Available online at www.sciencedirect.com
ScienceDirect
Procedia Computer Science 1 (2010) 955–963
Procedia Computer Science
www.elsevier.com/locate/procedia

International Conference on Computational Science, ICCS 2010

A coupled convection-diffusion level set model for tracking epithelial cells in colonic crypts☆

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Abstract

Colorectal cancer is initiated in colonic crypts as a consequence of alterations leading to the disruption of the normal colonic cellular process. We propose a model, which couples a convection-diffusion type equation with a level set equation, for tracking the time evolution of an epithelial cell set, inside a colonic crypt, until it reaches the top of the crypt. The convection-diffusion equation describes the evolution of the density of the cells in the epithelial cell set. The parameters of this equation regulate the geometric and temporal cellular mechanism, and different parameter choices lead to distinct cell behavior. The level set equation tracks the location and shape of the epithelial cell set, inside the crypt, as well as its interface, separating the cell set from the others cells, which reside within the crypt. The interfacial velocity of the epithelial cell set is obtained from the convection-diffusion type equation. Some *in silico* experiments are described. They are performed in a relative small time, with respect to the real biological evolution.

Keywords: convection-diffusion equation, level set method, fixed-point method, colonic crypt
2000 MSC: 76R99, 35M10, 65M06

1. Introduction

Colorectal Cancer (CRC) is one of the most frequent malignant tumors in the world [1], it forms in the large intestine (colon) or in the rectum (end of the colon). It is generally accepted that colorectal cancer is initiated in the small pits, called colonic crypts, that line the colon. A colonic crypt is a cylindrical tube, closed at the bottom and with a round opening in the top directed at the lumen's colon, that contains different populations of cells [2, 3]. These cells are aligned along the crypt wall: stems cells are believed to reside in the bottom of the crypt, transit cells along the middle part of the crypt axis and differentiated cells at the top of the crypt. In normal human colonic crypts the cells renew completely each $3-6$ days, through a programmed mechanism which includes the proliferation of cells, their migration along the crypt wall towards the top and their apoptosis, as they reach the top and the cell cycle

☆This work is part of the research project UTAustin/MAT/0009/2008 of the UT Austin | Portugal Program (http://www.utaustinportugal.org/).
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1877-0509
doi:10.1016/j.procs.2010.04.106

is finished. If this programmed mechanism changes, disease may appear leading to tumorigenesis. Nowadays it is accepted that the accumulation of several genetic modifications are responsible for the development of CRC [3]. The adenoma-carcinoma sequence is well established but there are no certainties about the molecular pathology of the adenoma. Two different processes are suggested to explain this behavior: the top-down [4] and the bottom-up [5] theories. The former is found on the fact that the mutant cells appear in the inter-cryptal zone between orifices. As the clone expands, the cells migrate laterally and downwards to displace the normal epithelium of adjacent crypts. In the bottom-up theory the migration kinetics is reversed, with the flux directed toward the top. Intensive research has been done on cell proliferation inside crypts in order to model the tumor growth. In particular we refer to [3, 6] for a literature review of colonic crypts, and cell-based models for colorectal cancer, and the references therein. Essentially these models can be distinguished in two large groups: continuum and cell-level models. The former are based on conservation and constitutive laws (such as Darcy or Stokes law), which simulate the cell growth and displacement. The latter rely on the fact that each cell is considered as a discrete entity which interacts with other cells (this leads in general to very expensive computational models); they describe the cell migration in small regions, using cell-cell interaction or cell-deformation forces (see [7], for instance).

In this paper we propose a new mathematical (continuum) model for tracking the evolution of an epithelial cell set, in a single colonic crypt. Our main goal is to improve the knowledge of the evolution of the early stages of colorectal cancer, based on theoretical assumptions and medical observations about colorectal crypts. Since it is impossible to conduct experiments in humans (and in general scarce clinical data are available), our model is meaningful for giving useful insight into many and dissimilar behaviors that a set of epithelial cells might have in a single colonic crypt. In fact, the model parameter manipulation permits to have different dynamical behaviors for the cell set, and the model predictions (see Section 4) are in good agreement with the medical observations for both normal and abnormal epithelial cells (for example, malignant cells are in part retained in the crypt whereas others are expelled out of the crypt, as suggested in [8]).

