University of Strasbourg
Master CSMI
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Mathematical Modeling and Simulations of Organ-on-Chip (OOC)

Internship Presentation

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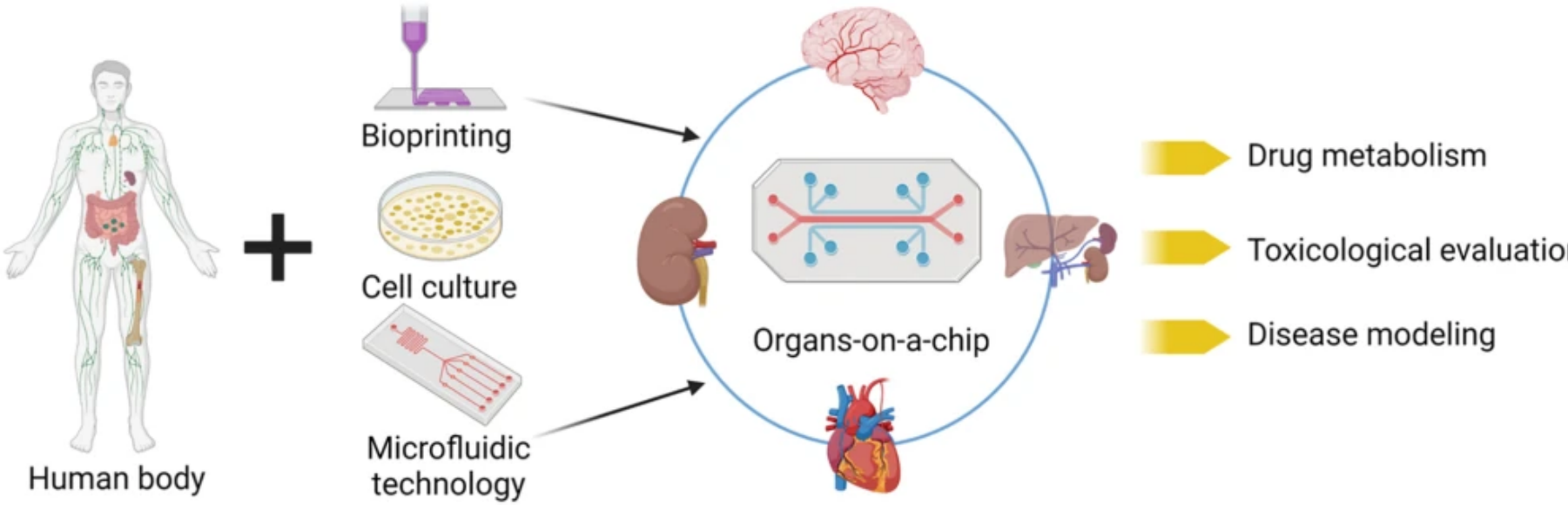
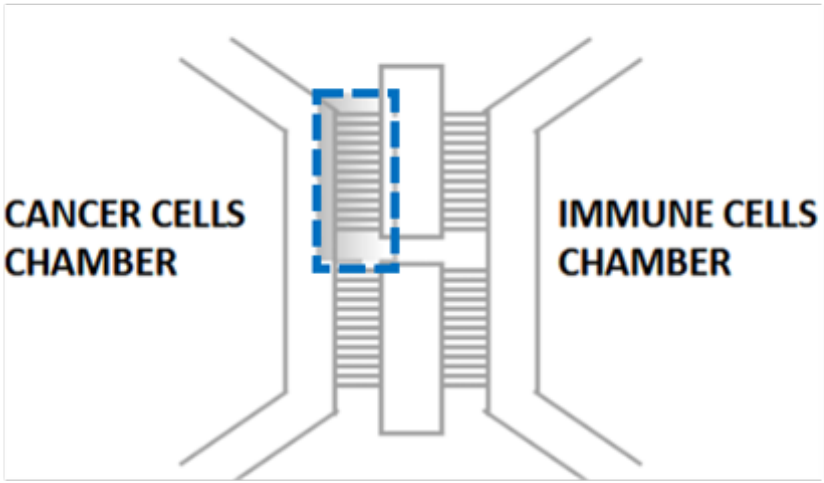
Organ-on-Chip: Context and Motivation

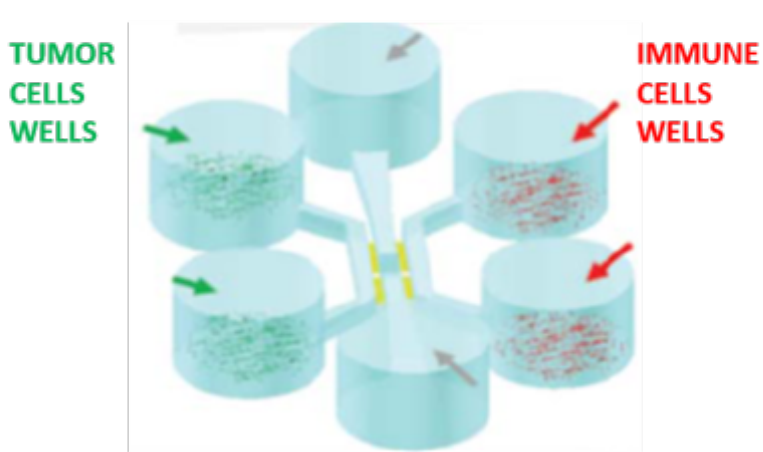
- **What is OOC?** A 3D microfluidic platform that mimics human tissue microenvironments to simulate cellular dynamics and interactions.

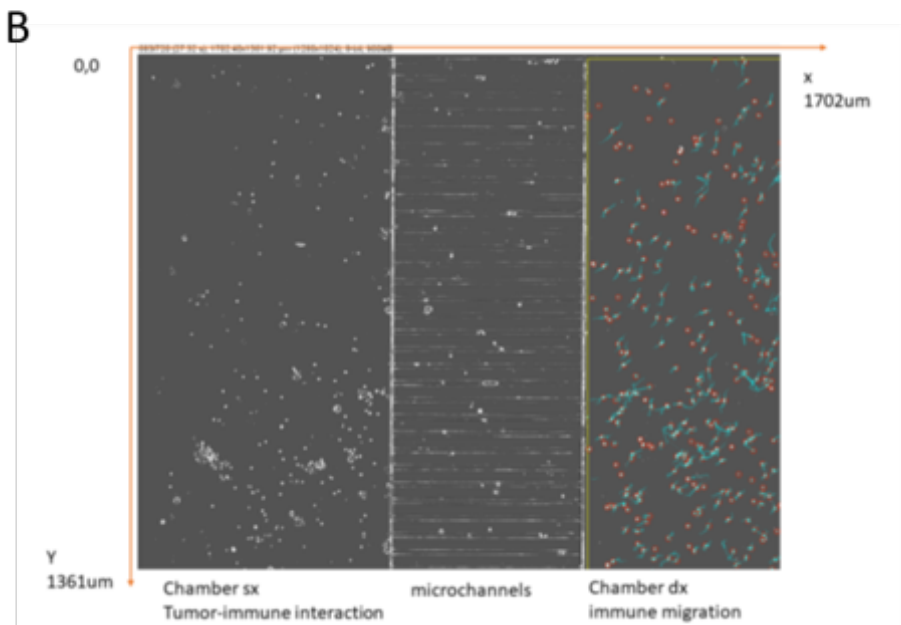


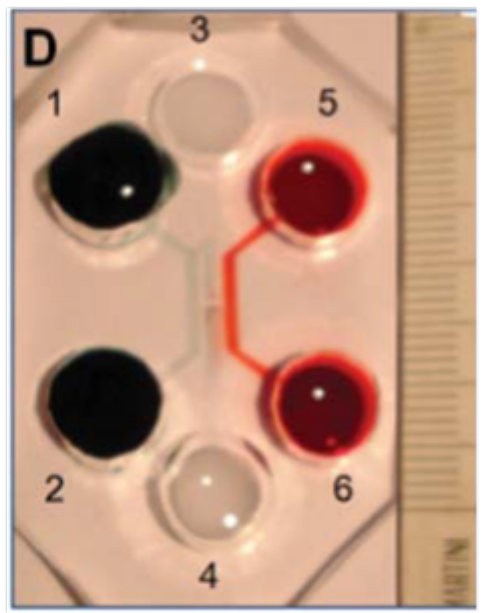
- **Motivation:**
  - Understand the mechanisms governing cell dynamics in microfluidic systems.
  - Investigate interactions between immune and tumor cells.

