

Bi-compartmental modelling of tumor and supporting vasculature growth dynamics for cancer treatment optimization purpose

Dávid Csercsik, Johanna Sápi, Tamás Gönczy and Levente Kovács

Abstract—We introduce a nonlinear bi-compartmental dynamic tumor cell and supporting vasculature volume growth model which takes into account nutrient and cell proliferation, necrosis and angiogenesis. Validation of the model requires measurement data on tumor volume during the therapy; for explicit identification of vasculature growth dynamic, in vivo measurement data on vasculature volume during the therapy are required as well. We show that the model can be used for the evaluation of drug dosage protocols.

I. INTRODUCTION

Recently it has been shown by [1] that innovative dosage delivery methods of anti-angiogenic drugs may be more effective for treating tumors, compared to conventional anti-angiogenic dosage protocols. In order to optimize such therapies with computer methods, we need a computational model, which is on the one hand capable of the integration of pathophysiological knowledge and measurement data. On the other hand, its computational complexity should be at a tractable level regarding optimization and controller design purposes. Controller design methodology is unavoidable if we wish to develop closed loop devices in the future for personalized tumor treatment purposes [2]. The drawbacks and shortcomings of models which are suitable for controller design are summarized in [3]. A common feature of these models is that either they do not explicitly consider angiogenesis, or they are far too complex for controller design [4]. For a recent review of integrative models of vascular remodeling during tumor growth see [5].

The Hahnfeldt model [6] considers vasculature volume changes during tumor growth; however, its validity has been already questioned by new biological results [7]. The model of Yang [8] considers basic angiogenic processes as well on a physical basis; however, since the proposed model is based on concentrations as state-variables, it is unable to describe tumor geometry and spatial aspects, which are, nevertheless, the most easiest aspects to measure.

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In this article we propose a new model which explicitly considers angiogenic processes and the effect of vasculature volume in the tumor. We suppose that vasculature concentration feeds back to tumor development by affecting the nutrition concentration in the tumor. As the proposed model takes into account exact geometrical aspect, viz. tumor volume is calculated, we are able to compare it with experimental results. Furthermore, we validate the behavior of the model via its response to various dosage protocols of anti-angiogenic drug.

The paper is organized as follows. In Section II, we present the modelling assumptions based on the newest biological findings; after that the model equations are discussed, particularly the choice of the variables. In Section III, first model calibration results based on experimental tumor volume data are presented, and then the response of the model to different delivery methods of antiangiogenic drugs are examined. The paper ends with the conclusions and future works in Section IV.

II. MATERIAL AND METHODS

A. Modelling Assumptions

Based on the newest biological findings [5], [7], and in accordance with our previous results [9], modelling assumptions are the following:

- We assume spherical tumor geometry, composed of a core and of a periphery layer.
- Living tumor cells of the periphery proliferate (cellular mitosis) on a rate which depends on the level of nutrient reaching them, and on the level of their actual concentration.
- Tumor cells of the core produce tumor angiogenic factor (TAF), if the nutrient concentration in the core is low.
- Tumor cells of the core necrotize, if the nutrient concentration in the core is too low.
- TAF stimulates new blood vessel formation and vasculature growth in the periphery.
- We assume that processes of cellular responses and synthesis of various factors (as TAF) are much faster than growth-related mechanisms.
- As the tumor grows and makes contact with external vasculature, blood vessels are accumulated in the periphery and they are partially incorporated from the environment to the tumor periphery, and then from tumor periphery to the tumor core.
- We assume that tumor cells basically stay in the same place; however, as the tumor grows, the same geo-

metrical position which has been considered earlier as periphery, will be considered as part of the core.

- We assume that the cells of the core/periphery are homogeneously distributed in the volume of the core/periphery.

B. Model Equations

The state equations are as follows

$$\frac{dr}{dt} = a_1 g([T_P]) \quad (1)$$

$$\frac{dT_C}{dt} = \frac{dV_C}{V_P} T_P - a_2 f_{necr}([N_C]) T_C$$

$$\frac{dT_P}{dt} = -\frac{dV_C}{V_P} T_P + a_3 f_{prot}([N_P], [T_P]) T_P$$

$$\frac{dT_{NC}}{dt} = a_2 f_{necr}([G_C]) T_C \quad (2)$$

$$\frac{dW_C}{dt} = a_4 r^\beta \frac{dV_C}{V_P} W_P + (a_5 e^{-[AI]\gamma_{AI}}) f_{TAF}([N_C]) W_P \quad (3)$$

