Simple tumour growth models with treatments

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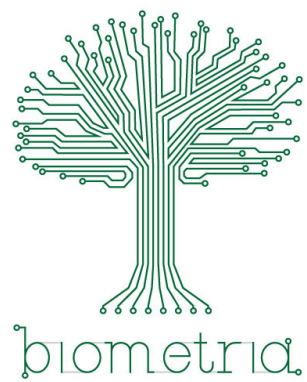

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Aims

Aims

Present a simple mathematical model that simulates the administration of a chemotherapeutic cycle-nonspecific agent, where the model takes into account the carrying capacity of tumour cells associated with the vascular endothelial cells as well as the chemotherapeutic action on vascular endothelial cells.

Introduction

Model

Four ordinary differential equations: normal and tumour cells, vascular endothelial cells and chemotherapeutic agent.

Modalities of chemotherapy under varying protocols: the conventional protocol and the metronomic schedule (smaller cycle time intervals T and lower dose-per-infusion than the conventional schedule) and continuous drug infusion

Introduction

Model

Angiogenic process involves a spatial structure well analysed by partial differential equations models [3].
We consider, as in other vascular tumour models for which the main focus is the treatment dynamic [5], [8], an ODE model, since cell growth in the vascular stage may be assumed to be a continuous process and the tumour may be considered, as a first approximation, an homogeneous population of cells.

Mathematical model

Model

Tumour angiogenesis is represented by the increase in carrying capacity due to neo-vascularization, which is related to the number of the vascular endothelial cells. To define the equation for vascular endothelial cells we follow [8].

We assume the logistic function for natural growth and intraspecific competition of tumour cells and k_1 is the carrying capacity of the tumour in the pre-vascular stage.

Mathematical model

Model

$$
\begin{cases}
\dfrac{dN_1}{dt} &= r_1 N_1 \left(1 - \dfrac{N_1}{k_1 + L_1} - \dfrac{\alpha_1 N_2}{k_1 + L_1}\right) - \dfrac{\mu N_1 Q}{a + Q} \\
\dfrac{dN_2}{dt} &= r_2 N_2 \left(1 - \dfrac{N_2}{k_2} - \dfrac{\alpha_2 N_1}{k_2}\right) - \dfrac{\nu N_2 Q}{b + Q} \\
\dfrac{dL_1}{dt} &= \sigma L_1 + \phi N_1 - \omega N_1 L_1 - \dfrac{\eta L_1 Q}{c + Q} \\
\dfrac{dQ}{dt} &= q(t) - \lambda Q
\end{cases}
. \quad (1)
$$

Mathematical model

Model

The contribution to the carrying capacity of tumour cells due to tumour angiogenesis is represented by L_1 - the number of the vascular endothelial cells; σ is related to the proliferation of the endothelial cells adjacent to the tumour and their movement into the peritumoural region; ϕ measures the angiogenic factors released by the tumour and ω models the neo-vascularization inhibition by the tumour itself.

Mathematical model

Model

Regarding the drug effect, we assume the classical log-kill functional response (i.e. the percentage of cells eliminated by the drug is always the same constant) hypothesized by [17] with a saturation of the Michaelis-Menten type for the amount of the drug; a, b and c determine the saturation of the drug functional response (they are the amount of the drug for which the respective effect is half of its maximum); μ is the treatment rate of the tumour cells; ν is the mortality rate of normal cells due to treatment; η models the intensity of the antiangiogenic effect of the chemotherapeutic drug; $\lambda > 0$ is the washout rate of a given cycle-nonspecific chemotherapeutic drug.

Mathematical model

Equilibrium solutions: untreated cancer

- $E_1(0,0,0)$ – Extinction of normal, endothelial and tumour cells.
- $E_2(0,k_2,0)$ – Spontaneous cure.
- $E_3(\widetilde{N_1},0,\widetilde{L_1})$ – Extinction of normal cells in the presence of tumour cells and endothelial vascular cells.
- $E_4(N_1^*,N_2^*,L_1^*)$ – Coexistence between cells.

