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Control Problems Related to Three Compartmental Model of Combined Anticancer Therapy

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***Abstract*— We present control problems related to a three-compartmental model of combinations of antiangiogenic treatment with chemotherapy. The line of reasoning is based on the idea of Hahnfeldt et al.(1999) with modifications resulting from the use of multiple modalities and effects of drug resistance. We present analysis of dynamic properties of the models and some simulation results for different treatment protocols.**

I. Introduction

The paper presents a model of anticancer therapy which combines chemotherapy considered as a direct control action and an indirect one in the form of antiangiogenic therapy. Across the last four decades, researches have revolutionized our understanding of cancer. In large part, this success was made possible by the development and application of the techniques of molecular biology, techniques that enabled researchers to probe and describe features of individual cells in ways unimaginable a century ago. Today, we know that cancer is a disease of molecules and genes, and we even know many of the molecules and genes involved. In fact, our increasing understanding of these genes is making possible the development of exciting new strategies for avoiding, preventing, and even correcting the changes that lead to cancer [1]. The site of action of almost all traditional cytotoxic drugs is the cellular DNA or the processes associated with this DNA. Drugs may interact directly with the DNA, intercalating between the bases, chemically altering the structure of DNA (adduct formation) or substituting the bases with analogous structures. Some agents may deplete the pool of bases required for DNA (and RNA) synthesis. Other group of drugs may affect the microtubules that organize the chromosomes during mitosis. Drug resistance in cancer is common. Some tumours are inherently unresponsive to cytotoxic chemotherapy. Others may respond well initially but relapse rapidly with drug-resistant disease. Many factors have been implicated in cellular resistance and these mechanisms may be drug or class specific. Pharmacokinetic factors also contribute towards mechanisms of resistance. For example, it is important to realize that for many anticancer drugs the administered form of the drug is not necessarily the active form. Variability in, for example, levels of activating or inactivating enzymes in the host tissues and in the tumour can lead to significant additional inter- and intraindividual variation in terms of normal tissue toxicity and anti-tumour efficacy from such drugs. All of the targets for traditional cytotoxics in malignant dividing cells are also expressed within normal dividing cells. The cells in the normal human body which turnover most rapidly and therefore are the most impacted by traditional cytotoxics are those of the bone marrow, skin, hair follicle, and gastrointestinal mucosa. Different normal tissues recover from a dose of chemotherapy at different rates. Malignant cells tend to have impaired DNA damage repair machinery compared to normal cells. If treatment is given intermittently, subsequent doses can be timed to occur when the host has recovered but the tumour has not. For each dose of chemotherapy it is thought that a constant fraction rather than an absolute number of malignant cells are killed (Skipper hypothesis). Over sixty years ago, Glenn Algire, studying physiological responses to tumour growth in mice at the National Cancer Institute, observed that the growth of tumour is dependent on the development of vascular supply. After observing the same phenomenon in 1971 Judah Folkman [2] suggested the substantial potential of tumour angiogenesis as a therapeutic target. Tumours, like normal tissues, have physiological constraints, on growth, such as access to oxygen and nutrients for metabolism. The diffusion of oxygen in tissues is limited to a distance of about 150μm, thus tissue growth is restricted to a few cubic millimeters if no new vasculature is formed. For this reason, tumours remain in a dormant state restricted to a few millimeters in diameter unless they develop in a well-vascularised area or are able to recruit their own vasculature. For vascularisation to occur, the nearest vessel or capillary needs to become destabilised so that the endothelial cells lining the vessel can loosen from their neighbours, migrate through the extracellular matrix towards the tumour. Only after a tumour has recruited its own blood supply it can expand in size. Tumours do this via the production of angiogenic factors secreted into local tissues and stroma; this process has been termed the angiogenic switch. The angiogenic switch is a discrete step in tumour development that can occur at different stages (Fig. 1.2) in the tumour-progression pathway, depending on the nature of the tumour and its microenvironment. Most tumours start growing as avascular nodules (dormant) until they reach a steady-state level of proliferating and apoptosing. cells. The initiation of angiogenesis, or the 'angiogenic switch', has to occur to ensure exponential tumour growth. The switch begins with perivascular detachment and vessel dilation, followed by angiogenic sprouting, new vessel formation and maturation, and the recruitment of perivascular cells. Blood-vessel formation will continue as long as the tumour grows, and the blood vessels specifically feed hypoxic and necrotic areas of the tumour to provide it with essential nutrients and oxygen. Activators of endothelial-cell proliferation and migration are

