Supporting Information

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SI Text

S1. Model Description

Intercell Cycle Transformation. Our model describes the dynamics of resting phase stem cell population N_t, and the distribution density of cell epigenetic states $f_t(x)$. Here x is a variable representing the epigenetic state of a cell, and subscript t indicates the tth cell cycle. At each cell cycle, cells undergo proliferation [with a probability $\beta_t(x)$], apoptosis [with a probability $\mu_t(x)$], and differentiation [with a probability $\delta_t(x)$], so that $(N_t, f_t(x))$ changes from one cell cycle to the next:

$$(N_t, f_t(x)) \mapsto (N_{t+1}, f_{t+1}(x)). \quad \text{[S1]}$$

During each cell cycle, $N_t \int f_t(x)\delta_t(x)dx$ cells leave the resting phase due to differentiation, and $N_t \int f_t(x)\beta_t(x)dx$ cells enter the proliferation phase. Each cell in the proliferation phase either goes through apoptosis with a probability $\mu_t(x)$ or produces two daughter cells. Here we omit the transitions between resting and quiescent phase. Hence, the cell population after mitosis is

$$\begin{aligned} N_{t+1} &= N_t - N_t \int f_t(x)\delta_t(x)dx - N_t \int f_t(x)\beta_t(x)dx \\ &\quad + 2N_t \int f_t(x)\beta_t(x)(1-\mu_t(x))dx \\ &= N_t\left(1 + \int f_t(x)[\beta_t(x)(1-2\mu_t(x)) - \delta_t(x)]dx\right). \end{aligned}$$

The integrals are taken over all possible epigenetic states. Define the observed proliferation probability as

$$\beta_{t,\text{obs}} = 1 + \int f_t(x)[\beta_t(x)(1-2\mu_t(x)) - \delta_t(x)]dx, \quad \text{[S2]}$$

then

$$N_{t+1} = N_t\beta_{t,\text{obs}}. \quad \text{[S3]}$$

Here $\beta_{t,\text{obs}}$ is the ratio of cell population numbers between two consecutive cell cycles.

To obtain the transformation of $f_t(x)$, we introduce a transition probability $p(x,y)$, representing the probability that a daughter cell of state x comes from a mother cell of state y. Then

$$\int p(x,y)dx = 1 \quad \text{[S4]}$$

for all y.

Similarly to the above argument, at each cell cycle, the number of cells with state x is $N_t f_t(x)$. After a cell division, $N_t f_t(x)(\delta_t(x)+\beta_t(x))$ cells with state x are removed from the resting phase due to differentiation and proliferation, and $2N_t \int f_t(y)\beta_t(y)(1-\mu_t(y))p(x,y)dy$ cells of state x are produced after mitosis. Thus, after mitosis, the number of cells with state x becomes

$$\begin{aligned} N_{t+1}f_{t+1}(x) &= N_t f_t(x) - N_t f_t(x)(\delta_t(x)+\beta_t(x)) \\ &\quad + 2N_t \int f_t(y)\beta_t(y)(1-\mu_t(y))p(x,y)dy, \end{aligned}$$

which gives

$$\begin{aligned} f_{t+1}(x) &= \frac{1}{\beta_{t,\text{obs}}}\Big[f_t(x)(1-(\delta_t(x)+\beta_t(x))) \\ &\quad + 2\int f_t(y)\beta_t(y)(1-\mu_t(y))p(x,y)dy\Big]. \end{aligned} \quad \text{[S5]}$$

Eqs. **S2**, **S3**, and **S5** together define transformation **S1**.

Evolutionary Fitness Function. To define an evolutionary fitness function akin to natural selection, we first introduce a tissue performance function Q, which depends on the cell population through a function $\varphi(x)$ and the distribution density $f_t(x)$ through a cell performance function $\chi(x)$:

$$Q(N_t, f_t(x)) = \varphi(N_t)\int \chi(x)f_t(x)dx. \quad \text{[S6]}$$

At each cell cycle, $(N_{t+1}, f_{t+1}(x))$ changes according to **[S3]** and **[S5]**, and depends on the quantities $\{\beta_t(x), \gamma_t(x), \delta_t(x)\}$. Thus, given $(N_t, f_t(x))$, we have

$$\begin{aligned} Q(N_{t+1}, f_{t+1}(x)) &= \varphi(N_{t+1})\int \chi(x)f_{t+1}(x)dx \\ &= \varphi(N_t\beta_{t,\text{obs}})\int \chi(x)\frac{1}{\beta_{t,\text{obs}}}\Big[f_t(x)\big(1-(\delta_t(x)+\beta_t(x))\big) \\ &\quad + 2f_t(y)\beta_t(y)\big(1-\mu_t(y)\big)p(x,y)dy\Big]dx \\ &= \frac{\varphi(N_t\beta_{t,\text{obs}})}{\beta_{t,\text{obs}}}\Big[\int \chi(x)f_t(x)(1-(\delta_t(x)+\beta_t(x)))dx \\ &\quad + 2\iint \chi(x)f_t(y)\beta_t(y)(1-\mu_t(y))p(x,y)dxdy\Big], \end{aligned}$$

where $\beta_{t,\text{obs}}$ is defined by **[S2]**. Let

$$\begin{aligned} &Q(N_t, f_t(x)|\beta_t(x), \mu_t(x), \delta_t(x)) \\ &= \frac{\varphi(N_t\beta_{t,\text{obs}})}{\beta_{t,\text{obs}}}\Big[\int \chi(x)f_t(x)\Big(1-\big(\delta_t(x)+\beta_t(x)\big)\Big)dx \\ &\quad + 2\iint \chi(x)f_t(y)\beta_t(y)\big(1-\mu_t(y)\big)p(x,y)dxdy\Big], \end{aligned} \quad \text{[S7]}$$

then

$$Q(N_{t+1}, f_{t+1}(x)) = Q\Big(N_t, f_t(x)|\beta_t(x), \mu_t(x), \delta_t(x)\Big), \quad \text{[S8]}$$

which depends on $\beta_t(x)$, $\mu_t(x)$ and $\delta_t(x)$.

In **[S7]**, the proliferation probability $\beta_t(x)$ varies at each cell cycle by epigenetic regulation; the apoptosis probability $\mu_t(x) = \bar{\mu}_G(x) + \hat{\mu}_t(x)$ in which $\bar{\mu}_G(x)$ is the average probability at homeostasis and is selected through genetic mutations and $\hat{\mu}_t(x)$ is random at each cell cycle due to epigenetic modulations. Similarly, the differentiation probability takes the form $\delta_t(x) = \bar{\delta}_G(x) + \hat{\delta}_t(x)$ in which $\bar{\delta}_G(x)$ is the average probability at homeostasis and $\hat{\delta}_t(x)$ represents the epigenetic uncertainty.

At each cell cycle, the proliferation $\beta_t(x)$ is controlled to achieve maximum tissue performance in Q after one cell division

in the face of uncertainties in apoptosis $\mu_t(x)$ and differentiation $\delta_t(x)$. This leads to solving the corresponding Bellman condition for $Q(N_{t+1}, f_{t+1}(x))$:

$$\mathrm{E}_{\mu_t(x),\delta_t(x)} \max_{\beta_t(x)} Q\Big(N_t, f_t(x)\big|\beta_t(x), \mu_t(x), \delta_t(x)\Big), \qquad \textbf{[S9]}$$

where $\mathrm{E}_{\mu_t(x),\delta_t(x)}$ is the expectation with respect to apoptosis and differentiation probabilities during cell division.

