

Mathematical modeling of cell population dynamics in the colonic crypt and in colorectal cancer

Matthew D. Johnston, Carina M. Edwards, Walter F. Bodmer, Philip K. Maini, and S. Jonathan Chapman

PNAS 2007;104:4008-4013; originally published online Feb 28, 2007;
doi:10.1073/pnas.0611179104

This information is current as of May 2007.

Online Information & Services	High-resolution figures, a citation map, links to PubMed and Google Scholar, etc., can be found at: www.pnas.org/cgi/content/full/104/10/4008
Related Articles	A related article has been published: www.pnas.org/cgi/content/abstract/92/24/11130
Supplementary Material	Supplementary material can be found at: www.pnas.org/cgi/content/full/0611179104/DC1
References	This article cites 24 articles, 9 of which you can access for free at: www.pnas.org/cgi/content/full/104/10/4008#BIBL This article has been cited by other articles: www.pnas.org/cgi/content/full/104/10/4008#otherarticles
E-mail Alerts	Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or click here .
Rights & Permissions	To reproduce this article in part (figures, tables) or in entirety, see: www.pnas.org/misc/rightperm.shtml
Reprints	To order reprints, see: www.pnas.org/misc/reprints.shtml

Notes:

Mathematical modeling of cell population dynamics in the colonic crypt and in colorectal cancer

Matthew D. Johnston^{*†}, Carina M. Edwards^{*†}, Walter F. Bodmer^{*§}, Philip K. Maini^{*¶}, and S. Jonathan Chapman[†]

Centres for ^{*}Mathematical Biology and [†]Industrial and Applied Mathematics, Mathematical Institute, University of Oxford, 24-29 St. Giles', Oxford OX1 3LB, United Kingdom; [‡]Cancer Research UK, Cancer and Immunogenetics Laboratory, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DS, United Kingdom; and [§]Oxford Centre for Integrative Systems Biology, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, United Kingdom

Contributed by Walter F. Bodmer, December 15, 2006 (sent for review November 23, 2006)

Colorectal cancer is initiated in colonic crypts. A succession of genetic mutations or epigenetic changes can lead to homeostasis in the crypt being overcome, and subsequent unbounded growth. We consider the dynamics of a single colorectal crypt by using a compartmental approach [Tomlinson IPM, Bodmer WF (1995) *Proc Natl Acad Sci USA* 92:11130–11134], which accounts for populations of stem cells, differentiated cells, and transit cells. That original model made the simplifying assumptions that each cell population divides synchronously, but we relax these assumptions by adopting an age-structured approach that models asynchronous cell division, and by using a continuum model. We discuss two mechanisms that could regulate the growth of cell numbers and maintain the equilibrium that is normally observed in the crypt. The first will always maintain an equilibrium for all parameter values, whereas the second can allow unbounded proliferation if the net per capita growth rates are large enough. Results show that an increase in cell renewal, which is equivalent to a failure of programmed cell death or of differentiation, can lead to the growth of cancers. The second model can be used to explain the long lag phases in tumor growth, during which new, higher equilibria are reached, before unlimited growth in cell numbers ensues.

age-structure | feedback | mutations | structural stability

The large intestine is one of the most frequent sites of carcinogenesis due, at least in part, to its continual self-renewal and the large numbers of daily cell divisions (1). There are millions of invaginations in the lining of the colon, called crypts, and it is widely believed that colorectal cancer is initiated when mutations or relatively stable epigenetic changes occur in the single layer of epithelial cells that line the crypt. Consequently, much work has been directed toward understanding the mechanisms involved in the dynamics of the cells in healthy and neoplastic (abnormally growing) crypts.

Stem cells are believed to reside near the bottom of the colorectal crypt (2), and these are capable of producing a variety of cell types that are required for tissue renewal and regeneration after injury (3). The stem cells divide to produce transit cells that migrate up the crypt wall toward the luminal surface. As the cells proceed up the crypt they differentiate into colonocytes, enteroendocrine cells, and Goblet cells (1). Once at the top, the cells either undergo apoptosis and/or are shed into the lumen and transported away (4, 5).

In the murine small intestine, the journey of the cells from the base of the crypt to its apex has been estimated to take between 2 and 3 days (6), and all the cells in the crypt, apart from the stem cells, will be renewed over this period. The stem cells are assumed to have a cycle time of between 12 and 32 h with an average of 24 h (7, 8). The transit cell population has an estimated cycle time of ≈ 11 –12 h (4, 9).

The crypt is homeostatic with an equilibrium maintained between cell proliferation and cell loss due to death and shedding. If this balance is shifted toward proliferation by, for example, mutations that promote proliferation or inhibit apoptosis, then neoplasia results (10–13). In the colon, such up-

regulated cell proliferation is the first step toward adenoma formation and subsequent carcinogenesis (14, 15). Here we present some simple mathematical models of the colorectal crypt with the aim of identifying the key processes that may initiate and accelerate tumorigenesis.

