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A multiscale model for Aberrant Crypt Foci

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Abstract

Colorectal cancer is believed to be initiated in colonic crypts as consequence of several genetic mutations in normal cells. Clusters of abnormal crypts, called Aberrant Crypt Foci (ACF), are thought to be the first manifestation of a possible carcinogenic process. Assuming that the formation of an ACF is due to the accumulation of abnormal cells we use multiscale technics to study their evolution. Starting from a 3-d crypt model we make its projection in a plane and then build a model in which the colon is a 2-d structure with crypts periodically distributed. Inside the crypts, the dynamics of the abnormal cells is governed by a convective-diffusive model, whose unknowns are the cell density of abnormal cells and a pressure. Outside the crypts, in the inter-cryptal region, a proliferative-diffusive model is assumed for the dynamics of abnormal cells. For the numerical implementation of this model, it is used a technique based on heterogeneous multiscale methods. Two scales are employed: a macro-scale and a micro-scale. The macro-scale corresponds to the region of the colon where the evolution of ACF is taking place, whilst the micro-scale is related to the region occupied by each crypt and its inter-cryptal region. Pressure and cell density are computed at the macro-scale level using the micro-scale structure in a neighborhood of the quadrature macro-scale points. This strategy reduces the computational cost of the simulations. Numerical results, simulating the ACF evolution, are shown and discussed.

Keywords: Convective-Diffusive Model, Heterogeneous Multiscale Methods, Colonic Crypts.

1. Introduction

Colorectal Cancer (CRC) is the third most frequent type of malignant tumors in the world [1], and the most incident men cancer in Portugal [2]. Unlike most other malignancies, it is possible to prevent colorectal cancer due to the long period of time elapsed between the appearance of an adenoma and the eclosion of the carcinoma. There are several stages in the colorectal cancer growth. The earliest expression of this process is the appearance of Aberrant Crypt Foci (ACF). These are clusters of abnormal crypts that are the precursors of the adenomas and can be detected by screening colonoscopy. A normal cell becomes abnormal as a consequence of several genetic mutations [3].

There is no scientific agreement about the way how these clusters are formed starting from the accumulation of abnormal cells. Two majors mechanisms have been proposed in order to explain these process, the top-down and the bottom-up morphogenesis. In the first one see [4] it is assumed that at the beginning abnormal cells appear in a superficial portion of the mucosae and spread laterally and downward inside the crypt. In the bottom-up

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morphogenesis [5], the first abnormal cells appear at the bottom of the crypt where they proliferate and fill all the crypt. It has also been suggested in [5] that a combination of these two mechanisms could be considered. An abnormal cell in the crypt base migrates to the crypt apex where it expands in agreement to the top-down morphogenesis model. The reader can refer to [6, 7, 8, 9, 3, 10, 11, 12, 13] for a review in colorectal cancer modeling and to [14, 15, 16, 5, 17, 4, 18] for the medical analysis of aberrant crypt foci and colorectal cancer.

Assuming that ACF are consequence of accumulation of abnormal cells, we will characterize the dynamics of these cells, in order to describe the evolution of ACF.

At the beginning we consider a 3-d crypt model, where a crypt is represented by a cylinder in \mathbb{R}^3 closed at the bottom and opened at the top, to which an inter-cryptal region closed to the crypt orifice is joined. The evolution of abnormal cells, inside the crypt, will be characterized by a convection-diffusion model similar to those described in [19, 20] whose solutions are the cell density of abnormal cells and a pressure due to the proliferative process. In the inter-cryptal region, where normal cells are apoptotic [11, 6], we use a proliferative-diffusive model. After making the projection of the 3-d crypt in a plane and obtaining then a 2-d model for the crypt, the colon is considered as a plain periodic spread structure composed by a crypt and a inter-crypt region. In this way we obtain a coupled parabolic-elliptic model in a domain $\Omega \subset \mathbb{R}^2$.

We simulate the ACF evolution using a multiscale model that describes the dynamics in space and time of the normal and abnormal cells in the colon. For the numerical implementation, we use an Heterogeneous Multiscale Method (HMM) [21] with a finite elements discretization in space. Two scales are used: a macro and a micro-scale. The macro-scale describes the region (measurable in decimeters) of the colon where the evolution of ACF is taking place, whilst the micro-scale describes the region (measurable in micrometers) occupied by a single crypt with an inter-cryptal region. Pressure and density are computed at the macro-scale level with the coefficients responsible for diffusion and proliferation, that are defined at the micro-scale.

