Mathematical model of colitis-associated colon cancer

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HIGHLIGHTS

First ever mathematical model of colitis-associated colon cancer.
Multiscale approach connecting genes mutations to epithelium proliferation.
TP53 mutation and inflammed colonic mucosa contribute to cancer early development.
TP53 mutations play a primary role, followed by APC mutation.

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ABSTRACT

As a result of chronic inflammation of their colon, patients with ulcerative colitis or Crohn's disease are at risk of developing colon cancer. In this paper, we consider the progression of colitis-associated colon cancer. Unlike normal colon mucosa, the inflammed colon mucosa undergoes genetic mutations, affecting, in particular, tumor suppressors TP53 and adenomatous polyposis coli (APC) gene. We develop a mathematical model that involves these genes, under chronic inflammation, as well as NF-κB, β-catenin, MUC1 and MUC2. The model demonstrates that increased level of cells with TP53 mutations results in abnormal growth and proliferation of the epithelium; further increase in the epithelium proliferation results from additional APC mutations. The model may serve as a conceptual framework for further data-based study of the early stage of colon cancer.

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1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide (Ferlay et al., 2010). Several gene mutations have been identified to have occurred in the early stages of the disease, including APC, TP53, K-RAS and SMAD (Rowan et al., 2000). In this paper, we focus on colon cancer; more specifically, on colitis-associated colon cancer. Patients with ulcerative colitis or Crohn’s disease are at risk of developing CRC as a result of chronic inflammation of their colon. Unlike cells of the normal colon mucosa, cells of the inflammed colon mucosa undergo genetic alteration, such as TP53 mutation, prior to dysplasia or cancer (Ullman and Itzkowitz, 2011). Mutations inactivating the APC gene are found in 80% of all human colon cancer (Kwong and Dove, 2009). While APC inactivation is believed to occur early in sporadic colon cancer (i.e., before early adenoma), the inactivation of TP53 occurs much earlier in colitis-associated colon cancer (Ullman and Itzkowitz, 2011). Loss of heterozygosity at p53 in colitis-associated colon cancer correlates with malignant progression, and was detected in 63% high grade dysplasia prior to APC inactivation (Ullman and Itzkowitz, 2011). As reported in Ullman and Itzkowitz (2011), TP53 mutations were found in inflammed mucosa of more than 50% of patients who did not have cancer.

The colonic mucosa forms a barrier against bacterial infection of the colonic epithelium. It consists of several mucins, primarily mucin 2 (MUC2) which is released from the epical membrane, and mucin 1 (MUC1) which is a transmembrane mucin that lines the surface of epithelial cells. MUC1 and MUC2, mainly MUC2, suppress inflammation in the intestinal tract and inhibit the development of colon cancer by forming a protective barrier (Ueno et al., 2008; Velcich et al., 2002). MUC2 expression is upregulated by p53 protein (Ookawa et al., 2002). When TP53 is mutated, MUC2 is downregulated resulting in a process that leads...
to colon cancer. Indeed, chronic inflammation sets in, activating NF-κB which promotes cell growth and proliferation \cite{Karin and Greten, 2005; Kojima et al., 2004}. NF-κB also upregulates MUC1 and this further induces proliferation by stabilizing β-catenin \cite{Huang et al., 2003; Kufe, 2009; Yamamoto et al., 1997}. APC mutations are present frequently in mucin-depleted foci (MDF) through an inflammation-related pathway \cite{Femia et al., 2007; Yang et al., 2008}. APC mutation promotes inappropriate proliferation by upregulating intracellular inventory of active β-catenin available to cadherins \cite{Bienz and Hamada, 2004}.

In this paper, we develop a mathematical model of colitis-associated colon cancer. The model involves MUC1, MUC2, TP53, APC, NF-κB and β-catenin. Chronic inflammation is an important component of the model, although we model it just in a generic fashion by lumping together all its components. The goal of our mathematical model is to demonstrate in qualitative terms how mutations (inactivation) in TP53, possibly also followed by mutation in APC, result in tumor growth. The biological background of the model is shown schematically in Fig. 1, with more details in the section on “Mathematical Model”.

van Leeuwen et al. \cite{van Leeuwen et al., 2006} reviewed the theoretical models of crypt dynamics and CRC, up to the year 2005, including hereditary syndromes, molecular dynamics and genetic instability, and CRC treatment; they also presented (see also van Leeuwen et al., 2007) a stochastic model of APC inactivation. Johnston et al. \cite{Johnston et al., 2007} developed a mathematical model of population dynamics in colonic crypt and in CRC. A population dynamics approach which involves CRC progression through APC → K → RAS → TP53 mutations was presented by Michor et al. \cite{Michor et al., 2005} and Delitala and Lorenzi \cite{Delitala and Lorenzi}.

