Solid Tumour Growth.
Analysis of Necrotic Core Formation.

Urszula Foryś and Anna Mokwa-Borkowska
Faculty of Mathematics, Informatics and Mechanics, UW
Institute of Applied Mathematics and Mechanics
Banacha 2, 02-097 Warsaw, Poland
e-mail: urszula@mimuw.edu.pl

Abstract

This paper deals with the analysis of simple model of an avascular solid tumour growth dynamics with a necrotic core. The analysis is focused to the conditions which guarantee existence and stability of a stationary solution to the model. The second part of the paper deals with the analysis of effects of an external source of nutrient on the process of necrotic core formation. This influence is visualised by numerical simulations.

Keywords: Solid avascular tumour, Proliferation, Apoptosis, Necrosis, Necrotic core, Reaction-diffusion equation, Implicit function.

1. INTRODUCTION

In the last years there appeared many papers devoted to the process of tumour growth and tumour dynamics [1] - [18]. Some of them dealt with the very early stage of this growth without necrotic core inside the tumour [5], [11] - [13], [18]. This paper is focussed on the next stage of the growth, i.e., the process of necrotic core formation. Therefore, we consider three cellular processes — proliferation, apoptosis and necrosis. The model is based on the idea of avascular multicellular spheroids (MCS) modelling. It is assumed that the growth of MCS under the diffusion of nutrient is governed by the mass conservation law (for the details of the model see e.g. [1, 2, 7]).

Finally, we study the following system of equations:

$$\sigma = \frac{1}{6}\Gamma R^2 - \frac{1}{2}\Gamma r_{nec}^2 + \frac{1}{3}\Gamma \frac{r_{nec}^3}{R} \tag{1}$$

$$\begin{array}{rcl} R^2\frac{dR}{dt} & = & \frac{s\Gamma}{30}(R^5 - r_{nec}^5) + \frac{s\Gamma}{6}R^2 r_{nec}^2 (r_{nec} - R) \\ & + & \frac{s\sigma_{min}-a}{3}R^3 - \frac{s\sigma_{min}-a+b}{3} r_{nec}^3, \end{array} \tag{2}$$

where:

- $R(t)$ and $r_{nec}(t)$ denote the external and necrotic radii of MCS at time t, respectively;
- $\sigma = \sigma_{ex} - \sigma_{min}$; σ_{ex} denotes the external source of nutrient, constant in the next Section; σ_{min} is the minimal source of nutrient needed to proliferation and we assume that

$$\sigma_{ex} > \sigma_{min}, \quad \text{i.e. } \sigma > 0; \tag{3}$$

- Γ, a, b are the model parameters responsible for processes of proliferation, apoptosis and necrosis and s is the scaling constant.

We consider Eqs. (1-2) with an initial condition $R(0) = R_0 > 0$.

2. ANALYSIS OF THE MODEL

This section deals with the analysis of existence and properties of solutions to Eqs. (1)-(2). The right-hand side of Eq. (2) comprises two unknown variables — $R(t)$ and $r_{nec}(t)$. Therefore, to study the solutions to Eq. (2) we should know the changes of r_{nec} with changing R. Eq. (1) describes the implicit function $r_{nec}(R)$. It is obvious that we are interested only in such a solution for which $0 \leq r_{nec}(R) < R$. It is easy to see that there is no solution to Eq. (1) such that $r_{nec} = R$. If there exists the solution $r_{nec} = R$, then Eq. (1) reduces to $\sigma = 0$ which contradicts inequalities (3).