The procedure of solving **[S9]** is given below. At each cell cycle, the expectations of $\mu_t(x)$ and $\delta_t(x)$ are given as

$$\mathrm{E}\mu_t(x) = \mu_{t-1}(x), \quad \mathrm{E}\delta_t(x) = \delta_{t-1}(x).$$

The proliferation rate $\beta_t(x)$ is obtained by solving the Bellman condition:

$$\max_{\beta_t(x)} \mathrm{E}Q\Big(N_t, f_t(x)\big|\beta_t(x), \mu_t(x), \delta_t(x)\Big)$$

$$\approx \max_{\beta_t(x)} \frac{\varphi\big(N_t \mathrm{E}\beta_{t,\mathrm{obs}}\big)}{\mathrm{E}\beta_{t,\mathrm{obs}}} \Big[\int \chi(x) f_t(x)\Big(1-\big(\delta_{t-1}(x)+\beta_t(x)\big)\Big)dx + 2\iint \chi(x) f_t(y)\beta_t(y)\big(1-\mu_{t-1}(y)\big)p(x,y)dxdy\Big],$$

where $\mathrm{E}\beta_{t,\mathrm{obs}}$ is the expectation of the observed proliferation probability

$$\begin{aligned}\mathrm{E}\beta_{t,\mathrm{obs}} &= 1+\int f_t(x)\Big[\beta_t(x)\big(1-2\mathrm{E}\mu_t(x)\big)-\mathrm{E}\delta_t(x)\Big]dx\\ &= 1+\int f_t(x)\Big[\beta_t(x)\big(1-2\mu_{t-1}(x)\big)-\delta_{t-1}(x)\Big]dx.\end{aligned}$$

After $\beta_t(x)$ is solved by the Bellman condition, stochastic perturbations for $\mu_t(x)$ and $\delta_t(x)$ are introduced, resulting in

$$\mu_t(x) = \overline{\mu}_G(x) + \hat{\mu}_t(x), \quad \delta_t(x) = \overline{\delta}_G(x) + \hat{\delta}_t(x). \qquad \textbf{[S10]}$$

Hence, the observed proliferation probability becomes

$$\beta_{t,\mathrm{obs}} = 1 + \int f_t(x)\Big[\beta_t(x)\big(1-2\mu_t(x)\big)-\delta_t(x)\Big]dx \qquad \textbf{[S11]}$$

with $\mu_t(x)$ and $\delta_t(x)$ given by **[S10]**. Consequently, the tissue state $\big(N_{t+1}, f_{t+1}(x)\big)$ becomes

$$N_{t+1} = N_t \beta_{t,\mathrm{obs}} \qquad \textbf{[S12]}$$

$$f_{t+1}(x) = \frac{1}{\beta_{t,\mathrm{obs}}}\Big[f_t(x)\Big(1-\big(\delta_t(x)+\beta_t(x)\big)\Big) + 2\int f_t(y)\beta_t(y)\big(1-\mu_t(y)\big)p(x,y)dy\Big]. \qquad \textbf{[S13]}$$

Given $(\overline{\mu}_G(x), \overline{\delta}_G(x))$ that are selected through genetic mutations in long time, **[S12]** and **[S13]** define a lifespan dynamics of $(N_t, f_t(x))$.

The evolutionary fitness function is defined as the performance at homeostasis after many cell divisions (i.e., $t\to\infty$):

$$W = \lim_{t\to\infty} Q\big(N_t, f_t(x)\big). \qquad \textbf{[S14]}$$

The fitness W is dependent on the probabilities $\overline{\mu}_G(x)$ and $\overline{\delta}_G(x)$ that are selected through genetic mutations.

S2. Homeostasis State

Nonlinear Integral Equations. During the development and maturation of an organism, $\big(N_t, f_t(x)\big)$ evolves following **[S3]** and **[S5]**. At homeostasis, $\big(N_t, f_t(x)\big)$ approaches an equilibrium state, which is represented as the limit as $t\to\infty$ (it may be more accurate to be referred to as the average of the limits when there are stochastic fluctuations).

Let $\big(N, f(x), \beta(x), \overline{\mu}_G(x), \overline{\delta}_G(x)\big)$ be averages of the limits $\big(N_t, f_t(x), \beta_t(x), \mu_t(x), \delta_t(x)\big)$ when $t\to\infty$. At homeostasis, the stem cell population reaches equilibrium and therefore $\beta_{t,\mathrm{obs}}\to 1$ as $t\to\infty$, which yields

$$\int f(x)\Big[\beta(x)\big(1-2\overline{\mu}_G(x)\big)-\overline{\delta}_G(x)\Big]dx = 0. \qquad \textbf{[S15]}$$

Furthermore, from **[S5]** the homeostasis tissue epigenetics $f(x)$ satisfies integral equation

$$\begin{aligned}f(x) = f(x)\big(1-\big(\overline{\delta}_G(x)+\beta(x)\big)\big) \\ +2\int f(y)\beta(y)\big(1-\overline{\mu}_G(y)\big)p(x,y)dy,\end{aligned} \qquad \textbf{[S16]}$$

or equivalently,

$$f(x) = \frac{2\int f(y)\beta(y)\big(1-\overline{\mu}_G(y)\big)p(x,y)dy}{\overline{\delta}_G(x)+\beta(x)}, \qquad \textbf{[S17]}$$

with a normalization condition

$$\int f(x)dx = 1. \qquad \textbf{[S18]}$$

Thus, for given functions $\overline{\mu}_G(x)$, $\overline{\delta}_G(x)$, and $p(x,y)$, the proliferation $\beta(x)$ and distribution density $f(x)$ are given by nonnegative solutions of the nonlinear integral Eqs. **S15**, **S17**, and **S18**.

The mathematical questions related to the existence and uniqueness of nonnegative solutions of **[S15]**, **[S17]**, and **[S18]** are left for future study. Here, we only investigate a simple case for illustration.

Heterogeneous Apoptosis Can Improve the Maintenance of Tissue Epigenetics. We assume all cells are homogeneous in proliferation so that $\beta(x)$ is independent of x. Consequently, **[S15]** gives

$$\beta = \frac{\int f(x)\overline{\delta}_G(x)dx}{\int f(x)\big(1-2\overline{\mu}_G(x)\big)dx}, \qquad \textbf{[S19]}$$

and **[S17]** can be rewritten as a nonlinear integral equation

$$f(x) = \frac{2\iint f(y)f(z)\overline{\delta}_G(z)\big(1-\overline{\mu}_G(y)\big)p(x,y)dydz}{\int f(y)\Big(\overline{\delta}_G(x)\big(1-2\overline{\mu}_G(y)\big)+\overline{\delta}_G(y)\Big)dy}. \qquad \textbf{[S20]}$$

Next we show that *if* $\overline{\mu}_G(x)$ is independent of x, the tissue epigenetics at homeostasis is abnormal. We consider a specific situation in which each cell only takes one of the two discrete epigenetic states, with $x\in\Omega_1$ implying a defective cell and $x\in\Omega_2$ a normal cell. The functions $\overline{\delta}_G(x)$ and $p(x,y)$ are given by piecewise constant functions:

$$\overline{\delta}_G(x) = \begin{cases}\delta_1, & x\in\Omega_1\\ \delta_2, & x\in\Omega_2,\end{cases}$$

and

$$p(x,y)=\begin{cases}p_1(x), & y\in\Omega_1\\ p_2(x), & y\in\Omega_2,\end{cases}$$

and let

$$p_{i,j}=\int_{x\in\Omega_i}p_j(x)dx,\quad (i,j=1,2). \tag{S21}$$

Furthermore, we make the following assumptions to induce normal differentiated cells and reduce defective cells number:

1. Defective cells have smaller differentiation probabilities than normal cells ($\delta_1\le\delta_2$).
2. The transition rate from defective to normal cells is smaller than that of the reverse transition ($p_{2,1}\le p_{1,2}$).

