Óbuda University

PhD thesisbook

Controller-managed automated therapy and tumor growth model identification in the case of antiangiogenic therapy for most effective, individualized treatment

by

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1 Background of the Research

The key of scientific success in every field nowadays depends on interdisciplinary design. Medical treatment is not an exception either; engineers and doctors have to work together to find more effective solutions in healing. Cancer is the leading cause of death all over the world. In the EU, the total estimated number of cancer casualties for 2014 is 1.323 million (Malvezzi et al. 2014). In the clinical practice, there are general protocols for cancer therapies (such as chemotherapy, radiotherapy). However, these treatments have many side effects and tumor cells can become resistant to chemotherapy drugs which on the one hand makes the usage of new drugs necessary (Perry 2008), and on the other hand it increases the treatment cost. That is the reason why a new dynamically-developing therapeutic group called Targeted Molecular Therapies (TMTs) (Gerber 2008) has appeared. These therapies gain more and more importance as they specifically fight against different cancer mechanisms, being more effective and having limited side effects compared to conventional cancer therapies (Kreipe and Wasielewski 2007). Nevertheless, protocols for cancer treatments (also for TMTs) are determined empirically and are comprised of constant drug dosage.

The aim of physiological modeling and control is to study, understand and model biological processes, then to apply identification and control strategies on it. By designing closed-loop control systems, the protocols could become model-based. Model-based design enables the automated treatment of cancer diseases by the personalized administration of TMT drugs. In this way, more effective solutions can be found in healing and offering individualized treatment for the patient. This approach is completely novel and may lead to a breakthrough in cancer therapies. Optimizing cancer treatments would improve efficiency, decrease treatment cost and minimize the side effects of cancer therapy (i.e. improves the patient's quality of life); thus analysis and synthesis of cancer therapies from an engineering point of view is needed.

In the outlined research field the basis of every therapy and further research is physiological and pathophysiological knowledge. This knowledge has to be applied paired with engineering knowledge to create a model which describes tumor growth.

Tumor growth dynamics can be modeled without therapy and under a certain cancer treatment as well. A promising targeted molecular therapy that arose in the last decade is antiangiogenic therapy (Pluda 1997; Kelloff et al. 1994) which aims to stop tumor angiogenesis (i.e. forming new blood vessels) as, without a blood supply, tumors cannot grow (Bergers and Benjamin 2003). A clinically validated tumor growth model under angiogenic inhibition was developed at Harvard University by Hahnfeldt et al. 1999. The

model describes the reduction of tumor volume based on endothelial reduction. The Hahnfeldt model and its simplified form has been used by most researchers working in the field of antiangiogenic control to design controllers and perform simulations.

Nevertheless, the Hahnfeldt model has some limitations according to the newest medical research in the field of angiogenic tumor growth (Döme et al. 2007; Femke and Griffioen 2007). The original theoretical concept of angiogenesis was endothelial sprouting; accordingly, new blood vessels sprout from existing ones (O'Reilly et al. 1997). Endothelial cells undergo disorganized sprouting, proliferation and regression, and become dependent on the vascular endothelial growth factor (VEGF) (McDonald 2008), one of the most important proangiogenic factors in tumor growth. Hence, in inhibiting VEGF in tumors, one can stop sprouting angiogenesis (Chang et al. 2012). Most of the angiogenic inhibitors act in that way and this is the key point in angiogenic inhibition studies.

However, later on, it has became clear that VEGF inhibition leads to apoptosis (process of programmed cell death) only in newly-built vessels in tumors, but does not have an effect on vessels which have already existed (Petersen 2007). That means that there is a strong need to revise the existing tumor growth model, since, according to the Hahnfeldt model, every blood vessel can be eliminated by the drug.

2 Directions and Goals of the Research

2.1 Controller Design for the Tumor Growth Model

Protocols for medical treatment comprise constant drug dosage, which can be effective in terms of reducing the progression of the diseases; however, nowadays the problem seems more complex. From multidisciplinary point of view the aim is to design a controller which is on the one hand able to minimize the input signal as far as possible (in order to have less side effects and greater cost-effectiveness) and on the other hand results in appropriately low tumor volume.

