

Stochastic elimination of cancer cells

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Tissues of multicellular organisms consist of stem cells and differentiated cells. Stem cells divide to produce new stem cells or differentiated cells. Differentiated cells divide to produce new differentiated cells. We show that such a tissue design can reduce the rate of fixation of mutations that increase the net proliferation rate of cells. It has, however, no consequence for the rate of fixation of neutral mutations. We calculate the optimum relative abundance of stem cells that minimizes the rate of generating cancer cells. There is a critical fraction of stem cell divisions that is required for a stochastic elimination ('wash out') of cancer cells.

Keywords: mathematical model; stem cells; cancer

1. INTRODUCTION

The development of multicellular organisms requires the organization of cells in morphologically stable functional units (Mintz 1971, 1977). Such units are made up of separate families of multiplying cells that are organized hierarchically. The most primitive cells are pluripotent stem cells capable of proliferation, self-renewal and production of many differentiated progeny (see Winton & Ponder 1990; Marshak *et al.* 2001; Tannishtha *et al.* 2001; Brittan & Wright 2002; Janes *et al.* 2002). Stem cells produce committed progenitor cells, which in turn produce even more committed cells. Differentiated cells typically proliferate to fulfil their organ-specific tasks (Turksen & Troy 1998). Once fully differentiated, however, such cells sometimes lose the ability to proliferate, as illustrated by the nuclear loss of erythrocytes and keratinocytes (Bach *et al.* 2000). In this paper, differentiated cells are considered to be partly or fully differentiated cells that retain proliferation abilities. The maintenance of homeostasis, i.e. constancy in cell number, reflects a highly regulated balance between the rates of cell proliferation and cell death. If the balance is shifted towards uncontrolled proliferation, cancer occurs. Therefore, cancer is breakdown of homeostasis.

Genetic alterations such as point mutations, chromosomal rearrangements, unequal crossing over, loss of heterozygosity, modification of DNA methylation and chromosome aberrations accumulate during the lifetime of an organism. They are caused by intrinsic errors of DNA replication and repair as well as by external factors such as exposure to mutagenic substances or radiation. They can happen in stem cells and differentiated cells. If those genetic alterations affect genes involved in cellular proliferation, cell-cycle regulation or apoptosis, then neoplastic growth might be initiated (Levine 1993; Mitelman *et al.* 1994; Kinzler & Vogelstein 1997, 1998; Lengauer *et al.* 1998; Knudson 2001; Hahn & Weinberg 2002). The

alteration of one gene, however, does not suffice to give rise to full-blown cancer. For progression towards malignancy and invasion, further mutational hits are necessary (Boveri 1914; Muller 1927; Knudson 2001). Hence the risk of cancer development does not only depend on mutations initiating tumourigenesis, but also on subsequent mutations driving tumour progression.

Mathematical modelling of cancer progression has a long history (Armitage & Doll 1957; Fisher 1958; Knudson 1971; Bell 1976; Moolgavkar & Knudson 1981; Wheldon 1988; Sherratt & Nowak 1992; Chaplain 1995; Gatenby & Gawlinski 1996; Tomlinson *et al.* 1996; Luebeck & Moolgavkar 2002; Nowak *et al.* 2002; Komarova *et al.* 2003; Little & Wright 2003; Michor *et al.* 2003), yet there is no comprehensive theory of somatic evolution (Gatenby & Maini 2003). Here, we explore how tissue design influences the probability to develop cancer, and we calculate the optimum tissue architecture to minimize this probability (Cairns 1975, 1981, 1998, 2002; Frank *et al.* 2003; Frank & Nowak 2003). In § 2a, we formulate a basic mathematical model. We assume that a population of cells is subdivided into a compartment of stem cells and a compartment of differentiated cells. Mutations in the latter compartment might be 'washed out' by the influx of unmutated cells from the stem cell compartment. In § 2b–d, we calculate the overall rate of fixation of cells that carry an advantageous mutation. We calculate the optimum fraction of stem cells. If there are too many stem cells, the rate of accumulation of mutated cells in the stem cell compartment is too high. If there are too few stem cells, then advantageous mutations among the differentiated cells are not washed out, but remain in some steady state. In § 2e, we show that the subdivision into stem cells and differentiated cells has no consequence for the accumulation of neutral mutations. In § 2f, we generalize from two to $n + 1$ compartments. There is one stem cell compartment and n compartments of differentiated cells. Compartment i feeds cells into compartment $i + 1$. We calculate the stack configuration that guarantees the wash-out of mutants from any compartment of differentiated cells. In § 2g, we discuss the possibility that a mutation