There have been a number of models that have studied cell population dynamics in the crypt, including the computational models by Paulus *et al.* (16, 17), Gerike *et al.* (18), and Meineke *et al.* (19), and the deterministic models by Boman *et al.* (20) and Hardy and Stark (21). One of the earliest and most influential models is that of Tomlinson and Bodmer (22), which we use as the starting point for our study. That model assumes that the cells in the crypt can be assigned to one of three different compartments: stem cells, semidifferentiated cells (transit-amplifying cells), and fully differentiated cells (Fig. 1). At the end of each cell cycle, stem cells and semidifferentiated cells are assumed to die (through apoptosis), differentiate, or renew with constant probabilities a_1 , a_2 , a_3 , and b_1 , b_2 , b_3 , respectively, where $a_1 + a_2 + a_3 = 1$ and $b_1 + b_2 + b_3 = 1$. These probabilities can also be interpreted as the proportions of each cell population dying, differentiating, and renewing. The fully differentiated cells are assumed to be removed from the system (through death or shedding) with probability (or proportion) c in a given time.

To formulate equations for the population of stem cells (denoted N_0), semidifferentiated cells (denoted N_1), and fully differentiated cells (denoted N_2) after each cell division, Tomlinson and Bodmer (22) implicitly assumed that the cell divisions in each population were synchronous, which requires the cell cycle time of stem cells (denoted t_0) to be an integer multiple of the cell cycle time of semidifferentiated cells (denoted t_1). The equations in ref. 22 are, however, not completely accurate, as they neglect the asynchronicity induced if t_0/t_1 is not an integer, as well as the compounding effect of semidifferentiated cells cycling more frequently than stem cells. Despite this, Tomlinson and Bodmer were able to predict that failure of apoptosis, or of differentiation, could lead to either exponential growth or a new equilibrium at higher cell numbers, and that failure of these processes was sometimes sufficient but not necessary for tumorigenesis, as this could also be achieved by a proliferative advantage. These observations can be used to explain premalignant growths, and the stepwise growth of tumors that occurs between long lag phases.

Our first aim in this paper is to remove the requirement of synchronicity from the model of Tomlinson and Bodmer, taking careful account of the different cell cycle times of stem and

Author contributions: C.M.E., W.F.B., P.K.M., and S.J.C. designed research; M.D.J., C.M.E., P.K.M., and S.J.C. performed research; and M.D.J. and S.J.C. wrote the paper.

The authors declare no conflict of interest.

Freely available online through the PNAS open access option.

[§]To whom correspondence should be addressed. E-mail: walter.bodmer@hertford.ox.ac.uk.

This article contains supporting information online at www.pnas.org/cgi/content/full/0611179104/DC1.

© 2007 by The National Academy of Sciences of the USA



$$N_0(t, a) = \hat{n}_0 \sum_{n=0}^{\infty} \delta(t - a - nt_0)(2a_3)^n, \quad [6]$$

$$N_1(t, a) = \hat{n}_1 \sum_{m=0}^{\infty} (2b_3)^m \delta(t - a - mt_1) + 2a_2\hat{n}_0 \sum_{n=1}^{\infty} \sum_{m=0}^{\infty} (2a_3)^{n-1}(2b_3)^m \times \delta(t - a - nt_0 - mt_1), \quad [7]$$

$$N_2(t, a) = \hat{n}_2 \sum_{p=0}^{\infty} (1-c)^p \delta(t - a - pt_2) + 2b_2\hat{n}_1 \sum_{m=1}^{\infty} \sum_{p=0}^{\infty} (2b_3)^{m-1}(1-c)^p \times \delta(t - a - mt_1 - pt_2) + 2a_2\hat{n}_0(2b_2) \sum_{n=1}^{\infty} \sum_{m=1}^{\infty} \sum_{p=0}^{\infty} (2a_3)^{n-1}(2b_3)^{m-1}(1-c)^p \times \delta(t - a - nt_0 - mt_1 - pt_2). \quad [8]$$

Note that while the stem cells remain synchronous, the semi-differentiated and fully differentiated cells become asynchronous if t_0 is not an integer multiple of t_1 .