$$\frac{dW_P}{dt} = dV_T \nu(r) - a_4 r^\beta \frac{dV_C}{V_P} W_P + (a_5 e^{-[AI]\gamma_{AI}}) f_{TAF}([N_C]) W_P \quad (4)$$

$$\frac{d[AI]}{dt} = -c_{AI} [AI] + I_{AI}(t) \quad (5)$$

where r , T_C , T_P , T_{NC} , W_C , W_P , and $[AI]$ denote the tumor radius, the number of living tumor cells in the core, the number of living tumor cells in the periphery, the number of necrotized tumor cells in the core, the volume of vasculature in the core, the volume of vasculature in the periphery, and the concentration of the angiogenic inhibitor respectively. The variable I_{AI} denotes the injection rate of the angiogenic inhibitor, considered as input to the system. Square brackets always denote concentration (or density).

The corresponding units of the model variables can be found in Table I.

var.	r	T_C	T_P	T_{NC}	W_C	W_P	$[AI]$
unit	mm	-	-	-	mm ³	mm ³	mg/kg

TABLE I
UNITS OF THE MODEL VARIABLES

The function $g([T_P])$ describes how the tumor expansion is derived from the density of tumor cells in the periphery ($[T_P]$).

$$g = \frac{1}{1 + e^{-\frac{p_g - [T_P]}{k_g}}}, \quad (6)$$

where p_g and k_g are parameters.

The actual tumor volumes of the core and the periphery are denoted with V_C and V_P , respectively. The actual volume increment of the core is dV_C , while the actual volume increment of the tumor is dV_T .

$$V_C = \frac{4}{3} (d_c r)^3 \pi \quad (7)$$

$$V_P = \frac{4}{3} (r)^3 \pi - V_C \quad (8)$$

$$dV_C = \frac{4}{3} (d_c (r + dr))^3 \pi - V_C \quad (9)$$

$$dV_T = \frac{4}{3} (r + dr)^3 - \frac{4}{3} r^3, \quad (10)$$

where d_c denotes the core-periphery ratio; as cells closer to the tumor center than $d_c r$ belong to the core, otherwise they belong to the periphery. This ratio is a function of the actual radius r , and always defines an outer layer of approximately 150 μm , which coincides with the diffusion distance [10].

$$d_c(r) = 1.1 \left(\frac{1}{1 + \exp\left(\frac{0.5-r}{0.333}\right)} \right)^{2.2} - 0.15. \quad (11)$$

In this way, the cells of the periphery are always supported with nutrients and oxygen from the environment. The vasculature density of the tumor environment is described as a function of the radius ($\nu(r)$), while γ_{AI} denotes the efficiency of the angiogenic inhibitor. The clearance rate of the angiogenic inhibitor is c_{AI} , its value is defined following [11].

We assume that tumor cells basically stay in the same place; however, as the tumor grows, the same geometrical position which has been considered earlier as periphery, will be considered as part of the core. The term $\frac{dV_C}{V_P} T_P$ (see (2) and (3)) describes this 'transmission' of periphery cells to core cells, since $\frac{T_P}{V_P}$ is the density of tumor cells in the periphery. Consequently, the increment of the core volume (dV_C) is the volume that is actually internalized from the periphery to the core.

The term $a_4 r^\beta \frac{dV_C}{V_P} W_P$ in (5) corresponds to the internalization of vasculature from the periphery to the core, which is supposed to be proportional to r^β where $\beta > 1$ is a constant parameter. This assumption is derived from the geometrical consideration that the same increment in the radius r causes a much larger volume growth, if the actual radius is larger, and the volume which needs blood support is increased more.

Nutrient concentration of the core and the periphery are $[N_C]$ and $[N_P]$ respectively, these are dimensionless normalized variables. If the nutrient concentration is 1, it is sufficient for proliferation, i.e. for tumor growth. Nutrient concentrations may be calculated as

$$[N_C] = \frac{r_C}{r_V^{ref}} \quad (12)$$

$$[N_P] = \frac{r_P}{r_V^{ref}}, \quad (13)$$

where $r_C = \frac{W_C}{V_C}$, $r_P = \frac{W_P}{V_P}$ and r_V^{ref} is the reference vasculature ratio, defining the necessary percentage of blood vessels in a unit volume of tissue to sufficiently support tumor cells with nutrients.

