Supporting information for the paper "Evolutionary dynamics of feedback escape and the development of stem cell driven cancers"

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The ode formulation of the model presented in the paper is given by equation (1), where S is the number of stem cells and D the number of differentiated cells. The self-renewal probability of stem cells $p(D)$ and the division rate $v(D)$ are decreasing functions of D. We add the conditions $p(D) \to 0$ and $v(D) \to 0$ as $D \to \infty$.

$$\begin{aligned} \dot{S} &= (2p(D) - 1)\, v(D)\, S \\ \dot{D} &= 2(1 - p(D))\, v(D)\, S - dD \end{aligned} \tag{1}$$

(i) *"System (1) has unique equilibrium point $(\hat{S}, \hat{D})$ as long as $1/2$ is in the range of the function $p(D)$. This point is asymptotically stable if and only if $-p'(\hat{D}) < 1/(2\hat{D})$."*

From equation (1) we note that the system has a unique non-trivial stationary point, characterized by the conditions:

$$p(\hat{D}) = 1/2 \quad \& \quad \hat{S} = \frac{d\hat{D}}{v(\hat{D})} \tag{2}$$

To study the stability of the stationary point we calculate the Jacobian evaluated at $(\hat{S}, \hat{D})$:

$$J(\hat{S}, \hat{D}) = \begin{bmatrix} 0 & 2dp'(\hat{D})\hat{D} \\ v(\hat{D}) & -d(2p'(\hat{D})\hat{D} + 1) \end{bmatrix}$$

Let B, C and D be given by:

$$\begin{aligned} x &= 2dp'(\hat{D})\hat{D} \\ y &= v(\hat{D}) \\ z &= -d(2p'(\hat{D})\hat{D} + 1) \end{aligned}$$

The corresponding eigenvalues of J are:

$$\lambda_1, \lambda_2 = \frac{z \pm \sqrt{z^2 + 4xy}}{2}$$

Note that $xy < 0$ for all $\hat{D}$, therefore if $z > 0$ the eigenvalues will have a positive real part and the stationary point would be unstable. If on the other hand $z < 0$ both eigenvalues are guaranteed to have a negative real part. Hence for the stationary point to be asymptotically stable it is necessary and sufficient that $z < 0$. This condition can be restated in the form:

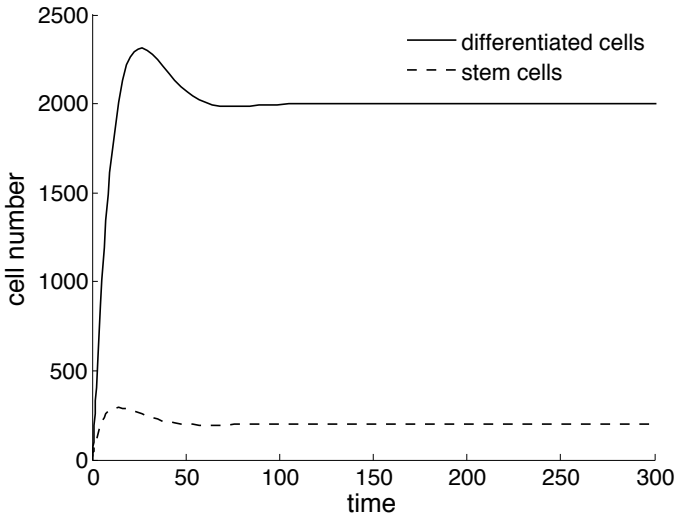

Figure 1: If the self-renewal probability for stem cells $p(D)$ satisfies the condition stated in **(i)** the system has a unique equilibrium point that is exponentially stable. The simulation started with a single stem cell at time $t = 0$.

$$-p'(\hat{D}) < 1/(2\hat{D}). \tag{3}$$

(ii) *"Feedback on the differentiation probability by itself is sufficient to control cell growth."*

We previously found a necessary and sufficient condition that guarantees the existence of a unique asymptotically stable stationary (equation 3). This condition is independent of $v(D)$. If there is no feedback on the division rate, the new equilibrium point $(\hat{S}, \hat{D})$ is defined by $p(\hat{D}) = 1/2$ and $\hat{S} = d\hat{D}/v_0$.

