

A Theoretical study of the optimal control problem for the metastases

We consider the problem

$$(1) \quad \begin{cases} \partial_t \rho(t, X; u) + \operatorname{div}(\rho(t, X; u)(G(X) - B(X)u(t))) = 0 &]0, T[\times \Omega \\ -\overline{G}(t, \sigma; u) \cdot \nu(\sigma) \rho(t, \sigma; u) = N(\sigma) \left\{ \int_{\Omega} \beta(X) \rho(t, X; u) dX + \beta(X_p(t; u)) \right\} &]0, T[\times \partial\Omega \\ \rho(0, X; u) = \rho^0(X) & \Omega \end{cases}$$

where we denoted $X = (V, K)$ and consider some general coefficients and initial data G, B, β, N and ρ^0 . Let us define $Q :=]0, T[\times \Omega$ and do the following assumptions on the data

$$(2) \quad \beta \in W^{1,\infty}(\Omega), \rho^0 \in W^{1,\infty}(Q), \rho^0 \geq 0, N \in W^{1,\infty}(\partial\Omega), N \geq 0, \int_{\partial\Omega} N(\sigma) d\sigma = 1.$$

Defining $\Sigma = \{(V_0, K); 1 < K < (\frac{c}{d})^{3/2}\}$ we also assume that there exists $\delta > 0$ such that

$$(3) \quad \operatorname{supp} N \subset \Sigma, \quad -\overline{G}(t, \sigma) \cdot \nu(\sigma) \geq \delta > 0, \text{ a.e. } (t, \sigma) \in [0, T] \times \Sigma.$$

Finally, although in the particular case of the coefficients of our model it is not true, we assume the following compatibility condition for regularity issues, in order to simplify the problem

$$(4) \quad -\overline{G}(t, \sigma) \cdot \nu(\sigma) \rho^0(\sigma) = N(\sigma) \left\{ \int_{\Omega} \beta(X) \rho^0(X) dX + \beta(X_p(0)) \right\}.$$

In the present theoretical analysis, we take the objective to be given by

$$J(u) = \int_{\Omega} a(X) \rho(t, X; u) dX$$

with $a \in C^\infty(\overline{\Omega})$, which covers both cases of total number of metastases and metastatic burden that we used in the simulations. We will prove existence of an optimal control and derive a first order optimality system.

A.1 Existence of an optimal solution

We first prove existence of a solution to the optimal control problem defined on the metastases (the following proposition as well as its proof still holds *verbatim* for J_M).

Theorem 1. *Under the assumptions (2), (3) and (4) there exists $u^* \in \mathcal{U}_{ad}$ such that*

$$J(u^*) \leq J(u), \quad \forall u \in \mathcal{U}_{ad}.$$

The proof of the theorem is based on the following proposition establishing $W^{1,\infty}$ bounds on the solution ρ of (1).

Proposition 2. *Under the assumptions (2), (3) and (4) if $\rho(u)$ is the solution of (1), then $\rho(u) \in W^{1,\infty}(Q)$ and there exists a continuous function C which can be explicitied in terms of $\|\beta\|_{W^{1,\infty}(\Omega)}$, $\|N\|_{W^{1,\infty}(\partial\Omega)}$, $\|G\|_{L^\infty(\Omega)}$ and $\|B\|_{L^\infty(\Omega)}$ such that, for all $u \in \mathcal{U}_{ad}$*

$$(5) \quad \|\rho(u)\|_{W^{1,\infty}(Q)} \leq C(\|u\|_{L^\infty(Q)}).$$

Proof. For $u \in \mathcal{U}_{ad}$, let $\rho(u) = \rho(t, X; u)$ be the solution of (1). Following the method of previous papers (17,18), we use the flow $\Phi(t, \tau, \sigma; u)$ associated to the EDO $\frac{d}{dt} \Phi = \overline{G}(\Phi; u)$, that is $\Phi(t, \tau, \sigma; u)$ is the

solution of this ODE being in σ at time τ . We consider the entrance time $\tau^t(X)$ and entrance point $\sigma^t(X)$ for a point $X \in \Omega$ given by