Consider the auxiliary function

$$f(r_{nec}) = \frac{1}{3}\Gamma r_{nec}^3 - \frac{1}{2}\Gamma R r_{nec}^2 + \frac{1}{6}\Gamma R^3 - \sigma R, \quad r_{nec} \geq 0$$

with the parameter $R > 0$. If R is small, i.e. $R < \tilde{R} = \sqrt{\frac{6\sigma}{\Gamma}}$, then $f(0) < 0$. For greater R the value $f(0)$ is positive. Calculating the derivative of f yields $f'(r_{nec}) = \Gamma r_{nec}^2 - \Gamma R r_{nec}$. Therefore, the auxiliary function is decreasing for $r_{nec} < R$ and increasing for $r_{nec} > R$. One calculates $f(R) = -\sigma R < 0$. Hence, to have the implicit function $r_{nec}(R)$ such that $0 \leq r_{nec} < R$ one requires

$$R > \tilde{R} = \sqrt{\frac{6\sigma}{\Gamma}}. \tag{4}$$

This shows that for small R there is no solution to Eq. (1) and then $r_{nec} = 0$. In this case Eqs. (1)-(2) reduces to

$$\left\{ \begin{array}{rcl} \sigma & = & -\frac{\Gamma}{6}R^2 \\ \dot{R} & = & \frac{s\Gamma}{30}R^3 + \frac{s\sigma_{min} - a}{3}R. \end{array} \right. \tag{5}$$

The parameter σ_{min} is connected with the process of necrosis and therefore, it should be excluded from the model in the case $r_{nec} = 0$. Combining both equations of Eqs. (5) one obtains one ordinary differential equation of the form

$$\dot{R} = \frac{R}{3}\left(-\frac{s\Gamma}{15}R^2 + s\sigma_{ex} - a\right) \tag{6}$$

with the following properties

1. If $s\sigma_{ex} > a$, then there exists the positive stationary solution $\bar{R} = \sqrt{\frac{15(s\sigma_{ex}-a)}{s\Gamma}}$ to Eq. (6). In this case R increases for $0 < R_0 < \bar{R}$ and decreases for greater R_0.

2. If $s\sigma_{ex} < a$, then R decreases for every $R > 0$.

We study the process of necrotic core formation and hence, we assume $R_0 < \tilde{R}$, i.e. there is no necrotic core at the beginning. Then we can consider three cases

1. If $s\sigma_{ex} < a$, then R decreases and therefore, the necrotic core is not formed.

2. If $s\sigma_{ex} > a$ and $\tilde{R} > \bar{R}$, then $\bar{R}$ attracts every solution with $R_0 < \tilde{R}$. Hence, there is no necrotic core, for $t > 0$.

3. If $s\sigma_{ex} > a$ and $\tilde{R} < \bar{R}$, then R increases and reaches the level $\tilde{R}$. Therefore, the necrotic core can occur.

From our point of view the only interesting Case is 3. Hence, in the following we assume that

$$5a < 3s\sigma_{ex} + 2s\sigma_{min} < 5s\sigma_{ex}, \tag{7}$$

which combines inequalities (3) with inequalities assumed in Case 3. Therefore, for $R \in (R_0, \tilde{R})$ there is no necrotic core and $R(t)$ increases according to Eq. (6). When R crosses the level $\tilde{R}$, the model switches from Eq. (6) to Eqs. (1)-(2).

Now, we study the behaviour of the fuction $r_{nec}(R)$. It is easy to calculate

$$r'_{nec}(R) = \frac{r_{nec}^2 + Rr_{nec} + R^2}{3Rr_{nec}},$$

which implies that the function $r_{nec}(R)$ is increasing for positive r_{nec}. Calculating the second derivative one obtains

$$r''_{nec}(R) = -\frac{2r_{nec}^4 - Rr_{nec}^3 - 3R^2r_{nec}^2 + R^3r_{nec} + R^4}{9R^2r_{nec}^3}.$$

We show that r_{nec} is concave, for $r_{nec} < R$. Let

$$g(r_{nec}) = 2r_{nec}^4 - Rr_{nec}^3 - 3R^2r_{nec}^2 + R^3r_{nec} + R^4$$

be a new auxiliary function. We see that $g(0) = R^4 > 0$, $g(R) = 0$ and

$$g'(r_{nec}) = 8r_{nec}^3 - 3Rr_{nec}^2 - 6R^2r_{nec} + R^3, \quad g''(r_{nec}) = 24r_{nec}^2 - 6Rr_{nec} - 6R^2.$$