Mathematical model

Stability analysis: untreated cancer

The non-biological equilibrium $E_1(0,0,0)$ and disease free equilibrium $E_2(0,k_2,0)$ are locally unstable for $\sigma > 0$ and any non-negative values of the other parameters (except for $k_1 > 0$ and $k_2 > 0$). If we assume $\sigma = 0$, we have to impose $k_1 > \alpha_1 k_2$ in order to guarantee the unstable character of $E_2(0,k_2,0)$. Without treatment, the system may evolve to $E_4(N_1^*, N_2^*, L_1^*)$ in the positive cone, if

$$\alpha_1\alpha_2 < 1 \text{ and } \frac{\sigma}{\omega} < N_1^* < \frac{k_2}{\alpha_2}. \tag{2}$$

Mathematical model

Table : Parameters related to the tumour, normal and endothelial cells for model (1).

Parameter	Value	Unity	Reference/Comments
r_1	10^{-2}	day^{-1}	[18]
r_2	10^{-3}	day^{-1}	$r_2 < r_1$
k_1	10^{8}	cells	estimated value
k_2	10^{12}	cells	[21]
α_1	9×10^{-5}	-	assumed value
α_2	9×10^{-2}	-	assumed value
σ	10^{-3}	day^{-1}	$\sigma \sim r_2$
ϕ	1	day^{-1}	assumed value
ω	10^{-12}	cells^{-1} dia^{-1}	assumed value