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mainly receptor tyrosine kinase ligands, such as vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF). Remarkably, many inhibitory molecules, such as 'statins', are derived from larger proteins that have no effect on angiogenesis. In general, the levels of activators and inhibitors dictate whether an endothelial cell will be in a quiescent or an angiogenic state. It is believed that changes in the angiogenic balance mediate the angiogenic switch.

Since in normal healthy adults, the process of angiogenesis is very limited, thus it should, at least in theory, be possible to inhibit tumour angiogenesis without affecting normal tissues. Antiangiogenic therapies have become one of the most promising approaches in the anti-cancer drug development. Successful preclinical research data lead to clinical trials based on different strategies. Approaches currently under evaluation for inhibiting angiogenesis may either be direct (targeting cell surface bound proteins/receptors) or indirect (targeting growth factor molecules). Because angiogenesis is a complex process with multiple, sequential, and interdependent steps, this complexity creates many potential targets for inhibition. Therefore, an antiangiogenic effect can be achieved by targeting angiogenic stimulators, angiogenic receptors, extracellular matrix proteins, extracellular matrix proteolysis, control mechanisms of angiogenesis, or the endothelial cells directly. The targeting of antigens selectively expressed on the surface of tumour capillary endothelial cells or tumour stromal fibroblasts is currently being explored for the immunotherapy of cancer. By targeting or preventing the generation of angiogenic blood vessels or tumour stroma, tumour lesions deprived of the essential support functions or nutrients required for survival and growth. This targeting approach may also be applicable to many tumour types because it is not dependent on a specific tumour cell type. The theoretical advantages that antiangiogenic therapeutics may have in the treatment of cancer are several-fold. First, endothelial cells involved in angiogenesis show several fundamental differences compared with quiescent endothelial cells, primarily their proliferation rate and antigen expression, which can be exploited so that antiangiogenic therapeutics specifically target tumour endothelial cells and not normal endothelium. Tumour blood vessels are also highly irregular (varying diameters), tortuous, have arterio-venous shunts, blind ends, lack smooth muscle, or enervation and have incomplete endothelial linings and basement membranes. As a result, blood flow is often slow or highly irregular, and the vessels are much 'leakier' than those in normal tissues, enabling the passage of large macromolecules. Second, antiangiogenic therapy may circumvent insufficient drug penetration into the interior of a tumour mass due to high interstitial pressure gradients within tumours because endothelial cells are highly accessible to circulating drugs. Third, unlike targeting of tumour cells where failure to destroy a proportion of the cells results in those cells proliferating and subsequent regrowth of the tumour, successful targeting of a few endothelial cells within a growing vessel may be sufficient to completely destroy that vessel. Consequently, disruption of a small percentage of the angiogenic vasculature may result in ischaemic necrosis of a substantial volume of tumour. Preclinical models support use of antiangiogenic therapy as a single agent for cancer treatment, but also suggest that the combination with chemotherapy might improve therapy effect [3]. A number of antiangiogenic clinical trials currently in progress have been designed to compare the effects of a particular cytotoxic agent alone with the effects of the same agent in combination with an angiogenesis inhibitor. The genetic instability and high mutation rate of tumour cells is responsible, in part, for the frequent emergence of acquired drug resistance with conventional cytotoxic anticancer therapy. However, vascular endothelial cells, like bone marrow cells, are genetically stable and have a low mutation rate. Therefore, Kerbel [4] proposed in 1991 a hypothesis that antiangiogenic therapy would be a strategy to bypass drug resistance. It is also worth mentioning, that antiangiogenic therapy was found to be efficient for slowly growing tumours, which are difficult target for classical chemotherapy. The administration of cytotoxic drugs, often results in significant side effects. Drug side-effects may reflect either the primary anti-proliferative action of the drug, some less well understood but predictable toxicological effects or they may be entirely idiosyncratic. Whereas over the years of application, side-effects of chemotherapy are already relatively well investigated, we still do not know much about side-effects of antiangiogenic therapy. Obvious complications might be related to menstruation, diabetes and wound healing. Nevertheless long-term effects of therapy require attention. Additionally it has been observed that antiangiogenic agents do require a very high dose to fulfill their function. The effects of combination therapy, which have also been observed for the combination of radiation therapy and angiogenesis inhibitors, could play a significant role in the clinical evaluation and effects of angiogenesis inhibitors. In some sense drawbacks of chemotherapy (induced drug resistance, smaller efficiency for slowly growing tumours) could be supported by advantages of antiangiogenic therapy and drawbacks of this therapy could be at least slightly moderated by the advantages of chemotherapy.

