Proceeding Series of the Brazilian Society of Applied and Computational Mathematics, Vol. 5, N. 1, 2017.

Trabalho apresentado no CNMAC, Gramado - RS, 2016.

Proceeding Series of the Brazilian Society of Computational and Applied Mathematics

Hierarchical Models of Tumor Growth

Anna Claudia Resende[1]
Regina C. Almeida[2]
Laboratório Nacional de Computação Científica (LNCC), Petrópolis/RJ, Brazil
Ernesto A. B. F. Lima[3]
Institute for Computational Engineering and Sciences (ICES), Austin/TX, USA

Abstract. We propose in this work a simple framework to build a hierarchical family of tumor growth models by selecting a subset of the most important parameters of our base model with respect to the evolution of the tumor volume. The importance of each parameter is identified through a model-free sensitivity analysis technique, the elementary effects (EE), due to its simplicity and low computational cost. This model framework encompasses the essential hypotheses and the limited set of important parameters acquired from the sensitivity analysis. In this way, we are able to create a family of models described by at least the same essential conditions and parameters but with different complexities regarding the number of parameters used. Numerical experiments are conducted to show the reasoning behind the hierarchical developed family of tumor growth models. The modeling framework in this manner provides a powerful way for studying a model itself or either its simplification or extension. The framework can also be tailored to form the basis for future models, incorporating new processes and phenomena.

Keywords. Tumor Growth, Sensitivity Analysis, Elementary Effects

1 Introduction

The purpose of this work is to model the basic aspects regarding solid tumor growth by developing a family of continuum models able to capture the vascular phase of tumor growth. This approach requires to deal with various parameters, the majority of them troublesome and relentless to be calibrated and validated [5]. From this point of view, the *"Occam's razor"* principle, which states that the simplest valid model is preferred, may help to select the simplest model that is able to represent well a desired quantity of interest. This approach was developed in [3], where a general adaptive modeling algorithm (The Occam-Plausibility (OP) Algorithm) for selection and validation of coarse-grained models of atomistic systems is presented. This algorithm represents a systematic approach to account parameter uncertainty during model calibration and validation stages, computing sensitivities index and making model adaptations (reducing parameters).

[1]annacmr@lncc.br
[2]rcca@lncc.br
[3]lima@ices.utexas.edu

The reasoning behind OP algorithm led us to pursue a simpler strategy to develop a hierarchical family of tumor growth models from the basic model derived from [4]. We use a simple sensitivity analysis method to investigate the influence of the input parameters on the tumor volume evolution. The set of influential parameters and some basic hypotheses are the core of the model family. In this way, sensitivity analysis is an essential tool to enhance the comprehension about the model itself and drives model alterations that eventually improve it in the *"Occam's razor"* sense.

2 Mathematical Model

Our modeling framework is based on the continuum hypothesis, built on mass conservation principles, that govern variables such as normoxic (n), hypoxic (h) and apoptotic (a) tumor cells densities, oxygen concentration (w), extracellular matrix (f) (ECM) and tumor-associated angiogenesis, captured by the interplay among endothelial cells (m) and the secretion of the vascular endothelial growth factor (g) (VEGF). The nondimensional model defined in $\Omega \times (0, \tau_{max})$ is given by the following set of seven nonlinear coupled partial differential equations:

