Optimal control of treatment time in a diffuse interface model of tumour growth

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joint work with

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Outline

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Setting

Tumours grown *in vitro* often exhibit "layered" structures:

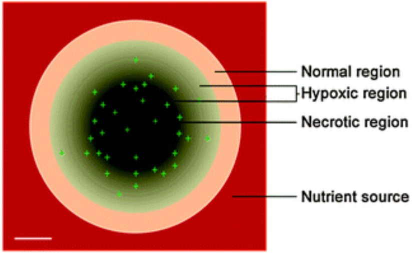

Figure: Zhang et al. *Integr. Biol.*, 2012, 4, 1072–1080. Scale bar $100\mu m = 0.1mm$

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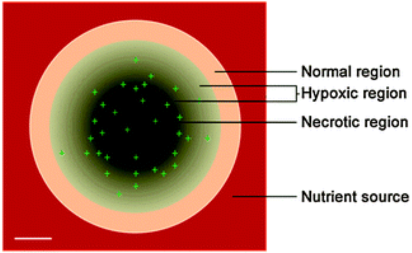

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Lack of a vasculature (blood supply) leads to the development of hypoxic and necrotic regions.

We would like to study the case where there are only proliferating tumour cells surrounded by (healthy) host cells, and a nutrient (e.g. glucose) is present.

Why optimise over the treatment time?

Common treatment for tumours are

- Cytotoxic drugs - target and damage rapidly dividing cells.
- Cytostatic drugs - blocks proliferation.
- Radiation therapy.
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Thus, aside from optimising the drug distribution, we should also consider optimising the treatment time.

Cahn–Hilliard + nutrient models with source terms

The simplest phase field model is a Cahn–Hilliard system with source terms

$$\begin{aligned} \partial_t \varphi &= \Delta \mu + \mathcal{M}, \\ \mu &= \Psi'(\varphi) - \Delta \varphi. \end{aligned}$$

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Examples:

- Linear kinetics [Cristini, Li, Lowengrub, Wise], [Wise, Lowengrub, Frieboes, Cristini], [Garcke, L.]

$$\mathcal{M} = h(\varphi)(\mathcal{P}\sigma - \mathcal{A}), \quad \mathcal{S} = h(\varphi)\mathcal{C}\sigma.$$

- Linear phenomenological laws for chemical reactions [Hawkins–Daarud, Prudhomme, van der Zee, Oden], [Colli, Gilardi, Hilhorst], [Frigeri, Grasselli, Rocca]

$$\mathcal{M} = \mathcal{S} = h(\varphi)(\sigma - \mu).$$

Cahn–Hilliard–Darcy models

Another variant is a Cahn–Hilliard–Darcy model with source terms:

$$\begin{aligned}
\mathrm{div}\boldsymbol{v} &= \mathcal{H}, \\
\boldsymbol{v} &= -K(\nabla p - \mu \nabla \varphi), \\
\partial_t \varphi + \mathrm{div}(\varphi \boldsymbol{v}) &= \Delta \mu + \mathcal{M}, \\
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which treats the tumour and host cells as inertial-less fluids.

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- Well-posedness/long-time behaviour studied in [Lowengrub, Titi, Zhao] ($\mathcal{H} = \mathcal{M} = 0$) and in [Jiang, Wu, Zheng] ($\mathcal{H} = \mathcal{M}$ prescribed).

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\mu &= \Psi'(\varphi) - \Delta\varphi - \sigma, \\
\partial_t\sigma + \mathrm{div}(\sigma\boldsymbol{v}) &= \Delta\sigma - \Delta\varphi - \mathcal{S},
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- The full model introduced in [Garcke, L., Sitka, Styles] couples an additional nutrient equation. Global weak existence established recently in [Garcke, L.] for $\mathcal{H}$ prescribed and $\mathcal{M}, \mathcal{S}$ with linear growth.

