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

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## Abstract

In this paper we develop a high order finite volume weighted essentially non-oscillatory (WENO) scheme for a tumor growth model with treatment. More precisely, we consider the case of a small cell lung cancer described by an hyperbolic partial differential equation which takes into account the evolution of tumors and its possible slowing down due to radio and chemotherapy treatments.

## Keywords

Tumor growth; Finite volume schemes.

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## I INTRODUCTION

We consider the following model introduced in [5] and taken back in [9]

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

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

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

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

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

where  $u(t, x)$  represents the colony size distribution of metastatic tumors with  $x$  cells at time  $t$ ,  $t_0$  and  $\bar{T}$  are the start and end times of treatment,  $u_0$  is the density in size at  $t_0$ . In the equation (1e),  $x_p(t)$  represents the number of cells present in a primary tumor at time  $t$ ,  $\beta(x)$  is the colonization rate and has the form  $\beta(x) = m \cdot x^\alpha$ ,  $m$  is the colonization coefficient and  $\alpha$  is the fractal dimension of the blood vessels infiltrated into the tumor see [5]. 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.  $G$  is the growth rate given by

$$G(t, x) = g(x) - K_c(x)C(t) - K_r(x)R(t), \quad (2)$$

where  $g$  is the Gompertzian growth rate given by

$$g(x) = ax \ln \left( \frac{b}{x} \right), \quad (3)$$

$b \geq 1$  is the maximal tumor size and  $a$  is a positive parameter that measures the rate of clonogenic proliferation. The term  $K_c(x)C(t)$  is associated with chemotherapy,  $C$  represents the drug's concentration and  $K_c$  measures its efficiency. Likewise,  $R$  represents the cell death induced by radiation and  $K_r(x)$  indicates the efficiency and the fact that radiotherapy is applied to tumors larger than  $\hat{x}$ . We note that the term associated to treatments will be discontinuous in time at isolated points  $t_i, i = 1, \dots, n$ , which correspond to the beginning and end of each therapy session.

Let  $E = \mathcal{C}_{MG}^1([t_0, T], L^1([1, b]))$  the set of continuous functions on  $[t_0, T]$  with values in  $L^1([1, b])$ , of class  $C^1$  on  $[t_0, T] \setminus \{t_i, i = 1, \dots, n\}$  and admitting right and left derivatives in time on each point. We have the following existence result.

*Theorem 1: Ben Abdeljalil, Ben Essid, and Mani Aouadi [9]*

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

$$u_0(b) = 0 \quad \text{and} \quad (Gu_0)(t_0, 1) = \int_1^b \beta(x)u_0(x)dx + \beta(x_p(t_0)). \quad (4)$$

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

$$G(t, 1) > 0, \quad \forall t \in ]t_0, T[, \quad (5a)$$

$$G(t_0, x) > 0, \quad \forall x \in [1, b[, \quad (5b)$$

$$G(t, b) < 0, \quad \forall t \in [t_0, T]. \quad (5c)$$

Then, there is a unique

$$u \in E(u_0) = \{w \in \mathcal{C}_{MG}^1([t_0, T], L^1([1, b])), w(t_0, \cdot) = u_0\} \quad \text{with} \quad Gu \in \mathcal{C}([t_0, T], W^{1,1}([1, b]))$$

that verifies the equations (1a), (1b) and (1c) respectively in

$$\mathcal{C}_{MG}([t_0, T], L^1([1, b])); \quad \mathcal{C}([t_0, T], \mathbb{R}); \quad \text{and} \quad L^1([1, b]).$$

## II NUMERICS

The Characteristic method used in [9] is expensive in terms of time and computer RAM. To overcome these faults, we use here the finite volume scheme of order 5, introduced 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 here between 1 and  $10^{12}$ , which makes it impossible to choose a small

step along the domain of variation of  $x$  that 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 [6], a change of variables with the aim of reducing, on the one hand, the spacial domain 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

$$\begin{cases} \partial_t v(t, y) + \partial_y F(t, y, v(t, y)) &= 0, \\ \tilde{G}(t, 0)v(t, 0) &= \int_0^{\log(b)} \tilde{\beta}(y)v(t, y)dy + \beta(x_p(t)), \\ v(0, y) &= 0. \end{cases} \quad (6)$$