$$
\begin{cases}
\dfrac{\partial w}{\partial t} = \nabla \cdot (D_w \nabla w) + \alpha_w m(1-w) - \beta_w (n+h+m)w - \gamma_w w; & \text{(1a)} \\
\dfrac{\partial n}{\partial t} = \nabla \cdot (D_n(\max\{n-\nu_c, 0\}+1)\nabla n) - \nabla \cdot (n\overline{\chi}_n \nabla f) + \alpha_n n \max\{1-v, 0\} - \alpha_h \mathcal{H}(\omega_h - w)n & \text{(1b)} \\
\qquad + h_n \alpha_h \mathcal{H}(w-\omega_h)h; & \\
\dfrac{\partial h}{\partial t} = \nabla \cdot (D_h \nabla h) + \alpha_h \mathcal{H}(\omega_h - w)n - h_n \alpha_h \mathcal{H}(w-\omega_h)h - \beta_h \mathcal{H}(\omega_a - w)h; & \text{(1c)} \\
\dfrac{\partial a}{\partial t} = \nabla \cdot (D_a \nabla a) + \beta_h \mathcal{H}(\omega_a - w)h; & \text{(1d)} \\
\dfrac{\partial m}{\partial t} = \nabla \cdot (D_m \nabla m) - \nabla \cdot (m\overline{\chi}_m \nabla g) + \alpha_m m g \max\{1-v, 0\}; & \text{(1e)} \\
\dfrac{df}{dt} = -\beta_f n f; & \text{(1f)} \\
\dfrac{\partial g}{\partial t} = \nabla \cdot (D_g \nabla g) + \alpha_g h \max\{1-g, 0\} - \beta_g m g. & \text{(1g)}
\end{cases}
$$

All types of cells and ECM are combined and assumed to occupy the whole microenvironment $v(\boldsymbol{x}, t)$ so that the total cell density is given by: $v(\boldsymbol{x}, t) = n(\boldsymbol{x}, t) + h(\boldsymbol{x}, t) + a(\boldsymbol{x}, t) + m(\boldsymbol{x}, t) + f(\boldsymbol{x}, t)$. The oxygen concentration is considered the only source of nutrients for cell viability, and it is assumed to diffuse randomly through the computational domain. The cell phenotypes, proliferative (normoxic), quiescent (hypoxic) and dead cells (apoptotic), depend on the oxygen availability in the system and are captured by a Heaviside function $\mathcal{H}$. The thresholds w_h and w_a represent the oxygen concentration below which the cell becomes hypoxic and apoptotic, respectively. Cells are transported mainly because diffusion, albeit directional fluxes are likewise considered. There is haptotactic

DOI: 10.5540/03.2017.005.01.0063

migration of normoxic cells towards the gradient of ECM and a chemotactic response of endothelial cells to the gradient of VEGF. The ECM degrades due to normoxic cells and tumor-associated angiogenesis is trigged by VEGF production, which drives the growth of endothelial cells. Some of the terms in (1) are indicated in red, which will be justified later in this work.

The approximate solution to system (1) is solved by developing a stabilized finite element method (FEM) and using an implicit Euler method to approximate the time derivatives. For details on model solution and numerical methodology, please see [1]. The resulting FEM method is implemented in C++ using the open source `libMesh` library. The 1D experiments shown here simulate the growth of a small tumor placed in the middle of the domain. Due to symmetry, only half of the computational domain is modeled so that $\Omega = (0, 3)$ is partitioned into 400 uniform elements. The time domain with $\tau_{max} = 350$ is also partitioned into uniform time step sizes equal to $\Delta t = 0.1$.

3 Sensitivity Analysis

The deterministic model (1) requires the knowledge of 22 input parameters (shown in Table 1). Some of them are obtained from the literature whereas there is either incomplete or lack of knowledge about the others. More seriously, we do not know *a priori* how they, and their uncertainties, affect the model outcome. Sensitivity analysis may help to identify this issue and drive model modifications.

Screening methods are well adapted to work with a large number of input parameters and were built to distinguish which ones are non-influential with a small number of model evaluations. Here we use the EE method due to its good properties and simplicity [6]. The model quantity of interest (QoI) is the tumor volume, which is represented by a function $Y(\mathbf{X})$, where $\mathbf{X} = (X_1, \ldots, X_d)$ is a vector of d independent input parameters. Considering that all variables in the input space are transformed into dimensionless variables in the unit hypercube, i.e., $\mathbf{X} \in [0, 1]^d$, then, for a given value $\mathbf{X}$, the elementary effect of the ith input factor is defined as:

$$EE_i = \frac{Y(X_1, \ldots, X_i + \Delta, \ldots, X_d) - Y(\mathbf{X})}{\Delta} = \frac{Y(\mathbf{X} + \mathbf{e}_i\Delta) - Y(\mathbf{X})}{\Delta}. \tag{2}$$