(iii) *"Feedback on the division rate alone cannot control cell growth i.e.: If* $p(D) \equiv p_0 > 0.5$ *then* $S, D \to \infty$*."*

Suppose that $S \nrightarrow \infty$, given that for all $t \quad \dot{S}(t) > 0$ this implies that $S \to \mathrm{M}$ (where M is a real positive number). Then for all t large enough:

$$\dot{D} < 2(1 - p_0)v(D)\mathrm{M} - dD$$

Consider the ode $\dot{x} = f(x)$ where $f(x) = 2(1-p_0)v(x)\mathrm{M} - dx$. Note that this ode has a unique equilibrium point $\hat{x}$, and furthermore $df/dx = 2(1-p_0)\mathrm{M}v'(x) - d < 0$ for all x, which implies that every trajectory converges to $\hat{x}$. Taking this fact together with (1) we find for all t large enough $D(t) < \hat{x}$, but given that v is a decreasing function, $\dot{S}(t) > (2p_0 - 1)v(\hat{x})S$, which implies that $S \to \infty$, which is a contradiction.

Finally, to prove that D also grows without bound, let us assume the opposite, that is $D \nrightarrow \infty$. Then for some M_1, $D < M_1$ for all t, and thus $v(D) \geq v(M_1)$, and $\dot{D} \geq 2(1 - p_0)v(M_1)S - dM_1$.

Since $S \to \infty$, we can see that $D \to \infty$.

(iv) *"If there is no feedback on differentiation and no feedback on the division rate differentiated cells and stem cells grow exponentially."*

If there is no feedback on differentiation nor the division rate, the system is described by a linear differential equation and we find that the solution is given by:

$$\begin{aligned} S(t) &= S(0)\, e^{\lambda_1 t} \\ D(t) &= \left(\tfrac{2(1-p_0)v_0 S(0)}{(2p_0-1)v_0+d}\right) e^{\lambda_1 t} + \left(D(0) - \tfrac{2(1-p_0)v_0 S(0)}{(2p_0-1)v_0+d}\right) e^{\lambda_2 t} \end{aligned} \tag{4}$$

where $\lambda_1 = (2p_0 - 1)v_0$ and $\lambda_1 = -d$. Given that $p_0 > 0.5$ there is exponential growth.

(v) *"If there is no feedback on differentiation but there is feedback on replication, cell growth is slower than any exponential." i.e: for all $k > 0$*

$$\lim_{t\to\infty} \frac{S(t) + D(t)}{\exp(kt)} = 0$$

Let k be an arbitrary positive number and $\epsilon < k$. Given that $v(x)$ is a decreasing function that goes to zero, and $D \to \infty$ (proven in **(iii)**), there is a positive number T such that for all $t > T$, $v(D) < \epsilon/(2p_0 - 1)$. We then have that for all t large enough $\dot{S} < \epsilon S$ and it follows that $0 < S(t) < \exp(\epsilon t) + C$ where C is some fixed constant. Dividing the previous inequalities by $\exp(kt)$ and taking the limit as $t \to \infty$ we get $S(t)/\exp(kt) \to 0$. An almost identical argument gives us $D(t)/\exp(kt) \to 0$ proving the result.

(vi) *"a). If there are no feedbacks, the ratio of stem cells to differentiated cells converges to a positive real number. b). If there is only feedback on the division rate, the number of differentiated cells cannot dominate the number of stem cells, i.e:* $\lim_{t\to\infty} S/D = \infty$. *"*

Statement (a) follows from equation 4, we note that

$$\lim_{t\to\infty} S/D = \frac{(2p_0 - 1)v_0 + d}{2(1 - p_0)v_0}$$

To prove (b) we argue by contradiction. Suppose that for some number M, $S/D < M$ for all t. Then

$$\dot{D} < D\,[2(1 - p_0)v(D)M - d]$$

In **(iii)** we found that when there is only feedback on the division rate $D \to \infty$. Thus given that $D > 0$ and $v(D) \to 0$ the right hand side of the equation is negative for all t large enough, which means that $\dot{D} < 0$ for all such t. We then have the contradiction $D \to \infty$ and $\dot{D} < 0$.

Mutations

Following the notation introduced in the paper we call wild type stem and differentiated cells S and D, and the mutant stem cells and differentiated cells S_m and D_m.