In control design, different goals can be taken into account. One can design controls which minimize the control transients using minimal control signal. These controls are optimal controls (e.g. Linear Quadratic (LQ) optimal control). However, there always will be model uncertainties and measurement noises; thus, there is a need for systems which satisfy the requirements not only for its nominal values but also in the presence of perturbations. These aspects can be taken into account using H_∞ control methodology. The goal of Thesis Group 1 is to design both optimal and robust controls and compare the results of the designed controllers.

2.2 Tumor Growth Model Identification

Examination of tumor growth belongs not only to basic medical research, but to the fields of biomedical engineering and applied informatics as well. Based on the experimental data, model identification can be carried out which describes the mathematical model of the investigated biological process. Using the mathematical model, different dosage algorithms can be designed for antiangiogenic cancer therapy and model-based treatment protocols can be created. These model-based protocols can be more effective than the current ones, since they provide individual treatment for the patients.

The goal of Thesis Group 2 is to create mathematical models which describe the tumor growth dynamics under angiogenic inhibition and without therapy. The resulted models have to be clinically valid and sufficiently simple to be manageable for both real-life applicability and controller design. Thesis Group 2 also aims to analyze the exparimental data to find the relationship between the measured tumor attributes (tumor volume, tumor mass and vascularization). In addition, the effectiveness of the applied therapies have to be examined based on the antiangiogenic drug administration (bevacizumab/ Avastin® (Mukherji 2010)).

3 Materials and Methods of Investigation

3.1 Controller Design for the Tumor Growth Model

Thesis Group 1 provides linear control synthesis for antiangiogenic therapy over the simplified tumor growth model of Hahnfeldt et al. 1999 (D'Onofrio and Gandolfi 2004):

$$\dot{x}_1(t) = -\lambda_1 x_1(t) \log\left(\frac{x_1(t)}{x_2(t)}\right) \tag{1}$$

$$\dot{x}_2(t) = b x_1(t) - d x_1(t)^{2/3} x_2(t) - e x_2(t) u(t) \tag{2}$$

$$y = x_1, \tag{3}$$

where x_1 is the tumor volume, x_2 is the endothelial volume and u is the concentration of the administered inhibitor. The parameters are the following: λ_1 is the tumor growth rate (1/day), b describes the stimulatory effect of the tumor on vasculature support growth (1/day), d presents the inhibitory effect of the tumor and the vasculature (1/day·mm^2) and the effect of the angiogenic inhibitor is desribed by e (kg/day·mg).

Two different control methods were applied to design linear controllers. The controller design was carried out according to the linearized model; however the simulations were

carried out with the nonlinear model.

Linear state-feedback control was designed with pole placement and LQ optimal control as well. Since not every state variables of the system can be measured, a linear observer was designed for both state-feedback methods; hence four different control strategies were realized under *MATLAB 7.9.0 (R2009b)* environment: (C1) state feedback with pole placement, (C2) LQ control method, (C3) state feedback with pole placement and observer, (C4) LQ control method with observer. Several parameter changes were investigated to observe the effect of the different control parameters: four operating points (low operating point: $x_{10} = 100$ mm^3, medium operating point: $x_{10} = 5000$ mm^3, high operating point: $x_{10} = 10000$ mm^3) and three saturation limits ($u_{max} = 25$ mg/kg, $u_{max} = 15$ mg/kg and $u_{max} = 13$ mg/kg) were analyzed. In the case of pole placement, three pole acceleration values ($a = 3$, $a = 5$ and $a = 8$) were examined; in the case of LQ optimal control, R weighting matrix was investigated over a wide range of values ($R = [10^3, 10^6]$). Every simulation result was evaluated based on three criteria: (i) the total concentration of the administered inhibitor during the treatment (mg/kg), (ii) the steady state inhibitor concentration at the end of the treatment (mg/kg), (iii) the steady state tumor volume at the end of the treatment (mm^3). These criteria are relevant from the medical and engineering points of view.

The other applied method is robust (H_∞) control. Taking into account the fact that every model contains uncertainties and measurement noises, I designed a stabilizing robust controller (Zhou 1996). The tumor growth model described by (1-3) was linearized in the $x_{10} = 100$ mm^3 operation point for controller design purposes. The system is unstable in that point but controllable and observable. The robust controller is a two-degrees of freedom controller, which consists of two parts: the feedforward and the feedback branches. Differences between the nominal model and the real system were taken into account using input multiplicative uncertainty (Bokor, Gáspár, and Szabó 2012). Weighting function W_n seeks to minimize the influence of sensor noise. Limitation of the control input is achieved by the weighting function W_u, which penalizes larger deflections. Ideal system is described by T_{id} transfer function. Weighting function W_{perf} seeks to penalize differences between the output of the nominal model and the ideal plant. The ideal system and weighting functions were chosen in the light of physiological aspects.

