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Tissue architecture, feedback regulation, and resilience to viral infection

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Abstract

Tissue homeostasis is one of the central requirements for the existence of multicellular organisms, and is maintained by complex feedback regulatory processes. Homeostasis can be disturbed by diseases such as viruses and tumors. Here, we use mathematical models to investigate how tissue architecture influences the ability to maintain tissue homeostasis during viral infections. In particular, two different tissue designs are considered. In the first scenario, stem cells secrete negative feedback factors that influence the balance between stem cell self-renewal and differentiation. In the second scenario, those feedback factors are not produced by stem cells but by differentiated cells. The model shows a tradeoff. If feedback factors are produced by stem cells, then a viral infection will lead to a significant reduction in the number of differentiated cells leading to tissue pathology, but the number of stem cells is not affected at equilibrium. In contrast, if the feedback factors are produced by differentiated cells, a viral infection never reduces the number of tissue cells at equilibrium because the feedback mechanism compensates for virus-induced cells death. The number of stem cells, however, becomes elevated, which could increase the chance of these stem cells to accumulate mutations that can drive cancer. Interestingly, if the virus interferes with feedback factor production by cells, uncontrolled growth can occur in the presence of the virus even in the absence of genetic lesions in cells. Hence, the optimal design would be to produce feedback factors by both stem and differentiated cells in quantities that strike a balance between protecting against tissue destruction and stem cell elevation during infection.

Keywords

virus dynamics; mathematical models; tissue architecture; tissue design; stem cells

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1. Introduction

The functioning of multicellular organisms requires tight regulation of cellular behavior such that the number of tissue cells is maintained at constant levels. Human adult tissue is thought to be maintained by tissue stem cells that have self-renewal capacity. The tissue stem cells differentiate into transit amplifying cells that are capable of a limited number of divisions, and further differentiation results in terminally differentiated cells that cannot divide anymore (Crosnier et al., 2006). Terminally differentiated cells perform their function that is required for the tissue, and die after a certain period of time. Homeostasis is thought to be achieved by various negative feedback loops (Daluiski et al., 2001; Elgjo and Reichelt, 2004; Lander et al., 2009; McPherron et al., 1997; Tzeng et al., 2011; Wu et al., 2003; Yamasaki et al., 2003). An important process that is subject to regulation is the decision for stem cells to self-renew upon division (giving rise to two daughter stem cells), or to differentiate, thus giving rise to two daughter cells that are on the path to terminal differentiation. As the number of cells grows, feedback factors have been shown to block self-renewal and promote differentiation instead, which limits tissue size through the eventual death of terminally differentiated cells. Other feedback factors down-regulate the rate of cell division as the number of cells grows, thus also preventing excessive growth. Such feedback loops have been observed in a variety of tissues (Daluiski et al., 2001; Elgjo and Reichelt, 2004; Lander et al., 2009; McPherron et al., 1997; Tzeng et al., 2011; Wu et al., 2003; Yamasaki et al., 2003) and many feedback factors have been found to belong to the transforming growth factor β (TGF-β) superfamily. For example, GDF11 is produced by neuronal cells in the mouse olfactory epithelium and provides feedback to inhibit the production of neurons. Lack of GDF11 leads to elevated production of neurons (Lander et al., 2009).

Tissue homeostasis can be disturbed by diseases. The development of tumors obviously leads to uncontrolled cell growth. Viral infection can lead to the depletion of tissue cells and compromised tissue function. There is also an interplay between viral infections and the development of tumors, with several viruses thought to contribute to tumor initiation (Butel, 2000; Zur Hausen, 2009). Because viral infections can destroy tissue cells, they thereby influence the feedback dynamics of the tissue, for example by reducing the level of feedback inhibition and thus inducing altered levels of cell proliferation and differentiation. In this paper we use mathematical models to study the consequences of viral infections for the dynamics of feedback regulation in otherwise healthy tissue. In particular, we ask how the design of regulatory circuits affects the protection against pathology. The models suggest the presence of an important tradeoff: If the regulatory mechanisms are designed to provide maximal protection against virus-induced tissue destruction, this can lead to increased levels of stem cell proliferation, which can promote the development of cancers. Interestingly, it is shown that in this case, viral interference with feedback factor production can lead to uncontrolled cellular proliferation even in the absence of induced genetic lesions in cells. In contrast, if tissue is designed to minimize the impact of the infection on stem cell proliferation, then virus-induced tissue destruction is maximized. Hence, evolution is likely to favor a tissue design that optimizes this tradeoff.

2. Results

2.1. The model

A model will be considered that includes two basic populations: (i) cells with self-renewal capacity, which includes both tissue stem cells and transit amplifying cells. For simplicity, this population will be collectively referred to as “stem cells”, and is denoted by S. (ii) terminally differentiated cells that cannot divide anymore, denoted by D. It is based on previous models (Lander et al., 2009; Lo et al., 2009; Rodriguez-Brenes et al., 2011) and given by the following set of ordinary differential equations that describe the time evolution of these cell populations.

$$\begin{aligned}\frac{dS}{dt}&=r'Sp'-(1-p')r'S\\ \frac{dD}{dt}&=2(1-p')r'S-aD\end{aligned} \quad (1)$$

This represents a minimally parameterized model to describe tissue dynamics, which allows us to obtain analytical insights. Stem cells divide with a rate r'. With a probability p', division results in two daughter stem cells (self-renewal). With a probability $1-p'$, division results in two differentiated cells. Differentiated cells die with a rate a. The primes in the notation mean that these parameters can be influenced by negative feedback. Feedback factors can either be produced by stem cells or by differentiated cells. In the context of differentiation, this is expressed as $p'=p/(n_1S+n_2D+1)$. Thus, the basic probability of self-renewal is given by p, and the parameters n_1 and n_2 describe the relative strength of feedback factors produced by stem and differentiated cells, respectively. Feedback on the rate of cell division is expressed by $r'=r/(m_1S+m_2D+1)$. The parameter r describes the intrinsic rate of cell division, and the relative strength of feedback factors produced by stem and differentiated cells is given by m_1 and m_2, respectively.