Outline

State equations

We consider the Cahn–Hilliard + nutrient model with linear kinetics and Neumann boundary conditions:

$$\begin{aligned}
\partial_t \varphi &= \Delta \mu + h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u), \\
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Here $h(s)$ is an interpolation function such that $h(-1) = 0$ and $h(1) = 1$, and

- $h(\varphi)\mathcal{P}\sigma$ - proliferation of tumour cells proportional to nutrient concentration,
- $h(\varphi)\mathcal{A}$ - apoptosis of tumour cells,
- $h(\varphi)\mathcal{C}\sigma$ - consumption of nutrient by the tumour cells,
- $h(\varphi)\alpha u$ - elimination of tumour cells by cytotoxic drugs at a constant rate α.

Objective functional

For positive β_T, β_u and non-negative $\beta_Q, \beta_\Omega, \beta_S$, we consider

$$
\begin{aligned}
J(\varphi, u, \tau) := \int_0^\tau \int_\Omega \frac{\beta_Q}{2} \left|\varphi - \varphi_Q\right|^2 + \int_\Omega \frac{\beta_\Omega}{2} \left|\varphi(\tau) - \varphi_\Omega\right|^2 \\
+ \int_\Omega \frac{\beta_S}{2} (1 + \varphi(\tau)) + \int_0^\tau \int_\Omega \frac{\beta_u}{2} \left|u\right|^2 + \beta_T \tau.
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- the variable τ denotes the unknown treatment time to be optimised,
- φ_Q is a desired evolution of the tumour over the treatment,
- φ_Ω is a desired final state of the tumour,
- the term $\frac{1+\varphi(\tau)}{2}$ measures the size of the tumour at the end of the treatment,
- the constant β_T penalizes long treatment times.

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In the case J is not dependent on τ (i.e. take $\tau = T$ fixed) and $\beta_S = \beta_T = 0$, a similar control problem has been recently studied in [Colli, Gilardi, Rocca, Sprekels].

Relaxed objective functional

Let $r > 0$ be fixed and let $T \in (0, \infty)$ denote a maximal time, we define

$$J_r(\varphi, u, \tau) := \int_0^\tau \int_\Omega \frac{\beta_Q}{2} |\varphi - \varphi_Q|^2 + \frac{1}{r} \int_{\tau - r}^{\tau} \int_\Omega \frac{\beta_\Omega}{2} |\varphi - \varphi_\Omega|^2$$
$$+ \frac{1}{r} \int_{\tau - r}^{\tau} \int_\Omega \frac{\beta_S}{2} (1 + \varphi) + \int_0^T \int_\Omega \frac{\beta_u}{2} |u|^2 + \beta_T \tau.$$

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The optimal control problem is

$$\min_{(\varphi, u, \tau)} J_r(\varphi, u, \tau)$$

subject to $\tau \in (0, T)$, $u \in \mathcal{U}_{\mathrm{ad}} = \{f \in L^\infty(\Omega \times (0, T)) : 0 \leq f \leq 1\}$, and

$$\begin{aligned}
\partial_t \varphi &= \Delta \mu + h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u) && \text{in } \Omega \times (0, T) = Q, \\
\mu &= \Psi'(\varphi) - \Delta \varphi && \text{in } Q, \\
\partial_t \sigma &= \Delta \sigma - \mathcal{C} h(\varphi) \sigma && \text{in } Q, \\
0 &= \partial_\nu \varphi = \partial_\nu \sigma = \partial_\nu \mu && \text{on } \partial\Omega \times (0, T), \\
\varphi(0) &= \varphi_0, \quad \sigma(0) = \sigma_0 && \text{in } \Omega.
\end{aligned}$$