The model introduced in this paper couples a convection-diffusion equation with a level set equation. In particular, it simulates the evolution of the boundary (or equivalently, of the shape) of this epithelial cell set, in time, by means of its single cell density. The level set equation permits to track efficiently the movement of the boundary of the cell set by solving an equation only inside the epithelial cell set (see for instance [9, 10], where the level set technique is also used to model the tumor's boundary in time). And to the best of our knowledge this is also the first cell-based model in colonic crypts which incorporates a level set method for tracking the cell movement inside the crypt.

To set up the model we use biological and medical information, and assume the evolution of the epithelial cell set is due to three main effects. The first describes the movement (mainly upwards) of the cells belonging to the set itself. The second is the the convective motion of the epithelial cell set generated by the others cells surrounding it, which, as a consequence of their normal behavior, tend to push the epithelial cell set out of the crypt. Finally, the third effect, is associated to the cell proliferation rate inside the epithelial cell set. All these effects are incorporated in the parameters and coefficients of the mathematical model here considered. Their values are based on the description of the phenomena reported in the literature (see for instance [2, 3, 5, 4, 11]). Basically, these parameters tend to capture both a normal and abnormal behavior of the epithelial cell set, with emphasis on the convection, diffusion and on the inner proliferative effect of the epithelial cell set itself.

Two numerical simulations are reported : with and without the proliferative effect. The results seem to reveal somewhat what is observed in reality, in normal crypts, with an extra information concerning the shape of the epithelial cell set and the distribution of the cell density.

We finish this introduction with a brief outline of the paper. It includes a short description of the coupled model, in Section 2, with details concerning the crypt geometry and the definition adopted for the flux of the cells belonging to the epithelial cell set. The numerical procedure proposed for the solution of the mathematical model is outlined in Section 3 (with a proof related to a fixed point argument). The corresponding numerical simulations are reported in Section 4. Finally some conclusions and future work are discussed in the last section.

2. Definition of the model

2.1. Geometry of a colonic crypt

To start with we define the geometrical domain of a colonic crypt. A crypt is a three-dimensional object (see Figure 1, middle), that we represent in an equivalent two-dimensional domain. If the colon is cut, open, and rolled out

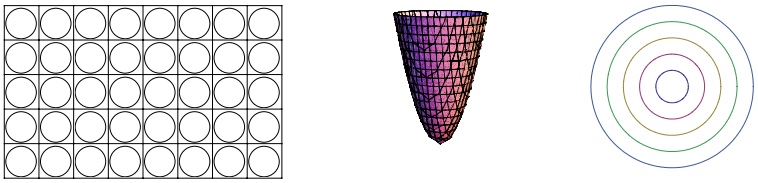

Figure 1: Colon in two dimensions (left), a colonic crypt in three and two dimensions (middle and right).

we obtain a two dimensional rectangular domain (see Figure 1, left), perforated by circles, periodically distributed. Each circumference (see Figure 1, left) represents the orthogonal projection of a crypt in the plan. In each crypt (see Figure 1, right) the concentric circumferences stand for different heights along the crypt's axis.

A colonic crypt of height R is then identified, in a (O, x, y) two-dimensional Cartesian reference system, with the closure of the open ball $B_R := \{(x, y) \in \mathbb{R}^2 : \sqrt{x^2 + y^2} < R\}$, with center $O = (0, 0)$ and radius R. In addition, we can also rewrite the crypt as $B_R = (0, R) \times (0, 2\pi)$ in the polar coordinate system, (O, r, θ), where O is the pole that matches the origin O of the Cartesian system and, r and θ stand for, respectively, the radial and angular component (this latter is also known as the polar angle). Moreover, we note that the point $r = 0$ is the origin O, and represents the bottom of the crypt, while $r = R$ is the top of the crypt, that is the crypt orifice linked with the lumen of the colon.