Studying the second derivative $g''(r_{nec})$ one can see that $g'(r_{nec})$ has a minimum at $\frac{1+\sqrt{17}}{8}R < R$ which is negative because $g'(R) = 0$. Therefore, there exists a point $R_c < \frac{1+\sqrt{17}}{8}R$ such that the auxiliary function g increases for $r_{nec} < R_c$ and decreases for $r_{nec} \in (R_c, R)$. Hence, $g(r_{nec}) > 0$, for $r_{nec} < R$ which proves concavity of the function $r_{nec}(R)$, for $r_{nec} < R$ obviously. An example of the graph of both curves that we obtain from Eq. (1) is presented in Fig. 1. We see that the function $r_{nec}(R)$ is approximately linear.

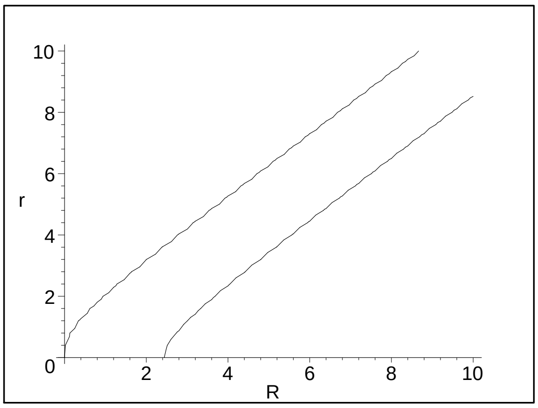

Figure 1: An example of the graph of $r_{nec}(R)$.

Now we study the asymptotic behaviour of $r_{nec}(R)$ as $R \to +\infty$. We see that $\frac{r_{nec}}{R}$ fulfills the equation

$$\frac{\sigma}{R^2} = \frac{\Gamma}{6} - \frac{1}{2}\Gamma(\frac{r_{nec}}{R})^2 + \frac{1}{3}\Gamma(\frac{r_{nec}}{R})^3,$$

which implies $\lim \frac{r_{nec}}{R} = 1$. Therefore, asymptotically one has $r_{nec}(R) \approx R + C$. Eq. (1) yields

$$3\Gamma C^2 + 2\Gamma \frac{C^3}{R} = 6\sigma,$$

and therefore, $C = -\sqrt{\frac{2\sigma}{\Gamma}}$. Hence, the asymptotic behaviour of r_{nec} is described by the following formula

$$r_{nec}(R) \approx R - \sqrt{\frac{2\sigma}{\Gamma}}. \tag{8}$$

The above analysis shows that the function $r_{nec}(R)$ is a smooth function of R, for $R > \tilde{R}$ and there is a unique solution to Eq. (1) such that $r_{nec} < R$. Therefore, the right-hand side of Eq. (2) is a smooth function of R, for $R > \tilde{R}$ which means that there exists a unique solution to Eqs. (1-2), for every $R_0 > \tilde{R}$. Hence, one can rewrite Eqs. (1)-(2) in the following form

$$\frac{30}{s\Gamma} R^2(t) \frac{dR}{dt}(t) = F(R(t)), \tag{9}$$

where

$$F(R) = -r_{nec}^5(R) + 5R^2 r_{nec}^3(R) - 10(\gamma+\beta) r_{nec}^3(R) - 5R^3 r_{nec}^2(R) + 10\gamma R^3 + R^5$$

with $\gamma = \frac{s\sigma_{min}-a}{s\Gamma}$, $\beta = \frac{b}{s\Gamma}$ and $r_{nec}(R)$ is implicitly defined by Eq. (1). The asymptotic behaviour of Eq. (9) depends on the shape of $F(R)$. We know that $R > \tilde{R}$ and $r_{nec}(\tilde{R}) = 0$. Therefore, $F(R) \to 10\gamma\tilde{R}^3 + \tilde{R}^5$ as $R \to \tilde{R}$. Inequalities (4) and (3) imply $10\gamma\tilde{R}^3 + \tilde{R}^5 > 0$.