## 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

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

where  $y_i$  is the center of the interval  $\mathcal{C}_i$ . By integrating (6) over the cell  $\mathcal{C}_i$ , we obtain

$$\frac{d}{dt} \bar{v}_i(t) = -\frac{1}{\Delta y} \left[ F_{i+\frac{1}{2}} - F_{i-\frac{1}{2}} \right], \quad (7)$$

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  $t$ . Therefore the equation (7) writes in the abstract form

$$\frac{d}{dt} \bar{v}_i(t) = \mathcal{L}(t, \bar{v}_{i-k}(t), \dots, \bar{v}_{i+k}(t)), \quad (8)$$

where  $\mathcal{L}$  is the spatial operator of the WENO scheme. Then, Eq. (8) is solved by the high-order TVD Runge-Kutta method [1, 7]. The fifth order polynomial  $P_i$ , which constitutes an

approximation of  $v$  to the right and left of the cell  $C_i$ , 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 defined in each one of the stencils  $S_i^{(r)}$ , as shown in Figure 1, for  $k = 3$ . More precisely, we

have

$$v_{i+\frac{1}{2}}^- = P_i(y_{i+1/2}) = \sum_{r=0}^2 \omega_r p_{r,i}^+, \quad v_{i-\frac{1}{2}}^+ = P_i(y_{i-1/2}) = \sum_{r=0}^2 \tilde{\omega}_r p_{r,i}^-$$

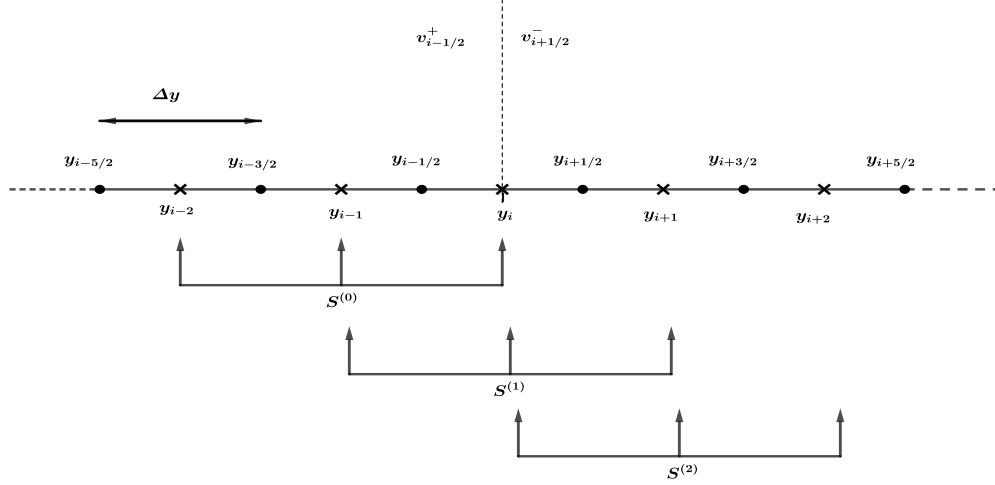


Figure 1: The stencils used by the WENO-5 numerical flux

The coefficients  $\omega_1$ ,  $\omega_2$  and  $\omega_3$  are called the nonlinear weights. The detailed reconstruction procedure for the 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

$$\omega_r = \frac{\alpha_r}{\sum_{r=0}^2 \alpha_r}, \quad \alpha_r = \frac{d_r}{(\varepsilon + \beta_r)^2}, \quad r = 0, 1, 2, \quad (9)$$

where  $d_0 = 1/10$ ,  $d_1 = 3/5$  and  $d_2 = 3/10$  are the linear weights which provide the 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  $\beta_r$  introduced in Shu [4]

$$\beta_r = \sum_{l=1}^2 \Delta y^{2l-1} \int_{C_i} \left( \frac{d^l}{dy^l} p_{r,i}(y) \right)^2 dy, \quad (10)$$

and therefore  $\beta_r$ , 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  $\omega_r$  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 (7) by the following conservative scheme

$$\frac{d}{dt}\bar{v}_i(t) = -\frac{1}{\Delta y} \left[ \hat{F}_{i+\frac{1}{2}} - \hat{F}_{i-\frac{1}{2}} \right], \quad (11)$$

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

$$\hat{F}_{i\pm\frac{1}{2}} = h(v_{i\pm\frac{1}{2}}^-, v_{i\pm\frac{1}{2}}^+), \quad i = 1, \dots, N_y, \quad (12)$$

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

$$\hat{F}_{i\pm\frac{1}{2}} = \frac{1}{2} \left[ \tilde{G}_{i\pm\frac{1}{2}} \left( v_{i\pm\frac{1}{2}}^- + v_{i\pm\frac{1}{2}}^+ \right) - \max_Q |\tilde{G}(t, y)| \left( v_{i\pm\frac{1}{2}}^+ - v_{i\pm\frac{1}{2}}^- \right) \right], \quad i = 1, \dots, N_y, \quad (13)$$

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 (8).

