IMO II Exam 1

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Consider a newly developed fluorescent biomarker (no lethal activity) that was tested on a pancreatic cancer cell line and the following cell uptake rates for different biomarker levels were recorded:

Concentration [μg/μm^3]	1	10	25	50	75	100	200	300	400	500
Uptake rate per cell [μg/s]	1.5x10^{-4}	3.7x10^{-4}	1.75x10^{-3}	0.011	0.018	0.021	0.019	0.021	0.019	0.02

1 Question 1

Use some graphical method to represent the above data (bar graphs, line graphs, ...). Estimate parameters $\mathcal{L}$ and κ of the following equation: $y(x) = \frac{\mathcal{L}}{1+e^{-\kappa(x-50)}}$ to fit the above uptake rate data for the given biomarker concentrations. Discuss how the drug uptake rate will change if you wary these parameters. Support your discussion with graphs **(25%)**.

1.1 Solution

In order to estimate the parameters $\mathcal{L}$ and κ of $y(x) = \frac{\mathcal{L}}{1+e^{-\kappa(x-50)}}$ I used the Nonlinear least-squares solver "`lsqcurvefit`" function of MATLAB (see the source code in the attached document).

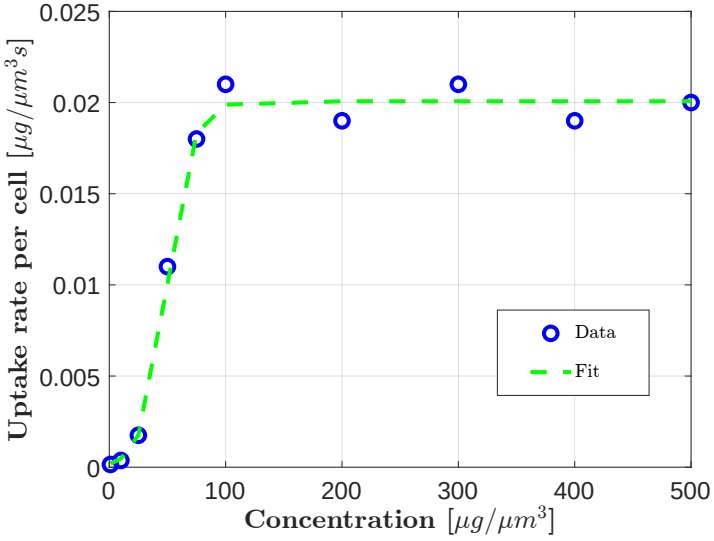


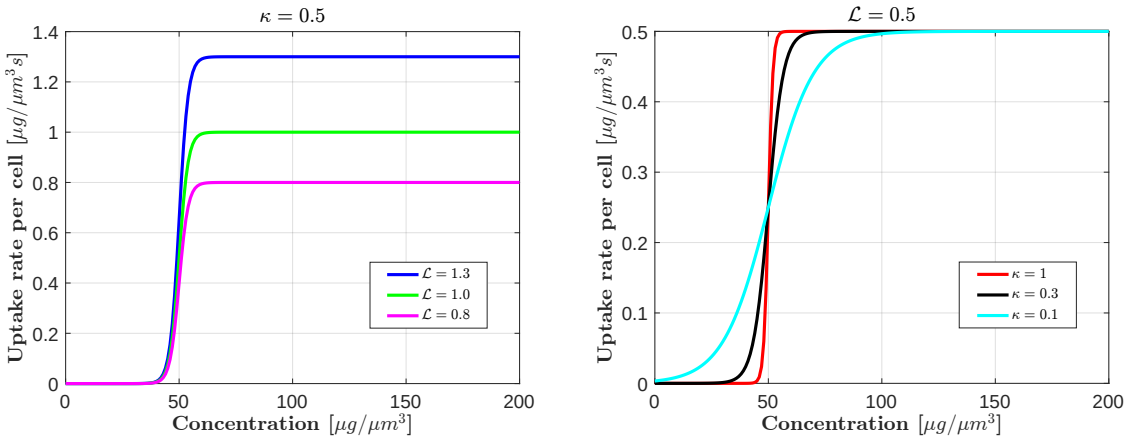
Figure 1: Fitting of the uptake rate data. The parameters of the model that best fit the data are $\mathcal{L} = 0.0201$ $[\mu g/\mu m^3 s]$ and $\kappa = 0.0937$ $[\mu m^3/\mu g]$.