Mutation Ddiv–

Stem cells that acquire this mutation give rise to differentiated cells that do not produce the division rate inhibiting factor.

$$\begin{aligned}
\dot{S} &= (2p(D+D_m)-1)\,v(D)\,S \\
\dot{D} &= 2(\,1-p(D+D_m)\,)\,v(D)\,S - dD \\
\dot{S}_m &= (2p(D+D_m)-1)\,v(D)\,S_m \\
\dot{D}_m &= 2(\,1-p(D+D_m)\,)\,v(D)\,S_m - dD_m
\end{aligned}$$

(vii) *"Mutation Ddiv– is 'neutral': it is neither disadvantageous nor does it confer a competitive advantage to the cells."*

Let us call $f(D,D_m) = (2p(D+D_m)-1)\,v(D)$. Then $\dot{S}(t) = f(D,D_m)\,S$ and $\dot{S}_m(t) = f(D,D_m)\,S_m \Rightarrow\ S(t) = S(0)\exp(\int_0^t f(D,D_m)dt)$ and $S_m(t) = S_m(0)\exp(\int_0^t f(D,D_m)dt)$. Then if $S(0)\neq 0$ we have $S_m(t) = cS(t)$ where $c = S_m(0)/S(0)$ and it follows that $\hat{S}_m = c\hat{S}$, i.e: the steady state ratio of mutant to wild type stem cells is the same as the initial ratio of mutant to wild type stem cells. Furthermore the steady state numbers of differentiated cells satisfy $\hat{D}_m = c\hat{D}$. This completes the proof of **(vii)**.

Let $\hat{D}$ be the unique real number that satisfies:

$$p(\hat{D}) = 1/2$$

If Mutation Ddiv– occurs the total steady state number of stem cells $\hat{S}_{\text{tot}} = \hat{S} + \hat{S}_m$ decreases and the total steady state number of differentiated cells $\hat{D}_{\text{tot}} = \hat{D} + \hat{D}_m$ remains the same. The steady state number of cells is given by:

$$p(\hat{D}_{\text{tot}}) = 0.5 \quad \text{and} \quad \hat{S}_{\text{tot}} = \frac{d\hat{D}_{\text{tot}}}{v(\hat{D}_{\text{tot}}/(1+c))}$$

Note that if c is very small, $S_m(0)\approx 1$ as one should expect from a random mutation, given the continuity of v the decrease in the steady state number of cells for the ode model should be very small. Furthermore in a stochastic formulation there is a very high chance that the mutated species would go extinct.

Mutation Ddiff–

Stem cells that acquire this mutation give rise to differentiated cells that do not produce the differentiation inhibiting factor:

$$\begin{aligned}
\dot{S} &= (2p(D)-1)\, v(D+D_m)\, S \\
\dot{D} &= 2(\,1-p(D)\,)\, v(D+D_m)\, S - dD \\
\dot{S}_m &= (2p(D)-1)\, v(D+D_m)\, S_m \\
\dot{D}_m &= 2(\,1-p(D)\,)\, v(D+D_m)\, S_m - dD_m
\end{aligned}$$

(viii) *"Mutation Ddiff– is 'neutral': it is neither disadvantageous nor does it confer a competitive advantage to the cells."*

Let us call $g(D, D_m) = (2p(D)-1)\, v(D+D_m)$ then $\dot{S}(t) = g(D, D_m)\, S$ and $\dot{S}_m(t) = g(D, D_m)\, S_m \Rightarrow$ $S(t) = S(0)\exp(\int_0^t g(D, D_m)dt)$ and $S_m(t) = S_m(0)\exp(\int_0^t g(D, D_m)dt)$. Then if $S(0) \neq 0$ we have $S_m(t) = cS(t)$ where $c = S_m(0)/S(0)$ and it follows that $\hat{S}_m = c\hat{S}$, i.e the steady state ratio of mutant to wild type stem cells is the same as the initial ratio of mutant to wild type stem cells. Furthermore the steady state numbers of differentiated cells satisfy $\hat{D}_m = c\hat{D}$. This completes the proof of **(viii)**.

If Mutation Ddiff– occurs the total steady state number of stem cells $\hat{S}_{\text{tot}} = \hat{S} + \hat{S}_m$ increases and so does the total steady state number of differentiated cells $\hat{D}_{\text{tot}} = \hat{D} + \hat{D}_m$. The steady state number of cells is given by:

$$\hat{D}_{\text{tot}} = \hat{D}(1+c) \quad \text{and} \quad \hat{S}_{\text{tot}} = \frac{d\hat{D}(1+c)}{v(\hat{D}(1+c))}$$

Note that if c is very small, $S_m(0) \approx 1$ as one should expect from a random mutation, given the continuity of v the increase in the steady state number of cells for the ode model should be very small. Furthermore in a stochastic formulation there is a very high chance that the mutated species would go extinct.