## 2.2 Numerical results

We consider the effect of treatments, by chemotherapy and by chemo-radiotherapy, on the evolution first of a primary tumor, then of a metastatic growing tumor. We consider the following parameters in [5, 8]

$$a = 0.0231, \quad b = 10^{12}, \quad m = 1.2 \times 10^{-9}, \quad \alpha = 2/3, \quad \alpha_{\text{eff}} = 1.133. \quad (14)$$

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

$$MI_{b_{\min}}(t) = \int_{b_{\min}}^b u(t, x) dx. \quad (15)$$

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.

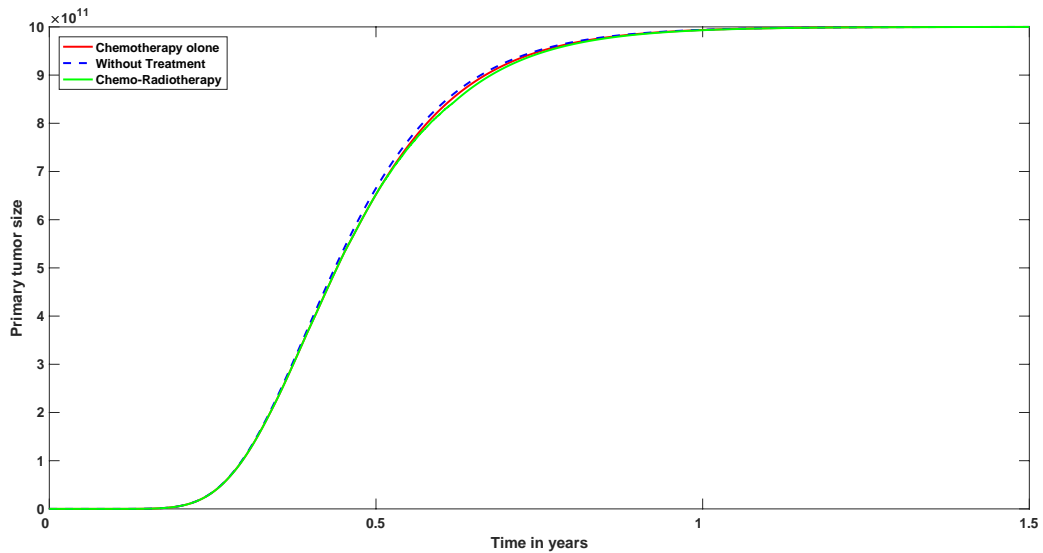


Figure 2: Primary tumor with and without treatments

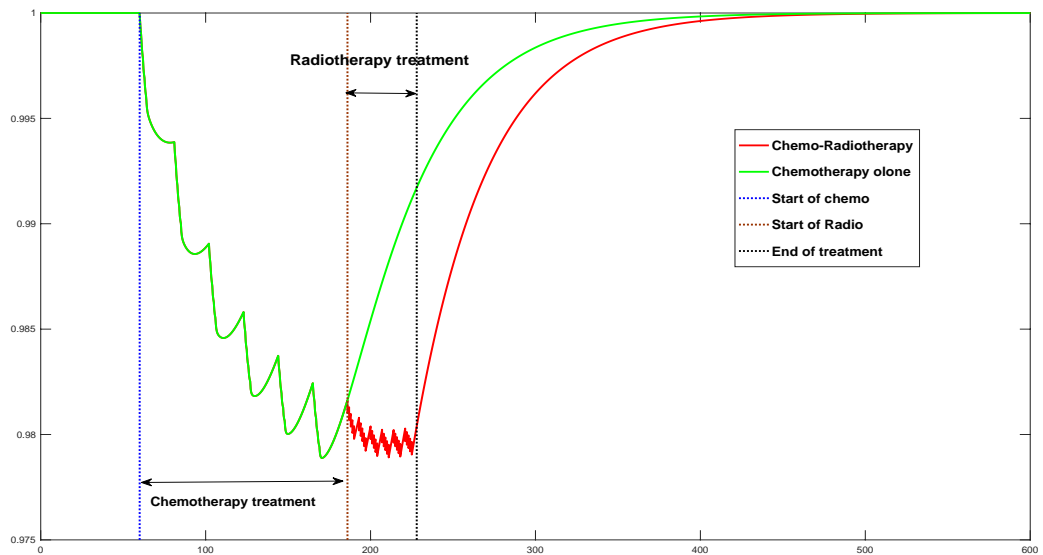


Figure 3: The ratio of the numbers of cells

### 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.

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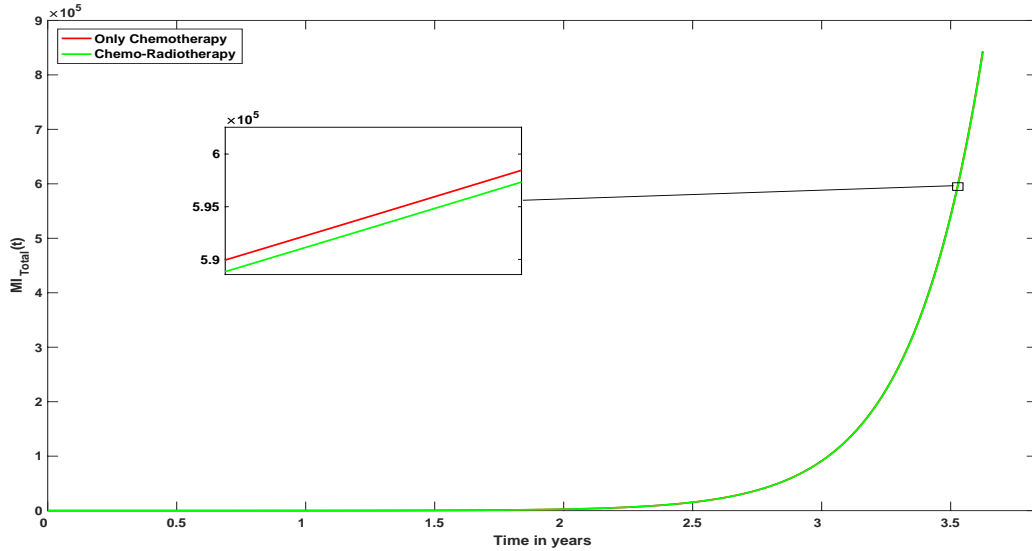


Figure 4: Total number of metastases ( $b_{min} = 1$ ).

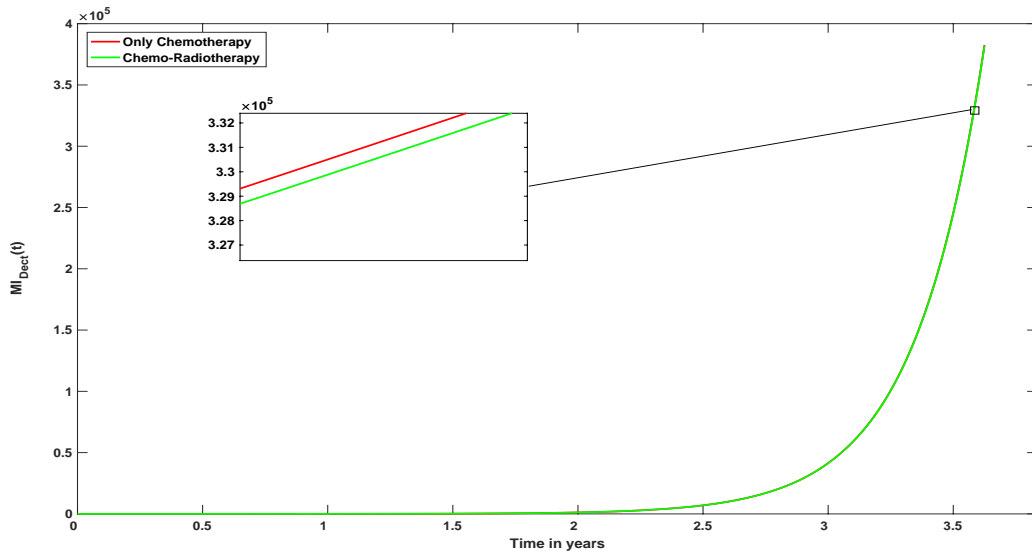


Figure 5: Number of metastases detectable ( $b_{min} = 10^8$ ).