Over the past decades, there has been considerable progress in mathematical modelling of tumour growth and associated vascular network development. Regrettably while most realistic models reflect these complex biological processes very accurately, due to their complexity, they become difficult or even not suitable for analysis of therapy protocols. Hopefully with a few simplifying assumptions, it is possible to propose and carefully validate models useful for analysis, preceding experimental and clinical studies.

II. Models of Cancer Growth Including Vascularization

The modelling of cancer is a very challenging topic. Complexity of the processes requires integrated, multiscale models, describing each of characteristics of cancer to truthfully reflect biological processes. Analysis of such models could potentially provide breakthroughs in understanding cancer and improving treatment. On the other hand, intricacy of models, results in difficulties during analysis, therefore it is a good strategy to start with

simplified models and then incorporate increasingly more complex and medically more realistic features into the model. Over the past decades, there has been a considerable progress in the mathematical modelling of tumour growth and cytotoxic treatments (see e.g. [5] for survey). This study presents models of growth involving only total number of tumour cells with either logistic or Gompertz-type growth. It is assumed that tumour cells multiply exponentially during the early phases of tumour growth. The growth rate declines, as tumour mass increases, which results in a sigmoid exponential growth curve. This assumption is justified by existence of a geometric gradient of availability of oxygen and nutrients, which causes stratification in viability of cells: usually cycling cells are near the surface or near blood vessels; further layers are occupied by dormant cells, while the deepest regions form a necrotic core. Self-limiting growth might be illustrated by non-linear Gompertz-type equation. Hahnfeldt *et al.*[6] proposed modifying original Gompertzian equation, in order to describe proportional relation between size of cancer cells population and parameter describing size of vascular network. To be more precise, Hahnfeldt suggested treating the carrying capacity, which constraints the tumour growth as a varying tumour volume sustainable by the vessels and roughly proportional to the vessel volume. Complete model requires additional equation describing changes of the volume of the vessels.

Equation below expresses Gompertz-type growth

$$\frac{dN}{dt} = -\beta N \ln \frac{N}{K} \tag{1}$$

where N represents tumour volume as size of cancerous cells population, K describes the maximum tumour volume sustainable by supporting vascular network, parameter β is responsible for growth rate. Likewise the process of angiogenesis is very complex, being a well-orchestrated sequence of events involving endothelial cell migration; proliferation; degradation of tissue; new capillary vessel (sprout) formation; loop formation (anastomosis) and crucially, blood flow through the network. Once there is blood flow associated with the nascent network, the subsequent growth of the network evolves both temporally and spatially in response to the combined effects of angiogenic factors, migratory cues via extracellular matrix and perfusion-related haemodynamic forces.