The results presented here follows our recent work [22], wherein a convection-diffusion type equation for pressure and density is modeled in 2-d, to track the time evolution of an epithelial cell set. The model presented in this work differs with respect to [22] in two main aspects. Here we start from a 3-d model and after a projection in a plane we obtain a 2-d model in the crypt, whereas in [22] the model was build directly in 2-d. The other point is that the multiscale structure permit us to model a region of the colon with millions of crypts whereas, in all our previous works [19, 20, 22] we modeled, using a single scale, a region of the colon occupied by few (one or two) crypts. We used, for instance in [19] and [20], a single-scale convective-diffusive model for colonic cells dynamics and colonic crypt morphogenesis, respectively. In [19, 22] we coupled the model with a level set equation to describe the dynamics of the boundary of a colonic cell set.

The outline of the paper is as follows. In Section 2 we describe the 3-d crypt geometry and the model for the colonic cell dynamics. The 3-d crypt is then projected on a plane in a 2-d crypt geometry, in Section 3. Afterwards, we present in Section 3 a multiscale model for the problem in a colon geometry represented as a periodical distribution of such 2-d crypt geometries. The implementation of Heterogeneous Multiscale Methods is discussed in Section 4 and includes the numerical discretization of the multiscale model, and the numerical algorithms for computing their solutions. Numerical results are shown and discussed in Section 5. Finally in the last section there are some comments and outlook work.

2. 3-d Crypt-geometry and cell model

In this model the colon is cut, open, and rolled out to give a three dimensional domain that consists of crypts periodically distributed. A crypt can be represented by a 3*d*-domain in \mathbb{R}^3 closed at the bottom and opened at the top.We also consider the inter-cryptal region closed to the crypt orifice. So, a "crypt" will be represented by a 2*d*-manifold *S* of \mathbb{R}^3 such that $S = S_1 \cup S_2 \cup S_3$, where

$$S_1 = \left\{ (x_1, x_2, x_3) \in \mathbb{R}^3 : r_S < \sqrt{x_1^2 + x_2^2} \text{ and } \max\{|x_1|, |x_2|\} \le \frac{1}{2}, \ x_3 = h \right\}$$
(1)

$$S_2 = \left\{ (x_1, x_2, x_3) \in \mathbb{R}^3 : \sqrt{x_1^2 + x_2^2} = r_S, \ x_3 \in]0, h] \right\}$$
(2)

$$S_3 = \left\{ (x_1, x_2, x_3) \in \mathbb{R}^3 : \sqrt{x_1^2 + x_2^2} \le r_S, \ x_3 = 0 \right\}$$
(3)

and where h is the height of the crypt and r_s is the radius of the crypt orifice (see Figure 1,left).

In the crypt region S we assume that there are two kinds of cells, normal and abnormal with densities $N(x_1, x_2, x_3, t)$ and $C(x_1, x_2, x_3, t)$, at time $t \in (0, T)$ respectively. An overall density hypothesis, N + C = 1, will be considered. This hypothesis describes a no-void condition (see [20]), it is used in the context of living tissue growth [23, 6] and for modeling the tumor growth [24, 25, 26].

Inside the crypt we use a transport/diffusion model describing cell dynamics [27, 24, 20], for both cells population. Therefore, in $(S_2 \cup S_3) \times (0, T)$ the densities N and C must verify

$$\begin{cases} \frac{\partial N}{\partial t} - \nabla \cdot (v_1 N) &= \nabla \cdot (D_1 \nabla N) + \alpha_1 N - \beta_1 N C, \\ \frac{\partial C}{\partial t} - \nabla \cdot (v_2 C) &= \nabla \cdot (D_2 \nabla C) + \beta_1 N C. \end{cases}$$
(4)

where D_1 , D_2 are the diffusion coefficient of normal and abnormal cells, respectively, α_1 the birth rate of normal cells and β_1 the death rate of normal cells. This latter corresponds to the birth rate of abnormal cells. The parameters v_1 and v_2 in (4) are the convective velocity of the normal and abnormal cells, respectively.

We assume $v_1 = v_2 = v$ (see [27]) and in order to simplify the model, a "fluid-like" behavior obeying to the following Darcy law $v = -\nabla p$ is also considered.

