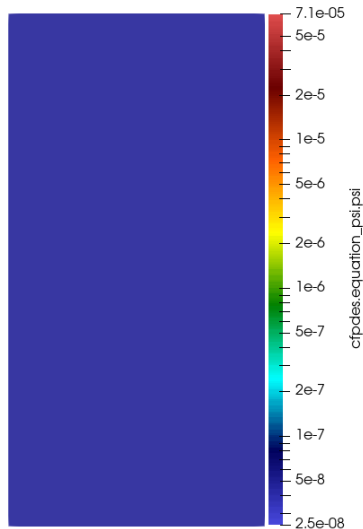


Figure: Chemoattractant  $\psi$

# Immune Cell Density Evolution (I)

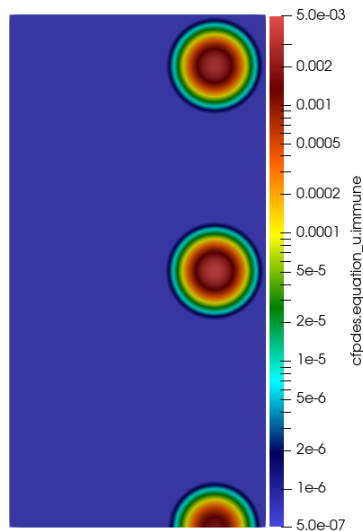


Figure: Immune  $u$  at  $t = 0$

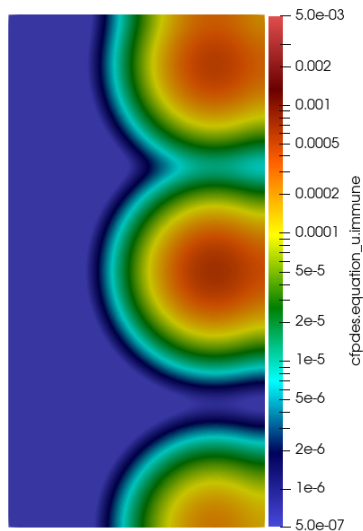


Figure: Immune  $u$  at  $t = 10$

# Immune Cell Density Evolution (II)

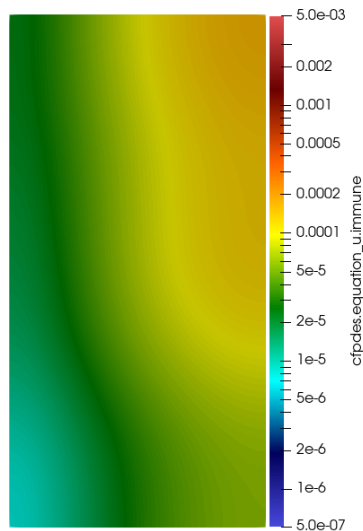


Figure: Immune  $u$  at  $t = 100$

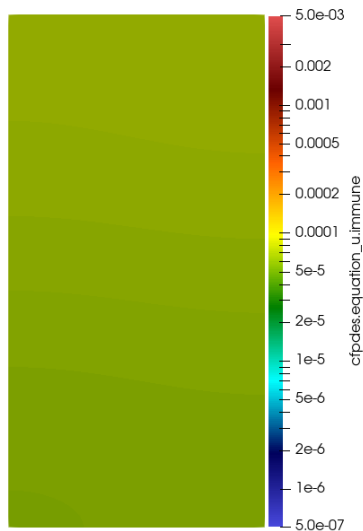


Figure: Immune  $u$  at  $t = 1000$



# Tumor Cell Density Evolution (I)

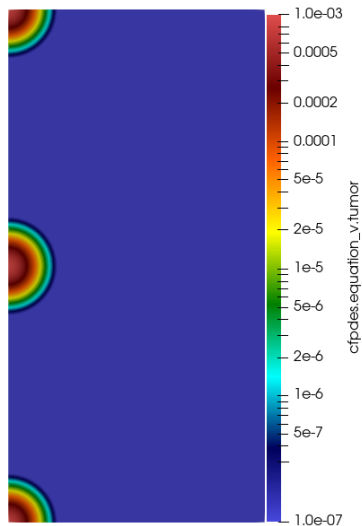


Figure: Tumor  $v$  at  $t = 0$

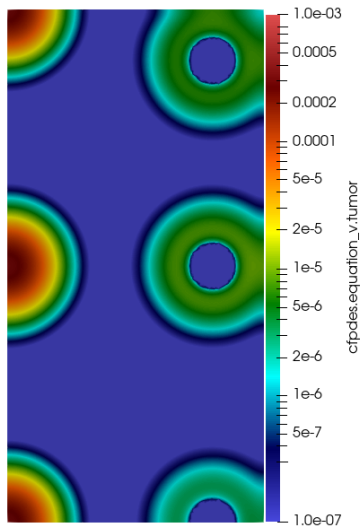


Figure: Tumor  $v$  at  $t = 10$

## Tumor Cell Density Evolution (II)

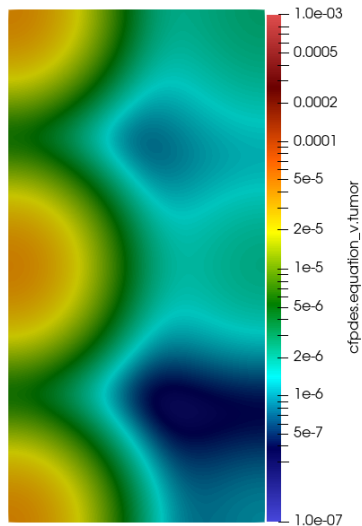