On the other hand, the asymptotic behaviour of the function $F(R)$ as $R \to +\infty$ is described by the following formula

$$\begin{aligned} F(R) \approx\; & -\left(R - \sqrt{\tfrac{2\sigma}{\Gamma}}\right)^5 + (5R^2 - 10(\gamma+\beta))\left(R - \sqrt{\tfrac{2\sigma}{\Gamma}}\right)^3 \\ & -5R^3\left(R - \sqrt{\tfrac{2\sigma}{\Gamma}}\right)^2 + 10\gamma R^3 + R^5 \\ =\; & -10\beta R^3 + \left(10R^2\sqrt{\tfrac{2\sigma}{\Gamma}} - 10R\sqrt{\tfrac{2\sigma}{\Gamma}}^2\right)\left(\tfrac{s\sigma_{ex}+2s\sigma_{min}-3a}{s\Gamma} + 3\beta\right) \\ & +2\sqrt{\tfrac{2\sigma}{\Gamma}}^3\left(\tfrac{s\sigma_{ex}+2s\sigma_{min}-3a}{s\Gamma} + 2\gamma + 5\beta\right) < 0, \end{aligned} \tag{10}$$

for large R. This shows that there exists at least one stable stationary solution to Eq. (9). Every solution to Eq. (9) tends to the stationary one. Moreover, the asymptotic behaviour of the necrotic radius r_{nec} described by Eq. (8) implies that for large R there is a thin proliferation layer surrounding a necrotic core inside MCS.

3. COMPUTER SIMULATIONS

In this section we consider two cases — constant external source of nutrient (as in the previous Section) and periodic one. The biological background of periodic function seems to be obvious — our food supplementation is periodic not constant and therefore, the diffusion of nutrient in MCS should also be periodic. The figures in what fallows show that the behaviour in these two cases is very similar. In the first case we obtain the stable stationary solution with a thin proliferation layer while for the second case the behaviour is asymptotically periodic. In the figures we compare the case of constant external source of nutrient on the left-hand side and the case of periodic function ($\cos + const$, where $const$ is the same as on the left-hand side) on the right-hand side. We study the dependence on the magnitude of different parameters of the model. At the beginning we use the following values of parameters

$$\sigma_{ex} = 3,\ \sigma_{min} = 1,\ \Gamma = 0.1,\ a = 0.1,\ b = 0.2,\ s = 0.3,\ R_0 = 5,\ t = 500. \tag{11}$$

Fig. 2 presents the solution for the above parameters. We see that the necrotic core occurs and the solution stabilizes very fast.

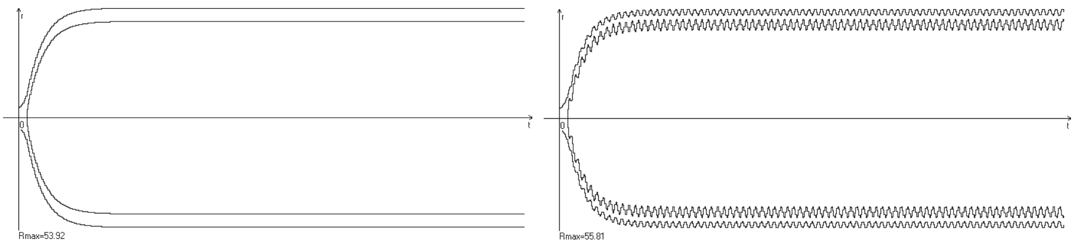

Figure 2: An example of the solution to Eqs. (1)-(2) for parameters defined by (11).

- Dependence on the proliferation coefficient Γ.

  Changing the proliferation coefficient Γ we observe that for smaller values the necrotic core forms later (an example of the solution in Fig. 3) and for greater values it forms at once (see Fig. 4).

