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A high-order WENO scheme of a model of tumor growth for treated small cell lung cancer

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Abstract

In this work we develop high order finite volume weighted essentially non-oscillatory (WENO) scheme for solving a model of tumor growth, with treatment, for small cell lung cancer.

Keywords

Tumor growth; Finite volume schemes; WENO scheme; High order accuracy

I INTRODUCTION

In this paper we develop high order finite volume weighted essentially non-oscillatory (WENO) schemes for a model of tumor growth, with treatment, for small cell lung cancer given by the following equations as in [11]

$$\frac{\partial}{\partial t} u(t, x) + \frac{\partial}{\partial x} [G(t, x)u(t, x)] = 0, \quad t \in]t_0, \bar{T}[, x \in]1, b[, \quad (1a)$$

$$(Gu)(t, 1) = \int_1^b \beta(x)u(t, x)dx + \beta(x_p(t)), \quad t \in]t_0, \bar{T}[, \quad (1b)$$

$$(Gu)(t, b) = 0, \quad t \in]t_0, \bar{T}[, \quad (1c)$$

$$u(t_0, x) = u_0(x), \quad (1d)$$

$$\frac{dx_p}{dt}(t) = G(t, x_p(t)), \quad t > t_0, x_p(t_0) = x_0, \quad (1e)$$

where t_0 and \bar{T} are the start and end times of treatment, u_0 is the density in size at t_0 .

The equation (1b) means that the number of metastatic single cells newly created per unit time is the total rate of new metastases due to metastases already present and to the primary tumor. In the equation (1e) $x_p(t)$ represents the number of cells present in a primary tumor at time t . The colonization rate $\beta(x)$ has the form

$$\beta(x) = m.x^\alpha, \quad (2)$$

where m is the colonization coefficient and α is the fractal dimension of the blood vessels infiltrated into the tumor see [5]. Equation (2) indicates that the rate of metastases from a tumor of size x is proportional to the number of tumor cells in contact with the blood vessels. The parameter α expresses how the blood vessels are geometrically distributed in the tumor. G is

given by

$$G(t, x) = g(x) - \underbrace{\gamma(x - \bar{x}_c)(1 + \tanh(\theta(x - \bar{x}_c)))C(t)}_{\text{Chemotherapy treatment}} - \underbrace{\gamma_r(x - \hat{x}_r)(1 + \tanh(\theta(x - \hat{x}_r)))R(t)}_{\text{Radiotherapy treatment}}, \quad (3)$$

with a Gompertzian growth rate

$$g(x) = ax \ln \left(\frac{b}{x} \right) \quad (4)$$

where $b \geq 1$ is the maximal tumor size and a is a positive parameter that measures the rate of clonogenic proliferation. The term $C(t)$, represents the drug's concentration for more details see [10], where \bar{x} is a threshold from which drugs start, moreover from a mathematical point of view \bar{x} is a constant strictly greater than 1 imposed to guarantee that $G(t, 1) > 0$, and γ is a positive constant that quantifies the drug's effectiveness. Likewise, R represents cell death induced by radiation. Using a linear-quadratic model, we have the following expression of radiotherapy treatment

$$R(t) = 1 - \exp \left(-\alpha_{\text{eff}} \frac{d_r}{2\varepsilon} \sum_{i=1}^m \chi_{[t_i - \varepsilon, t_i + \varepsilon]}(t) \right),$$

where d_r is a radiation dose, and α_{eff} is a constant that translates radiations into cell death, said relative effective radiosensitivity parameter [6, 9, 11].