Figure: Tumor  $v$  at  $t = 100$

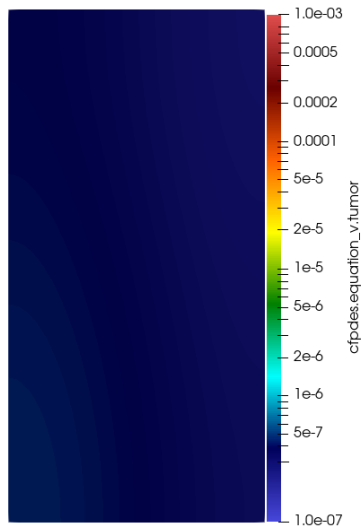


Figure: Tumor  $v$  at  $t = 1000$

# Chemoattractant $\varphi$ Evolution (I)

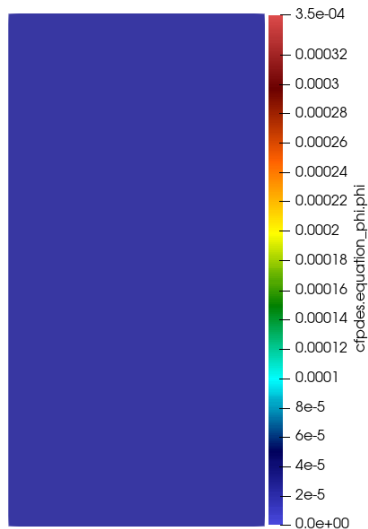


Figure:  $\varphi$  at  $t = 0$

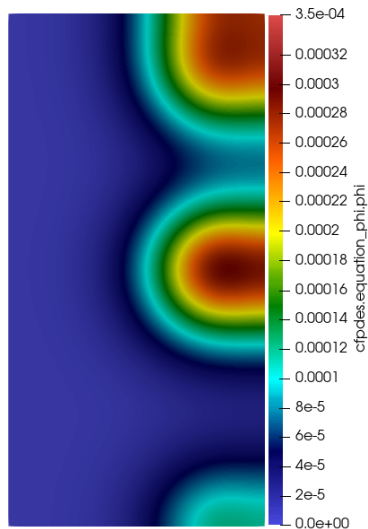


Figure:  $\varphi$  at  $t = 10$

## Chemoattractant $\varphi$ Evolution (II)

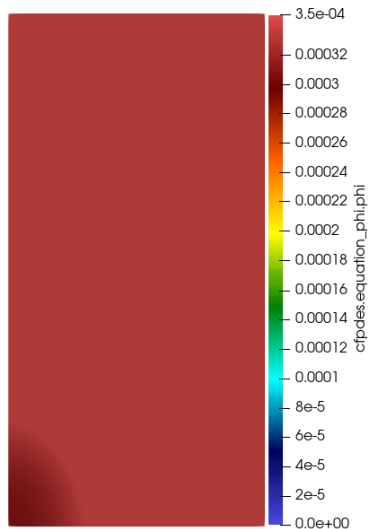


Figure:  $\varphi$  at  $t = 100$

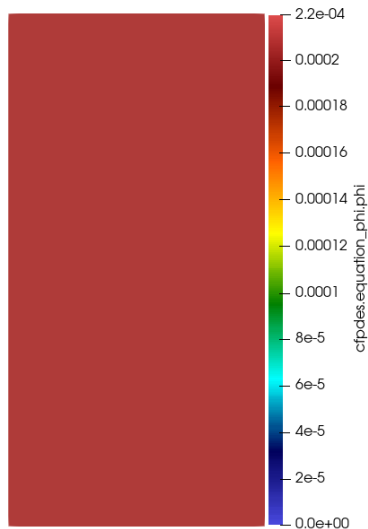


Figure:  $\varphi$  at  $t = 500$

# Chemoattractant $\psi$ Evolution (I)

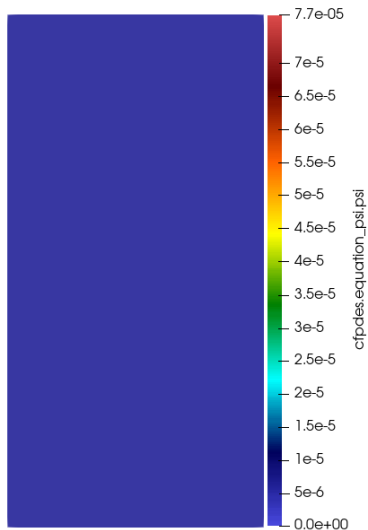


Figure:  $\psi$  at  $t = 0$

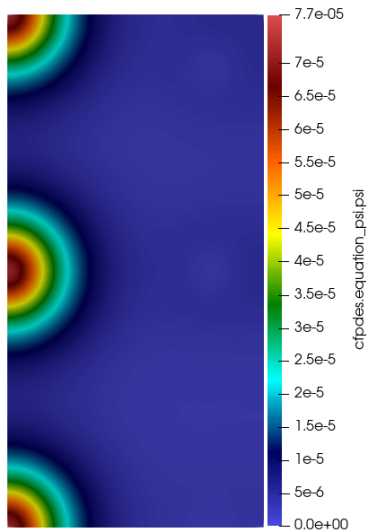