$$\tau^t(X) := \inf\{0 \leq \tau \leq t; \Phi(\tau; t, X) \in \Omega\}, \quad \sigma^t(X) := \Phi(\tau^t(X); t, X).$$

and introduce the sets

$$\Omega_1^t = \{X \in \Omega; \tau^t(X) > 0\}, \quad \Omega_2^t = \{X \in \Omega; \tau^t(X) = 0\}$$

as well as

$$Q_1 := \{(t, X) \in [0, T] \times \bar{\Omega}; X \in \bar{\Omega}_1^t\}, \quad Q_2 := \{(t, X) \in [0, T] \times \bar{\Omega}; X \in \bar{\Omega}_2^t\}$$

and also define $\widetilde{Q}_1 := \{(t, \tau, \sigma); 0 \leq \tau \leq t \leq T, \sigma \in \partial\Omega\} = \Phi^{-1}(Q_1)$. We define the two following changes of variables

$$\Phi_1 : \begin{array}{ccc} \widetilde{Q}_1 & \rightarrow & Q_1 \\ (t, \tau, \sigma) & \mapsto & (t, \Phi(t; \tau, \sigma; u)) \end{array} \quad \text{and} \quad \Phi_2 : \begin{array}{ccc} [0, T] \times \bar{\Omega} & \rightarrow & Q_2 \\ (t, Y) & \mapsto & (t, \Phi(t; 0, Y; u)) \end{array}$$

and set

$$(6) \quad \widetilde{\rho}_1(t, \tau, \sigma; u) := \rho(\Phi_1(t; \tau, \sigma; u))J_1(t; \tau, \sigma; u) \quad \text{and} \quad \widetilde{\rho}_2(t, Y; u) := \rho(\Phi_2(t; 0, Y; u))J_2(t, Y; u)$$

with

$$(7) \quad J_1(t, \tau, \sigma; u) = |\overline{G}(\tau, \sigma) \cdot \nu(\sigma)| e^{\int_{\tau}^t \operatorname{div} \overline{G}(s, \Phi(s, \tau, \sigma; u)) ds} \quad \text{and} \quad J_2(t, Y; u) = e^{\int_0^t \operatorname{div} \overline{G}(\Phi(s, 0, Y; u)) ds}.$$

We have

$$(8) \quad \rho(t, X; u) := \widetilde{\rho}_1(\Phi_1^{-1}(t, X; u))J_1^{-1}(\Phi_1^{-1}(t, X; u))\mathbf{1}_{(t, X) \in Q_1} + \widetilde{\rho}_2(\Phi_2^{-1}(t, X; u))J_2^{-1}(\Phi_2^{-1}(t, X; u))\mathbf{1}_{(t, X) \in Q_2}$$

with $(\widetilde{\rho}_1, \widetilde{\rho}_2)$ solving the problems

$$(9) \quad \begin{cases} \partial_t \widetilde{\rho}_1(t, \tau, \sigma; u) = 0 & 0 < \tau \leq t < T, \sigma \in \partial\Omega \\ \widetilde{\rho}_1(\tau, \tau, \sigma; u) = N(\sigma) \left\{ \widetilde{B}(\tau, \widetilde{\rho}_1, \widetilde{\rho}_2) + \beta(X_p(\tau; u)) \right\} & 0 < \tau < T, \sigma \in \partial\Omega \end{cases}$$

where we denoted

$$\widetilde{B}(\tau, \widetilde{\rho}_1, \widetilde{\rho}_2) = \int_0^{\tau} \int_{\partial\Omega} \beta(\Phi(\tau; s, \sigma; u)) \widetilde{\rho}_1(\tau, s, \sigma; u) d\sigma ds + \int_{\Omega} \beta(\Phi(\tau; 0, Y; u)) \widetilde{\rho}_2(\tau, Y; u) dY,$$

and

$$(10) \quad \begin{cases} \partial_t \widetilde{\rho}_2(t, Y; u) = 0 & t > 0, Y \in \Omega \\ \widetilde{\rho}_2(0, Y; u) = \rho^0(Y) & Y \in \Omega. \end{cases}$$

We prove now the following lemma on the regularity of $\widetilde{\rho}_1$ solving (9).