Based on these hypothesis we obtain from (4) the following elliptic-parabolic coupled model in $(S_2 \cup S_3) \times (0, T)$

$$\begin{cases} \frac{\partial C}{\partial t} - \nabla \cdot (\nabla pC) = \nabla \cdot (D_2 \nabla C) + \beta_1 C(1 - C), \\ -\Delta p = \nabla \cdot ((D_2 - D_1) \nabla C) + \alpha_1 (1 - C). \end{cases}$$
(5)

Since in the inter-cryptal region S_1 , there is no high proliferative activity, as in inner crypt region, we will consider the same equation for the density *C*, without the convective term, that is we have in $S_1 \times (0, T)$

$$\frac{\partial C}{\partial t} = \nabla (D_2^* \nabla C) + \beta_1 C (1 - C) \tag{6}$$

where D_2^* is the diffusion coefficient of the abnormal cells in S_1 .

In normal colonic crypts it has been observed, see [28], that the proliferative activity is present in the lower two thirds of the crypt, and that this activity is larger at the bottom of the crypt and decreases upwards towards the orifice. We define therefore the proliferative coefficients α_1 and β_1 , as decreasing functions, in $S_2 \cup S_3$, with respect the height of the crypt, thus

$$\alpha_1(x_3) = \begin{cases} \tau_{\alpha_1}(x_3 - 2/3h)^2 & \text{if } x_3 \le \frac{2}{3}h \\ 0 & \text{elsewhere} \end{cases}$$
$$\beta_1(x_3) = \begin{cases} \tau_{\beta_1}(x_3 - 2/3h)^2 + \gamma_{\beta_1} & \text{if } x_3 \le \frac{2}{3}h \\ \gamma_{\beta_1} & \text{elsewhere} \end{cases}$$

where τ_{α_1} is larger than τ_{β_1} to guarantee that α_1 is larger than β_1 . Considering the new parameters

$$D^{S} = \begin{cases} D_{2} & \text{in } S_{2} \cup S_{3} \\ D_{2}^{*} & \text{in } S_{1} \end{cases}, \qquad E^{S} = \begin{cases} D_{2} - D_{1} & \text{in } S_{2} \cup S_{3} \\ 0 & \text{in } S_{1} \end{cases},$$
(7)

$$\alpha^{S} = \begin{cases} \alpha_{1} & \text{in } S_{2} \cup S_{3} \\ 0 & \text{in } S_{1} \end{cases} , \qquad \beta^{S} = \begin{cases} \beta_{1} & \text{in } S_{2} \cup S_{3} \\ \beta_{2} & \text{in } S_{1} \end{cases} ,$$

$$(8)$$

where β_2 is defined as a constant function in S_1 such that $\beta_2 = \gamma_{\beta_1}$, we can rewrite (5)-(6) in all $S \times (0, T)$ as follows

$$\begin{cases} \frac{\partial C}{\partial t} - \nabla \cdot (\nabla pC) &= \nabla \cdot [D^S \nabla C] + \beta^S C(1 - C), \\ -\Delta p &= \nabla \cdot (E^S \nabla C) + \alpha^S (1 - C). \end{cases}$$
(9)

3. 2-d Multiscale colon model

In this section we describe the projection of the 3-d "crypt" *S* in a 2-d crypt domain $P = \left[-\frac{1}{2}, \frac{1}{2}\right] \times \left[-\frac{1}{2}, \frac{1}{2}\right]$ and make the correspondent changes in system (9). The multiscale model is then presented in a two dimensional colonic region Ω that is formed by a periodic distribution of the crypt micro-domain ϵP . Here ϵ is a small positive parameter that represents roughly on the ratio of the crypt orifice with respect the dimension of the colon region examined. By considering the bijective transformation $\Pi: S \to P$ defined by

$$\Pi(x_1, x_2, x_3) = (X_1, X_2) := \begin{cases} (x_1, x_2), & \text{if } (x_1, x_2, x_3) \in S_1 \\ \left(\frac{1}{r_S} \left[r + \frac{x_3}{h}(r_S - r)\right] x_1, \frac{1}{r_S} \left[r + \frac{x_3}{h}(r_S - r)\right] x_2 \right), & \text{if } (x_1, x_2, x_3) \in S_2 \\ \frac{r_S}{r_S}(x_1, x_2), & \text{if } (x_1, x_2, x_3) \in S_3 \end{cases}$$
(10)

we have that $\forall i = 1, 2, 3$ $\Pi(S_i) = P_i$ where, see Figure 1,

$$P_1 = P - B_{r_S}(0,0), \quad P_2 = B_{r_S}(0,0) - B_r(0,0), \quad P_3 = B_r(0,0) \quad \text{and } 0 < r < r_S < \frac{1}{2}.$$