Denoting

$$f_1=\int_{y\in\Omega_1}f(y)dy,\quad f_2=\int_{y\in\Omega_2}f(y)dy, \tag{S22}$$

and taking $x\in\Omega_1$, [**S20**] becomes [we note $\overline{\mu}_G(y)=\mu$ being a constant]

$$f(x)=\frac{2(f_1\delta_1+f_2\delta_2)(1-\mu)\left(f_1p_1(x)+f_2p_2(x)\right)}{\delta_1(1-2\mu)+f_1\delta_1+f_2\delta_2}. \tag{S23}$$

Integrating [**S23**] over $x\in\Omega_1$, we obtain

$$f_1=\frac{2(f_1\delta_1+f_2\delta_2)(1-\mu)\left(f_1p_{1,1}+f_2p_{1,2}\right)}{\delta_1(1-2\mu)+f_1\delta_1+f_2\delta_2}. \tag{S24}$$

Since $f_2=1-f_1$, [**S24**] is an equation of f_1 in the form

$$F_1(f_1)=F_2(f_1), \tag{S25}$$

where

$$F_1(f_1)=f_1\left(\delta_1(1-2\mu)+\delta_2-(\delta_2-\delta_1)f_1\right),$$

$$F_2(f_1)=2(1-\mu)\left(\delta_2-(\delta_2-\delta_1)f_1\right)\left(f_1\left(p_{1,1}-p_{1,2}\right)+p_{1,2}\right).$$

We note that both $F_1(f_1)$ and $F_2(f_1)$ are quadratic functions of f_1. There are two roots of $F_1(f_1)=0$ $\left(0 \text{ and } \frac{(1-2\mu)\delta_1+\delta_2}{\delta_2-\delta_1}\right)$, and two roots of $F_2(f_1)=0\left(-\frac{p_{12}}{p_{11}-p_{12}}(<0) \text{ and } \frac{\delta_2}{\delta_2-\delta_1}\left(<\frac{(1-2\mu)\delta_1+\delta_2}{\delta_2-\delta_1}\right)\right)$. Then the equation $F_1(f_1)=F_2(f_1)$ has a unique solution f_1^* in the interval $\left(0,\frac{\delta_2}{\delta_2-\delta_1}\right)$ (Fig. S1). Here f_1^* gives the percentage of defective cells. Furthermore, if $F_1(z)\le F_2(z)$ then $f_1^*\ge z$ (see Fig. S1 for an illustration).

Now, from the above two assumptions,

$$\begin{aligned}F_1\left(\frac{1}{2}\right)&=\frac{1}{2}\left((1-2\mu)\delta_1+\frac{1}{2}(\delta_1+\delta_2)\right)\\&=\frac{1}{2}(1-\mu)(\delta_1+\delta_2)-\frac{1}{2}\left(\delta_2+\mu(\delta_2-\delta_1)\right)\\&\le\frac{1}{2}(1-\mu)(\delta_1+\delta_2),\end{aligned}$$

and

$$\begin{aligned}F_2\left(\frac{1}{2}\right)&=\frac{1}{2}(1-\mu)(\delta_1+\delta_2)(p_{11}+p_{12})\\&\ge\frac{1}{2}(1-\mu)(\delta_1+\delta_2)(p_{11}+p_{21})\\&=\frac{1}{2}(1-\mu)(\delta_1+\delta_2).\end{aligned}$$

Thus, $F_1\left(\frac{1}{2}\right)<F_2\left(\frac{1}{2}\right)$ and hence $f_1^*\ge\frac{1}{2}$. This result indicates that more than half of the cells are defective at homeostasis, an abnormal or a disease state for a tissue.

S3. Optimal Control Strategies

The Problem of Variation. At each cell cycle, the proliferation probability $\beta_t(x)$ is determined by Bellman condition **S9**. From [**S9**], the function $\beta_t(x)$ is taken so that the expectation of $Q\left(N_{t+1},f_{t+1}(x)\right)$ reaches the maximum, with $\left(N_{t+1},f_{t+1}(x)\right)$ given by $\left(N_t,f_t(x)\right)$ through [**S2**], [**S3**], and [**S5**].

First, we show that Bellman condition **S9** alone is not sufficient to determine the function $\beta_t(x)$, and thus additional restrictions are required for a well-posed problem.

We assume that in the tissue $\mu_t(x)$ and $\delta_t(x)$ are known before the proliferation $\beta_t(x)$ is chosen. Define a functional

$$A[\beta_t]=Q(N_{t+1},f_{t+1}(x))=\varphi(N_{t+1})\int\chi(x)f_{t+1}(x)dx. \tag{S26}$$

Here N_{t+1} and $f_{t+1}(x)$ depend on β_t through [**S2**], [**S3**], and [**S5**]. If $A[\beta_t]$ attains its local minimum at β_0 and $\eta(x)$ is an arbitrary function,

$$A[\beta_0]\le A\left[\beta_0+\varepsilon\eta\right] \tag{S27}$$

for any small number ε. Therefore, the variation of A at $\beta_t=\beta_0$ must vanish,

$$\begin{aligned}\left.\frac{dA[\beta_0+\varepsilon\eta]}{d\varepsilon}\right|_{\varepsilon=0}&=\left[\varphi'(N_{t+1})\int\chi(x)f_{t+1}(x)dx\frac{dN_{t+1}}{d\varepsilon}\right.\\&\left.+\varphi(N_{t+1})\frac{d\int\chi(x)f_{t+1}(x)dx}{d\varepsilon}\right]\Bigg|_{\varepsilon=0}=0.\end{aligned} \tag{S28}$$

A direct calculation yields

$$\left.\frac{dN_{t+1}}{d\varepsilon}\right|_{\varepsilon=0}=N_t\int\eta(x)f_t(x)(1-2\mu_t(x))dx$$

and

$$\begin{aligned}&\left.\frac{d\int\chi(x)f_{t+1}(x)dx}{d\varepsilon}\right|_{\varepsilon=0}\\&=\frac{1}{\beta_{t,\text{obs}}}f_{t+1}(x)\left(\int\eta(x)f_t(x)\left(1-2\mu_t(x)\right)dx\right)\\&+\frac{1}{\beta_{t,\text{obs}}}\\&\times\left(-\eta(x)f_t(x)+2\int\eta(y)f_t(y)(1-\mu_t(y))p(x,y)dy\right).\end{aligned}$$

Here $\beta_{t,\mathrm{obs}}$ and $f_{t+1}(x)$ are given by [**S2**] and [**S5**], respectively, but with $\beta_t=\beta_0$. Thus, Eq. **S28** yields, for an arbitrary function $\eta(x)$,

$$\begin{aligned}0=&\varphi'(N_{t+1})N_{t+1}\\&\times\left(\int\chi(x)f_{t+1}(x)dx\right)\left(\int\eta(x)f_t(x)\left(1-2\mu_t(x)\right)dx\right)\\&+2\varphi(N_{t+1})\int\eta(y)f_t(y)\left(1-\mu_t(y)\right)p(x,y)dy\\&+\varphi(N_{t+1})f_{t+1}(x)\int\eta(y)f_t(y)\left(1-2\mu_t(y)\right)dy\\&-\varphi(N_{t+1})\eta(x)f_t(x).\end{aligned}\qquad[\mathbf{S29}]$$

It is impossible to find a function $\beta_0(x)$ that solves [**S29**] with arbitrary x and function $\eta(x)$.

The above argument shows that Bellman condition **S9** does not have a solution for a general function $\beta_t(x)$, and thus additional conditions are required.

For a particular biological system, there are additional restrictions to the proliferation. We consider two types of stem cells often seen in biological systems, namely either homogeneous or heterogeneous in their proliferation. For stem cells homogenous in their proliferation, the function $\beta_t(x)$ is independent of x (but may change with t); for stem cells heterogeneous in proliferation, the function $\beta_t(x)$ varies with x.

Homogeneous in Proliferation (Strategy A). ***Formulation of the proliferation probability.*** For cells homogeneous in their proliferation, the proliferation probability β_t is independent of the epigenetic state x. It is implicitly assumed that cells know the expected apoptosis probability $\mu_t(x)$ and the differentiation probability $\delta_t(x)$ before determining the proliferation probability β_t. For example, a simple strategy is to assume the expectations of these two probabilities equal the current values while determining β_t, i.e., assuming $\mathrm{E}\mu_t(x)=\mu_{t-1}(x)$ and $\mathrm{E}\delta_t(x)=\delta_{t-1}(x)$.