The parameters out of the simulation are: $\mathcal{L} = 0.0201$ $[\mu g/\mu m^3 s]$ and $\kappa = 0.0937$ $[\mu m^3/\mu g]$ (see figure 1), which fit the data with a squared 2-norm of the residual equal to 5.4386x10^{-6}.

1.1.1 Variation of parameters:

In the following analysis the parameters are considered to be always positive, in order to replicate the relationship seen in the uptake rate data.

When keeping constant κ and increasing only the parameter $\mathcal{L}$, the plateau of the drug uptake rate increases and the steepness of the curve remains constant (see figure 2a), no change in its dynamics. On the contrary, when $\mathcal{L}$ is constant and κ increases, the plateau is the same and the steepness increases (figure 2b).



(a) (b)

Figure 2: Behavior of the uptake rate function when varying its parameters $\mathcal{L}$ and κ. (a) Variation of $\mathcal{L}$ with a constant $\kappa = 0.5$, and (b) Variation of κ with a constant $\mathcal{L} = 0.5$.

2 Question 2

Use a hybrid agent-based model of your choice (on-lattice, off-lattice, or another) to mimic in vitro Petri-dish experiments in which cells are seeded within the domain (seeding density of 35%) and exposed to a biomarker of a specified concentration (from the table above). The biomarker is supplied uniformly in the whole domain once—at the beginning of the experiment, can diffuse within the domain (with a constant diffusion coefficient of $10\mu m^2/s$), is taken up by each cell according to the above uptake equation, and is accumulated inside each cell over time (there is no lethal effect). Provide model description and equations. List model parameters and numerical stability conditions, if any **(25%)**.

2.1 Solution

Model: I am going to use an hybrid agent-based model that considers the cells $C_i, i = 1, ..., N$ as off-lattice agents and the amount of biomarker $\gamma(\mathbf{x}, t)$ on-lattice. Each cell i is characterized by its position $\mathbf{X}_i$, radius R (constant for all cells), age A_i, maturation age A^{mat} (same for all cells), number of neighbors N_i^{neigh}, and the amount of biomarker inside the cell C_i^{γ}.

2.1.1 Rules for Cells:

- *Cell division:*
  When the age of a cell i becomes equal to its maturation age, it divides. The position of the daughter cells, $i1$ and $i2$, can then be described by the following equations:

$$\mathbf{X}_{i1} = \mathbf{X}_i \tag{1}$$

$$\mathbf{X}_{i2} = \mathbf{X}_i + 0.5 * R * (cos(\alpha), sin(\alpha)) \tag{2}$$

where one daughter cell remains at the same position of the mother $\mathbf{X}_i$, see equation (1), and the second is placed at a random angle $\alpha \in (0, 2\pi)$ of $\mathbf{X}_i$ (equation (2)).

The ages of these new cells are reset ($A_{i1} = A_{i2} = 0$), and to avoid division synchronization their maturation ages are changed by $\pm 20\%$ (noise) of the maturation age of the mother A_i^{mat}.

Finally, the concentration of biomarker within the mother cell is redistributed to its daughters: $C_{i1}^{\gamma} = C_{i2}^{\gamma} = 0.5 C_i^{\gamma}$.

- *Repulsive forces:*
  In order to avoid cell overlapping, there is a need to add repulsive forces. In this case, I considered Hookean forces between the cells as follows:

$$\mathbf{F}_{ij} = k(\|\mathbf{X}_j - \mathbf{X}_i\| - 2R)\frac{\mathbf{X}_j - \mathbf{X}_i}{\|\mathbf{X}_j - \mathbf{X}_i\|} \tag{3}$$

  where $\mathbf{F}_{ij} = -\mathbf{F}_{ji}$

- *Cell Relocation:*
  From the net repulsion forces acting on a cell i, a cell relocation follows, i.e., a passive movement. Calculated using the Newton's second law:

$$\sum_{i \neq j}^{N_i^{neigh}} \mathbf{F}_{ij} - \nu \frac{d\mathbf{X}_i}{dt} = 0 \tag{4}$$

- *Biomarker uptake:*
  The function that describes the uptake rate of biomarker by each cell is:

$$\frac{dC_i^{\gamma}}{dt} = \sum_{j}^{N_i^{in}} \frac{\mathcal{L}}{1 + e^{-\kappa(\gamma(\mathbf{x}_j, t) - 50)}} \tag{5}$$

  where the sum is performed over all grid points inside the cell i (N_i^{in}), i.e., where $\|\mathbf{X}_i(t) - \mathbf{x}_j\| < R$. Therefore $\gamma(\mathbf{x}_j, t)$ is the concentration at the grid point $\mathbf{x}_j$ inside the cell i.