Here, Δ is a predetermined integer in $\{1/(p-1), \ldots, 1 - 1/(p-1)\}$, p is the number of levels into which the unit hypercube is discretized, $(\mathbf{X} + \mathbf{e}_i\Delta)$ is equal to $\mathbf{X}$ apart for its ith component, that has been increased by a total amount of Δ, and $\mathbf{e}_i$ is a vector of zeros but a unit at its ith component [6]. According to an one-(parameter)-at-a-time (OAT) sampling strategy, the distribution of elementary effects associated with the ith input factor can be obtained. Global SA measures are then calculated by averaging the elementary effects, using as sensitivity measures the estimates of the absolute mean μ_i^* and the standard deviation σ_i of this distribution. The mean μ_i^* evaluates the general impact of the ith parameter on the output (QoI), while the standard deviation σ_i assesses the overall interplay of parameter effects, including linear/nonlinear interactions among

DOI: 10.5540/03.2017.005.01.0063

parameters. They are computed for each ith input parameter as:

$$\mu_i^* = \frac{1}{r}\sum_{j=1}^{r}|EE_i^j|; \quad \sigma_i^2 = \frac{1}{r-1}\sum_{j=1}^{r}(EE_i^j - \mu_i)^2, \tag{3}$$

where r is the number of trajectories by which the hyperspace is "sampled". Higher μ_i^* indicates a more influential parameter while higher σ_i is an evidence of increased correlation or nonlinearity between parameters. The details regarding the construction of the trajectories are provided in [1].

Table 1: Nondimensional parameters.

Par.	**Value**	**Meaning**	**Par.**	**Value**	**Meaning**
D_w	0.58	nutrient diffusion coeff.	β_w	0.57	oxygen consumption rate
D_n	5.8×10^{-5}	normoxic cells diffusion coeff.	β_h	0.32	transfer rate from h to a
D_h	1.0×10^{-5}	hypoxic cells diffusion coeff.	β_f	0.5	rate of ECM degradation
D_a	1.0×10^{-6}	apoptotic cells diffusion coeff.	β_g	5.0	VEGF consumption rate
D_m	5.8×10^{-5}	endothelial cells diffusion coeff.	ω_h	0.4	threshold n to h
D_g	0.02	VEGF diffusion coeff.	ω_a	0.3	threshold h to a
α_w	1.0	rate of oxygen growth	χ_n	1.4×10^{-4}	haptotatic constant (n)
α_n	$log2$	rate of normoxic cells prolif.	χ_m	2.1×10^{-6}	hapoptatic constant (m)
α_h	1.6	transfer rate from n to h	γ_w	0.025	oxygen decay rate
α_m	0.7	rate of endothelial cells growth	ν_c	0.8	crowding constant
α_g	10.0	rate of growth of VEGF	h_n	0.1	% transfer rate from h to n

Some analysis are shown in Figure 1 for the basic one-dimensional tumor growth model presented in Section 2. Figures 1(a) and 1(b) depict the elementary effects using $r = 20$ and $r = 50$ for a fixed value of $p = 4$, respectively. Some parameter related measures are explicitly indicated. Clearly, there are two different regions: the less important parameters are those whose measures are close to zero and the most influential parameters are those for which $\mu_i^* > 0.1$. Moreover, higher σ_i is an evidence of increased correlation or nonlinearity between parameters. Remarkably, the set of influential parameters does not depend on r. This behavior is highlighted in Figure 1(d), which shows μ_i^* for r up to 50. The rank of importance is clearly defined: D_n is the most influential parameter, followed by ω_a, β_w, β_f, α_n, and D_w. The uncertainties of the other 15 model parameters do not significantly impact the QoI.