2.2. Definition of the cell flux

Let $[0, T]$ be a given time interval, the goal of the model is to track the evolution of an epithelial cell set since a starting time $t = 0$ and until a final time $t = T$. For each $t \in [0, T]$, and in each point (r, θ) of the crypt, the density of the cells, inside the set, is denoted by $c(r, \theta, t)$. Moreover, we denote by $D(t)$ this epithelial cell set, at time t. For each fixed polar angle θ, intersecting $D(t)$, the numbers $r_1(\theta, t) = \min\{r : (r, \theta) \in D(t)\}$ and $r_2(\theta, t) = \max\{r : (r, \theta) \in D(t)\}$ represent, respectively, the minimum and the maximum distance from the bottom of the crypt to $D(t)$, measured along the polar angle θ. Likewise, for each fixed radial component r, intersecting $D(t)$, $\theta_1(r, t) = min\{\theta : (r, \theta) \in D(t)\}$ and $\theta_2(r, t) = max\{\theta : (r, \theta) \in D(t)\}$ are the minimum and maximum angle in $D(t)$, respectively, measured along the circumference of radius r.

We describe now the flux $F(r, \theta, t)$, of the cell population within the domain $D(t)$ (outside the region $D(t)$ we implicitly suppose this flux is zero; see the second equation of (3), where this assumption is enforced explicitly). By definition, this flux $F(r, \theta, t)$ controls the rate of loss or increase of $c(r, \theta, t)$ through the boundary of $D(t)$. The formula for the flux is based on several assumptions, which rely on biological and medical information, regarding the mechanism of epithelial cells in colonic crypts. More precisely we split the flux into the sum of its radial and angular components. Then, $F(r, \theta, t) := g(r, \theta, t)\,\hat{r} + h(r, \theta, t)\,\hat{\theta}$, where $\hat{r}$ and $\hat{\theta}$ are the unit vectors of the polar coordinate system and g and h are defined by

$$\begin{cases} g(r, \theta, t) & := & -\alpha(r) \int_{r_1(\theta,t)}^{r} c_t(s, \theta, t)\, ds + \gamma(r) \int_{r}^{r_2(\theta,t)} c_t(s, \theta, t)\, ds + v^0(r)\, c(r, \theta, t) \\ h(r, \theta, t) & := & -\beta(r) \int_{\theta_1(r,t)}^{\theta} r c_t(r, \varphi, t)\, d\varphi + \beta(r) \int_{\theta}^{\theta_2(r,t)} r c_t(r, \varphi, t)\, d\varphi. \end{cases} \tag{1}$$

In the following part of this section we describe the definitions for $g(r, \theta, t)$ and $h(r, \theta, t)$ used in (1). In this model, the flux $F(r, \theta, t)$, in the point (r, θ) within $D(t)$, represents the number of cells crossing a unit of area placed in (r, θ) in unit of time. We assume that this flux depends on the cell density variation (with respect to time) $c_t(r, \theta, t)$. Thus, the four integrals in (1) represent the diffusion flux contribution in two different directions (in the radial direction, along the crypt height, outwards and inwards the crypt, and in the angular direction, towards the sides). The remaining fifth term stands for the convective flux contribution to the cell transport. More precisely:

i) The term $-\alpha(r) \int_{r_1(\theta,t)}^{r} c_t(s, \theta, t)\, ds$ represents the pressure exerted by the cells laying in $D(t)$, along the radial direction (for θ fixed) that are behind the point (r, θ). The function α is a decreasing weight function of r. In the numerical

tests we use $\alpha(r) = \frac{1}{4}\left(1 - \frac{r}{R}\right)$. This choice relies on the medical observation that at the bottom of the crypt (where there are many semi-differentiated cells) the cells move rapidly towards the crypt orifice, due to their high rate of differentiation, and, when they are ascending to the top, they become fully-differentiated cells and start then to move slowly to the top of the crypt (see [3]).

ii) The term $\gamma(r)\int_r^{r_2(\theta,t)} c_t(s,\theta,t)\,ds$ describes the pressure exerted in the radial direction by the cells laying in $D(t)$ ahead the point (r,θ). It accounts for the fact that when the cells approach the top of the crypt, many of them try to go outside simultaneously, thus that the exit from the crypt is penalized. This term is proportional to the number of cells, within $D(t)$, that lay along the radial direction (with θ fixed), but that are near the crypt orifice, at the top. In our numerical simulations we use $\gamma(r) = \frac{r}{8R}$.

iii) The remaining two integrals in (1) define the angular flux component. They describe the pressure exerted by the cells, which are inside $D(t)$, and lay in the circumference with radius r, between the minimum and maximum polar angles $\theta_1(r,t)$ and $\theta_2(r,t)$. We use $\beta(r) = \frac{r}{16R}$.

iv) Finally, the term $v^0(r)\,c(r,\theta,t)$ represents the transport of the cells with the unknown cell density $c(r,\theta,t)$ by the flow $v^0(r)$. This flow is due to the normal renewal cell mechanism inside the colonic crypt (that includes the proliferation, of the semi-differentiated and fully-differentiated cells, and also their apoptosis, see for instance [2, 3]). In this model we set $v^0(r) = 0.8\,\frac{r}{R}$ (based on [3], p.261: *"cells produced at the bottom of the crypt move upwards with increasing velocity, reaching a rate of 0.7-1 positions per hour at the top of the crypt"*).