The process of proliferation is described by a bi-sigmoid function (f_{prot}), as proliferation depends on two main factors. On the one hand, if the concentration of living tumor cells ($[T_P]$) is too high, proliferation is limited. On the

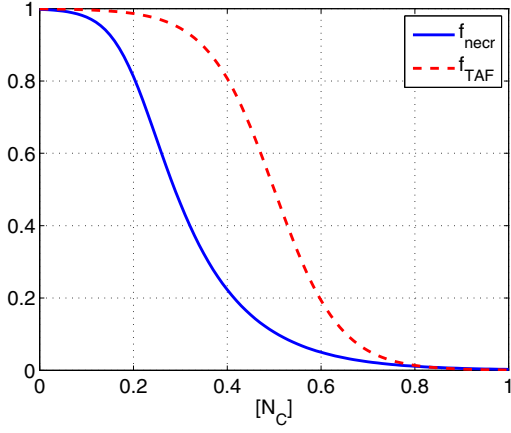


Fig. 1. Cell necrosis (f_{necr}) and TAF production (f_{TAF}) as a function of nutrient concentration of the core ($[N_C]$)

other hand, proliferation is also limited by low nutrient concentration of the periphery ($[N_P]$). The function shows saturation in both variables.

$$f_{prol} = \frac{1}{1 + e^{\frac{p_1 - [N_P]}{k_1}}} \frac{1}{1 + e^{\frac{p_2 - [T_P]}{k_2}}}. \quad (14)$$

Cell necrosis (f_{necr}) and TAF production (f_{TAF}) are sigmoid functions:

$$f_{necr} = \left(\frac{1}{1 + e^{\frac{p_3 - [N_C]}{k_3}}} \right)^{b_3} \quad (15)$$

$$f_{TAF} = \left(\frac{1}{1 + e^{\frac{p_4 - [N_C]}{k_4}}} \right)^{b_4}, \quad (16)$$

where p_3 , p_4 , k_3 , k_4 , b_3 and b_4 are parameters. As the nutrient concentration decreases, tumor cells begin to produce TAF in order to start and afterwards enhance vascularization and get more nutrient; and besides, if the nutrient concentration decreases further, they necrotize (Fig. 1).

Table II summarizes the values and units of the model parameters.

III. RESULTS

A. Model Calibration Based on Experimental Tumor Volume Data

Tumor volume data from experimental measurements [1] were used to calibrate the model. In the experiment C57Bl/6 mice were implanted with C38 mouse colorectal carcinoma. Mice C_1 - C_5 received one 10 mg/kg bolus of bevacizumab (an angiogenic inhibitor [12]) on day 3 of the experiment. Fig. 2 shows the measured tumor volumes. For model calibration, the initial condition is $x(0) = [0.13 \ 3 \ 495 \ 0 \ 0 \ 0 \ 0 \ 0]$, the external vasculature density is $\nu(r) = 0.002$, and the values of the parameters are described in Table II. Fig. 2 illustrates the calibrated model which shows good agreement with the experimental tumor volume data.

parameter	value	unit
a_1	1.2	mm/day
a_2	1	mm ³ /day
a_3	12	1/day
a_4	0.06	
a_5	1	kg/(mg day)
b_3	0.3	
b_4	0.3	
c_{AI}	$\log(2)/3.9$	1/day
c_{CDT}	$\log(2)/3.9$	1/day
k_1	0.17	
k_2	-45000	1/mm ³
k_3	-0.04	
k_4	-0.06	
k_q	55000	1/mm ³
p_1	1	
p_2	$4 \cdot 10^5$	1/mm ³
p_3	0.2	
p_4	0.45	
p_q	$4 \cdot 10^9$	1/mm ³
r_V^{ref}	0.005	
β	1.2	
γ_{AI}	0.8	

TABLE II
VALUES AND UNITS OF THE MODEL PARAMETERS

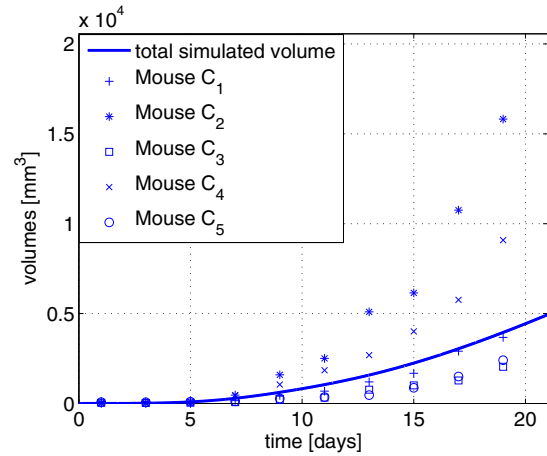


Fig. 2. Simulated and measured tumor volume data (total simulated volume refers to $V = V_P + V_C$)

In Fig. 3, we can see that at the beginning of the tumor growth process, vasculature is accumulated in the periphery at a rate higher than the volume growth of the periphery, thus the vasculature concentration of the periphery increases. Later as the radius of the tumor and the term r^β grows, it is internalized at an increasing rate. TAF-dependent vascularization (see Fig. 4), which is proportional to the (constantly increasing) vasculature volume of the periphery, also contributes to core angiogenesis. However, while these two mechanisms increase the vasculature volume in the core, the volume of the core also increases with growth, as a consequence, the vasculature concentration (vasculature volume of the core/total volume of the core) of the core is close to constant (apart from the initial transients, caused by very small volumes as denominators at the beginning).