To the authors’ knowledge, the present paper is the first mathematical model of colitis-associated colon cancer. Although the genetic pathway leading to this carcinoma is quite complex, we believe that our simplified model is a useful first step to gain qualitative understanding of the early evolution of the disease.

2. Mathematical model

The mathematical model of colitis-associated CRC is based on the schematics of biological network shown in Fig. 1. The geometry of the colonic crypt is shown in Fig. 2A. In the mathematical model, we simplify this geometry, as shown in Fig. 2B, by resorting to a one-dimensional geometry where the apical membrane of the epithelium is a flat surface \(x = 0\), above which lies the mucus layer \((0 < x < x_{\top})\), and below which is the epithelium tissue \((-x_m < x < 0)\).

\[\text{A} \quad \text{Colonic Crypt} \]
\[\text{B} \quad \text{Mucus Layer} \]

Fig. 2. The geometry of the model. (A) The colonic crypt and basement membrane. (B) A simplified one-dimensional model. The line \(x = 0\) is the apical surface of the colonic crypt. The region \((0 < x < x_{\top})\) represents the colonic crypt occupied by MUC2. The region \((-x_m < x < 0)\) represents the colonic epithelium; in this region, there are goblet cells, enterocytes, neuroendocrine cells, and colonic stems cells \cite{Humphries and Wright, 2008}. For simplification, we lump all the cells together and, furthermore, assume that tumor invasion goes only downwards.
2.1. Notations

We introduce the following notation:

- \( p \) = level, or prevalence, of cells with TP53 mutation
- \( M_1(t) \) = concentration of MUC1 in tumor tissue (g/cm³)
- \( M_2(x,t) \) = concentration of MUC2 (g/cm³) in the region \( 0 < x < x_{\text{top}} \) above the apical membrane outside of the cells
- \( l(t) \) = level of inflammatory response in tumor tissue
- \( N(t) \) = concentration of active NF-κB (g/cm³) in tumor tissue
- \( B(t) \) = concentration of active β-catenin in tumor tissue (g/cm³)
- \( x_m(t) \) = thickness of tumor cells tissue (cm)

The variables satisfy a system of ordinary differential equations and the parameters of the system are given in Tables B1 and B2.

2.2. Mucins

MUC1 is a transmembrane mucin which lines the apical surface of epithelial cells and provides a protective barrier that can be upregulated to suppress inflammation caused by pathogenic bacteria (Linden et al., 2008; McGuckin et al., 2011). The expression of MUC1 is induced by inflammatory cytokines such as TNFα, IFNγ and IL-6 through NF-κB pathway (Saeland et al., 2012). The dynamic of the concentration of MUC1 is modeled as

\[
\frac{dM_1}{dt} = \lambda_{11} + \frac{\alpha N}{N+K_d} - \lambda_{12}M_1,
\]

where \( \lambda_{11} \) is the basal production rate of MUC1 and \( \lambda_{12} \) is the degradation rate of MUC1.

MUC2 is a major secreted mucin which is released from the apical membrane to the region above \( x = 0 \) and below same level \( x = x_{\text{top}} \). It is a protective gel that suppresses the inflammatory response (Velcich et al., 2002; Linden et al., 2008; Allen et al., 1998; Byrd and Bresalier, 2004). MUC2 is diffusive above the apical surface with a diffusion coefficient \( D_m \). We assume that the concentration of MUC2 satisfies a diffusion equation in the region \( 0 < x < x_{\text{top}} \).

\[
\frac{\partial M_2}{\partial x} = D_m \frac{\partial^2 M_2}{\partial x^2} - \lambda_{22}M_2,
\]

where \( \lambda_{22} \) is the degradation coefficient of MUC2.

MUC2 production is upregulated by NF-κB and TP53 so that the combined production rate is proportional to \( \lambda_{21}(p) + \beta N/(N+K_2) \) where \( \lambda_{21}(p) \) depends on TP53 in the following way: as the number of cells that developed TP53 mutation is increased, the parameter \( \lambda_{21}(p) \) is correspondingly decreased. We assume that this production rate results in a flux at the apical surface of the colon,

\[
\frac{\partial M_2}{\partial x} \bigg|_{x=0} = -\left( \lambda_{21}(p) + \beta \frac{N}{N+K_2} \right).
\]

We also assume that MUC2 does not diffuse beyond the edge \( x = x_{\text{top}} \), so that

\[
\frac{\partial M_2}{\partial x} \bigg|_{x=x_{\text{top}}} = 0.
\]

By integrating both sides of Eq. (2) from \( x=0 \) to \( x=x_{\text{top}} \) and using the flux conditions, we obtain

\[
\frac{d}{dt} \int_0^{x_{\text{top}}} M_2 dx = D_m \left( \lambda_{21}(p) + \beta \frac{N}{N+K_2} \right) - \lambda_{22} \int_0^{x_{\text{top}}} M_2 dx.
\]