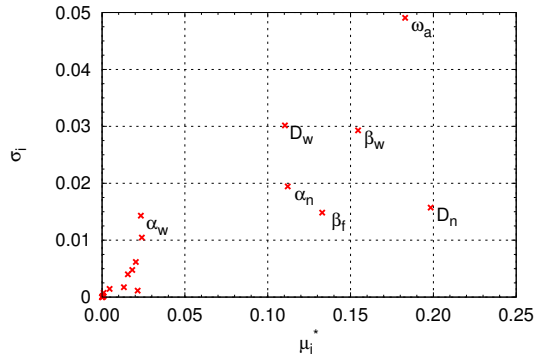
4 Hierarchical Family of Tumor Growth Models

Guided by the results obtained from the sensitivity analysis, we propose a simple model-building framework for model development, including model simplification and enhancement. This model framework encompasses the essential hypotheses and the limited set of important parameters acquired from the sensitivity analysis. We assume that the hierarchical family of models satisfies the following hypotheses: (i) the medium is heterogeneous; (ii) angiogenesis is triggered during the tumor evolution thus implying that tumor cells undergo different phenotypic stages (normoxic, hypoxic and apoptotic); (iii) only normoxic cells proliferate at rate α_n; (iv) the transitions between cell stages mainly depend on the threshold ω_a (and so on ω_h); (v) the oxygen transport depends on the

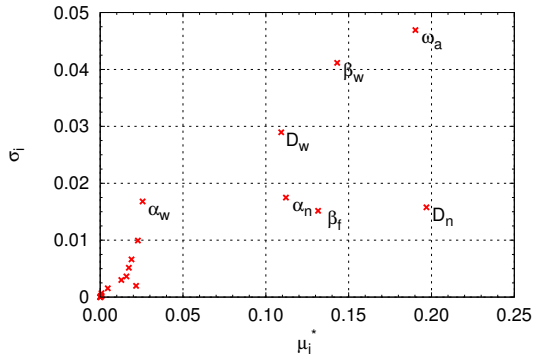
DOI: 10.5540/03.2017.005.01.0063

diffusion coefficient D_w and oxygen uptake rate β_w; (vi) tumor evolution depends on the extracellular matrix degradation (β_f); (vii) tumor evolution also depends on normoxic cells motility due to diffusion (D_n).

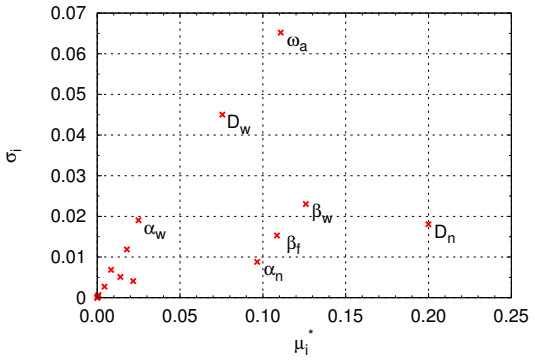
Here, we develop a simpler member of the family (for a model enhancement, see [1]). This simplified model is built by disregarding the following phenomena: (i) the natural oxygen decay; (ii) the increase of the oxygen diffusion coefficient to avoid crowding; (iii) the haptotactic movement of normoxic cells towards ECM's gradient; (iv) the chemotactic movement of endothelial cells towards VEGF's gradient. This means that we disregard the **red** terms highlighted in system (1). With these assumptions, the number of model parameters decreases to 18. The tumor evolution obtained for this model is compared with the evolution of the base model depicted in Figure 2. We perform a sensitivity analysis to this model through the elementary effects method (under the same assumptions selected for the base model) to verify that the set of important parameters indeed remains the same. As shown in Figure 1(c), this indeed occurs.



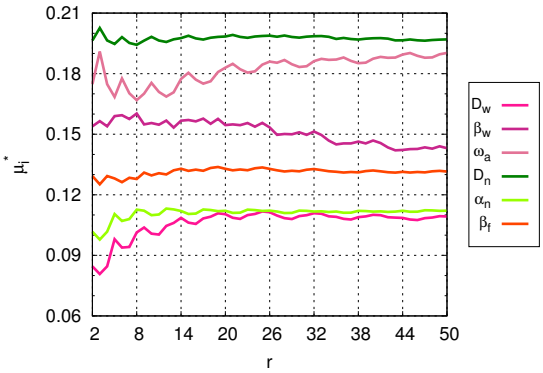
(a) Original Model: $\mu_i^* \times \sigma$ for $r = 20$ and $p = 4$.



