

## Chapter 3

# Modeling Colorectal Cancer: A Stability Analysis Approach

**Svetoslav Nikolov**

*University of Rostock, Germany & Institute of  
Mechanics and Biomechanics, Bulgaria*

**Mukhtar Ullah**

*University of Rostock, Germany*

**Momchil Nenov**

*Institute of Mechanics and Biomechanics,  
Bulgaria*

**Julio Vera Gonzalez**

*University of Rostock, Germany*

**Peter Raasch**

*University of Rostock, Germany*

**Olaf Wolkenhauer**

*University of Rostock, Germany*

## ABSTRACT

*Mathematical modeling is increasingly used to improve our understanding of colorectal cancer. In the first part of this chapter, the authors give a review of systems biology approaches to investigate colorectal cancer. In the second part, the mathematical model proposed by Johnston et al. (2007) is expanded to include time delays and analysed for its stability. For both models, the original and the extended version, the authors obtain the necessary and sufficient conditions for stability. This is confirmed by numerical simulations. Thus, some new mathematical and biological results are obtained.*

## INTRODUCTION

The prevailing view has been that cancer is a disease related to modifications of the DNA, particularly mutations. Colorectal cancer provides an example in which it has become clear that this phenomenon emerges across various level of organisation, from molecular events, to the cell-cell interactions to tissue organisation. At the level of an organ or the organism, cancer represents the

collapse of cooperation between millions of cells (Wodarz & Komarova, 2005). The prevailing view has been that cancer is initiated and progresses through sequential accumulation of mutations, i.e. through clonal evolution and successive phenotypic stages (Bernards & Weinberg, 2002; Siegmund, Marjoram, Tavaré, & Shibata, 2009). A system, where these mechanisms are understood in considerable detail is colorectal cancer (Sjoberg, et al., 2006; Walther, et al., 2009; Wodarz & Komarova, 2005).

DOI: 10.4018/978-1-4666-2506-8.ch003

Recent studies of Colorectal Cancer (CRC) show that it remains a major health risk with over one million cases worldwide and a disease-specific mortality of approximately 33% in the developed world (Wolpin & Mazer, 2008; Walther, et al., 2009). For now, it is not clear why some patients respond to therapy and others do not, and why some patients relapse, whereas others do not. Based on current investigations, it appears that the CRC consists of an uncontrolled growth of abnormal cells in that part of the intestine (Boursi & Alber, 2007; Stein & Schlag, 2007). It is a multistep process, consisting of several genetic alterations, that alters the protein milieu of the cell and drives it to malignant transformation (Sjoblom, et al., 2006).

As indicated by its name, CRC is a cancer that affects the colon or the rectum. The colon consists of many microscopic structures called crypts. At the base of the crypt are located stem cells, which are undifferentiated cells. They can keep dividing and differentiate to epithelial cells. The differentiating cells travel up the crypt, perform their function, and die by apoptosis after about a week (Siegmund, et al., 2009; Wolpin & Mazer, 2008; Wodarz & Komarova, 2005). The epithelial cells are relatively short lived, which is why stem cell division has to give rise to new differentiated cells continuously in order to replenish the tissue. For this process to be in normal boundaries, it is crucial that the differentiated cells die by apoptosis. If the death of these cells fails, then a dysplastic crypt appears due to the accumulation of transformed cells around the crypt (formation of a polyp called adenoma). Recent studies of the multi-stage progression of CRC indicate that dysplastic crypt is the first stage of this disease (Kinzler & Vogelstein, 1998; Wodarz & Komarova, 2005). On the other hand, one of the molecular causes of CRC emergence and progression is a dysfunction in the *Wnt* signaling pathway, usually involving the tumor suppressor APC (Adenomatous Polyposis Coli) (Markowitz & Bertagnolli, 2009). It is well

known that causation is complex and can involve several mutations and depends on the interaction between the different components of the pathway.