Illustration of the Organ-on-Chip Device and Geometries





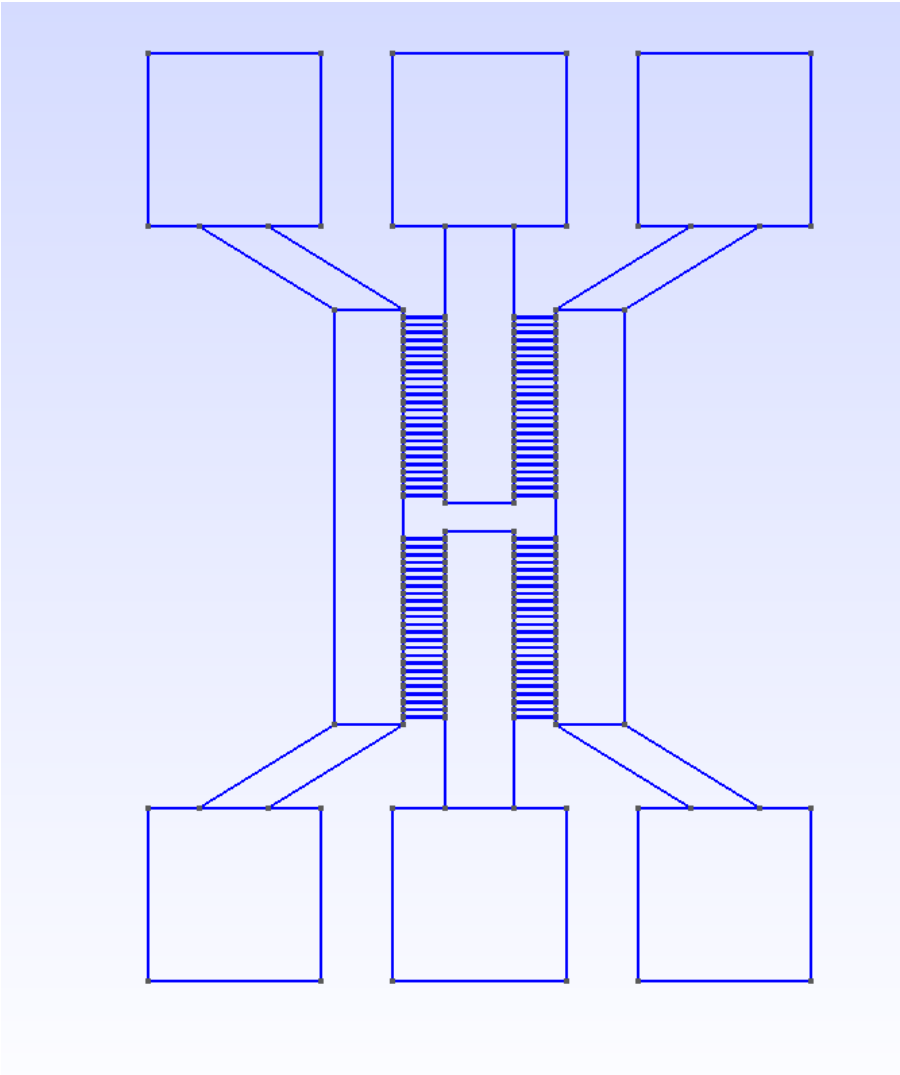


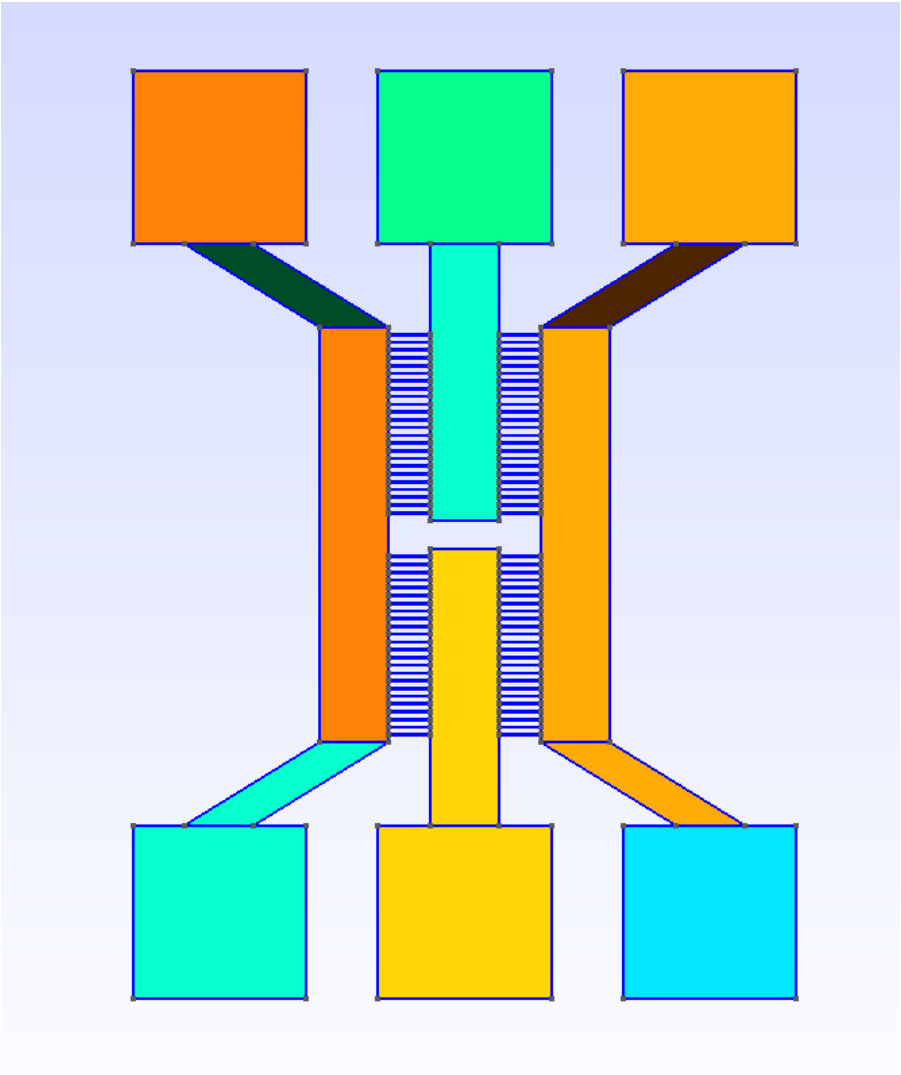


Typical

Organ-on-Chip schematic: microchannels, chambers, and zones of cellular interaction [?].

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 τ affects convergence:
  - Table of convergence rates:

τ	$\mathbf{u}_h$	p_h	$\bar{p}_h$	k
$O(h)$	$k+1$	k	$k+2$	≥ 1
$O(1)$	$k+1$	$k+1$	$k+2$	≥ 1
$O(1/h)$	k	$k+1$	$k+1$	≥ 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 Γ_D, $\mathbf{u} \cdot \mathbf{n} = h_N$ on Γ_N.
- **Notations:**
  - Mesh $\mathcal{T}_h$, faces $\mathcal{E}_h = \mathcal{E}_h^o \cup \mathcal{E}_h^\partial$.
  - 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 $\hat{p}_h$.

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:**

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

- **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 Γ_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 Γ_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: $\mathbb{M}\widehat{\mathbf{p}} = \mathbf{F} + \mathbf{G}_N$.
  - 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 φ.
  - Equations:

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

- **Auxiliary Variables:**

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

- **Expected:**
  - Preserve non-negativity of u, φ.
  - 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:

$$\left(\frac{\partial u_h}{\partial t}, w\right)_\Omega + (\widehat{j_h} \cdot n, w)_{\mathcal{E}_h} - (j_h, \nabla w)_{\mathcal{T}_h} = (f_u, w)_\Omega,$$

$$\left(\frac{\partial \varphi_h}{\partial t}, \tau\right)_\Omega + (\widehat{\psi_h} \cdot n, \tau)_{\mathcal{E}_h} - (\psi_h, \nabla \tau)_{\mathcal{T}_h} + (a\varphi_h, \tau)_\Omega - (bu_h, \tau)_\Omega = (f_\varphi, \tau)_\Omega,$$

$$(\beta \psi_h, \theta)_\Omega - (\varphi_h, \nabla \cdot \theta)_{\mathcal{T}_h} + (\widehat{\varphi_h}, \theta \cdot n)_{\mathcal{E}_h} = 0,$$

$$(\alpha j_h + \beta \chi u_h \psi_h, q)_\Omega - (u_h, \nabla \cdot q)_{\mathcal{T}_h} + (\widehat{u}_h, q \cdot n)_{\mathcal{E}_h} = 0,$$

OOC model: One chamber model Description

- Domain: $\Omega = [0, 500] \times [0, 1000]\,(\mu\text{m})$.
- 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.

Explanation of the model

Coefficient descriptions and modelling Choices

Symbol	Description	Value	Units
D_v	Tumor-cell diffusivity	5.6×10^1	$\mu\mathrm{m}^2/\mathrm{s}$
D_u	Immune-cell diffusivity	2.0×10^2	$\mu\mathrm{m}^2/\mathrm{s}$
D_φ	Diffusivity of φ	9.0×10^2	$\mu\mathrm{m}^2/\mathrm{s}$
D_ψ	Diffusivity of ψ	9.0×10^2	$\mu\mathrm{m}^2/\mathrm{s}$
χ	Chemotactic sensitivity	10^6-10^{10}	$M\mu\mathrm{m}^2/(\mathrm{s}\cdot\mathrm{cell})$
α	Production rate of φ per immune cell	1.0×10^{-1}	$\mathrm{s}^{-1}\cdot\mathrm{cell}^{-1}$
β	Decay rate of φ	1.0×10^{-4}	s^{-1}
a_ψ	Decay rate of ψ	1.0×10^{-4}	s^{-1}
b_ψ	Production rate of ψ per tumor cell	1.0×10^{-1}	$\mathrm{s}^{-1}\cdot\mathrm{cell}^{-1}$
$k_{\varphi_1}, k_{\varphi_2}$	Killing parameters	1.0, 1.0	—
k_1	cellular drift velocity	1.0	$M\cdot\mu m^2/s$
k_2	receptor dissociation constant	1.0	M
k_3	drift velocity	1.56×10^{10}	$M\cdot\mu m^2/s$
L_x, L_y	chambers dimensions	500, 1000	$\mu\mathrm{m}$
c_L	Channel length	600	$\mu\mathrm{m}$
c_w	Channel width	12	$\mu\mathrm{m}$
c_d	Width beetween channels	100	$\mu\mathrm{m}$

Initial and Boundary Conditions and Experimental Setup

- **Initial Conditions:**
  - Gaussian distributions:

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

$$u(0,x,y) = 5.10^{-3}\exp\left(-\frac{(x-400)^2+(y-500)^2}{1000}\right) + 4.10^{-3}\exp\left(-\frac{(x-400)^2+(y-900)^2}{1000}\right) + 2.10^{-3}\exp\left(-\frac{(x-400)}{1000}\right.$$

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

- **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 $h = 5\,\mu$m.
- **Time Integration**: Θ-scheme with $\Delta t = 1\,$s, up to $T = 10\,000\,$s.