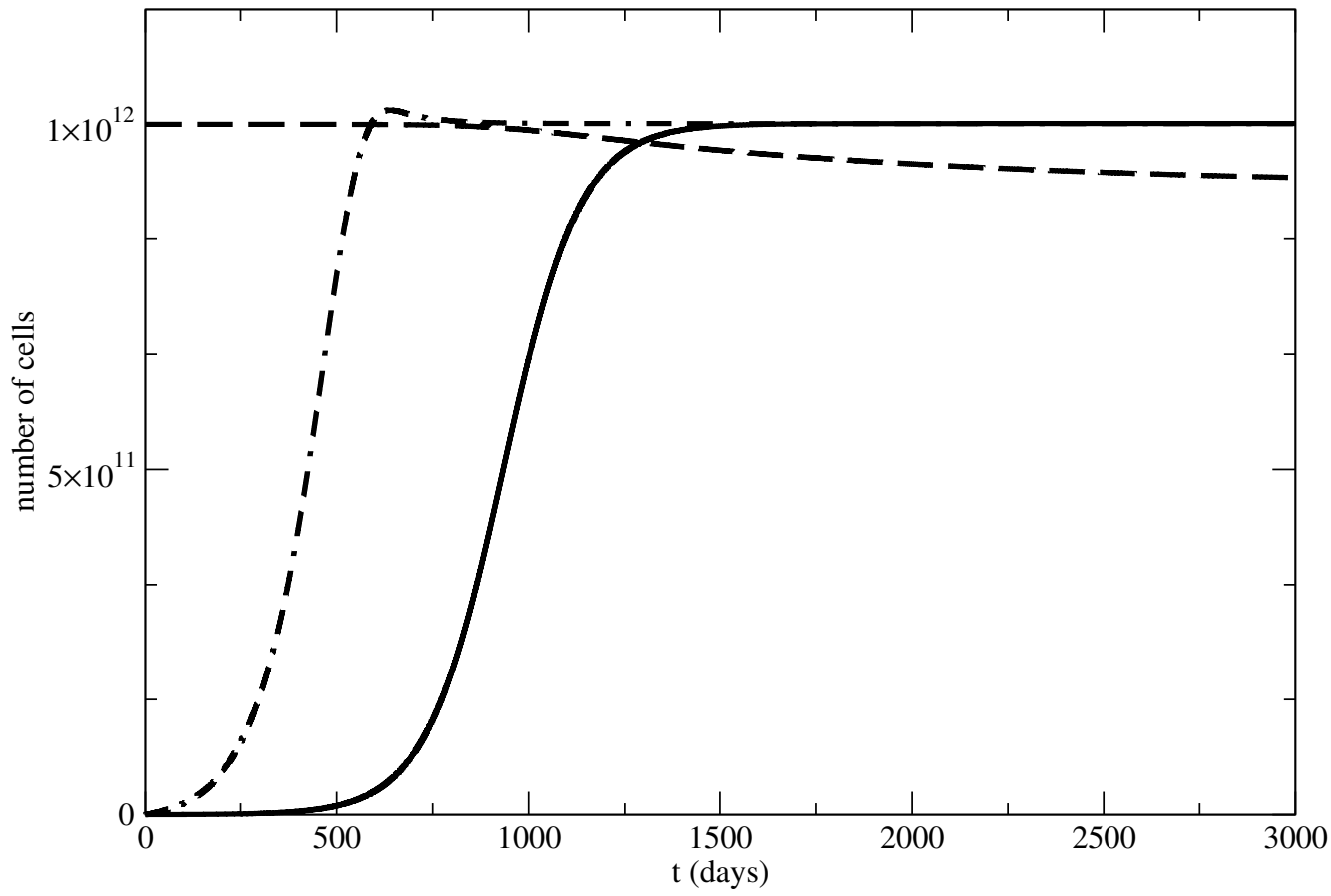

Figure : Tumour evolution for no treatment model (with $Q(t) \equiv 0$, $\forall\ t$). Initial conditions: $N_1(0) = 10^8$ tumour cells (solid line), $N_2(0) = 10^{12}$ normal cells (dashed line) and $L_1(0) = 0$ vascular endothelial cells (dash-dotted line).

Mathematical model

Anti-cancer chemotherapy: continuous administration

- $P_1\left(0, 0, 0, \frac{q}{\lambda}\right)$ – Elimination of normal and tumour cells due to high dose.
- $P_2\left(0, \widehat{N}_2, 0, \frac{q}{\lambda}\right)$ – Curing disease through continuous chemotherapy.
- $P_3\left(\widehat{N}_1, 0, \widehat{L}_1, \frac{q}{\lambda}\right)$ – Elimination of normal cells by treatment in the presence of tumour cells and vascular endothelial cells.
- $P_4\left(\underline{N_1}, \underline{N_2}, \underline{L_1}, \frac{q}{\lambda}\right)$ – Coexistence between normal and tumour cells in the presence vascular endothelial cells.

Mathematical model

Anti-cancer chemotherapy: continuous administration

Let us consider the details for the cure state $P_2(0, \widehat{N}_2, 0, q/\lambda)$:

$$\widehat{N}_2 = \frac{k_2 \left(r_2 b\lambda + q(r_2 - \nu)\right)}{r_2 \left(b\lambda + q\right)}. \tag{3}$$

From a biological point of view, we have $\widehat{N}_2 > 0$, which occurs if

$$0 < q < q_{\text{threshold}} \quad \text{com} \ \ \nu > r_2. \tag{4}$$

where

$$q_{\text{threshold}} = \frac{r_2 b\lambda}{\nu - r_2}, \tag{5}$$

corresponds to the rate of infusion of the drug required to cure.

Mathematical model

Anti-cancer chemotherapy: continuous administration

The cure state $P_2(0, \widehat{N}_2, 0, q/\lambda)$ is locally stable when

- $$\eta_{\text{threshold}} = \sigma\left(1 + \frac{c\lambda}{q}\right) \tag{6}$$

  below that, there is no cure for the disease. There is a transcritical bifurcation in the bifurcation diagram, assuming η to be a control parameter, since P_2 changes from unstable to stable equilibrium. Therefore, above $\eta_{\text{threshold}}$, the tumour is eliminated.

- $$\alpha_1 > \mathcal{E}/\mathcal{D} \tag{7}$$

Mathematical model

Anti-cancer chemotherapy: continuous administration

where

$$\begin{aligned} \mathcal{D} &= -r_1 k_2 (a\lambda + q)\big(r_2(b\lambda + q) - \nu q\big), \\ \mathcal{E} &= -r_2 k_1 (b\lambda + q)\big(r_1(a\lambda + q) - \mu q\big), \end{aligned}$$

sets up an inequality expressed in terms of the infusion rate q, which is, from a clinical perspective, a parameter that can be controlled. The critical parameters q and η, given, respectively by (5) and (6) corresponds, respectively, to the upper and lower values for the cure state; condition (7) is also necessary to guarantee the local stable character of the cure state.

Mathematical model

Table : Parameters related to the chemotherapy action.

Parameter	Value	Unity	Reference/Comment
μ	8	day^{-1}	assumed value
ν	8×10^{-2}	day^{-1}	$\nu \ll \mu$
λ	4.16	day^{-1}	[11]
a	2×10^{3}	mg	assumed value
b	5×10^{6}	mg	assumed value
c	2×10^{3}	mg	$c \sim a$

Mathematical model

Anti-cancer chemotherapy: conventional schedule

From [13] we estimate that the body surface of a patient with a weight of 70 kg and height 1.70m is 1.8m^2, thus establishing a dose of 900 mg per cycle. We assume that this dose is infused over 3 hours because we assume that the drug interacts immediately with the tumour and also because cyclophosphamide's peak plasma concentration occurs approximately 3 hours after infusion [11]. An infusion of 3 hours (1/8 day) implies an infusion rate of $8 \times 900 = 7200$ mg/day. This corresponds to an standard protocol which will be called the *conventional schedule*.