The spatial aspects are usually approximated by simple reaction-diffusion process, thus relating the change in number of tumour cells to their diffusion in space, as well as their proliferation. As another point of view, there are several models of angiogenesis, mainly focused on the proliferation and migration of the endothelial cells in response to different molecular signals, e.g. those associated with tumour angiogenesis factors. Recently, blood flow modelling in a tumour-induced micro-capillary network has been suggested in order to study the application of antiangiogenic and chemotherapy agents. Majority of models mentioned above, intend to fully reflect the complexity of the biological process and allow accurate simulations. Nevertheless, following the reasoning explained earlier, it is thoughtful to start analysis with models under simplifying assumptions. Models considered in this study, are based on the model proposed by Hahnfeldt *et al.*[6] who have developed and biologically validated a two-dimensional model of ordinary differential equations for interactions between primary tumour volume and the carrying capacity of the vasculature. network which in turn is proportional to the square of the tumour diameter. For simplification, it was necessary to assume spherical symmetry of tumour mass. Therefore the expression for K has the following form

$$\frac{dK}{dt} = \gamma N - \lambda N^{\frac{2}{3}} K - \mu K \tag{2}$$

where γ represents the effect of the stimulation, λ the effect of the inhibition, μ the natural cell death. Taking into account, that tumour growth is relatively slow comparing to the rate of releasing pro- and antiangiogenic factors, it was possible to assume that parameters γ, λ, μ are constant. The model (1), (2) may be modified by introducing logistic type growth equation instead of the Gompertz-type one and by changing ratio between stimulating and blocking angiogenic factors (see [7], [8]). It leads to a set of models which although behave similarly when uncontrolled may have different control properties (see [9]). For example all the models have the same equilibrium point which is both locally and globally asymptotically stable. On the other hand conditions of tumour eradication under periodic therapy [7] are both sufficient and necessary for all the models except of the original Hanhfeldt model for which they are only necessary. Similar differences are observed when optimal antiangiogenic treatment protocols are considered. Once more the original Hahnfeldt model contains singular arcs in optimal trajectories which are absent in other models (see [9]-[13]). The authors of [12], [13] treat singular arcs as a generic property of optimal protocols of antiangiogenic therapy. We suggest [9], [10] that it is rather exception than a rule.

III. Analysis of Models with Cancer Growth and Therapy

The model presented so far lacked the term describing use of any anticancer therapy. Application of combined antiangiogenic and chemotherapy requires the following modification of the model (see [11], [10]):

$$\begin{aligned} \frac{dN}{dt} &= -\beta N \ln \frac{N}{K} - \psi N v(t) \\ \frac{dK}{dt} &= \gamma N - \lambda N^{\frac{2}{3}} K - \mu K - \eta K u(t) - \xi K v(t) \end{aligned} \tag{3}$$

where $u(t)$ denotes the dose of the antiangiogenic agent scaled to its effect on vascular network and η is a constant parameter. This factor increases multiplicatively the mortal loss rate of the vessels. Primary purposes of individual therapy differ. It has been already mentioned, that antiangiogenic drug indirectly affects tumour by destabilizing tumour vasculature. On the other hand cytotoxic agents affect cancer cells directly, but additionally influencing healthy tissue, including endothelial cells. Therefore to both equations term $v(t)$ was added. It denotes the dose of the chemotherapy scaled to its effect on tumour

and normal tissues, with ψ and ξ being constant scaling parameters. Both *u(t)* and *v(t)* might be either constant or periodic functions representing constant drug infusion or periodic administration of the drug respectively. From clinical point of view, it is important to 'push' tumour back to avascular stage, opening possibility for surgical intervention. Although models based on original Hahnfeldt model were carefully validated and might be suitable for development and improvement of therapy protocols, they neglect a few major obstacles in successful treatment, among which it is worth to mention drug resistance, phase dependence and pharmacodynamics / pharmacokinetics.