Theorem 1: Ben Abdejlil, Ben Essid, and Mani-Aouadi [11]

We suppose that the initial data u_0 belongs to $W^{1,1}([1, b])$ and verifies the compatibility conditions

$$u_0(b) = 0 \quad \text{and} \quad (Gu_0)(t_0, 1) = \int_1^b \beta(x)u_0(x)dx + f(t_0). \quad (5)$$

We suppose that G is of class C^2 in x for all t , has a finite number of discontinuities denoted by t_i , $i = 1, \dots, n$, and is of class C^2 on the connected components of $\mathcal{Q} = [t_0, T] \times [1, b]$ delimited by the curves $\Sigma_i = \{(t_i, x), x \in [1, b]\}$, $i = 1, \dots, n$, verifies the conditions

$$G(t, 1) > 0, \quad \forall t \in]t_0, T], \quad (6a)$$

$$G(t_0, x) > 0, \quad \forall x \in [1, b[, \quad (6b)$$

$$G(t, b) < 0, \quad \forall t \in [t_0, T]. \quad (6c)$$

Then, there is a unique $u \in E(u_0) = \{w \in C_{MG}^1([t_0, T], L^1([1, b])), w(t_0, \cdot) = u_0\}$ with $Gu \in \mathcal{C}([t_0, T], W^{1,1}([1, b]))$ that verifies the equations (1a), (1b) and (1c) respectively in $\mathcal{C}([t_0, T], L^1([1, b]))$, $\mathcal{C}([t_0, T], \mathbb{R})$ and $L^1([1, b])$.

II NUMERICS

The Characteristic method use [11] is expensive in terms of time and computer RAM. To overcome this difficulties, we use here the finite volume scheme of order 5, developed in 1996 by

Guang-Sh and Chi-Wang Shu [3], this scheme known as WENO (Weighted Essentially Non-Oscillatory) scheme is one of the most popular method to approximate the hyperbolic conservation laws with high order accuracy in the regions where the solution is regular and by eliminating the oscillations in the regions of discontinuities. Nowadays, there are several WENO schemes, similar in principle to the first one introduced in 1994 by Liu, Osher and Chan [2] the difference lies in the way the non-oscillatory weights are determined in order to increase the order and reduce the dissipation of the solution. The WENO schemes are based on cell averages and a Runge-Kutta TVD (Total Variation Diminishing) discretization. The number of cells x varies between 1 and 10^{12} , which makes it impossible to choose a small step along the domain of variation of x which verifies the CFL condition. Moreover for a non-uniform subdivision the maximum of the steps is of the order of 10^8 , and the solution explodes quickly. We make as in [7] a change of variable in order to reduce on the one hand the domain of the space and on the other hand to preserve the nature of the differential system. We set

$$\begin{aligned} y &= \log(x), \\ \tilde{G}(t, y) &= G(t, e^y)e^{-y}, \\ \tilde{\beta}(y) &= \beta(e^y), \\ v(t, y) &= e^y u(t, y), \\ F(t, y, v(t, y)) &= \tilde{G}(t, y)v(t, y). \end{aligned}$$

We obtain a new system of conservation law on $\mathcal{Q} = [0, T] \times [0, \log(b)]$ made of N_y cells

$$\begin{cases} \partial_t v(t, y) + \partial_y F(t, y, v(t, y)) = 0, \\ \tilde{G}(t, 0)v(t, 0) = \int_0^{\log(b)} \tilde{\beta}(y)v(t, y)dy + \beta(x_p(t)), \\ v(0, y) = 0. \end{cases} \quad (7)$$

2.1 Numerical scheme

We consider a uniform subdivision of the interval $[0, \log(b)]$ made of N_y cells

$$0 = y_{\frac{1}{2}} < y_{\frac{3}{2}} < \dots < y_{N_y - \frac{1}{2}} < y_{N_y + \frac{1}{2}} = \log(b).$$

We define, for any $i = 1 \dots N_y$, the cells and the centers of each cell by

$$\begin{aligned} \mathcal{C}_i &= [y_{i-\frac{1}{2}}, y_{i+\frac{1}{2}}], \\ y_i &= \frac{1}{2} \left(y_{i+\frac{1}{2}} + y_{i-\frac{1}{2}} \right), \\ \Delta y &= y_{i+\frac{1}{2}} - y_{i-\frac{1}{2}} = \frac{\log(b)}{N_y}, \\ \bar{v}_i(t) &= \frac{1}{\Delta y} \int_{\mathcal{C}_i} v(t, y)dy, \end{aligned}$$

