Preprints of the 21st IFAC World Congress (Virtual)
Berlin, Germany, July 12-17, 2020

Reaction kinetic interpretation of mechanisms related to vascular tumor growth with respect to structural identifiability ⋆

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Abstract: Anti-angiogenic drugs are relatively new tools in cancer therapy with very low side-effects compared to earlier approaches. These drugs inhibit the formation of new blood vessels in the tumor, thus cutting its cells from nutrient supply. As proliferating tumor cells have very intensive metabolism, the lack of nutrients provides a significant barrier for the growth rate of the tumor. In the recent years it has been shown that the dosage protocol of these drugs may be critical in terms of their efficiency. In addition, several papers are considering model-based methods for therapy optimization and potential feedback control of tumor growth, based on the application of anti-angiogenic drugs. In this paper we use the framework of reaction kinetic systems to formulate simple models for important mechanisms present in vascular tumor growth, and analyze their identifiability properties assuming various plausible measurable variables. The conclusions of the article may contribute to experiment design regarding identification of such and similar models.

Keywords: Biomedical systems, identifiability, nonlinear systems

1. INTRODUCTION

Several computational models of tumor growth have been described in the literature, from simple ones (Sápi et al., 2015a) to complex and spatially detailed approaches as (Bauer et al., 2007; Gevertz and Torquato, 2006). One of the main motivations behind developing tumor growth models is to use their predictive power to estimate the effects of possible therapeutic approaches in cancer treatment (Levine et al., 2000; Arakelyan et al., 2002; Poleszczuk et al., 2015).

Angiogenesis, an important form of neuvascularization, plays an important role in tumor development (Folkman, 1992, 2002). During the process of angiogenesis, new blood vessels are formed, which contribute to the nutrient support of the intensively metabolizing tumor cells. Anti-angiogenic drugs as Avastin (active substance of the pharmacological agent bevacizumab) inhibit the process of angiogenesis, thus cutting the proliferating tumor cells from nutrient supply (Ferrara et al., 2005). These drugs have significantly less side effects compared to conventional chemotherapeutic drugs used in cancer therapy. Recently it has been described that the dosage of these drugs is very critical regarding their efficiency. Sápi et al. (2015b) detail the benefits of quasi-continuous therapy over traditional one-shot protocols, and shows that even applying a significantly lower total drug amount, the treatment can be made more effective.

Some of the recently developed simple models have also been used for feedback approaches, namely optimal discrete time control (Drexler et al., 2017c; Sápi et al., 2017) and positive nonlinear control (Drexler et al., 2017d).

Recent models (Drexler et al., 2017b; Csercsik and Kovács, 2019) aim to describe the tumor growth under the anti-angiogenic effect of bevacizumab, in a control oriented-manner with few parameters and state-variables. These approaches already use concepts from the theory of reaction kinetic networks or chemical reaction networks (CRN) to describe various processes taking place during tumor progression (e.g. cell proliferation and drug effect).

CRNs are nonnegative systems, capable of producing important qualitative dynamical phenomena as stable / unstable equilibria, limit cycles, multistability and even chaotic behavior). Therefore CRNs can be regarded as "prototypes of nonlinear systems" (Érdi and Tóth, 1989). The theory of chemical reaction networks has significant results relating qualitative dynamical properties and network structure (Horn and Jackson, 1972; Feinberg, 1987).

Considering a nonlinear ordinary differential equation (ODE) state space model in CRN or any other time-invariant form, to fit the model for experimental data, one must perform parameter estimation, the quality of which

⋆ This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 679681).

is a key point regarding the subsequent performance of the obtained model (Ljung, 1987).

Structural identifiability properties of a system describe whether there is a theoretical possibility for the unique determination of system parameters from theoretically perfect input-output measurements or not. Identifiability is a property related to the model structure itself, and its analysis should ideally precede any experiment design or parameter estimation process. Early references for studying identifiability properties of dynamical systems are (Walter, 1982, 1987). Davidescu and Jorgensen (Davidescu and Jorgensen, 2008) discuss the problem of structural parameter identifiability for CRNs. Meshkat et al. analyze identifiable parameter combinations in nonlinear dynamic systems biology models (Meshkat et al., 2014). Identifiable parameter combinations in nonlinear ODE models and the method of rational reparameterization is described in (Meshkat et al., 2011). Structural identifiability analysis via symmetries of differential equations is performed in (Yates et al., 2009).