Fig. 1. Crypt projection, R stays for r_S

Note that *h* is the height of the crypt, r_S is the radius of P_2 and of the crypt orifice, and *r* is the radius of P_3 . For an arbitrary function *g* defined in *S*, a correspondent g^* function is defined in *P* by

$$g^*(X_1, X_2) = g(x_1, x_2, x_3),$$

where $(X_1, X_2) = \Pi(x_1, x_2, x_3)$. Using the relation between the space derivatives of $g(x_1, x_2, x_3)$ and the space derivatives of $g^*(X_1, X_2)$, system (9) can be rewritten in $P \times]0, T[$ as follows

$$\frac{\partial C^*}{\partial t} - \mathcal{R}^*_{ij} \frac{\partial}{\partial X_i} (C^* \frac{\partial p^*}{\partial X_j}) = \mathcal{R}^*_{ij} \frac{\partial}{\partial X_i} (D^* \frac{\partial C^*}{\partial X_j}) + \beta^* C^* (1 - C^*),$$

$$- \mathcal{R}^*_{ij} \frac{\partial^2 p^*}{\partial X_i \partial X_j} = \mathcal{R}^*_{ij} \frac{\partial}{\partial X_i} (E^* \frac{\partial C^*}{\partial X_j}) + \alpha^*_1 (1 - C^*),$$
(11)

where $p^*, C^* : P \to \mathbb{R}$ are respectively the pressure and the cell density in *P* and for i = 1, 2

$$\mathcal{A}_{ii}^{*}(X_{1}, X_{2}) = \begin{cases} 1, & \text{in } P_{1} \\ g_{i}(X_{1}, X_{2}), & \text{in } P_{2} \\ \left(\frac{r}{r_{s}}\right)^{2}, & \text{in } P_{3} \end{cases}; \quad \mathcal{A}_{12}^{*}(X_{1}, X_{2}) = \mathcal{A}_{21}^{*}(X_{1}, X_{2}) = \begin{cases} 1, & \text{in } P_{1} \\ g_{3}(X_{1}, X_{2}), & \text{in } P_{2} \\ \left(\frac{r}{r_{s}}\right)^{2}, & \text{in } P_{3} \end{cases}$$

with

$$g_1(X_1, X_2) = \frac{X_1^2 + X_2^2}{r_s^2} + \frac{(r_s - r)^2}{h^2(X_1^2 + X_2^2)} X_1^2; \quad g_2(X_1, X_2) = \frac{X_1^2 + X_2^2}{r_s^2} + \frac{(r_s - r)^2}{h^2(X_1^2 + X_2^2)} X_2^2; \quad g_3(X_1, X_2) = \frac{(r_s - r)^2}{h^2(X_1^2 + X_2^2)} X_1 X_2.$$

Let ϵ be the size of the crypt in the colon. The two dimensional multiscale problem is modeled now in the rectangular domain Ω formed by the domain (ϵP) that is periodically distributed, see Figure 2. In order to define



Fig. 2. Colon as a periodic structure

a problem in Ω we consider the periodic coefficients $A_{ij}^{\epsilon}, D^{\epsilon}, E^{\epsilon}, \alpha^{\epsilon}$ and β^{ϵ} defined in all the domain Ω in the following way: $\forall X \in \Omega$

Similar definitions are valid for the other periodic coefficients D^{ϵ} , E^{ϵ} , α^{ϵ} and β^{ϵ} . Using these coefficients, we define a new model (12) -(13) in Ω to which we add initial conditions and homogeneous boundary conditions for pressure and cell density, that is we have in $\Omega \times (0, T)$

$$\frac{\partial C^{\epsilon}}{\partial t} - A^{\epsilon}_{ij} \frac{\partial}{\partial X_i} (C^{\epsilon} \frac{\partial p^{\epsilon}}{\partial X_j}) = A^{\epsilon}_{ij} \frac{\partial}{\partial X_i} (D^{\epsilon} \frac{\partial C^{\epsilon}}{\partial X_j}) + \beta^{\epsilon} C^{\epsilon} (1 - C^{\epsilon}),$$
(12)

$$-A_{ij}^{\epsilon} \frac{\partial^2 p^{\epsilon}}{\partial X_i \partial X_j} = A_{ij}^{\epsilon} \frac{\partial}{\partial X_i} (E^{\epsilon} \frac{\partial C^{\epsilon}}{\partial X_j}) + \alpha^{\epsilon} (1 - C^{\epsilon}).$$
(13)