Since β_t is a constant, the optimal value is given by $\partial Q(N_{t+1},f_{t+1}(x))/\partial\beta_t=0$, which yields

$$\begin{aligned}0=&\varphi'(N_{t+1})\frac{\partial N_{t+1}}{\partial\beta_t}\int\chi(x)f_{t+1}(x)\\&+\varphi(N_{t+1})\int\chi(x)\frac{\partial f_{t+1}(x)}{\partial\beta_t}dx.\end{aligned}\qquad[\mathbf{S30}]$$

Let

$$\overline{\mu}_t=\int f_t(x)\mu_t(x)dx,\quad\overline{\delta}_t=\int f_t(x)\delta_t(x)dx,$$

$$\overline{\chi}_t=\int f_t(x)\chi(x)dx,\quad\overline{d}_t=\int f_t(x)\chi(x)\delta_t(x)dx,$$

$$\sigma(y)=\int\chi(x)p(x,y)dx,\quad\overline{\sigma}_t=\frac{\int f_t(y)(1-\mu_t(y))\sigma(y)dy}{1-\overline{\mu}_t},$$

then we have

$$\begin{aligned}\frac{\partial N_{t+1}}{\partial\beta_t}&=N_t(1-2\overline{\mu}_t),\\\frac{\partial f_{t+1}(x)}{\partial\beta_t}&=-\frac{f_{t+1}(x)}{N_{t+1}}\frac{\partial N_{t+1}}{\partial\beta_t}+\frac{N_t}{N_{t+1}}\\&\quad\times\left[-f_t(x)+2\int f_t(y)(1-\mu_t(y))p(x,y)dy\right].\end{aligned}$$

Thus, [**S30**] becomes

$$\frac{N_t\beta_{t,\mathrm{obs}}\varphi'\left(N_t\beta_{t,\mathrm{obs}}\right)}{\varphi\left(N_t\beta_{t,\mathrm{obs}}\right)}=A_t,\qquad[\mathbf{S31}]$$

where

$$A_t=1-\frac{\overline{\sigma}_t}{\overline{\chi}_{t+1}}-\frac{\overline{\sigma}_t-\overline{\chi}_t}{(1-2\overline{\mu}_t)\overline{\chi}_{t+1}},$$

$$\overline{\chi}_{t+1}=\frac{\overline{\chi}_t-\overline{d}_t+\beta_t(2(1-\overline{\mu}_t)\overline{\sigma}_t-\overline{\chi}_t)}{\beta_{t,\mathrm{obs}}}$$

and

$$\beta_{t,\mathrm{obs}}=1+\beta_t(1-2\overline{\mu}_t)-\overline{\delta}_t.\qquad[\mathbf{S32}]$$

The theoretical optimal strategy β_t is obtained from a solution of [**S31**] and [**S32**]. In addition, we note a biologically acceptable proliferation probability is always nonnegative, and must be less than a maximum value $\beta_{\max}$ that is limited by its biological capability. Thus, the possible proliferation probability takes values within the interval $[0,\beta_{\max}]$. We set the probability $\beta_t=0$ if the β_t obtained above is less than 0, and set $\beta_t=\beta_{\max}$ if it is larger than $\beta_{\max}$.

Assume the population performance $\varphi(N)$ is maximum at $N=N_*$, i.e., $\varphi'(N_*)=0$ and $\varphi''(N_*)<0$. Here N_* is by definition the fittest cell population of the tissue. In [**S31**], if A_t is close to 0, we have approximately

$$\beta_{t,\mathrm{obs}}\approx\frac{1}{N_*}\left(N_*+\frac{A_t\varphi(N_*)}{N_*\varphi''(N_*)}\right),\qquad[\mathbf{S33}]$$

or equivalently,

$$\beta_t\approx\frac{\frac{1}{N_t}\left(N_*+\frac{A_t\varphi(N_*)}{N_*\varphi''(N_*)}\right)-1+\overline{\delta}_t}{1-2\overline{\mu}_t}.\qquad[\mathbf{S34}]$$

Therefore,

$$N_{t+1}\approx N_*+\frac{A_t\varphi(N_*)}{N_*\varphi''(N_*)},\qquad[\mathbf{S35}]$$

which yields $N_t\approx N_*$ when A_t is close to 0. Thus, [**S34**] indicates a negative feedback when the cell population is close to the value of the fittest population (Fig. S2*A*).

Tissue dynamics based on strategy A. Fig. S2 shows numerical simulations obtained from the above control strategy. Fig. S2*A* plots the decreasing dependence of proliferation probability on cell population. Fig. S2*B* shows the time course of the performance $Q(N_t,f_t(x))$ in a simulation of 5,000 cell cycles. Fig. S2*C* gives $f_t(x)$ at the early, intermediate, and later temporal points in the simulation.

Epigenetic dependences are required for robust development and evolution. In this study, the dependences of δ,μ,χ on the epigenetic state are significant in regulation. Here we study the importance of epigenetic dependence in robust development and evolution.

From [**S3**] and [**S5**], the dynamics of population and average cell performance $(N_t,\overline{\chi}_t)$ are given by

$$\begin{bmatrix}N_t\\\overline{\chi}_t\end{bmatrix}\mapsto\begin{bmatrix}N_t\beta_{t,\mathrm{obs}}\\\dfrac{\overline{\chi}_t-\overline{d}_t+\beta_t(2(1-\overline{\mu}_t)\sigma_t-\overline{\chi}_t)}{\beta_{t,\mathrm{obs}}}\end{bmatrix}\qquad[\mathbf{S36}]$$

Here

$$\beta_t = \frac{\beta_{t,\mathrm{obs}} - 1 + \bar{\delta}_t}{1 - 2\bar{\mu}_t}. \quad \textbf{[S37]}$$

Eqs. **S5**, **S31**, **S36**, and **S37** together define a dynamical system for $(N_t, \bar{\chi}_t)$. This dynamical system reaches a statistical equilibrium state when $t \to \infty$. Thus, the expectation $\mathrm{E}\beta_{t,\mathrm{obs}} \to 1$ and the limits

$$N = \lim_{t\to\infty} \mathrm{E}N_t, \quad \bar{\chi} = \lim_{t\to\infty} \mathrm{E}\bar{\chi}_t$$

are well defined. In this case, we have

$$\frac{N\varphi'(N)}{\varphi(N)} = \lim_{t\to\infty} \mathrm{E}A_t \quad \textbf{[S38]}$$

and

$$\bar{\chi} = \lim_{t\to\infty} \mathrm{E}\left[\bar{\sigma}_t + (1 - 2\bar{\mu}_t)\left(\bar{\sigma}_t - d_t/\bar{\delta}_t\right)\right]. \quad \textbf{[S39]}$$

Eqs. **S38** and **S39** give the population N and average performance $\bar{\chi}$ at homeostasis.

If the performance function χ is independent of the state x (i.e., $\bar{\chi}_t = \bar{\sigma}_t = \chi$ for any t), we have $N = N_*$ and therefore the evolutionary fitness $W = \bar{\chi}\varphi(N_*)$ is independent of the apoptosis probability $\mu(x)$. Hence, the apoptosis response fails to evolve based on the evolutionary fitness W. This result suggests that variability in cell performance is necessary for successful natural selection for apoptosis.