Mathematical model

Anti-cancer chemotherapy: conventional schedule

We define such a regimen by [12]

$$q(t) = \begin{cases} 7200, & l \leq t < l + \frac{1}{8}, \\ 0, & l + \frac{1}{8} \leq t < l + 21, \end{cases} \tag{8}$$

where $l = 0, 21, 42, 63$ ($n_{inf} = 4$ infusions), with $q(t \geq 84) \equiv 0$.

Mathematical model

Table : Parameters related to chemotherapy administration in cycles for model (1). Chemotherapeutic drug: cyclophosphamide.

Parameter	Conventional	Metronomic
Drug infusion rate (q_{cycle})	7200 mg/day	$q < 7200$ mg/day
Cycle time interval (T)	21 days	$T < 21$ days
Number of infusions (n_{inf})	4	$n_{\mathrm{inf}} > 4$
Drug infusion time (τ)	$1/8$ day $= 3$h	$1/8$ day $= 3$h
Total drug dose ($D = q_{\mathrm{cycle}}\, n_{\mathrm{inf}}\, \tau$)	$D_{\mathrm{c}} = 3600$ mg	$D \geq 3600$ mg
Antiangiogenic effect (η)	$\eta > 0$ day^{-1}	$\eta > 0$ day^{-1}

We set both total dose D at $D_{\mathrm{c}} = 3600$ mg. We simulate three metronomic schedules with n_{inf} equal to 8, 12 or 16 infusions. As we can see in Figure, the lower and more frequent the dose, the greater the tumoural reduction will be.

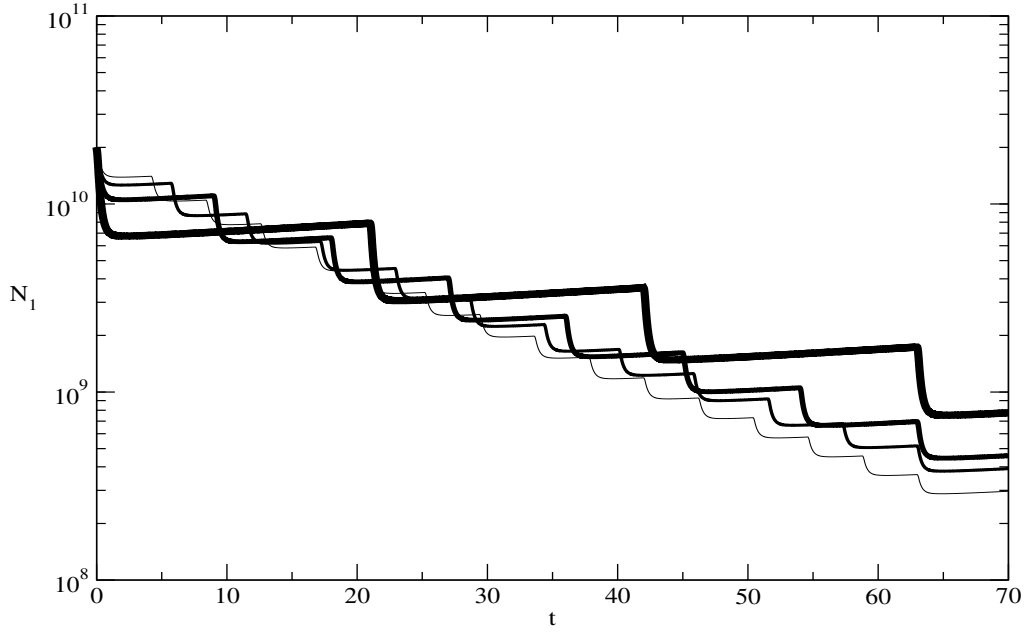

Figure : Number of tumour cells. Conventional (the thickest solid line) and metronomic schedules (the three thinnest solid lines correspond to $n_{\mathrm{inf}} = 16, 12$ and 8) until 70 days (the last day of infusion is the 63th).