The articles (Chis et al., 2011; Raue et al., 2014) perform critical comparison of methods regarding structural identifiability analysis for systems biology models.

In this paper our aim is to create models of the basic mechanisms of vascular tumor growth in the CRN framework, while also provide some basic results about their identifiability with respect to realistic outputs.

2. METHODS

Probably the most cited article related to structural identifiability of nonlinear systems is (Ljung and Glad, 1994). In section 6 of (Ljung and Glad, 1994) the importance of the linear regression form is discussed. The parameters are denoted with θ, while y and u stand for the output(s) and input(s) of the system. The argument in (Ljung and Glad, 1994) states that if the model equations may be rearranged to the form

$$P_i(u,y)\theta_i - Q_i(u,y) = 0 \quad i = 1,...,d \quad , \tag{1}$$

the model structure is globally identifiable (where d is the number of parameters). P and Q may be arbitrary complex functions of u and y and of their higher order derivatives.

In the following, we formulate simple reaction mass action kinetic (Horn and Jackson, 1972) descriptions for mechanisms playing important roles in vascular tumor development, and analyze the identifiability of the implied model structures via the simple method of searching for rearrangements to obtain a regression form linear in parameters – described in eq. (1).

3. RESULTS

We formulate the pathophysiological mechanisms in question as reactions. Reactions in the proposed framework are interpreted as stoichiometric relations between a source complex and a product complex. Complexes in this terminology are considered as positive linear combination of species. Species stand for the elementary components present in the reaction. For example in the reaction

$$2H + O \rightarrow H_2O$$

H, O and H_2O are the species while $2H + O$ and H_2O are the complexes.

The CRN framework was originally developed for chemical reactors where the state variables were interpreted as concentrations, but assuming constant density the molecule numbers can be also interpreted as volumes.

3.1 Simple proliferation

Let us start with the most simple reaction kinetic mechanism which can be related to tumor growth, namely simple proliferation. If T denotes the volume of tumor cells, the proliferation process is simply described as

$$T \xrightarrow{k_1} 2T,$$

which implies the system equation

$$\dot{T} = k_1 T, \tag{2}$$

corresponding to the classic exponential growth model.

In this case, we neglect any other mechanism like necrosis of the tumor cells or vasculature-dynamics. Considering that modern medical imaging technologies like e.g. magnetic resonance imaging (MRI) and computed tomography (CT) are available for the description of the spatial characteristics of the tumor, we can assume that the measurable output is the tumor size, which is in this case equal to the volume of the tumor cells. As equation (3) shows, in this case the only parameter k_1 is clearly identifiable.

$$y = T, \quad \dot{y} = k_1 T \quad k_1 = \frac{\dot{y}}{y} \tag{3}$$

3.2 Proliferation and necrosis

It is known that due to multiple factors, tumor cells (typically inside the tumor) tend to necrotize. From the prospect of tumor growth modelling, it is important to distinguish these necrotized cells, since they do not proliferate. On the other hand, they also contribute to the total tumor volume.

$$T \xrightarrow{k_1} 2T \quad T \xrightarrow{k_2} N$$

$$\begin{aligned} \dot{T} &= k_1 T - k_2 T \\ \dot{N} &= k_2 T \end{aligned} \tag{4}$$

Let us still assume that the measurable output is the tumor size, which is now the total volume of living and necrotic tumor cells. In this case,

$$\begin{aligned} y &= T + N \\ \dot{y} &= \dot{T} + \dot{N} = k_1 T \\ \ddot{y} &= k_1(k_1 T - k_2 T) = \dot{y}(k_1 - k_2) \end{aligned} \tag{5}$$

from which it can be seen that $(k_1 - k_2)$ is identifiable.