OOC model: Two chamber model Description

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

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

- **Governing equations in the channel** (ω):

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

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

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

Chemotactic Sensitivity and Killing Functions

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

$$\boxed{\chi := k_3}$$

with drift velocity k_3 (see table 14).

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

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

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

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

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

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

Results for the one chamber model: Statistics and Visualization

Temporal evolution of immune cell concentrations for different chemotactic sensitivity values χ

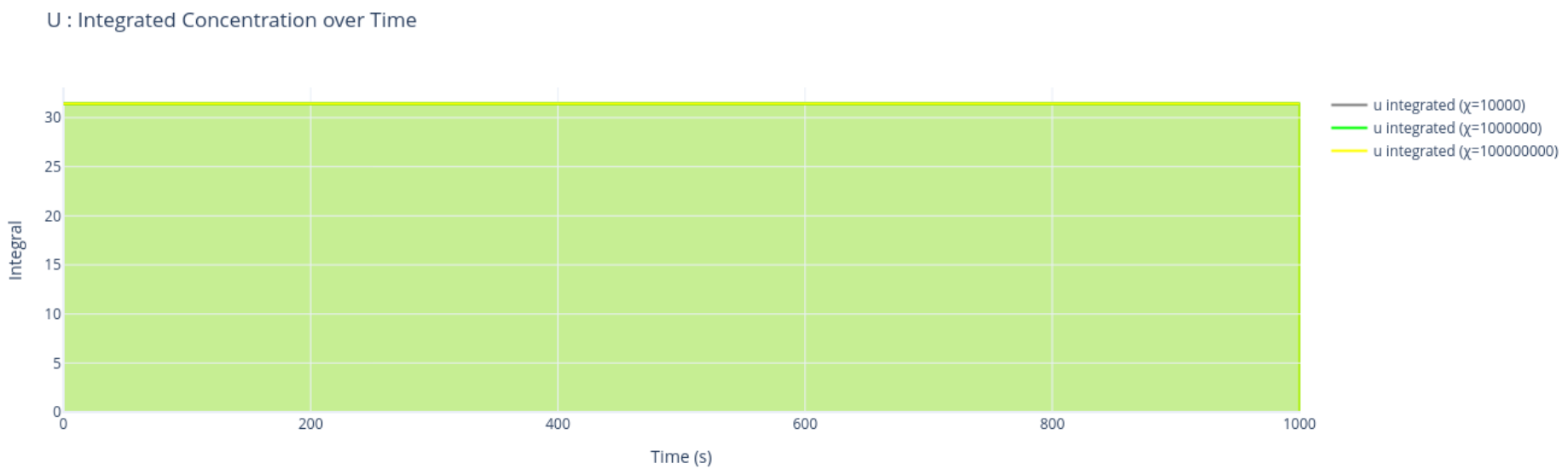


Figure: Immune cells

Explanation...

Statistics and Visualization

Evolution of tumor cell concentrations over time for different chemotactic sensitivity values χ

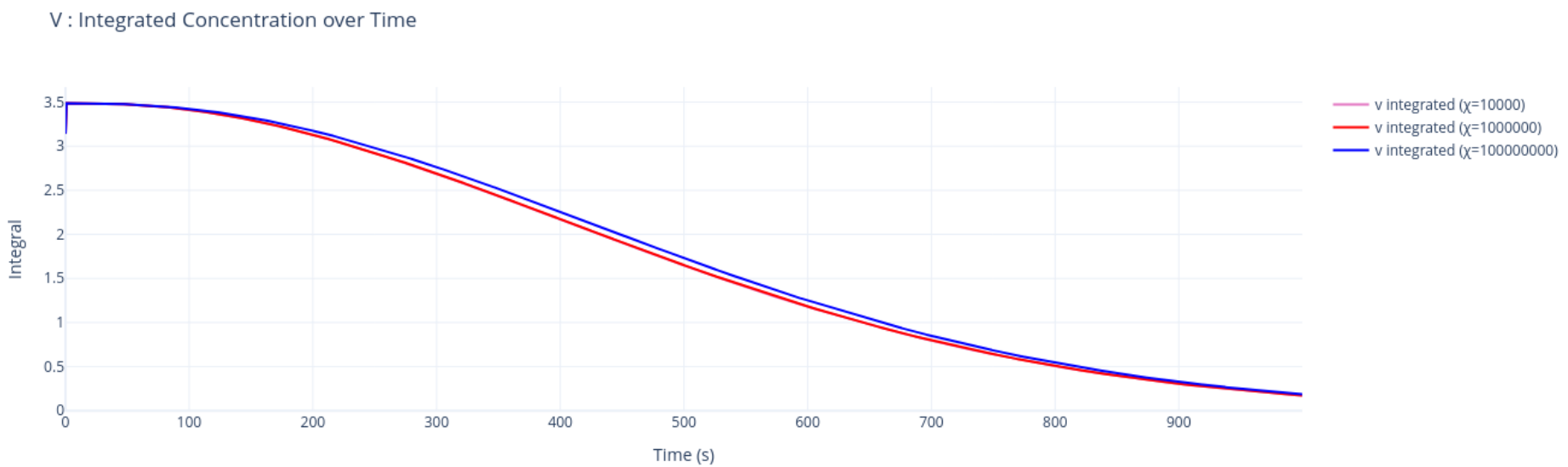


Figure: tumor cells

Explanation...