2.1.2 PDE for biomarker concentration dynamics:

The equation that models the biomarker concentration $\gamma(\mathbf{x}, t)$ diffusion is:

$$\frac{\partial \gamma(\mathbf{x}, t)}{\partial t} = D_{\gamma} \nabla^2 \gamma(\mathbf{x}, t) - \sum_{i}^{N} \frac{dC_i^{\gamma}}{dt} \tag{6}$$

where the second term is the total uptake rate (sum over all cells uptake), described by the equation (5).

To solve this equation I used the Forward Time Centered Space (FTCS), finite difference method. Therefore, in a 2D domain the **numerical stability condition** is equal to:

$$\frac{D_{\gamma} \Delta t}{h^2} < \frac{1}{4}$$

where D_{γ} is the diffusion coefficient, Δt is the time step, and $\Delta x = \Delta y = h$ is the mesh width.

2.1.3 Model Parameters:

Maturation Age (Doubling time)	$A^{mat} = 20\ [h]$
Cell radius	$R = 6\ [\mu m]$
Overcrowding cell number	$N_{max}^{neigh} = 6$
Neighborhood radius	$R_{neigh} = 3.5R$
Force constant	$k = 100\ \mu g/\mu m s^2]$
Medium viscosity	$\nu = 120\ [\mu g/\mu m s]$
Maximum uptake rate	$\mathcal{L} = 0.0201\ [\mu g/\mu m^2 s]$
Steepness of uptake rate function	$\kappa = 0.0937\ [\mu m^2/\mu g]$
Diffusion coefficient	$D_\gamma = 10\ [\mu m^2/s]$
Domain size	$(-500, 500) \times (-500, 500)\ [\mu m^2]$
Mesh width	$h = 6\ [\mu m]$
Time step	$\Delta t = 0.6\ [s]$

Initial conditions:

Number of cells	$Ncells = 0.35 * mesh\ area/cell\ area$
Biomarker concentration outside cells	γ_0 vary from $1 - 500\ [\mu g/\mu m^2]$
Biomarker concentration inside cells	$\gamma_0^{incell} = 0\ [\mu g/\mu m^2]$
Cells' coordinates	random over the domain size $(-500, 500); (-500, 500)\ [\mu m]$
Cells' ages	randomly sampled from A^{mat}

Boundary conditions:

- Erase cells when go out of the domain.
- Neumann Boundary condition:

$$\frac{\partial \gamma(\mathbf{x}, t)}{\partial \mathbf{n}} = 0$$

which in the code is solved in a central difference approximation.

3 Question 3

For this biomarker to be detectable in clinic, its concentration inside the cells must reach a level of $200\mu g/\mu m^3$. Using the model designed above determine which biomarker concentrations listed above (if any) will result in at least 75% of cells having the detectable level of the accumulated biomarker after the 2-hour long experiment. Summarize your results graphically **(25%)**.

3.1 Solution

For the uptake rate defined in section 1, an initial concentration of $75[\mu g/\mu m^2]$ will already lead to a 100% of cells having a total biomarker concentration equal or greater than 200 $[\mu g/\mu m^2]$, in $2[h]$ experiment. For an initial concentration of $50[\mu g/\mu m^2]$, approximately 70% of cells reach this biomarker concentration threshold (see figures 3 and 4, green bars).

These results are specific to the cell configuration shown in figures 4a and 4b (random seed equal to 7).