2.3. Chronic inflammation

Chronic inflammation is not always in response to bacterial infection. The etiology of chronic inflammation includes autoimmune disease, viral or fungal infections, and other toxins. However, in the case of inflammatory bowel disease (ulcerative colitis and Crohn’s disease), the main cause and accelerator of chronic inflammation are the bacterial infection (Ullman and Itzkowitz, 2011; Aggarwal et al., 2006). When the mucosal layer is damaged, the opportunity of bacterial infection increases and the inflammatory response is upregulated. We assume that the level of inflammatory response per cell, \( I \), increases when the concentrations of MUC1 and MUC2 decrease, and take it to be

\[
l = (1-M_1/M_1-M_2/M_2)^+,
\]

where \( s^+ = s \) if \( s > 0 \) and \( s^+ = 0 \) if \( s \leq 0 \). The parameters \( \mu_1 \) and \( \mu_2 \) are the normalizing factors of \( M_1 \) and \( M_2 \), respectively.

2.4. NF-κB and β-catenin

NF-κB is activated by inflammatory cytokines during colitis-associated inflammation,

\[
\frac{dN}{dt} = \lambda_{31} \left( 1 + \frac{I}{K_b} \right) - \lambda_{32}N,
\]

where \( \lambda_{31} \) is the basal growth rate, \( \lambda_{32} \) is the deactivation rate and \( K_b \) is the normalizing factor of \( I \).

MUC1 cytoplasmic tail interacts with β-catenin and blocks the phosphorylation-dependent degradation of β-catenin. Overexpression of MUC1 increases stabilization of β-catenin (Huang et al., 2003). APC inactivation by chronic inflammation also reduces the APC-mediated β-catenin destruction (Bienz and Hamada, 2004). For simplicity, we assume that the effect of APC mutation on the degradation of β-catenin is proportional to the level of inflammatory response. The equation of β-catenin can then be written as follows:

\[
\frac{dB}{dt} = \frac{\lambda_{41}B}{(1+(M_1/M_1)+\frac{V_1}{1+\eta_A(I/K_{R_1})}) + \frac{V_2}{1+\eta_A(I/K_{R_2})}} - \lambda_{42}B,
\]

where \( \lambda_{41} \) is the basal production rate of β-catenin per cell, \( \lambda_{42} \) is the degradation coefficients of β-catenin in a natural turnover, and \( \eta_A \) is the parameter controlling the level of APC mutation(\( \eta_A = 0 \) if APC is not mutated). \( K_{R_1} \) and \( K_{R_2} \) are the normalizing factors of \( M_1 \) and \( I \), respectively.

2.5. Tumor cell

The tumor tissue consists of the extracellular matrix and several types of cells, including endothelial cells, macrophages, lymphocytes, fibroblasts, smooth muscle cells and, of course, (epithelial) cancer cells. Since the cancer cells are proliferating abnormally, the tumor tissue grows, and the cancer cells move with the growing tissue at some velocity \( V(x,t) \). We denote density of the cancer cells by \( C(x,t) \). Then, by conservation of
mass,
\[
\frac{\partial C}{\partial t} + \frac{\partial (VC)}{\partial x} = \lambda_c(B,N)C,
\]
proliferation
\[\text{(6)}\]
in \((-x_m < x < 0)\), where \(\lambda_c\) is the proliferation rate of cancer cells. The proliferation rate depends on the concentration of active NF-κB (Karlin and Greten, 2005; Kojima et al., 2004) and active β-catenin (Aust et al., 2001; Calvisi et al., 2004; Chen et al., 2008); we assume that NF-κB plays a somewhat larger role than β-catenin, and cancer cells do not proliferate if the sum of normalized \(B\) and \(N\) is less than a threshold \(K_c\), accordingly we take
\[
\lambda_c(B,N) = \lambda_{51} \frac{(0.8B/B_{ss} + N/N_{ss} - K_C)^+}{(0.8B/B_{ss} + N/N_{ss} - K_C)^+ + 1},
\]
where \(N_{ss}\) and \(B_{ss}\) are the steady state concentrations of NF-κB and β-catenin, respectively, in healthy tissue.