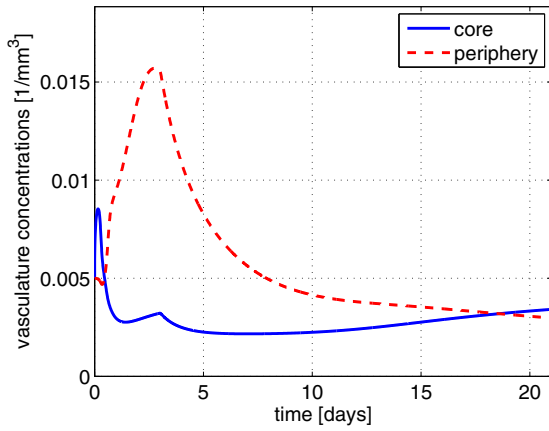


Fig. 3. Simulated vasculature concentrations in the calibrated model

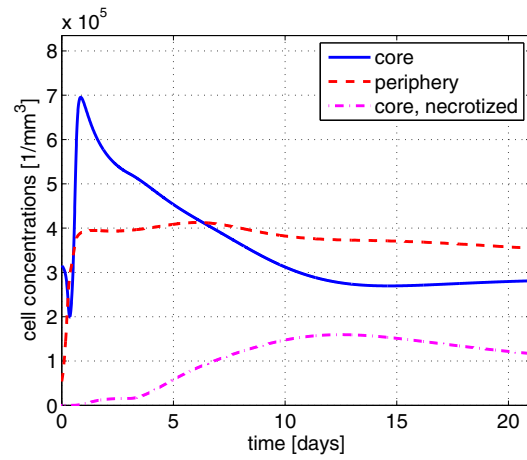


Fig. 5. Simulated tumor cell concentrations in the calibrated model

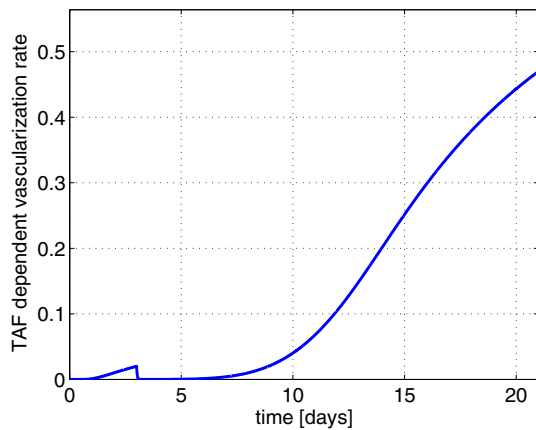


Fig. 4. Simulated TAF-dependent angiogenesis in the calibrated model – the term $(a_5 e^{-[AI]^{\gamma_{AI}}}) f_{TAF}([N_C]) W_P$ is depicted

We may clearly see the effect of the anti-angiogenic drug braking the increasing trend in Fig 3 at day 3.

Fig. 5 depicts tumor cell concentrations in the core and in the periphery; and necrotized tumor cell concentration in the core.

B. Model Calibration Based on Response to Different Delivery Methods of Antiangiogenic Drugs

In [3] two delivery methods of bevacizumab were compared. In the first group, mice received one large dose according to the prescribed medical protocol; while in the second group, a significantly smaller dose was applied every day of the therapy (quasi-continuous therapy). Mice in the second group received a fraction of what mice received in the first group in all. The results have shown that the quasi-continuous therapy was still more effective.

In order to verify these results with the new bi-compartmental model, we considered the following simulation scenarios (in every case the treatment period was 20 days):

- In Therapy 0, no angiogenic inhibitor was administered.