Initial Distributions: Tumor and Immune Cells

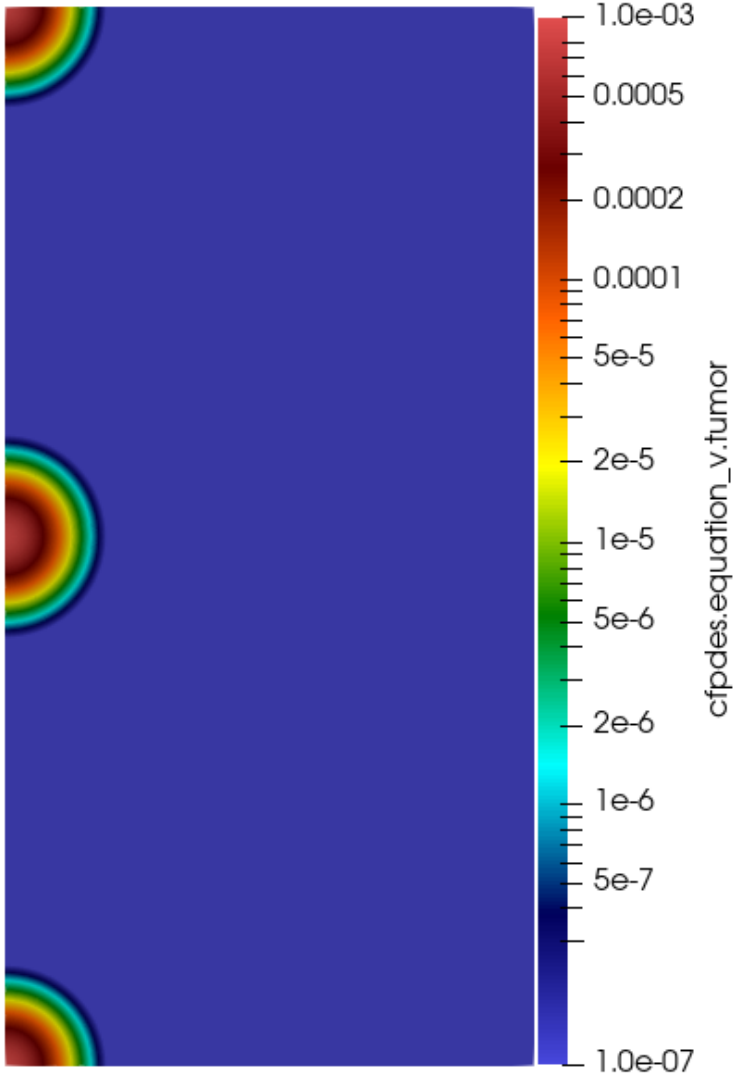


Figure: Tumor v

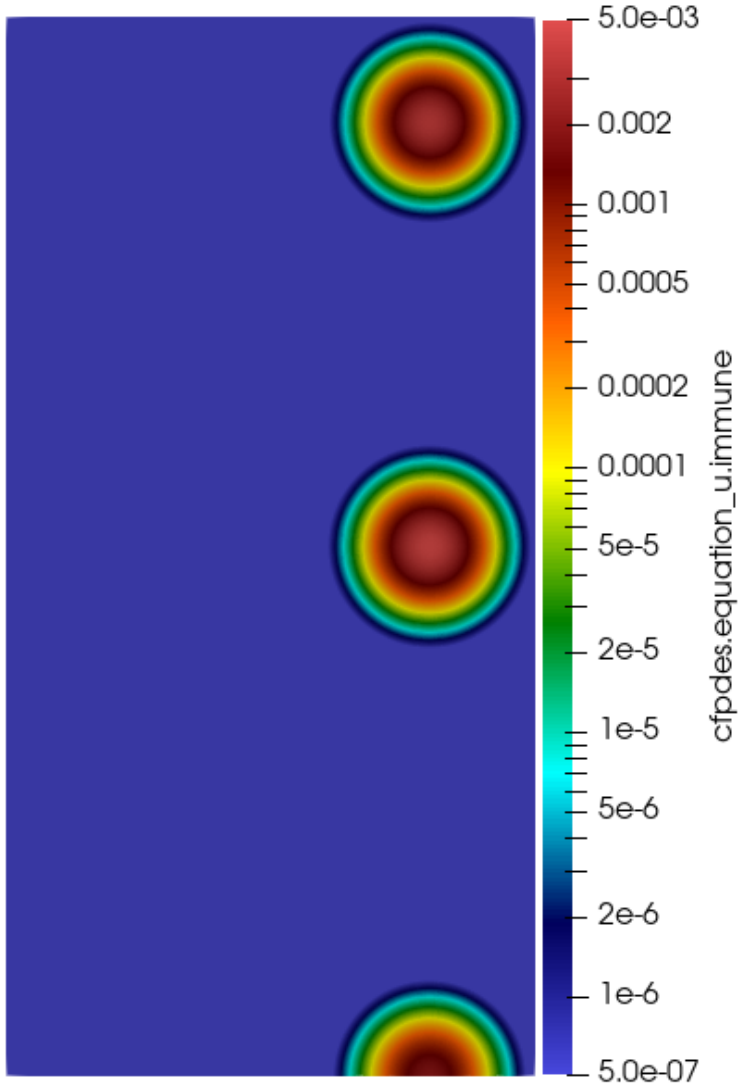


Figure: Immune u

Initial Distributions: Chemoattractants

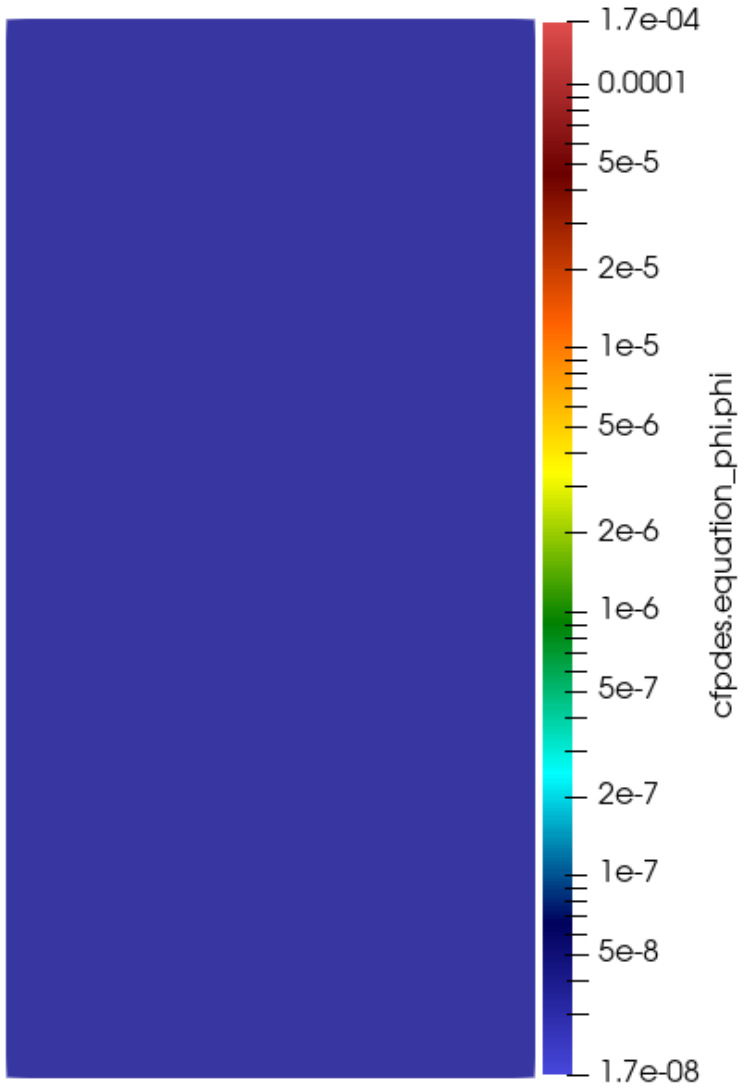


Figure: Chemoattractant φ

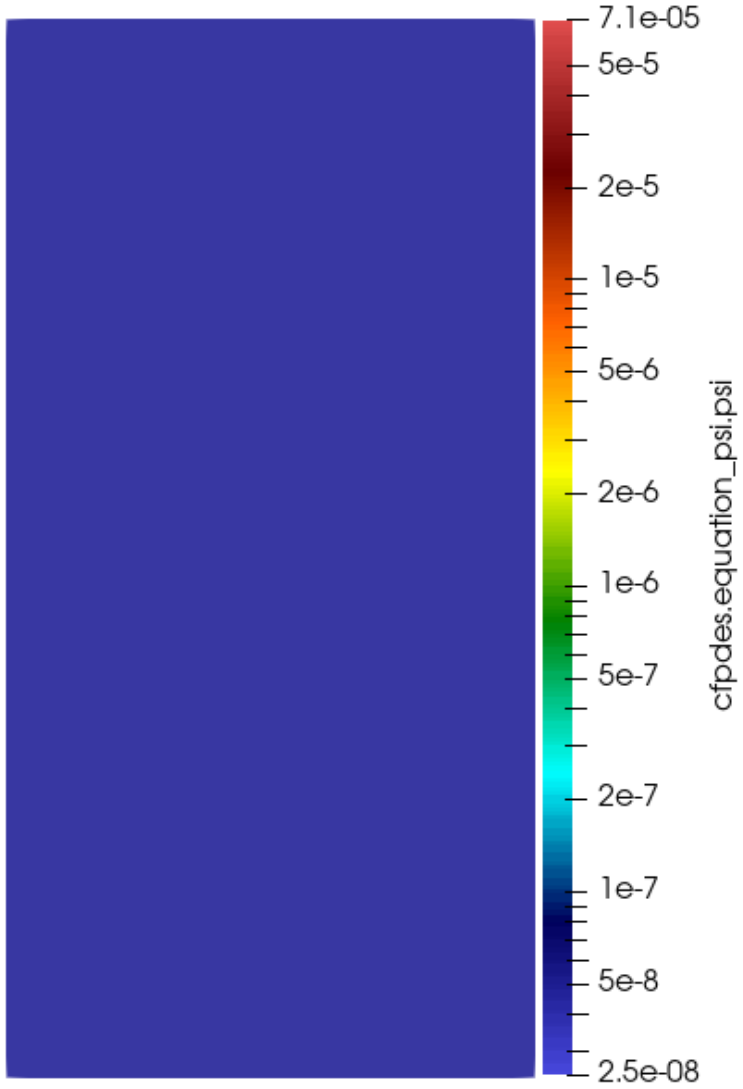


Figure: Chemoattractant ψ

Immune Cell Density Evolution (I)