Mutation Sdiff–

Stem cells that acquire this mutation do not respond to the differentiation inhibiting factor:

$$\begin{aligned}
\dot{S} &= (2p(D)-1)\, v(D)\, S \\
\dot{D} &= 2(\,1-p(D)\,)\, v(D)\, S + 2(1-p_0)\, v(D)\, S_m - dD \\
\dot{S}_m &= (\;\; 2p_0 - 1 \;\;)\, v(D)\, S_m
\end{aligned}$$

(ix) *"Mutation Sdiff–confers a competitive advantage to stem cells who carry it. If a single stem cell acquires this mutation, the cell population grows without bound and the number of wild type stem cells goes to zero."*

We previously proved that feedback inhibition by itself is incapable of controlling cell growth (see **(iii)**), this proves the first part of the proposition.

Since $D \to \infty$, there is a t_0 such that $p(D) < 1/4$ for all $t > t_0$. Let us consider the equation $\dot{y} = -(1/2)v(D)y$, with the additional condition $y(t_0) = S(t_0)$. We have $S(t) < y(t)$ for all $t > t_0$. Comparing the equations for S_m and y, we can see that $y(t) = cS_m^{-\frac{1}{2(2p_0-1)}}$ for $t > t_0$. Since $S_m \to \infty$, we have $y \to 0$, and therefore $S \to 0$.

Mutation Sdiv–

Stem cells that acquire this mutation do not respond to the replication inhibiting factor. The model is described by the following system of differential equations:

$$\begin{aligned} \dot{S} &= (2p(D)-1)\,v(D)\,S \\ \dot{D} &= 2(\,1-p(D)\,)\,v(D)\,S + 2(1-p(D))\,v_0\,S_m - dD \\ \dot{S}_m &= (2p(D)-1)\,v_0\,S_m \end{aligned}$$

(x) *"Mutation Sdiv– cannot take over the stem cell population. If a small number of stem cells acquires this mutation, in the new steady state mutant stem cells will only be a small percentage of the total stem cell population."*

The system has a family of stationary points $(\hat{S}, \hat{D}, \hat{S}_m)$ defined by

$$p(\hat{D}) = 1/2, \quad \hat{S}v(\hat{D}) + \hat{S}_m v_0 = d\hat{D}. \tag{5}$$

If we call the total number of stem cells $S_{\rm tot}(t) = S(t) + S_m(t)$ then the pair $(S_{\rm tot}, D)$ satisfies the original system (1). In **(i)** we proved that that this two dimensional system is exponentially stable, which means that in a vicinity of its unique equilibrium point $(\hat{S}_{\rm tot}, \hat{D})$ $D(t)$ approaches $\hat{D}$ at an exponential rate.

Now taking into account that $p(\hat{D})= 1/2$, noting that $v(D) \le v_0$ and considering Taylor's expansion of $p(D)$ around $\hat{D}$ we find that $|(2p(D)-1)v(D)| = {\rm O}(|D-\hat{D}|)$. Then, given that $D(t)$ approaches $\hat{D}$ at an exponential rate, there are positive constants α and M such that for all t large enough $|(2p(D(t))-1)v(D(t))| \le Me^{-\alpha t}$ which means that the integral $\int_0^\infty (2p(D(\tau))-1)v(D(\tau))\,d\tau$ is absolutely convergent and the number of wild type stem cells converges to a unique number defined by

$$\hat{S} = S(0)exp\left\{\int_0^\infty (2p(D(\tau))-1)v(D(\tau))\,d\tau\right\} \tag{6}$$

In the absence of mutants, the unique stable fixed point is given by $(\hat{S}^{old}, \hat{D}^{old}, \hat{S}_m^{old})$, where

$$p(\hat{D}^{old}) = 1/2, \quad \hat{S}^{old} = d\hat{D}^{old}/v(\hat{D}^{old}), \quad \hat{S}_m^{old} = 0.$$