We note that due to i)-iii) the flux components g and h are pressure differences, along the radial and angular directions, respectively. Therefore, as for the Darcy Law, the flux F depends on the pressure in both the radial and angular directions. This accounts for the diffusive motion of the cells in the model.

By definition the divergence of F is $\mathrm{div}F = g_r + \frac{g}{r} + \frac{h_\theta}{r}$, where here, and always hereafter in the text, the lower subscripts "r" and "θ" mean partial derivative with respect to the variables r and θ, respectively. Using the definitions of g and h, then

$$\begin{aligned}\mathrm{div}F(r,\theta,t) \;=\; & -\Big(\alpha(r)+\gamma(r)+2\beta(r)\Big)\,c_t(r,\theta,t) - E(r,\theta,t)\\ & -A(r)\int_{r_1(\theta,t)}^{r} c_t(s,\theta,t)\,ds - B(r)\int_{r}^{r_2(\theta,t)} c_t(s,\theta,t)\,ds,\end{aligned} \tag{2}$$

where, with the definitions of the parameters v^0, α and γ, $A = \left(\alpha_r + \frac{\alpha}{r}\right) = \frac{R-2r}{4Rr}$, $B = -\left(\gamma_r + \frac{\gamma}{r}\right) = -\frac{1}{4R}$, and $E = -c_r\,v^0 - c\,\left(v^0_r + \frac{v^0}{r}\right) = -c_r\,r\,\frac{0.8}{R} - c\,\frac{1.6}{R}$.

2.3. The coupled convection-diffusion level set model

The model has two unknowns: the cell density $c(r,\theta,t)$ and the domain $D(t)$ (*i.e.*, the location and geometry of the epithelial cell set at time t, inside the crypt). We use a convection-diffusion type equation for determining $c(r,\theta,t)$, coupled with a level set function $\phi(r,\theta,t)$ (see [12, 13]) for representing $D(t)$, its boundary $\Gamma(t)$ and time evolution. More exactly, the coupled model can be summarized by the following system of partial differential equations: find $c(r,\theta,t)$ and $\phi(r,\theta,t)$, such that

$$\begin{cases} \phi_t(r,\theta,t) + v(r,\theta,t)\cdot\nabla\phi(r,\theta,t) = 0 & \text{in} \quad B_R\times(0,T),\\ c_t(r,\theta,t) + \mathrm{div}\big(F(r,\theta,t)\,H(\phi(r,\theta,t))\big) = G(r,\theta,t) & \text{in} \quad B_R\times(0,T),\\ \phi(r,\theta,0) = \phi_0(r,\theta) & \text{in} \quad B_R,\\ c(r,\theta,0) = c_0(r,\theta) & \text{in} \quad B_R, \end{cases} \tag{3}$$

where $c_0 \neq 0$ in $D(0)$, $c_0 = 0$ in $B_R \setminus D(0)$, and with

$$D(t) := \{(r,\theta)\in B_R \,:\, \phi(r,\theta,t)\le 0\} \quad \text{and} \quad \Gamma(t) := \{(r,\theta)\in B_R \,:\, \phi(r,\theta,t) = 0\}, \tag{4}$$

for each time $t\in[0,T]$. In (3), F is the flux defined by (1), $H(.)$ is the Heaviside function ($H(z) = 1$, if $z\ge 0$, and $H(z) = 0$ if $z < 0$), v is the velocity of the boundary $\Gamma(t)$ of $D(t)$ and the function $G(r,\theta,t)$ is a cell proliferation rate. The velocity v depends on the flux and cell density. It is defined in $D(t)$ by

