The Abdus Salam International Centre for Theoretical Physics

Postgraduate Diploma Programme
Quantitative Life Sciences

Mathematical models of proliferative control

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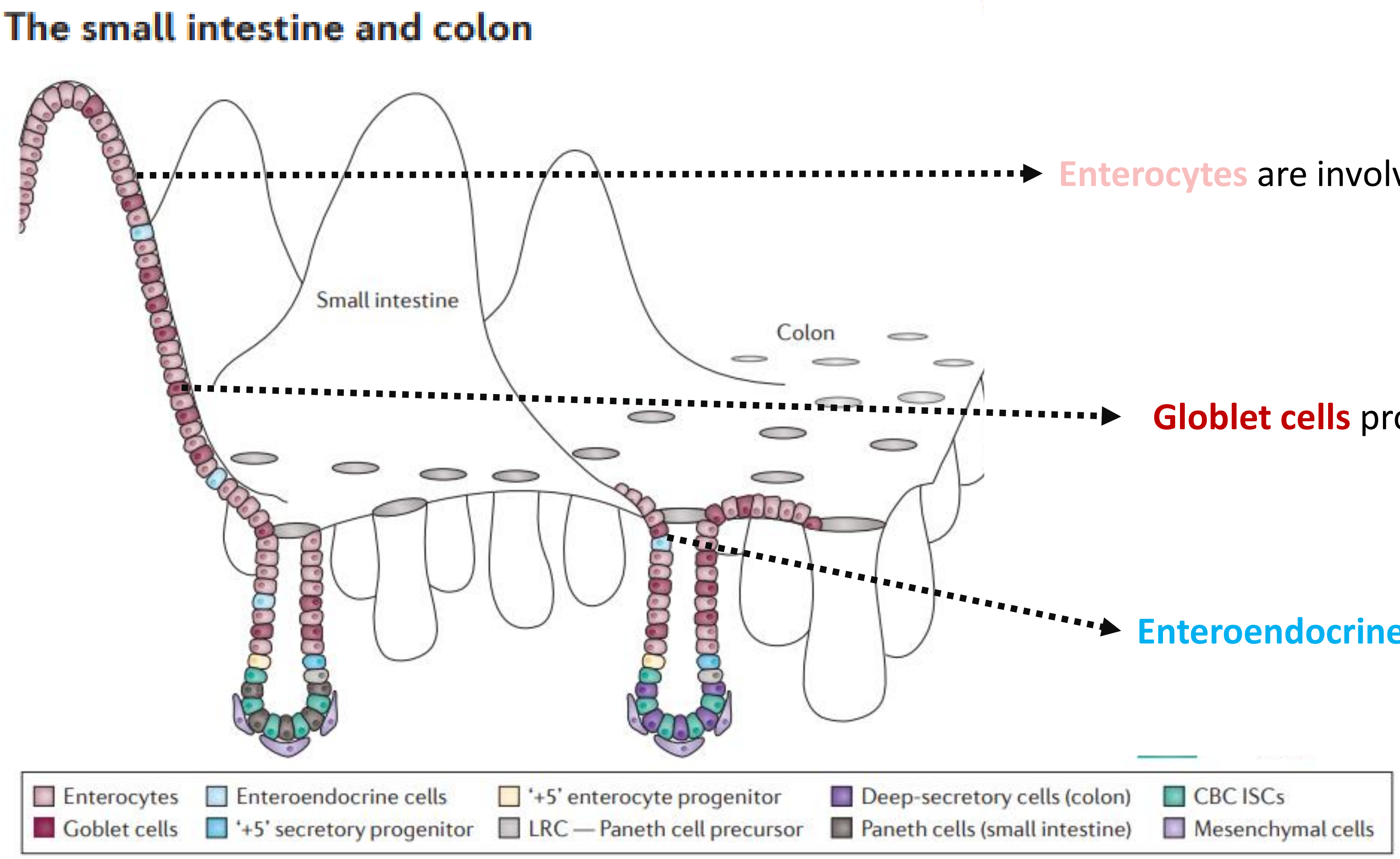
Tissues are organized communities of cells performing different functions