Let us set the initial condition corresponding to a perturbation of this stable point, such that $S(0) = \hat{S}^{old}$, $D(0) = \hat{D}^{old}$ and $S_m(0) = X$. We then have:

$$\hat{S} = \hat{S}^{old}exp\left\{\int_0^\infty (2p(D(\tau))-1)v(D(\tau))\,d\tau\right\} \le \hat{S}^{old}.$$

The inequality follows from the expressions for the neutrally stable point, equations (5). If the sign is "=", then the proof is complete because this means that $\hat{S}_m = 0$, and no invasions has occured. If the sign is "<", we conclude that

$$\int_0^\infty (2p(D(\tau))-1)v(D(\tau))\,d\tau < 0. \tag{7}$$

Let us next consider the trajectory for $S_m(t)$: $S_m(t) = S_m(0)exp\left\{v_0\int_0^t (2p(D(\tau))-1)\,d\tau\right\}$. Taking $t\to\infty$, we have

$$\hat{S}_m = Xexp\left\{v_0\int_0^\infty (2p(D(\tau))-1)\,d\tau\right\}.$$

We need to prove that $\hat{S}_m < X$, which is equivalent to proving that

$$\int_0^\infty (2p(D(\tau)) - 1)\, d\tau < 0. \tag{8}$$

To prove the latter inequality, let us split the time-axis into intervals, $I_0 = [t_0, t_1)$, $I_1 = [t_1, t_2)$, ... such that $D(t_i) = \hat{D}$, and therefore $p(D(t_i)) = 1/2$. Inside the intervals, the quantity $2p(D)-1$ does not change sign. Let us call the set of intervals where $2p(D(t)) - 1 > 0$, I_+, and the complimentary set, I_-. Inequality (7) is equivalent to the following: (note that both infinite sums are finite because the integral in (6) is absolutely convergent)

$$\sum_{I_+} \int_{I_k} (2p(D(\tau)) - 1)v(D(\tau))\, d\tau < \sum_{I_-} \int_{I_k} (1 - 2p(D(\tau))v(D(\tau))\, d\tau.$$

Let us denote by v_2 the quantity $v(\hat{D})$. Note that inside intervals in I_+, $v(D(t)) > v_2$, and inside intervals in I_-, $v(D(t)) < v_2$. Then the following chain of inequalities can be written:

$$v_2 \sum_{I_+} \int_{I_k} (2p(D(\tau)) - 1)\, d\tau < \sum_{I_+} \int_{I_k} (2p(D(\tau)) - 1)v(D(\tau))\, d\tau <$$
$$\sum_{I_-} \int_{I_k} (1 - 2p(D(\tau))v(D(\tau))\, d\tau < v_2 \sum_{I_-} \int_{I_k} (1 - 2p(D(\tau))\, d\tau.$$

Therefore, inequality (8) holds. We conclude that the resulting amount of mutants cannot exceed the initial amount of mutants, and thus invasion cannot occur.

(xi) *"If Mutation Sdiv– occurs in a cell population that carries Mutation Sdiff– the cell population grows exponentially and the percentage of stem cell that only carry Mutation Sdiff– goes to zero."*

Cells that carry both mutations do not have any of the two feedback mechanisms and thus grow exponentially **(iv)** Cells that only carry mutation Sdiff– do not have differentiation feedback, but they have feedback on the cell division rate so their growth is slower than any exponential **(v)**. Hence the percentage of stem cells that only carries mutation Sdiff– goes to zero.

Multiple mutations

We have proved that there is only one mutation that confers a competitive advantage to stem cell that carry it (Mutation Sdiff–) so when we analyze multiple mutations we only need to consider stem cells that acquire this mutation first.

Mutation Sdiff– followed by Mutation Ddiv–

If Mutation Sdiff– occurs we can assume that the wild type stem cell population is negligible. The model is then described by the following system of differential equations:

$$\begin{aligned}
\dot{S} &= (2p_0 - 1)\, v(D)\, S \\
\dot{D} &= 2(\,1 - p_0\,)\, v(D)\, S - dD \\
\dot{S}_m &= (2p_0 - 1)\, v(D)\, S_m \\
\dot{D}_m &= 2(\,1 - p_0\,)\, v(D)\, S_m - dD_m
\end{aligned}$$

Given that $\dot{S}= \dot{S_m}$ it follows that if c is such that $S_m(0) = cS(0)$ then $S_m(t) = cS(t)$ for all t (look at the proof of **(iv)**). Hence if c is very small at any time t the percentage of stem cells with both mutations will be very small.