Figure:  $\psi$  at  $t = 10$

## Chemoattractant $\psi$ Evolution (II)

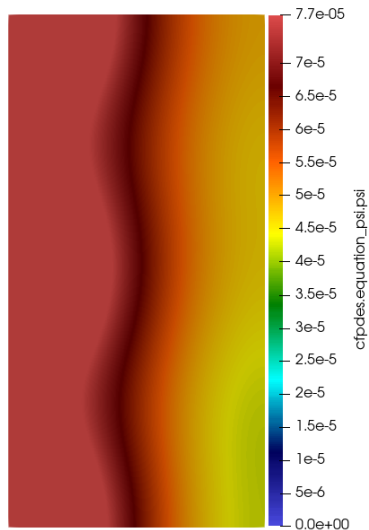


Figure:  $\psi$  at  $t = 100$

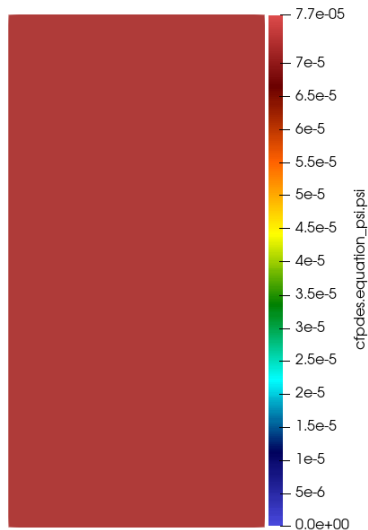


Figure:  $\psi$  at  $t = 500$

## Conclusion and Future Work

- **Summary:**

- Developed a one-chamber model based on diffusion-reaction-chemotaxis equations.
- Simulated cellular and chemical interactions on a rectangular domain ( one chamber case), using feelp toolboxes.

- **Challenges:**

- Extend the model to a two-chamber geometry with HDG coupling.
- Validate results with experimental Organ-on-Chip data.
- Solve the inverse problem for parameter calibration.

Thank you all for your attention.  
Any questions ?