Another relatively simple case to consider is a uniform initial distribution of ages, so that $n_i(a) = \hat{n}_i/t_i$. A closed form solution is possible whenever t_0/t_1 is rational, and is given in the [supporting information \(SI\) Text](#). In the biologically realistic case of, for example, $t_0 = 2t_1$, the solution for N_1 at the points where $t - a = 2nt_1$ satisfies

$$N_1(t, a) = \frac{\hat{n}_1}{t_1} (2b_3)^{2n} + \frac{a_2\hat{n}_0(1+2b_3)}{t_1[2a_3 - (2b_3)^2]} [(2a_3)^n - (2b_3)^{2n}]. \quad [9]$$

Combining like terms in the double summation in 7 when $t_0 = 2t_1$ gives

$$N_1(t, a) = \sum_{n=0}^{\infty} [\delta(t - a - 2nt_1) + 2b_3\delta(t - a - (2n+1)t_1)] \times \left[\hat{n}_1(2b_3)^{2n} + \frac{2a_2\hat{n}_0}{2a_3 - (2b_3)^2} [(2a_3)^n - (2b_3)^{2n}] \right]. \quad [10]$$

The similarity between expressions 9 and 10 indicates that the distribution of cell ages, while necessary for consistency when modeling on the time scale of the cell cycle, is not crucial in determining the long-time behavior of the solution, and can make the solutions overly complicated. We therefore now develop a much simpler ordinary-differential equation (ODE) model which allows for continuous cell division.

The Continuous Model. Here we assume that we are interested in times much greater than the cell cycle time, and that the cell

populations are large enough that we can assume that they vary continuously with time, rather than taking only integer values.

Denoting the per-capita rate of stem (respectively semidifferentiated) cell proliferation by α_3 (respectively β_3), differentiation by α_2 (respectively β_2), and death by α_1 (respectively β_1), and the per-capita removal rate of fully differentiated cells by γ , the ODE model is

$$\frac{dN_0}{dt} = (\alpha_3 - \alpha_1 - \alpha_2)N_0, \quad [11]$$

$$\frac{dN_1}{dt} = (\beta_3 - \beta_1 - \beta_2)N_1 + \alpha_2N_0, \quad [12]$$

$$\frac{dN_2}{dt} = \beta_2N_1 - \gamma N_2. \quad [13]$$

Note that these rates are analogous but not equivalent to the corresponding proportions of the cell populations in the age-structured model; the relationship between the two sets of parameters will be determined in the following section.

Eqs. 11–13 are much easier to solve than their age-structured equivalents. Given initial cell populations $N_i = \hat{n}_i$, we find

$$N_0(t) = \hat{n}_0 e^{\alpha t}, \quad [14]$$

$$N_1(t) = A e^{\alpha t} + (\hat{n}_1 - A) e^{\beta t}, \quad [15]$$

$$N_2(t) = B e^{\alpha t} + C e^{\beta t} + (\hat{n}_2 - B - C) e^{-\gamma t}, \quad [16]$$

where $\alpha = \alpha_3 - \alpha_1 - \alpha_2$ and $\beta = \beta_3 - \beta_1 - \beta_2$ are the net stem and semidifferentiated cell per-capita growth rates, respectively, and the constants A , B , and C are given by

$$A = \frac{\alpha_2 \hat{n}_0}{\alpha - \beta}, \quad B = \frac{\beta_2 A}{\gamma + \alpha}, \quad \text{and} \quad C = \frac{\beta_2 (\hat{n}_1 - A)}{\gamma + \beta}. \quad [17]$$

Comparing the Age-Structured and Continuous Models. In the age-structured model, we consider proportions of the cell populations dying, differentiating, or renewing at discrete time intervals, whereas in the continuous model, we assume that these processes occur continuously and we work with the rates at which they occur. To compare the models, it is important to be able to relate the two sets of parameters, which is the goal of this section.

In the age-structured model, for the case where all the cells in each population are initially synchronous in their cell cycles, we have the general solution 6–8. The total population of each cell type is given by integrating over all possible ages

$$\hat{N}_i(t) = \int_0^{t_i} N_i(t, a) da. \quad [18]$$

It is shown in the [SI Text](#) that integrating 6–8 over all ages gives

$$\hat{N}_0(t) \approx \hat{n}_0 (2a_3)^{t/t_0}, \quad [19]$$

$$\hat{N}_1(t) \approx \hat{A} (2a_3)^{t/t_0} + (\hat{n}_1 - \hat{A}) (2b_3)^{t/t_1}, \quad [20]$$

$$\hat{N}_2(t) \approx \hat{B} (2a_3)^{t/t_0} + \hat{C} (2b_3)^{t/t_1} + (\hat{n}_2 - \hat{B} - \hat{C}) (1-c)^{t/t_2}, \quad [21]$$

for constants \hat{A} , \hat{B} , and \hat{C} that can be determined. Comparing 14–16 and 19–21, we see immediately that the renewal proportions and proliferation rates are related by

$$(2a_3)^{1/t_0} = e^{\alpha}, \quad (2b_3)^{1/t_1} = e^{\beta}, \quad (1-c)^{1/t_2} = e^{-\gamma}. \quad [22]$$