Mutation Sdiff– followed by Mutation Ddiff–

Once again if Mutation Sdiff– occurs we can assume that the wild type stem cell population is negligible. For a cell population consisting entirely of cells that carry Mutation Sdiff– the addition of Mutation Ddiff– is redundant

Mutation Sdiff–/partial

There is a less acute version of Mutation Sdiff– in which mutant stem cells do not completely loose the ability to recognize the differentiation promoting factors but instead have a waker response to them. This system is described by the following equations,

$$\begin{aligned} \dot{S} &= (2p(D) - 1)\, v(D)\, S \\ \dot{D} &= 2(\, 1 - p(D)\,)\, v(D)\, S + 2(1 - \tilde{p}(D))v(D)\, S_m - dD \\ \dot{S}_m &= (2\tilde{p}(D) - 1)\, v(D)\, S_m, \end{aligned}$$

with $\tilde{p}(D) \geq p(D)$.

(xii) *"If both functions $p(D)$ and $\tilde{p}(D)$ satisfy condition (3), then the following holds for Mutation Sdiff–/partial: (a) The number of differentiated cells increases to $\tilde{D}$ where $\tilde{p}(\tilde{D}) = 1/2$. (b) The wild type stem cells become extinct. (c) The total number of stem cells increase to $\tilde{S}_{\rm tot} = (d/v(\tilde{D}))\tilde{D}$."*

Consider the fixed point of the system, $(\tilde{S}, \tilde{D}, \tilde{S}_m)$ defined by $\tilde{S} = 0$, $\tilde{p}(\tilde{D}) = 1/2$ and $\tilde{S}_m = d\tilde{D}/v(\tilde{D})$. Statements (a,b,c) follow from the fact that this fixed point is stable, which is proven below.

The eigenvalues of the appropriate Jacobian are given by $(2p(\tilde{D}) - 1)v(\tilde{D})$ and the two roots of the following quadratic equation,

$$\lambda^2 + \lambda d[1 + 2\tilde{D}\tilde{p}'(\tilde{D}) - \tilde{D}v'(\tilde{D})/v(\tilde{D})] - 2\tilde{p}'(\tilde{D})v^2(\tilde{D})\tilde{S}_m.$$

The first eigenvalue is negative from the condition $\tilde{p}(D) \geq p(D)$. The quadratic equation has two roots with negative real parts because the term in front of the first power of λ is positive by condition (3), and the term in front of λ^0 is positive because $\tilde{p}'(\tilde{D})$ is negative. Therefore, the fixed point is stable.

Mutation Sdiv–/partial

There is also the possibility that a mutation arises that only produces a partial loss in the ability to respond to the division rate feedback factors (denoted by Sdiv–/partial). From the proof of **(x)** it follows that this mutation does not confer a competitive advantage to a population of wild type stem cells. However, if this mutation arises in a population of cells that carry mutation Sdiff– this additional mutation may produce an acceleration in the growth rate of the tumor size. In this scenario, the system is described by the following equations,

$$\begin{aligned}\dot{S} &= (2p_0 - 1)\, v(D)\, S \\ \dot{D} &= 2(\,1 - p_0\,)\, v(D)\, S + 2(1 - p(D))\tilde{v}(D)\, S_m - dD \\ \dot{S}_m &= (2p_0 - 1)\, \tilde{v}(D)\, S_m,\end{aligned}$$

with $\tilde{v}(D) \geq v(D)$.

(xiii) *"If mutation Sdiv–/partial arises in a population of cells that carry mutation Sdiff– the number of cells carrying mutation Sdiv–/partial $\to \infty$. Furthermore if $\lim_{t\to\infty} v(D)/\tilde{v}(D) = M < 1$ the fraction of stem cells not carrying mutation Sdiv–/partial becomes a negligible part of the stem cell population."*

Let us suppose that in a population of cells carrying mutation Sdiff– mutation Sdiv–/partial arises in a single cell at time t^*. Then if we define $y(t)$ by the differential equation $\dot{y} = (2p_0 - 1)\tilde{v}(D)y$ and $y(t^*) = S(t^*)$ we have $S_m(t) = y(t)/S(t^*)$ and $y(t) \geq S(t)$ for $t \geq t^*$. Since $S(t) \to \infty$ (see (iii)) $S_m(t) \to \infty$ proving the first part of the proposition.