Lemma 3. *Let $F, \beta \in W^{1,\infty}(\widetilde{Q}_1)$, $N \in W^{1,\infty}(\partial\Omega)$, $T > 0$ and $\rho \in L^\infty(\widetilde{Q}_1)$ be the solution of the following problem*

$$(11) \quad \begin{cases} \partial_t \rho = 0 & \widetilde{Q} \\ \rho(\tau, \tau, \sigma) = N(\sigma) \int_0^{\tau} \int_{\partial\Omega} \beta(\tau, \tau', \sigma') \rho(\tau, \tau', \sigma') d\tau d\sigma' + F(\tau, \sigma) & [0, T] \times \partial\Omega \end{cases}$$

We also assume $\operatorname{supp} N, \operatorname{supp}_\sigma F \subset \Sigma$. Then $\rho \in W^{1,\infty}(\widetilde{Q}_1)$, with support in $R := \{(t, \tau, \sigma) \in \widetilde{Q}; \sigma \in \Sigma\}$ and

$$\|\rho\|_{W^{1,\infty}} \leq C(\|\beta\|_{L^\infty}, \|\partial_t \beta\|_{L^\infty}, \|N\|_{W^{1,\infty}}, \|F\|_{W^{1,\infty}})$$

with C being a continuous function.

Proof. From the equation, we have $\partial_t \rho \in L^\infty(\tilde{Q}_1)$. Then, the solution of (11) is given by, for almost every $(t, \tau, \sigma) \in \tilde{Q}_1$

$$(12) \quad \rho(t, \tau, \sigma) = N(\sigma) \int_0^\tau \int_{\partial\Omega} \beta(\tau, s, \sigma') \rho(\tau, s, \sigma') ds d\sigma' + F(\tau, \sigma)$$

from which we get, in the distribution sense

$$\begin{aligned} \partial_\tau \rho(t, \tau, \sigma) &= N(\sigma) \left\{ \int_{\partial\Omega} \beta(\tau, \tau, \sigma') N(\sigma') \int_0^\tau \int_{\partial\Omega} \beta(\tau, s, \sigma'') \rho(\tau, s, \sigma'') ds d\sigma'' + F(\tau, \sigma') \right. \\ &\quad \left. + \int_0^\tau \int_{\partial\Omega} \partial_\tau \beta(\tau, s, \sigma') \rho(\tau, s, \sigma') + \beta(\tau, s, \sigma') \partial_t \rho(\tau, s, \sigma') ds d\sigma' \right\} + \partial_\tau F(\tau, \sigma) \end{aligned}$$

as well as

$$\partial_\sigma \rho(t, \tau, \sigma) = \partial_\sigma N(\sigma) \int_0^\tau \int_{\partial\Omega} \beta(\tau, s, \sigma') \rho(\tau, s, \sigma') ds d\sigma' + \partial_\sigma F(\tau, \sigma)$$

and prove that $\rho \in W^{1,\infty}(\tilde{Q}_1)$. Formula (12) also proves the assertion on the support of ρ .

The $W^{1,\infty}$ bound (5) comes from the above explicit expressions and the following L^1 bound : for all $t \in [0, T]$

$$\int_0^t \int_{\partial\Omega} |\rho(t, s, \sigma)| ds d\sigma \leq \int_0^t e^{(t-s)\|\beta\|_{L^\infty}} \int_{\partial\Omega} |F(s, \sigma)| ds d\sigma.$$

It is derived by applying a Gronwall lemma to the following inequality, obtained from equation (11)

$$\frac{d}{dt} \int_0^t \int_{\partial\Omega} |\rho(t, \tau, \sigma)| d\sigma d\tau \leq \|\beta\|_{L^\infty} \int_0^t \int_{\partial\Omega} |\rho(t, \tau, \sigma)| d\sigma d\tau + \int_{\partial\Omega} |F(t, \sigma)| d\sigma.$$

□

We apply the previous lemma to $\tilde{\rho}_1$ solving (9) by using $\tilde{\beta}(t, \tau, \sigma) = \beta(\Phi(t, \tau, \sigma; u))$ and

$$\begin{aligned} F(\tau, \sigma) &= N(\sigma) \left\{ \int_{\Omega} \beta(\Phi(\tau, 0, Y; u)) \tilde{\rho}_2(\tau, Y) dY + \beta(X_p(\tau)) \right\} \\ &= N(\sigma) \left\{ \int_{\Omega} \beta(\Phi(\tau, 0, Y; u)) \rho^0(\tau, Y) dY + \beta(X_p(\tau)) \right\}. \end{aligned}$$