$$v(r,\theta,t) = \frac{F(r,\theta,t)}{c(r,\theta,t)}, \tag{5}$$

and by a continuous extension of (5) in a neighbourhood of $\Gamma(t)$, and zero elsewhere in B_R. We consider two possible proliferation rates $G(r,\theta,t)$ (see Section 4): either $G = 0$, which means there is no growth of cells within the region $D(t)$, and so there is conservation of the total number of cells in $D(t)$, or

$$G(r,\theta,t) := H(\phi(r,\theta,t))\,\frac{N_t(t)}{|D(t)|}, \quad \text{with} \quad \begin{cases} N_t = \lambda N - k\frac{N^2}{1+mN}, & \text{in } (0,T) \\ N(0) = \int_{B_R} c_0(r,\theta)\, r\, dr\, d\theta. \end{cases} \tag{6}$$

Here $|D(t)|$ is the area of $D(t)$, and N is the number of cells generated in $D(t)$. The latter is obtained by solving the ordinary differential equation in (6) with $\lambda = 0.9$, and $k = m = 0.01$ (see [2]). From the convection-diffusion type equation (second equation in (3)) we get

$$\int_{B_R} c(x,y,t)\,dx\,dy = N(t) - \int_0^t \left(\int_{\partial B_R} F(x,y,t)\, H(\phi(x,y,t)\cdot n\, dx\, dy \right), \tag{7}$$

where n is the outward unit normal vector to the boundary ∂B_R of B_R. In (7), the left hand side represents the total number of cells belonging to $D(t)$ at time t, that is then equal to the number of cells $N(t)$, generated inside $D(t)$ at the time interval $[0,t]$, minus the total number of epithelial cells of $D(t)$ that are shed into the colon's lumen in the same time interval. The definition of N is based on [2]: the ordinary differential equation used in (6) represents a feedback model, with a saturating feedback. It expresses that the rate at which the epithelial cell density increases is not only linear (the term λN), but there is also a maximum per-capita rate of cell density (the term $-k\frac{N^2}{1+mN}$) taken into account.

Finally, we emphasize that the convection-diffusion type equation can be written, in $D(t)$, as $c_t = Lc_t$, where the operator L is defined by

$$Lc_t(r,\theta,t) = \frac{4}{3}\left(A(r) \int_{r_1(\theta,t)}^{r} c_t(s,\theta,t)\,ds + B(r) \int_{r}^{r_2(\theta,t)} c_t(s,\theta,t)\,ds + E(r,\theta,t) \right) + G(r,\theta,t). \tag{8}$$

3. Numerical procedure

In this section we describe the numerical procedure used for solving the coupled model (3). It involves a finite difference discretisation, for both the convection-diffusion and the level set equations. In addition, we are able to resolve the convection-diffusion type equation with a fixed-point algorithm, since the associated operator L (see (8)) becomes a contraction, as shown in step 3 below. This is due to the chosen discretization scheme.

In order to start with the numerical procedure, we first define a mesh in the spatial domain $B_R = (0,R)\times(0,2\pi)$, using the radial and angular step sizes, dr and $d\theta$, respectively. The step size of the time interval $[t_0,T]$ is denoted by dt. In the numerical simulations we set $t_0 = 0$.

The following steps characterize the algorithm used for the numerical simulations of $D(t)$ and the cell density $c(r,\theta,t)$.

Step 1 Set the initial conditions at time $t = t_0$: $D(t_0)$, $\Gamma(t_0)$ and $c(r,\theta,t_0) = c_0(r,\theta)$, where c_0 is non null only in $D(t_0)$.

Step 2 Measure the area $|D(t_0)|$ of the epithelial cell set and the total number of cells inside $D(t_0)$, at time t_0, using respectively $\int_{B_R} H(\phi(r,\theta,t_0))\, r dr\, d\theta$ and $\int_{B_R} c(r,\theta,t_0)\, r\, dr\, d\theta$.