Mathematical model

CASE STUDY I – Computing the antiangiogenic effect

For the same tumoural curves, the lowest value of tumour cells reached during each respective protocol is (63 days of treatment):

- Conventional schedule: 7.53×10^8 tumour cells;
- Metronomic chemotherapy:
  - $n_{\text{inf}} = 8$ and $T = 7$ days: 4.45×10^8 tumour cells.
  - $n_{\text{inf}} = 12$ and $T = 63/11 = 5.\underline{72}$ days: 3.79×10^8 tumour cells.
  - $n_{\text{inf}} = 16$ and $T = 63/15 = 4.2$ days: 2.87×10^8 tumour cells.

Table : Analysis of the cycle time interval T apart from the antiangiogenic chemotherapeutic effect itself. Total treatment time: 42 days; total dose: $D = 3600$ mg.

n_{inf}	T (days)	η (day^{-1})	Min. of tumour cells ($\times 10^9$)
8	6	0	**1.069**
		500	0.380
12	$3.\underline{81}$	0	**1.075**
		500	0.328
16	2.8	0	0.920
		500	0.252

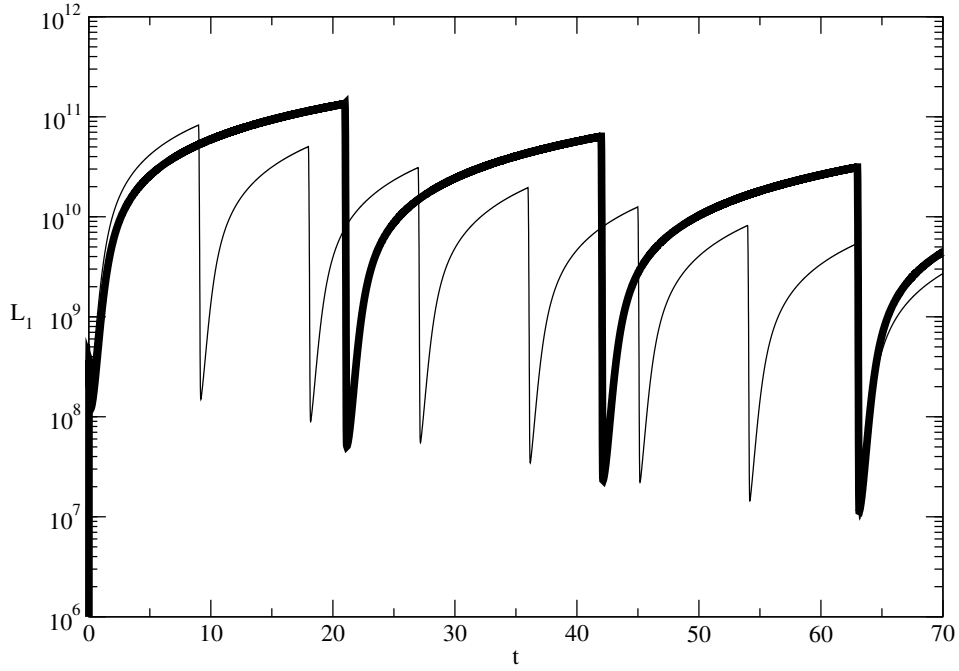

Figure : Number of vascular endothelial cells for a conventional schedule (thickest line) and for metronomic chemotherapy schedule with $n_{\mathrm{inf}} = 8$ (thinnest line).

Mathematical model

CASE STUDY II – Antiangiogenic protocols and human survival time

We compare a conventional schedule and a metronomic one, both with total dose D_{c} and $2D_{\mathrm{c}}$. Our goal is to investigate the differences between them in respect to the argument that metronomic chemotherapy increases human survival time.

Note that, unlike the conventional schedule at dose D_{c}, for the other three cases, the number of tumour cells is reduced from an order of magnitude of 10^{10} cells to less than 10^{9} cells, that is, they become clinically undetectable tumours.