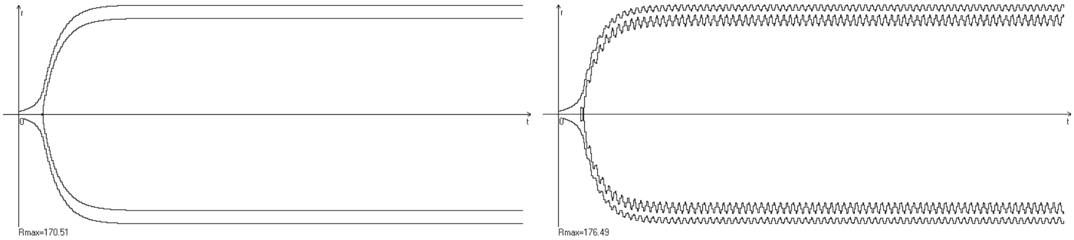

Figure 3: An example of the solution to Eqs. (1)-(2) for $\Gamma = 0.01$.

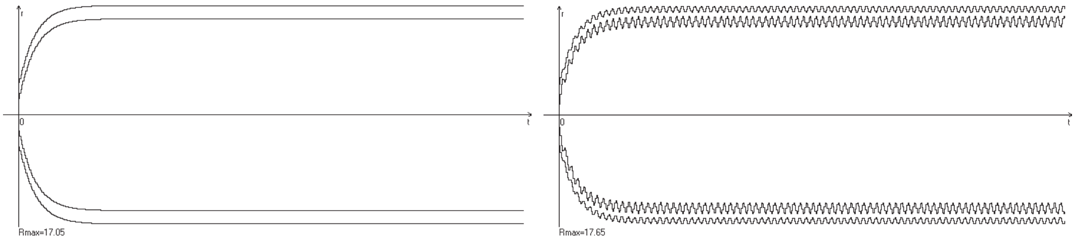

Figure 4: An example of the solution to Eqs. (1)-(2) for $\Gamma = 1$.

- Dependence on the apoptosis parameter a.

  It occurs that the dependence on the apoptosis parameter a is not significant until the necrotic core is formed (compare Fig. 2 and Fig. 5). When a increases the initial radius $R_0 = 5$ is closer and closer to the stationary solution and finally reaches this value (see the left-hand side of Fig. 6). If $a > 0.375$, then Inequalieties (7) are not satisfied and moreover, the solution decreases to 0 (see the right-hand side of Fig. 6).

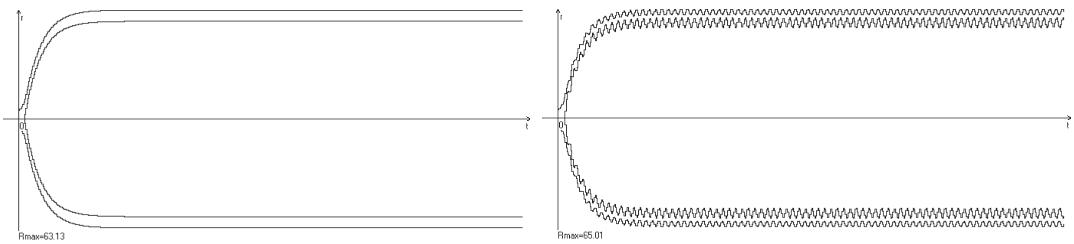

Figure 5: An example of the solution to Eqs. (1)-(2) for $a = 0.001$.

- Dependence on the necrosis parameter b.

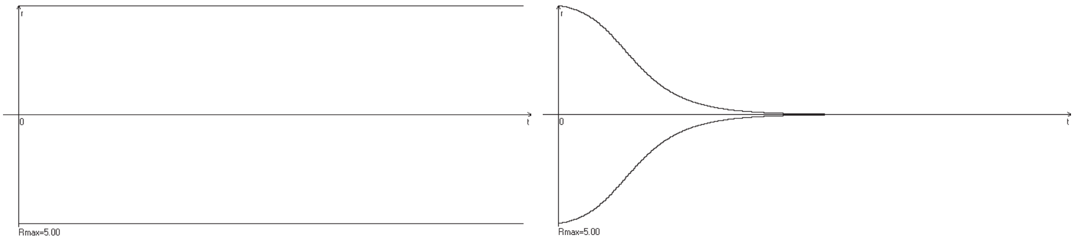

Figure 6: An example of the solution to Eqs. (1)-(2) for $a = 0.375$ (on the left-hand side) and $a = 0.38$ (on the right-hand side).