3.3 Vasculature-independent growth

In this subsection we consider the mechanism describing vasculature-independent growth (proliferation), considering also vasculature internalization. In this model, in addition to the volume of the tumor cells, we also consider the volume of the vasculature, which is a potentially critical factor for tumor growth, regarding the nutrient supply of cells in the tumor core. Under the tumor core, we mean the volume inside the tumor, which is not supported by nutrients via diffusion from the environment. Modelling of vasculature dynamics is especially important if one aims to optimize the dosage of anti-angiogenic drugs like bevacizumab (Sápi et al., 2015b), since these drugs have a direct effect on angiogenesis, thus an indirect effect on vasculature volumes.

In the initial phase of the growth when the tumor is small, and its full volume is sufficiently supplied with nutrients from the environment by diffusion, it can be assumed that vasculature is not needed for the growth of the tumor.

Our aim in this case is to describe the phenomenon that as the tumor grows, it internalizes vasculature from the surrounding host tissue. This phenomenon is called blood vessel incorporation or vessel co-option (Döme et al., 2007), and its importance is more significant in densely vascularized tissues, as the liver.

In the following the variable V denotes the volume of vasculature in the tumor. The tumor growth and the simultaneous vessel incorporation may be described by the reaction

$$T \xrightarrow{k_1} 2T + \alpha V,$$

where the parameter $\alpha \geq 0$ is proportional to vasculature density in the host tissue of the tumor. The implied differential equations describing the dynamics of the tumor cell and vasculature volumes are as

$$\begin{aligned} \dot{T} &= k_1 T \\ \dot{V} &= k_1 \alpha T. \end{aligned} \tag{6}$$

The measurable output (the total tumor volume) in this case is the sum of the tumorous cell volume and the volume of the tumor vasculature, formally $y = T + V$. According to this, we may write

$$\begin{aligned} \dot{y} &= k_1 T + k_1 \alpha T = (1+\alpha) k_1 T \\ \ddot{y} &= k_1 \alpha (k_1 T) = (1+\alpha) k_1^2 T = \dot{y} k_1 \\ k_1 &= \frac{\ddot{y}}{\dot{y}}, \end{aligned} \tag{7}$$

thus k_1 is identifiable. On the other hand, α (or $(1+\alpha)$) could be expressed in this formalism only, if the single trajectory of T (not the sum $T+V$) would have been known.

3.4 Vasculature-dependent growth without angiogenesis

After the initial phase of tumor growth, if we neglect the cells on the periphery, which have sufficient access of nutrients via diffusion, it is plausible to assume that proliferation is dependent on nutrient supply thus on vasculature presence. In this case we may write the reaction describing vasculature dependent proliferation as

$$T + V \xrightarrow{k_1} 2T + (1+\alpha)V,$$

where the term $(1+\alpha)V$ describes the internalization of vasculature from the environment as the tumor grows (α still denotes the vasculature density in the environment of the tumor).

$$\begin{aligned} \dot{T} &= k_1 T V \\ \dot{V} &= k_1 \alpha T V \end{aligned} \tag{8}$$

We still assume that the measurable output is the total tumor volume, composed of tumor cells and vasculature. The output derivatives in this case are as follows.

$$\begin{aligned} y &= T + V \\ \dot{y} &= k_1 T V + k_1 \alpha T V = (1+\alpha) k_1 T V \end{aligned} \tag{9}$$

$$\begin{aligned} \ddot{y} &= (1+\alpha) k_1 (\dot{T} V + T \dot{V}) \\ &= (1+\alpha) k_1 (k_1 T V^2 + k_1 \alpha T^2 V) \\ &= k_1^2 T V^2 + k_1^2 \alpha T^2 V + k_1^2 \alpha T V^2 + k_1^2 \alpha^2 T^2 V \\ &= (1+\alpha) k_1 T V (k_1 V + k_1 \alpha T) = \dot{y}(k_1 V + k_1 \alpha T) \\ \dddot{y} &= \ddot{y}(k_1 V + k_1 \alpha T) + \dot{y}(k_1 (k_1 \alpha V T) + k_1 \alpha (k_1 T V)) \\ &= \ddot{y}(k_1 V + k_1 \alpha T) + \dot{y}(2 k_1^2 \alpha V T) \\ &= \frac{\ddot{y}^2}{\dot{y}} + \dot{y}^2 \frac{2 k_1 \alpha}{(1+\alpha)} \end{aligned} \tag{10}$$

which shows that the term $\frac{2k_1\alpha}{(1+\alpha)}$ is identifiable.