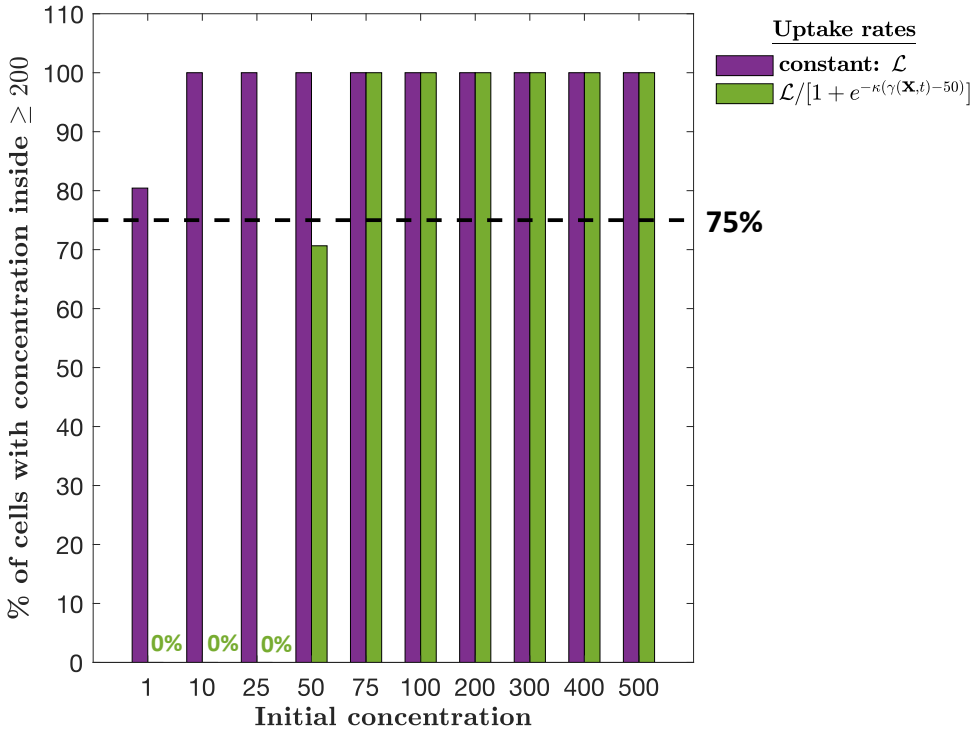


Figure 3: Percentage of cells with concentration of biomarker inside them greater or equal than 200 $[\mu g/\mu m^2]$. Purple bars correspond to the constant uptake rate, and green bars to the uptake rate defined in section 1 (logistic function). The dashed line indicates the 75% threshold.

Figure 4 shows the final distribution of concentrations inside cells and on the domain, for initial concentrations of 50 and 75$[\mu g/\mu m^2]$. Top figure 4a shows the histogram for the case of initial concentration of 50$[\mu g/\mu m^2]$, the one that could not reach the 75% threshold. Final concentrations inside cells for this case range from $\sim$ 120 to $\sim$ 270$[\mu g/\mu m^2]$. Contrary, for an initial concentration of biomarker equal to 75$[\mu g/\mu m^2]$, the final concentrations inside cells range from 200 to $\sim$ 500$[\mu g/\mu m^2]$ (figures 4b).