We assume for simplicity that the cells density in the tissue \((-x_m < x < 0)\) is a constant, \(C_0\), so that Eq. (6) becomes
\[
C_0 \frac{\partial V}{\partial x} = \lambda_c(B,N)C_0.
\]
Assuming also that the velocity at the top of the epithelium is zero, we get
\[
-V(-x_m) = \lambda_c(B,N)x_m.
\]
Hence the dynamic of \(x = -x_m\) is governed by the following equation,
\[
\frac{dx_m}{dt} = \lambda_c(B,N)x_m.
\]
Combining all the above equations, we have
\[
\frac{dM_1}{dt} = \lambda_{11} + \frac{\alpha N}{N + K_2} - \lambda_{12}M_1.
\]
\[\text{(11)}\]
\[
\frac{dM_2}{dt} = D_M \left( \frac{\lambda_{21}(p) + \beta N}{N + K_2} - \lambda_{22}M_2 \right),
\]
production by cells
\[\text{degradation}\]
\[\text{(12)}\]
\[
\frac{dN}{dt} = \lambda_{31} \left( 1 + \gamma \frac{(l/K_N)}{(l/K_N)+1} \right) - \lambda_{32}N.
\]
activation
\[\text{deactivation}\]
\[\text{(13)}\]
\[
\frac{dB}{dt} = \lambda_{41} \left( 1 + \frac{V_1}{1 + \frac{M_1}{K_B}} + \frac{v_2}{1 + \eta_A(l/K_B)} \right) B,
\]
production deactivation
\[\text{(14)}\]
\[
\frac{dx_m}{dt} = \lambda_c(B,N)x_m.
\]
\[\text{(15)}\]
with
\[I = (1 - M_1/\mu_1 - M_2/\mu_2)^+\]
\[\text{(16)}\]
and
\[
\lambda_c(B,N) = \lambda_{51} \frac{(0.8B/B_{ss} + N/N_{ss} - K_C)^+}{(0.8B/B_{ss} + N/N_{ss} - K_C)^+ + 1}.
\]
\[\text{(17)}\]

3. Simulations

The simulations described in this section were performed using the Matlab build-in solver ode23. The parameters used in the simulations were determined in Appendix A and are summarized in Tables B1 and B2.

Figs. 3–5 show how the thickness of the epithelium, \(x_m\), increases in time under mutations of TP53 and APC; time, along the horizontal axis, is measured in hours, and \(x_m\), along the vertical axis, is measured in cm.

Mutation in TP53 is represented by the parameter \(\lambda_{21}(p)\): as more cells undergo TP53 mutation, this parameter \(\lambda_{21}(p)\) decreases, and the thickness \(x_m = x_m(t)\) increases. Similarly, as more cells undergo APC mutation, the parameter \(\eta_A\) increases, and \(x_m\) still further increases.

In Fig. 3 we see, at different fixed values of \(\eta_A\), a dramatic increase in \(x_m\), as \(\lambda_{21}(p)\) decreases from 3.31 (low level of TP53 mutation).
mutations among the epithelial cells) to 0.662 (high level of TP53 mutations). Fig. 4 shows, at different fixed values of $\lambda_{21}^p$, an increase in $x_m$ as the parameter $\eta_A$ is increased from 0.48 (low level of APC mutation among the epithelial cells) to 2 (high level of APC mutations). We note that the increase in $x_m$ as a result of APC mutations is relatively mild compared with the increase resulting from TP53 mutations. This is consistent with the fact that in colitis-associated colon cancer, the initial mutation of TP53 plays a more major role than APC mutation.

In Fig. 5A, we plotted the thickness $x_m$ after 720 h as a function of the parameter $\lambda_{21}^p$ for different values of $\eta_A$; as $\lambda_{21}^p$ decreases (more TP53 mutations occurred among the cells), $x_m$ increases. For larger values of $\eta_A$ (more cells underwent also APC mutations), the level of $x_m$ is increased, although the relative increase, as $\eta_A$ increases, is rather mild.

On the other hand, Fig. 5B shows a much larger increase of $x_m$ after 720 h as $\lambda_{21}^p$ decreases from 3.31 (no TP53 mutation) to 0 (high level of TP53 mutations). The depth of the proliferating epithelium, $x_m$, is further increased with additional APC mutations, i.e., as $\eta_A$ increases so does the $x_m$-graph. This increase, however, is very mild when the level of TP53 mutation is small ($\lambda_{21}^p = 2.648, 3.31$) and it becomes more
pronounced when the level of TP53 mutations is high ($\lambda_21(p) = 0.0662$).

The simulations in Figs. 3–5 show that TP53 inactivation plays a major role in colitis-associated tumor growth, while APC inactivation plays only a secondary role, which is quite minor, unless the level of TP53 mutations among the epithelial cells has become large enough. This lends support to the hypothesis that in colitis-associated colon cancer, TP53 mutation plays more significant role than APC mutation, at least in the early stage of the disease.

4. Sensitivity analysis

Since the normalizing factors (i.e., $K_z$, $K_N$, $KB_1$, $KB_2$, $\mu_1$, $\mu_2$, $B ss$ and $N ss$) in the model were only roughly estimated, we performed sensitivity analysis to determine the robustness of the simulation results and effect of the parameters on $x_m$. We used the method of Partial Rank Correlation Coefficient (PRCC) (Marino et al., 2008) for our sensitivity analysis. We ran 5000 simulations in which the parameters were varied according to Latin hypercube sampling scheme with the ranges shown in Table B3. In all the simulations, $\eta_A = 1$ and $\lambda_21(p) = 0.662$. The results of the sensitivity analysis are summarized in Table B3. Fig. 6 shows the scatter plots of rank transformed $x_m$ at 720 h versus the rank transformed parameters with significant correlation; the title of each subplot shows its PRCC value and statistical significance.

