Optimal Control of Free Boundary Models for Tumor Growth

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ICERM Workshop: Fostering Cross-Disciplinary Collaboration in Biology, Medicine, and Computational Science

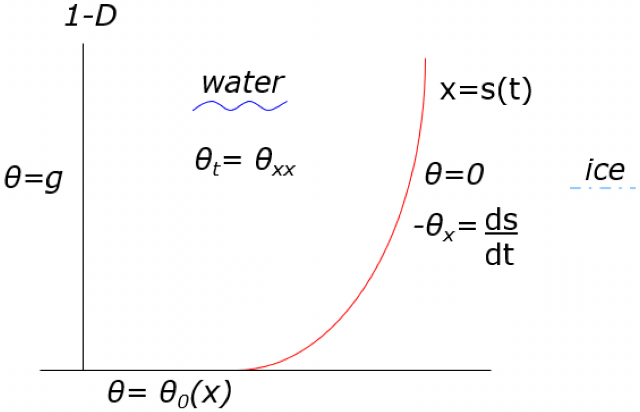
Outline

1. Introduction to free boundary problems
   - Free boundary problems
   - Two well-known examples
2. Tumor growth model
   - Model setup
   - Preliminary results
3. Optimal control of the tumor growth model
   - Optimal control theory
   - Numerical simulations

Free boundary problem and its applications

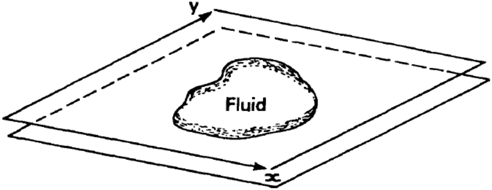
- In mathematics, a free boundary problem (FBP) is a partial differential equation to be solved for both an unknown function u and an unknown domain Ω.
- FBPs have a wide range of applications in:
  - **physics and engineering** (e.g., melting or solidification of materials, contact problems);
  - **finances** (e.g., credit rating migration, optimal exercise value in the Black-Scholes model);
  - **biology** (e.g., tumor growth, wound healing, atherosclerotic plaque formation)
  - **ecology** (e.g., introducation of a new species, propagation of diseases)
- Two examples: Stefan problem (melting of solid), and Hele-Shaw problem (a drop of water between two parallel plates).

Stefan problem



- In the case of two-phase, several space dimensions, the problem is much harder. Even if the data are very smooth, the solution need not be smooth [Friedman, 1968, Trans. Am. Math. Soc]

Hele-Shaw problem

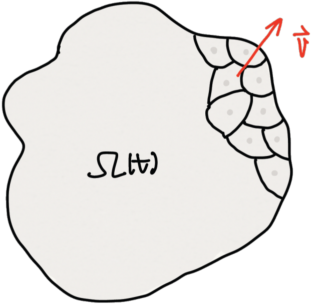


Elliott & Ockendon 1982

- $u(x,t)$ denotes the pressure
- $\Omega(t)$ denotes the unknown domain
- velocity $\vec{v} = -\nabla u$
- $$\begin{aligned} \Delta u &= 0 && \text{in } \Omega(t), \\ u &= \kappa && \text{on } \partial\Omega(t), \\ V_n &= -\tfrac{\partial u}{\partial n} && \text{on } \partial\Omega(t). \end{aligned}$$
- Stationary solutions are radially symmetric.

Outline

Basic tumor growth model



- Diffusion of the nutrients:

$$
\begin{aligned}
&\sigma_t = \Delta\sigma - \sigma && \text{in the tumor region } \Omega(t),\\
&\sigma = 1 && \text{on the tumor boundary } \partial\Omega(t).
\end{aligned}
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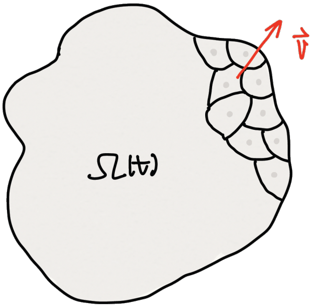
Basic tumor growth model