Next, we introduce a viral infection into this model, assuming that the virus can only infect differentiated cells and not the stem cells. Denoting infected differentiated cells by I, this is formulated as follows according to standard virus dynamics equations.

$$\begin{aligned}\frac{dS}{dt}&=r'Sp'-(1-p')r'S\\ \frac{dD}{dt}&=2(1-p')r'S-aD-bDI\\ \frac{dI}{dt}&=bDI-a_dI\end{aligned} \quad (2)$$

The infection is modeled based on established virus dynamics formulations (Nowak and May, 2000; Perelson, 2002). Upon contact with uninfected differentiated cells, infection occurs with a rate b. Infected cells die with a rate a_d. Free virus particles are not explicitly taken into account but are assumed to be in a quasi-steady state. This is a well justified assumption in the field (Nowak and May, 2000) because the turnover of free virus is much faster than that of infected cells. In the presence of the virus infection, two types of differentiated cells exist (uninfected and infected), and both can potentially secrete feedback factors. Infected cells can maximally produce the same amount of feedback factors as uninfected cells, but may produce less due to viral impairment. Thus, the self-renewal

feedback is now given by $p'=p/(n_1S + n_2D + fn_2I +1)$, where $f \leq 1$. Similarly, the division feedback is given by $r'=r/(m_1S + m_2D + gm_2I +1)$, where $g \leq 1$.

We will start by analyzing a scenario where there is only feedback on self-renewal/differentiation (p′). No feedback on the rate of cell division will be assumed to exist for now. Feedback on self-renewal is the most important feedback loop that enables the existence of a stable equilibrium in this system (Lander et al., 2009; Lo et al., 2009), and this simplification helps us obtain some key results. Subsequently, feedback on the rate of cell division is introduced and examined.

2.2. Feedback on self-renewal only

This section considers the scenario where there is feedback on self-renewal only, and the rate of cell division is simply given by the parameter r ($m_1=m_2=0$). The following outcomes are observed. Persistence of the tissue requires that $p>0.5$. In this case the system can converge to two different equilibria depending on the parameter values. If the infection is not established, the following equilibrium is observed:

$$S^{(0)}=\frac{a(2p-1)}{n_2 r+an_1}$$
$$D^{(0)}=\frac{r(2p-1)}{n_2 r+an_1}$$
$$I^{(0)}=0$$

If the virus does establish an infection, the dynamics converge to the following steady state:

$$S^{(1)}=\frac{a_d[b(2p-1)-n_2(a_d-fa)]}{b(rfn_2+a_d n_1)}$$
$$D^{(1)}=\frac{a_d}{b}$$
$$I^{(1)}=\frac{rb(2p-1)-a_d(rn_2+an_1)}{b(rfn_2+a_d n_1)}$$

Successful infection is established if the basic reproductive ratio of the virus (Anderson and May, 1991; Nowak and May, 2000) is greater than one, given by $R_0 = bD^{(0)}/a_d$.

We are interested in the effect of the infection on tissue homeostasis. Therefore, we compare the number of stem cells and differentiated cells in the presence of the infection with the number in the absence of the infection at equilibrium, expressed as ratios $S_{frac}=S^{(1)}/S^{(0)}$ and $D_{frac}=(D^{(1)}+I^{(1)})/D^{(0)}$. Let us first examine the dependence of these ratios on the viral replication rate, b (Figure 1). We consider the effect of infection in the context of two different tissue designs. First we assume that feedback factors are only produced by stem cells and not by differentiated cells ($n_1>0$; $n_2=0$). Figure 1a shows that in this case, the fraction of stem cells during infection, S_{frac}, is independent of the viral replication rate, b. The fraction of differentiated cells, D_{frac}, declines with b towards an asymptote because a faster replicating virus leads to a higher degree of cell depletion (Figure 1a). If the basic reproductive ratio of the virus, R_0, is around its threshold value of one, there is a strong dependence. But if $R_0>>1$, the dependence is weak while converging to the asymptote. Now, the opposite scenario is explored where all feedback factors are produced by differentiated cells and none by stem cells ($n_1=0$; $n_2>0$). The fraction of stem cells during infection, S_{frac},

increases asymptotically with b (figure 1b). The reason is that a faster replicating virus kills more differentiated cells, which triggers the feedback mechanism to compensate for this, achieved through an elevation of the stem cell compartment. This dependence is again strong for R_0 around one, and becomes weak for R_0>>1. Because of the feedback induced compensation for the death of differentiated cells, this population does not depend on the viral replication rate in this case (Figure 1b).

Figure 1 shows some interesting differences between the tissue designs. To explore this further, we make a simplification. Because the fractions S_{frac} and D_{frac} do not strongly depend on the viral replication rate b for R_0>>1, we will consider these fractions at the limit b$\to\infty$, i.e. $S_{frac}^{b\to\infty}$ and $D_{frac}^{b\to\infty}$. The expressions are given by

$$S_{frac}^{b\to\infty}=\frac{a_d\ (n_2\ r+an_1)}{(rfn_2+a_d\ n_1)\ a},\ D_{frac}^{b\to\infty}=\frac{n_2\ r+an_1}{r\ fn_2+a_d\ n_1}. \quad (3)$$

Let us now investigate the properties of the two tissue designs in more detail.

If feedback factors are only produced by stem cells (n_1>0; n_2=0), the expressions simplify as follows.

$$\begin{aligned} S_{frac}^{b\to\infty}&=1\\ D_{frac}^{b\to\infty}&=\frac{a}{a_d} \end{aligned} \quad (4)$$

That is, the presence of infection does not alter the number of stem cells, but it lowers the total number of differentiated cells. This is also shown without the simplification b$\to\infty$ in Figure 2a. Since many tumors are thought to arise by mutations in stem cells, a lack of increase of this population means that the infection is not likely to increase the risk of carcinogenesis. Tissue size is compromised, however, and the degree of reduction in the number of differentiated cells is given by the virus-induced death rate of infected cells, a_d, compared to the death rate of uninfected cells, a. Therefore, if the virus kills the cells relatively fast (cytopathic virus), the degree of pathology is predicted to be large.