We see that the only statistically significant PRCC values are $B ss$, $N ss$, $\mu_1$, $\mu_2$, $KB_1$, $KB_2$ and $KN$; among them, the parameters $B ss$, $N ss$ and $\mu_1$ have PRCC values larger than 0.5 in magnitude. The parameters $B ss$ and $N ss$ are negatively correlated to $x_m$, which is indeed natural: when these normalizing factors increase, the velocity $\lambda_{V}(B,N)$ of $x_m$ decreases. On the other hand, $\mu_1$ and $\mu_2$ are positively correlated to $x_m$; as they increase, the inflammation $I$ increases and so does $x_m$. Note that $\mu_2$ correlates more strongly to $x_m$ than $\mu_1$, indicating that MUC2 is more prominent than MUC1 in providing protective barrier against inflammation. Finally, according to Table B3 and Fig. 6, the other normalizing factors ($K_z$, $K_N$, $KB_1$, $KB_2$) as well as the other parameters do not affect $x_m$ appreciably.

5. Conclusion and discussion

Colorectal cancer is one of the most common types of cancer around the world. A significant number of colon cancer cases are associated with chronic inflammation resulting from ulcerative colitis or Crohn’s disease. This inflammation arises from the immune system response to bacterial infection, which occurs when the colonic mucosa undergoes genetic alterations. Such alterations can be traced to tumor suppressor gene TP53 which regulates MUC2 production. Other mutations may also subsequently occur, such as APC inactivation. Although APC is involved in a number of signaling pathways, here we consider its effect just in terms of its response to inflammation, where it plays only a secondary role.

Our model includes TP53, NF-κB and $\beta$-catenin, MUC1 and MUC2, and the level of chronic inflammation. We measure the degree of tumor cells proliferation by the combined levels of NF-κB and $\beta$-catenin. The simulations illustrate how increased level of TP53 mutation among colonic epithelial cells results in increased proliferation of the epithelium into the stroma. Mutations in APC in the context of colitis-associated colon cancer contributed only slightly to cells proliferation, as compared to TP53 mutations.

Our model is multi-scale: it includes processes that occur within cells, and, at the same time, it treats cells proliferation at the tissue level, showing increase in the thickness of the epithelium as a result of TP53 and APC mutations. The model is formulated by a system of differential equations. Most of the parameters have been determined from the literature, directly or indirectly, but a few parameters, especially the “normalizing
We shall take a degradation rate of MUC1 of $\lambda_{12} = (\ln(2)/16.5) h^{-1} = 1.17 \times 10^{-3} s^{-1}$ in Eq. (11).

$\lambda_{13}, K_1, \alpha$: To estimate $\lambda_{13}$ and $K_1$, we shall use the steady state values of MUC1 ($M_{1ss}$) and NF-κB ($N_{ss}$) for healthy colon and for tumor colon. For healthy tissue, $M_{1ss} = 0.5 - 2 g/cm^3$ (Agrawal et al., 1998); we take $M_{1ss} = 1.25 \times 10^{-6} g/cm^3$. Next, according to Hoffmann et al. (2002), the steady state concentration of NF-κB for healthy tissue is around $0.04 \mu M$ where $1 M = 1 Molar = 1 mol/L = 1 mol/dm^3$, 1 mol is the amount of a substance that contains as many entities as there are atoms in $12 g$ of $^{12}C$. Since the weight of NF-κB molecule is 60 kDa where 1 Da = $1 g/mol$ (1 Da is 1/12 of the rest mass of $^{12}C$), we get $N_{ss} = (0.04 \times 60)(\mu M \times kDa) = 2.4 \times (10^{-9} \times 10^9) g/cm^3 = 2.4 \times 10^{-6} g/cm^3$. In colon tumor, the concentration of MUC1 is 50% more than that of healthy tissue (Saeland et al., 2012) while the concentration of NF-κB is double that of healthy tissue (Kojima et al., 2004). Hence we get two steady state equations for solving $\lambda_{13}$ and $K_1$:}

$$\lambda_{13} + 2 \frac{N_{ss}}{N_{ss} + K_1} - \lambda_{12} M_{1ss} = 0, \quad (A.1)$$

$$\lambda_{13} + 2 \frac{N_{ss}}{2N_{ss} + K_1} - \lambda_{12}(1.5 M_{1ss}) = 0. \quad (A.2)$$

We shall take $K_1$ to be at least 10 times larger than $N_{ss}$. The effect of NF-κB on MUC1 production should be at least comparable to the production when there is no infection. Hence, the term $\alpha N_{ss}/(N_{ss} + K_1)$ should not be too small compared to $\lambda_{13}$; we take it to be $\alpha = 20\lambda_{13}$. Then, from Eqs. (A.1) and (A.2), we obtain $K_1 = 3.36 \times 10^{-5} g/cm^3$, $\lambda_{13} = 6.26 \times 10^{-12} g^-1/cm^3$ and $\alpha = 20 \lambda_{13} = 1.25 \times 10^{-16} g^-4/cm^3$.

