

Partial Differential Equations and Homogenization for Simulating Aberrant Crypt Foci Dynamics

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Outline

- Brief introduction.
Colonic crypts and Aberrant Crypt Foci (ACF).
- Motivation and Main Goal.
Conventional endoscopy images.
- Description of the Heterogenous and Periodic Model.
Representation of the ACF evolution in the colon.
- Homogenized Model.
Heuristic procedure: two-scale asymptotic expansion.
- Existence of Solution of the Homogenized Model.
Fixed point argument.
- Numerical Results.
- Conclusions.

Aberrant Crypt Foci (ACF)

- ACF are clusters of aberrant (deviant from normal) crypts. ACF are thought to be the precursors of colorectal cancer.
- Crypts are small pits, which are compartments of cells, in the colon epithelium.

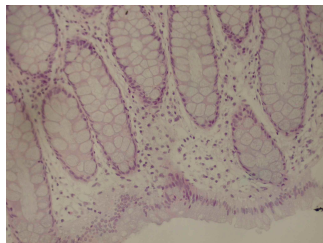
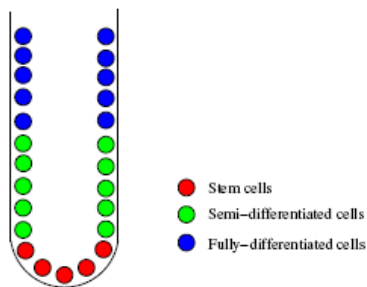


Figure: Schematic representation of a crypt (left) and microscopic image (Faculty of Medicine UC and HUC) (right)

Aberrant Crypt Foci - Colonoscopy

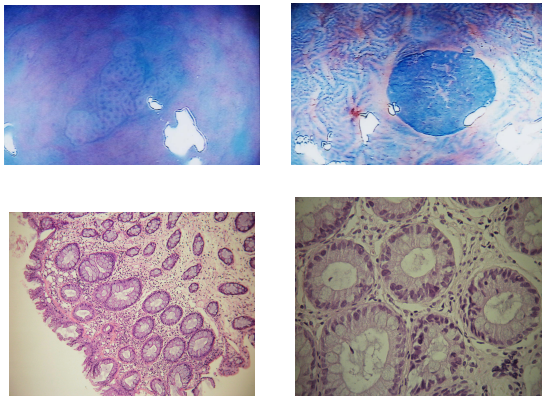


Figure: Medical endoscopic images (upper figures) and corresponding microscopic images (lower figures). Images - Faculty of Medicine, Univ. of Coimbra and HUC.

Aberrant Crypt Foci - Colonoscopy

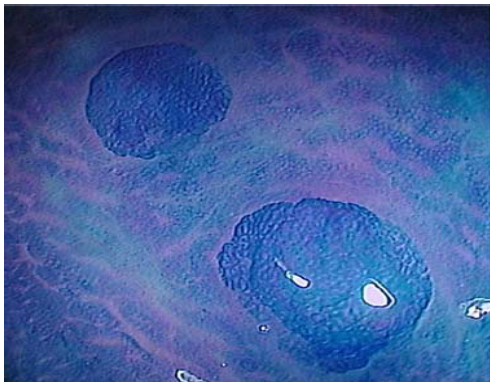


Figure: Colonoscopy image (obtained with a conventional endoscope), showing two big ACF in the human colon of a patient (Courtesy: Faculty of Medicine, University of Coimbra, Portugal).

Motivation and Main Goal

- To define a model for the **evolution of ACF**, *i.e.*, the evolution of groups of several aberrant crypts, as **observed in colonoscopy images**.
- Our goal is **to reproduce *in silico* the dynamics of ACF at the tissue level**, by using appropriate mathematical models and tools.
- Firstly, we propose a **cell dynamics model for describing the evolution of abnormal colonic cells in a single crypt**.
It is a PDE model that confines itself to two populations of colonic cells, normal and abnormal, and that is afterwards re-written only in terms of the abnormal cell population.
- Subsequently, **using the periodic structure of the colon**, we resort to **homogenization techniques** for simulating the evolution of ACF at the tissue level in a 2D framework.