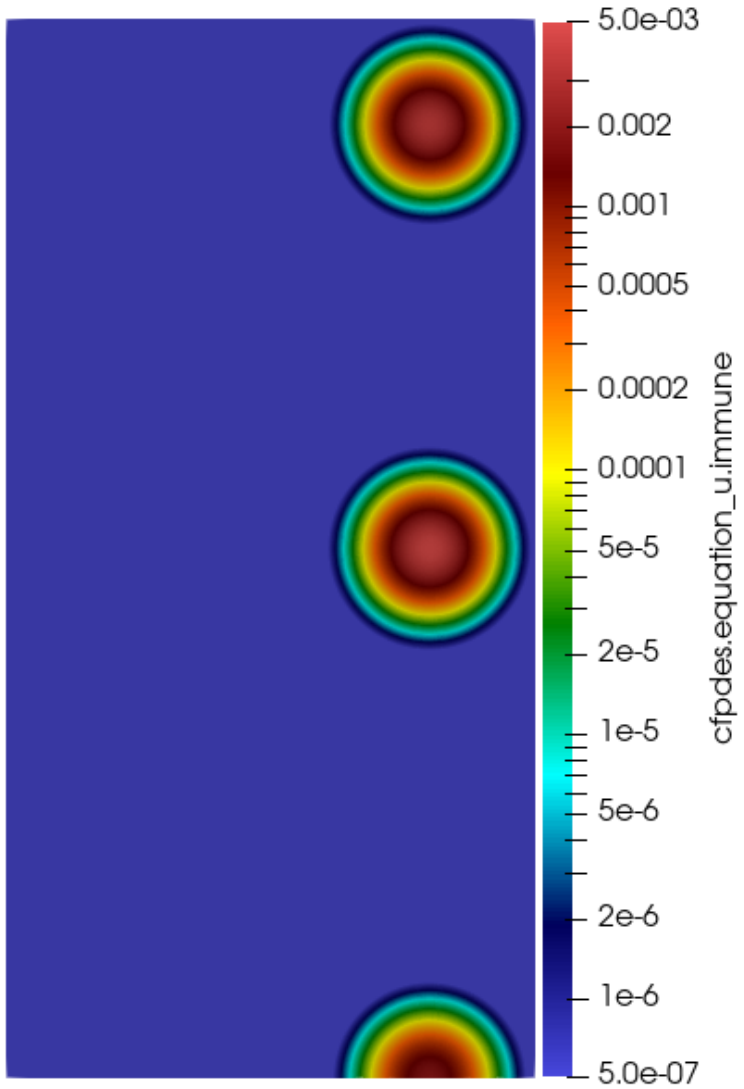


Figure: Immune u at $t = 0$

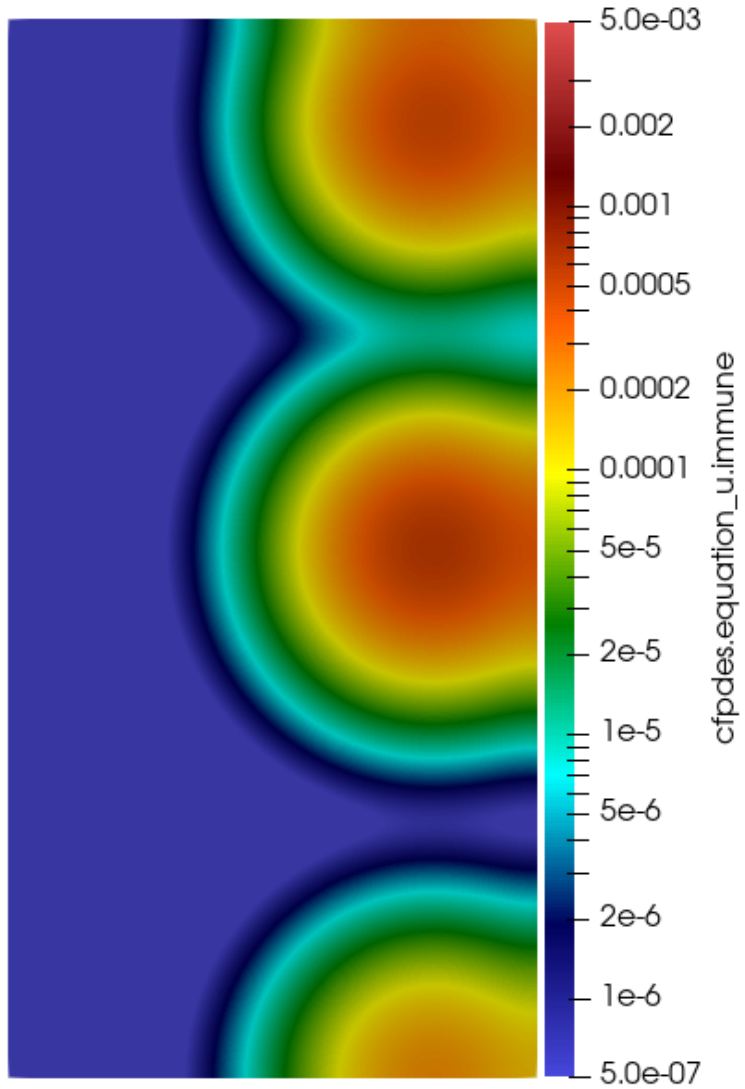


Figure: Immune u at $t = 10$

Immune Cell Density Evolution (II)

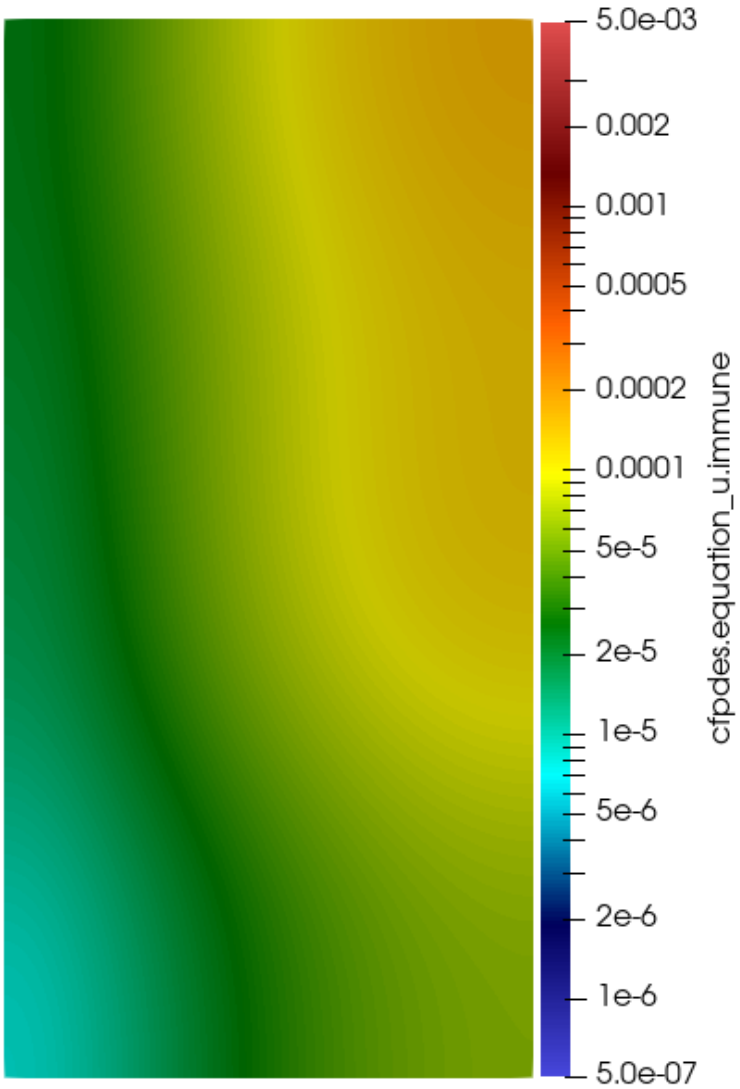


Figure: Immune u at $t = 100$

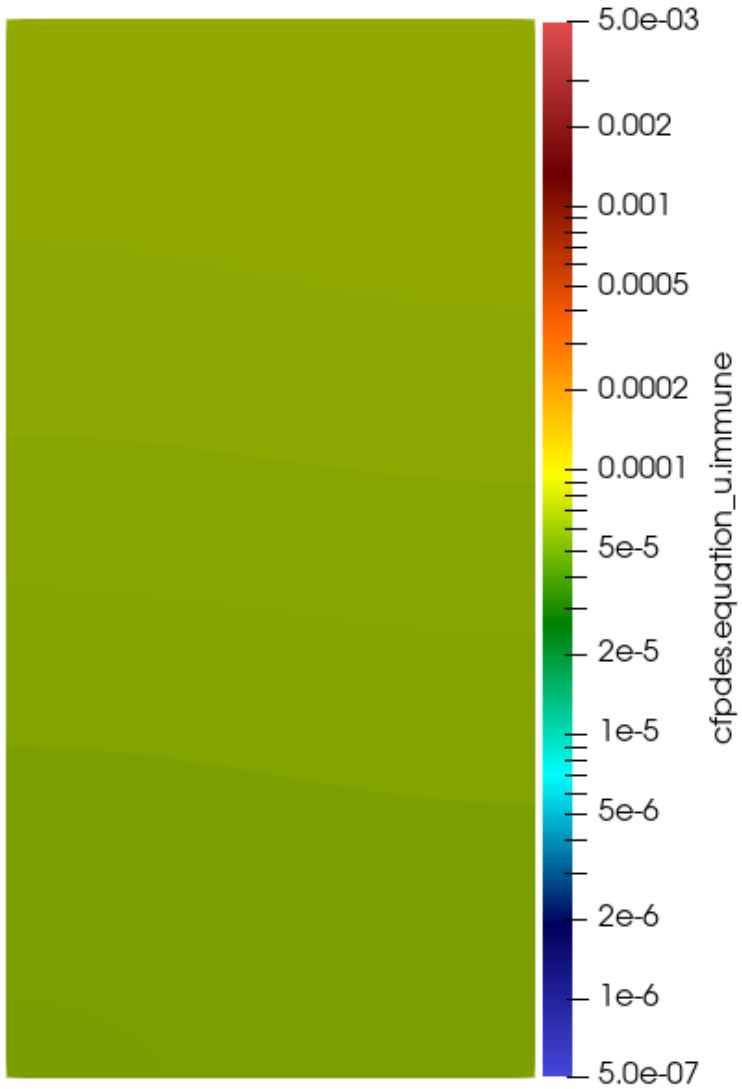


Figure: Immune u at $t = 1000$

Tumor Cell Density Evolution (I)

