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► **To cite this version:**

Pierfrancesco Moschetta, Corrado Mascia, Chiara Simeoni. Numerical investigation of the Gatenby-Gawlinski model for tumour dynamics. SHARE SCIENCE WORKSHOP SAPIENZA 2019, Oct 2019, Rome, Italy. hal-02520865

HAL Id: hal-02520865

<https://hal.science/hal-02520865v1>

Submitted on 27 Mar 2020

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Numerical investigation of the Gatenby-Gawlini model for tumour dynamics



Modelle Calcolo

Pierfrancesco Moschetta, Corrado Mascia and Chiara Simeoni

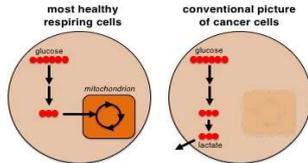
Email: moschetta@mat.uniroma1.it mascia@mat.uniroma1.it simeoni@unice.fr

Research fields: mathematical modeling, numerical analysis and scientific computing.

From a phenomenological point of view, the Gatenby-Gawlini model of cancer invasion is inspired by the Warburg effect and relies on the acid-mediated invasion hypothesis. The main purpose consists in improving the understanding of its structural aspects, by means of a numerical approach based on finite volume approximations, and provide a space-averaged propagation speed estimate as a tool to investigate the phenomenon of traveling fronts. In particular, the multidimensional environment is explored with emphasis on some important qualitative aspects strongly linked to experimental observations.

Biomedical context and model presentation

The **Warburg effect** concerns the metabolism of cancer cells, essentially providing their glucose uptake rates: tumour cells tend to rely on glycolytic metabolism even in presence of huge oxygen amounts, while normal cells undergo glucose metabolism by employing oxidative phosphorylation pathways, which is the most effective process in terms of ATP production and requires oxygen as main resource. Tumour cells seem to forgo the conventional pathway and appeal to glycolysis, inducing lactic acid fermentation (generally released in hypoxia), thus leading to the so-called **acid-mediated invasion hypothesis**.



The model [Gatenby and Gawlini, 1996] is developed to reproduce cancer cells invasion within a healthy tissue: we deal with a **reaction-diffusion system**. The **degenerate diffusion term** within the second equation prevents tumour from spreading, unless the surrounding healthy tissue concentration is diminished from its carrying capacity. A generalized version of the model is proposed in [McGillen et al., 2014], including terms for acid-mediated tumour cells death and mutual competition between healthy and cancer cells.

$$\begin{cases} \frac{\partial u}{\partial t} = u(1-u) - duw \\ \frac{\partial v}{\partial t} = rv(1-v) + D \frac{\partial}{\partial x} \left[(1-u) \frac{\partial v}{\partial x} \right] \\ \frac{\partial w}{\partial t} = c(v-w) + \frac{\partial^2 w}{\partial x^2} \end{cases}$$

- $u(\mathbf{x},t)$ healthy tissue density;
- $v(\mathbf{x},t)$ tumour cells density;
- $w(\mathbf{x},t)$ extracellular lactic acid concentration;
- d death rate for healthy cells;
- r growth rate for tumour cells;
- c growth and reabsorption rate for lactic acid;
- D diffusion constant for tumour cells;
- $[-1, 1]$ experimental domain;
- the homogeneous Neumann problem is considered for the boundary data.

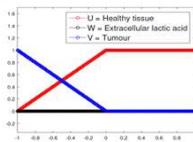
A numerical algorithm based on **cell-centered finite volume approximations** is employed for the spatial discretization: the interfacial quantities are approximated by building weighted averages involving the size of the adjacent finite volumes and the first order derivatives are discretized by means of an upwind formula. For the time discretization a **semi-implicit approach** is invoked: the reaction terms are treated explicitly, while the differential terms on the right-hand sides are approximated implicitly.

$$\begin{cases} u_j^{n+1} = u_j^n + \Delta t [u_j^n(1-u_j^n) - du_j^n w_j^n] \\ v_j^{n+1} = v_j^n + r \Delta t v_j^n (1-v_j^n) \\ \quad + D \frac{\Delta t}{(\Delta x)^2} \left[(1-u_j^{n+1})(v_{j+1}^{n+1} - 2v_j^{n+1} + v_{j-1}^{n+1}) \right. \\ \quad \left. - \frac{1}{2}(v_{j+1}^{n+1} - v_j^{n+1})(u_{j+1}^{n+1} - u_j^{n+1}) - \frac{1}{2}(v_j^{n+1} - v_{j-1}^{n+1})(u_j^{n+1} - u_{j-1}^{n+1}) \right] \\ w_j^{n+1} = w_j^n + c \Delta t (v_j^n - w_j^n) + \frac{\Delta t}{(\Delta x)^2} (w_{j-1}^{n+1} - 2w_j^{n+1} + w_{j+1}^{n+1}) \end{cases}$$