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Basic tumor growth model

- Conservation of mass: $\operatorname{div}\vec{V} = S$, $S =$ proliferation rate.
  Simplified assumption: linear dependence on σ: $S = \mu(\sigma - \widetilde{\sigma})$, (here $\widetilde{\sigma} > 0$ comes from apoptosis;μ tumor aggressiveness parameter)
- Extra Cellular Matrix $\Rightarrow$ porous medium: Darcy's law: $\vec{V} = -\nabla p$.

$$\Delta p = -\mu(\sigma - \widetilde{\sigma}) \quad \text{in } \Omega(t).$$

- Cell-to-cell adhesiveness gives the boundary condition

$$p = \kappa \quad \text{on } \partial\Omega(t).$$

- Continuity: $V_n = -\dfrac{\partial p}{\partial n} \quad$ on $\partial\Omega(t)$
  where V_n= velocity in the normal n direction.
- Initial conditions $\sigma|_{t=0} = \sigma_0 \quad$ in $\Omega(0)$, where $\Omega(0)$ is given.

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Well-posedness:

- Local in time problem is well posed [Chen-Friedman, 2003, SIAM J. Math. Anal.]
- However, the global existence of a classical solution is still open.

Basic tumor growth model

- If $0 < \widetilde{\sigma} < 1$, the model admits a unique radially symmetric stationary solution [Friedman-Reitich, 2001, Trans. Amer. Math. Soc.], [Friedman-Reitich, 1999, J. Math. Bio.]
- The radially symmetric solution is linearly stable when μ is small and unstable when μ is large [Friedman-Hu, 2006, Arch. Rat. Mech. Anal.], [Friedman-Hu, 2006, J. Diff. Eqn.]
- There exists a sequence of symmetry-breaking bifurcation branches [Fontelos-Friedman, 2003, Asymptot. Anal.], [Friedman-Reitich, 2001, Trans. Amer. Math. Soc.],[Friedman-Hu, 2008, Tran. Amer. Math.]
- Extensions by Cui, Escher, Hao, Lam, Wu, Wang, Huang, ... Including necrotic, inhibitors, the effect of angiogenesis, ...

A systematic survey of tumor model studies:

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Adding a control

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\end{aligned}
$$

- m: anti-cancer strategy, which acts by reducing nutrient levels inside the tumor

Adding a control

- For simplicity, we first consider spatially independent controls
- We define the set of admissible controls,

$$U_M = \{m \in L^\infty(0,T) : 0 \leqslant m(t) \leqslant M \; \forall t \in (0,T)\},$$

  where $M > 0$ is the maximal level of treatment
- The objective functional is

$$J(m) = \int_0^T \Big(|\Omega(t)| + \beta m^2(t)\Big)\mathrm{d}t,$$

  where β quantifies the importance of minimizing side effects within the overall objective
- The goal is to determine an optimal control $m^* \in U_M$ such that

$$J(m^*) = \min_{m \in U_M} J(m)$$

Adding a control

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such that

$$\begin{aligned}
&\sigma_t = \Delta\sigma - (1+m)\sigma && \text{in } \Omega(t),\\
&\Delta p = -\mu(\sigma - \widetilde{\sigma}) && \text{in } \Omega(t),\\
&\sigma = 1 && \text{on } \partial\Omega(t),\\
&p = \kappa && \text{on } \partial\Omega(t),\\
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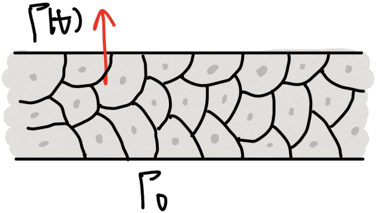
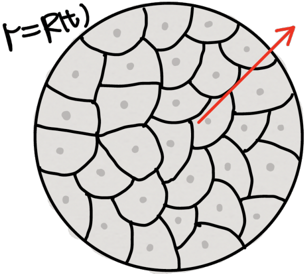
Special Geometries





Radially symmetric case

$$
\begin{aligned}
\sigma_t - \Delta_r \sigma + (1+m)\sigma = 0 \qquad & \text{in } B_{R(t)},\ 0 < t < T, \\
\sigma = 1 \qquad & \text{on } \partial B_{R(t)},\ 0 < t < T. \\
R'(t) = \frac{\mu}{R^2(t)} \int_0^{R(t)} (\sigma - \widetilde{\sigma}) r^2 \mathrm{d}r \qquad & 0 < t < T, \\
\sigma = \sigma_0 \qquad & \text{in } B_{R_0},\ t = 0,
\end{aligned}
$$