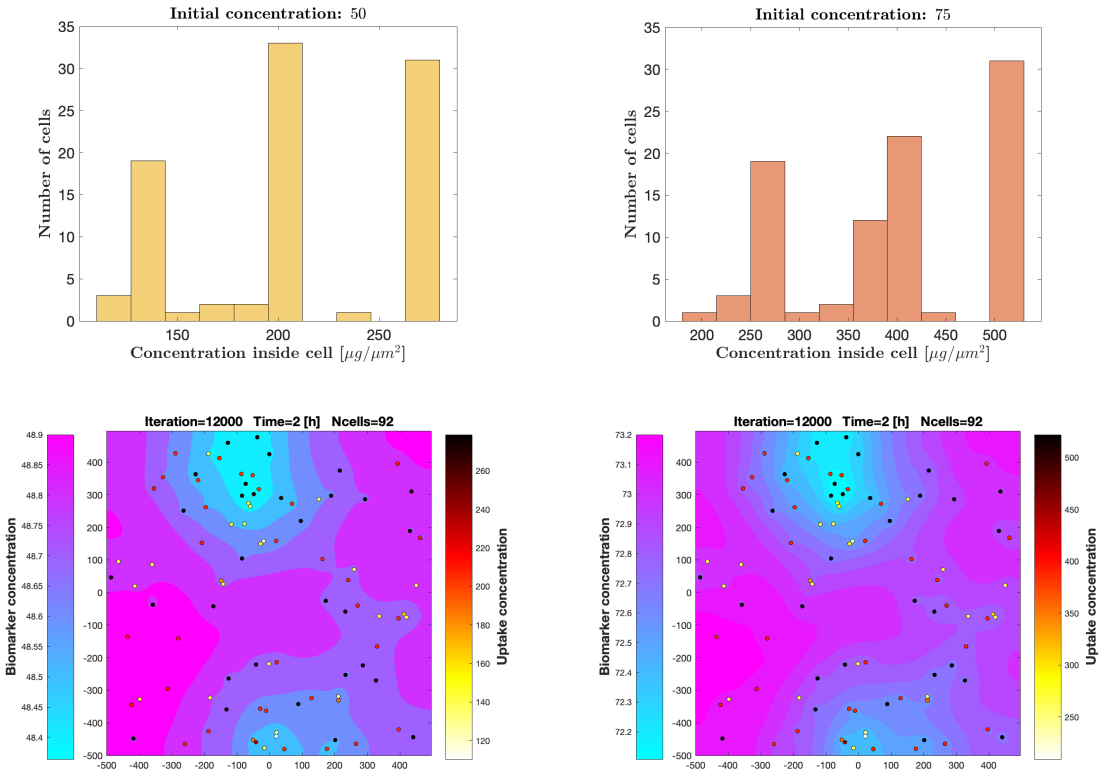
4 Question 4

Choose a different uptake function and check if it will provide a more efficient treatment, i.e., if a lower biomarker concentration than the one found in the previous step, will achieve the same effect (the detectable biomarker level in at least 75% of cells). Justify your answer **(25%)**.

4.1 Solution

For this question I chose a constant uptake rate $\mathcal{L} = 0.0202[\mu g/\mu m^2 s]$. Since this is not dependant on the biomarker concentration available, in order to avoid the cell to take more than is available in a grid point, one must include the following condition: $uptake = min(\mathcal{L} * dt, \gamma(\mathbf{x}, t))$. Therefore, the cell will always take rather the concentration related to the constant uptake rate or the actual value of the concentration at the grid point. Whichever is smaller.

As can be seen in figures 3 (purple bars) and 5, more than the 75% of the cells will have already taken a concentration of 200$[\mu g/\mu m^2]$ or more at the end of the simulation, for an initial concentration of 1$[\mu g/\mu m^2]$. Final concentrations inside cells for this case range from $\sim$ 125 to $\sim$ 470$[\mu g/\mu m^2]$.



(a) (b)

Figure 4: Histograms (top) and ABM colormaps (bottom) of the biomarker uptake - after 2 hours experiment - for two initial concentrations and logistic uptake rate function. Initial concentrations of (a) $50[\mu g/\mu m^2]$ and (b) $75[\mu g/\mu m^2]$.

This constant uptake rate function is more efficient than the logistic one -with maximum rate equal to the constant case-, which achieves the goal at an initial concentration of $75[\mu g/\mu m^2]$. This happens because, for a same value of time the cells are always taken the same amount of biomarker, that during the most part of the simulation is greater than the amount of biomarker taken by the logistic case. A comparison between the colormaps of figures 4 and 5 reflect this fact better, where a mostly biomarker depleted domain is shown after $2[h]$ experiment for the constant rate uptake function.

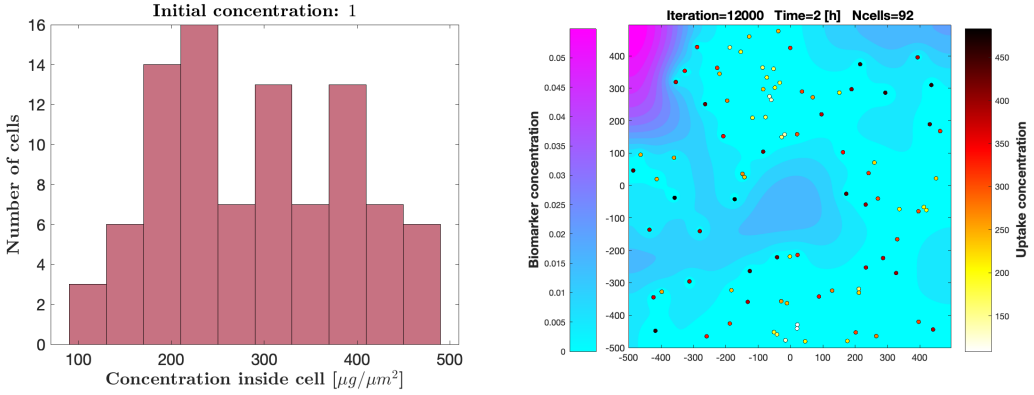


Figure 5: Histogram (left) and ABM colormap (right) of the biomarker uptake - after 2 hours experiment - for an initial concentration of $1[\mu g/\mu m^2]$ and constant uptake rate $\mathcal{L}$.