with y_i is the center of the interval \mathcal{C}_i . By integrating (7) over the cell \mathcal{C}_i , we obtain

$$\frac{d}{dt} \bar{v}_i(t) = -\frac{1}{\Delta y} \left[F_{i+\frac{1}{2}} - F_{i-\frac{1}{2}} \right], \quad (8)$$

where $F_{i\pm\frac{1}{2}} = F(t, y_{i\pm\frac{1}{2}}, v(t, y_{i\pm\frac{1}{2}}))$. For semi-discrete spatial approximations, the time variable t is absent. The basic idea is to express $v_{i\pm\frac{1}{2}}(t) \equiv v(t, y_{i\pm\frac{1}{2}})$ as a function of $\bar{v}_j(t)$, for all t , and therefore the equation (8) is written in the abstract form

$$\frac{d}{dt}\bar{v}_i(t) = \mathcal{L}(t, \bar{v}_{i-k}(t), \dots, \bar{v}_{i+k}(t)), \quad (9)$$

where \mathcal{L} is the spatial operator of the WENO scheme, and then solves Eq. (9) by the high-order TVD Runge-Kutta methods developed by Shu and Osher [1, 8]. The fifth order polynomial P_i is an approximation of v to the right and left of the cell \mathcal{C}_i , it is constructed by the convex combination of the interpolated value $p_{r,i}^\pm = p_{r,i}(y_{i\pm 1/2})$, where $p_{r,i}(y)$ is the polynomial of the second degree below, defined in each of the stencils $S_i^{(r)}$, as shown in Figure 1, for $k = 3$

$$v_{i\pm\frac{1}{2}}^\pm = P_i(y_{i\pm 1/2}) = \sum_{r=0}^2 \omega_r p_{r,i}(y_{i\pm 1/2}) \quad (10)$$

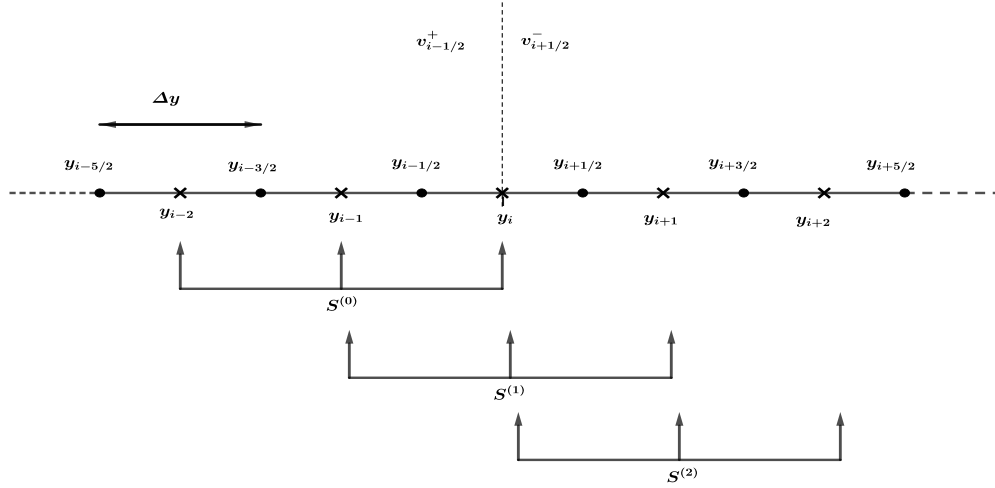


Figure 1: The stencils used by the WENO-5 numerical flux

The coefficients ω_1 , ω_2 and ω_3 are called the nonlinear weights. The detailed reconstruction procedure for the three third order fluxes $\hat{F}_{i\pm\frac{1}{2}}^{(r)}$, are given by