Theorem

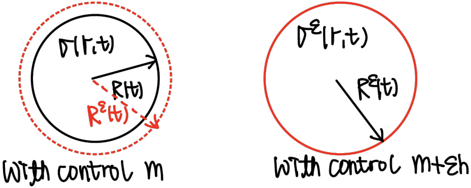
There exists a unique solution (σ, R), where $\sigma \in W^{2,1,p}$ for any $p > 1$ and $R \in C^1$. The solution exists for all $T > 0$.

Theorem

For a fixed $T > 0$, there exists $m^* \in U_M$ that minimizes the objective functional $J(m)$.

Sensitivity system

- Differentiability of the mapping $m \longmapsto (\sigma, R)$



- $\xi = \frac{r}{R(t)}$, $\sigma(r,t) = u(\xi,t) = u\left(\frac{r}{R(t)}, t\right)$, $\sigma_0(r) = u_0(\xi) = u_0\left(\frac{r}{R(t)}\right)$

$$\begin{cases} u_t - \dfrac{R'}{R}\xi u_\xi - \dfrac{1}{\xi^2 R^2}\dfrac{\partial}{\partial \xi}(\xi^2 u_\xi) + (1+m)u = 0 & 0 < \xi < 1,\ 0 < t < T, \\ u = 1 & \xi = 1,\ 0 < t < T, \\ u_\xi = 0 & \xi = 0,\ 0 < t < T, \\ R' = R\mu \displaystyle\int_0^1 (u - \widetilde{\sigma})\xi^2 \mathrm{d}\xi & 0 < t < T, \\ u = u_0 & 0 < \xi < 1,\ t = 0, \\ R = R_0 & t = 0. \end{cases}$$

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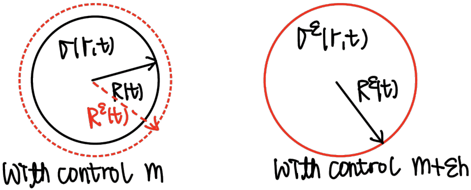

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Sensitivity system

Theorem

The mapping $m \to (u,R)$ is differentiable: as $\varepsilon \to 0$,

$$\frac{u^\varepsilon - u}{\varepsilon} \rightharpoonup v \text{ weakly in } W^{2,1,p}(Q_T) \text{ and } \frac{R^\varepsilon - R}{\varepsilon} \rightharpoonup \rho \text{ weakly in } W^{1,p}(0,T).$$

$$\begin{cases} v_t - \dfrac{R'}{R}\xi v_\xi - \dfrac{1}{\xi^2 R^2}\dfrac{\partial}{\partial \xi}(\xi^2 v_\xi) + (1+m)v = & \\ \qquad \dfrac{\rho'}{R}\xi u_\xi - \dfrac{R'\rho}{R^2}\xi u_\xi - \dfrac{2\rho}{\xi^2 R^3}\dfrac{\partial}{\partial \xi}(\xi^2 u_\xi) - uh & 0<\xi<1,\ 0<t<T, \\ v = 0 & \xi = 1,\ 0<t<T, \\ v_\xi = 0 & \xi = 0,\ 0<t<T, \\ \rho' = \rho\mu \displaystyle\int_0^1 (u-\widetilde{\sigma})\xi^2 \mathrm{d}\xi + R\mu \int_0^1 v\xi^2 \mathrm{d}\xi & 0<t<T, \\ v = 0 & 0<\xi<1,\ t=0, \\ \rho = 0 & t = 0. \end{cases}$$