When the cell fitness $\chi(x)$ varies with x, **[S35]** indicates $N \neq N_*$, i.e., the cell population at homeostasis differs from the value of the fittest population, and the difference $\Delta N = |N - N_*|$ is proportional to $\Delta\chi = |\sigma - \chi|$. We note that $\Delta\chi$ measures the difference between the performance of mother cells and their daughter cells, and is in turn determined by $p(x,y)$—the variation between daughter cells and the mother cell due to epigenetic state transition in cell division. Simulations show that if the daughter cells are identical to their mother cells, i.e.,

$$p(x,y) = \begin{cases} 1 & x = y \\ 0 & x \neq y, \end{cases} \quad \textbf{[S40]}$$

then $N = N_*$, and the tissue epigenetics $f(x)$ at homeostasis is dependent on the initial cell distributions (Fig. S3). We note that changes in cell distributions during a lifetime can be induced by accidental injury. Thus, the above analysis suggest that the transition of epigenetic state in cell division is necessary for a robust tissue epigenetics at homeostasis with respect to accidental changes in life span, but can shift the stem cell population away from the value of the fittest population.

Heterogeneous in Proliferation (Strategy B). ***Formulation of the proliferation probability.*** For stem cells heterogeneous in proliferation, $\beta_t(x)$ varies with the epigenetic state x. Here we study a simple situation in which cells take two distinct proliferation probabilities.

We divide all stem cells into two phenotypes by their epigenetic state x, with $x \in \Omega_1$ for type I cells, and $x \in \Omega_2$ for type II cells. Proliferation probabilities are the same for cells of the same type:

$$\beta_t(x) = \begin{cases} \beta_{t,1}, & x \in \Omega_1 \\ \beta_{t,2}, & x \in \Omega_2 \end{cases}. \quad \textbf{[S41]}$$

We assume that the proliferation of type II cells is modulated such that $\beta_{t,2}$ changes at each cell cycle, while the proliferation of type I cells is unmodulated over the lifetime ($\beta_{t,1} \equiv \bar{\beta}_{1,G}$ is genetically regulated).

Based on the above assumptions, the proliferation $\beta_{t,2}$, for given $\beta_{t,1} \equiv \bar{\beta}_{1,G}$, $\mu_t(x)$ and $\delta_t(x)$, is determined by $\partial Q(N_{t+1}, f_{t+1}(x))/\partial\beta_{t,2} = 0$, i.e.,

$$\bar{\chi}_{t+1}\varphi'(N_{t+1})\frac{\partial N_{t+1}}{\partial\beta_{t,2}} + \varphi(N_{t+1})\frac{\partial\bar{\chi}_{t+1}}{\partial\beta_{t,2}} = 0, \quad \textbf{[S42]}$$

which gives

$$N_{t+1}\frac{\varphi'(N_{t+1})}{\varphi(N_{t+1})} = 1 - \frac{2\int_{\Omega_2} f_t(y)(1-\mu_t(y))\sigma_t(y)dy - \int_{\Omega_2} f_t(x)\chi(x)dx}{\bar{\chi}_{t+1}\int_{\Omega_2} f_t(x)(1-2\mu_t(x))dx}, \quad \textbf{[S43]}$$

with $N_{t+1} = N_t\beta_{t,\mathrm{obs}}$.

At each cell cycle, the optimal proliferation probability $\beta_{t,2}$ is obtained based on Eq. **S43**.

To solve Eq. **S43**, we denote

$$\bar{f}_{t,1} = \int_{\Omega_1} f_t(x)dx, \quad \bar{f}_{t,2} = \int_{\Omega_2} f_t(x)dx,$$

$$\bar{\mu}_{t,1} = \int_{\Omega_1} f_t(x)\mu_t(x)dx, \quad \bar{\mu}_{t,2} = \int_{\Omega_2} f_t(x)\mu_t(x)dx,$$

$$\bar{\chi}_{t,1} = \int_{\Omega_1} f_t(x)\chi(x)dx, \quad \bar{\sigma}_{t,1} = \frac{\int_{\Omega_1} f_t(x)(1-\mu_t(x))\sigma(x)dx}{f_{t,1} - \bar{\mu}_{t,1}},$$

$$\bar{\chi}_{t,2} = \int_{\Omega_2} f_t(x)\chi(x)dx, \quad \bar{\sigma}_{t,2} = \frac{\int_{\Omega_2} f_t(x)(1-\mu_t(x))\sigma(x)dx}{f_{t,2} - \bar{\mu}_{t,2}}.$$

Then,

$$\beta_{t,\mathrm{obs}} = 1 + \bar{\beta}_{1,G}\left(\bar{f}_{t,1} - 2\bar{\mu}_{t,1}\right) + \beta_{t,2}\left(\bar{f}_{t,2} - 2\bar{\mu}_{t,2}\right) - \bar{\delta}_t, \quad \textbf{[S44]}$$

and

$$\begin{aligned}\bar{\chi}_{t+1} &= \frac{1}{\beta_{t,\mathrm{obs}}}\int \chi(x)f_t(x)(1-\delta_t(x)-\beta_t(x))dx \\ &\quad + \frac{2}{\beta_{t,\mathrm{obs}}}\int f(y)\beta_t(y)(1-\mu_t(y))\sigma(y)dy \\ &= \frac{1}{\beta_{t,\mathrm{obs}}}\Big[\left(\bar{\chi}_t - \bar{d}\right)_t - \bar{\beta}_{1,G}\bar{\chi}_{t,1} - \beta_{t,2}\bar{\chi}_{t,2} \\ &\quad + 2\bar{\beta}_{1,G}\left(\bar{f}_{t,1} - \bar{\mu}_{t,1}\right)\bar{\sigma}_{t,1} + 2\beta_{t,2}\left(\bar{f}_{t,2} - \bar{\mu}_{t,2}\right)\bar{\sigma}_{t,2}\Big] \\ &= \frac{1}{\beta_{t,\mathrm{obs}}}\Big[\left(\bar{\chi}_t - \bar{d}\right)_t - \bar{\beta}_{1,G}\left(\bar{\chi}_{t,1} - 2\left(\bar{f}_{t,1} - \bar{\mu}_{t,1}\right)\bar{\sigma}_{t,1}\right) \\ &\quad - \beta_{t,2}\left(\bar{\chi}_{t,2} - 2\left(\bar{f}_{t,2} - \bar{\mu}_{t,2}\right)\bar{\sigma}_{t,2}\right)\Big]. \end{aligned} \quad \textbf{[S45]}$$

Thus, we can rewrite **[S43]** as

$$N_t\beta_{t,\mathrm{obs}}\frac{\varphi'\left(N_t\beta_{t,\mathrm{obs}}\right)}{\varphi\left(N_t\beta_{t,\mathrm{obs}}\right)}=A_t' \qquad \textbf{[S46]}$$

with

$$A_t'=1-\frac{\overline{\sigma}_{t,2}}{\overline{\chi}_{t+1}}-\frac{f_{t,2}\overline{\sigma}_{t,2}-\overline{\chi}_{t,2}}{\overline{\chi}_{t+1}\left(f_{t,2}-2\overline{\mu}_{t,2}\right)}. \qquad \textbf{[S47]}$$

The proliferation $\beta_{t,2}$ is obtained from the positive solution of Eqs. **S44**–**S47**.

Similarly to the previous argument, when $N_t\approx N_*$ and $A_t'\approx 0$, we have

$$\beta_{t,\mathrm{obs}}\approx\frac{1}{N_*}\left(N_*+\frac{A_t'\varphi(N_*)}{N_*\varphi''(N_*)}\right), \qquad \textbf{[S48]}$$

and hence

$$\beta_{t,2}\approx\frac{\frac{1}{N_t}\left(N_*+\frac{A_t'\varphi(N_*)}{N_*\varphi''(N_*)}\right)-1-\overline{\beta}_{1,G}\left(\overline{f}_{t,1}-2\overline{\mu}_{t,1}\right)+\overline{\delta}_t}{\overline{f}_{t,2}-2\overline{\mu}_{t,2}}. \qquad \textbf{[S49]}$$

Tissue dynamics based on strategy B. Based on the previous arguments, the proliferation probability of type II cells at homeostasis, denoted as β_2, is dependent on the probability of type I cells $\overline{\beta}_{1,G}$. Fig. S4*A* shows the dependences of β_2 and the evolutionary fitness W on $\overline{\beta}_{1,G}$ (varying from 0 to 0.1). Simulations suggest that the proper value of the unmodulated proliferation probability $\overline{\beta}_{1,G}$ can improve the evolutionary fitness compared with the case of homogeneous proliferation (the corresponding evolutionary fitness is shown by the red dashed line in Fig. S4*A*). We also note that if $\overline{\beta}_{1,G}$ is too large ($\overline{\beta}_{1,G}>0.08$ in the current simulation), it is possible to induce uncontrolled growth such that the fitness decreases to 0. Fig. S4*B* shows tissue epigenetics $f(x)$ at homeostasis with $\overline{\beta}_{1,G}=0.02$ and $\overline{\beta}_{1,G}=0.06$, respectively. When $\overline{\beta}_{1,G}=0.02$, the tissue epigenetics has the same profile as in the case of homogenous proliferation (Fig. S2*C*), and when $\overline{\beta}_{1,G}=0.06$ (with better fitness), the epigenetic distribution shows apparent shift to the region of better performance (corresponding to the region of larger x).