(b) Original Model: $\mu_i^* \times \sigma$ for $r = 50$ and $p = 4$.

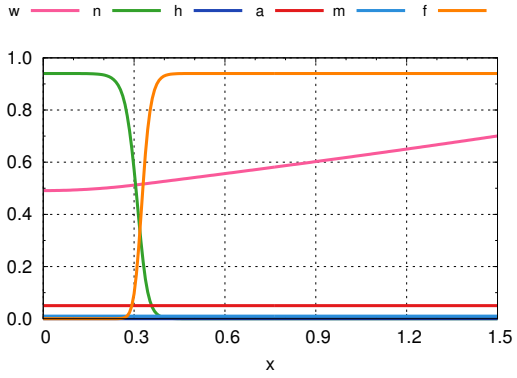


(c) Simplified Model: $\mu_i^* \times \sigma$ for $r = 20$ and $p = 4$.

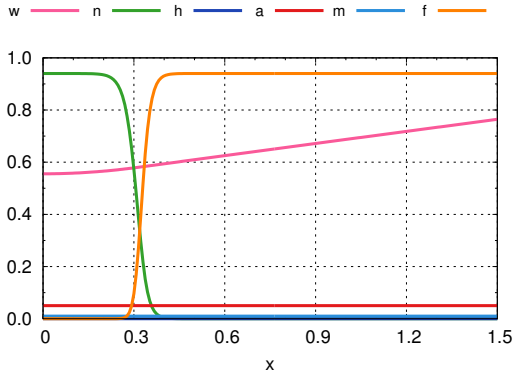


(d) Original Model: $r \times \mu_i^*$, using $p = 4$.

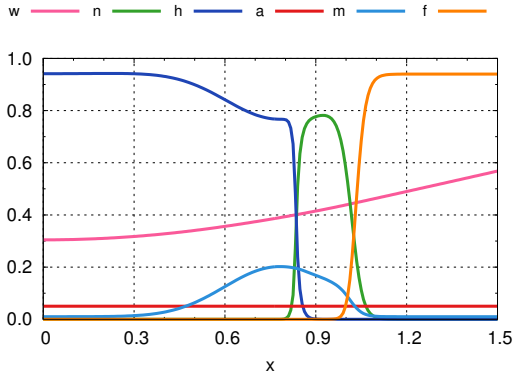
Figure 1: Global EE measures for the original and simplified models using specific values of r and p. For $p = 4$, Figures 1(a), 1(b) and 1(c) show absolute means (μ_i^*) and standard deviation (σ_i) for $r = 20$ and $r = 50$. Figure 1(d) shows the dependence of μ_i^* with respect to the number of trajectories r for the original model.



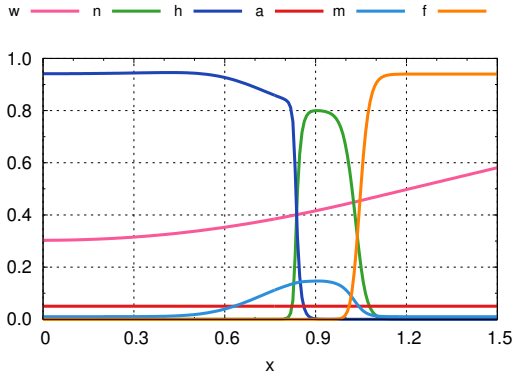
(a) Original Model. Time: t = 70.



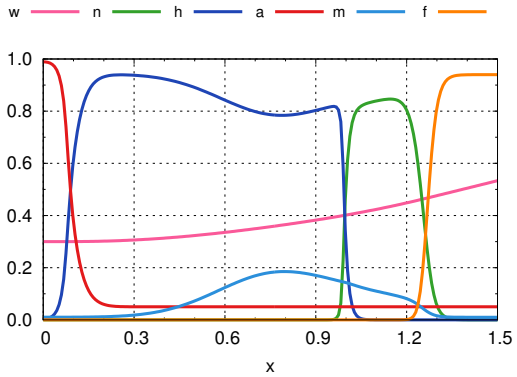
(b) Simplified Model. Time: t = 70.