Most of cytotoxic agents affect cells being at specific phase of cell cycle. Model describing phase dependence should consist of disjoint compartments for respective phases and incorporate drug action only to susceptible ones. Pharmacodynamics and pharmacokinetics are terms related to drug delivery, more precisely to the drug. dosage, its concentration in the body and effectiveness. Models presented so far, employ common approximation that the concentration of a drug is equal to the drug dose and its effects are instantaneous. For obvious reasons such approximation is far from being accurate. More adequate models are beyond the scope of this thesis. When it comes to the emergency of the drug resistance in tumour chemotherapy, a possible solution might be a model combining one of the previously discussed models of angiogenesis with the simplest model of drug resistance. The simplest model of this type, proposed in [10] consists of three compartments. Population of cancer cells is divided into sensitive and resistant subpopulations. Remaining compartment describes dynamics of supporting vascular network. The model employs Hahnfeldt equation of angiogenesis with both antiangiogenic and cytotoxic agents incorporated into equations. A logistic type equation limits an effect of the vascular network dynamics (instead of the Gompertz – type model discussed previously).

$$\begin{aligned}\frac{dS}{dt} &= -aS + (1 - v - \frac{S}{K})(2-q)aS + rcR \\ \frac{dR}{dt} &= -cR + (2-r)(1-\frac{R}{K})cR + (1-v)qaS \\ \frac{dK}{dt} &= \gamma N - \lambda N^{\frac{2}{3}} K - \mu K - \eta K u - \xi K v\end{aligned} \qquad (4)$$

An average number of cells in the sensitive and the resistive populations are represented by *S* and *R* respectively. A sum of cells from both populations is denoted with *N*. Coefficients *a* and *c* stand for the inverse of the average transit times through compartments. Probability of mutations occurring during the process are described with *q* - probability of mutation into resistive cell, $0 < q < 1$ and *r* - probability of mutation into sensitive cell, $0 \le r < 1$. Chemotherapy and antiangiogenic therapy are already incorporated into equations, with *v* – representing dose of cytostatic killing agent , $0 \le v \le 1$ and *u* – representing dose of antiangiogenic drug , $0 \le u \le 1$.

To start analysis of dynamical properties of the model it is necessary to predict its asymptotic behavior. The simplest way to this is to find equilibrium points for the model and estimate at least local stability conditions given by the analysis of its linear approximation in the neighbourhood of these points. Equilibrium points of model (4) were calculated under assumption of uncontrolled growth. Assuming $u = v = 0$ simplified the problem of finding equilibrium point but still overall number of equilibrium points equals seven. Nevertheless five of them were excluded from stability analysis basing on assumptions regarding ranges of values of the parameters, assumption of uncontrolled growth with stable gene amplification ($r=0$) and results of the simulations. More specifically parameters *c* and *a* are chosen to ensure that cells resistant to the anticancer drugs divide with abnormal rate. Therefore remaining two equilibrium points are:

$$S_1^* = 0 \qquad K_1^* = \frac{\gamma}{\lambda} R_1^{*\frac{1}{3}} \qquad R_1^* = \left(\frac{\gamma}{2\lambda}\right)^{\frac{3}{2}}$$

$$S_2^* = K_2^*\left(\frac{1-q}{2-q}\right) \qquad R_2^* = \frac{K_2^{*3} - S_2^*\left(\frac{\gamma}{\lambda}\right)^3}{\left(\frac{\gamma}{\lambda}\right)^3}$$

$$K_2^* = \sqrt{\left(\frac{\gamma}{\lambda}\right)^3 \frac{\left(\frac{5q^2}{4} - 4q + 3\right)}{(q-2)^2} + \left(\frac{\gamma}{\lambda}\right)^3 \frac{\sqrt{-c(q-2)^3\left(2c + 8aq - cq - 8aq^2\right)}}{4c(q-2)^2}}$$

For simplification of calculations, investigation of stability was limited to the set of fixed values of parameters. Therefore:

$$a = 0.02; \qquad c = 0.2; \qquad q = 0.9;$$
$$\gamma = 5.85; \qquad \lambda = 0.00873;$$