We observe that $\|\tilde{\beta}\|_{L^\infty(\tilde{Q})} = \|\beta\|_{L^\infty(\Omega)}$ and

$$\partial_t \tilde{\beta} = \nabla \beta \cdot \partial_t \Phi = \nabla \beta \cdot G(X) - \nabla \beta \cdot Bu$$

so

$$\|\partial_t \tilde{\beta}\|_{L^\infty(\tilde{Q})} \leq \|\nabla \beta\|_{L^\infty(\Omega)} \left\{ \|G\|_{L^\infty(\Omega)} + \|B\|_{L^\infty(\Omega)} \|u\|_{L^\infty(0,T)} \right\}.$$

Thus we have, since the $W^{1,\infty}$ norm of F is controlled by the $W^{1,\infty}$ norms of N , β and ρ^0 that

$$\|\tilde{\rho}_1(u)\|_{W^{1,\infty}(\tilde{Q}_1)} \leq C(\|u\|_{L^\infty(0,T)})$$

with C a continuous function.

We wish now to end the proof by recovering regularity on ρ using formula (8).

- From the assumption (3), we have that Φ_1 is an homeomorphism bilipschitz on R . Hence the chain rule applies on R and $\tilde{\rho}_1 \circ \Phi_1^{-1} \in W^{1,\infty}(\Phi_1(R))$ and also

$$\rho_1 := \tilde{\rho}_1 \circ \Phi_1^{-1} J_1^{-1} \in W^{1,\infty}(\Phi_1(R)).$$

- Since $\text{supp } \tilde{\rho}_1 \subset R$, then $\tilde{\rho}_1 \circ \Phi_1^{-1} J_1^{-1} = \tilde{\rho}_1 \circ \Phi_1^{-1} J_1^{-1} \mathbf{1}_{\{\Phi_1(R)\}} \in W^{1,\infty}(Q_1)$
- Φ_2 is always bilipschitz thus $\rho_2 := \tilde{\rho}_2 \circ \Phi_2^{-1} J_2^{-1} \in W^{1,\infty}(Q_2)$.

Now we rewrite formula (8) as $\rho = \rho_1 \mathbf{1}_{\{Q_1\}} + \rho_2 \mathbf{1}_{\{Q_2\}}$. Since $Q_1 \cap Q_2 = \{\Phi(t, 0, \sigma; u), ; t \in [0, T], \sigma \in \partial\Omega\}$, we compute

$$\begin{aligned} \rho_1(t, \Phi(t, 0, \sigma; u)) &= (\bar{G}(0, \sigma) \cdot \nu(\sigma))^{-1} \tilde{\rho}_1(t, 0, \sigma) e^{-\int_0^t \text{div } \bar{G}(s, \Phi(s, \tau, \sigma; u)) ds} \\ &= (\bar{G}(0, \sigma) \cdot \nu(\sigma))^{-1} N(\sigma) \left\{ \int_{\Omega} \beta(\Phi(\tau, 0, Y; u)) \rho^0(\tau, Y) dY + \beta(X_p(\tau)) \right\} e^{-\int_0^t \text{div } \bar{G}(s, \Phi(s, \tau, \sigma; u)) ds} \end{aligned}$$

and

$$\rho_2(t, \Phi(t, 0, \sigma; u)) = \tilde{\rho}_2(t, \sigma) e^{-\int_0^t \text{div } \bar{G}(s, \Phi(s, \tau, \sigma; u)) ds} = \rho^0(\sigma) e^{-\int_0^t \text{div } \bar{G}(s, \Phi(s, \tau, \sigma; u)) ds}.$$

