Partial Differential Equations and Homogenization for Simulating Aberrant Crypt Foci Dynamics [1]

Isabel Narra Figueiredo, Carlos Leal, Giuseppe Romanazzi
Dep. of Mathematics, University of Coimbra, Portugal.
isabelf@mat.uc.pt, carlosl@mat.uc.pt, roman@mat.uc.pt

Björn Engquist
Dep. of Mathematics and ICES, University of Texas at Austin, USA.
engquist@ices.utexas.edu

Abstract

The human colon epithelium is characterized by millions of very small pits, called crypts. Each crypt is a compartment containing different types of cells. In normal human colonic crypts, the cells renew completely each 5-6 days, through an harmonious and ordered procedure which includes the proliferation of cells, their migration along the crypt wall towards the top and their apoptosis, as they reach the orifice of the crypt. Colorectal carcinoma occurs as a consequence of several genetic mutations in normal colonic mucosa, determining phenotypic modifications with biological and morphologic consequences [1]. Those modifications lead to dysfunction of the cellular process and cause loss of homeostasis in colonic crypts.

It is believed that aberrant crypt foci (ACF) are the precursors of colon cancer [2]. These are clusters of crypts, that present an abnormal morphology, because they contain cells with a deviant behavior with respect to the normal ones. ACF can be detected *in vivo* in conventional colonoscopy, by the instillation of a dye. In fact, it is known that a few minutes after the instillation ACF stain 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 [3]. 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 cellular proliferation rate, and after they migrate to the crypt orifice [4].

[1]This work was partially supported by the project PTDC/MATNAN/0593/2012 and also by CMUC and FCT (Portugal) through European program COMPETE/ FEDER and project PEst-C/MAT/UI0324/2011.

We propose a cell dynamics model, based on homogenization techniques, for simulating *in silico* the evolution of ACF (see [5]).

The colon is modeled as an heterogeneous two-dimensional media perforated by crypts, that are periodically distributed. The model consists of a system coupling a parabolic and an elliptic equation, whose unknowns are respectively, the density of abnormal cells and the pressure generated by the cell proliferation. We note that we assume that these abnormal cells have the property to proliferate not only inside the crypt as done by normal cells, but also outside the crypt. This property is believed to be responsible for abnormal cells to invade neighbor crypts and can induce crypt fission and the formation of an adenoma [1, 6]. Then, to the heterogenous periodic model, homogenization techniques are applied, to find a simpler model, whose solution symbolizes the averaged behavior of ACF at the tissue level. We emphasize that with the homogenization technique we can perceive alterations at the surface of the colon epithelium, by using the information of what happens inside the crypts at the cellular level. 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 heterogeneous periodic model to the homogenized one are also presented.

Keywords: Homogenization, Convection-Diffusion Equations, Cell Dynamics.

References

[1] P. Figueiredo, M. Donato, M. Urbano, H. Goulão, H. Gouveia, C. Sofia, M. Leitão, and Diniz Freitas. Aberrant crypt foci: endoscopic assessment and cell kinetics characterization. International Journal of Colorectal Disease, 24(4):441–450, 2009.

[2] R. P. Bird and C. K. Good. The significance of aberrant crypt foci in understanding the pathogenesis of colon cancer. Toxicology Letters, 112-113:395–402, 2000.

[3] I-M. Shih et al. Top-down morphogenesis of colorectal tumors. Proceedings of the National Academy of Sciences of the United States, 98(5):2640–2645, 2001.

[4] S. L. Preston et al. Bottom-up histogenesis of colorectal adenomas: Origin in the monocryptal adenoma and initial expansion by crypt fission. Cancer Research, 63:3819–3825, 2003.

[5] Isabel N. Figueiredo, Carlos Leal, Giuseppe Romanazzi, Bjorn Engquist. An homogenization model for aberrant crypt foci. arXiv:1405.1386 [math.AP], 2014.

[6] I. M. M. van Leeuwen, C. M. Edwards, M. Ilyas, and H. M. Byrne. Towards a multiscale model of colorectal cancer. World Journal of Gastroenterology, 13(9):1399–1407, 2007.