Well-posedness of state equations

Theorem

Let $\varphi_0 \in H^3, \sigma_0 \in H^1$ *with* $0 \leq \sigma_0 \leq 1$, $h \in C^{0,1}(\mathbb{R}) \cap L^\infty(\mathbb{R})$ *non-negative, and* Ψ *is a quartic potential, then for every* $u \in \mathcal{U}_{\mathrm{ad}}$ *there exists a unique triplet*

$$\varphi \in L^\infty(0,T;H^2) \cap L^2(0,T;H^3) \cap H^1(0,T;L^2) \cap C^0(\overline{Q}),$$
$$\mu \in L^2(0,T;H^2) \cap L^\infty(0,T;L^2),$$
$$\sigma \in L^\infty(0,T;H^1) \cap L^2(0,T;H^2) \cap H^1(0,T;L^2), \quad 0 \leq \sigma \leq 1 \text{ a.e. in } Q$$

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satisfying the state equations.

Key points:

- Compact embedding $L^\infty(0,T;H^2) \cap H^1(0,T;L^2) \subset\subset C^0(\overline{Q})$,
- Boundedness of σ comes from a weak comparison principle applied to

$$\partial_t \sigma = \Delta\sigma - \mathcal{C}h(\varphi)\sigma.$$

- Proof utilises a Schauder fixed point argument (Reason: the weak comparison principle cannot be applied to the discrete approximations σ_k from a Galerkin approximation).

Existence of a minimiser

- Using that $\varphi \in L^1(0,T;L^1)$, J_r is bounded from below:

$$J_r(\varphi,u,\tau) := \int_0^\tau \int_\Omega \frac{\beta_Q}{2}|\varphi-\varphi_Q|^2 + \frac{1}{r}\int_{\tau-r}^\tau \int_\Omega \frac{\beta_\Omega}{2}|\varphi-\varphi_\Omega|^2 + \frac{1}{r}\int_{\tau-r}^\tau \int_\Omega \frac{\beta_S}{2}(1+\varphi) + \int_0^T \int_\Omega \frac{\beta_u}{2}|u|^2 + \beta_T\tau$$

$$\geq -\frac{\beta_S}{2r}\int_{\tau-r}^\tau \int_\Omega |\varphi| \geq -\frac{\beta_S}{2r}\|\varphi\|_{L^1(0,T;L^1)} \geq -C.$$

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- Minimising sequence $(u_n, \tau_n) \in \mathcal{U}_{\text{ad}} \times (0, T)$, with corresponding state variables $(\varphi_n, \mu_n, \sigma_n)$ such that

$$\lim_{n \to \infty} J_r(\varphi_n, u_n, \tau_n) = \inf_{(\phi, w, s)} J_r(\phi, w, s).$$

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- We extract a convergent subsequence $u_n \rightharpoonup^* u_* \in L^\infty(Q)$ and limit functions $(\varphi_*, \mu_*, \sigma_*)$ satisfying the state equations and

$$\varphi_n \to \varphi_* \text{ in } C^0([0,T];L^2) \cap L^2(Q).$$

Key point: All of the convergence are with respect to the interval $[0, T]$.

Existence of a minimiser

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- As $\{\tau_n\}_{n \in \mathbb{N}}$ is a bounded sequence, we extract a convergent subsequence $\tau_n \to \tau_* \in [0, T]$.

Existence of minimiser

To pass to the limit in:

$$J_r(\varphi_n, u_n, \tau_n) := \int_0^{\tau_n} \int_\Omega \frac{\beta_Q}{2} |\varphi_n - \varphi_Q|^2 + \frac{1}{r} \int_{\tau_n - r}^{\tau_n} \int_\Omega \frac{\beta_\Omega}{2} |\varphi_n - \varphi_\Omega|^2 + \frac{1}{r} \int_{\tau_n - r}^{\tau_n} \int_\Omega \frac{\beta_S}{2} (1 + \varphi_n) + \int_0^T \int_\Omega \frac{\beta_u}{2} |u_n|^2 + \beta_T \tau_n,$$