3D Crypt \longrightarrow 2D Crypt

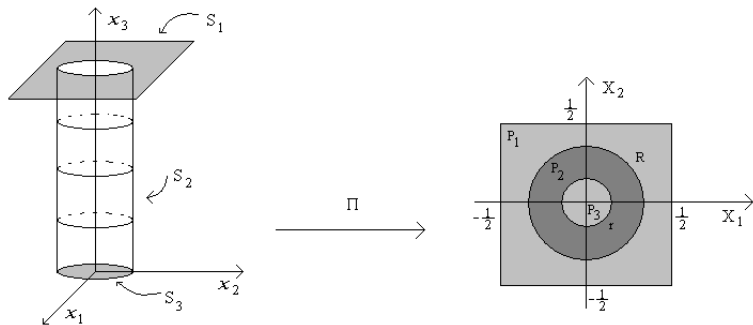


Figure: Left: Schematic representation of a general region $S = S_1 \cup S_2 \cup S_3$ in the colon, containing a 3D crypt and a small surrounding neighborhood (depicted as S_1). Right: The region S projected in a plane region $P = P_1 \cup P_2 \cup P_3$ using the operator Π , where $P_i := \Pi(S_i)$ for $i = 1, 2, 3$.

Cell Dynamics Model

System defined in $S \times]0, T] \subset \mathbb{R}^3 \times \mathbb{R}$

$$\begin{cases} \frac{\partial N}{\partial t} + \nabla \cdot (v_N N) = \nabla \cdot (D_N \nabla N) + \gamma N - \beta C(1 - C), \\ \frac{\partial C}{\partial t} + \nabla \cdot (v_C C) = \nabla \cdot (D_C \nabla C) + \beta C(1 - C). \end{cases}$$

- N and C - normal and abnormal cell densities : $N + C = 1$.
- D_N and D_C - diffusion coefficients of normal and abnormal cells.
- γ and β - birth rates of normal and abnormal cells.
- v_N and v_C - convective velocities of normal and abnormal cells.

Parabolic-elliptic system in the 3D crypt-time domain

Assumptions : $v_N = v_C = v$ and that the interior of the colonic crypt is "fluid-like", the cells obey to Darcy's law $v = -\mu \nabla p$, where p is an internal pressure and μ is a positive constant describing the viscous-like properties of the medium ($\mu = 1$).

- the unknown is the pair (C, p)
- C - abnormal cell density
- p - the pressure generated by the cells

$$\begin{cases} \frac{\partial C}{\partial t} - \nabla \cdot (\nabla p C) = \nabla \cdot (D_C \nabla C) + \beta C(1 - C), \\ -\Delta p = \nabla \cdot ((D_C - D_N) \nabla C) + \gamma(1 - C), \end{cases}$$

Parabolic-elliptic system in the 2D crypt-time domain

System redefined in $P \times]0, T] \subset \mathbb{R}^2 \times \mathbb{R}$

- the unknown is the pair (C^*, p^*)
- C^* - abnormal cell density
- p^* - the pressure generated by the cells
- D^* , E^* , β^* and γ^* stand for physiologic parameters
- A_{ij}^* , for $j, i = 1, 2$ are parameters resulting from the transformation from S into P

$$\begin{cases} \frac{\partial C^*}{\partial t} - \mathcal{A}_{ij}^* \frac{\partial}{\partial X_i} (C^* \frac{\partial p^*}{\partial X_j}) = \mathcal{A}_{ij}^* \frac{\partial}{\partial X_i} (D^* \frac{\partial C^*}{\partial X_j}) + \beta^* C^* (1 - C^*) \\ -\mathcal{A}_{ij}^* \frac{\partial^2 p^*}{\partial X_i \partial X_j} = \mathcal{A}_{ij}^* \frac{\partial}{\partial X_i} (E^* \frac{\partial C^*}{\partial X_j}) + \gamma^* (1 - C^*). \end{cases}$$

2D heterogeneous and periodic model

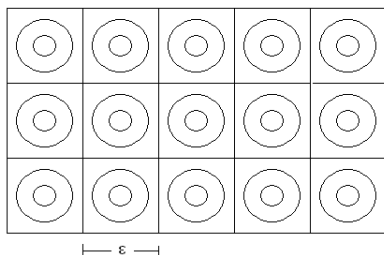


Figure: Two-dimensional top view of part of the colon wall, considered as an heterogeneous material with a periodic distribution of small heterogeneities, εP .

Inside each square, there is a crypt, containing colonic cells, represented by the two concentric circles. The region inside the square and outside the big circle is the region surrounding the crypt orifice.