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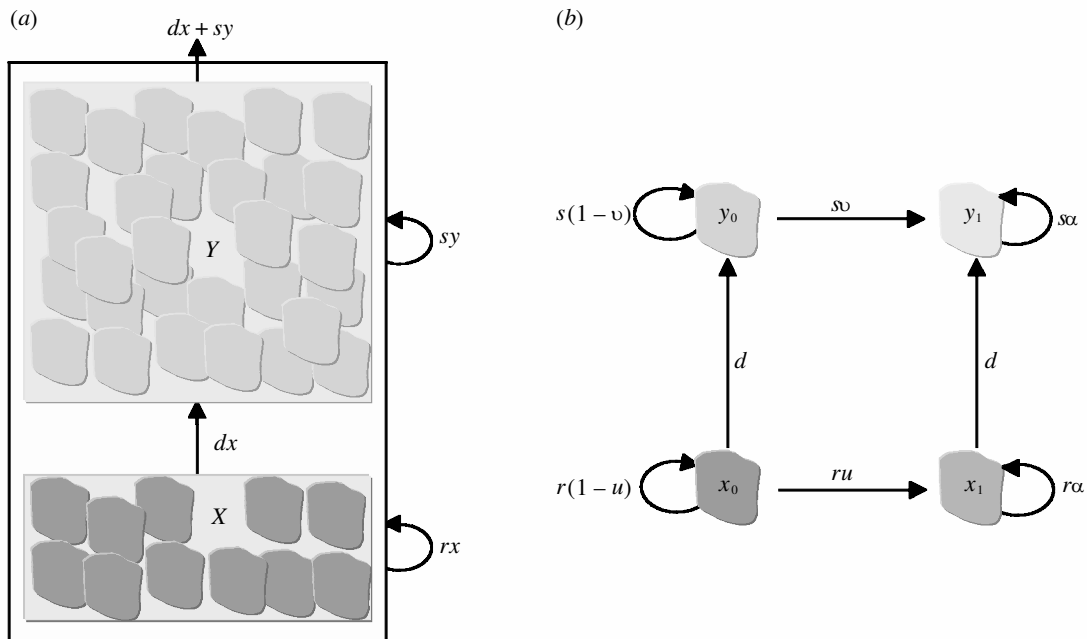


Figure 1. Tissue architecture. Tissues of multicellular organisms consist of compartments of stem cells, X , and compartments of differentiated cells, Y . (a) Stem cells, x , replicate at a growth rate r and export cells at a rate d into the Y compartment where differentiated cells, y , proliferate at a growth rate s . Cells are removed from the system at a rate $dx + sy$. (b) Wild-type stem cells, x_0 , proliferate at a rate r and give rise to mutated stem cells, x_1 , with probability u per cell division. Stem cells are exported at a rate d into the differentiated cell compartment. Wild-type differentiated cells, y_0 , proliferate at a rate s and give rise to mutated differentiated cells, y_1 , with probability v per cell division. Mutated cells, x_1 and y_1 , have a somatic fitness α . If $\alpha = 1$, the mutation is neutral; if $\alpha > 1$, the mutation is advantageous. The scheme outlines the stochastic differential equations (equation (2.1)).

confers different fitness values to stem cells and differentiated cells. In § 2h, we explore optimum proliferation dynamics and tissue design to minimize the risk of cancer initiation via mutations that immediately break through compartment boundaries if not washed out. The main point of the paper, summarized in § 3, is that the detailed structure of cell populations is extremely important for understanding the principles of somatic evolution. Tissue architectures may have evolved to maximize the duration of cancer-free cooperation among cells.

2. RESULTS

(a) *The basic mathematical model*

Consider a tissue of a multicellular organism. The tissue is organized into units. Each unit is subdivided into a compartment of stem cells, X , and a compartment of differentiated cells, Y (figure 1a). These two cell types are linked in a precursor–progeny relationship. Stem cells, x , have self-renewal and differentiation capabilities, replenishing the X compartment at a growth rate r and fuelling cells into the Y compartment at a rate d . Differentiated cells, y , proliferate at a rate s ; we assume that $s > 0$. In a healthy tissue, constancy in cell number is obtained by removing cells from the Y compartment at a rate $dx + sy$. The first step towards cancer can be made in either of the compartments. A mutation in a tumour suppressor gene, oncogene or gene causing genetic instability increases the probability of developing cancer. We study the random fixation or elimination of a particular mutation which may be neutral or advantageous. A neutral mutation, like the inactivation of one allele of a tumour suppressor gene, does not alter

the fitness of a cell. The inactivation of the second allele of a tumour suppressor gene or the activation of an oncogene, however, can confer a growth advantage to the cell.

The population dynamics of the compartments are illustrated in figure 1b. Wild-type stem cells are denoted by x_0 . They divide at rate r and give rise to mutated stem cells, x_1 , with probability u per cell division. Wild-type differentiated cells are denoted by y_0 . They divide at rate s and produce mutated differentiated cells, y_1 , with probability v per cell division. Mutated cells, x_1 and y_1 , have a somatic fitness α . If $\alpha = 1$, the mutation is neutral. If $\alpha > 1$, the mutation is advantageous. Here, we assume that the mutation confers the same fitness α both to stem cells and differentiated cells. We consider the case of different fitness values in § 2g.

The basic model neglecting stochasticity takes the form

$$\left. \begin{aligned} \dot{x}_0 &= r(1-u)x_0 - dx_0 - \Psi x_0, \\ \dot{x}_1 &= rux_0 + r\alpha x_1 - dx_1 - \Psi x_1, \\ \dot{y}_0 &= dx_0 + s(1-v)y_0 - \Phi y_0, \\ \dot{y}_1 &= dx_1 + svy_0 + s\alpha y_1 - \Phi y_1. \end{aligned} \right\} \quad (2.1)$$

The homeostatic factors Ψ and Φ ensure constancy in stem cell number and differentiated cell number, respectively. We have $\Psi = (rx_0 + r\alpha x_1 - dx)/x$ and $\Phi = (dx + sy_0 + s\alpha y_1)/y$.