$$\begin{aligned} p_{0,i}^+ &= -\frac{1}{6}\bar{v}_{i-2} + \frac{5}{6}\bar{v}_{i-1} + \frac{2}{6}\bar{v}_i & p_{0,i}^- &= \frac{2}{6}\bar{v}_{i-2} - \frac{7}{6}\bar{v}_{i-1} + \frac{11}{6}\bar{v}_i \\ p_{1,i}^+ &= \frac{2}{6}\bar{v}_{i-1} + \frac{5}{6}\bar{v}_i - \frac{1}{6}\bar{v}_{i+1} & p_{1,i}^- &= -\frac{1}{6}\bar{v}_{i-1} + \frac{5}{6}\bar{v}_i + \frac{2}{6}\bar{v}_{i+1} \\ p_{2,i}^+ &= \frac{11}{6}\bar{v}_i - \frac{7}{6}\bar{v}_{i+1} + \frac{2}{6}\bar{v}_{i+2} & p_{2,i}^- &= \frac{2}{6}\bar{v}_i + \frac{5}{6}\bar{v}_{i+1} - \frac{1}{6}\bar{v}_{i+2} \end{aligned}$$

and

$$\omega_r = \frac{\alpha_r}{\sum_{r=0}^2 \alpha_r}, \quad \alpha_r = \frac{d_r}{(\varepsilon + \beta_r)^2}, \quad r = 0, 1, 2, \quad (11)$$

where $d_0 = 3/10$, $d_1 = 3/5$ and $d_2 = 1/10$ are the linear weights which can assure fifth order accuracy, and $\varepsilon = 10^{-6}$ introduced to avoid the denominator to become 0 Shu [4]. To measure the smoothness of the r th polynomial approximation $p_{r,i}$ in the stencil $S_i^{(r)}$, we adopt the smoothness indicators β_r introduced in Shu [4]

$$\beta_r = \sum_{l=1}^2 \Delta y^{2l-1} \int_{C_i} \left(\frac{d^l}{dy^l} p_{r,i}(y) \right)^2 dy, \quad (12)$$

and therefore β_r , for all $r = 0, 1, 2$, is written as a function of \bar{v}

$$\begin{aligned} \beta_0 &= \frac{13}{12}(\bar{v}_{i-2} - 2\bar{v}_{i-1} + \bar{v}_i)^2 + \frac{1}{4}(\bar{v}_{i-2} - 4\bar{v}_{i-1} + 3\bar{v}_i)^2, \\ \beta_1 &= \frac{13}{12}(\bar{v}_{i-1} - 2\bar{v}_i + \bar{v}_{i+1})^2 + \frac{1}{4}(\bar{v}_{i+1} - \bar{v}_{i-1})^2, \\ \beta_2 &= \frac{13}{12}(\bar{v}_i - 2\bar{v}_{i+1} + \bar{v}_{i+2})^2 + \frac{1}{4}(3\bar{v}_i - 4\bar{v}_{i+1} + \bar{v}_{i+2})^2, \end{aligned}$$

and the weights ω_r are constructed to avoid oscillations in the points of discontinuity, $\omega_r = d_r + O(\Delta y^2)$ in smooth region of v and $\omega_r = d_r + O(1)$ if v is not regular.

We approximate (8) by the following conservative scheme

$$\frac{d}{dt} \bar{v}_i(t) = -\frac{1}{\Delta y} \left[\hat{F}_{i+\frac{1}{2}} - \hat{F}_{i-\frac{1}{2}} \right], \quad (13)$$

where the numerical flux \hat{F} is defined by

$$\hat{F}_{i\pm\frac{1}{2}} = h(v_{i\pm\frac{1}{2}}^-, v_{i\pm\frac{1}{2}}^+), \quad i = 1, \dots, N_y, \quad (14)$$

the two argument function h is a monotone flux see Liu, Osher, and Chan [2] and Shu [4] for more details. Here, we choose the Lax-Friedrichs flux

$$\hat{F}_{i\pm\frac{1}{2}} = \frac{1}{2} \left[\tilde{G}_{i\pm\frac{1}{2}} \left(v_{i\pm\frac{1}{2}}^- + v_{i\pm\frac{1}{2}}^+ \right) - \max_Q |\tilde{G}(t, y)| \left(v_{i\pm\frac{1}{2}}^+ - v_{i\pm\frac{1}{2}}^- \right) \right], \quad i = 1, \dots, N_y, \quad (15)$$

where $\tilde{G}_{i\pm\frac{1}{2}} = \tilde{G}(t, x_{i\pm\frac{1}{2}})$. For WENO procedure, we need the value in two ghost cells $v_{\frac{1}{2}}^-$ and $v_{N_y+\frac{1}{2}}^+$. We set $v_{N_y+\frac{1}{2}}^+ = 0$ and we use the boundary condition to compute $v_{\frac{1}{2}}^-$. For the non local boundary condition we use a Newton-Cotes quadrature formula of order 5. Finally we use TVD Runge-Kutta to solve the equations (1e) and (9).