The dependence on the necrosis parameter b is much more significant then on the parameter of apoptosis a. For large b the solution stabilizes faster, the maximal radius of MCS is smaller and for periodic source of nutrient we observe oscillations with larger amplitude (see Fig. 7) while for small b we see very thin proliferation layer which causes that the growth is very slow and oscillations in the second case are almost not observed (compare Fig. 8).

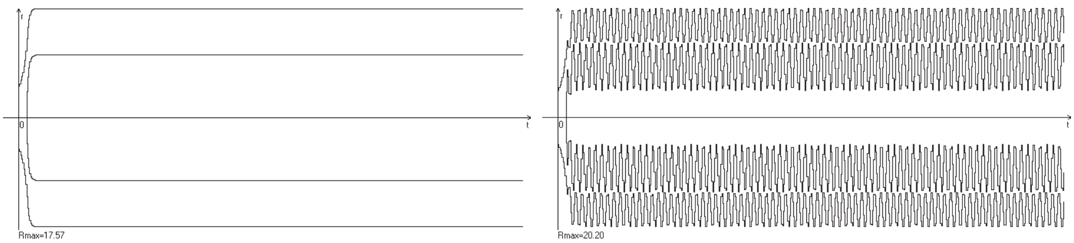

Figure 7: An example of the solution to Eqs. (1)-(2) for $b = 2$.

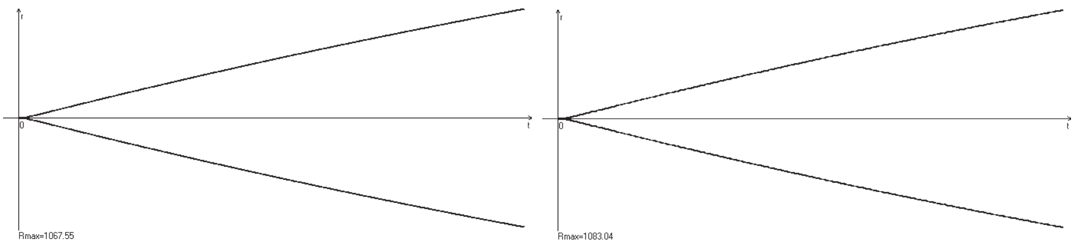

Figure 8: An example of the solution to Eqs. (1)-(2) for $b = 0.002$.

- Dependence on the external source of nutrient σ_{ex}.

In conclusion we consider the dependence on the magnitude of the external source of nutrient. This dependence is rather evident — larger values of σ_{ex} cause larger growth of MCS (compare Fig. 2 and Fig. 9).

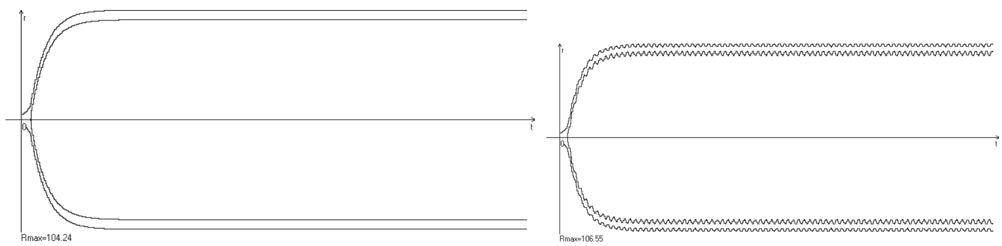

Figure 9: An example of the solution to Eqs. (1)-(2) for $\sigma_{ex} = 5$.