Let z be the fraction of mutated stem cells, $z = x_1/x$, and ω the fraction of mutated differentiated cells, $\omega = y_1/y$. Then we have, including stochasticity,

$$\dot{z} = ru(1-z) + r(\alpha-1)z(1-z) + A\xi_x(t), \quad (2.2a)$$

$$\dot{\omega} = sv(1 - \omega) + (dx/y)(z - \omega) + s(\alpha - 1)\omega(1 - \omega) + B\xi_y(t). \tag{2.2b}$$

Stochastic fluctuations are represented by $A\xi_x(t)$ and $B\xi_y(t)$ and can be derived from a diffusion approximation. We have $A = [2rz(1 - z)/x]^{1/2}$ and $B = [2s\omega(1 - \omega)/y]^{1/2}$. The functions ξ_z and ξ_ω provide white noise. Stochastic fluctuations are caused by the finiteness of cell numbers. This is known as demographic stochasticity in ecology and as random genetic drift in population genetics. Here, we introduce stochastic fluctuations according to the Moran model (Moran 1962). In this model, cells are randomly chosen to divide or to die without changing the total abundance. In the Moran model, there are overlapping generations. In the Wright–Fisher model, more commonly used in theoretical population genetics, there are discrete generations. Consequently, populations in the Moran model display more random drift than in the Wright–Fisher model (Durrett 2002).

(b) A Markovian jump process

If the mutation rate in both cell types is sufficiently small, a mutant cell with a growth advantage $\alpha > 1$ will either go extinct or take over the compartment before the next mutation occurs. In this case, a compartment will almost always consist of a homogeneous cell population. We can approximate the transition from a wild-type compartment to a mutated compartment by a Markovian jump process (Kimura & Ohta 1968; Iizuka & Ogura 1991). The time of fixation of a mutant is of the order of the population size; the waiting time until a successful mutant appears is of the order of the inverse of the mutation rate (Kimura & Ohta 1968). Hence the latter is much larger than the time of fixation.

Consider the situation where the mutation confers an increase in somatic fitness, $\alpha > 1$. In this case, the system can be in one of three different states. The stochastic dynamics are defined by transitions among the three states (figure 2). Initially, the system is in the state (X_0, Y_0) ; that is, both compartments contain only unmutated cells. If a mutation occurs and is fixed in the stem cell compartment, then the mutation will also become fixed among the differentiated cells. The system moves to state (X_1, Y_1) . The transition from (X_0, Y_0) to (X_1, Y_1) occurs at the rate $p_x = rx\rho_x$, where ρ_x denotes the probability that one mutated cell with a relative selective advantage α reaches fixation in the X compartment. It is given by $\rho_x = (1 - 1/\alpha)/(1 - 1/\alpha^x)$.

Suppose that the gene is first mutated in a differentiated cell. If the somatic fitness of the cell is less than a critical value, $\alpha < 1 + \alpha_0$, then the mutation will be ‘washed out’ by the influx of unmutated cells from the stem cell compartment. Here, $\alpha_0 = dx/(sy)$ denotes the wash-out rate. If the fitness advantage exceeds the wash-out rate, $\alpha > 1 + \alpha_0$, then mutated cells can be maintained in the differentiated cell compartment at a frequency of $\hat{w} = 1 - [\alpha_0/(\alpha - 1)]$. Let Y_2 denote the state of a partly mutated compartment of differentiated cells. The transition from (X_0, Y_0) to (X_0, Y_2) occurs at rate $p_y = syv\rho_y$, where ρ_y denotes the probability that the mutation reaches the steady-state frequency, \hat{w} , in the Y compartment. It is given by $\rho_y = [1 - 1/(\alpha - \alpha_0)]/[1 - 1/(\alpha - \alpha_0)^y]$. Finally, the system can move from state (X_0, Y_2) to state (X_1, Y_1)

with a mutation in the X compartment. This takes place at the rate p_x .

Let us now consider the timing of the mutational events. The probability that the transition from (X_0, Y_0) to (X_1, Y_1) occurs before time t is $\Pr(T_x < t) = 1 - \exp(-p_x t)$. The probability that the transition from (X_0, Y_0) to (X_0, Y_2) occurs before time t is $\Pr(T_y < t, T_x > t) = \exp(-p_x t)(1 - \exp(-p_y t))$.

We want to calculate the optimum subdivision into stem cells and differentiated cells that minimizes the incidence of cancer. Consider the following scenario: a first mutation arises and becomes fixed in the compartment; a second mutation leads to a clonal expansion which initiates cancer progression. In this case, the probability that cancer has been initiated by a tissue compartment at time t is $P(t) = 1 - \exp[-CR(t)]$ where C is a constant and $R(t) = rux_1(t) + svy_1(t)$. We obtain

$$R(t) = (rux + svy)(1 - e^{-p_x t}) + svy\hat{w}e^{-p_x t}(1 - e^{-p_y t}). \tag{2.3}$$

For the appropriate time-scale we have $p_x t \ll 1$ and $p_y t \ll 1$. This simply means that most compartments of a tissue remain unmutated with respect to a particular gene for the lifetime of the organism. In this case, we can approximate

$$R(t) \approx [(rux + svy)p_x + svy\hat{w}p_y]t. \tag{2.4}$$

At the minimum $R(t)$, we have $r = d$, because $r > d$ implies unnecessary cell divisions in the X compartment that provide additional risk. Furthermore, we want to minimize $R(t)$ subject to the constraint $c = rx + sy = \text{constant}$. This means the tissue compartment has to generate a fixed number of differentiated cells per time. Without such a constraint, the optimum design would use cells that never divide.