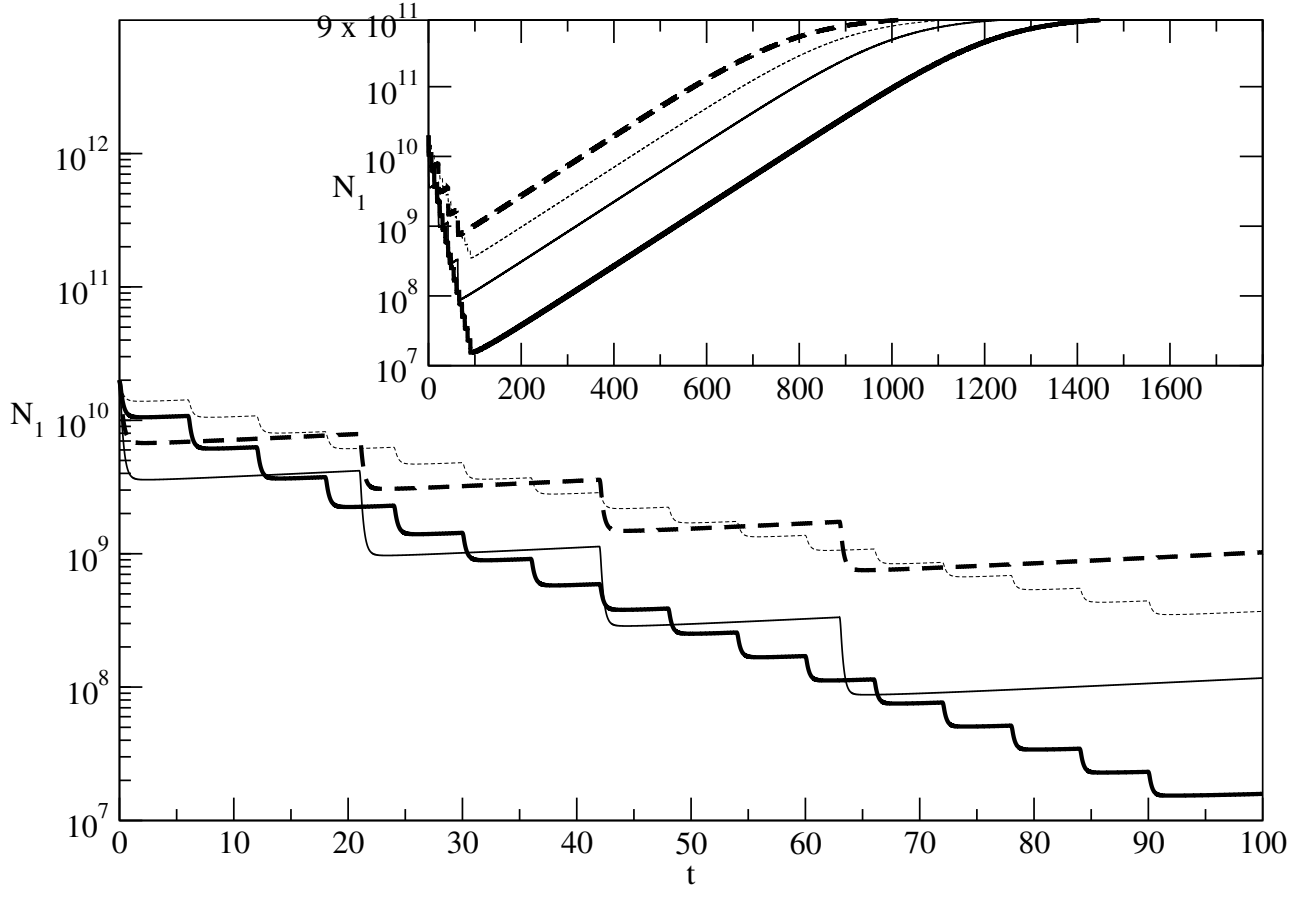

Figure : Number of tumour cells for conventional schedule with dose $D_{\mathrm{c}} = 3600$ mg (thickest dashed line), conventional schedule with *doubled* dose $2D_{\mathrm{c}} = 7200$ mg (thinnest solid line), metronomic chemotherapy with dose $D_{\mathrm{c}} = 3600$ mg (thinnest dashed line) and metronomic chemotherapy with dose $2D_{\mathrm{c}} = 7200$ mg (thickest solid line). $\eta = 500$ day^{-1}.

Table : Analysis of patient's survival time.