Adjoint system

- Rewrite the sensitivity system as $\mathscr{L}\begin{pmatrix} v \\ \rho \end{pmatrix} = \begin{pmatrix} -uh \\ 0 \end{pmatrix}$,

  where $\mathscr{L}\begin{pmatrix} v \\ \rho \end{pmatrix} = \begin{pmatrix} L_1 v \\ L_2\rho \end{pmatrix} + \mathscr{B}\begin{pmatrix} v \\ \rho \end{pmatrix}$

  $$\mathscr{B}\begin{pmatrix} v \\ \rho \end{pmatrix} = \begin{pmatrix} -\frac{\rho'}{R}\xi u_\xi + \frac{R'}{R^2}\rho\xi u_\xi + \frac{2\rho}{\xi^2 R^3}\frac{\partial}{\partial\xi}\left(\xi^2 u_\xi\right) \\ -R\mu\int_0^1 v\xi^2 \mathrm{d}\xi \end{pmatrix}$$

- The adjoint operator $\mathscr{L}^*\begin{pmatrix} \lambda_1 \\ \lambda_2 \end{pmatrix} = \begin{pmatrix} L_1^*\lambda_1 \\ L_2^*\lambda_2 \end{pmatrix} + \mathscr{B}^*\begin{pmatrix} \lambda_1 \\ \lambda_2 \end{pmatrix}$,

  $$\mathscr{B}^*\begin{pmatrix} \lambda_1 \\ \lambda_2 \end{pmatrix} = \begin{pmatrix} -\mu\int_0^1 \lambda_1\xi^3 u_\xi \mathrm{d}\xi - \mu R\lambda_2 \\ \int_0^1 \lambda_1\xi^2\left(\frac{2}{R^3}u_{\xi\xi} + \frac{4}{R^3\xi}u_\xi\right)\mathrm{d}\xi \end{pmatrix}$$

Adjoint system

$$
\begin{cases}
-(\lambda_1)_t - \dfrac{1}{\xi^2 R^2}\dfrac{\partial}{\partial \xi}\left(\xi^2(\lambda_1)_\xi\right) + \dfrac{R'}{R}\xi(\lambda_1)_\xi + \dfrac{3R'}{R}\lambda_1 + \lambda_1(1+m) & \\
\qquad\qquad -\mu\displaystyle\int_0^1 \lambda_1 \xi^3 u_\xi \mathrm{d}\xi - \mu R \lambda_2 = 0 & 0<\xi<1,\ 0<t<T, \\
\lambda_1 = 0 & \xi = 1,\ 0<t<T, \\
(\lambda_1)_\xi = 0 & \xi = 0,\ 0<t<T, \\
-\lambda_2' + \displaystyle\int_0^1 \lambda_1 \xi^2 \left(\dfrac{2}{R^3}u_{\xi\xi} + \dfrac{4}{R^3\xi}u_\xi\right)\mathrm{d}\xi - \lambda_2\mu\displaystyle\int_0^1 (u-\widetilde{\sigma})\xi^2 \mathrm{d}\xi & \\
\qquad\qquad = 4\pi R^2 & 0<t<T, \\
\lambda_1 = 0 & 0<\xi<1, t=T, \\
\lambda_2 = 0 & t = T.
\end{cases}
$$

Optimality system

- $\lim_{\varepsilon\to 0^+} \frac{J(m+\varepsilon h)-J(m)}{\varepsilon} \geq 0 \;\Rightarrow\; \int_0^T h\left(2\beta m - \int_0^1 u\lambda_1\xi^2 \mathrm{d}\xi\right)\mathrm{d}t \geq 0$
- On the set $\{(\xi,t) : 0 < u^*(\xi,t) < M\}$, the variation $h \in L^\infty(0,T)$ is arbitrary. Therefore, we obtain

$$2\beta m - \int_0^1 u\lambda_1\xi^2 \mathrm{d}\xi = 0$$

- We derive a characterization of the optimal control:

$$m^*(t) = \min\left\{M, \max\left\{0, \frac{\int_0^1 u^*(\xi,t)\lambda_1(\xi,t)\xi^2 \mathrm{d}\xi}{2\beta}\right\}\right\}.$$

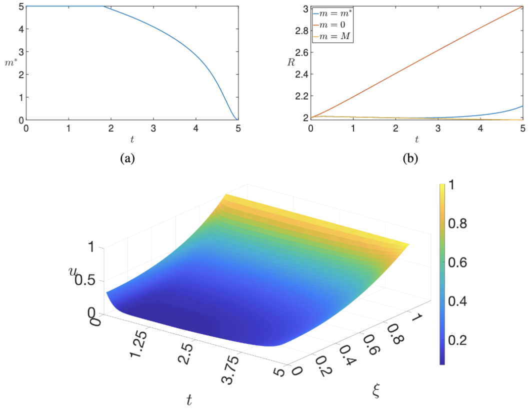
- Optimality system = state system + adjoint systems + characterization of the optimal control

Theorem

If $T > 0$ is sufficiently small or β is sufficiently large, then there is a unique solution $(u, R, \lambda_1, \lambda_2)$ of the optimality system, where $u, \lambda_1 \in W^{2,1,p}(Q_T)$ for any $p > 1$ and $R, \lambda_2 \in C^1[0,T]$.