In § 2h, we consider a different scenario: the first mutation immediately leads to clonal expansion beyond the compartment boundaries. In this case, the rate of cancer initiation is minimized by minimizing the sum $p_x + p_y$. Again, this leads to an optimum fraction of stem cells per tissue compartment.

(c) Optimum design to protect against very advantageous mutations

Let us now calculate the optimal partitioning of cells into stem cells, x , and differentiated cells, y , that minimizes the risk of cancer initiation via highly advantageous mutations, $\alpha \gg 1$. In this case, the probability that a cell with fitness α reaches fixation in the stem cell compartment can be approximated by $\rho_x = 1 - 1/\alpha$. The probability that a cell with fitness $\alpha - \alpha_0$ is fixed in the differentiated cell compartment can be approximated by $\rho_y = 1 - 1/(\alpha - \alpha_0)$ if $\rho_y > 0$ and $\rho_y = 0$ otherwise. These approximations hold if $\alpha^x \gg 1$ and $(\alpha - \alpha_0)^y \gg 1$. Let us introduce a rate $\zeta = rx/c$, which is a number between 0 and 1 and denotes the fraction of cellular proliferation in a tissue that arises from divisions of stem cells. With $c = rx + sy$, we have $1 - \zeta = sy/c$. Thus, for $\alpha \gg 1$, we obtain from equation (2.4)

$$R(t) = u^2 c^2 \left[\left(\zeta + \frac{v}{u}(1 - \zeta) \right) \zeta + \left(\frac{v}{u} \right)^2 (1 - \zeta)^2 \right] t. \tag{2.5}$$

The evaluation of the risk function depends on the

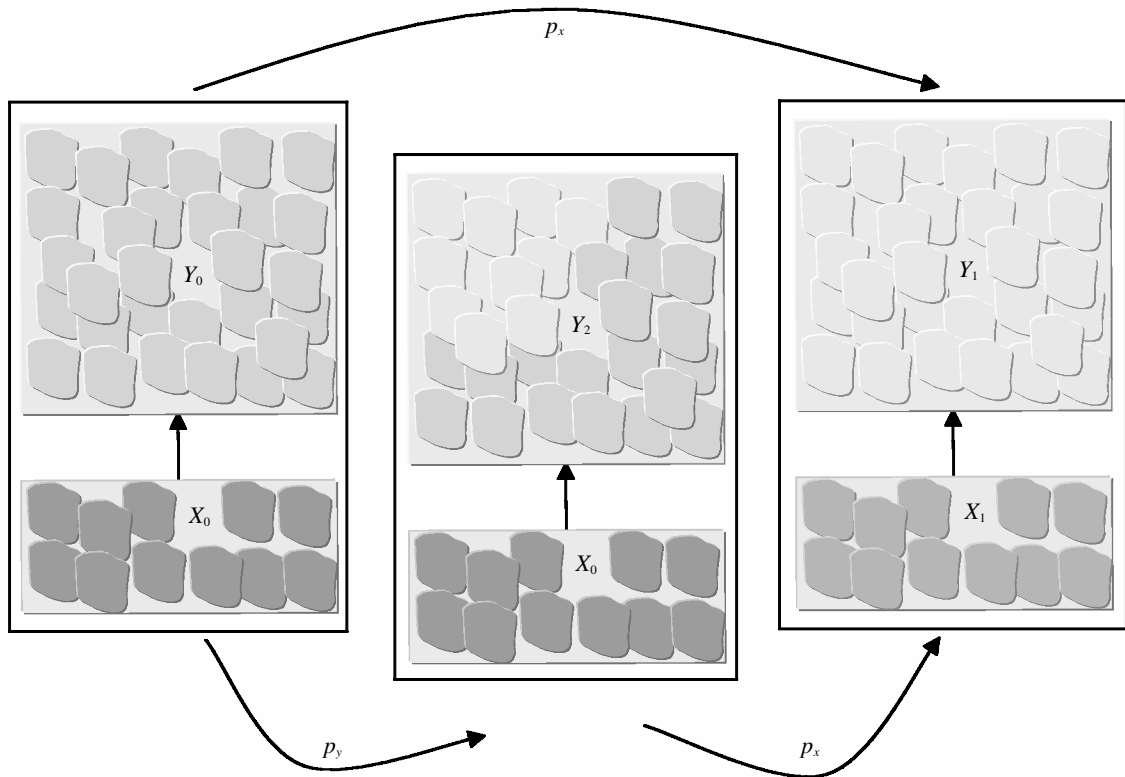


Figure 2. Transition dynamics. The system can be in three different states: both compartments can be unmutated, (X_0, Y_0) , both compartments can be mutated, (X_1, Y_1) , or the stem cell compartment can be unmutated while the differentiated cell compartment is partly mutated, (X_0, Y_2) . The transition from (X_0, Y_0) or (X_0, Y_2) to (X_1, Y_1) occurs at a rate p_x . The transition from (X_0, Y_0) to (X_0, Y_2) occurs at a rate p_y .

mutation rates in stem cells and differentiated cells. If $u = v$, the risk of initiating neoplastic growth takes its minimum at the value $rx/c = \zeta = 1/2$, where both compartments have the same numbers of cell divisions per time. Figure 3a shows the numerical simulation for the case $u = v$.