Hence, using the compatibility condition (4) we obtain that $\rho \in \mathcal{C}(Q)$ which, combined with $\rho|_{Q_1} \in W^{1,\infty}(Q_1)$ and $\rho|_{Q_2} \in W^{1,\infty}(Q_2)$ gives $\rho \in W^{1,\infty}(Q)$. The $W^{1,\infty}$ bound (5) follows from formula (8), the $W^{1,\infty}$ bounds on $\tilde{\rho}_1$ and on $\tilde{\rho}_2$ (this last one coming from explicit solution of (10)), the chain rule and $W^{1,\infty}$ estimates on $\Phi_1^{-1}|_{\Phi(R)}$ (using assumption (3)) as well as on Φ_2^{-1} , J_1^{-1} and J_2^{-1} . \square

Since $\{J(u); u \in \mathcal{U}_{ad}\}$ is bounded by zero by below from the positivity of the solution it has a finite lower bound and there exists a sequence u_n in \mathcal{U}_{ad} such that

$$(13) \quad J(u_n) \xrightarrow{n \rightarrow \infty} \inf_{u \in \mathcal{U}_{ad}} J(u).$$

Since \mathcal{U}_{ad} is bounded, from the estimate (5) we obtain that the family $\rho(u_n)$ is bounded in $W^{1,\infty}(Q)$. Using Ascoli-Arzelà theorem there exists $\rho^* \in \mathcal{C}(Q)$ and a subsequence still denoted $\rho(u_n)$ such that $\rho(u_n) \xrightarrow[n \rightarrow \infty]{\mathcal{C}(Q)} \rho^*$. The weak formulation of the problem (1) writes : for all $\phi \in \mathcal{C}_c^1([0, T] \times \bar{\Omega})$

$$\begin{aligned} &\int_0^T \int_{\Omega} \rho(t, X; u_n) [\partial_t \phi(t, X) + G(X) \cdot \nabla \phi(t, X) - u_n(t) B(X) \cdot \nabla \phi(t, X)] dt dX + \\ &\int_{\Omega} \rho^0(X) \phi(0, X) dX + \int_0^T \int_{\partial\Omega} \phi(t, \sigma) N(\sigma) \left\{ \int_{\Omega} \beta(X) \rho(t, X; u_n) dX + \beta(X_p(t; u_n)) \right\} d\sigma dt = 0 \end{aligned}$$

and thus the convergence of $\rho(u_n)$ in $\mathcal{C}(Q)$ and the $*$ - weak L^∞ convergence of u_n are sufficient to pass to the limit in order to obtain, using uniqueness of the solution to the problem (1) (see (18)), that $\rho^* = \rho(u^*)$. Now

$$J(u_n) = \int_{\Omega} a(X) \rho(T, X; u_n) dX \xrightarrow{n \rightarrow \infty} \int_{\Omega} a(X) \rho(T, X; u^*) dX = J(u^*)$$

Using (13) we get $J(u^*) = \inf_{u \in \mathcal{U}_{ad}} J(u)$, which ends the proof of the theorem.

A.2 Optimality system

We shall now derive first order necessary conditions on the optimal control. Let u^* is a solution of the optimal control problem, we have

$$J'(u^*) \cdot (v - u^*) \geq 0, \quad \forall v \in \mathcal{U}_{ad}.$$

Here we have, for all $u, v \in L^2(Q)$

$$J'(u) \cdot (v - u) = \int_{\Omega} a(X) z(T, X; \rho^*, u^*, v) dX.$$

where $z = z(\rho^*, u^*, v) = D_u \rho(u^*) \cdot (v - u^*)$ and $\rho^* = \rho(u^*)$. Hence

$$(14) \quad \int_{\Omega} a z(T; \rho^*, u^*, v) dX \geq 0, \quad \forall v \in \mathcal{U}_{ad},$$

Notice that z solves the following problem

$$(15) \quad \begin{cases} \partial_t z + \operatorname{div}(z \overline{G}(X, u^*)) = \operatorname{div}(\rho^* B(X) \cdot (v - u^*)) \\ -\overline{G} \cdot \nu(t, \sigma; u^*) z(t, \sigma; u^*) = N(\sigma) \left\{ \int_{\Omega} \beta(X) z(t, X; u^*) dX + \nabla \beta(X_p(t; u^*)) \cdot D_u X_p(t; u^*) \cdot (v - u^*) \right\} \\ z(0, X; u^*) = 0. \end{cases}$$