In the opposite case, where only differentiated cells produce feedback factors (n_1=0; n_2>0), the expressions or $S_{frac}^{b\to\infty}$ and $D_{frac}^{b\to\infty}$ simplify as follows.

$$\begin{aligned} S_{frac}^{b\to\infty}&=\frac{a_d}{fa}\\ D_{frac}^{b\to\infty}&=\frac{1}{f} \end{aligned} \quad (5)$$

Let us first assume that the virus does not impair feedback production by infected cells, i.e. f=1. Now, we find that the virus infection does not reduce the number of tissue cells, thus leading to absence of virus-induced pathology. The number of differentiated cells remains identical compared to the level in the absence of the infection. Note that this result is independent of the rate of virus-induced cell death and also applies to cytopathic viruses. Virus-induced cell death is compensated for by feedback modulation. The number of stem

cells, however, is increased by the infection, proportional to the degree of viral cytopathicity, a_d. The higher the death rate of infected relative to uninfected cells, the larger the elevation of the stem cell population. These trends are also shown in the absence of the simplification $b \to \infty$ in Figure 2b. A higher number of stem cells means more stem cell divisions, which increases the chances of mutations. This in turn increases the chances of cancer initiation. Next, assume that the virus impairs the production of feedback factors in infected cells, i.e. $f<1$. In the extreme case, $f=0$, we find that both the differentiated and the stem cell populations increase towards infinity (Figure 2c). In other words, unbounded proliferation of stem cells is observed, which would correspond to a tumor. Interestingly, unbounded growth does not necessarily rely on any genetic alteration in the cells. If viral replication compromises the function of differentiated cells, resulting in the lack of feedback factor production, the tissue becomes dysregulated, leading to cancerous growth. If feedback factor production is not completely abolished but reduced ($0<f<1$), the cell populations rise towards a new steady state (Figure 2d), the level of which is determined by the value of f. While growth is not unbounded anymore, this can also be considered cancerous growth. In fact, many cancers are characterized by growth periods, followed by periods of stasis.

In the above analysis it was assumed that virus infection can reduce the level of feedback factor production ($f<1$). This is a reasonable assumption because viruses can compromise cellular function in a variety of ways. Theoretically, it is also possible that the presence of the virus enhances feedback factor production ($f>1$), e.g. by up-regulating gene expression. As is clear from the above expressions for $S_{frac}^{b\to\infty}$ and $D_{frac}^{b\to\infty}$, this would reduce both the number of stem and differentiated cells, thus promoting tissue pathology.

In summary, there is a tradeoff in the design of regulatory circuits in the context of viral infections. If feedback factors are produced mostly by stem cells, then stem cell homeostasis remains unaltered during viral infections, but maximal virus-induced tissue destruction is observed. In contrast, if feedback factors are produced mostly by differentiated cells, then tissue destruction will not be observed, but there is a high risk of developing cancer due to elevated stem cell replication. Therefore, the best design, i.e. the one most likely favored by evolution, will be a balance of feedback factor production by stem and differentiated cells that optimizes this tradeoff. It is currently not possible to calculate this optimal tradeoff. As can be seen from the full expressions for or $S_{frac}^{b\to\infty}$ and $D_{frac}^{b\to\infty}$ (3), a change in either parameter results in an equal change in $S_{frac}^{b\to\infty}$ and $D_{frac}^{b\to\infty}$. For example, a 2-fold increase in n_1 leads to the same fold reduction in the values of $S_{frac}^{b\to\infty}$ and $S_{frac}^{b\to\infty}$. That is, the number of stem cells during infection is reduced towards its pre-infection levels (thus reducing risk of carcinogenesis), and the number of differentiated cells is reduced below its pre-infection level by the same amount, thus increasing the degree of pathology.

The uncertain part is how to interpret this. Although a given change in the degree of feedback inhibition changes the number of stem cells by as much as it changes the number of differentiated cells, it is unclear how this change in homeostasis relates to disease development. For example it is possible that a 2-fold reduction in the number of stem cells only marginally reduces the chances to generate carcinogenic mutations, but that a 2-fold

reduction in the number of differentiated tissue cells kills the organism. These types of considerations will determine the optimal balance between n_1 and n_2, and hence this is currently not possible to calculate.

2.3. Feedback on self-renewal and cell division rate

Here, we consider the additional negative feedback on the rate of cell division, i.e. $m_1>0$ and $m_2>0$. Feedback factors can again be produced either by stem cells (m_1) or differentiated cells (m_2). This model is studied numerically because equilibrium expression are very complex and not insightful and hence not written down here. The results described in the previous section still hold in this more complex situation. If the viral infection leads to increased cell growth, the growth rate is slower in the presence of this additional feedback (Figure 3). This makes sense because the feedback slows down the rate of cell division. Such a slow growth pattern in the presence of feedback on cell division has recently been described (Rodriguez-Brenes et al., 2011).

2.4. Infection of stem cells

So far, it was assumed that only differentiated cells become infected. Here it will be assumed that stem cells can also become infected. This has been documented to occur in retroviruses and other viruses (Banerjee et al., 2010), although typically the virus does not tend to be very active in stem cells but can be transmitted by cell division. The following model describes stem cell infection.

$$\begin{aligned}\frac{dS}{dt}&=r'Sp'-(1-p')r'S-b_SS(I_d+\eta I_s)\\ \frac{dD}{dt}&=2(1-p')r'S-aD-b_dD(I_d+\eta I_S)\\ \frac{dI_s}{dt}&=b_sS(I_d+\eta I_S)-a_sI_s+rI_sp-(1-p')rI_s\\ \frac{dI_d}{dt}&=b_dD(I_d+\eta I_S)-a_dI_d+2(1-p')rI_s\end{aligned} \quad (6)$$

Now there are two infected cell populations instead of one. The infected differentiated cells are denoted by I_d, while the infected stem cells are denoted by I_s. Both populations die with rate a_d and a_s, respectively. Infection of differentiated and stem cells occurs with a rate b_d and b_s, respectively, and the rate of virus production is assumed to be different in stem and differentiated cells, expressed by the factor η. We will only consider feedback on differentiation, described by $p'=p/(n_1S+f_sn_1I_s+n_2D+f_dn_2I_d+1)$. The difference compared to model (2) is that virus infection can not only inhibit feedback production in differentiated cells but also in stem cells, described by parameters f_d and f_s, respectively. This model gives rise to equilibrium expressions that are too complex to obtain, so the model is explored numerically.

In model (2), which only took account of differentiated cell infection, there were two basic outcomes. Either the infection was not established or the infection was established in which case the dynamics converged to the internal equilibrium. With stem cell infection, there are two internal equilibria (Figure 4). In one case, all populations persist, as before (Figure 4a). In the alternative case, the population of uninfected stem cells goes extinct and only infected stem cells persist (Figure 4b). Consequently, the number of uninfected differentiated cells also goes extinct. Extinction of uninfected cells occurs because of indirect competition

(Holt, 1977). Both infected and uninfected stem cells proliferate, and their population sizes are regulated by the production of negative feedback signals. While proliferation is assumed to occur with the same rate in both populations, the infected cell population gains at the expense of the uninfected cell population due to the process of infection. Hence, the infected cells can grow to higher levels and produce more negative feedback signals than the uninfected cell population, which is consequently driven to extinction through feedback-induced terminal differentiation and death.