$\lambda_{22}$: Estimates of the MUC2 turnover in the distal colon suggest a half-life of a few hours (Hansson, 2011); thus we assume that half life of MUC2 is around 3 h and the degradation rate coefficient of MUC2 in Eq. (12) is then $(\ln(2)/3) h^{-1} = 2.79 \times 10^{-3} s^{-1}$.

$D_{M2}$: The diffusion rate $D_{M2}$ of MUC2 in mucus layer is similar to that of human cervical mucin in water (Axelsson et al., 1998), which is $4.7 \times 10^{-8} cm^2/s$ (Sheehan and Carlstedt, 1984).

$K_{\alpha}, \beta, \lambda_{21}$: For healthy colon, the density of MUC2 is around $M_{2ss} = 1.3 g/cm^3$ (Aksoy et al., 1999) and the thickness of mucus layer is around $\lambda_{top} = 0.01 cm$ (Atuma et al., 2001; Corfield et al., 2001), so the steady state, $\bar{M}_{2ss}$, of total amount of MUC2 is $\int_{0}^{\lambda_{top}} M_{2ss} d\lambda = M_{2ss} \times \lambda_{top} = 1.3 \times 10^{-2} g/cm^2$. From the steady state equation of (12), we get

$$\lambda_{21}(p) + \beta \frac{N_{ss}}{N_{ss} + K_2} = \frac{\lambda_{22} \bar{M}_{2ss}}{D_M}. \quad (A.3)$$

We assume that the relative change of MUC2 in tumor colon is comparable to the increase in MUC1 concentration, so we take $\beta = 20\lambda_{21}(p)$ and $K_2 = K_1 = 3.36 \times 10^{-5} g/cm^3$ in Eq. (12). From Eq. (A.3), we then obtain $\lambda_{21}(p) = 3.31 g/cm^4$ for healthy tissue, and then $\beta = 20\lambda_{21}(p) = 66.15 g/cm^4$.

### A.2. Chronic inflammation

$\mu_1$ and $\mu_2$ are normalizing factors of $M_1$ and $\bar{M}_2$, respectively. We assume that MUC2 blocks inflammation better than MUC1 and take $\mu_1 = 10 M_{1ss} = 1.25 \times 10^{-5} g/cm^3$ and $\mu_2 = \bar{M}_{2ss} = 1.3 \times 10^{-2} g/cm^2$.

### A.3. NF-κB

$\lambda_{31}, \lambda_{32}$: As mentioned before, the steady state $N_{ss}$ of NF-κB in healthy tissue is $N_{ss} = 2.4 \times 10^{-6} g/cm^3$ (Hoffmann et al., 2002). This number equals to $\lambda_{31}/\lambda_{32}$ when $I = 0$ (no inflammation) in Eq. (13). On the other hand, the deactivation rate $\lambda_{32}$ of NF-κB is estimated by nuclear export rate (into the nuclear) of NF-κB which is equal to $\lambda_{32} = 8 \times 10^{-5} s^{-1}$ (Hoffmann et al., 2002). Hence $\lambda_{31} = N_{ss} \lambda_{32} = (2.4 \times 10^{-6} g/cm^3) \times (8 \times 10^{-5} g/cm^3) = 1.92 \times 10^{-10} g/cm^3$.

$K_\gamma$: Note, by (13), that $I$ decreases when $M_1$ and $M_2$ increase, and $K_\gamma$ is the normalizing factor of $I$. The range of $I$ is from 0 to 1, and we shall take $K_\gamma = 0.1$.

$\gamma$: From Eq. (13), the steady state concentration of NF-κB for tumor colon (1/$K_\gamma$ is large) is $(1 + \gamma)\lambda_{31}/\lambda_{32}$ whereas in healthy tissue it is $\lambda_{31}/\lambda_{32}$. Since the concentration of NF-κB in tumor colon is double that of healthy tissue (Kojima et al., 2004), we get $\gamma = 1$.