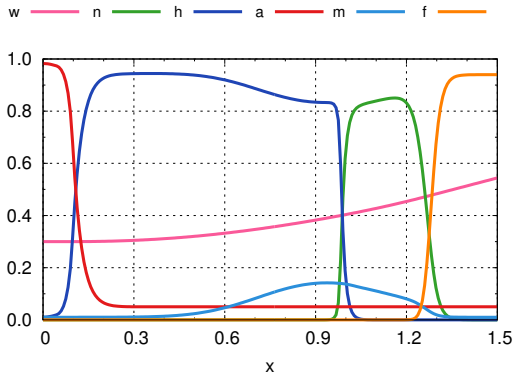
(c) Original Model. Time: t = 280.



(d) Simplified Model. Time: t = 280.



(e) Original Model. Time: t = 350.



(f) Simplified Model. Time: t = 350.

Figure 2: Behavior of the nondimensional models presented in this work. The left column refers to the original model (1) and the right column refers to the simplified model (system (1) without the **red** terms). As the tumor grows, hypoxic cells appear in Figure 2(c), yielding the growth of endothelial cells towards the tumor. This allows the increase of proliferative cells depicted in Figure 2(e), which ends up increasing the nutrient uptake resulting in cell death where $w < \omega_a$.

DOI: 10.5540/03.2017.005.01.0063

5 Conclusion

In this work we focus on the development of a family of hierarchical deterministic tumor growth model capable of capturing both avascular and vascular phases of cancer. The impact of parameter uncertainty was assessed by performing a sensitivity analysis through the elementary effects technique. This method was able to identify the set of most influential parameters with respect to the evolution of the tumor volume, chosen as the model quantity of interest. We showed that oxygen diffusion and uptake, oxygen thresholds that drive phenotypic transitions, ECM degradation, normoxic cells diffusion and proliferative rate play major role in tumor progression.

Guided by the results obtained from the sensitivity analysis, we proposed a simple model-building framework for model development. We built a hierarchical family of tumor growth models that share common hypotheses (and the same set of most influential parameters) with different complexities regarding the number of parameters used. We built a simpler model, disregarding the terms related to some non-influential parameters and addressed the uncertainty in this model through sensitivity analysis, that showed that indeed the same set of influential parameters are identified.

Acknowledgments

The authors would like to thank the support through CNPq (132591/2014-6 and 305612/2013-1).

References

[1] A. C. M. de Resende, Sensitivity Analysis as a Tool for Tumor Growth Modeling. Dissertação de Mestrado, LNCC/MCTI, 2016.

[2] R. V. M. de Souza, Modelos de crescimento tumoral espacialmente heterogêneos com aplicação de quimioterapia. Dissertação de Mestrado, LNCC/MCTI, 2013.

[3] K. Farrell, J. T. Oden and D. Faghihi. A Bayesian framework for adaptive selection, calibration, and validation of coarse-grained models of atomistic systems, *Journal of Computational Physics*, 295:189–208, 2015. DOI: 10.1007/S00466-014-1028-Y.

[4] P. Hinow et al. A spatial model of tumor-host interaction: Application of chemotherapy, *Math. Biosci. Eng.*, 6(3):521–546, 2009. DOI: 10.3934/MBE.2009.6.521.

[5] J. T. Oden, E. E. Prudencio and A. Hawkins-Daarud. Selection and assessment of phenomenological models of tumor growth, *Mathematical Models and Methods in Applied Sciences*, 23(7):1309–1338, 2013. DOI: 10.1142/S0218202513500103.

[6] A. Saltelli, M. Ratoo, T. Andres, F. Campolongo, J. Cariboni, D. Gatelli, M. Saisana, and S. Tarantola. *Global Sensitivity Analysis: The Primer*. John Wiley & Sons, Chichester, 2008.