2D heterogeneous and periodic model

We define periodic coefficients $A_{ij}^\varepsilon, D^\varepsilon, E^\varepsilon, \gamma^\varepsilon, \beta^\varepsilon$ as follows:

$$A_{ij}^\varepsilon(X) = A_{ij} \left(\frac{X}{\varepsilon} \right), \quad A_{ij} = \begin{cases} \mathcal{A}_{ij}^* & \text{in } P \\ \text{by periodicity (with period } P) & \text{elsewhere in } \mathbb{R}^2 \end{cases}$$

where $X = (X_1, X_2) \in \Omega \subset \mathbb{R}^2$. Analogous formulas are used for defining the other periodic physiologic coefficients $D^\varepsilon, E^\varepsilon, \gamma^\varepsilon, \beta^\varepsilon$.

$$\begin{cases} \frac{\partial C^\varepsilon}{\partial t} - A_{ij}^\varepsilon \frac{\partial}{\partial X_i} \left(C^\varepsilon \frac{\partial p^\varepsilon}{\partial X_j} \right) = A_{ij}^\varepsilon \frac{\partial}{\partial X_i} \left(D^\varepsilon \frac{\partial C^\varepsilon}{\partial X_j} \right) + \beta^\varepsilon C^\varepsilon (1 - C^\varepsilon) \\ -A_{ij}^\varepsilon \frac{\partial^2 p^\varepsilon}{\partial X_i \partial X_j} = A_{ij}^\varepsilon \frac{\partial}{\partial X_i} \left(E^\varepsilon \frac{\partial C^\varepsilon}{\partial X_j} \right) + \gamma^\varepsilon (1 - C^\varepsilon). \end{cases}$$

Homogenization technique

- In short the homogenization technique applied to the previous system, consists in considering a sequence of problems indexed by ε , and taking the **limit of this sequence**, when the small parameter ε **tends to zero**.
- Equivalently, the objective is to find the **limit (C^0, p^0)** of the sequence of solution pairs $\{(C^\varepsilon, p^\varepsilon)\}_{\varepsilon>0}$ of the system, in an appropriate topological space.
- The **homogenization model (or equivalently, the limit problem) will be the model for which (C^0, p^0) is the solution**.
- We use an heuristic procedure, that consists in forming a two-scale $(X, Y = X/\varepsilon)$ asymptotic expansion in ε for C^ε and p^ε defined by

$$C^\varepsilon(X, t) = \sum_{i=0}^{+\infty} \varepsilon^i C^i(X, Y, t) \quad \text{and} \quad p^\varepsilon(X, t) = \sum_{i=0}^{+\infty} \varepsilon^i p^i(X, Y, t)$$

Homogenized Model

The (formal) homogenization model, defined in $\Omega \times]0, T]$, is the following system whose unknown is the pair (C^0, p^0)

$$\begin{cases} \frac{\partial C^0}{\partial t} - \widetilde{A}_{ijm} \frac{\partial C^0}{\partial X_i} \frac{\partial p^0}{\partial X_j} = D \widetilde{A}_{ijm} \frac{\partial^2 C^0}{\partial X_i \partial X_j} + (\widetilde{\beta m} - \widetilde{\gamma m}) C^0 (1 - C^0) \\ - \widetilde{A}_{ijm} \frac{\partial^2 p^0}{\partial X_i \partial X_j} = \widetilde{\gamma m} (1 - C^0) \end{cases}$$

Theorem (Existence) - Let Ω an open and bounded domain in \mathbb{R}^2 with boundary $\partial\Omega$ regular enough, T a fixed positive real number and $(\widetilde{\gamma m}), (\widetilde{\beta m} - \widetilde{\gamma m})$ sufficiently small. Then, the homogenization model has a solution (p^0, C^0) such that $p^0 \in C^{\frac{\alpha}{2}}([0, T]; C^{1,\alpha}(\overline{\Omega}))$ and $C^0 \in C^\alpha(\overline{\Omega} \times [0, T])$.

Coefficients

By using Fredholm alternative, $m : P \rightarrow \mathbb{R}$ is the unique solution of

$$\left\{ \begin{array}{l} -\frac{\partial^2(A_{ij}m)}{\partial Y_i \partial Y_j} = 0, \\ \text{with } m \text{ } P\text{-periodic, } m > 0, \int_P m dY = 1. \end{array} \right.$$

$\widetilde{A_{ij}m} = \int_P A_{ij}m dY$ is the average of $A_{ij}m$ in P .

$$\widetilde{\gamma m} = \int_P \gamma m dY, \quad \widetilde{\beta m} = \int_P \beta m dY.$$

Proof [Existence Theorem]

- Based on Schauder's fixed point theorem.
- Appropriate norms in function spaces.
- Existence and regularity properties for:
 - The semilinear parabolic problem
[A. Friedman. *Partial differential equations of parabolic type*. Prentice-Hall, Englewood Cliffs, NJ., 1964].
 - Elliptic problem
[C. V. Pao. *Nonlinear parabolic and elliptic equations*. Plenum Press, New York, 1992].
- The operator $S : B_M(0) \rightarrow B_M(0)$, defined as $S = Q \circ G \circ D \circ I \circ E$ verifies Schauder's fixed point theorem.