Step 3 Determine c_t in $D(t_0)$, at time $t = t_0$, using a fixed point iteration method for the modified operator L, also denoted by L. This means use the iterative algorithm $c_t^{k+1} = Lc_t^k$, for $k = 1,2,\ldots$. In effect, since the time $t = t_0$ is fixed, in the definition (8) of L, the terms $E(r,\theta,t)$ and $G(r,\theta,t)$ are considered as data, because they do not involve the unknown c_t, only the given cell density $c(r,\theta,t_0)$. Thus, from (8), for any scalar functions v and w

$$\begin{aligned} |Lv - Lw| &\le \left|\frac{R-2r}{3Rr}\right| \left| \int_{r_1(\theta,t)}^{r} (v-w)(s,\theta,t)\,ds \right| + \frac{1}{3R}\left| \int_{r}^{r_2(\theta,t)} (v-w)(s,\theta,t)\,ds \right| \\ &\le \left(\left|\frac{R-2r}{3Rr}\right| r + \frac{1}{3R}(R-r) \right) \max_{(r,\theta)} |v-w|\,. \end{aligned} \tag{9}$$

But

$$\frac{|R-2r|+R-r}{3R} = \left\{ \begin{array}{ll} \frac{2R-3r}{3R}, & \text{if } 0 \le r \le \frac{R}{2} \\ \\ \frac{r}{3R}, & \text{if } \frac{R}{2} \le r \le R \end{array} \right\} \le \frac{2}{3} < 1.$$

Therefore the modified operator L is a contraction and then it exists a unique fixed point, which is the solution c_t, for fixed time $t = t_0$, of the equation $c_t = Lc_t$.

Step 4 Compute F, using (1), and also $F_\epsilon(r,\theta,t_0) = F(r,\theta,t_0)\, H_\epsilon(\phi(r,\theta,t_0))$ in all B_R. Here $H_\epsilon(z) = 1-\frac{1}{2}\left(1+\frac{2}{z}\arctan\frac{z}{\epsilon}\right)$ is a smooth regularization of the Heaviside function $H(z)$ (defined before in (3)), for a small ϵ (when ϵ goes to zero $H_\epsilon(z)$ converges to $H(z)$, see [14]). F_ϵ is now a regularized extension of F, defined in B_R. Then, compute the regularized velocity v_ϵ as in (5), using F_ϵ instead of F.

Step 5 Solve the level set equation, using the velocity v_ϵ of step 4, to determine $\phi(t_0+dt)$ and afterwards $\Gamma(t_0+dt)$ and $D(t_0+dt)$. We use an integration forward in time to approximate the level set equation, with CFL (Courant, Friedrichs and Lewy) constrained time-steps and a first order forward Euler scheme, with upwind.

Step 6 Update c_t in $B_R \setminus D(t)$ at time t_0, using the new level set function $\phi(t_0+dt)$, obtained in the previous step 5. That is, $c_t(r,\theta,t_0) = -\mathrm{div}(F_\epsilon(r,\theta,t_0+dt)) + G(r,\theta,t_0)$, with $G(t_0)$ defined by (6), and $F_\epsilon(r,\theta,t_0+dt) = F(r,\theta,t_0+dt)\, H_\epsilon(\phi(r,\theta,t_0+dt))$.

Step 7 Update the cell density c in all B_R, at time t_0+dt, using $c(t_0+dt) = c(t_0) + c_t(t_0)\, dt$, with $c_t(t_0)$ defined in steps 3 and 6.

Step 8 Set $t_0 := t_0 + dt$ and repeat the steps $2-7$.

Step 9 The method proceeds until we get $\phi(T)$, $D(T)$, and $c(r,\theta,T)$ at the final time T.

4. Numerical simulations

In the human colon epithelium there are millions of crypts (approximately 10 millions according to [15]). In each crypt, the cells are aligned along the crypt wall and the average number in humans is about: 120 cells in height (from the bottom to the top of the crypt) and 60 cells in perimeter. The cell size is about $6-10$ microns, thus the size of a crypt is approximately 900 microns, from the closed bottom to the orifice, and 150 microns in perimeter.

We recall that the main goal in this paper is to track the evolution of an epithelial cell set $D(t)$, at any time t, starting with a given initial set $D(0)$ and until a final prescribed time T. This is done tracking the zero level set of the function $\phi(r,\theta,t)$, which solves, with the unknown cell density $c(r,\theta,t)$, the system (3).

We show the results of two numerical simulations: the first corresponding to a null cell proliferation rate, $G = 0$, and the second with G defined in (6). In both cases we take $R = 20$, which means we consider 20 levels of height in the colonic crypt (thus one level is associated to 6 levels of the human colonic crypt). We also set $T = 20$, symbolizing 20 hours of simulation. Moreover, we consider at the initial time $t = 0$ an epithelial cell set $D(0)$ equal to a circle of radius 4, and for the corresponding cell density, we take $c_0(r,\theta) = 1$, if $(r,\theta) \in D(0)$ and $c_0(r,\theta) = 0$, if $(r,\theta) \in B_R \setminus D(0)$ (see the first picture in the left, in Figures 2 and 3).