If the mutation rate in stem cells is less than the mutation rate in differentiated cells, $u < v$, then the risk function takes its minimum at the value

$$\zeta = \frac{(2v/u - 1)v/u}{2(1 - v/u + (v/u)^2)}. \quad (2.6)$$

This equation satisfies $0 < \zeta < 1$ if $1 < v/u \leq 2$. If $v/u > 2$, then the optimum takes the value $\zeta = 1$, which means all cells are stem cells. Figure 3b–d shows numerical simulations for the cases $v = 1.5u$, $v = 2u$ and $v = 3u$.

(d) Optimum design to protect against slightly advantageous mutations

If the relative fitness α is only slightly larger than 1, then we approximate $\rho_x = \alpha - 1$ and $\rho_y = (\alpha - \alpha_0) - 1$. From equation (2.4), we obtain

$$R(t) = u^2 c^2 \left[\left(\zeta + \frac{v}{u}(1 - \zeta) \right) \zeta \left(1 - \frac{1}{\alpha} \right) + \left(\frac{v}{u} \right)^2 \frac{(1 - \zeta)[(\alpha - 1) - \alpha \zeta]^2}{(\alpha - 1)(\alpha - (\alpha + 1)\zeta)} \right] t. \quad (2.7)$$

This function of ζ has two different minima depending on the ratio v/u . If $v/u > 2\alpha - 1/(\alpha - 1)$, the function takes its minimum at $\zeta = 1$. This implies that the optimum is achieved if all cells are stem cells. If $v/u < 2\alpha - 1/(\alpha - 1)$, the minimum lies at $\zeta < 1 - 1/\alpha$. This indicates

that the optimal fraction of stem cells is smaller than the wash-out threshold. Figure 3b–d also shows numerical simulations for these cases.

(e) Neutral mutations

Some mutations, such as the inactivation of one allele of a tumour suppressor gene, imply a step towards cancer without altering the phenotype of the cell. They confer neither a selective advantage nor a selective disadvantage to the cell, i.e. $\alpha = 0$. However, they provide a risk for cancer initiation.

In this case, there is no intermediate optimum of tissue design. If $rx = c$, the risk of initiating cancer is $R(t) = ru^2 ct$. If $ry = c$, the risk is $R(t) = sv^2 ct$. The tissue consists entirely of the cell type with the lower mutation rate. If $ru^2 < sv^2$, all cells are stem cells, x . Otherwise, there are only ‘differentiated’ cells, y . Obviously, in the absence of stem cells, the y cells have to act like stem cells. Hence the subdivision into stem cells and differentiated cells does not affect the rate of accumulation of neutral mutations.

This result should not be surprising. Intuitively, neutral mutations can only become fixed if they arise in the stem cell compartment. Kimura (1968) showed that the rate of neutral evolution is independent of the population size. Thus the size of the stem cell compartment does not matter.

(f) Stack design

So far, we have considered cell populations consisting of one compartment of stem cells and one compartment of differentiated cells. Let us now generalize to a stack of