Figure 5 explores numerically, under which conditions these two outcomes are achieved. Two parameters were varied: the rate of stem cell infection, b_s, and the rate of infected stem cell death, a_s. Simulations were run until the population of uninfected stem cells either reached equilibrium (persistence) or declined to extinction. The outcome was coded by different colors and symbols, with blue (×) indicating persistence and red (+) extinction. In many virus infections, it is thought that there is a correlation between the rate of virus production and the death rate of infected cells. Hence, in Figure 5, we assumed that the parameters η and a_s are positively correlated, i.e. a higher rate of virus production leads to a higher rate of cell death in the infected stem cells. A seen in Figure 5, a higher rate of stem cell infection (higher b_s) and a lower death rate of infected cells (lower a_s) promote the extinction of uninfected stem cells. As mentioned above, stem cell infecting viruses tend to be characterized by a relatively low replicative activity in the stem cells, indicating a low degree of cell killing. Hence, it is likely that such viruses will lead to the infection of the whole stem cell population (Figure 5).

In order to examine the impact of the infection on tissue homeostasis, let us therefore first assume that the virus is weakly cytopathic in stem cells (i.e. small value of a_s) and that hence all stem cells are infected. Now the expression for S_{frac} and D_{frac} do not depend on the infection rates anymore, because all susceptible cells are infected and virus spread is driven only by the division of infected cells. For the case $n_1=0$ and $n_2>0$, we obtain:

$$S_{frac}=\frac{ra_d\,[r(2q-1)-a_s]}{f_d a_d\,(2q-1)(r^2-a_s^2)}$$
$$D_{frac}=\frac{r(2q-1)-a_s}{f_d\,(2q-1)(r+a_s)}.$$

If the value of a_s is small relative to r, this converges to

$$S_{frac}=\frac{a_d}{f_d a}$$
$$D_{frac}=\frac{1}{f_d},$$

which is identical to expression (5) above. For the case $n_1>0$ and $n_2=0$, we obtain:

$$S_{frac}=\frac{r(2q-1)-a_s}{f_s\,(r+a_s)(2q-1)}$$
$$D_{frac}=\frac{a[r^2\,(2q-1)+a_s\,(a_s-2rq)]}{f_s a_d r(r+a_s)(2q-1)}$$

If the value of a_s is small relative to r, this converges to

$$S_{frac}=\frac{1}{f_s}$$
$$D_{frac}=\frac{a}{f_s a_d}.$$

This is similar to expression (4) above, with the addition that feedback signal impairment in stem cells, f_s, now influences the outcome of infection. Thus, if the virus impairs feedback factor production in stem cells, uncontrolled cellular growth is possible in this scenario as well, brought about by compromised feedback regulation in the absence of genetic transformation of cells.

Therefore, the basic conclusions obtained for the model without stem cell infection hold. The only difference is that impairment of feedback factor production in stem cells can also contribute to uncontrolled cancerous growth. Note, however, that viral persistence in stem cells can further have other effects not accounted for in the model, such as the genetic transformation of cells, which can again promote the initiation of cancer in the long term.

In contrast, if the value of a_s is larger and consequently both uninfected and infected stem cells persist, the situation is more complex. In principle, the conclusions reached from model (2) hold (Figure 6), but the population sizes of both the stem cells and the differentiated cells are lower, leading to tissue pathology due to a stem cell killing. Thus, in the cases when population levels were predicted to remain constant in the face of infection in model (2), infection can now reduce them due to virus-induced stem cell death (Figure 6). Since in most cases of stem cell infection the virus does not show significant replicative activity in stem cells, this scenario is not further explored.

To conclude, this section showed that taking into account stem cell infection does not lead to significant changes to our results derived from the model without stem cell infection. In the biologically realistic scenario where the virus does not kill the stem cells with significant rates, the whole tissue stem cell population becomes infected, and the results regarding tissue homeostasis remain largely unchanged. In the less realistic scenario when the virus kills stem cells with relatively large rates, additional tissue pathology can occur due to stem cell death. Interestingly, this suggests that at least in the short term, the infection is less detrimental to the host if the entire stem cell population becomes infected, although the long-term cost can be a higher chance of genetic transformation and hence the development of cancer.

3. Discussion and Conclusion

We investigated how the design of feedback control influences the tissue response to infection. An important difference was observed depending on whether the feedback factors are secreted from the differentiated cells or the stem cells. Secretion from stem cells only ensures that during a viral infection, the stem cell population remains constant, thus minimizing the risk of mutagenesis which could come about from increased levels of cell division. This, however, comes at the cost of maximally possible virus-induced tissue pathology. On the other hand, if feedback factors are secreted from differentiated cells only, then virus-induced tissue pathology is entirely absent because any cell death is compensated

for by reduction of feedback inhibition. The price to pay is a significantly enhanced level of stem cell division, which could sharply increase stem cell mutagenesis and thus the incidence of cancer. Moreover, if the virus impairs cell function (Butel, 2000) such that feedback factors are produced at reduced levels, then excessive tissue growth is observed, i.e. the organism develops cancer as a result of the disrupted feedback mechanisms by the virus. Therefore, it is likely that the optimal design (i.e. favored by selection) is the one where feedback factors are produced by both stem and differentiated cells at relative levels that optimize this tradeoff. The notion that in the context of tissue design there is a tradeoff between protection against pathology and protection against excess proliferation during infection provides a new perspective for understanding how tissue architecture relates to function.

It is clear that there is an important connection between viral infections and cancer (Butel, 2000; Damania, 2007; Elgui de Oliveira, 2007; Helt and Galloway, 2003). Viruses can carry oncogenes (Tarbouriech et al., 2006) and they are thought to induce cancer by causing mutations, typically by inserting themselves into the genome of the host (Helt and Galloway, 2003). Our model suggests a different mode of virus-induced carcinogenesis that does not rely on the generation of mutations in the cells (Banerjee et al., 2010). If the virus simply impairs cell function such that feedback factors in infected cells are not produced, then the corruption of this feedback itself can lead to unbounded cellular growth as long as the virus is present.