Parameters *a* and *c* (in day^{-1}) were chosen according to previously mentioned assumptions, moreover their adjustment allows to reduce overshoots in the simulation of uncontrolled growth of resistive and sensitive subpopulations. Coefficients λ (in $day^{-1}mm^{-2}$) and γ (in day^{-1}) were based on the analysis presented in [6]. Similarly as in [7] and [8] for simulations the natural mortality factor for cancer cells μ = 0. Then equilibrium points are:

$$S_1^* = 0 \qquad K_1^* = 4811.1 \qquad R_1^* = 370.0815$$

$$S_2^* = 1220.5 \qquad K_2^* = 13425 \qquad R_2^* = 6820.6$$

(all in mm^3)

Derived characteristic equations are:

$$1: \quad s^3 + 0.3905s^2 - 0.0675s + 0.000134$$
$$2: \quad s^3 + 3.7124s^2 + 0.5291s + 0.000965$$

As we can see only for the second equilibrium point the necessary conditions of local stability are met. We proceed with checking sufficient conditions, which according to the Hurwitz criterion are fulfilled. We can state that since the

linear approximation of the system in the second equilibrium point is asymptotically stable, therefore this equilibrium point is also asymptotically locally stable.

Influence of combined antiangiogenic and chemotherapy on three compartmental systems was tested. Mathematical intricacy provoked generalization of the problem analysis. Instead of deriving necessary and sufficient conditions for tumour eradication, followed by deriving optimality conditions (as it was developed for simpler models e.g. in [8]-[13]), most promising therapy protocols proposed in previous studies [10], [11] were used. Some examples of simulation experiments are presented (Fig.1-3). It appears that for chosen set of parameters tumour volume is slightly declining. Population of cells resistive to the action of cytotoxic agents is decreasing, as size of vascular network is decreasing. For such set of scaling parameters we may treat an outcome of the therapy as preventing further expansion of the disease rather than an actual eradication of the tumour (compare [14]). Within the population of endothelial cells we initially observe growth in number of cells, followed by slow declining. Period of forty days was chosen, while both cytotoxic and angiogenic agents were administrated to the patient. Outcome of such therapy might be considered as satisfying, due to significantly decreased tumour volume and size of vascular network. Nevertheless it is not recommended to treat the patient with such therapy regime, since it might be devastating for patients overall condition. Surprisingly on the contrary to original Hahnfeldt model and its modifications, in case of the three compartmental model periodic combined therapy which for these models theoretically guarantees asymptotic eradication of tumour population [11] brings significantly worse results than constant drug infusion. Results of the simulation of application of both agents in successive manner in which drugs switching occurs every two and a half days show that as expected volume of the tumour and size of vascular network decrease, however final therapy outcome is poor.

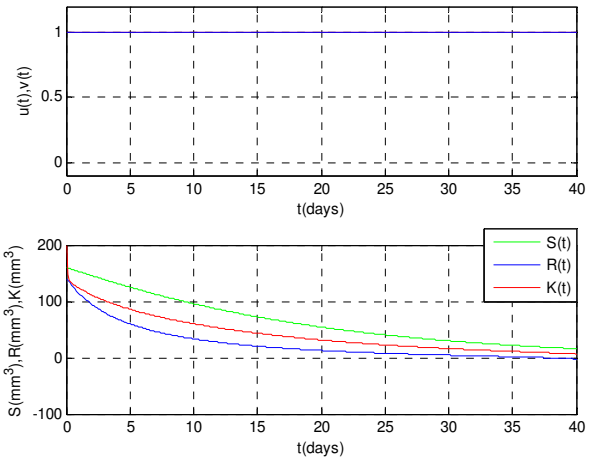

Fig. 1 Three compartmental model under constant combined therapy.