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we make use of

$$\chi_{[0,\tau_n]}(t) \to \chi_{[0,\tau_*]}(t), \quad \varphi_n - \varphi_Q \to \varphi_* - \varphi_Q \text{ strongly in } L^2(Q)$$

to obtain

$$\lim_{n \to \infty} \int_0^{\tau_n} \int_\Omega |\varphi_n - \varphi_Q|^2 = \lim_{n \to \infty} \int_Q |\varphi_n - \varphi_Q|^2 \chi_{[0,\tau_n]}(t) = \int_0^{\tau_*} \int_\Omega |\varphi_* - \varphi_Q|^2 .$$

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Weak lower semi-continuity of the $L^2(Q)$ norm then yields

$$\inf_{(\phi,w,s)} J_r(\phi, w, s) \geq \liminf_{n\to\infty} J_r(\varphi_n, u_n, \tau_n) \geq J_r(\varphi_*, u_*, \tau_*).$$

That is, (u_*, τ_*) is a minimiser.

Outline

Fréchet differentiability with respect to the control

We set $\mathcal{S}(u) = (\varphi, \mu, \sigma)$ as the solution operator on the interval $[0, T]$, and introduce the linearized state variables $(\Phi^w, \Xi^w, \Sigma^w)$ corresponding to w as solutions to

$$\begin{aligned}
\partial_t \Phi &= \Delta \Xi + h(\varphi)(\mathcal{P}\Sigma - \alpha w) + h'(\varphi)\Phi(\mathcal{P}\sigma - \mathcal{A} - \alpha u), \\
\Xi &= \Psi''(\varphi)\Phi - \Delta\Phi, \\
\partial_t \Sigma &= \Delta\Sigma - \mathcal{C}(h(\varphi)\Sigma + h'(\varphi)\Phi\sigma),
\end{aligned}$$

with Neumann boundary conditions and zero initial conditions.

Fréchet differentiability with respect to the control

We set $\mathcal{S}(u) = (\varphi, \mu, \sigma)$ as the solution operator on the interval $[0, T]$, and introduce the linearized state variables $(\Phi^w, \Xi^w, \Sigma^w)$ corresponding to w as solutions to

$$\begin{aligned}
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\end{aligned}$$

with Neumann boundary conditions and zero initial conditions.

Theorem

For any $w \in L^2(Q)$ there exists a unique triplet (Φ, Ξ, Σ) with

$$\begin{aligned}
\Phi &\in L^\infty(0,T;H^1) \cap L^2(0,T;H^3) \cap H^1(0,T;(H^1)^*) =: \mathbb{X}_1, \\
\Xi &\in L^2(0,T;H^1) =: \mathbb{X}_2, \\
\Sigma &\in L^\infty(0,T;H^1) \cap H^1(0,T;L^2) \cap L^2(0,T;H^2) =: \mathbb{X}_3,
\end{aligned}$$

and

$$\|\Phi\|_{\mathbb{X}_1} + \|\Xi\|_{\mathbb{X}_2} + \|\Sigma\|_{\mathbb{X}_3} \leq C\|w\|_{L^2(Q)}$$

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with Neumann boundary conditions and zero initial conditions.

Expectation: The Fréchet derivative of $\mathcal{S}$ at $u \in \mathcal{U}_{\mathrm{ad}}$ in the direction w is

$$\mathrm{D}_u \mathcal{S}(u) w = (\Phi^w, \Xi^w, \Sigma^w).$$

Fréchet differentiability with respect to the control

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Theorem

Let $\mathcal{U} \subset L^2(Q)$ be open such that $\mathcal{U}_{\mathrm{ad}} \subset \mathcal{U}$. Then $\mathcal{S} : \mathcal{U} \subset L^2(Q) \to \mathcal{Y}$ is Fréchet differentiable, where

$$\begin{aligned}
\mathcal{Y} = &\left[L^2(0, T; H^2) \cap L^\infty(0, T; L^2) \cap H^1(0, T; (H^2)^*) \cap C^0([0, T]; L^2)\right] \\
&\times L^2(Q) \times \left[L^\infty(0, T; H^1) \cap H^1(0, T; L^2)\right]
\end{aligned}$$