When the *Wnt* receptor is not engaged,  $\beta$ -catenin is bound to a complex comprising two tumor suppressor proteins: APC and Axin. The kinases CKI and GSK3, which are also part of the complex, phosphorylate a set of Serine and Tyrosine residues in the amino-terminus of  $\beta$ -catenin. The resulting phosphorylated footprint recruits a  $\beta$ -TrCP-containing E3 ubiquitin ligase, which targets  $\beta$ -catenin for proteasomal degradation. In the presence of the *Wnt* ligand the kinase activity is inhibited allowing for the accumulation of  $\beta$ -catenin, which translocates into the nucleus and binds to the N-terminus of DNA-binding proteins Lef/Tcf which repress target genes in direct association with co-repressors such as Groucho, thereby converting them into transcriptional activators (Rattis, Voermans, & Reya, 2004). *Wnt* signaling therefore causes the transcription of the genes controlled by Tcf/Lef. Several pieces of evidence indicate that the *Wnt* pathway is the most important factor in controlling cell fate and differentiation in the epithelium of the intestine. Thus, *Wnt* signaling is required to preserve the crypt progenitor phenotype (Reya & Clevers, 2005) and inhibition of the *Wnt* receptor leads to a complete loss of crypts in mice models (Korinek, et al., 1998). The gradient of *Wnt* signaling in the crypt causes the dysfunction of cell proliferation and the ability to divide indefinitely and differentiation for the cells that travel upwards towards the surface. Consequently, mutations that lead to the stabilization and accumulation of  $\beta$ -catenin lead to the preservation of the progenitor phenotype and proliferation of undifferentiated cells.

The increasing risk of CRC with age suggests several stages of development caused by the accumulation of mutations. The earliest observed precursors of colon carcinoma are the Aberrant Crypt Foci (ACF) or microadenoma, which frequently show the loss of the APC gene. These can

21 more pages are available in the full version of this document, which may be purchased using the "Add to Cart" button on the publisher's webpage:

[www.igi-global.com/chapter/modeling-colorectal-cancer/71976](http://www.igi-global.com/chapter/modeling-colorectal-cancer/71976)

## Related Content

---

### Analysis and Quantification of Motion within the Cardiovascular System: Implications for the Mechanical Strain of Cardiovascular Structures

Spyretta Golemati, John Stoitsis and Konstantina S. Nikita (2009). *Handbook of Research on Advanced Techniques in Diagnostic Imaging and Biomedical Applications* (pp. 34-47).

[www.irma-international.org/chapter/analysis-quantification-motion-within-cardiovascular/19586](http://www.irma-international.org/chapter/analysis-quantification-motion-within-cardiovascular/19586)

### Can Activated Platelet Rich Plasma Combined with Adipose-Derived Stem Cells Be Used to Treat Skin Wrinkles?: A Mechanism Study

Phuc Van Pham, Loan Thi-Tung Dang, Nhung Hai Truong and Ngoc Kim Phan (2013). *Medical Advancements in Aging and Regenerative Technologies: Clinical Tools and Applications* (pp. 313-329).

[www.irma-international.org/chapter/can-activated-platelet-rich-plasma/71987](http://www.irma-international.org/chapter/can-activated-platelet-rich-plasma/71987)

### Analysis of Doppler Embolic Signals

Ana Leiria and M. M. M. Moura (2011). *Biomedical Diagnostics and Clinical Technologies: Applying High-Performance Cluster and Grid Computing* (pp. 249-277).

[www.irma-international.org/chapter/analysis-doppler-embolic-signals/46693](http://www.irma-international.org/chapter/analysis-doppler-embolic-signals/46693)

### Nursing Informatics History and its Contributions to Nursing Knowledge

Heather Strachan, Peter Murray and William Scott Erdley (2011). *Evidence-Based Practice in Nursing Informatics: Concepts and Applications* (pp. 78-97).

[www.irma-international.org/chapter/nursing-informatics-history-its-contributions/48924](http://www.irma-international.org/chapter/nursing-informatics-history-its-contributions/48924)

### Exploring Type-and-Identity-Based Proxy Re-Encryption Scheme to Securely Manage Personal Health Records

Luan Ibraimi, Qiang Tang, Pieter Hartel and Willem Jonker (2011). *Clinical Technologies: Concepts, Methodologies, Tools and Applications* (pp. 391-411).

[www.irma-international.org/chapter/exploring-type-identity-based-proxy/53597](http://www.irma-international.org/chapter/exploring-type-identity-based-proxy/53597)