### A.4. β-catenin

$\lambda_{41}, \lambda_{42}$: In Murray et al. (2010), the production rate $\lambda_{41}$ and the degradation coefficient $\lambda_{42}$ of β-catenin in a natural-turnover (destruction-complex-independent manner) are $\lambda_{41} = 25.38 nM/h$ and $\lambda_{42} = 1.54 \times 10^{-2} h^{-1} = 4.28 \times 10^{-6} s^{-1}$, respectively. Since the weight of β-catenin is around 92 kDa, we get $\lambda_{41} = 92 \times 25.38 \times 10^{-12} kg/(cm^3 h) = 6.49 \times 10^{-10} g/(cm^3 s)$.

$K_{B1}, K_{B2}$: In Eq. (14), $K_{B1}$ is the normalizing factor of $M_1$, so we take it to be $K_{B1} = M_{1ss} = 1.25 \times 10^{-5} g/cm^3$. Similarly, we take $K_{B2} = K_{B1} = 0.1$.

$\nu_1, \nu_2$: APC mutation cells exhibit over 8-fold increased concentration of β-catenin (Austen et al., 2001; Murray et al., 2010). According to Eq. (14), $\nu_2$ should be larger than 7; we take $\nu_2 = 8$. In the abnormal tissue with no APC mutation, the fold change of β-catenin level is appreciably less than that in the tissue with APC mutation (Austen et al., 2001; Ninomiya et al., 2000); correspondingly we take $\nu_1 = \frac{\nu_2}{4} = 2$.

## A.5. Tumor cell

According to Eq. (14), for healthy tissue ($I = 0$), $B = (\lambda_{41}/\lambda_{42})(1 + \nu_1 + \nu_2/(1 + (M_{1ss}/K_{B2})))^{-1} = 1.37 \times 10^{-5} g/cm^3$. In Eq. (17), we take $N_{ss} = 2.4 \times 10^{-6} g/cm^3$.

For healthy colon, the proliferation rate $\lambda_c$ should be zero. In Eq. (17), $\lambda_c$ equals $\lambda_{51}(1.8 - K_c)/((1.8 - K_c)^+ + 1)$ for healthy colon, so $K_c$ has to be larger than 1.8; thus we take $K_c = 1.9$. It is difficult
Table B1
Parameters used in Eqs. (11) and (12).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Definition</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_{MUC1}$</td>
<td>$1.25 \times 10^{-6}$ g/cm$^3$</td>
<td>Steady state concentration of MUC1 for healthy tissue</td>
<td>Agrawal et al. (1998)</td>
</tr>
<tr>
<td>$\lambda_{MUC1}$</td>
<td>$6.26 \times 10^{-12}$ gs$^{-1}$/cm$^3$</td>
<td>Production parameter of MUC1</td>
<td>Estimated from Agrawal et al. (1998), Saeland et al. (2012), Hoffmann et al. (2002), Kojima et al. (2004)</td>
</tr>
<tr>
<td>$\lambda_{MUC2}$</td>
<td>$1.17 \times 10^{-5}$ s$^{-1}$</td>
<td>Degradation parameter of MUC1</td>
<td>Pimental et al. (1996)</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>$1.25 \times 10^{-10}$ gs$^{-1}$/cm$^3$</td>
<td>Upregulation rate parameter of MUC1 by NF-$\kappa$B</td>
<td>Estimated from Agrawal et al. (1998), Saeland et al. (2012), Hoffmann et al. (2002), Kojima et al. (2004)</td>
</tr>
<tr>
<td>$K_1$</td>
<td>$3.36 \times 10^{-3}$ g/cm$^3$</td>
<td>Upregulation parameter of MUC1 by NF-$\kappa$B</td>
<td>Estimated from Agrawal et al. (1998), Saeland et al. (2012), Hoffmann et al. (2002), Kojima et al. (2004)</td>
</tr>
</tbody>
</table>

