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Modeling and Simulating Colonic Cell Renewal Disruption

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Abstract

Colorectal cancer is believed to be initiated as a consequence of several genetic mutations in colonic cells. Colon epithelium is densely perforated by small holes (called crypts) wherein a strong cellular activity occurs. Aberrant Crypt Foci (ACF) are one of the first manifestations of the carcinogenesis process. In this paper we summarize different models, that have been recently proposed, for simulating and predicting the evolution of ACF. In all these models, it is assumed that the dynamics of colonic cells is characterized by a transport/diffusion equation coupled with an elliptic type equation, and involving some physiological parameters, as the birth and death rates of proliferative cells. First, a model for the cell dynamics in a single crypt is described. This model yields crypt fission in which a crypt follows a process of splitting due to an increase of the birth rate of proliferative cells. This reproduces a morphological pattern similar to that observed in medical images. The second model, here presented, is used to estimate the birth rate of proliferative cells along the colonic crypt wall. It is an inverse problem formulated as a PDE-constrained optimization model. Finally, by appropriately extending, to the entire colon, the above mentioned cell dynamics model, a periodic two-dimensional model is obtained for simulating the ACF appearance. To solve this last model two different approaches are applied and compared : one relies on heterogeneous multi-scale methods and the other on homogenization techniques.

Key words: Convection-diffusion, Cell Dynamics, Colonic Crypt, Fixed-Point Theorem, Homogenization, Multi-Scale Methods
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Colorectal cancer is one of the most common types of cancer that has a high rate of death, in the Western World [1]. It is generally accepted that colorectal cancer has its origin in

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genetic mutations in colonic cells. Due to the large period of time elapsed between genetic mutations in colonic cells and the appearance of carcinoma (20-40 years according to [2]), it is possible to prevent the formation of carcinomas through an early detection of adenomas. The carcinogenesis process can be in fact stopped by the identification and removal of adenomas that otherwise could develop further into carcinomas. One of the first manifestations of colorectal cancer, detectable by conventional colonoscopy, is the appearance of the so-called Aberrant Crypt Foci (ACF)[3]. These are clusters of abnormal crypts (crypts are small cavities, in the colonic epithelium, containing the colonic cells) that present an abnormal morphology. ACF can be detected in colonoscopy, by the instillation of a dye. In fact, it is known that a few minutes after the instillation ACF become darker than normal crypts. There is no scientific agreement about the ACF morphogenesis. In the top-down theory, the appearance of abnormal cells occurs in the mucosa surface and afterwards they spread laterally and inside the crypts [4]. Instead, in the bottom-up theory, abnormal cells appear first in the bottom of the crypt, where they are prone to accumulate genetic alterations due to high birth rate, and after they migrate to the crypt orifice [5]. For a review of ACF and colorectal cancer medical analysis the reader can refer to [6, 7].

This paper presents a brief summary of our recent results, concerning the modeling and simulation of ACF morphogenesis (for a detailed explanation we refer to [8, 9, 10, 11]).

In [8] it is proposed a hybrid convection-diffusion-shape model, that simulates and predicts aberrant colonic crypt morphogenesis, similar to that observed in medical images. [12, 13, 5]. This model shows crypt fission, where a single crypt follows a subdivision process that starts at the bottom of the crypt, when there is an higher proliferative birth rate than that observed in normal crypts. The overall model couples the cell movement and proliferation equations with the crypt geometry. It relies on classical continuum transport/mass conservation laws and the changes in the crypt shape are driven by the pressure exerted by the cells on the crypt wall. This pressure is related to the cell velocity by a Darcy-type law. Numerical simulations are performed and comparisons with medical results are discussed.

In [9] a cell crypt based parameter estimation model is proposed. It is assumed that the cellular kinetics, occurring inside a single crypt, is governed by the convection-diffusion-shape model introduced in [8]. This latter involves some important physiologic parameters, as the birth and death rate of proliferative cells, for which only qualitative information is available in the literature. These parameters have a crucial role in ACF dynamics and evolution. By resolving an inverse problem (that minimizes the misfit between two proliferative cell densities: one observed and the other predicted by the model), we estimate the birth rate of proliferative cells (considered as a parameter field), along the colonic crypt wall. The location where the birth rate deviates from normal qualitative values can then be determined, and used for further clinical research and better understanding of the abnormal process leading to the increase or decrease of proliferative cells, and the emergence of ACF.

In [10] a multiscale model for aberrant crypt foci is presented. Starting from a three-

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dimensional single crypt, we perform its projection into a plane and then build a model in which the colon is a two-dimensional structure with crypts periodically distributed therein. Inside each crypt, 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, as described in [8]. 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 the multiscale model, it is used a technique based on heterogeneous multiscale methods (see for example [14]). 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 local 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.

In [11] an homogenization model is described and used to represent the cellular dynamics in the colon epithelium, with the goal of simulating and predicting, *in silico*, the spread and evolution of ACF, as it can be observed in colonoscopy. By assuming that the colon is an heterogeneous media, exhibiting a periodic distribution of very small cavities (the crypts), the periodic model, introduced in [10], is adopted for describing the ACF cell-dynamics in a two-dimensional setting. Then, to this periodic model, homogenization techniques are applied, to find a simpler model, whose solution symbolizes the averaged behavior of ACF. Some theoretical results concerning the existence of solution of the homogenized model are proven, applying a fixed point theorem. Numerical results showing the convergence of the periodic model to the homogenized one are also presented.

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