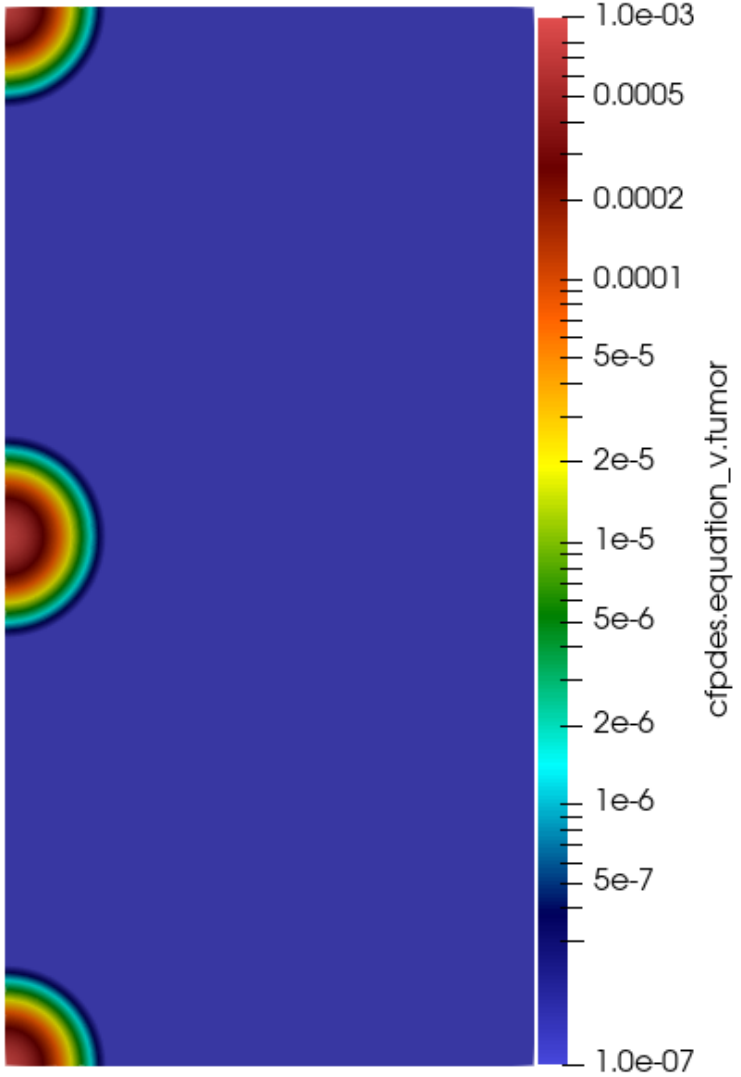


Figure: Tumor v at $t = 0$

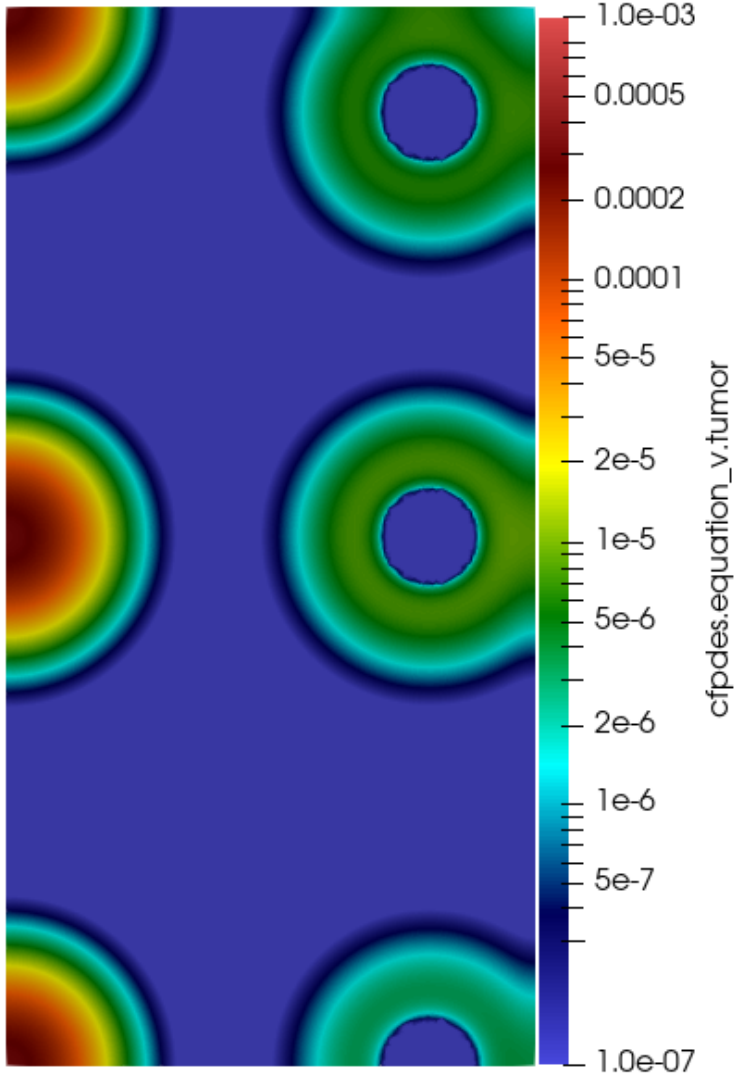


Figure: Tumor v at $t = 10$

Tumor Cell Density Evolution (II)

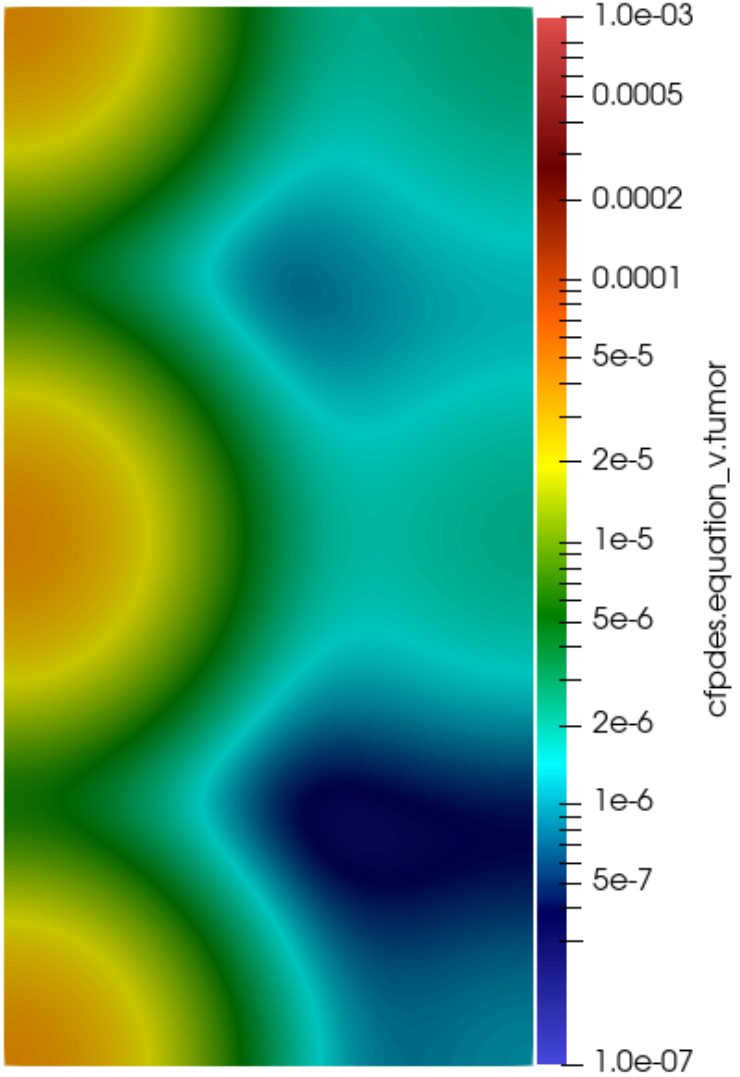


Figure: Tumor v at $t = 100$

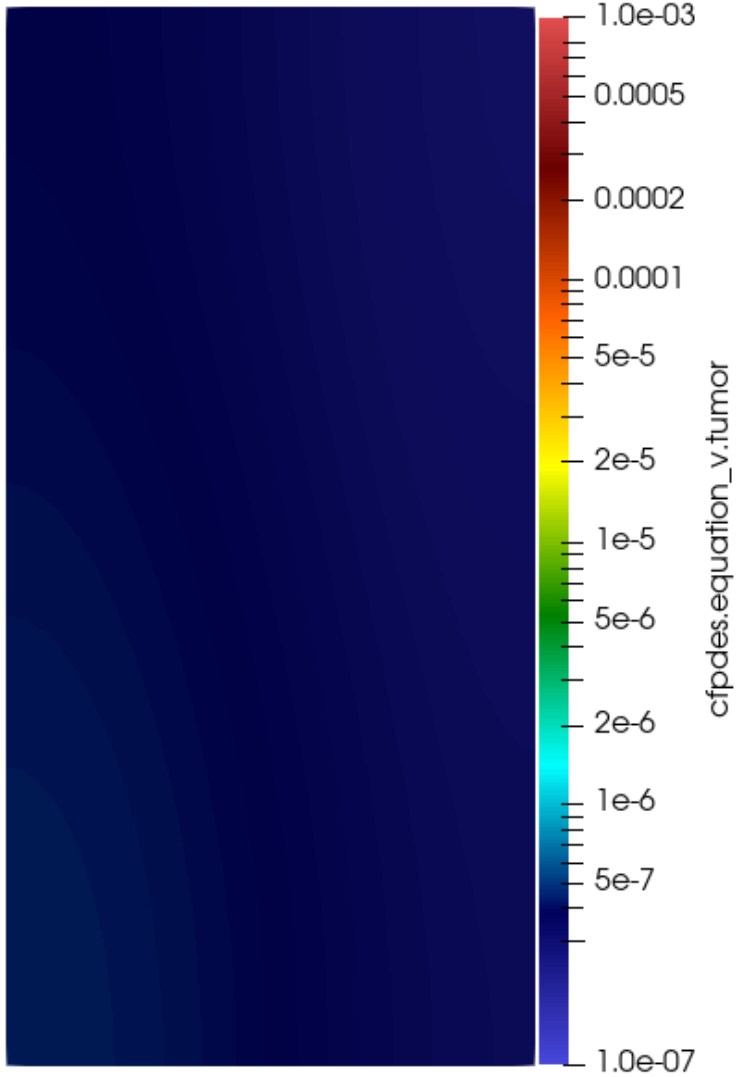


Figure: Tumor v at $t = 1000$

Chemoattractant φ Evolution (I)