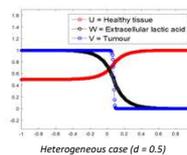
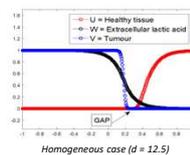
Simulations results

Parameters and initial profiles

- $D = 4 \cdot 10^{-5}$
- $r = 1$
- $c = 70$
- $d \in \{0.5, 12.5\}$
- $T = 20$ final time
- $\Delta x = 0.005$ space-step
- $\Delta t = 0.01$ time-step



Recognition of tumour invasions



LeVeque-Yee wave speed estimate

$$s^n = \frac{\Delta x}{[v] \Delta t} \sum_j (v_j^n - v_{j-1}^{n+1}), \text{ where } [v] = v(+\infty) - v(-\infty)$$

Investigation case	Numerical	Analytical
Homogeneous i.e. $d = 12.5$	0.0124	$s \approx 2\sqrt{Dr} = 0.0126$
Heterogeneous i.e. $d = 0.5$	0.0058	$s \approx \sqrt{2Ddr} = 0.0063$

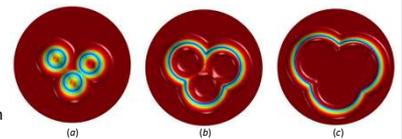
Propagating fronts are moving from left to right. The **heterogeneous invasion** (coexistence between tumour and healthy cells behind the wave front) takes place if $d < 1$; the **homogeneous invasion** (healthy tissue destruction behind the wave front) happens if $d \gg 1$. In this last scenario, from the experimental point of view, is remarkable the formation of the **tumour-host hypocoellular interstitial Gap**, namely a separation zone between cancer and healthy cells fronts.

To get information about the propagating fronts speed, the **LeVeque-Yee space-averaged approximation** [LeVeque and Yee, 1990] is invoked: its strength lies in the absolute independence from the dynamics of the system solutions.

Multidimensional simulations

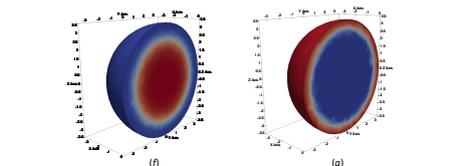
Gap detection for two-dimensional configurations

Three initial distinct cancerous peaks surrounded by the healthy tissue ($d = 12.5$). By adopting a bird-eye viewpoint, it is possible to appreciate the **Gap** formation around the cancerous peaks: **smaller blue rings**, namely null zone densities, are detectable within the circular crowns located between the fronts. Through an intermediate evaluations (b), it is shown how these rings gradually increase their size and are opening, as the corresponding cancerous peaks are colliding and going into meltdown. Eventually, once the novel tumour core is well defined (c), the **resultant Gap** consists of a **single contour** cordoning off the cancerous crown from the surrounding marginal area, where the local healthy tissue is regressing.

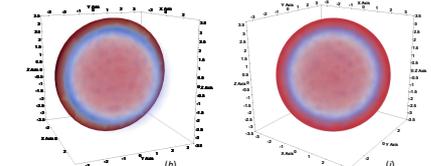


Gap detection for three-dimensional configurations

Graphs of the tumour (d) and healthy (e) cells densities at the final time instant for the homogeneous invasion ($d = 12.5$) by means of the transparency technique. The initial profile is a single cancerous peak surrounded by healthy tissue.



Half balls for the tumour (f) and healthy (g) cells densities arising from domain sectioning and provided with numerical data throughout the external spherical surface. Through symmetry arguments, it is possible to infer that data distributions retain an analogous behaviour inside any inner layer.



Graphical proof for assessing the presence of a separation zone between the tumour and healthy cells densities: simultaneous plot (h) of data merging from (d) and (g); simultaneous plot (i) of data from (d) and (e) allowing to notice the **three-dimensional Gap**, appearing as a null density **solid shell**.

References:

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