Suppose that $\lim_{t\to\infty} v(D)/\tilde{v}(D) = M < 1$, then we can choose N such that $M < N < 1$ and there is a real number T that satisifies $v(D)/\tilde{v}(D) < N$, for all $t \geq T$. Define $x(t)$ by the differential equation $\dot{x} = (2p_0 - 1)N\tilde{v}(D)x$ and $x(T) = S(T)$. We then have for $t \geq T$, $x(t) = cS_m(t)^N$ where c is a positive constant. It it follows that:

$$\frac{S(t)}{S_m(t)} \leq \frac{x(t)}{S_m(t)} = cS_m(t)^{N-1}$$

Since $S_m(t) \to \infty$ and $N - 1 < 0$ the fraction on the left hand side goes to zero proving the second part of the proposition.

Symmetric and asymmetric stem cell division

In this section we consider the possibility that stem cells divide in two possible ways: symmetrically giving rise to either two stem cell or two differentiated cells; or asymmetrically, giving rise to one stem cell and one differentiated cell. Suppose that stem cells divide symmetrically into two stem cells with probability $p_{\rm S}(D)$ or asymmetrically with probability $p_{\rm A}(D)$, where $p_{\rm S}(D) + p_{\rm A}(D) \leq 1$. Then the rate of change of stem cells and differentiated cell is given by:

$$\begin{aligned}\dot{S} &= 1 \times p_{\rm S}(D)v(D)S + 0 \times p_{\rm A}(D)v(D)S - 1 \times (1 - p_{\rm S}(D) - p_{\rm A}(D))v(D)S \\ &= [2(p_{\rm S}(D) + 0.5p_{\rm A}(D)) - 1]v(D)S.\end{aligned}$$

$$\begin{aligned}\dot{D} &= 2 \times (1 - p_{\rm S}(D) - p_{\rm A}(D))v(D)S + 1 \times p_{\rm A}(D)v(D)S - dD \\ &= 2[1 - (p_{\rm S}(D) + 0.5p_{\rm A}(D))]v(D)S - dD\end{aligned}$$

The introduction of the new division pattern does not change any of our previous results. Indeed, if we make $p(D) = p_{\rm S}(D) + 0.5p_{\rm A}(D)$ and substitute this expression into the previous equations we recover the original model (system (1)).

	p_0	v_0	d	h	g
Figures 1,2,S1	0.60	6.93 time^{-1}	6.93e-2 time^{-1}	4.50e-3 cells^{-1}	1.00e-4 cells^{-1}
Figure 3	0.80	1.39 time^{-1}	1.39e-2 time^{-1}	1.50e-3 cells^{-1}	0.00 cells^{-1}
Figure 4a	0.71	0.31 hr^{-1}	7.36e-1 hr^{-1}	2.22e-3 cells$^{-1/2}$	0.00 cells$^{-1/2}$
Figure 4b	0.55	295 hr^{-1}	126 hr^{-1}	3.67e-3 cells$^{-1/2}$	0.00 cells$^{-1/2}$
Figure 4c	0.62	6.29 days^{-1}	2.51e-1 days^{-1}	0.00 cells$^{-1/2}$	0.00 cells$^{-1/2}$
Figure 4d	0.68	1.46 days^{-1}	1.46e-1 days^{-1}	0.00 cells$^{-1/2}$	0.00 cells$^{-1/2}$
Figure 4e	0.67	2.91 days^{-1}	5.93 days^{-1}	0.00 cells$^{-1/2}$	1.74e-4 cells$^{-1/2}$
Figure 4f	0.60	6.93 time^{-1}	11.54e-3 time^{-1}	4.50e-3 cells^{-1}	1.00e-4 cells^{-1}

Supplementary Table 1. Parameters used in the manuscript figures. In Figures 1-3 and S1 the functional forms used are $p(D) = p_0/(1 + gD)$ and $v(D) = v_0/(1 + hD)$. In Figure 2c, $\tilde{p}(D) = 0.1p(D)$. In Figure 2e, $\tilde{v}(D) = 0.05p(D)$. Time is expressed in units of $\ln 2/v(\hat{D})$, the expect duration of one cell cycle at equilibrium. In Figure 4, $p(D) = p_0/(1 + g\sqrt{D})$ and $v(D) = v_0/(1 + h\sqrt{D})$ (see **Methods**). In Figure 4b a weight of one nanogram per cell is assumed.