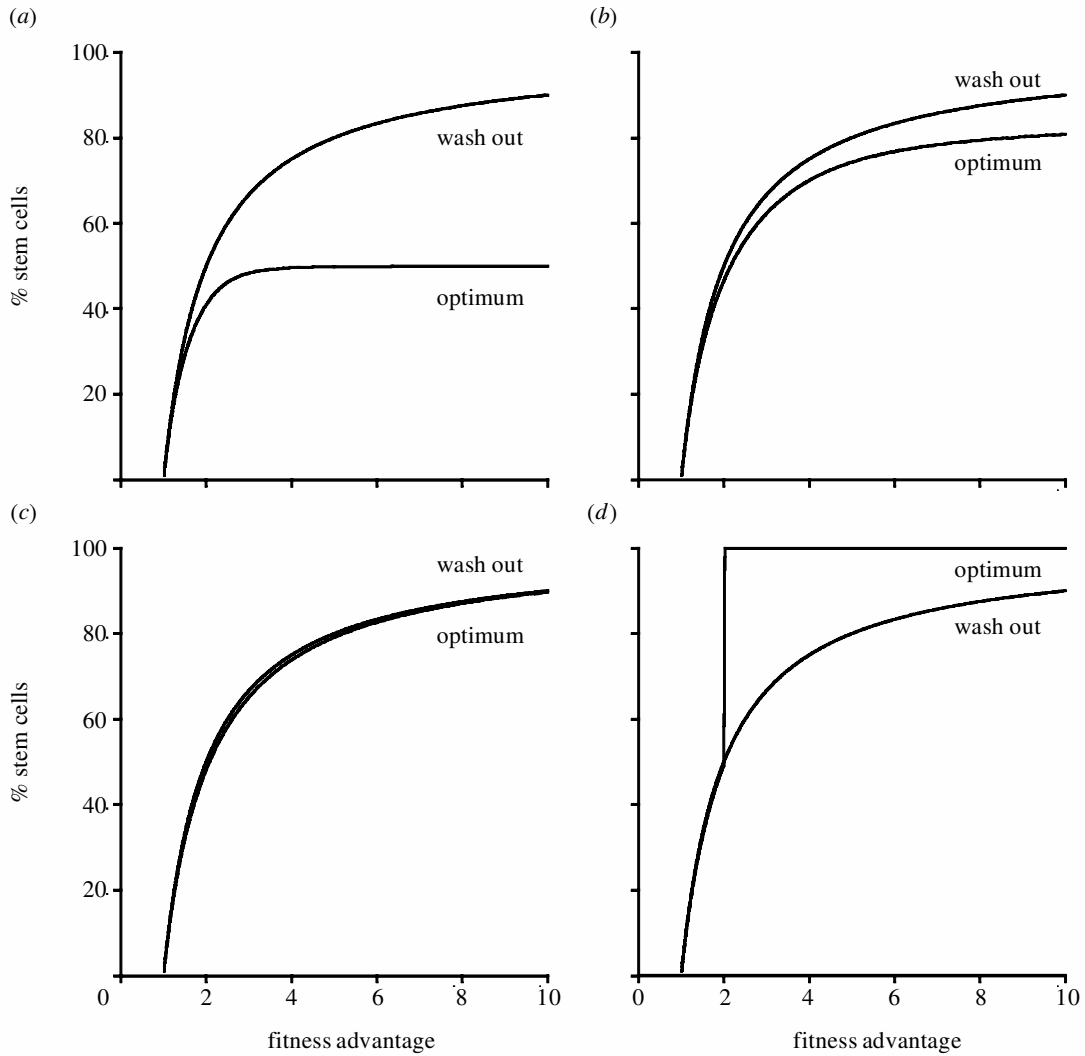


Figure 3. Optimum design and wash-out threshold as function of the mutant fitness, α . We plot the optimum fraction of stem cells that minimizes the risk function $R(t) = [(rux + svy) p_x + svy\hat{w} p_y]t$. We also plot the fraction of stem cells that guarantees wash out, $x = c/r(1 - 1/\alpha)$. The optimum depends on the mutation rate in stem cells, u , and the mutation rate in differentiated cells, v . The ratio v/u is 1 in (a), 1.5 in (b), 2 in (c) and 3 in (d). If $v/u = 1$, the optimal stem cell fraction converges to 1/2. If $v/u < 2\alpha - 1/(\alpha - 1)$, the optimal stem cell fraction is smaller than the wash-out threshold. If $v/u > 2\alpha - 1/(\alpha - 1)$, the optimum is achieved if all cells are stem cells.

$n + 1$ compartments (figure 4). The bottom compartment (the stem cell compartment) exports cells into the second compartment which feeds cells into the next compartment and so on. Cells are discarded from the top compartment. We call this a stack design. This set-up approximates the design of colon and epidermal compartments, in which stem cells reside at the bottom of the tissue and differentiated cells push towards the epithelial surface.

Enumerate the compartments $i = 0, 1, \dots, n$. The size of compartment i is denoted by x_i . Cells in compartment i proliferate at a rate r_i and give rise to mutated cells at rate u_i . Cells are transported from compartment 0 to compartment 1 at a rate r_0x_0 , from compartment 1 to compartment 2 at a rate $r_0x_0 + r_1x_1$, etc. Hence the export rate from compartment i to compartment $i + 1$ is given by $\sum_{k=0}^i r_k x_k$.

Consider a mutant with selective advantage $\alpha > 1$. For this mutant, the wash-out condition from compartment i is given by

$$r_i x_i (\alpha - 1) \leq \sum_{k=0}^{i-1} r_k x_k \tag{2.8}$$

The stack design that guarantees wash out of the mutant in compartment $i = 1, 2, \dots, n$ is

$$r_i x_i = \frac{1}{\alpha - 1} \left(\frac{\alpha}{\alpha - 1} \right)^{i-1} r_0 x_0 \quad \text{for } i = 1, 2, \dots, n. \tag{2.9}$$

At the top of the stack, cells are discarded at the rate

$$c = \sum_{i=0}^n r_i x_i = \left(\frac{\alpha}{\alpha - 1} \right)^n r_0 x_0. \tag{2.10}$$

As before, we are interested in minimizing the risk of cancer initiation subject to a constant value c . The optimization calculation for a stack of n compartments gives complicated expressions. We know, however, that the stack design that is optimum for protecting against a specific mutant with fitness advantage α is close to the stack