The numerical procedure described in Section 3 has been implemented using the software MATLAB® [16] and the level set toolbox [17]. The simulations were obtained in a computer with an Intel Q9550 CPU (quad-core at 2.83GHz).

For the first simulation, whose results are shown in Figure 2, G is zero, and the cell density is depicted with a color proportional to its intensity: light color for a lower cell density and dark color for a higher density (the color bar ranges from white, corresponding to $c = 0$, to the darkest color, for which $c = 2$). As expected the cell density in $D(t)$ decreases as time t increases. In fact, the cells start to spread rapidly, due to the diffusion and convection, and at time $t = 10$, we can observe they concentrate more at the top of $D(10)$, because there is a higher cell density ($c = 1.7$). This behavior is in good agreement with the natural renewal of the cells that move rapidly to the top of the crypt and when they are close to it they decrease their velocity and so they concentrate themselves in the higher parts of the epithelial cell set, before being released out of the crypt. We note that at time $t = 20$ the cells of $D(20)$ have reached the top of

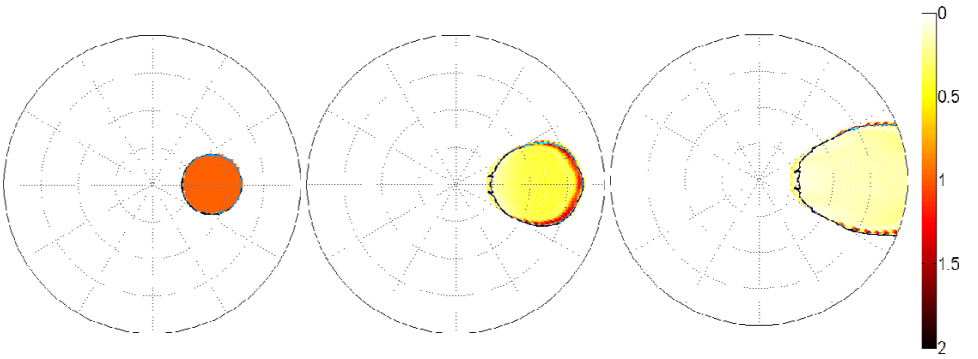

Figure 2: Simulation of the evolution of an epithelial cell set and its cell density, when no extra cell proliferation rate is added. The three pictures show, from left to right, the simulations obtained at time $t = 0,\ 10,\ 20$ respectively. The computer simulation time is 4719 secs.

the crypt, and some of them have been already shed into the colon lumen. In effect, we obtain, numerically, that the total number of cells (given by $\int_{B_R} c(r,\theta,t)\, r\, dr\, d\theta$) is 50.52 for times $t = 0$, $t = 10$ (*i.e.* when the set $D(t)$ is still inside the crypt there is conservation of the total number of cells of $D(t)$) and 34.33 for time 20.

Still in Figure 2, the curve, surrounding the epithelial cell set $D(t)$, represents the approximation of the boundary $\Gamma(t) := \{(r,\theta) \in B_R \ :\ \phi(r,\theta,t) = 0\}$. We note that almost all the "colored cells", represented by the light color, are contained inside the approximated $\Gamma(t)$, except a few that are left at the bottom of $D(t)$ (see in Figure 2, the left part of $D(t)$ for the cases $t = 10, 20$). The coupling of the convection-diffusion and level-set equations permits to determine, almost accurately, the evolution of the region $D(t)$ and its boundary $\Gamma(t)$ in its forwarding move up to the top of the crypt. The approximation is however not fully accurate because some cells with a very small density that lay at the bottom of the $D(t)$ are not caught inside the simulated $D(t)$. This problem can be improved by refining the finite difference mesh. Actually, for the pictures displayed in Figure 2 we have considered a 60×60 grid for the spatial domain $[0, 20] \times [-\pi/4, \pi/4]$. This is a rather coarse grid for detecting all the cells at the bottom of $D(t)$, but is quite satisfactory to catch the large number of cells (which are well marked by the dark color in the figures) that are at the top of the epithelial cell set $D(t)$.