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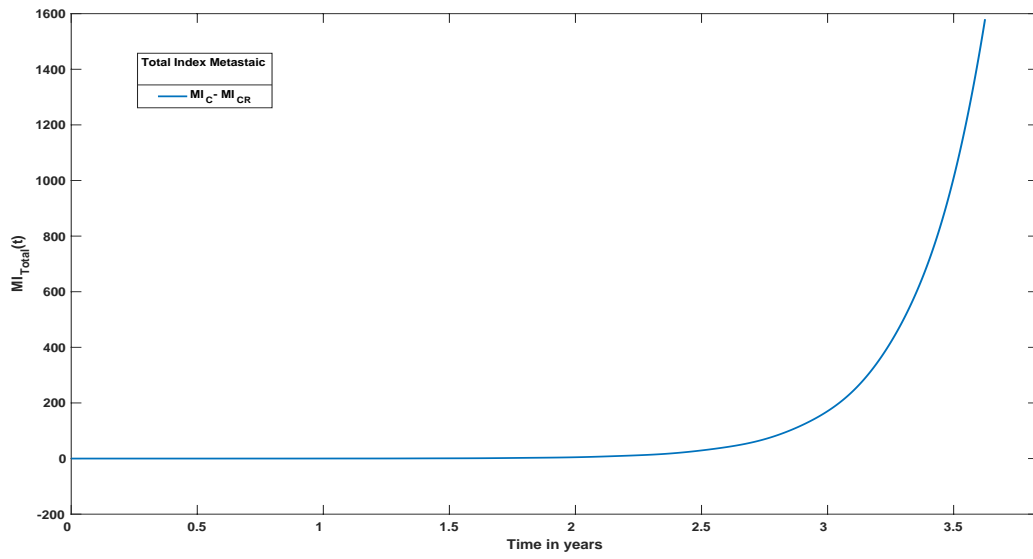


Figure 6: The difference in total metastatic index between chemotherapy alone and chemo-radiotherapy.

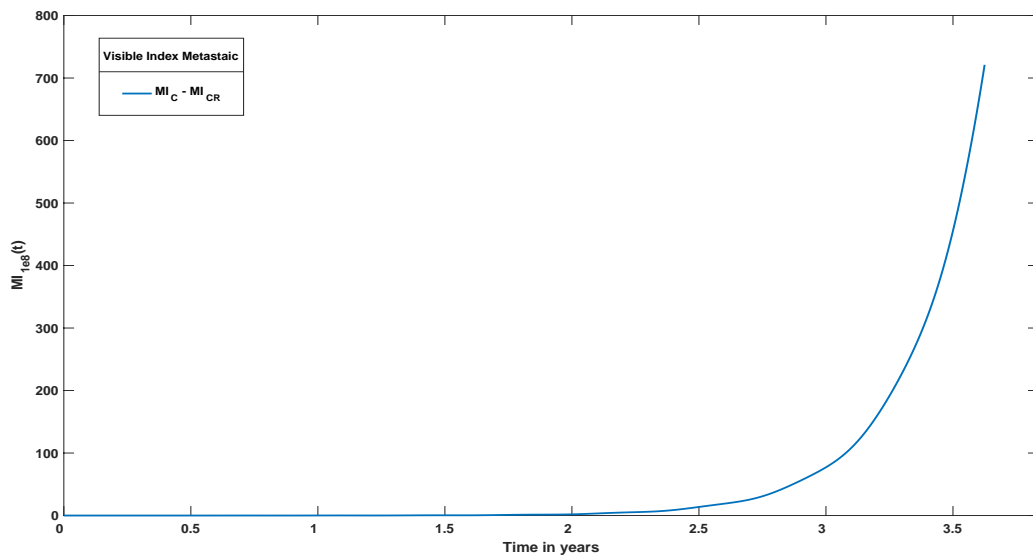


Figure 7: The difference in visible metastatic index between chemotherapy alone and chemo-radiotherapy.