4. Solution of the 2-d multiscale colon model

In this section we describe the multiscale method that is used to determine a numerical solution of (12)-(13). A finite element method, that results from a macro and a micro-scale discretization, is used. While macro-scale finite elements, that have edges of size $H >> \epsilon$, are used to approximate numerically p^{ϵ} and C^{ϵ} in all Ω , the micro-scale elements, that have edges of size $h \le \epsilon$, permit us to catch the high oscillations of the coefficients $A_{ij}^{\epsilon}, D^{\epsilon}, \ldots$ used

in (12)-(13). Multiscale finite element methods avoid the inefficient use of a single scale to discretize the multiscale problem in all the domain Ω . A single scale can be, in fact, too coarse to catch the oscillations of the micro-scale periodic coefficients that vary with ϵ , or when the scale is of order ϵ , it can require an high computational cost and a large memory allocation for the numerical implementation of the method.

The multiscale method used here is based on the FE-HMM method [29] and it is briefly described in Paragraph 4.1. The implementation of FE-HMM to solve problem (12)-(13) is presented in Paragraph 4.2.

4.1. Brief Description of FE-HMM

This method has been presented by Assyr Abdulle in [29, 30]. His works are applied to multiscale problems involving elliptic PDE equations in divergence form or with parabolic PDE equations. Parabolic equations are reduced to PDE elliptic equations after approximating the derivatives in time by the Euler formula. Convergence results for FE-HMM are proved in [31], when the multiscale coefficients of the problem are uniform elliptic, symmetric and bounded.

This method uses a macro-scale finite element discretization with edge size H in all the domain Ω and a micro-scale finite elements with a step-size h, only in a neighborhood of the quadrature points, that are used in the quadrature formulae to approximate the integrals of the variational macro-scale formulation, see Figure 4.1. Therefore this strategy reduces the computational cost of the numerical implementation with respect to the use of classical FEM methods, with a micro-scale discretization used in all Ω , as discussed before.

We describe now the application of FE-HMM for solving a simple second order elliptic equation

$$-\nabla \cdot (a^{\epsilon} \nabla u^{\epsilon}) = f \quad \text{with } u^{\epsilon} = 0 \text{ in } \partial\Omega, \tag{14}$$

where $a^{\epsilon}(x) \in L^{\infty}(\Omega)$ is an high oscillating parameter, that is periodic in the square micro-domain ϵP , and it is symmetric, uniformly elliptic and bounded in Ω .

Let \mathcal{T}_H be a partition of Ω with quadrilaterals of edge H and $H_0^1 = \{v \in H^1(\Omega) : v = 0 \text{ in } \partial\Omega\}$, we define the macro-scale finite element space

$$V^{H} = \left\{ v^{H} \in H_{0}^{1}(\Omega) \mid u^{H} \mid_{K} \text{ is a (bi)linear polynomial } \forall K \in \mathcal{T}_{H} \right\}.$$
(15)

From (14) we have the following variational formulation: find $u^H \in V^H$ such that

$$\sum_{K\in\mathcal{T}_H} \int_K a^{\epsilon} \nabla u^H \cdot \nabla v^H dx = \sum_{K\in\mathcal{T}_H} \int_K f v^H dx, \quad \forall v^H \in V^H.$$
(16)



Fig. 3. HMM Finite Element Discretization using macroelements K with edges H. Micro square elements are used in a neighborhood K_{δ_l} of a limited number of quadrature points inside each element K. K_{δ_l} have edges δ with $\epsilon \leq \delta \ll H$.