- In Therapy A, we applied one large bolus at day 3, administering one-off 10 mg/kg angiogenic inhibitor (simulation of the prescribed medical protocol).
- In Therapy B, we applied 0.2 mg/kg boluses every day, thus the total injected amount of angiogenic inhibitor is 4 mg/kg (simulation of the quasi-continuous therapy using constant dose/input).
- According to model predictions, we defined one more quasi-continuous therapy (Therapy C). In this case, the input (angiogenic inhibitor dose) varies from period to period. The model predicts that too early injections are not effective, since angiogenesis is proportional to W_P which is small in the beginning (even if its concentration may have large peaks). Nevertheless, injections in the late period are not effective either, since the tumor has already grown and developed a vasculature in the core. Consequently, in Therapy C, we applied the following doses: 0.1 mg/kg in day 1 – day 5, 0.3 mg/kg in day 6 – day 10, 0.25 mg/kg in day 11 – day 15, and 0.15 mg/kg in day 16 – day 20, resulting in a total amount of 4 mg/kg, similarly to Therapy B.

Table III summarizes the simulation results. Final tumor volume refers to the value of tumor volume at the end of the simulation, $\max([AI])$ denotes the maximal value of the angiogenic inhibitor concentration during the simulation, while $\int_0^\infty I_{AI}(t)$ denotes the total administered amount of angiogenic inhibitor. Note that Therapy A is the same treatment which was used for model calibration, and simulated tumor volume of Therapy A is shown in Fig. 2.

Simulation results show that the model predictions are in good agreement with experimental results. The quasi-continuous administration turns out to be more effective than the prescribed medical protocol in terms of final tumor volume, even if the total injected amount of angiogenic inhibitor was significantly smaller. Moreover, the quasi-continuous therapy when angiogenic inhibitor dose varies from period to period (according to model predictions), was found to be the most effective. In addition, Fig. 6 shows that in the case of Therapy C, the TAF-dependent angiogenesis

therapy	final tumor volume [mm ³]	max([AI]) [mg/kg]	$\int_0^\infty I_{AI}(t)$ [mg/kg]
0	$5.85 \cdot 10^3$	0	0
A	$4.94 \cdot 10^3$	9.62	10
B	$4.91 \cdot 10^3$	1.27	4
C	$4.76 \cdot 10^3$	1.45	4

TABLE III

SIMULATION RESULTS OF THERAPIES BASED ON DIFFERENT DELIVERY METHODS

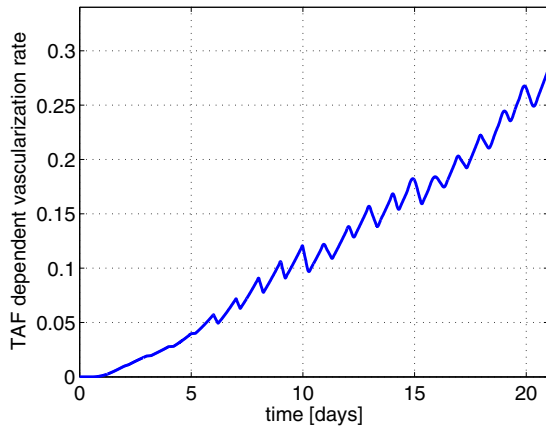


Fig. 6. Simulated TAF-dependent angiogenesis in the case of Therapy C

is much more slower than in Therapy A (Fig. 4). This means that quasi-continuous therapy is more effective than one large bolus dose, not just in terms of final tumor volume, but in terms of TAF-dependent angiogenesis as well.

IV. CONCLUSIONS AND FUTURE WORKS

A. Conclusions

We proposed a bi-compartmental model describing tumor cell and supporting vasculature growth dynamics based on physical principles. The model accounts for conservation equations regarding tumor cells and vasculature volumes. A simplified model of nutrient supply by vasculature is included in the model, as well as angiogenic mechanisms, which are initiated in the case of low nutrient concentration. The model has been validated with real experimental data regarding volume growth, and the explicit consideration of vasculature volumes makes possible to test it by measurement data. As we have shown, the prediction of the model regarding one-off bolus and daily quasi-continuous dosage therapies is in good agreement with the observed experimental results [1].

B. Future Works

The experimental implementation of the in-silico implemented therapy C may provide further measurement data for model validation. The other main objective for the future is further validation of the model with vasculature volume time series data. On the one hand, tumors implanted in various tissues with different vascularization may be studied

to compare their growth profile with model predictions. On the other hand, it would be necessary to continuously monitor vasculature volumes in the core and the periphery during tumor growth in the same time with the continuous measurement of tumor volume.

Other important scenarios are to investigate inhomogeneous vasculature environment (variable nutrient concentration), and simulation of combined therapies where not only an antiangiogenic drug is applied (monotherapy) but antiangiogenic drug is combined with cytostatic drugs.

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