2.2 Numerical results

We consider the effect of treatments (only chemotherapy and chemo-radiotherapy) on the evolution, first of a primary tumor, then of a metastatic growing tumor. We consider the following parameters in [5, 10]

$$a = 0.0231, \quad b = 10^{12}, \quad m = 1.2 \times 10^{-9}, \quad \alpha = 2/3, \quad \alpha_{\text{eff}} = 1.133. \quad (16)$$

We introduce as in [5], the metastatic index defined by

$$MI_{b_{\min}}(t) = \int_{b_{\min}}^b u(t, x) dx. \quad (17)$$

We opt for a time discretization with variable steps. Let $(t_n)_{0 \leq n \leq N}$ be a nonuniform subdivision of $[0, T]$ with steps $k_n = t_{n+1} - t_n$. Care will be taken to consider the points of discontinuity of G as nodes of the mesh.

Primary tumor.

Figure 2, shows the effect of the treatment in terms of reduction of the number of tumor cells. Figure 3 clearly shows the advantage of concomitant therapy over chemotherapy alone.

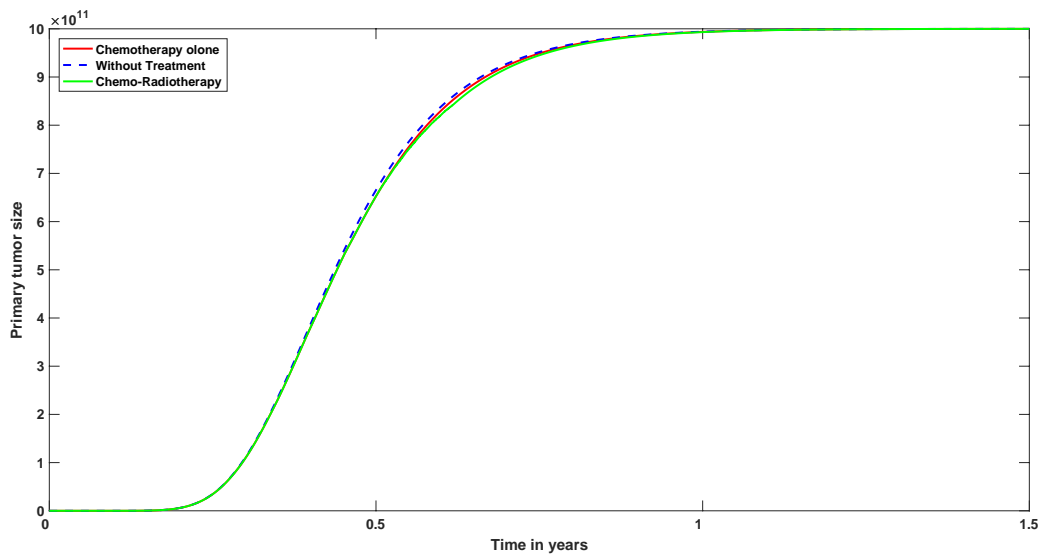


Figure 2: Primary tumor with and without treatments

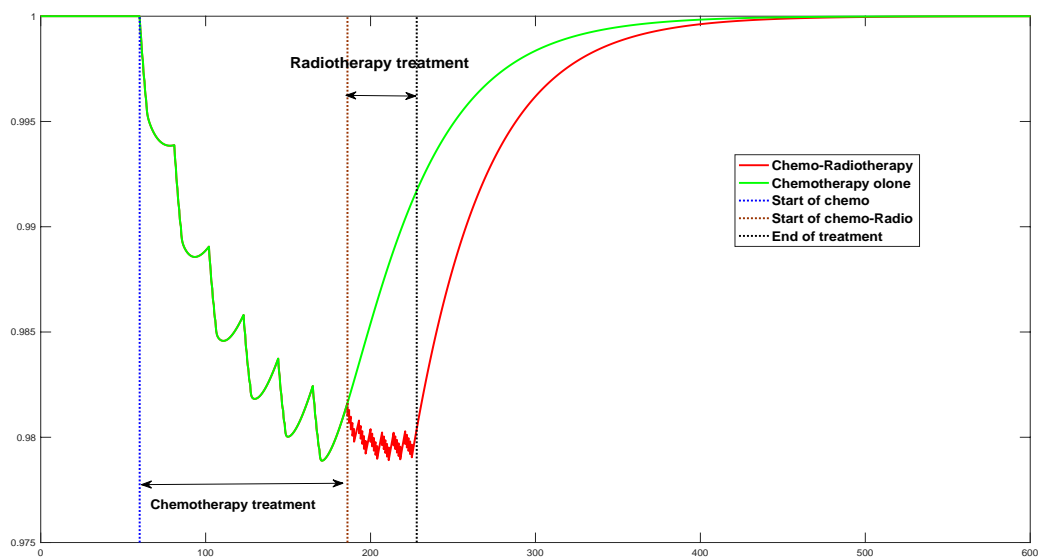


Figure 3: The ratio of the numbers of cells

Growing tumor.

Figure 4 and Figure 5 show respectively the benefit of concomitant treatment compared to chemotherapy alone in reducing the number of total and detectable metastases. The difference in metastatic index between chemotherapy alone and chemo-radiotherapy, is presented in Figure 6 and Figure 7.

REFERENCES

- [1] C.-W. Shu and S. Osher. "Efficient implementation of essentially non-oscillatory shock-capturing schemes". In: *Journal of Computational Physics* 77.2 (1988), pages 439–471. ISSN: 0021-9991.

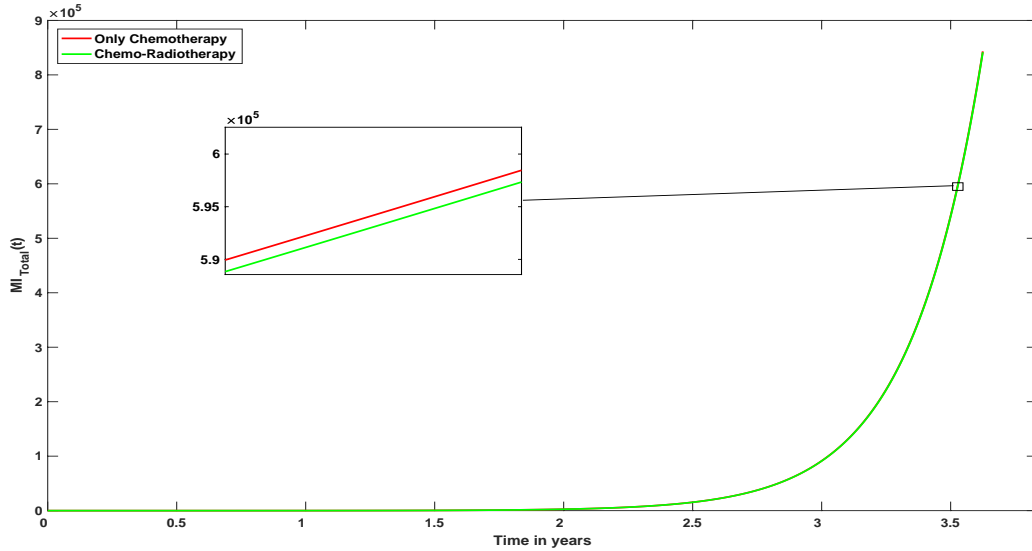


Figure 4: Total number of metastases ($b_{min} = 1$).