3.2 Tumor Growth Model Identification

Thesis Group 2 provides tumor growth model identification. Specific animal experiments were performed to investigate tumor growth dynamics and create new tumor growth

models. Tumor growth was investigated without therapy and under angiogenic inhibition. Linear model identification of tumor growth dynamics without therapy using parametric identification was carried out on two tumor types (C38 colon adenocarcinoma and B16 melanoma). Linear model identification of C38 colon adenocarcinoma growth dynamics under bevacizumab inhibition was performed using parametric identification as well. The resulting models are clinically valid and sufficiently simple to be manageable for both real-life applicability and controller design.

The relationship between the measured tumor attributes during the experiments (tumor mass, tumor volume and vascularization) was examined using linear regression analysis (Montgomery, Peck, and Vining 2012). To decide whether the relationship is significant or not between two variables, I used the following statistics. Pearson correlation coefficient (R) describes strength of the correlation (linear dependence) between the variables. Coefficient of determination (R^2) tells how many percent of the variability in a data can be explained by the given statistical model (which is a linear model in every investigated cases). Using Analysis of Variance (ANOVA) test (Larson 2008) we can decide that the regression analysis is valid or not (level of significance was chosen to $p = 0.05$).

Effective dosage of angiogenic inhibitor for optimal cancer therapy was also investigated. To compare the results of the investigated cases, statistical analysis was used. Before the usage of any statistical tests, one has to examine the normality and homogeneity of variance (homoscedasticity) of the distributions. Normality was investigated with one-sample Kolmogorov-Smirnov test, and homogeneity of variance (homoscedasticity) was examined with Levene's test. After confirming normality and homoscedasticity, parametric statistical analysis can be used. Analysis of Variance (ANOVA) test was used to compare more than two samples. To find those samples, which have significantly different means, pairwise comparison was done. Tukey's honest significant difference (HSD) test was used as post hoc test.

4 New Scientific Results

Thesis Group 1: Controller Design for the Tumor Growth Model.

I provided a linear control synthesis for antiangiogenic therapy over the reduced tumor growth model of Hahnfeldt et al. 1999. I provided new cancer treatment opportunity based on two different controller-managed automated angiogenic inhibitor administration. The usage of controller-based treatment can ensure effective individual treatment for the patients.

Thesis 1.1

I developed the basis of a new, controller-managed automated therapy which provides optimal drug administration in the case of cancer treatments. The control method which implements this therapy is linear state-feedback control (using pole placement, LQ optimal control and linear observer). The designed controllers ensure alternatives to optimal treatments, from which the clinical doctor can choose the most appropriate, patient and tumor-specific solution. This new approach can handle the therapeutic efficacy, the cost-effectiveness and the side-effect moderation aspects as well.

Thesis 1.2

I developed the basis of a new, controller-managed automated anticancer therapy, which provides robust control and effective treatment also in the case of arising measurement noise and model uncertainties in the control loop. The stabilizing robust (H_∞) controller was designed in the light of physiological aspects, limitations and applicability. I proved using in silico simulations, that the robust controller-based treatment is more efficient than the medical protocol-based treatment.

Relevant own publications pertaining to this thesis group: [S-14; S-11; S-18; S-8; S-9; S-5; S-6; S-1; S-2; S-20; S-10; S-17; S-19; S-3; S-12].

Thesis Group 2: Tumor Growth Model Identification.

I provided mathematical models which describe the tumor growth dynamics without therapy and under angiogenic inhibition. I investigated the relationship between the measured tumor attributes and applied the results to create a new model for precise tumor volume evaluation. I examined the effective dosage of angiogenic inhibitor for optimal cancer therapy.

Thesis 2.1

I provided linear model identification of tumor growth dynamics without therapy using parametric identification for two tumor types (C38 colon adenocarcinoma and B16 melanoma). The resulted models are clinically valid.

Thesis 2.2

I provided linear model identification of C38 colon adenocarcinoma growth dynamics under bevacizumab inhibition using parametric identification. The resulted models are clinically valid and sufficiently simple to be manageable for both real-life applicability and controller design.