Robust recovery after sudden changes. Fig. S5 shows tissue response (cell population, differentiated cell population, and cell distributions) to temporal changes in differentiation. In simulations, the immigration of dormant cells from the quiescent phase to the resting phase is taken into account in a simple way by introducing a sudden increase (10%) of the resting phase cell population at the time point $(t=1,000)$ along with an increase in the differentiation probability. We observe a transient rise and fall of cell populations in the resting phase due to the addition of resting-phase cells to the model, however, with similar long-time dynamics shown in Fig. 4. The overall features are found to be similar to those obtained without considering the effect of the quiescent phase.

Fig. S6 shows cell population dynamics, under three different strategies, when there are temporary changes in the apoptosis probability. The results indicate that heterogeneity in proliferation induces less changes in cell populations than the cases of homogeneous proliferation.

S4. Evolution

The evolutionary fitness W defined by **[S14]** is a function of $\overline{\mu}_G(x)$ and $\overline{\delta}_G(x)$. Here we keep $\overline{\delta}_G(x)$ unchanged and study the evolution of the apoptosis probability $\overline{\mu}_G(x)$ via the fitness function W.

Fig. S7 shows a numerical simulation for the evolution of $\overline{\mu}_G(x)$ when the cells are homogeneous in proliferation. In the simulation, the apoptosis $\overline{\mu}_G(x)$ starts from a constant function ($\overline{\mu}_G(x)\equiv 0.07$) with a low fitness ($W=0.18$), and automatically evolves to yield a high fitness ($W=1.8$) at the end of the simulation. The resulting apoptosis is taken such that cells with lower performance (cells with $x<60$) have larger apoptosis probability. Consequently, the tissue epigenetics $f(x)$ at homeostasis shifts from the profile of low-performance cells being dominant to that of high-performance cells being dominant (Fig. S7*B*). Furthermore, simulations show that the evolution obviously increases the average cell fitness ($\overline{\chi}$ increases from 0.10 to 0.98 in the simulation), but only results in small changes in the cell population N. Further simulations show that the results are robust and insensitive to the choices of initial apoptosis probability (Fig. S8).

We also test our results using different functions for the differentiation $\overline{\delta}_G(x)$ (Fig. S9). Simulations suggest that different differentiation probabilities can give the same value of evolutionary fitness after a number of mutations, and the resulting apoptosis probability and tissue epigenetics at homeostasis are insensitive to $\overline{\delta}_G(x)$.

S5. Details for Numerical Simulations

Parameter Values and Choices of Functions in the Model. In simulating the model, we need to specify the five functions $p(x,y)$, $\overline{\mu}_G(x)$, $\overline{\delta}_G(x)$, $\chi(x)$, and $\varphi(N)$.

For simplicity, we assume the epigenetic state can be represented as a scalar variable $x\in[0,X_{\max}]$. For example, x can be the expression level of one gene, or the number of nucleosome modifications of a DNA region. In general, x represents an intrinsic cellular state that may change after each cell division. Without loss of generality, the four functions $\chi(x)$, $\overline{\delta}_G(x)$, $\overline{\mu}_G(x)$, and $p(x,y)$ are chosen in a consistent way, as seen in Fig. S10. In particular, because x can be transformed into different values by shifting and reflecting its values, without loss of generality, the region of small values of x corresponds to the low value of the performance function $\chi(x)$. Together, we assume the following characteristics of the five functions:

i) A cell has low performance (low capability of accomplishing its physiological function) when $x<60$, and it has high performance when $100<x<X_{\max}=300$.
ii) Cells defined in the region of $100<x<140$ at resting phase have larger differentiation probability ($\overline{\delta}_G(x)$) than the other cells.
iii) Cells with $80<x<160$ at the proliferative phase have smaller apoptosis probability ($\overline{\mu}_G(x)$), as they have larger differentiation probability.
iv) The transition probability $p(x,y)$ is taken in a form such that only local changes in the epigenetic state are allowed in each cell division.
v) Function $\varphi(N)$ is concave with a maximum value at $N=1$ since we normalize the fittest population to $N_*=1$.

All simulation codes are written in MATLAB (MathWorks) (available upon request). Those functions, as plotted in Fig. S10, then take the following forms in MATLAB:

$$\chi(x)=0.1+0.9\times\mathrm{gamcdf}(x,40,2),$$

$$\overline{\delta}_G(x)=0.01+0.4\times\mathrm{normpdf}(x,120,20),$$

$$\overline{\mu}_G(x)=0.35-27\times\mathrm{normpdf}(x,120,40),$$

$$\varphi(N)=(cN)^2e^{-(cN-1)^2},\quad c=\left(\sqrt{5}+1\right)\Big/2,$$

and for $(x,y)\in[0,300]\times[0,300]$

$$p(x,y)=\begin{cases}\dfrac{1}{C(y)}\psi\left(\dfrac{x}{y}-1;\dfrac{\sqrt{2}}{2},10\right) & \left|\dfrac{x}{y}-1\right|<\dfrac{\sqrt{2}}{2}\\ 0 & \text{otherwise}\end{cases}$$

where

$$\psi(z;a,s)=\left(a^2-z^2\right)^s, C(y)=\int_0^{300}\psi\left(\frac{x}{y}-1;\frac{\sqrt{2}}{2},10\right)dx.$$

Here the functions gamcdf and normpdf are taken for the convenience of programming. The values of 0.9, 0.4, and 27 in $\chi(x)$, $\overline{\delta}_G(x)$ and $\overline{\mu}_G(x)$ can be changed to adjust the difference between the maximum and minimum of these functions. We take the initial population $N_0=0.8$ and the initial distribution density $f_0(x)=1/300$.

For the simple feedback (strategy C), a standard Hill function is used for the feedback function:

$$\beta_t=\beta_0\frac{1+\rho(N_t/K)^m}{1+(N_t/K)^m}, \qquad \textbf{[S50]}$$

in which $\beta_0=0.25$, $\rho=0.05$, $K=0.2$, and m varies from 1 to 10.

Proliferation at Each Cell Cycle. At each step, N_t and $f_t(x)$ are known. We first solve **[S31]** (or **[S46]** for cells heterogeneous in proliferation) for β_t [let $\mu_t(x)=\mu_{t-1}(x)$ and $\delta_t(x)=\delta_{t-1}(x)$ while solving these equations]. Next, we apply random perturbations to the average probabilities $\overline{\mu}_G(x)$ and $\overline{\delta}_G(x)$ to obtain $\mu_t(x)$ and $\delta_t(x)$ at the current step:

$$\mu_t(x)=\overline{\mu}_G(x)+0.08\eta_{t,1}+0.04\xi_{t,1}(x),$$

and

$$\delta_t(x)=\overline{\delta}_G(x)+0.006\eta_{t,2}+0.0008\xi_{t,2}(x).$$

Here $\eta_{t,i}$ represent the external noise to the whole population and are independent random values uniformly distributed in $[-1,\ 1]$ and $\xi_{t,i}(x)$ represent the intrinsic noise to each individual cell and are independent uniform distribution random values in $[-1,\ 1]$ for each value of x. The observed proliferations $\beta_{t,\text{obs}}$ is calculated from the calculated β_t, $\mu_t(x)$ and $\delta_t(x)$. Finally, N_{t+1} and $f_{t+1}(x)$ are obtained from **[S3]** and **[S5]**. The procedure is repeated for 5×10^4 steps until the stationary state is reached. Then calculation of the evolutionary fitness W is carried out.