The method approximates each integral of the first member in (16), by using the two point Gauss quadrature formula

$$\sum_{l=1,\dots,4} \omega_{K_l} q^H(x_{K_{\delta_l}}) \approx \int_K q^H(x) dx, \quad \text{with } \omega_{K_l} = \frac{|K|}{4} \text{ and } x_{K_{\delta_l}} = F_K \left(\pm \frac{\sqrt{3}}{6}, \pm \frac{\sqrt{3}}{6} \right), \quad l = 1,\dots,4,$$
(17)

where F_K is the affine mapping of $I = (-\frac{1}{2}, \frac{1}{2}) \times (-\frac{1}{2}, \frac{1}{2})$ into K. The values $q^H(x_{K_{\delta_l}})$ in (17) are approximated by the average $\frac{1}{|K_{\delta_l}|} \int_{K_{\delta_l}} q^h_{K_l}(x) dx$ of some micro-functions $q^h_{K_l}$ that are defined in next paragraph.

Applying such integral approximation to the first member of (16), the macro-scale variational formulation becomes : find $u^H \in V^H$ such that

$$\mathcal{B}(u^{H}, v^{H}) := \sum_{K \in \mathcal{T}_{H}} \sum_{l \in \mathcal{L}} \frac{\omega_{K_{l}}}{|K_{\delta_{l}}|} \int_{K_{\delta_{l}}} a^{\epsilon}(x) \nabla u^{h} \nabla v^{h} dx = \int f v^{H} dx, \quad \forall v^{H} \in V^{H}.$$
(18)

4.1.1. Micro-Functions

We describe here the properties of the micro-functions v^h (and u^h), that define $\mathcal{B}(u^H, v^H)$ in (18), and their relation with the associated v^H (and u^H). Each v^h is defined in $K_{\delta_l} = x_{K_{\delta_l}} + \delta I$, with $l = 1, ..., 4, \delta \ge \epsilon$ and satisfy

•
$$v^h - v^H|_{K_{\delta_l}} \in S = \left\{ z : K_{\delta_l} \to \mathbb{R} : z \text{ is periodic in } K_{\delta_l}, \forall T \in \mathcal{T}_h \ z|_T \text{ is linear and } \int_{K_{\delta_l}} z dx = 0 \right\}$$
 (19)

•
$$\int_{K_{\delta_l}} a^{\epsilon}(x) \nabla v^h \nabla z^h dx = 0 \quad \forall z^h \in S$$
(20)

A possible v^h satisfying (20) in K_{δ_l} is the function w such that

$$w_{|_{K_{\delta_{\epsilon}}}} \in S \quad \text{and} \quad F'_{\epsilon}(w)(z) = 0 \quad , \ \forall z \in S$$

$$\tag{21}$$

where $F'_{\epsilon}(w)$ is the Fréchet derivative in w of the functional $F_{\epsilon} = A^{\epsilon}(w, w)$ with $A^{\epsilon}(w, z) = \frac{1}{2} \int a^{\epsilon} \nabla w \cdot \nabla z dx$.

Since $A^{\epsilon}(\cdot, \cdot)$ is a bilinear and symmetric operator in $S \times S$, the problem (21) is equivalent to determining $w \in S$ that minimize $F_{\epsilon}(v)$ in S, with v verifying (19). This minimization problem can be solved by using Lagrange multipliers: determine $w \in S$ and $\Lambda \in \mathbb{R}$ such that

$$\begin{cases} F'(w) + D^T \Lambda = 0\\ Dw = \beta \end{cases}$$
(22)

where $Dw = \beta$ describes numerically the condition (19).

4.1.2. Convergence

An important property of FE-HMM is that it has a number of computations that does not depend on the size of ϵ . Moreover, it can be proved, see [31, 32], that if the multiscale problem (14) has multiscale coefficient a^{ϵ} , with the properties described at the beginning of Section 4.1 the following result of a priori estimate in $L^2(\Omega)$ is valid

$$\|u^{\epsilon} - u^{H}\|_{L^{2}(\Omega)} \leq C \left(H + \sqrt{\epsilon} + \frac{h}{\epsilon}\right).$$

Here u^{ϵ} and u^{H} are, respectively, the theoretical solution of the continuous multiscale problem and the numerical solution of the method FE-HMM. A similar results is valid after using a post-processing procedure in $H^{1}(\Omega)$.