We will also need the Cauchy problem solved by $Y(t; u^*) := D_u X_p(t; u^*) \cdot (v - u^*) \in \mathbb{R}^2$ which is

$$(16) \quad \begin{cases} \dot{Y}(t; u^*) = D_X \overline{G}(X_p(t; u^*)) Y(t; u^*) - B(X_p(t; u^*)) (v - u^*) \\ Y(0; u^*) = 0 \end{cases}$$

In order to simplify the optimality condition (14), we introduce the adjoint problem of (15). Let $p^* \in H^1(Q)$ solving

$$(17) \quad \begin{cases} -\partial_t p^*(t, X; u^*) - \overline{G}(X; u^*) \nabla p^*(t, X; u^*) - \beta(X) \int_{\partial\Omega} N(\sigma) p^*(t, \sigma) d\sigma = 0 \\ p^*(T, X) = -a(X). \end{cases}$$

We also introduce the adjoint $\xi^*(t; u) \in \mathbb{R}^2$ of the problem (16) with a particular source term

$$\begin{cases} \dot{\xi}(t; u^*) = - (D_X \overline{G})^T (t, X_p^*(t; u^*)) \xi(t; u^*) - \nabla \beta(X_p^*(t; u^*)) \int_{\partial\Omega} N(\sigma) p^*(t, \sigma; u^*) d\sigma \\ \xi(T) = 0 \end{cases}$$

We replace a from the first equation of (17) into (14) to obtain

$$\int_{\Omega} p^*(T, X) z(T, X) dx \leq 0, \quad \forall v \in \mathcal{U}_{ad}.$$

By integration by part in time we have

$$\int_Q (-\overline{G}(X; u^*) \nabla p^*(t, X; u^*) - \beta(X) \int_{\partial\Omega} N(\sigma) p(t, \sigma) d\sigma) z dx dt \leq 0, \quad \forall v \in \mathcal{U}_{ad}.$$

$$\int_0^T \int_{\Omega} p^* \operatorname{div}(\rho^* B(v - u^*)) dX - \left[\dot{\xi} + (D_X \overline{G})^T \xi \right] \cdot Y dt \leq 0 \quad \forall v \in \mathcal{U}_{ad}$$

and another integration by part in time yields

$$\int_0^T \int_{\Omega} p^* \operatorname{div}(\rho^* B(v - u^*)) dX - \xi B(X_p(u^*)) (v - u^*) dt \leq 0 \quad \forall v \in \mathcal{U}_{ad}$$

We deduce the following optimality system :

$$(18) \quad \left\{ \begin{array}{l} \partial_t \rho^* + \operatorname{div}(\rho^* \overline{G}(u^*)) = 0 \\ -G \cdot \nu(t, \sigma; u^*) \rho^*(t, \sigma; u^*) = N(\sigma) \left\{ \int_{\Omega} \beta(X) \rho^*(t, X; u^*) dX + \beta(X_p(t; u^*)) \right\} \\ \rho^*(0, X; u^*) = \rho^0 \\ \dot{X}_p(t; u^*) = \overline{G}(t, X_p(t; u^*); u^*) \\ X_p(0; u^*) = 0 \\ -\partial_t p^*(t, X; u^*) - \overline{G}(X; u^*) \nabla p^*(t, X; u^*) - \beta(X) \int_{\partial\Omega} N(\sigma) p^*(t, \sigma) d\sigma = 0 \\ p^*(T) = -a \\ \dot{\xi}(t; u^*) = - (D_X \overline{G})^T (t, X_p^*(t; u^*)) \xi(t; u^*) - \nabla \beta(X_p^*(t; u^*)) \int_{\partial\Omega} N(\sigma) p^*(t, \sigma; u^*) d\sigma \\ \xi(T) = 0 \\ \langle \int_{\Omega} \operatorname{div}(B \rho^*) p^* dX - \xi B(X_p(u^*)) \cdot (v - u^*) \rangle_{L^2(0, T)^2} \leq 0, \quad \forall v \in \mathcal{U}_{ad}. \end{array} \right.$$

where $\operatorname{div}(\rho^* B)$ stands for the vector $(\operatorname{div}(\rho^* B^1), \operatorname{div}(\rho^* B^2))$ with B^1, B^2 being the columns of B .