In mimicking the cells heterogeneous in proliferation, we take $\Omega_1=(200,300]$ and therefore $\Omega_2=[0,200]$. At each cell cycle, after obtaining $\beta_{t,2}$ from **[S46]**, the proliferation probability is given as

$$\beta_t(x)=\overline{\beta}_{1,G}+\left(\beta_{t,2}-\overline{\beta}_{1,G}\right)\frac{1}{1+(x/200)^{100}} \qquad \textbf{[S51]}$$

to smooth out $\beta_t(x)$ at $x=200$.

Evolution of the Apoptosis. To study the evolution of apoptosis probability $\overline{\mu}_G(x)$ akin to natural selection, we start from an initial $\overline{\mu}_G(x)$, and apply a small change to generate a new function μ_{new}. We ask whether the change increases the fitness W. If it does increase the fitness, then it survives, and otherwise, it only survives with a probability $\exp[(W_{\text{new}}-W_{\text{old}})/T]$ with a constant T. In simulations, $\overline{\delta}_G(x)$ remains unchanged. The simulation procedure is given below:

1. Start from an initial function $\overline{\mu}_G(x)$.
2. Calculate the evolutionary fitness $W_{\text{old}}=W(\overline{\mu}_G(x))$ following the above procedure.
3. Perform a mutation [perturb the function $\overline{\mu}_G(x)$ at a randomly selected x] to obtain a new function $\overline{\mu}_{G,\text{new}}(x)$ (for heterogeneous cells, we perturb β_1 as well), and calculate the corresponding evolutionary fitness $W_{\text{new}}=W(\overline{\mu}_{G,\text{new}})$.
4. Accept the new function with a probability $\exp[(W_{\text{new}}-W_{\text{old}})/T]$ ($T=0.01$ in simulations) and let $W=W_{\text{new}}$, $\overline{\mu}_G(x)=\overline{\mu}_{G,\text{new}}(x)$.
5. Go to step 3 or stop the simulation.

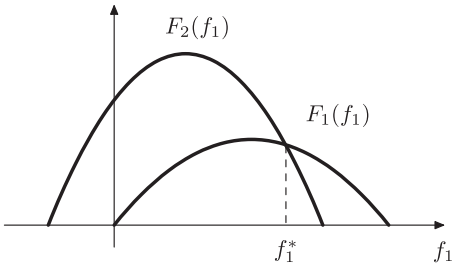

Fig. S1. Illustration of functions $F_1(f_1)$ and $F_2(f_1)$.

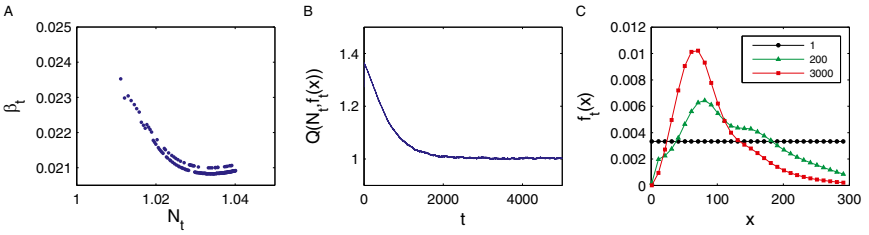

Fig. S2. Simulations for stem cells homogeneous in proliferation. (*A*) Dependence of the proliferation β_t on the size of cell population N_t. (*B*) Time course of the performance $Q(N_t,f_t(x))$. (*C*) Tissue epigenetic $f(x)$ at the cell cycle $t=1$ (black circles), 200 (green triangles), and 3,000 (red squares). See the main text and *SI Text*, section S5 for details.

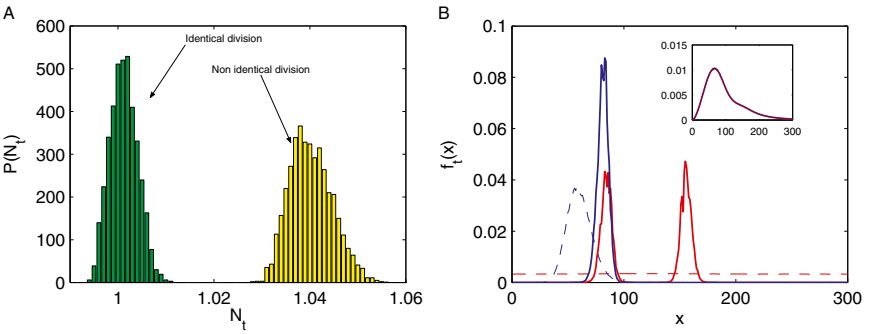

Fig. S3. Simulations with different partition functions $p(x,y)$. (*A*) Distributions of cell populations at homeostasis for identical cell division ($p(x,y)$ given by [**S40**]) and nonidentical cell division [$p(x,y)$ as in Fig. S2], respectively. (*B*) Distributions of epigenetic states obtained from identical cell division but with different initial states (shown by dashed curves of the same color). *Inset* shows distributions obtained from nonidentical cell division but with different initial distributions (the two resulting curves are indistinguishable).

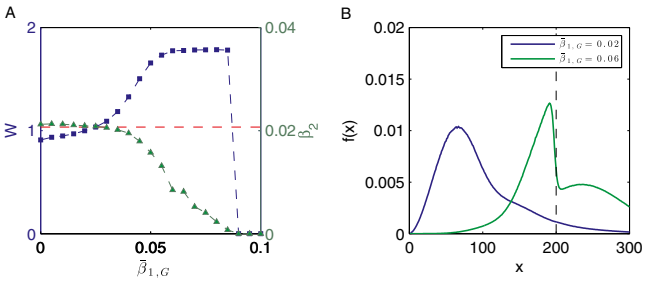

Fig. S4. Numerical simulations for heterogeneous stem cells. (*A*) The fitness (*W*, left-hand ordinate and blue squares) as well as proliferation probability of type II cells (β_2, right-hand ordinate and green triangles) at homeostasis as functions of proliferation probability of type I cells $\bar{\beta}_{1,G}$. The red dashed line shows the evolutionary fitness *W* at homeostasis when we assume homogeneous proliferation (strategy A). (*B*) Tissue epigenetics $f(x)$ at homeostasis with $\bar{\beta}_{1,G}=0.02$ (blue) and $\bar{\beta}_{1,G}=0.06$ (green), respectively. The dashed vertical line indicates the separation of type I and II cells. In simulations, all functions are the same as those used in Fig. S2, type I cells are those with $200<x\leq 300$, and type II cells are those with $0\leq x\leq 200$.