Numerical simulations

- Algorithm: Forward-Backward Sweep Method



(a) (b) (c)

- $J(0) = 345.7407$ (no control); $J(m^*) = 196.8044$ (optimal control); $J(M) = 204.2545$ (maximal control)

Numerical simulations

- M stands for the maximal level of treatment that can be achieved and tolerated.

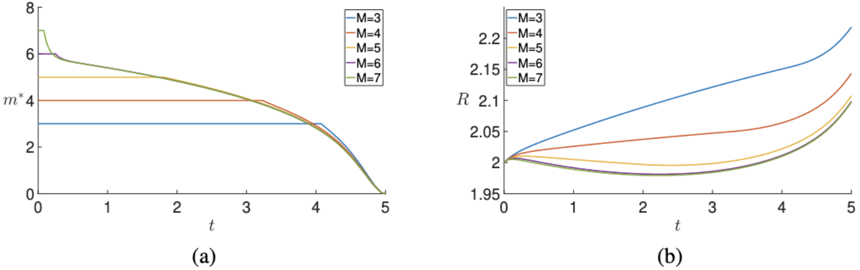


Figure: Optimal control and tumor radius when varying parameter value of M.

Numerical simulations

- β measures the severity/importance of side effects.

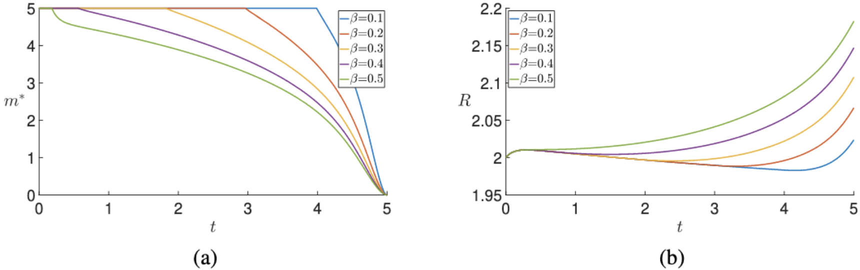
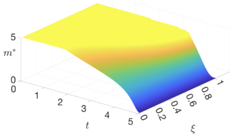


Figure: Optimal control and tumor radius when varying parameter value of β.

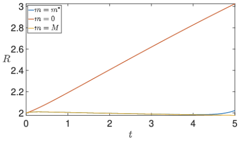
- Side effects limit the magnitude and benefits of the control.

Can we let the control be spatially dependent? Yes!

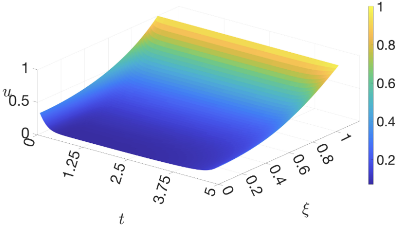
- Admissible set $U_M = \{m \in L^\infty((0,1)\times(0,T)) : 0 \leqslant m \leqslant M\}$
- Objective functional $J(m) = \int_0^T \frac{4}{3}\pi R^3(t)\mathrm{d}t + \int_0^T \int_0^1 \beta m^2(\xi,t)\mathrm{d}\xi\,\mathrm{d}t$
- Characterization $m^*(\xi,t) = \min\left\{M, \max\left\{0, \frac{u(\xi,t)\lambda_1(\xi,t)}{2\beta}\right\}\right\}$



(a)



(b)



(c)

Can we put control elsewhere? Yes!