This brings us to a caveat. If the basic reproductive ratio of the virus is greater than one, a persistent infection is established and the virus will remain in the host forever in the model. In this way, the growth of a tumor can be continuously driven by the corruption of feedback factor production. Our model does not include immune responses to infection, since this is beyond the scope of the current study. If immune responses are mounted, viral infections can potentially be cleared, as is the case for many infections. If a virus that is eventually cleared impairs production of feedback factors, then the resulting cellular growth will only be temporary and stop once the infection has been removed by the immune system. In this case, whether the overabundance of cells persists in the long term depends on whether stem cells are infected or not. If stem cells are infected and can be removed by the immune system, the number of cells can be brought back to homeostatic levels. If only differentiated cells are infected, the excess stem cell population that resulted from proliferation cannot be removed because they are not visible to the immune system. In either scenario, the growth that occurred during the presence of the infection can significantly promote accumulation of mutations due to the relatively large number of cell divisions, thus increasing the chances of genetic transformation. There are many viruses that establish persistent infections and that are not cleared, a large fraction of which is probably unknown because they do not cause any overt symptoms. Such viruses could pose an oncogenic danger if they interfere with feedback factor production in infected cells, even if they cannot genetically transform cells.

4. Methods

The results reported in this paper are based on the analysis of ordinary differential equations (ODEs). They were analyzed by a combination of analytical and numerical techniques.

Numerical simulations were performed with Matlab, using the Runge Kutta 4th order ODE solver. In the simulations, parameters were chosen for illustrative purposes only. Currently, the parameters connected to feedback-mediated tissue regulation are not known, so measured parameters cannot be used. In addition, the paper is conceptual in nature rather than describing the dynamics of one particular virus infection.

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- Tissue homeostasis is required for multi-cellular organisms
- Tissue homeostasis is maintained by feedback regulation
- Feedback regulation can be influenced by viral infections
- We investigate the effect of viral infections on tissue homeostasis
- Protection against tissue pathology is found to increase vulnerability to cancer

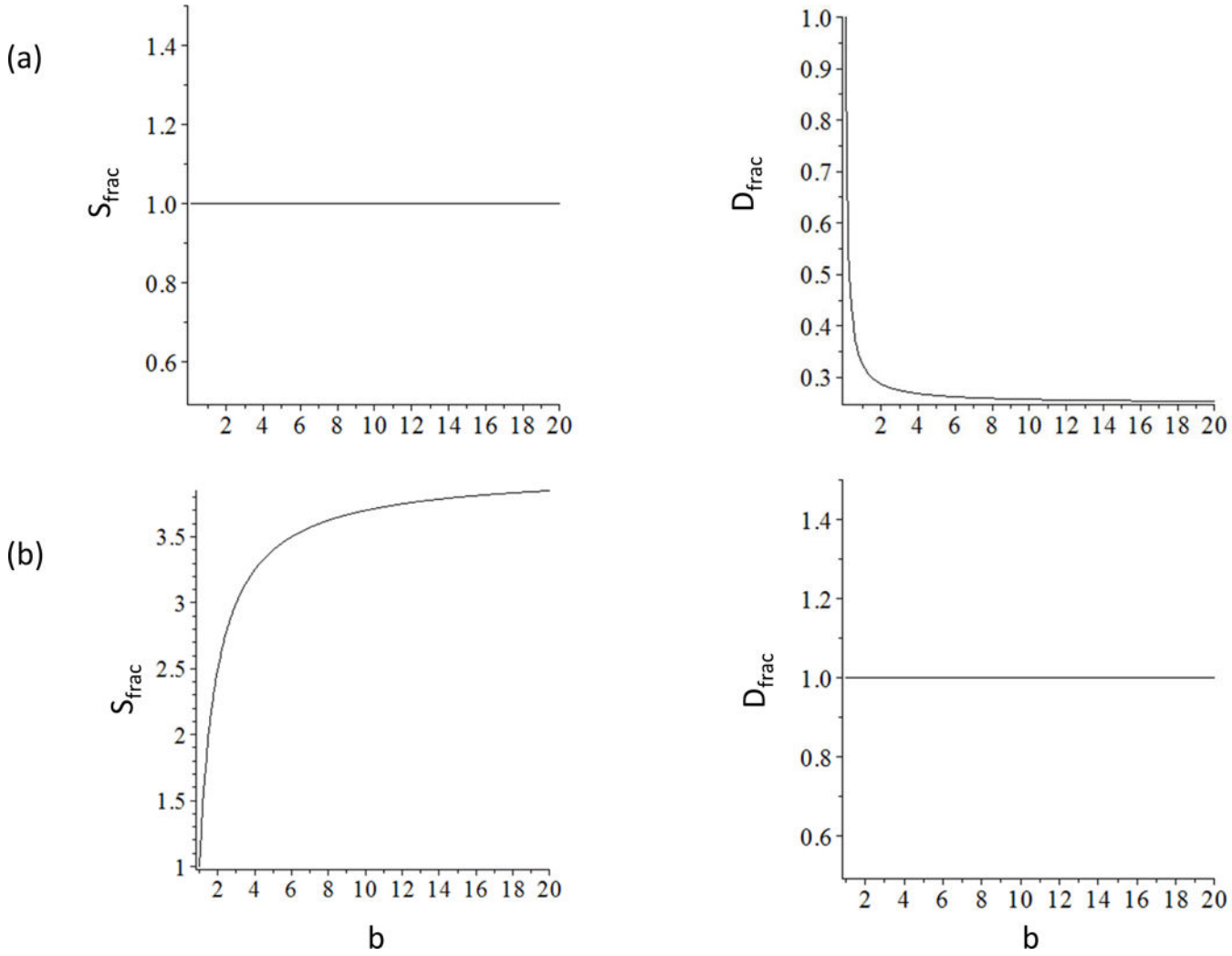

Figure 1.

Dependence of the measures S_{frac} and D_{frac} on the replication rate of the virus, b, according to model (2). (a) Scenario where we assume $n_1=1$ and $n_2=0$. (b) Scenario $n_1=0$ and $n_2=1$. Other parameters were chosen as follows. $p=0.6$, $r=0.5$; $a=0.05$; $a_2=0.2$; $m_1=m_2=0$; $f=1$.