Thesis 2.3

I provided a new model for tumor volume evaluation from caliper measured data, based on the results of linear regression analysis of three measured tumor attributes (tumor mass, tumor volume and vascularization). The model uses two tumor diameters (width and length) of the tumor to evaluate precisely the tumor volume without requiring the approximation of the third diameter (height) and assumption of the tumor shape. I have demonstrated that this model results in a more precise tumor volume evaluation than the currently recommended Xenograft Tumor Model Protocol.

Thesis 2.4

I compared the effectiveness of bevacizumab administration in the case of protocol-based therapy and quasi-continuous therapy. I have demonstrated that the effectiveness of the quasi-continuous (daily) very low dose administration was more effective than one large dose. I provided a methodology for effective dosage of angiogenic inhibitor for optimal cancer therapy, which opens a new treatment opportunity based on closed-loop control.

Relevant own publications pertaining to this thesis group: [S-13; S-15; S-4; S-7; S-16].

5 Discussion and Practical Applicability of the Results

5.1 Controller Design for the Tumor Growth Model

Thesis Group 1 discusses the results of controller for the tumor growth model. Simulation results of linear state-feedback controls demonstrated that the nonlinear model has to be linearized at a low operating point in order to achieve successful control; in increasing the operating point, the control signals become too low to sufficiently reduce the tumor volume (because of the nonlinearity). According to various aspects, the most effective control was the LQ control method: (a) for two criteria (total concentration of the administered inhibitor during the treatment and steady state inhibitor concentration at the end of the treatment), this controller had the best results; (b) the minimal value of the third criterion (steady state tumor volume at the end of the treatment) can be well approximated with the LQ control method; (c) this was the only controller which ensures successful control for high operating points. I provided a set of controllers which can handle the therapeutic efficacy, cost-effectiveness and side-effect moderation aspects as well.

To deal with model uncertainties and measurement noises, a stabilizing robust (H_∞) controller was designed where ideal system and weighting functions were chosen in light of physiological aspects. The results of robust control were compared to the results based on LQ optimal control and THE Hungarian OEP (National Health Insurance Fund of Hungary) protocol (Hungary(OEP) 2010). As would be expected, the LQ optimal control provides better results, but only in the case of good model identification and minimal sensor noise. If the system contains significant uncertainties and the measurement noise is large, only the robust control method can provide near-optimal results. Simulations show that the intermittent dosing used by the OEP chemotherapy protocol is not effective; the tumor volume reduced slightly as a result of a one-day dose, but between the treatment phases, the tumor grows back again. At the end of the whole treatment period, there is no large difference between the therapy with OEP protocol and the case without therapy.

5.2 Tumor Growth Model Identification

Thesis Group 2 discusses newly created mathematical models which describe the tumor growth dynamics without therapy and under angiogenic inhibition. Besides this, a two-dimensional mathematical model for tumor volume evaluation from caliper-measured data was also provided. This model results in more precise tumor volume evaluation than the Xenograft Tumor Model Protocol. The results of parametric identification show that tumor growth dynamics can be described with a second order linear system. Examining

the tumor attributes, I found that not each attribute correlates, thus not only tumor mass and tumor volume is important to be measured. The relevant tumor attribute that has to be measured is based on the therapy applied.

Tumor volumes were calculated using caliper-measured data and small animal MRI measurement results. A two-dimensional mathematical model was created for tumor volume evaluation from caliper-measured data.

Tumor growth was investigated under antiangiogenic therapy using protocol-based and quasi-continuous (daily) administration. The effectiveness of the antiangiogenic therapy strongly depends on the administration, and a drug which is effective on a molecular level can be applied in a less effective way because of the incorrectly chosen administration. Phase III/2 (where tumor volume was measured by digital caliper) results showed that a daily $^1/_{180}$ dosage is comparable with the effectiveness of one large dose (protocol). Furthermore Phase III/3 (where tumo volumer was measured by digital caliper and also small animal MRI) results showed that the effectiveness of small daily doses is even better than one large dose. Taking into account the physiological aspects as well, on the one hand, a small daily dosage is better than one large dose, because it enables the normalization of blood vessels; hence bevacizumab could be used more efficiently. On the other hand, if antiangiogenesis is persistent, it can completely destroy the vascular network which leads to tumor necrosis (death of tumor). Furthermore, it should not be ignored that a considerably lower dose has considerably lower side-effects (or virtually nothing).

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