Total dose (mg)	Schedule	Min. of tumour cells	Survival time (days)
$3600\ (D_{\mathrm{c}})$	conventional	7.526×10^{8}	1000
$3600\ (D_{\mathrm{c}})$	metronomic	3.495×10^{8}	1100
$7200\ (2D_{\mathrm{c}})$	conventional	0.876×10^{8}	1200
$7200\ (2D_{\mathrm{c}})$	metronomic	0.154×10^{8}	1450

Conclusion

Conclusion

Conclusion

a) The killing action of chemotherapeutic drug on vascular endothelial cells is more relevant to the reduction of a tumour than the metronomic schedule of chemotherapy. Applying a metronomic schedule for a chemical efficient in killing endothelial cells enhances the antiangiogenic effect, which leads to a more effective tumour reduction.

b) Increasing the total dose is a better strategy for increasing the survival of a patient (after the total treatment time), even for conventional or metronomic schedules. However, for metronomic schedules, at the end of treatment, larger dose are effective for tumoural reduction.

c) In the limit case of continuous drug administration, there are critical values for dose per infusion and chemotherapeutic action on endothelial cells that guarantee the elimination of cancer cells.

A simple tumour growth model with treatments II

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Model

We propose the following model based on [4] and [16]:

$$
\begin{cases}
\dfrac{dN_1}{dt} &= r_1 N_1 \left(1 - \frac{N_1}{k_1+L} - \frac{\alpha_{12}\, N_2}{k_1+L}\right) - c_1\, I\, N_1 - \frac{\mu\, N_1\, Q}{a+Q} \\
\dfrac{dN_2}{dt} &= r_2 N_2 \left(1 - \frac{N_2}{k_2} - \frac{\alpha_{21}\, N_1}{k_2}\right) - \frac{\nu\, N_2\, Q}{b+Q} \\
\dfrac{dI}{dt} &= s - d_1\, I + \frac{\rho\, I\, N_1}{\gamma+N_1} - c_2\, I\, N_1 - \frac{\delta\, I\, Q}{d+Q} \\
\dfrac{dL}{dt} &= \sigma\, L + \phi\, N_1 - \omega\, N_1\, L - \frac{\eta\, L\, Q}{c+Q} \\
\dfrac{dQ}{dt} &= q(t) - \lambda\, Q
\end{cases}
\quad . \quad (9)
$$

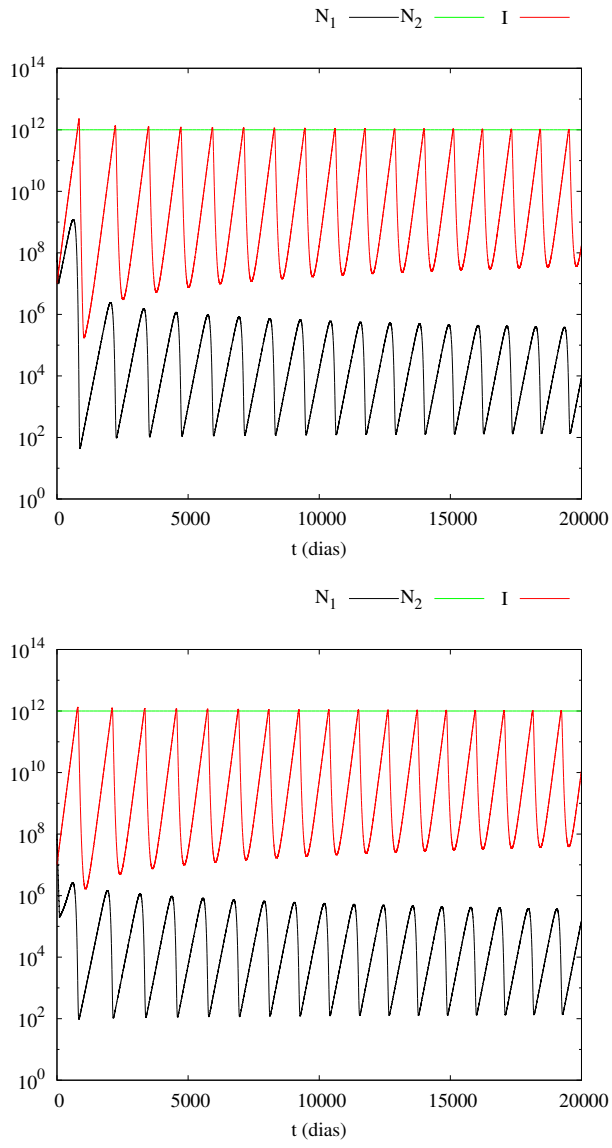

Figure : Conventional and metronomic: $\rho = 0.215$ day^{-1}, $s = 10^4$ cells day^{-1}, $N_1(0) = 10^8$, $N_2(0) = 10^{12}$, $I(0) = 10^7$ and $L(0) = 10^2$.