Table B2
Parameters used in Eqs. (13)-(17).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Definition</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_{NF-\kappa}$</td>
<td>$2.4 \times 10^{-6}$ g/cm$^3$</td>
<td>Steady state concentration of NF-$\kappa$B for healthy tissue</td>
<td>Hoffmann et al. (2002)</td>
</tr>
<tr>
<td>$\lambda_{NF-\kappa}$</td>
<td>$1.92 \times 10^{-15}$ gs$^{-1}$/cm$^3$</td>
<td>Activation parameter of NF-$\kappa$B</td>
<td>Estimated by Hoffmann et al. (2002)</td>
</tr>
<tr>
<td>$\lambda_{NF-\kappa}$</td>
<td>$8 \times 10^{-6}$ s$^{-1}$</td>
<td>Degradation parameter of NF-$\kappa$B</td>
<td>Hoffmann et al. (2002)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>$1$</td>
<td>Upregulation parameter of NF-$\kappa$B by inflammation</td>
<td>Estimated from Kojima et al. (2004)</td>
</tr>
<tr>
<td>$K_{NF}$</td>
<td>$0.1$</td>
<td>Normalizing factor of $I$</td>
<td>This work</td>
</tr>
<tr>
<td>$\beta$-catenin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda_{\beta}$</td>
<td>$6.49 \times 10^{-16}$ gs$^{-1}$/cm$^3$</td>
<td>Production rate of $\beta$-catenin</td>
<td>Murray et al. (2010)</td>
</tr>
<tr>
<td>$\lambda_{\beta}$</td>
<td>$4.28 \times 10^{-6}$ s$^{-1}$</td>
<td>Degradation parameter of $\beta$-catenin</td>
<td>Murray et al. (2010)</td>
</tr>
<tr>
<td>$\gamma_{\beta}$</td>
<td>$4$</td>
<td>Upregulation parameter of $\beta$-catenin by MUC1</td>
<td>Estimated from Aust et al. (2001), Ninomiya et al. (2000)</td>
</tr>
<tr>
<td>$\gamma_{\beta}$</td>
<td>$8$</td>
<td>Upregulation parameter of $\beta$-catenin by APC mutation induced by inflammation</td>
<td>Estimated from Aust et al. (2001), Murray et al. (2010)</td>
</tr>
<tr>
<td>$K_{M1}$</td>
<td>$1.25 \times 10^{-6}$ g/cm$^3$</td>
<td>Normalizing factor of $M_1$</td>
<td>This work</td>
</tr>
<tr>
<td>$K_{M2}$</td>
<td>$0.1$</td>
<td>Normalizing factor of $M_2$</td>
<td>This work</td>
</tr>
<tr>
<td>$B_{in}$</td>
<td>$1.37 \times 10^{-5}$ g/cm$^3$</td>
<td>Steady state concentration of $\beta$-catenin for healthy tissue</td>
<td>This work</td>
</tr>
<tr>
<td>$\eta_{B}$</td>
<td>$0$</td>
<td>Parameter controlling the level of APC mutation</td>
<td>Variable</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
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</tr>
<tr>
<td>$\mu_1$</td>
<td>$1.25 \times 10^{-5}$ g/cm$^3$</td>
<td>Normalizing factor of $M_1$</td>
<td>This work</td>
</tr>
<tr>
<td>$\mu_2$</td>
<td>$1.3 \times 10^{-5}$ g/cm$^2$</td>
<td>Normalizing factor of $M_2$</td>
<td>This work</td>
</tr>
<tr>
<td>Tumor cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda_{T}$</td>
<td>$1.5 \times 10^{-6}$ s$^{-1}$</td>
<td>Proliferation parameter of tumor cell</td>
<td>Eisenberg et al. (2011), Kim and Friedman (2010), Kim et al. (2010)</td>
</tr>
<tr>
<td>$K_{C}$</td>
<td>$1.9$</td>
<td>Threshold of normalized $B$ and $N$</td>
<td>This work</td>
</tr>
</tbody>
</table>

Table B3
PRCC values and ranges of parameters for the PRCC simulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
<th>PRCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_{11}$</td>
<td>$[3.13,9.39] \times 10^{-12}$ gs$^{-1}$/cm$^3$</td>
<td>0.0005</td>
</tr>
<tr>
<td>$\lambda_{12}$</td>
<td>$[0.585,1.755] \times 10^{-5}$ s$^{-1}$</td>
<td>0.0341</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>$[0.625,1.875] \times 10^{-10}$ gs$^{-1}$/cm$^3$</td>
<td>0.0315</td>
</tr>
<tr>
<td>$K_1$</td>
<td>$[1.68,5.04] \times 10^{-5}$ g/cm$^3$</td>
<td>-0.0064</td>
</tr>
<tr>
<td>$D_{MUC}$</td>
<td>$[2.35,7.05] \times 10^{-8}$ cm$^2$/s$^{-1}$</td>
<td>0.0090</td>
</tr>
<tr>
<td>$\beta$</td>
<td>$[1.395,4.185] \times 10^{-5}$ s$^{-1}$</td>
<td>0.0023</td>
</tr>
<tr>
<td>$K_{MUC1}$</td>
<td>$[33.075,99.225]$ g/cm$^3$</td>
<td>-0.0068</td>
</tr>
<tr>
<td>$K_{MUC2}$</td>
<td>$[1.68,5.04] \times 10^{-5}$ g/cm$^3$</td>
<td>0.0120</td>
</tr>
<tr>
<td>$\lambda_{31}$</td>
<td>$[0.96,2.88] \times 10^{-10}$ gs$^{-1}$/cm$^3$</td>
<td>-0.0037</td>
</tr>
</tbody>
</table>
to determine directly the proliferation rate of colon cancer, but in other cancers, rates of order $10^{-6}$ s$^{-1}$ were used [Eisenberg et al., 2011; Kim and Friedman, 2010; Kim et al., 2010]. We correspondingly take $\lambda_{S1} = 1.5 \times 10^{-6}$ s$^{-1}$.

Appendix B. Tables

(See Tables B1–B3).

References