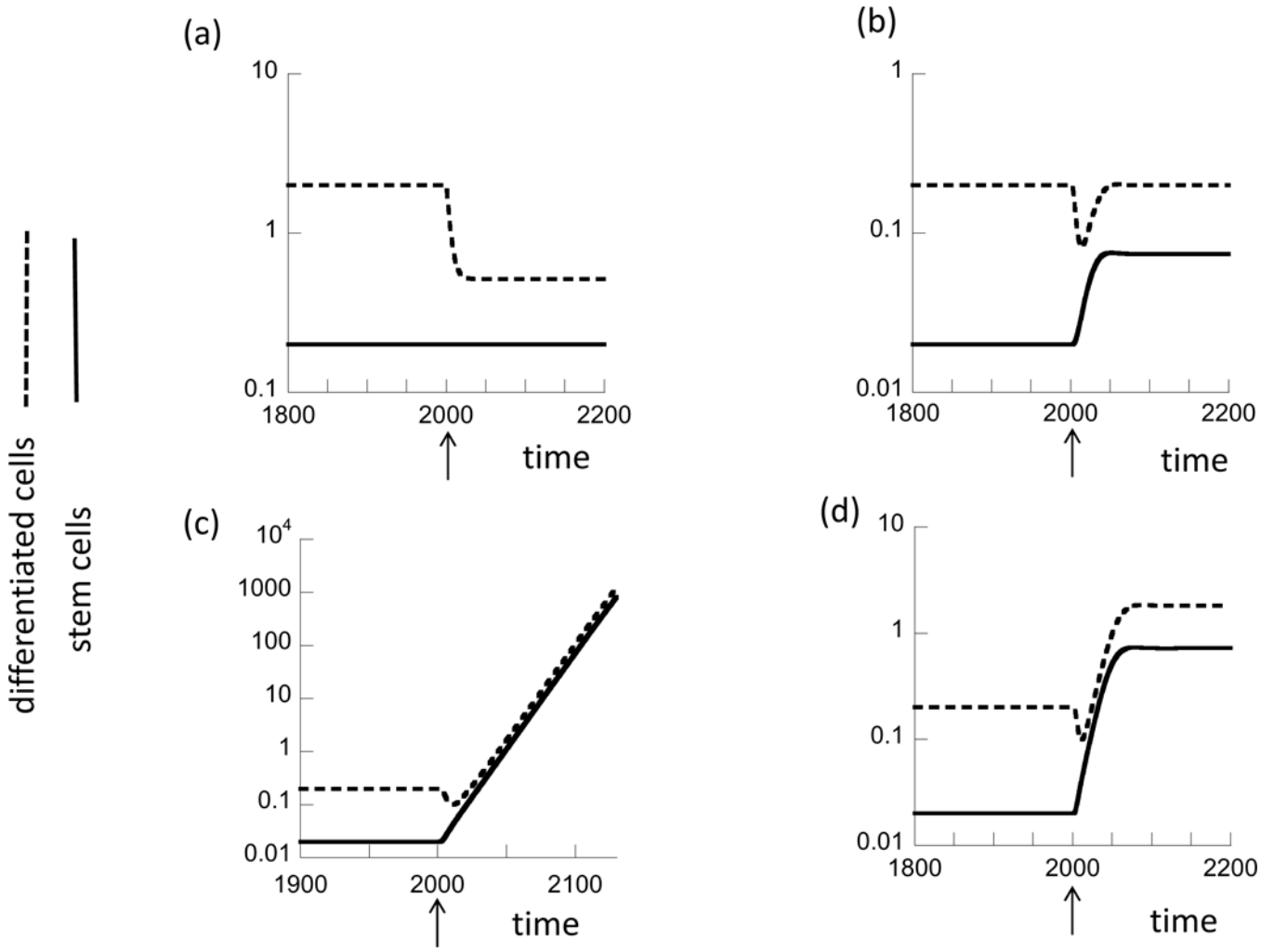

Figure 2.

Tissue architecture and resilience to infection, according to model (2). Arrow indicates infection. (a) Scenario where we assume $n_1=1$ and $n_2=0$ as well as $f=1$. Stem cell numbers remain steady during infection but differentiated cells decline. (b) Scenario where we assume $n_1=0$ and $n_2=1$ as well as $f=1$. Infection does not alter the equilibrium number of differentiated cells, but the number of stem cells grows. For $n_1=0$ and $n_2>0$, uncontrolled tissue growth is observed if $f<1$, shown in (c) $f=0$ and (d) $f=0.1$. Other parameters were chosen as follows. $b = 10$; $p=0.6$, $r=0.5$; $a=0.05$; $a_2=0.2$; $m_1=m_2=0$.

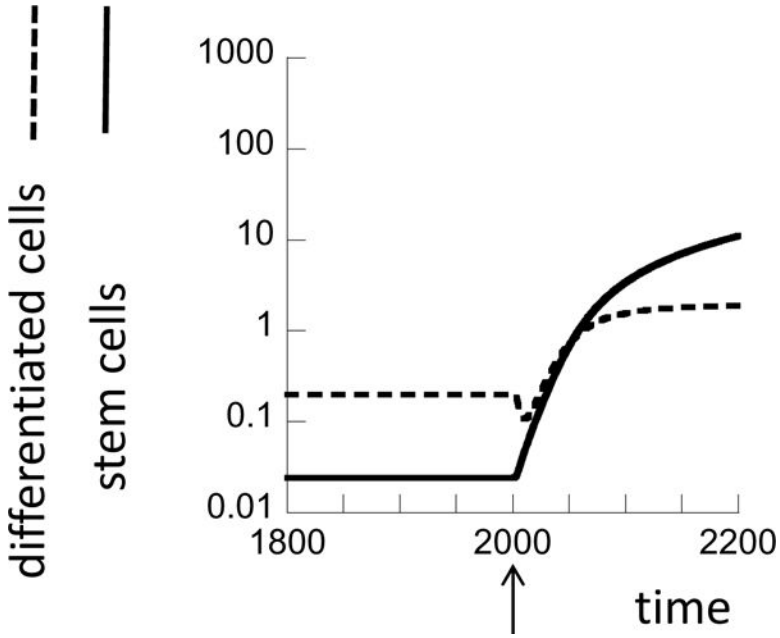

Figure 3.

Uncontrolled growth in the context of negative feedback on the cell division rate, according to model (2). Arrow indicates infection. Parameters were chosen as follows. $b = 10$; $n_1=0$; $n_2=1$. $p=0.6$, $r=0.5$; $a=0.05$; $a_2=0.2$; $m_1=m_2=1$; $f=0$; $g=0$.