Fréchet differentiability with respect to the control

We set $\mathcal{S}(u) = (\varphi, \mu, \sigma)$ as the solution operator on the interval $[0, T]$, and introduce the linearized state variables $(\Phi^w, \Xi^w, \Sigma^w)$ corresponding to w as solutions to

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$$\mathrm{D}_u \mathcal{S}(u) w = (\Phi^w, \Xi^w, \Sigma^w).$$

Consequence: For the reduced functional $\mathcal{J}_r(u, \tau) := J_r(\varphi, u, \tau)$,

$$\begin{aligned} \mathrm{D}_u \mathcal{J}_r(u_*, \tau)[w] = \beta_Q \int_0^T \int_\Omega (\varphi_* - \varphi_Q)\Phi^w + \int_Q \beta_u u_* w \\ + \frac{1}{2r} \int_{\tau - r}^{\tau} \int_\Omega \left(\beta_\Omega(\varphi_* - \varphi_\Omega)\Phi^w + \beta_S \Phi^w\right). \end{aligned}$$

Fréchet differentiability with respect to time

Lemma

For $f \in H^1(0,T;L^2) \subset C^0([0,T];L^2)$,

$$\mathrm{D}_\tau \left(\int_0^\tau \int_\Omega |f|^2 \right) = \int_\Omega |f(\tau)|^2 .$$

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Then, for

$$J_r(\varphi, u, \tau) = \int_0^\tau \int_\Omega \frac{\beta_Q}{2} |\varphi - \varphi_Q|^2 + \frac{1}{r} \int_{\tau - r}^\tau \int_\Omega \frac{\beta_\Omega}{2} |\varphi - \varphi_\Omega|^2 + \frac{1}{r} \int_{\tau - r}^\tau \int_\Omega \frac{\beta_S}{2} (1 + \varphi) + \int_0^T \int_\Omega \frac{\beta_u}{2} |u|^2 + \beta_T \tau,$$

we have

$$\mathrm{D}_\tau \mathcal{J}_r(u, \tau_*) = \beta_T + \frac{\beta_Q}{2} \|\varphi(\tau_*) - \varphi_Q(\tau_*)\|_{L^2}^2 + \frac{\beta_\Omega}{2r} \left(\|(\varphi - \varphi_\Omega)(\tau_*)\|_{L^2}^2 - \|(\varphi - \varphi_\Omega)(\tau_* - r)\|_{L^2}^2 \right) + \int_\Omega \frac{\beta_S}{2r} (\varphi(\tau_*) - \varphi(\tau_* - r)).$$

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we have

$$\begin{aligned} \mathrm{D}_\tau \mathcal{J}_r(u, \tau_*) = \beta_T + \frac{\beta_Q}{2} \|\varphi(\tau_*) - \varphi_Q(\tau_*)\|_{L^2}^2 \\ + \frac{\beta_\Omega}{2r} \left(\|(\varphi - \varphi_\Omega)(\tau_*)\|_{L^2}^2 - \|(\varphi - \varphi_\Omega)(\tau_* - r)\|_{L^2}^2 \right) \\ + \int_\Omega \frac{\beta_S}{2r} (\varphi(\tau_*) - \varphi(\tau_* - r)). \end{aligned}$$

Note that the control u does not appear explicitly.