In the second simulation, see Figure 3, we use the same initial conditions, for time $t = 0$, as in the previous case, but now we suppose there is a non zero cell proliferation rate G. The Figure 3 shows the evolution of the epithelial cell set $D(t)$, for time $t = 0$, $t = 10$, and $t = 20$. The color-bar in this Figure 3 goes from 0 (marked by the white

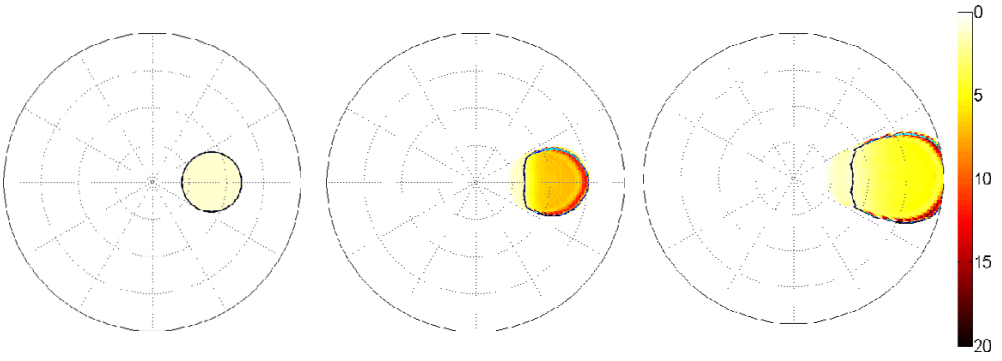

Figure 3: Simulation of the evolution of an epithelial cell set and its cell density, when an extra cell proliferation rate is added. The three pictures show, from left to right, the simulations obtained at time $t = 0,\ 10,\ 20$ respectively. The computer simulation time is 9915 secs.

color) to 20 (marked by the dark color). We remark that at time $t = 10$ the cell density increases significantly. In fact, at this time, the total number of cells (given by $\int_{B_R} c(r, \theta, t)\, r\, dr\, d\theta$) is equal to 467.5, which might disrupt the normal balance of cells in the crypt. As in the previous simulation (without source term), the cells tend to accumulate at the top (rightest part of $D(t)$). Moreover we observe that the epithelial cell set $D(t)$ reaches the top of the crypt before $t = 20$ with a slightly less growth in the angular and radial directions, with respect the previous no-source case. This can be explained because the cells are now more equally distributed and more compacted with respect the first numerical simulation. Biological evidence suggests that mutant cells are more viscous and then they are more retained in the bottom of the crypt [8, 6], our model is able to catch this retention of the set when a positive proliferation rate is considered. Finally, we note that in the two cases examined we are able to simulate 20 hours of a biological evolution in less than 2 and 3 hours of computing simulation, respectively, in the first and in the second simulation considered.

5. Conclusion and future work

In this paper we have proposed a new coupled model to represent the time evolution of an epithelial cell set in a colonic crypt. The numerical results shown are quite satisfactory for tracking the contour of the epithelial cell set, as well as, the evolution of its cell density. This model is able to reproduce some particular aspects of the behavior of cells in colonic crypts, and to reveal processes/mechanisms that would be impossible to reach with real-life experiments.

One drawback of the model, observed in the numerical simulations, is that for a rather coarse mesh, it is not possible to detect a small number of cells that are always located at the bottom of the epithelial cell set. We think that this problem could be solved using very fine and adaptive spatial grids. However this will involve a larger computer simulation time. As future work we intend to improve the efficiency and speed of our numerical codes in order to better approximate the epithelial cell set using a smaller computing simulation time. In addition, we also plan to generalise this single crypt model to multiple colonic crypts (see Figure 1, left). Moreover, another mathematical model, such as a pure diffusive-convective model, is under study in order to better track the evolution of the epithelial cell set.

Extensions of the present work, interesting for medical doctors, focus on numerical simulations able to predicting the appearance of aberrant crypt foci (see [18]) and *a posteriori* colorectal polyps. This amounts to introducing appropriate changes in the definition and values used for the parameters involved in the coupled model. In particular we intend to apply multiscale methods to account for the several events that can occur in colonic crypts, at the very different cellular and tissue levels.

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