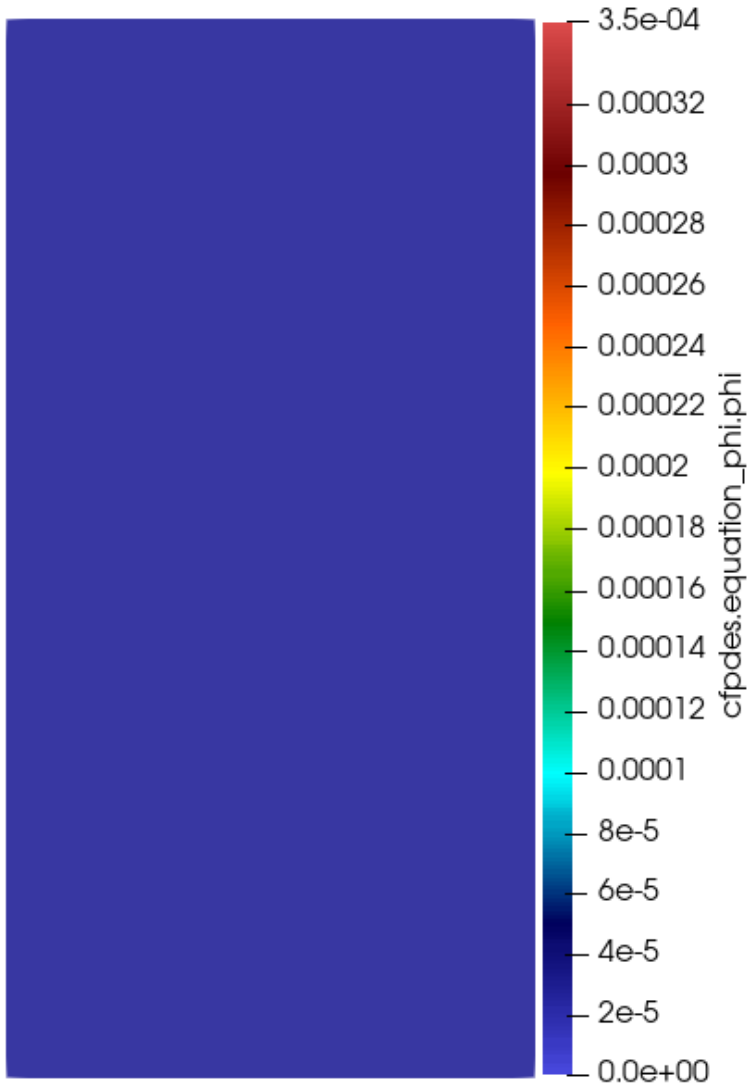


Figure: φ at $t = 0$

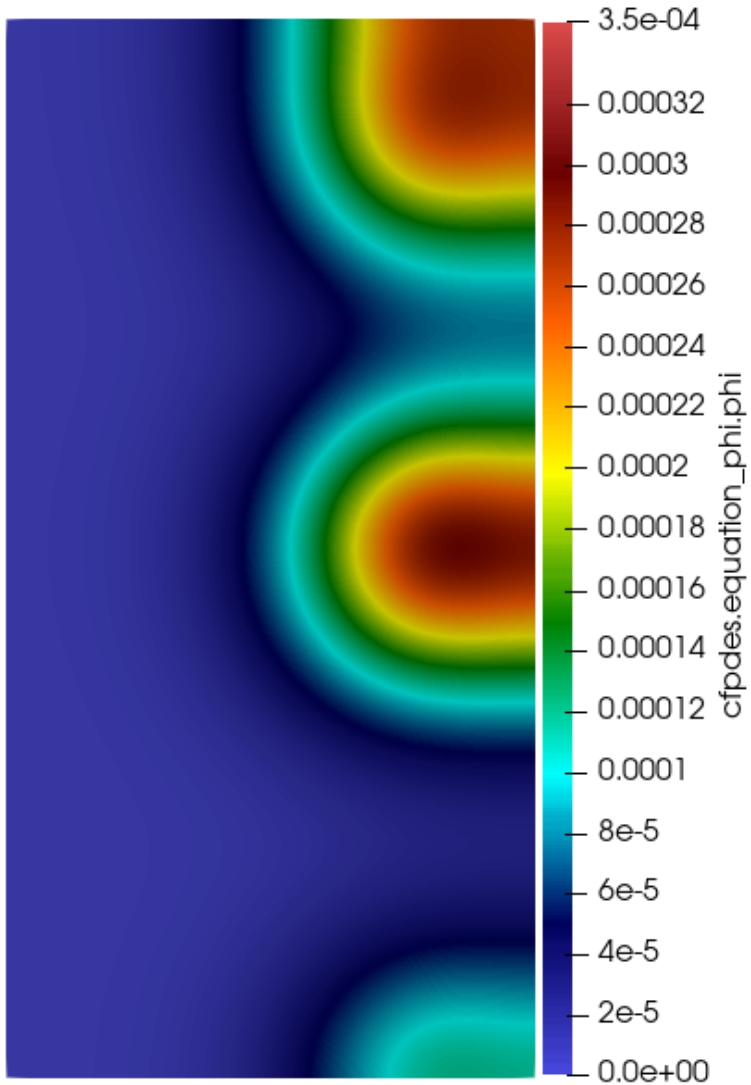


Figure: φ at $t = 10$

Chemoattractant φ Evolution (II)

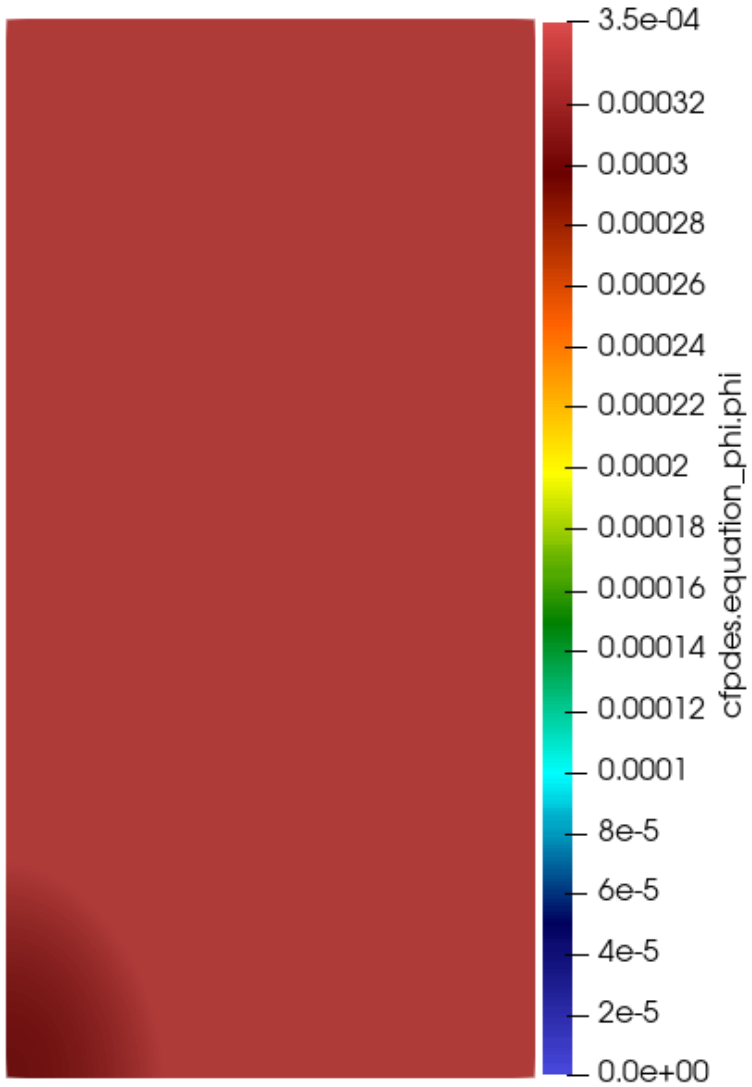


Figure: φ at $t = 100$

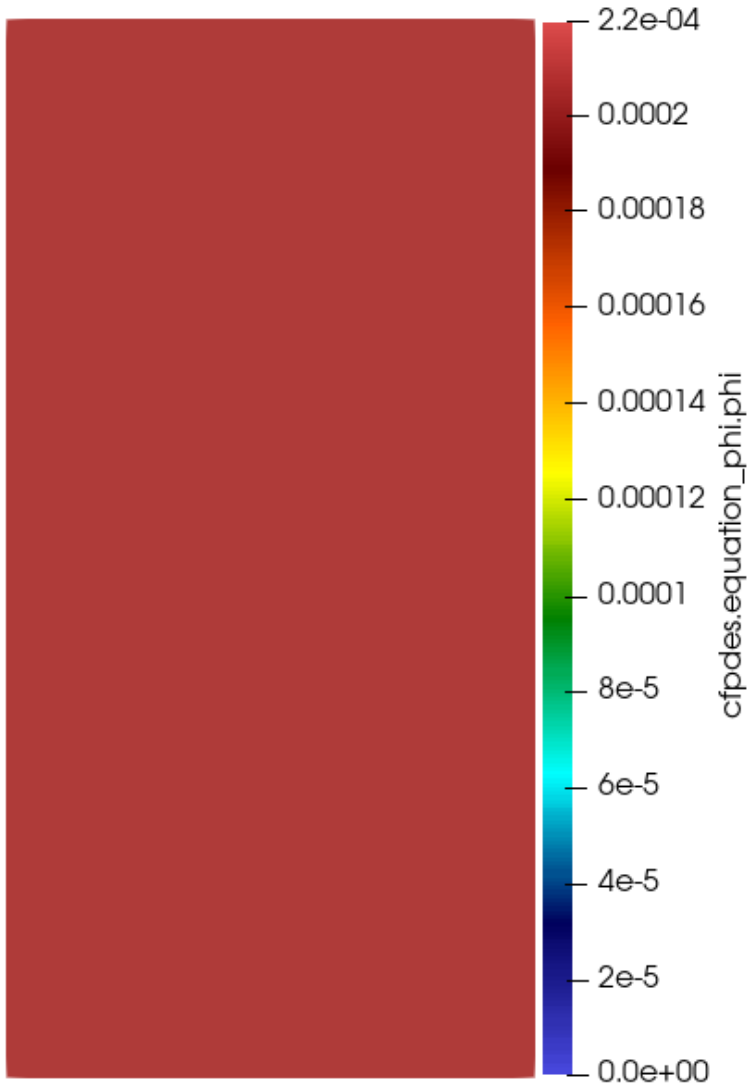


Figure: φ at $t = 500$

Chemoattractant ψ Evolution (I)