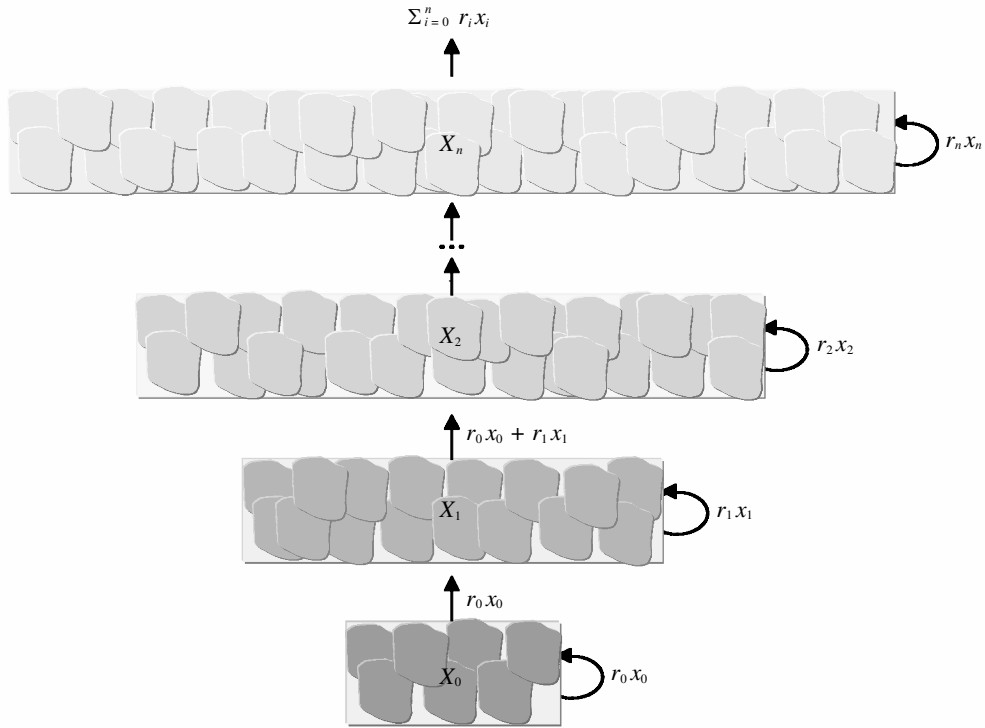


Figure 4. Stack design. Consider a tissue consisting of $n + 1$ compartments enumerated $i = 0, 1, \dots, n$. Cells in compartment i proliferate at rate r_i and are exported to compartment $i + 1$ at a rate $\sum_{k=i}^n r_k x_k$. Cells are discarded at the top of the stack at a rate $\sum_{i=0}^n r_i x_i$. The risk of initiating cancer can be reduced by increasing the number of compartments. Wash out of mutated cells in compartments $i = 1, 2, \dots, n$ is guaranteed by the geometric series given by equation (2.11).

design that guarantees wash out in the compartments $i = 1, 2, \dots, n$. For a fixed c this design is

$$r_0 x_0 = c \left(1 - \frac{1}{\alpha}\right)^n,$$

$$r_i x_i = \frac{c}{\alpha} \left(1 - \frac{1}{\alpha}\right)^{n-i} \quad \text{for } i = 1, 2, \dots, n. \quad (2.11)$$

All compartments except for the stem cell pool, $i = 0$, follow a geometric series, i.e. each two successive compartments are in the same ratio (figure 5). The overall risk of cancer initiation is greatly reduced by adopting a stack design. Using the critical wash-out parameters, the risk becomes

$$R(t) = \left(\sum_{i=0}^n u_i r_i x_i \right) u_0 r_0 x_0 \rho_0 t = \left[\sum_{i=1}^n u_i \frac{c}{\alpha - 1} \left(\frac{\alpha}{\alpha - 1} \right)^{i-1-n} + u_0 c \left(\frac{\alpha}{\alpha - 1} \right)^{-n} \right] u_0 c \left(\frac{\alpha}{\alpha - 1} \right)^{-n} \rho_0 t. \quad (2.12)$$

Here, $\rho_0 = (1 - 1/\alpha)/(1 - 1/\alpha^x)$. If the mutation rate is the same for all compartments, $u_0 = u_1 = \dots = u_n = u$, the risk takes the form

$$R(t) = c^2 u^2 \left(\frac{\alpha}{\alpha - 1} \right)^{-n} \rho_0 t. \quad (2.13)$$

Here, we have the constraint that $R(t) \geq cu^2 t$ if $n \rightarrow \infty$.

(g) Dependence of somatic fitness on differentiation stages

We can also consider a mutation conferring different fitness advantages α_x and α_y , to mutated stem cells and