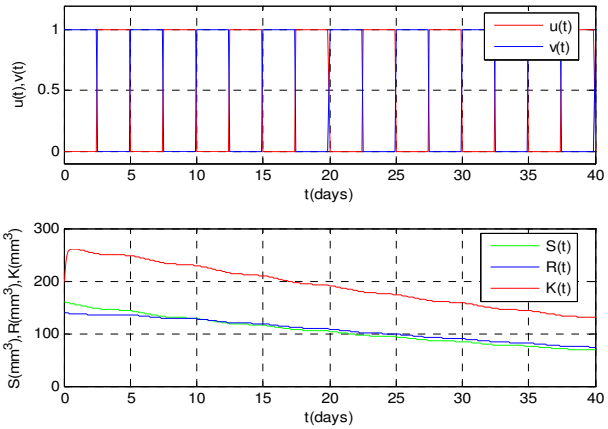

Fig.2 Three compartmental model under periodic combined therapy.

An interesting outcome of combined therapy is found for therapy protocol scheduled for five days. During the first four days cytotoxic agent is administrated, antiangiogenic drug is included with a delay of one day. Results might be difficult to interpret. Therapy protocol is divided into three sections. In absence of antiangiogenic agent we can observe initial growth of vascular network, which is limited and slowed by low amount of angiogenic stimulators and presence of cytotoxic agent. Population of cells sensitive to the drug action is slowly decreasing, while number of cells resistant to the drug action remains approximately constant. In the second section both drugs are administrated simultaneously for three days. Combination of drugs had the most significant influence on population of endothelial cells.

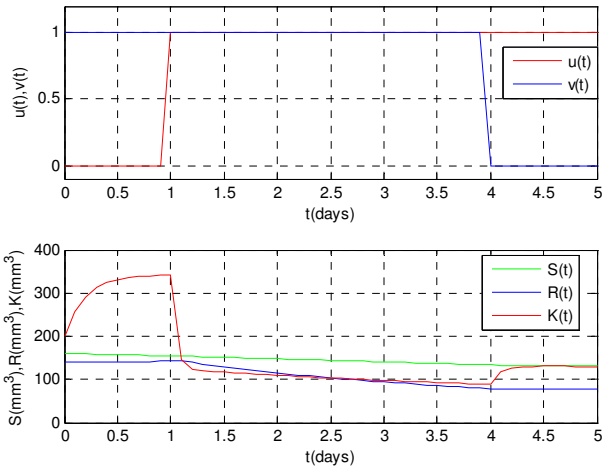

Fig.3 Three compartmental model under combined therapy; $\eta = 9.1$, $\xi = 4.7$

Once cytotoxic agent is switched off, again vascular network slowly re-grows. Overall evaluation and final outcome of considered protocol seems to be of less importance than features of the model revealed during the simulation.

IV. Conclusion

In this research main attention was focused on combined antiangiogenic treatment and chemotherapy incorporated into models from the class of models proposed by Hahnfeldt *et al*. Strategies designed at crippling a tumour by targeting vascular network supporting it, were first proposed almost 40 years ago by Folkman and co-workers. Nevertheless tumour anti-angiogenesis is still considered to be a novel treatment approach. This indirect approach targets endothelial cells, rather than fast duplicating, continuously mutating and genetically less stable tumour cells. As it was emphasized combinations of antiangiogenic agents together with other types of therapies are one of the most inspiring approaches in modern oncology. Combining the therapies seems to be reasonable, considering disadvantages related to conventional treatment. Early clinical experiments bring hope, that this approach may become a new possibility for cancer cure accomplishment. Nevertheless from mathematical point of view this becomes a multi-control problem, making study of satisfying solution significantly more complex. Over past decades, there has been considerable progress in mathematical modelling of tumour growth and associated vascular network development. Regrettably while most realistic models reflect these complex biological processes very accurately, due to their complexity, they become difficult or even not suitable for analysis of therapy protocols. Hopefully with a few simplifying assumptions, it is possible to propose and carefully validate models useful for analysis, preceding experimental and clinical studies. Presented models truthfully describe biological processes of tumour growth and associated angiogenesis, under crucial simplifying assumptions. Mathematical models might be useful for design of modern therapy protocols. Treatment protocol design requires obviously more rigorous analysis and deep investigation of each parameter involved. Future research may include careful estimation of parameters values and refiormulation of models, into more realistic.

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