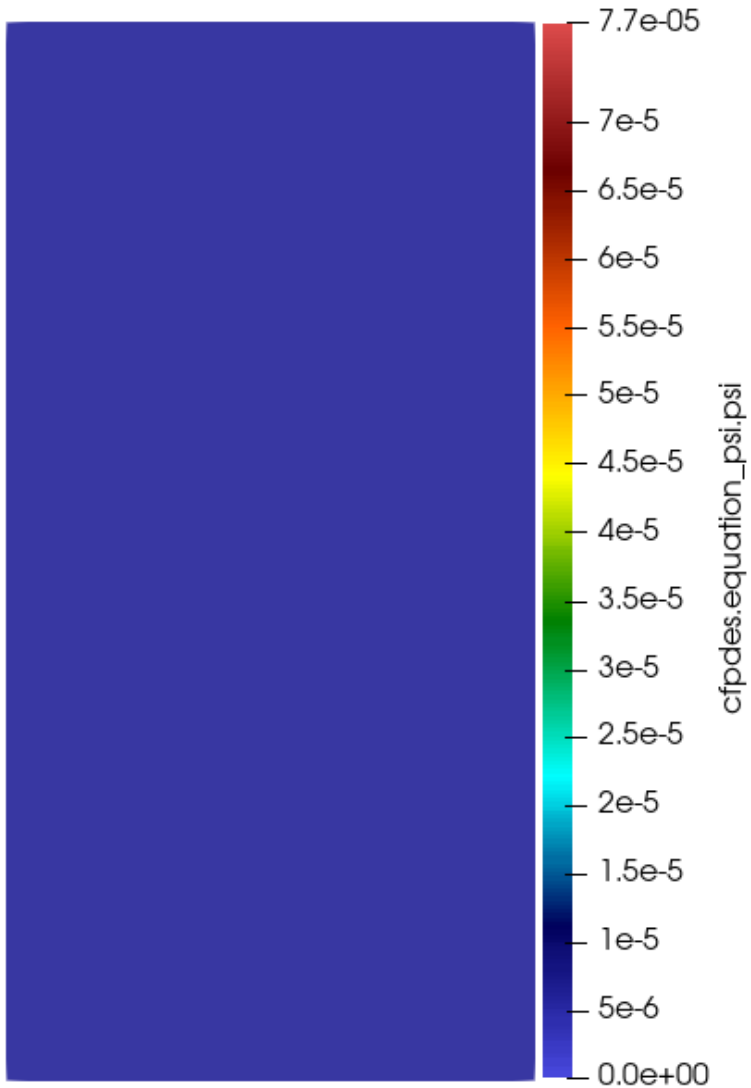


Figure: ψ at $t = 0$

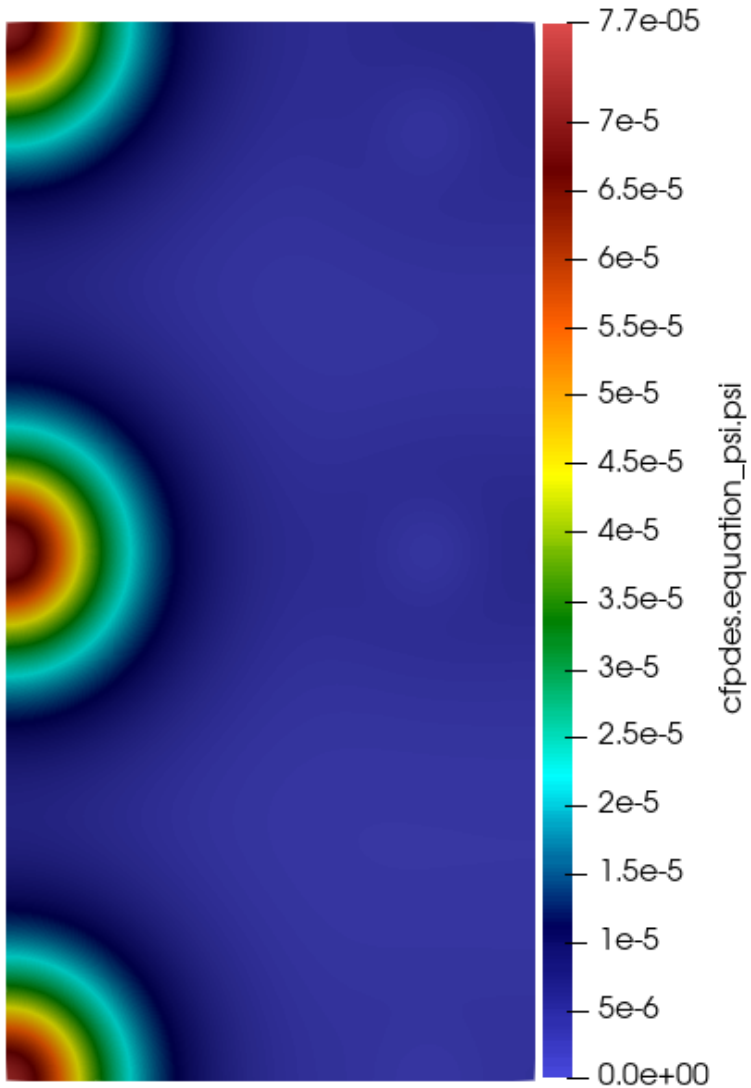


Figure: ψ at $t = 10$

Chemoattractant ψ Evolution (II)

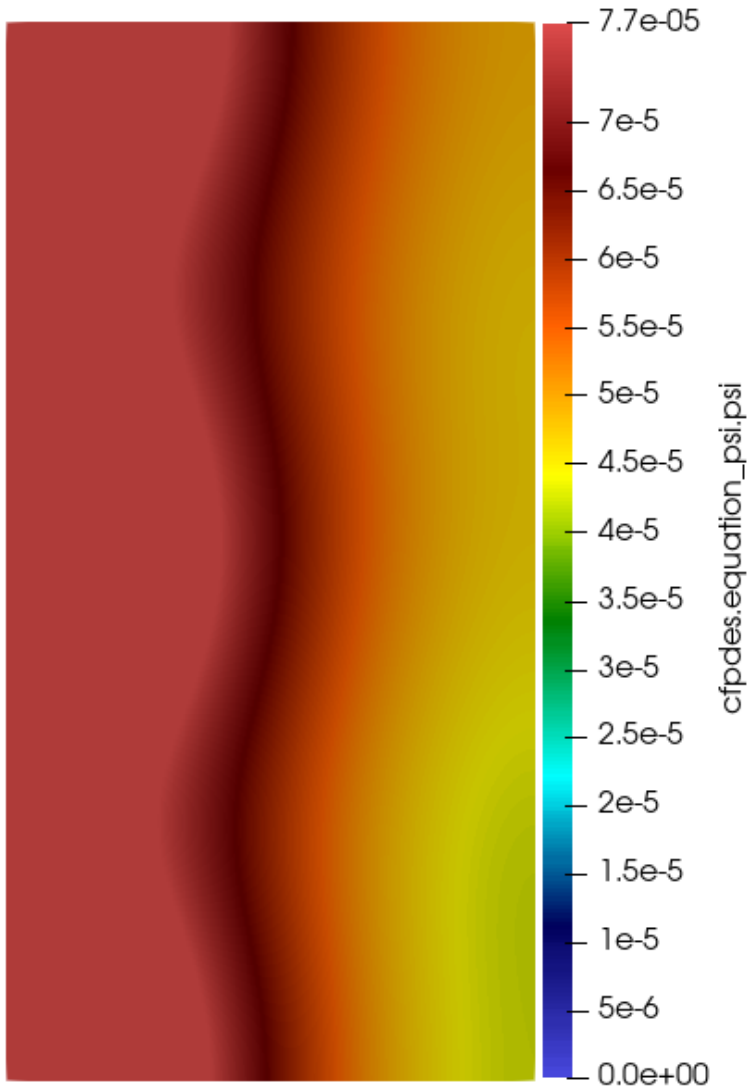


Figure: ψ at $t = 100$

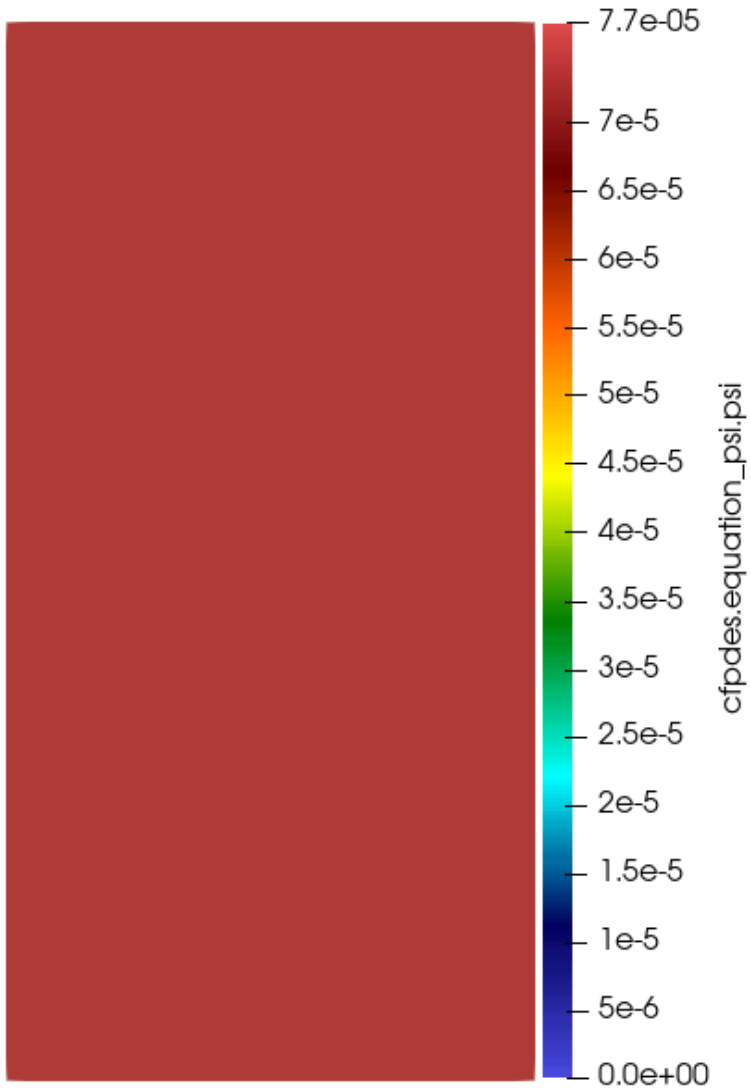


Figure: ψ at $t = 500$

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 feelpp 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 ?