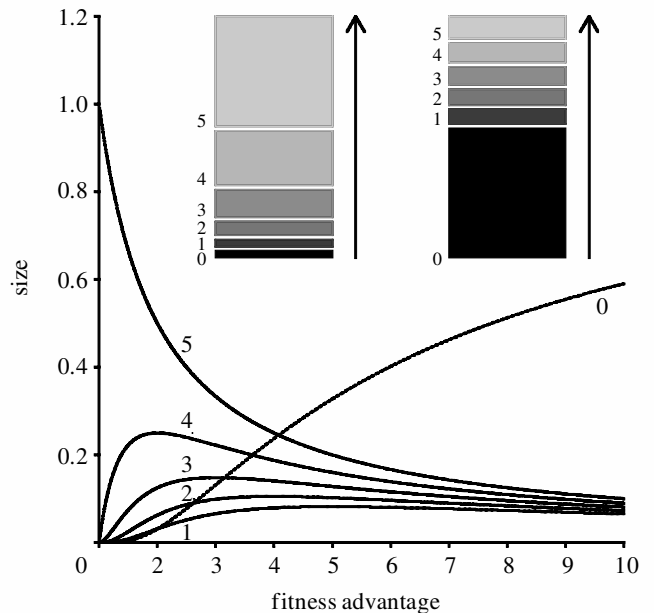


Figure 5. Optimal stack design. We plot equation (2.11) for stacks $i = 0, \dots, n = 5$ to explore the stack sizes optimal to prevent tumour initiation by mutations with varying fitness values, α . The optimal size function of the stem cell compartment, $i = 0$, increases monotonically with α : the higher the fitness advantage of the mutation, the more stem cells are needed to guarantee wash out. The functions of compartments $i = 1, \dots, 4$ have intermediate optima. The function of compartment $i = 5$ decreases monotonically. The left stack design shows the compartment sizes for $\alpha = 2$. The right stack design shows the compartment sizes for $\alpha = 10$. Cells are moved upwards and discarded at the top of the stack.

mutated differentiated cells, respectively. The transition from state (X_0, Y_0) to state (X_1, Y_1) occurs at rate $p_x = rxup_{x_0}$ where $p_x = (1 - 1/\alpha_x)/(1 - 1/\alpha_x^2)$. The transition from state (X_0, Y_0) to state (X_0, Y_2) occurs at rate $p_y = syvp_{y_0}$, where $p_y = [1 - 1/(\alpha_y - \alpha_0)]/[1 - 1/(\alpha_y - \alpha_0)^2]$. The wash-out rate is denoted by $\alpha_0 = dx/(sy)$. The transition from state (X_0, Y_2) to state (X_1, Y_1) occurs at rate p_x . The risk function of cancer initiation via slightly advantageous mutations, equation (2.7) now takes the form

$$R(t) = u^2 c^2 \left[\left(\zeta + \frac{v}{u}(1 - \zeta) \right) \zeta \left(1 - \frac{1}{\alpha_x} \right) + \left(\frac{v}{u} \right)^2 \frac{(1 - \zeta)[(\alpha_y - 1) - \alpha_y \zeta]^2}{(\alpha_y - 1)(\alpha_y - (\alpha_y + 1)\zeta)} \right] t. \quad (2.14)$$

Again, there is an optimal compartment size to protect against mutations initiating tumorigenesis. This property of the calculation remains unchanged even if fitness values differ between the X and the Y compartments.

(h) Mutations that ignore compartment boundaries

So far, we have considered mutations that are at least initially constrained by the boundaries of the compartment in which they arise. Cells bearing such mutations can proliferate to take over the respective compartment, but are then confined within the compartment boundaries. They cannot proliferate to exceed the constant compartment size without further mutations. Let us now consider advantageous mutations that, if not washed out, immediately give rise to cellular proliferation that exceeds the compartment boundary.

In that case, we want to maximize the expected time the system will remain in state (X_0, Y_0) . This is equivalent to minimizing $p_x + p_y$ subject to the constraint $c = rx + sy = \text{constant}$. The optimum tissue design again depends on the mutation rates in stem cells and differentiated cells. If $v/u > (\alpha - 1)/(\alpha - 1 + d/r)$, then the optimum abundance of stem cells is the one guaranteeing wash out of mutants in the differentiated cell compartment, $x = [c(\alpha - 1)]/[\alpha - 1 + d/r]$. If however, $v/u < (\alpha - 1)/(\alpha - 1 + d/r)$, then the optimum tissue design does not contain any stem cells, $x = 0$.

3. DISCUSSION

We propose that multicellular organisms have evolved complex tissue designs to minimize the rate of somatic evolution that leads to cancer. Tissues evolved to be subdivided into stem cells and lineage-committed cells. Stem cells might have reduced mutation rates due to preservation of immortal strands and defection in DNA repair (Cairns 2002). Stem cells replenish the whole tissue by asymmetrical cell divisions and export of lineage-committed cells into differentiated cell compartments. Lineage-committed cells of various differentiation stages proliferate to fulfil their organ-specific tasks. The subdivision into stem cells and differentiated cells effectively reduces the risk of accumulating mutations that make the respective cell prone to selfish unregulated proliferation.

We show that tissue design has no effect on the emergence and spread of neutral mutations and does not alter

the fitness of the cell. The spread of cells harbouring advantageous mutations, however, is dramatically affected by tissue design. An advantageous mutation arising in a differentiated cell pool can be washed out by the continuous influx of unmutated cells from the precursor compartment. The continuous renewal of differentiated cell compartments might succeed to prevent the spread of selfish cells that would otherwise initiate neoplastic growth. Advantageous mutations arising in the stem cell compartment, however, are likely to reach fixation in the stem cell compartment as well as in differentiated cell compartments. The abundance of stem cells takes an intermediate optimum: if there are too many stem cells, then the risk of receiving stem cell mutations is too high. If there are too few stem cells, then the wash-out rate of mutated differentiated cells is too low. Here, we show how the optimum architecture depends on fitness advantages and mutation rates. We also calculate the configuration of a stack of cellular compartments that guarantees wash out of mutants.

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