- Add a control in the equation of the tumor proliferation rate $S = \mu(\sigma - \widetilde{\sigma} - Bm)$
- More complicated objective functional $J(m) = A_1 R(T) + \int_0^T A_2 R(t)\mathrm{d}t + \int_0^T A e^{-\gamma t} m^2(t)\mathrm{d}t$
- The model in the radially symmetric case becomes

$$\min_{m \in U_M} J(m) = A_1 R(T) + \int_0^T A_2 R(t)\mathrm{d}t + \int_0^T A e^{-\gamma t} m^2(t)\mathrm{d}t$$

subject to

$$\begin{aligned}
&\sigma_t - \Delta_r \sigma + \sigma = 0 && \text{in } B_{R(t)},\ 0 < t < T,\\
&\sigma = 1 && \text{on } \partial B_{R(t)},\ 0 < t < T,\\
&R'(t) = \frac{\mu}{R^2(t)} \int_0^{R(t)} (\sigma - \widetilde{\sigma} - \beta m) r^2 \mathrm{d}r && 0 < t < T,\\
&\sigma = \sigma_0 && \text{in } B_{R_0}.
\end{aligned}$$

- Assuming $m \in L^\infty$, we can prove $\sigma \in W^{2,1,p}$ and $R \in W^{1,\infty}$

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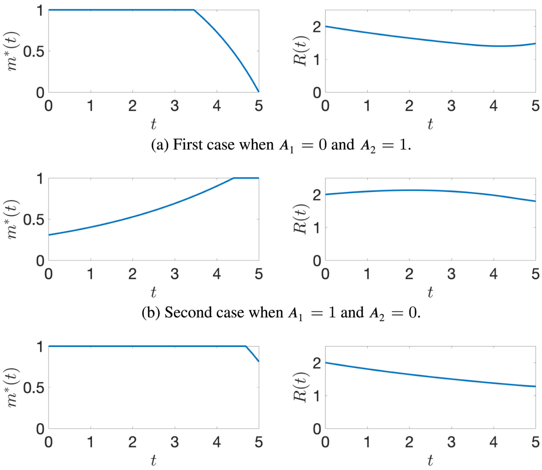
Numerical simulations



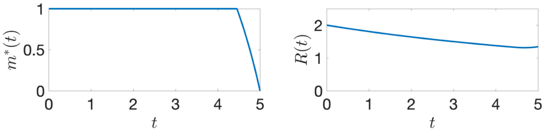
(a) First case when $A_1 = 0$ and $A_2 = 1$.

(b) Second case when $A_1 = 1$ and $A_2 = 0$.

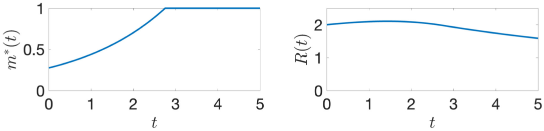
(c) Third case when $A_1 = 1$ and $A_2 = 1$.

Numerical simulations

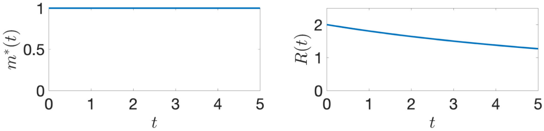
- γ measures the decay rate of side effects.
- All other parameter values are kept the same, while γ is increased from 0.2 to 0.4.



(a) First case when $A_1 = 0$ and $A_2 = 1$.



(b) Second case when $A_1 = 1$ and $A_2 = 0$.



(c) Third case when $A_1 = 1$ and $A_2 = 1$.

Summary and future work

- In summary, we have developed the optimal control framework for the free boundary tumor growth model within some special geometries (multilayered and radially symmetric).
- In future work, we plan to relax the restrictions on geometry.

- Zhao, X. E., Wu, Y., Leander, R., Ding, W., & Lenhart, S. (2024). Optimal control of treatment in a free boundary problem modeling multilayered tumor growth. arXiv preprint arXiv:2410.14114.
- Wu, Y., Zhao, X. E., Leander, R., & Ding, W. (2025). Optimal Control for a Free Boundary Tumor Growth Model. EECT.
- Zhao, X. E. (2025). Analysis and optimization of tumor inhibitor treatments in a free boundary tumor growth model. Nonlinear Anal. Real World Appl., 86, 104406.

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Thank you!