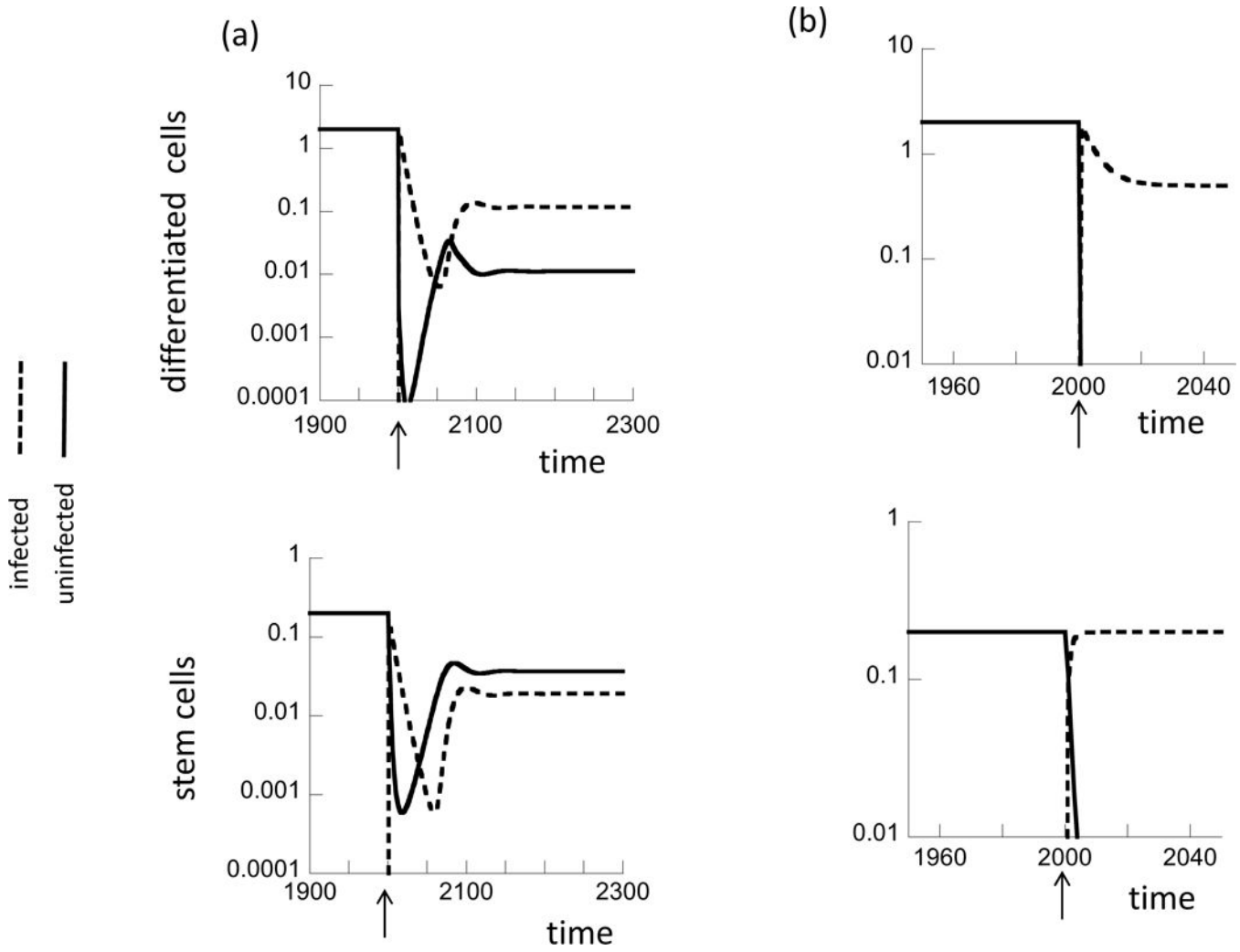

Figure 4.

Two different virus persistence equilibria in the stem cell infection model (6), illustrated for case where $n_1=1$ and $n_2=0$. Arrows indicate infection. (a) Either both uninfected and infected cells persist or (b) only infected cells persist and the uninfected cells go extinct. Parameters were chosen as follows. $b_d = 10$; $b_s=0.5$; $p=0.6$, $r=0.5$; $a=0.05$; $a_d=0.2$; $m_1=m_2=0$; $f_s=f_d=1$, $\eta=1$. (a) $a_s=0.2$ (b) $a_s=0$.

