Control-oriented modelling of tumor and tumor vasculature growth

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Tumor growth - processes

Let us consider what occurs in cancer growth (relevant to our perspective):

1. there is an initial amount of cancer cells appearing in a completely health organ
2. these cells proliferate, the tumor grows, and as some tumor cells will not have access to enough nutrient, they induce the formation of pre-vascular cells from existing vascular network
3. after a period of time, the formation of new blood vessels is initiated
4. both normal and cancer cells compete for nutrients and space
5. cells not getting enough nutrient necrotize

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Literature of tumor and vasculature growth modelling

- Very simple (linear-exponential or sigmoid growth) tumor growth models - not describing angiogenesis.
- Apoptosis-based tumor growth model (McElwain and Morris, 1978) - PDEs and multi-phase approach
- Multiscale models of angiogenesis (Qutub, 2009, Jiang, 2005)
- Yang 2012 'Mathematical modeling of solid cancer growth with angiogenesis'

See the review Rieger and Welter 2015

Tumor and vasculature growth modelling for control purposes - Challenges

- Complexity of metabolic, signaling and vascularization processes - what is the right level of complexity to consider?
- The volume of the tumor increases during the process - concentration based methods can not assume constant volume as usual. What is the space region the model is intended to describe?

We need a model complex enough to describe angiogenic processes (because that is what we aim to influence) and their relation to tumor growth and necrosis, but simple enough to be identifiable, and possible to use for controller design purposes.

Modelling approaches

Two modelling approaches:

- Model 1: Proliferation-driven approach
- Model 2: Balloon and cobweb model

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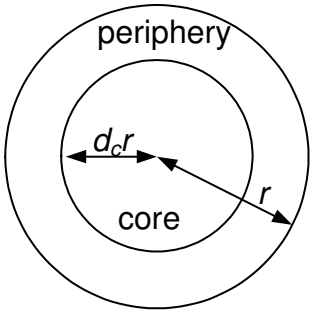
Assumptions of Model 1



- 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.
- Living tumor cells of the core necrotize if the level of nutrient reaching them is too low.
- Separation of time scales: we assume that processes of cellular responses are much faster than growth-related mechanisms.

Model 1

An initial model has been developed which is capable of

- Describe the geometrical tumor growth as a result of the increase in tumor cell density
- Describe the number of living and necrotic cells in the core and the periphery
- Describe the density and nutrition dependent cell proliferation process which leads to increase in tumor cell density

The current model considers nutrition as input, later it will be dependent on the angiogenic state of the model.

A bicompartmental dynamic tumor growth model D. Csercsik, J. Sápi, L. Kovács - accepted to IFAC WC 2017.

Model 1 - variables and equations

The fundamental state equations of the model are as follows

$$\begin{aligned}
\frac{dr}{dt} &= a_1 g([T_P]) \\
\frac{dT_C}{dt} &= \frac{dV_C}{V_P} T_P - a_2 f_{necr}([G_C]) T_C \\
\frac{dT_P}{dt} &= -\frac{dV_C}{V_P} T_P + a_3 f_{prol}([G_P], [T_P]) T_P \\
\frac{dT_{NC}}{dt} &= a_2 f_{necr}([G_C]) T_C
\end{aligned} \tag{1}$$

r - radius, T_C and T_P - the number of tumor cells in the core and in the periphery. T_{NC} - the number of necrotic tumor cells in the core.
$[G]$ - nutrient concentration.

$+$ further differential equations corresponding to healty/pathological vasculature in the tumor core/periphery, affecting $[G]$.

Assumptions of Model 2

- We assume that the proliferation of tumor cells is much faster than vascularization processes and tumor cells fill all volume where the nutrient concentration is high enough - close to blood vessels -, and necrotize anywhere else. $\rightsquigarrow$ the volume and vasculature state of the model uniquely determines the number of living and necrotized tumor cells.
- As the tumor grows, it behaves like an inflated balloon in a box full of cobweb: blood vessels in the environment are accumulated on the surface of the tumor, where angiogenesis also takes place.
- Blood vessels form the surface of the tumor are internalized at a certain rate.
- Blood vessels inside the tumor are decomposed at a certain rate.

$\rightsquigarrow$ Conservation equations in this model are applied to vasculature volumes

Model 2 - variables and equations

Fundamental equations of model 2

$$\begin{aligned} \frac{dW_B}{dt} &= d_{ve}\frac{dV}{dt} - W_B\lambda_i \\ \frac{dW_P}{dt} &= W_B\lambda_i - W_P\lambda_i \\ \frac{dW_C}{dt} &= W_P\lambda_i - r_{deg}W_C \end{aligned} \tag{2}$$

(no angiogenesis included)

$W_B/W_P/W_C$ - vasculature volume at the border/periphery/core, d_{ve} vasculature density in the environment, λ_i internalization parameter, r_{deg} - rate of degradation

Conclusions

- We consider 2 modelling approaches to describe tumor growth and angiogenesis for control purposes.
- The first model is based on the description of the number and proliferation of tumor cells.
- The second model (balloon and cobweb) is based on the description of the vasculature volumes and their position.
- Open questions are to be discussed (eg. how to derive growth rate in the second model).

Thank you for your attention!

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