First order optimality conditions

Introducing the adjoint system

$$
\begin{aligned}
-\partial_t p &= \Delta q + \Psi''(\varphi_*)q - \mathcal{C}h'(\varphi_*)\sigma_* r + h'(\varphi_*)(\mathcal{P}\sigma_* - \mathcal{A} - \alpha u_*)p \\
&\quad + \beta_Q(\varphi_* - \varphi_Q) + \frac{1}{2r}\chi_{(\tau_* - r, \tau_*)}(t)(2\beta_\Omega(\varphi_* - \varphi_\Omega) + \beta_S), \\
q &= \Delta p, \\
-\partial_t r &= \Delta r - \mathcal{C}h(\varphi_*)r + \mathcal{P}h(\varphi_*)p
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with Neumann boundary conditions and final time condition $r(\tau_*) = p(\tau_*) = 0$. We have

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\end{aligned}
$$

with Neumann boundary conditions and final time condition $r(\tau_*) = p(\tau_*) = 0$. We have

Theorem

There exists a unique (p, q, r) to the adjoint system such that

$$
\begin{aligned}
& p \in L^2(0,\tau_*; H^2) \cap H^1(0,\tau_*; (H^2)^*) \cap L^\infty(0,\tau_*; L^2) \cap C^0([0,\tau_*]; L^2), \\
& q \in L^2(0,\tau_*; L^2), \\
& r \in L^2(0,\tau_*; H^2) \cap L^\infty(0,\tau_*; H^1) \cap H^1(0,\tau_*; L^2) \cap C^0([0,\tau_*]; L^2).
\end{aligned}
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\end{aligned}$$

with Neumann boundary conditions and final time condition $r(\tau_*) = p(\tau_*) = 0$. We have

Theorem

The optimal control (u_*, τ_*) satisfy

$$\int_0^T \int_\Omega \beta_u u_*(v - u_*) - \int_0^{\tau_*} \int_\Omega h(\varphi_*)\alpha p(v - u_*) \geq 0 \quad \forall v \in \mathcal{U}_{\mathrm{ad}},$$

and

$$\begin{aligned}
&\beta_T + \frac{\beta_Q}{2}\|(\varphi_* - \varphi_Q)(\tau_*)\|_{L^2}^2 + \frac{\beta_S}{2r}\int_\Omega \varphi_*(\tau_*) - \varphi(\tau_* - r)\,\mathrm{dx} \\
&\quad + \frac{\beta_\Omega}{2r}\left(\|(\varphi_* - \varphi_\Omega)(\tau_*)\|_{L^2}^2 - \|(\varphi - \varphi_\Omega)(\tau_* - r)\|_{L^2}^2\right) = 0.
\end{aligned}$$

Summary

1. We introduced an optimal control problem for optimising treatment time of a cancer therapy involving cytotoxic drugs:

$$\partial_t \varphi = \Delta \mu + h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u), \quad \mu = \Psi'(\varphi) - \Delta \varphi,$$
$$\partial_t \sigma = \Delta \sigma - \mathcal{C} h(\varphi)\sigma.$$

2. The (relaxed) objective functional penalises long treatment times, and contains various tracking-type objectives:

$$J_r := \int_0^\tau \int_\Omega \frac{\beta_Q}{2} |\varphi - \varphi_Q|^2 + \frac{1}{2r} \int_{\tau - r}^\tau \int_\Omega \Big(\beta_\Omega |\varphi - \varphi_\Omega|^2 + \beta_S (1 + \varphi) \Big)$$
$$+ \int_Q \frac{\beta_u}{2} |u|^2 + \beta_T \tau.$$

3. Existence of an pair (u_*, τ_*) for the optimal drug distribution and treatment time is shown.
4. Two first order optimality conditions are derived.

Outline

Recall the original functional:

$$J(\varphi, u, \tau) = \int_0^\tau \int_\Omega \frac{\beta_Q}{2} |\varphi - \varphi_Q|^2 + \int_\Omega \frac{\beta_\Omega}{2} |\varphi(\tau) - \varphi_\Omega|^2 + \int_0^\tau \int_\Omega \frac{\beta_u}{2} |u|^2 + \beta_T \tau.$$

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We can prove that:

Lemma

Let $f \in H^2(0, T; L^2)$, i.e., $\partial_{tt} f \in L^2(0, T; L^2)$, then

$$\mathrm{D}_\tau \left(\int_\Omega |f(\tau)|^2 \, \mathrm{dx} \right) = 2 \int_\Omega f(\tau) \partial_t f(\tau) \, \mathrm{dx}.$$