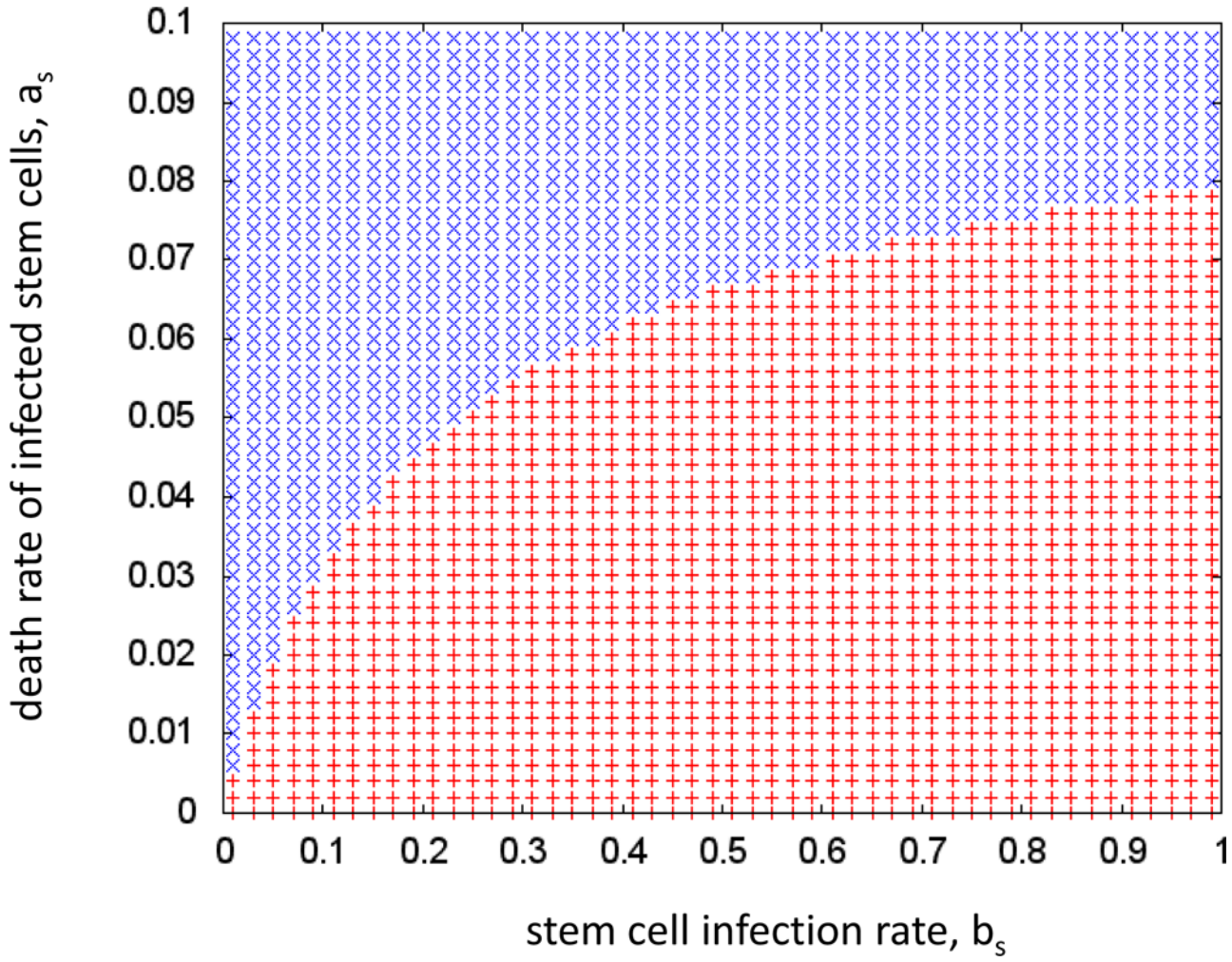

Figure 5.

Whether uninfected stem cells persist or not in the stem cell infection model (6) depends on parameters, which is explored numerically. The rate of stem cell infection, b_s, and the death rate of infected stem cells, a_s, was varied and the outcome is coded by different colors and symbols. Persistence of uninfected stem cells is shown in blue (×), and extinction in red (+). Parameters were chosen as follows. $b_d = 10$; $p=0.6$, $r=0.5$; $a=0.05$; $a_d=0.2$; $m_1=m_2=0$; $f_s=f_d=1$, $\eta=a_s$.

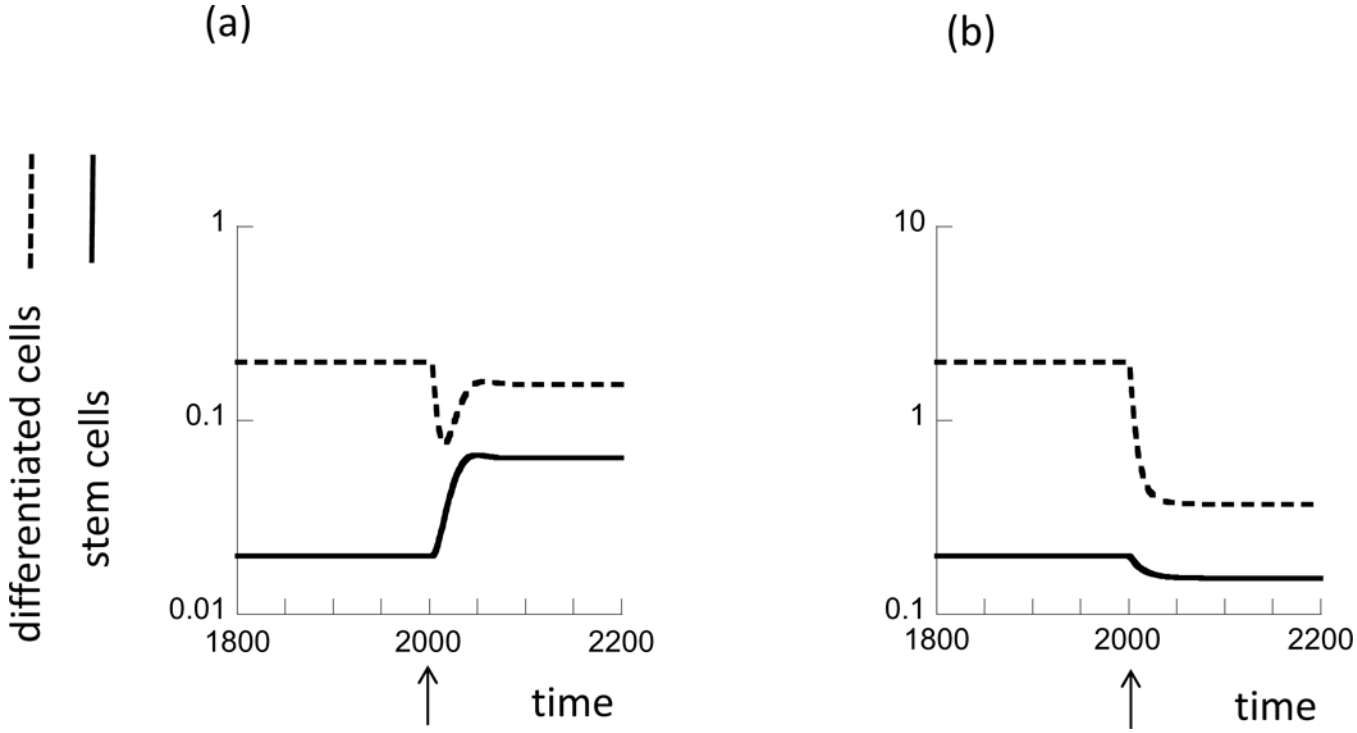

Figure 6.

Effect of the virus in the stem cell infection model (6) in the parameter regime where uninfected and infected cells coexist. (a) $n_1=0$; $n_2=1$ and (b) $n_1=1$; $n_2=0$. Basic properties shown in Figure 2 still hold, but both the population of stem and differentiated cells can be lower due to virus-induced stem cell killing. Arrows indicate infection. The remaining parameters were chosen as follows. $b_d = 10$; $b_s=0.5$; $p=0.6$, $r=0.5$; $a=0.05$; $a_d=0.2$; $a_s=0.02$; $m_1=m_2=0$; $f_s=f_d=1$, $\eta=1$.