Summarizing the results of simulations we notice that the behaviour of solutions to the model with constant external source of nutrient and with periodic one are very similar. In most of the cases the difference is not significant and therefore, we can approximate the growth of MCS using the easier case. However, in some cases, namely for large values of the necrotic parameter b the observed oscillations have large amplitudes. Modelling such a case we should to remember of these differences.

Acknowledgements This paper was prepared in the framework of RTN "Using Mathematical Modelling and Computer Simulation to Improve Cancer Therapy" (CT - 2000 - 00105).

References

[1] H.P. Greenspan, Models for the growth of a solid tumour by diffusion, *Stud. Appl. Math.,* **52**, 317-340 (1972).

[2] J. Adam and S. Maggelakis, Diffusion regulated growth characteristics of a spherical prevascular carcinoma, *Bull. Math. Biol.,* **52**, 549-589 (1990).

[3] N. Bellomo and G. Forni, Dynamics of tumor interaction with the host immune system, *Math. Comput. Modelling,* **20**, 107-122 (1994).

[4] R. Schuster and H. Schuster, Reconstruction models for the Ehrlich Ascites Tumor of the mouse, in *Mathematical population dynamics*, vol 2, edited by O. Arino, D. Axelrod, M. Kimmel, Wuertz, Winnipeg (1995).

[5] H.M. Byrne and M. Chaplain, Growth of non-necrotic tumours in the presence and absence of inhibitors, *Math. Biosci.,* **130**, 151-181 (1995).

[6] H.M. Byrne and M. Chaplain, Growth of necrotic tumours in the presence and absence of inhibitors, *Math. Biosci.,* **135**, 187-216 (1996).

[7] H.M. Byrne, The effect of time delays on the dynamics of avascular tumour growth, *Math. Biosci.,* **144**, 83 - 117 (1997).

[8] *A survey models for tumor-immune system dynamics*, eds. J. Adam and N. Bellomo, Birkhäuser, Boston (1997).

[9] N. Bellomo and E. De Angelis, Strategies of applied mathematics towards an immuno mathematical theory an tumors and immune system interactions, *Math. Mod. Meth. Appl. Sci.,* **8**, 1403-1429 (1998).

[10] E. De Angelis and L. Preziosi, Advection-diffusion models for solid tumors in vivo and related free-boundary problems, *Math. Models Methods Appl. Sci.*, **10**, 379-408 (2000).

[11] M. Bodnar and U. Foryś, Time delays in proliferation process for solid avascular tumour, *Math. Comput. Model.*, **37**, 1201-1210 (2003).

[12] M. Bodnar and U. Foryś, Time delays in regulatory apoptosis for solid avascular tumour, *Math. Comput. Model.*, **37**, 1211-1220 (2003).

[13] U. Foryś and M. Kolev, Time delays in proliferation and apoptosis for solid avascular tumour, preprint Warsaw University, RW 02-10 (110) (2002), to appear in *Banach Center Publications.*

[14] M. Kolev, Mathematical modelling of the competition between tumours and immune system considering the role of the antibodies, *Math. Comp. Model.*, **37**, 1143-1152 (2003).

[15] D. Ambrosi, N. Bellomo and L. Preziosi, Modelling the immune response to tumor heterogeneity and progression, *J. Theor. Medicine,* **4** (1), 51-66 (2002).

[16] L. Arlotti, A. Gamba and M. Lachowicz, A kinetic model of tumor/immune sustem cellular interactions, *J. Theor. Medicine*, **4** (1), 39-50 (2002).

[17] E. De Angelis and P. E. Jabin, Qualitative analysis of a mean field model of tumour immune system competition, *Math. Mod. Meth. Appl. Sci.*, **13**, 187-206 (2003).

[18] J. Valenciano and M. Chaplain, Computing higly accurate solutions of a tumour angiogenesis model, *Math. Mod. Meth. Appl. Sci.*, **13**, 747-766 (2003).