4.2. FE-HMM applied to the colon multiscale problem

In this section we apply the FE-HMM method to the coupled multiscale problem (12)-(13), with some modifications with respect to its original version presented in the previous paragraph. In our case we have a parabolic equation (12) that is coupled with an elliptic problem (13). This latter is not in divergence form. Consequently the bilinear form associated to the variational formulation is not symmetric. In order to overcome this difficulty we will introduce some terms in the variational formulation of (12)-(13) that enables to solve the arising microproblems with Lagrange multipliers following, the same procedure and technique described in Paragraph 4.1. Let consider the macro-scale Finite Element space V^H defined in (15) with basis $\{\phi_m\}$, we define the following matrices F_a , G_a and M_a for a general function a(x) by

$$F_{a} = \left(\int a(x)\phi_{k}\sum_{i}^{2}\frac{\partial A_{i}^{\epsilon}}{\partial x_{i}}\cdot\nabla\phi_{l}dx\right)_{k,l}, \quad G_{a} = \left(\int a(x)\nabla\phi_{k}\cdot(A^{\epsilon}\nabla\phi_{l})dx\right)_{k,l}, \quad M_{a} = \left(\int a(x)\phi_{k}\phi_{l}dx\right)_{k,l}, \quad (23)$$

where $\frac{\partial A_i^{\epsilon}}{\partial x_i} = \left(\frac{\partial A_{ij}^{\epsilon}}{\partial x_i}\right)_{j=1,2}$. These matrices are used later in the description of the numerical method with a(x) having different expressions, see (24)-(25).

The coupled system (12)-(13) can be discretized using the Galerkin Finite Element method in the space V^H defined in (15) with partition \mathcal{T}_H . The variational problems associated to (12)-(13) determine an algebraic problem in the vectors p^H, C^H that are defined respectively by the values of p^{ϵ} and C^{ϵ} in the macro-nodes of the partition \mathcal{T}_H . Consider a discretization in time $\{t_n\}$ with time step Δ_t , we apply as first the Backward Euler method in the interval $[t_{n-1}, t_n]$ to the macro finite element discretization of the parabolic equation (13). Therefore we have that, known $C^{H,n-1}$ and $p^{H,n-1}$ that are respectively the approximation at time t_{n-1} of C^H and p^H , the numerical solution $C^{H,n}$ is obtained by solving

$$(M_1 + \Delta_t A_C)C^{H,n} = M_1 C^{H,n-1} \text{ with } A_C = B_{\nabla p} + D_{\nabla p} + F_{D^{\epsilon}} + G_{D^{\epsilon}} - M_{\beta(1-C^{H,n-1})}$$
(24)

where $B_{\nabla p} = M_{p^{H,n-1},b}$ with $b = \left(\sum_{i=1}^{2} \frac{\partial A_i}{\partial x_i} \cdot \nabla \phi_m\right)_m$ and $D_{\nabla p} = ((d \cdot \nabla \phi_k)\phi_l)_{k,l}$ with $d = p^{H,n-1} \cdot (A\nabla \phi_m)_m$.

After computing $C^{H,n}$ using (24), we get $p^{H,n}$ by solving the macro finite element discretization of (13) at time t_n

$$(F_1 + G_1)p^{H,n} = -(F_{E^{\epsilon}} + G_{E^{\epsilon}})C^{H,n} + M_{\alpha}(1 - C^{H,n}).$$
(25)

We remark that the linear operators $F_a(u, v) = \int a(x)u \sum_{i=1}^2 \frac{\partial A_i^{\epsilon}}{\partial x_i} \nabla v dx$ and $D_{\nabla p}(u, v) = (d \cdot \nabla u)v$ associated to the matrices F_a and $D_{\nabla p}$ in (24)-(25) are not symmetric. In order to have symmetric operators in the first members of

matrices F_a and $D_{\nabla p}$ in (24)-(25) are not symmetric. In order to have symmetric operators in the first members of (24)-(25), and apply then the technique described in Paragraph 4.1, we modify system (24)-(25) into

$$(M_1 + \Delta_t \widetilde{A}_C)C^{H,n} = (M_1 + \Delta_t \widetilde{B}_C)C^{H,n-1}$$
(26)

$$(F_1 + F_1^T + G_1)p^{H,n} = -(F_{E^{\epsilon}} + G_{E^{\epsilon}})C^{H,n} + M_{\alpha}(1 - C^{H,n-1}) + F_1^T p^{H,n-1}$$
(27)