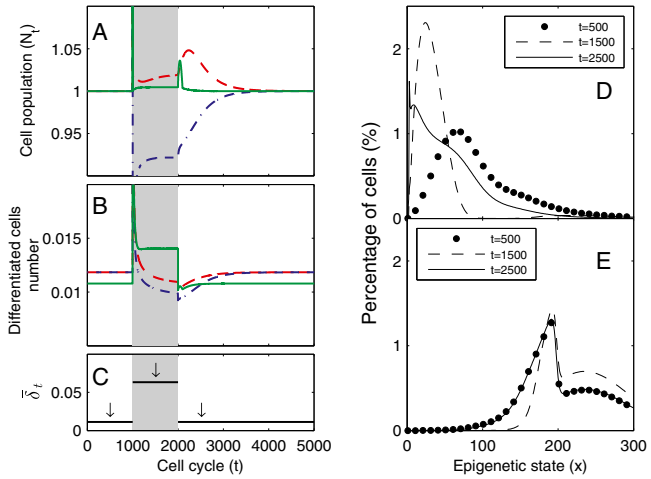

Fig. S5. Tissue response to temporal changes in differentiation. (*A*) Time courses of cell population, under three different strategies for the proliferation. The red dashed line represents strategy A, the green solid line strategy B, and the blue dashed/dotted line strategy C with Hill coefficient $m = 10$. (*B*) Time course of the number of differentiated stem cell $(N_t\bar{\delta}_t)$. (*C*) Time course of the average differential $\bar{\delta}_t$. Shadows indicate the time window of increasing differentiation. (*D*) Cell distributions (strategy A) at three time points (marked with arrows in *C*), before (filled circles, $t = 500$), during (dashed line, $t = 1{,}500$), and after (solid line, $t = 2{,}500$) the sudden change of differentiation. (*E*) Same as *D* but using strategy B.

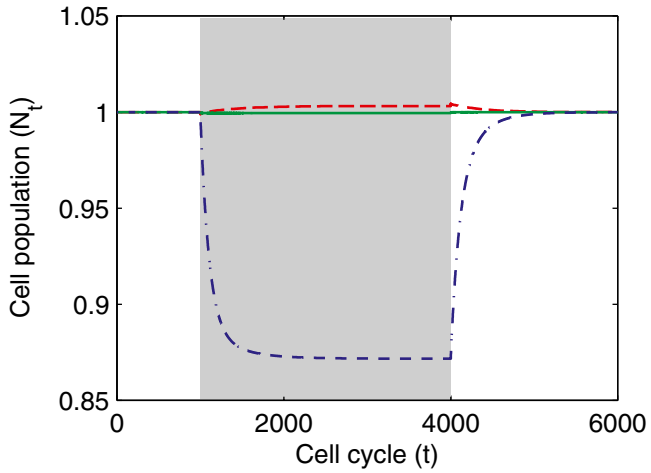

Fig. S6. Simulation of cell population dynamics when there are temporary changes in the apoptosis probability. Different colored lines correspond to different control strategies for proliferation. The red dashed line represents strategy A, the green solid line strategy B, and the blue dashed/dotted line strategy C. The shadow region indicates the time window of increasing the apoptosis probability [$\bar{\mu}_G(x) = 0.35 - 22 \times \text{normpdf}(x, 120, 40)$ in the shadow region].

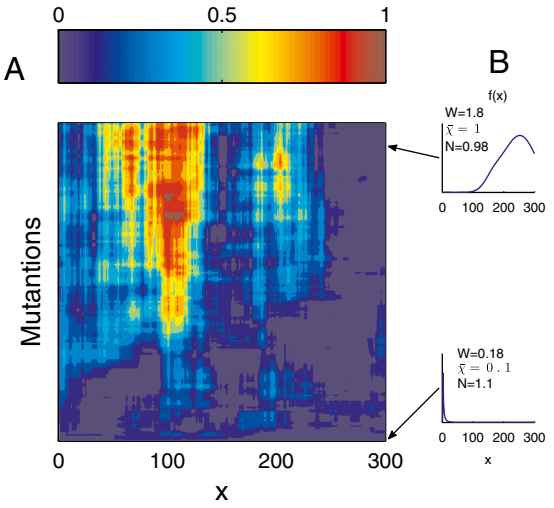

Fig. S7. Evolution of apoptosis probability $\bar{\mu}_G(x)$ of homogenous cells. (*A*) The function $\bar{\mu}_G(x)$ at different times, with an initial constant function $\bar{\mu}_G(x) = 0.07$. (*B*) Tissue genetics $f(x)$, evolutionary fitness W, average cell fitness $\bar{\chi}$, and population number N at two temporal points (indicated by arrows, early and later in the evolution, respectively). See *SI Text*, section S5 for simulation details.

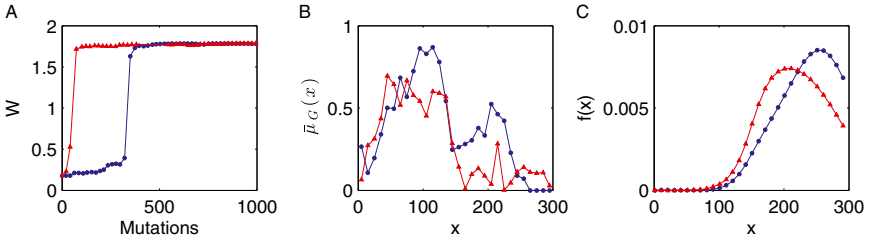

Fig. S8. Evolution of the apoptosis probability starting from different initial functions. (*A*) Dependence of the evolutionary fitness W on the number of mutations. (*B*) Apoptosis probability function at the end of the simulation. (*C*) Tissue epigenetics $f(x)$ at the end of simulation. Blue circles are obtained from the initial $\bar{\mu}_G(x) = 0.07$, and red triangles from the initial $\bar{\mu}_G(x) = 0.01 + 0.03 \times \text{chi2pdf}(x,200)$.

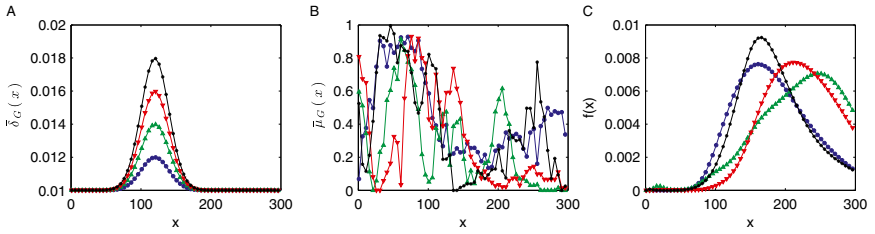

Fig. S9. Evolution of the apoptosis probability $\bar{\mu}_G(x)$ with different forms of $\bar{\delta}_G(x)$. (*A*) The function $\bar{\delta}_G(x)$ used in simulations. We take $\bar{\delta}_G(x) = 0.01 + r \times \text{normpdf}(x,120,20)$ with $r = 0.1$ (blue circles), 0.2 (green up triangles), 0.3 (red down triangles), and 0.4 (black asterisks). (*B*) Apoptosis probability at the end of simulation. (*C*) Tissue epigenetics $f(x)$ at the end of simulation.

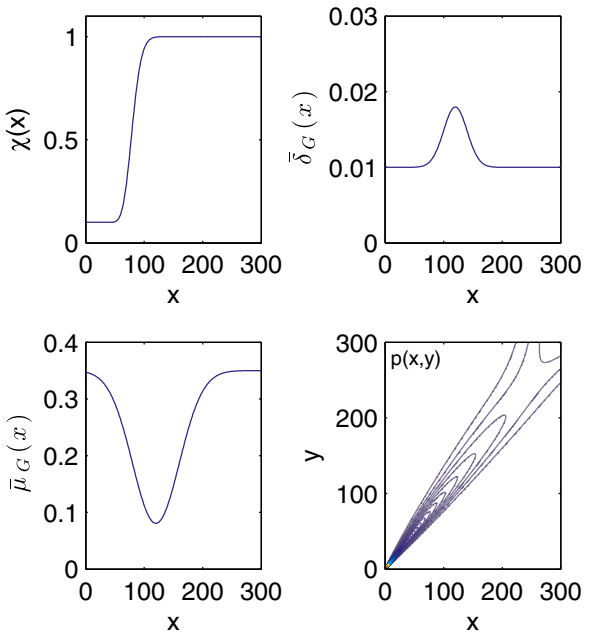

Fig. S10. The functions $\chi(x)$, $\bar{\delta}_G(x)$, $\bar{\gamma}_G(x)$, and $p(x,y)$ (contour plot) used in the simulations.