Operator $S = Q \circ G \circ D \circ I \circ E$

$$E : \begin{array}{l} B_M(0) \subset C^\alpha(\bar{\Omega}_T) \\ C \end{array} \longrightarrow \begin{array}{l} C^{\frac{\alpha}{2}}([0, T]; W^{2,q}(\Omega)) \\ p \text{ (solution of the elliptic problem)} \end{array}$$

$$\|u\|_{C^\alpha(\bar{\Omega}_T)} = \sup_{(X,t) \in \bar{\Omega}_T} |u(X,t)| + \sup_{(X,t),(\xi,\tau) \in \bar{\Omega}_T} \frac{|u(X,t) - u(\xi,\tau)|}{(|t - \tau| + |X - \xi|^2)^{\frac{\alpha}{2}}}$$

$$I : \begin{array}{l} C^{\frac{\alpha}{2}}([0, T]; W^{2,q}(\Omega)) \\ p = E(C) \end{array} \longrightarrow \begin{array}{l} C^{\frac{\alpha}{2}}([0, T]; C^{1,\alpha}(\bar{\Omega})) \\ p \text{ (Sobolev imdedding)} \end{array}$$

$$D : \begin{array}{l} C^{\frac{\alpha}{2}}([0, T]; C^{1,\alpha}(\bar{\Omega})) \\ p \end{array} \longrightarrow \begin{array}{l} \in H^{1+\alpha,\alpha}(\bar{\Omega}_T) \\ \hat{p} \end{array}$$

Operator $S = Q \circ G \circ D \circ I \circ E$

$$G : H^{1+\alpha,\alpha}(\overline{\Omega}_T) \longrightarrow (C^\alpha(\overline{\Omega}_T))^2$$
$$\hat{p} \longmapsto \nabla \hat{p} = \left(\frac{\partial \hat{p}}{\partial X_1}, \frac{\partial \hat{p}}{\partial X_2} \right).$$

$$Q : (C^\alpha(\overline{\Omega}_T))^2 \longrightarrow \in C^\alpha(\overline{\Omega}_T)$$
$$\nabla \hat{p} \longmapsto C \quad (\text{solution of the parabolic problem})$$

[For $Q : (\widetilde{\gamma}m), (\widetilde{\beta}m - \widetilde{\gamma}m)$ small enough].

Numerical solution of the homogenization model

- Compute \mathbf{p}^0 the approximation of the pressure at time $t = 0$, by using $\tilde{G}_m \mathbf{p}^0 = \tilde{\gamma} \tilde{m} M (\mathbf{1} - \mathbf{C}^0)$, and set $n = 0$.

- While $t_n < T$

- 1 Build the matrix $\tilde{D}_{m, \nabla p}$, for \mathbf{p}^n , i.e

$$(\tilde{D}_{m, \nabla p})_{l, k} := \sum_s p_s^n \int_{\Omega} \nabla \varphi_l \cdot \tilde{A} m \nabla \varphi_s \varphi_k dX_1 dX_2.$$

- 2 Compute \mathbf{C}^{n+1} using the backward Euler method with $\tilde{D}_{m, \nabla p}$ computed in the previous step 1, i.e

$$\left(M + \Delta t \left(-\tilde{D}_{m, \nabla p}^T + \tilde{G}_{m, D} - M_{\tilde{\beta} m - \tilde{\gamma} \tilde{m}} (\mathbf{1} - \mathbf{C}^n) \right) \right) \mathbf{C}^{n+1} = M \mathbf{C}^n.$$

- 3 Compute \mathbf{p}^{n+1} using $\tilde{G}_m \mathbf{p}^{n+1} = \tilde{\gamma} \tilde{m} M (\mathbf{1} - \mathbf{C}^{n+1})$.

- 4 Increment n , that is $n = n + 1$, and go to step 1.

- Stop when $t_n = T$.

Parameters - Proliferative and Diffusion coefficients

$$\gamma(x_3) = \begin{cases} \tau_\gamma(x_3 - 2/3L)^2 & \text{if } x_3 \leq \frac{2}{3}L \\ 0 & \text{elsewhere} \end{cases}$$

$$\beta(x_3) = \begin{cases} \tau_{\beta_1}(x_3 - 2/3L)^2 + \beta_2 & \text{if } x_3 \leq \frac{2}{3}L \\ \beta_2 & \text{elsewhere} \end{cases}$$

$$D_N = 0.1$$

$$D_C = 0.1$$

[Qualitative behavior of normal colonic cells : they have a high proliferation at the bottom of the crypt (where $x_3 = 0$) that decreases going upwards in direction of the orifice (where $x_3 = L$) along the crypt axis with respect x_3 .]