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References I

[1] Brasil.
Bases do Tratamento. In: Inca (Ed.). **Ações de enfermagem para o controle do câncer: uma proposta de integração de ensino**. Rio de Janeiro: INCA, p.57;414;449, 2008.

[2] Browder, T.; Butterfield, C.E.; Kraling, B.M.; Shi, B.; Marshall, B.; O'Reilly, M.S.; Folkman J.
Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. **Cancer Res.**, v.60, p.1878-1886, 2000.

[3] Chaplain, M. A. J.; McDougall, S. R.; Anderson, A. R. A.
Mathematical modelling of tumour-induced angiogenesis **Annu. Rev. Biomed. Eng.**, v.8, p.233–257, 2006.

References II

[4] de Pillis, L. G.; Radunskaya, A.
A mathematical tumor model with immune resistance and drug therapy: an optimal control approach, **J. Theor. Med.**, 3, 79–100, 2001.

[5] d'Onofrio, A.; Gandolfi, A.
Tumor eradication by antiangiogenic therapy: analysis and extensions of the model by Hahnfeldt et. al. (1999). **Math. Biosc.**, v.191, p.159-184, 2004.

[6] Folkman, J.
Tumour angiogenesis: therapeutic implications. **N. Engl. J. Med.**, v.285, n.21, p.1182–1186, 1971.

[7] Gatenby, R. A.
Application of competition theory to tumour growth: implications for tumour biology and treatment. **Eur. J. Cancer**, v.32A, p.722–726, 1996.

References III

[8] Hahnfeldt, P.; Panigrahy, D.; Folkman, J.; Hlatky, L.
Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy. **Cancer Res.**, v.59, p.4770–4775, 1999.

[9] Levine H. A.; Sleeman, B. D.; Nilsen-Hamilton, M.
Mathematical model for the roles of pericytes and macrophages in the initiation of angiogenesis I: the role of protease inhibitors in preventing angiogenesis. **Math. Biosci.**, v.168, p.77–115, 2000.

[10] Maggelakis, S. A.
The effects of stimulator and inhibitor factors on tumour vascularization: a mathematical model. **Mathl. Comput. Model.**, v.23, n.6, p.121–133, 1996.

References IV

[11] MeadJohnson Oncology Products [internet] http:// patient.cancerconsultants.com/ druginserts/ Cyclophosphamide.pdf

[12] Martin, R.; Teo, K. L.
Optimal control of drug administration in cancer chemotherapy. Singapore: World Scientific, 1993. 187p.

[13] Mosteller, R. D.
Simplified calculation of body surface area. **N. Engl. J. Med.**, p.1098, 1987.

[14] Nani, F.; Freedman H. I.
A mathematical model of cancer treatment by immunotherapy. **Math. Biosc.**, v.163, n.4, p.159–199, 2000.

References V

[15] Norton, L.
Introduction. In: Silver, R. T.; Lauper, R. D.; Jarowski, C. I. (Ed.). **A synopsis of cancer chemotherapy**. New York: Yorke Medical Books, 1987. p.24.

[16] Rodrigues., D. S.
Modelagem matemática em câncer: dinâmica angiogênica e quimioterapia anti-neoplásica. Dissertação de mestrado, Unesp, IBB, 2011. (In portuguese)

[17] Skipper, H. E.; Schaebel-Jr., F. M.; Wilcox, W. S.
Experimental evaluation of potential anticancer agents XIII: on the criteria and kinetics associated with curability of experimental leukemia. **Cancer Chemother. Rep.**, v.35, p.1–111, 1964.

References VI

[18] Spratt, J. S.; Meyer, J. S.; Spratt, J. A.
Rates of growth of human neoplasms: Part II. **J. Surg. Oncol.**, v.61, n.2, p.68–73, 1996.

[19] Stamatakos, G. S.; Kolokotroni, E. A.; Dionysiou, D. D.; Georgiadi, E. C.; Desmedt, C.
An advanced discrete state-discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study. **J. Theor. Biol.**, v.266, n.1, p.124–139, 2010.

[20] Pinho, S. T. R.; Freedman, H. I.; Nani, F. K.
A chemotherapy model for the treatment of cancer with metastis. **Math. Comp. Model.**, v.36, p.773–803, 2002.

[21] Weinberg, R. A.
The biology of cancer. New York, Garland Science.

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