where $\widetilde{A_C} = B_{\nabla p} + D_{\nabla p} + D_{\nabla p}^T + F_{D^{\epsilon}} + F_{D^{\epsilon}}^T + G_{D^{\epsilon}} - M_{\beta(1-C^{\epsilon})}$ and $\widetilde{B_C} = F_{D^{\epsilon}}^T + D_{\nabla p}^T$. We obtain (26) by adding $\Delta_t(F_{D^{\epsilon}}^T + D_{\nabla p}^T)C^{H,n+1}$ and $\Delta_t(F_{D^{\epsilon}}^T + D_{\nabla p}^T)C^{H,n}$ respectively to the first and second member of (24). Equation (27) is instead obtained by adding $F_1^T p^{H,n}$ and $F_1^T p^{H,n-1}$ respectively to the first and second member of (25). We have now that the first member of equations in the system (26)-(27) have symmetric operators. We observe also that system (26)-(27) is equivalent to (24)-(25) when a sufficient small Δ_t is used.

5. Numerical Results

In this section we describe the evolution of two ACF in the colon by solving the numerical system (26)-(27) with $\epsilon = 5e - 05$ and with homogeneous boundary conditions for both p^H and C^H . We have implemented the numerical procedure, described in the previous section, using MATLAB in a computer with an Intel Q9550 CPU (quad-core at 2.83GHz) with 3.77 GByte of total RAM memory. In the simulation we suppose that the two ACF are initially located in the region $\Omega = [-2, 2] \times [-1, 1]$ and that they have a uniform malignant cell density C = 0.9 (see the two regions colored by red in the first picture on the left of Figure 4). These conditions define the initial numerical solution $C^{H,0}$ of the system (26)-(27) that is solved at different time steps $t_n = t_{n-1} + \Delta_t$ with $\Delta_t = 5e - 03$. We use the proliferative coefficients $D_1 = 0.1$ and $D_2 = D_2^* = 0.2$, and a multiscale discretization with macro and micro finite elements (quadrilaterals) that have edges of size H = 0.125 and $h = \epsilon/4$, respectively. The numerical solution $C^{H,n}$ obtained at time $t_n = 0, 0.5, 1, 1.5, 2, 2.5$ are depicted in Figure 4. The maximum value of the associated density is shown in Table 1.



Fig. 4. Simulation of the evolution of two aberrant crypt foci and its abnormal cell density. The six pictures show, from left to right and top to bottom, the simulations obtained at time $t_n = 0, 0.5, 1, 1.5, 2, 2.5$ respectively. The colored bar on the right of each picture describes the density distribution in an interval that goes from zero, depicted in dark blue, to the maximum density depicted in red, see also Table 1.

We observe that as the time advances the density of the malignant cells decreases and becomes more uniformly distributed. At the final time of the simulation, t = 2.5 the two ACF join and form a unique ACF. Based on the results in Table 1 and in the Figures 1 and 2, we can say that the malignant cells propagate quickly with an high loss of density in the initial instants of time, when the two ACF are not in contact, and as the two ACF become closer the propagation of cells in the colon decrease and the density of the cells becomes more homogeneously distributed in Ω . In fact, we can deduce a loss of 75% of the maximum density in [0, 1] and a loss of 51% in [1, 2].

Table 1. Maximum density located in the centre of the ACF simulated

Table 1. Maximum density ideated in the centre of the field simulated						
Time t_n	0	0.5	1	1.5	2	2.5
$\max C^{H,n}$	0.900	0.399	0.223	0.149	0.109	0.085

6. Conclusions and future work

In this paper we have proposed a coupled multiscale model to describe the time evolution of the aberrant crypt foci in a region of the colon. 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. In particular we can model both the top-down and bottom-up theories for the dynamics of the colonic cells and also the interaction of normal with abnormal cells in a region of the colon, with milions of crypts. The multiscale method used allows to catch the high oscillations of the multiscale parameters, with a reduction of the computational time, compared to a single micro-scale model. In fact a single micro-scale code has a computational time that increases for a decreasing epsilon. Based on our simulations with $h = \epsilon/4$, it requires in each time-step 1727.2 and 3488.7 seconds for $\epsilon = 5e - 02$ and $\epsilon = 4e - 02$ respectively, whereas the FE-HMM approach has a computational time independent of ϵ , a time-step run requires only 729.7 seconds for H = 0.125.

The drawback of this multiscale method is the lackness of convergence results due to the complexity of the problem investigated. An analysis of the approximation error involves the study of the associated homogenized problem [29, 31, 32] and it will be studied in future.

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