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Then, the optimality condition for τ_* is

$$\mathrm{D}_\tau \mathcal{J}|_{(u_*, \tau_*)} = \int_\Omega \frac{\beta_Q}{2} |(\varphi_* - \varphi_Q)(\tau_*)|^2 + \frac{\beta_\Omega}{2} (\varphi_*(\tau_*) - \varphi_\Omega) \partial_t \varphi_*(\tau_*) + \frac{\beta_u}{2} |u_*(\tau_*)|^2 \, \mathrm{dx} + \beta_T.$$

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Issues: For the above expression to be well-defined and to apply the lemma, we need

$$\partial_{tt} \varphi_* \in L^2(0, T; L^2), \quad u_* \in H^1(0, T; L^2).$$

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$$\partial_{tt} \varphi_* \in L^2(0, T; L^2), \quad u_* \in H^1(0, T; L^2).$$

If we define $\mathcal{U}_{\mathrm{ad}} = \{u \in H^1(0, T; L^2) : 0 \leq u \leq 1, \|\partial_t u\|_{L^2(Q)} \leq K\}$ for some fixed $K > 0$, and impose $\varphi_0 \in H^5$, $\sigma_0 \in H^3$, then it is possible to obtain

$$\varphi \in H^2(0, T; L^2) \cap W^{1,\infty}(0, T; H^1).$$

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However, boundedness of the functional J does not give an a priori bound on $\|\partial_t u\|_{L^2(Q)}$, thus the our previous method cannot be applied with J to deduce the existence of a minimiser.

Issues with the well-posedness

The state equations

$$\begin{aligned}
\partial_t \varphi &= \Delta \mu + h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u), \\
\mu &= \Psi'(\varphi) - \Delta \varphi, \\
\partial_t \sigma &= \Delta \sigma - \mathcal{C} h(\varphi)\sigma.
\end{aligned}$$

satisfies the energy identity

$$\frac{\mathrm{d}}{\mathrm{dt}} \underbrace{\int_\Omega \left(\Psi(\varphi) + \frac{1}{2} |\nabla \varphi|^2 + \frac{1}{2} |\sigma|^2 \right)}_{=:\mathcal{E}} + \int_\Omega \left(|\nabla \mu|^2 + |\nabla \sigma|^2 + h(\varphi)\mathcal{C} |\sigma|^2 \right)$$

$$= \int_\Omega h(\varphi) \left(\mathcal{P}\sigma - \mathcal{A} - \alpha u \right) \mu.$$

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$$= \int_\Omega h(\varphi)\left(\mathcal{P}\sigma - \mathcal{A} - \alpha u\right)\mu.$$

We can estimate the right-hand side as

$$\delta \|\mu\|_{L^2}^2 + \frac{C}{\delta}(\mathcal{P}^2 \|\sigma\|_{L^2}^2 + \dots) \quad \text{for some } \delta > 0,$$

leading to

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$$\delta \|\mu\|_{L^2}^2 + \frac{C}{\delta}(\mathcal{P}^2 \|\sigma\|_{L^2}^2 + \dots) \quad \text{for some } \delta > 0,$$

leading to

$$\begin{aligned} \mathcal{E}(t) &+ \int_0^t \int_\Omega \left(|\nabla \mu|^2 + |\nabla \sigma|^2 \right) \\ &\leq \mathcal{E}(0) + \int_0^t \int_\Omega \left(\delta\,|\mu|^2 + \text{ other terms...} \right). \end{aligned}$$

Issues with the well-posedness

$$\mathcal{E}(t) + \int_0^t \int_\Omega \left(|\nabla \mu|^2 + |\nabla \sigma|^2 \right) \leq \mathcal{E}(0) + \int_0^t \int_\Omega \left(\delta \, |\mu|^2 + \text{ other terms...} \right).$$