Heterogeneous Periodic Model / Homogenized model

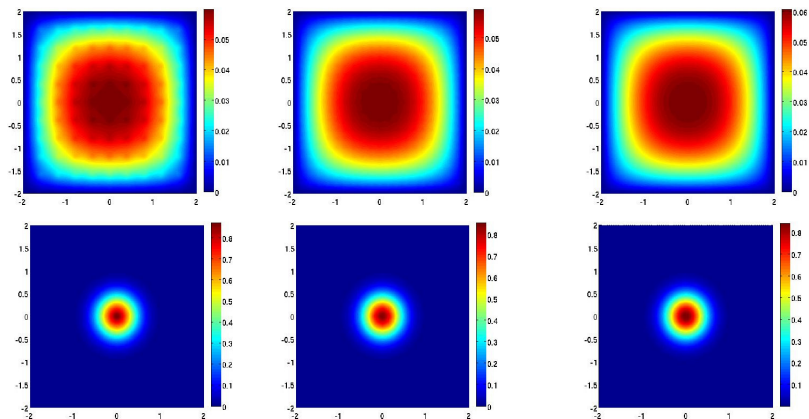


Figure: Left and middle columns: Pressure p^ϵ (top) and cell density C^ϵ (bottom) for $\epsilon = 0.4$ (100 crypts) and $\epsilon = 0.2$ (400 crypts), respectively. Right column: Homogenized pressure p^0 (top) and cell density C^0 (bottom). Time $t = 0.05$.

Relative errors between the heterogeneous and homogenized solutions - $(p^\varepsilon, C^\varepsilon)$ and (p^0, C^0)

$\ p^\varepsilon - p^0\ _2 / \ p^0\ _2$	$\varepsilon = 8e - 01$	$\varepsilon = 4e - 01$	$\varepsilon = 2e - 01$	$\varepsilon = 1e - 01$
t=1e-02	5.6720e-02	3.2261e-02	2.9908e-02	1.8665e-02
t=3e-02	5.6624e-02	3.1586e-02	2.9112e-02	1.7835e-02
t=5e-02	5.6560e-02	3.0886e-02	2.8282e-02	1.6983e-02

$\ C^\varepsilon - C^0\ _2 / \ C^0\ _2$	$\varepsilon = 8e - 01$	$\varepsilon = 4e - 01$	$\varepsilon = 2e - 01$	$\varepsilon = 1e - 01$
t=1e-02	5.9151e-03	5.6067e-03	5.0236e-03	4.4482e-03
t=3e-02	1.68321e-02	1.6036e-02	1.3912e-02	1.2729e-02
t=5e-02	2.6861e-02	2.5810e-02	2.2391e-02	2.1140e-02

Relative Errors for pressure and cell density in L^2 norm at times 0.01, 0.03, 0.05 with space step size $h = 5e - 03$ and time step size $\Delta t = 5e - 03$.

Conclusions and Outlook

- It is proposed an **homogenization model**, for **simulating the ACF spread and dynamics**, with the goal of reproducing *in silico*, what is observed in **conventional colonoscopy images**.
- This is a macro-model that represents the evolution of ACF at the surface of the colon, by **using the information of the cell dynamics in the crypts**.
- The **advantage of this homogenization model** is the possibility to perform experiments *in silico*, that represent simulations of the ACF evolution at the tissue level, starting with an arbitrary density (small or big) of abnormal cells that can be located in an arbitrary colon region: inside a single crypt or in several crypts, adjacent or not, or outside the crypts.

References

- Isabel N. Figueiredo, Carlos Leal, Giuseppe Romanazzi, Bjorn Engquist:
An Homogenization Model for Aberrant Crypt Foci,
ARXIV:1405.1386 [MATH.AP]
submitted, 2014.
- Isabel N. Figueiredo, Carlos Leal, Giuseppe Romanazzi, Bjorn Engquist,
Pedro N. Figueiredo:
**A convection-diffusion-shape model for aberrant colonic crypt
morphogenesis**,
COMPUTING AND VISUALIZATION IN SCIENCE
14, 4 (2011) 157-166.
- Isabel N. Figueiredo, Carlos Leal:
Physiologic parameter estimation using inverse problems,
SIAM JOURNAL ON APPLIED MATHEMATICS
73(3), (2013) 1164 - 1182.

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