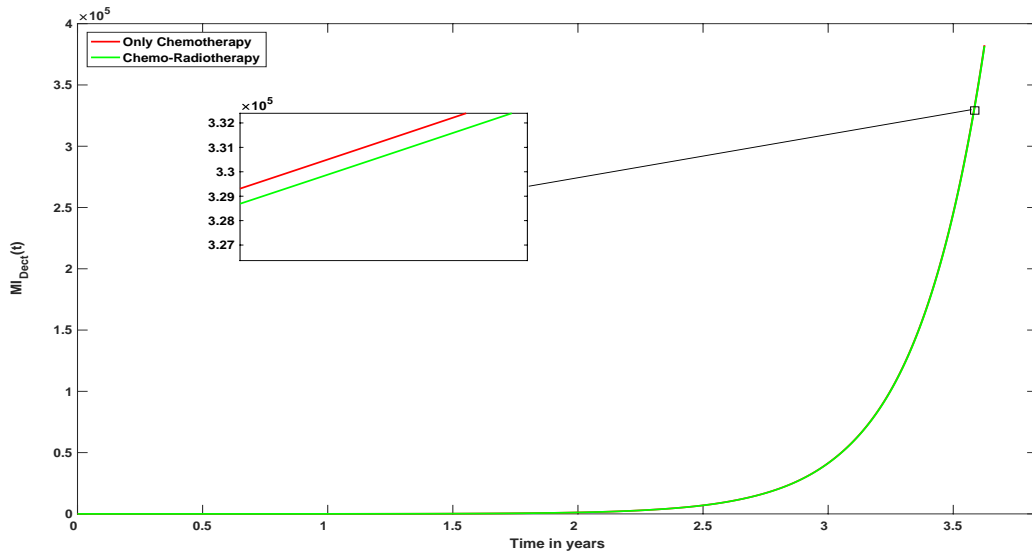


Figure 5: Number of metastases detectable ($b_{min} = 10^8$).

- [2] X.-D. Liu, S. Osher, and T. Chan. “Weighted Essentially Non-oscillatory Schemes”. In: *Journal of Computational Physics* 115.1 (1994), pages 200–212. ISSN: 0021-9991.
- [3] X.-D. Liu, S. Osher, and T. Chan. “Efficient Implementation of Weighted ENO Schemes”. In: *Journal of Computational Physics* 126.1 (1996), pages 202–228. ISSN: 0021-9991.
- [4] C.-W. Shu. “Essentially non-oscillatory and weighted essentially non-oscillatory schemes for hyperbolic conservation laws”. In: Springer Berlin Heidelberg, 1998, pages 325–432.
- [5] K. Iwata, K. Kawasaki, and N. Shigesada. “A Dynamical Model for the Growth and Size Distribution of Multiple Metastatic Tumors”. In: *Journal of theoretical biology* 203 (Apr. 2000), pages 177–186.
- [6] R. Rockne, E. Alvord, J. Rockhill, and K. Swanson. “A mathematical model for brain tumor response to radiation therapy”. In: *Journal of mathematical biology* 58 (Sept. 2008), pages 561–78.
- [7] A. Devys, T. Goudon, and P. Lafitte. “A model describing the growth and the size distribution of multiple metastatic tumors”. In: *Discrete and Continuous Dynamical Systems - Series B* 12 (Nov. 2009).