To apply Poincaré inequality to the $\|\mu\|_{L^2(L^2)}$ on the RHS, we need to estimate the square of the mean of μ using

$$\mu = \Psi'(\varphi) - \Delta\varphi.$$

If $|\Psi'(s)| \leq C(1 + |s|^p)$ for some p, then we have

$$\left\| \frac{1}{|\Omega|} \int_\Omega \mu \right\|_{L^2(L^2)}^2 \leq C(1 + \|\varphi\|_{L^{2p}(L^{2p})}^{2p}) + \text{ other terms } \ldots$$

But, to control $\|\varphi\|_{L^{2p}(L^{2p})}^{2p}$ in the absence of any a priori estimate, we need $p = 1$!
I.e., Ψ can only be a quadratic potential [Garcke, L.].

Issues with the well-posedness

If σ is bounded in Q, then

$$\left| \int_\Omega h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u)\mu \right| \leq C\|\mu\|_{L^1}$$

and by the Poincaré inequality, we have

$$\|\mu\|_{L^1} \leq C\|\nabla\mu\|_{L^1} + C\left|\frac{1}{|\Omega|}\int_\Omega \mu\right|.$$

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$$\begin{aligned}\mathcal{E}(t) &+ \int_0^t \int_\Omega \left(|\nabla\mu|^2 + |\nabla\sigma|^2\right) \\ &\leq \mathcal{E}(0) + C\int_0^t \left(\delta\|\nabla\mu\|_{L^1} + \|\Psi'(\varphi)\|_{L^1} + \text{ other terms...}\right).\end{aligned}$$

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With an assumption like

$$|\Psi'(s)| \leq C_1\Psi(s) + C_2,$$

we obtain a priori estimates for potentials with higher polynomial growth.

The Schauder argument

Given $\phi \in L^2(Q)$, consider the mapping

$$\begin{aligned} M_1 : L^2(Q) &\to L^\infty(0,T;H^1) \cap L^2(0,T;H^2) \cap H^1(0,T;L^2) \cap L^\infty(Q), \\ \phi &\mapsto \sigma, \end{aligned}$$

where σ solves

$$\partial_t \sigma = \Delta \sigma - \mathcal{C} h(\phi) \sigma.$$

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where σ solves

$$\partial_t \sigma = \Delta \sigma - \mathcal{C} h(\phi)\sigma.$$

Then define the mapping

$$\begin{aligned} M_2 : L^2(Q) &\to L^\infty(0,T;H^2) \cap L^2(0,T;H^3) \cap H^1(0,T;L^2), \\ \phi &\mapsto \varphi, \end{aligned}$$

where φ solves

$$\partial_t \varphi = \Delta \mu - h(\varphi)(\mathcal{P} M_1(\phi) - \mathcal{A} - \alpha u), \quad \mu = \Psi'(\varphi) - \Delta \varphi.$$

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$$\begin{aligned} M_1 : L^2(Q) &\to L^\infty(0,T;H^1) \cap L^2(0,T;H^2) \cap H^1(0,T;L^2) \cap L^\infty(Q), \\ \phi &\mapsto \sigma, \end{aligned}$$

where σ solves

$$\partial_t \sigma = \Delta \sigma - \mathcal{C} h(\phi)\sigma.$$

Then define the mapping

$$\begin{aligned} M_2 : L^2(Q) &\to L^\infty(0,T;H^2) \cap L^2(0,T;H^3) \cap H^1(0,T;L^2), \\ \phi &\mapsto \varphi, \end{aligned}$$

where φ solves

$$\partial_t \varphi = \Delta \mu - h(\varphi)(\mathcal{P} M_1(\phi) - \mathcal{A} - \alpha u), \quad \mu = \Psi'(\varphi) - \Delta \varphi.$$

The solution to the fixed point problem

$$z = M_2(z)$$

yields a triplet (φ, μ, σ) which solves the state equations.