In general, re-parametrization of models may affect their identifiability properties (Meshkat and Sullivant, 2014). In this case however, as we will see, the re-parametrization $p_1 = k_1$, $p_2 = \alpha k_1$ results in the same linear regression form.

$$\begin{aligned} \dot{T} &= p_1 T V \\ \dot{V} &= p_2 T V \end{aligned} \tag{11}$$

$$\begin{aligned} y &= T + V \\ \dot{y} &= p_1 T V + p_2 T V = (p_1 + p_2) T V \end{aligned} \tag{12}$$

$$\ddot{y} = (p_1 + p_2)(p_1 T V^2 + p_2 T^2 V) \tag{13}$$

from which with similar derivations as in the case of the original parametrization we get

$$= \frac{\ddot{y}^2}{\dot{y}} + \dot{y}^2 \frac{2p_1p_2}{(p_1+p_2)}, \tag{14}$$

which is equivalent to eq. (10).

Up to this point our assumption was that the only measurable input is the tumor size. Recently, however, several novel imaging techniques have been developed, which make the mapping of vascular micro-structures possible: Functional photoacoustic microscopy (Zhang et al., 2006) and doppler optical frequency domain imaging (Vakoc et al., 2009) are used today already in *in vivo* setups for the reconstruction of vascular networks, while diffusible iodine-based contrast-enhanced computed tomography (Gignac et al., 2016) may be used in terminal experimental animals. Based on these methods, the tracking of the development of tumorous vasculature may be possible. In the following we assume that in addition to the total tumor size, an other input, namely the total volume of the vasculature is also available for measurement.

According to our model

$$\begin{aligned} \dot{T} &= k_1 TV \\ \dot{V} &= k_1 \alpha TV, \end{aligned} \tag{15}$$

this implies

$$\begin{aligned} &y_1 = T + V \quad y_2 = V \\ &T = y_1 - y_2 \\ \\ &\dot{y}_1 = (1+\alpha)k_1 TV \\ &\dot{y}_2 = k_1 \alpha TV \\ \\ &k_1 = \frac{\dot{y}_1 - \dot{y}_2}{y_2(y_1 - y_2)} \\ &\alpha = \frac{\dot{y}_1}{\dot{y}_1 - \dot{y}_2} - 1, \end{aligned} \tag{16}$$

which clearly show the identifiability of k_1 and α in this case.

3.5 Vasculature-dependent growth with angiogenesis

Regarding our reaction kinetic formulation, we capture the mechanism of angiogenesis in the simplest form as

$$T + V \xrightarrow{k_1} 2T + (1+\alpha)V \qquad V \xrightarrow{k_2} 2V,$$

where the first reaction describes the vasculature-dependent proliferation and the vessel incorporation during tumor growth, while the second reaction corresponds to angiogenesis.

This implies the dynamic equations

$$\begin{aligned} \dot{T} &= k_1 TV \\ \dot{V} &= k_1 \alpha TV + k_2 V \end{aligned} \tag{17}$$

If we consider the previously introduced two outputs to the system, we can write

$$\begin{aligned} &y_1 = T + V \quad y_2 = V \quad T = y_1 - y_2 \\ \\ &\dot{y}_1 = (1+\alpha)k_1 TV \\ &\dot{y}_2 = k_1 \alpha TV + k_2 V \\ \\ &\dot{y}_1 = (\dot{y}_1 - \dot{y}_2)(1+\alpha) + k_2 y_1, \end{aligned} \tag{18}$$

where the last equation is a linear regression form regarding the parameters $(1+\alpha)$ and k_2. k_1 may be derived as in eq. (16).