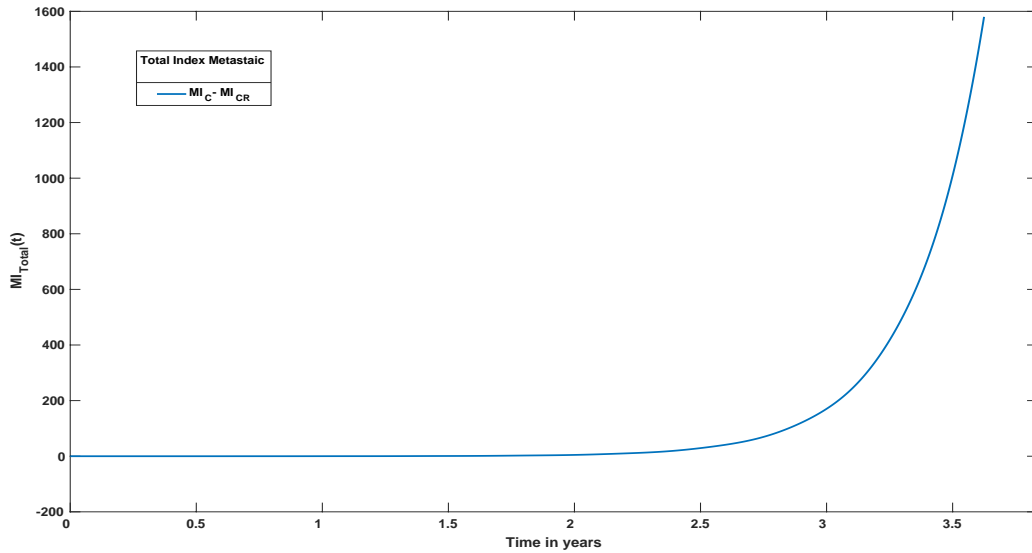


Figure 6: The difference in total metastatic index between chemotherapy alone and chemo-radiotherapy.

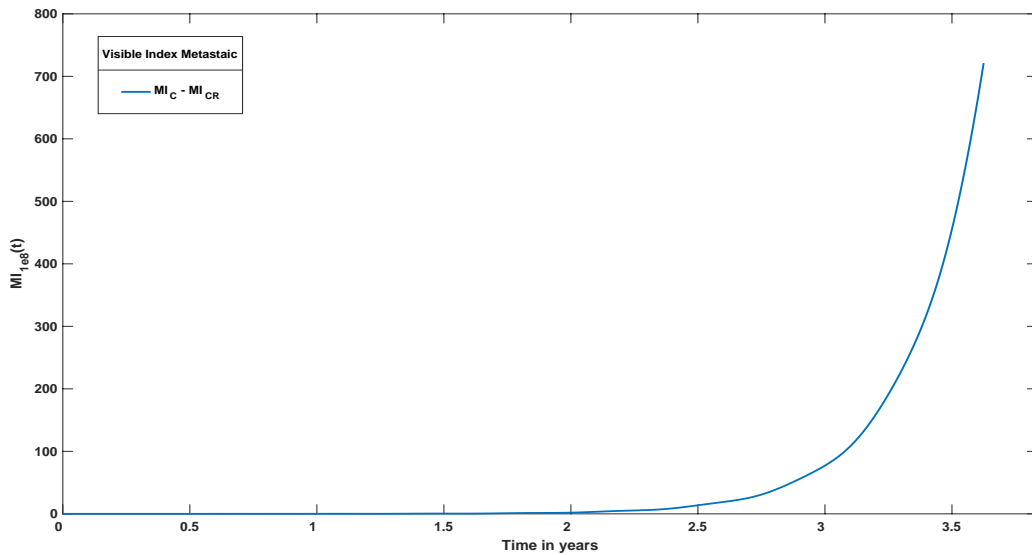


Figure 7: The difference in visible metastatic index between chemotherapy alone and chemo-radiotherapy.

- [8] S. Gottlieb, D. Ketcheson, and C.-W. Shu. *Strong Stability Preserving Runge-Kutta and Multistep Time Discretizations*. WORLD SCIENTIFIC, 2011.
- [9] Z. Liu and C. Yang. "A Mathematical Model of Cancer Treatment by Radiotherapy". In: *Computational and mathematical methods in medicine* 2014 (Nov. 2014), page 172923.
- [10] C. Faivre, R. El Cheikh, D. Barbolosi, and F. Barlesi. "Mathematical optimisation of the cisplatin plus etoposide combination for managing extensive-stage small-cell lung cancer patients". In: *British Journal of Cancer* 116 (Jan. 2017).
- [11] S. E. Ben Abdejilil, A. Ben Essid, and S. Mani-Aouadi. "Analysis of a model of tumor growth including a PDE-ODE coupling with a nonlocal boundary condition". Manuscript submitted. 2021.