3.6 Vasculature-dependent growth with angiogenesis and necrosis

Finally, let us consider the scenario where all the previously detailed mechanisms are at work simultaneously. We consider the reactions

$$T + V \xrightarrow{k_1} 2T + (1+\alpha)V \quad T \xrightarrow{k_2} N \quad V \xrightarrow{k_3} 2V,$$

which imply the dynamical equations

$$\begin{aligned} \dot{T} &= k_1 TV - k_2 T \\ \dot{V} &= k_1 \alpha TV + k_3 V \\ \dot{N} &= k_2 T. \end{aligned} \tag{19}$$

Let us still assume that the first output of the system is the total volume, which now is the sum of living tumor cells, necrotic tumor cells and the vasculature $y_1 = T + N + V$. The second output is still the vasculature volume $y_2 = V$.

$$\begin{aligned} &\dot{y}_1 = (1+\alpha)k_1 TV + k_3 V \\ \\ &\dot{y}_2 = k_1 \alpha TV + k_3 V \\ \\ &\dot{y}_1 = k_1 TV + \dot{y}_2 \\ \\ &\ddot{y}_1 = k_1(\dot{T}V + t\dot{V}) + \ddot{y}_2 \\ \\ &\quad = k_1\left((k_1 TV - k_2 T)V + (k_1 \alpha TV + k_3 V)T\right) + \ddot{y}_2 \\ \\ &\quad = k_1^2 TV^2 - k_1 k_2 TV + k_1^2 \alpha T^2 V + k_1 k_3 TV + \ddot{y}_2 \\ \\ &\quad = k_1 TV\left(k_1 V - k_2 + k_1 \alpha T + k_3\right) + \ddot{y}_2 \end{aligned} \tag{20}$$

Using the equation $k_1 \alpha T + k_3 = \frac{\dot{y}_2}{y_2}$, and by rearrangement we get

$$\ddot{y}_1 - \ddot{y}_2 - (\dot{y}_1 - \dot{y}_2)\frac{\dot{y}_2}{y_2} = (\dot{y}_1 - \dot{y}_2)y_2 k_1 - (\dot{y}_1 - \dot{y}_2)k_2 \tag{21}$$

which is a linear regression form regarding parameters k_1 and k_2.

On the other hand

$$\dot{y}_2 = k_1 \alpha TV + k_3 V = (\dot{y}_1 - \dot{y}_2)\alpha + y_2 k_3. \tag{22}$$

which is a linear regression form regarding parameters k_3 and α.

4. CONCLUSIONS AND FUTURE WORK

In the current paper we considered various simple reaction kinetic models of pathophysiological mechanisms taking place during tumor development. Assuming on the one hand the tumor size as a measurable output and the vasculature volume as a potential second output on the other, we analyzed the structural identifiability properties of the proposed models. The results clearly show that the measurement of vasculature volume may be critical regarding the experiment design and parameter estimation related to such kinetic tumor growth models where the description of vascular dynamics is also explicitly included in the formulation. The importance of these models is significant in the optimization of the dosage protocols of anti-angiogenic drugs, regarding especially potential feedback approaches.

The state space models discussed in this article were autonomous. One possible future research task is to extend the proposed models with inputs describing the dosage of various drugs. In this case reactions describing the drug effects must be taken into account as well. Such extensions will increase the number of parameters to be estimated, but also the number of known functions (the input and its derivatives).

An other straightforward question is how the proposed models perform regarding parameter estimation in experiments, which provide enough measured signals according to the results of the identifiability analysis. Recently published models (Drexler et al., 2017a,b; Csercsik and Kovács, 2019) use volume measurement data for model calibration, originating from experiments, where anti-angiogenic drugs were administered to animals, according to various protocols (Sápi et al., 2015b). The results of the current article show that the identification of models which incorporate more complex mechanisms of angiogenesis and vascular tumor growth, may require also measurement data about vasculature volume and dynamics.

Experiments with simultaneous measurement of the tumor and vasculature volumes are planned to be carried out in the foreseeable future in the framework of the Tamed Cancer ERC grant of the European Union's Horizon 2020 research and innovation programme (grant agreement No 679681).

ACKNOWLEDGEMENTS

The authors would like to thank the Gábor Szederkényi and Dániel András Drexler for their help in the preparation of the manuscript.

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