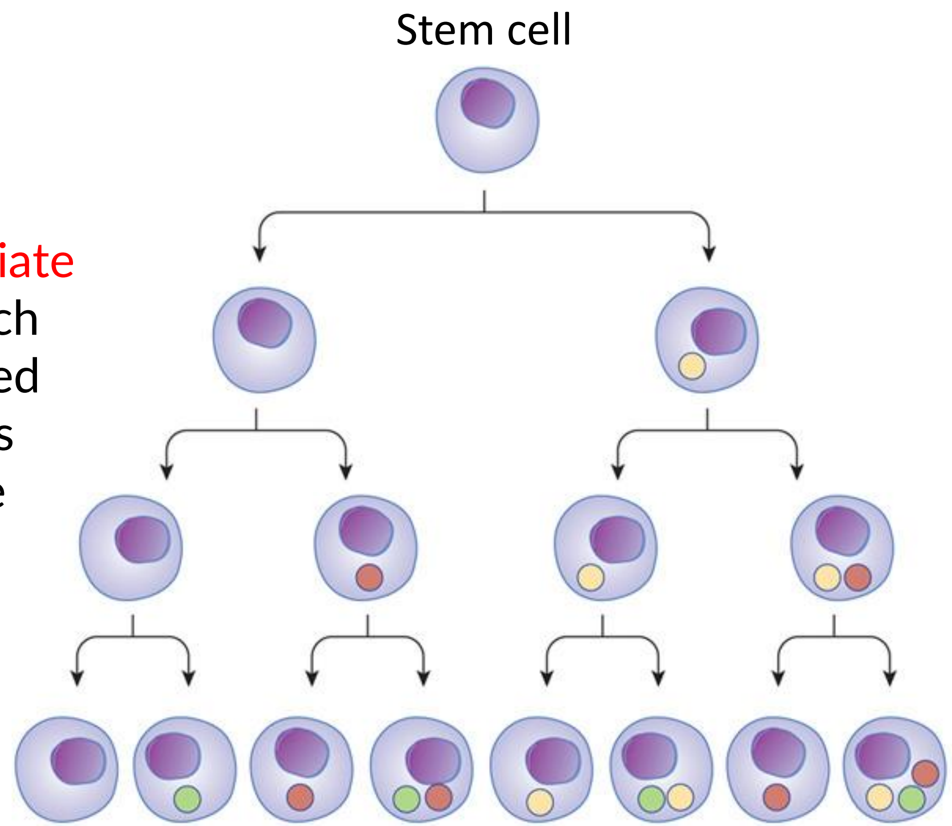
Enterocytes are involved in the uptake of nutrients.

Goblet cells produce mucus.

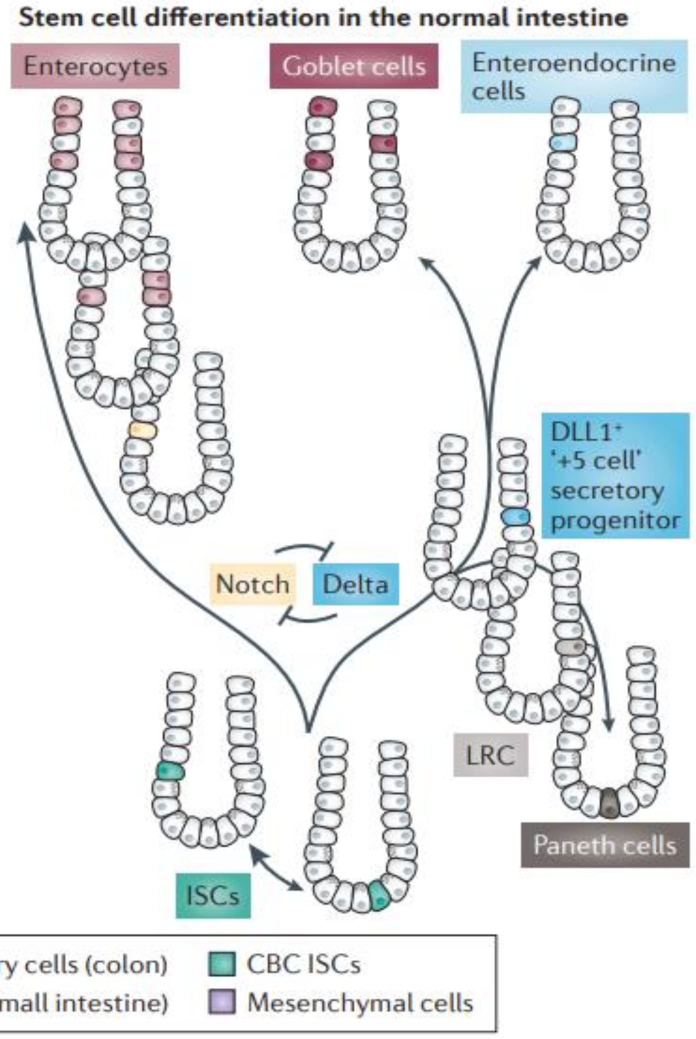
Enteroendocrine cells produce hormones.

Cell lineages track cellular differentiation

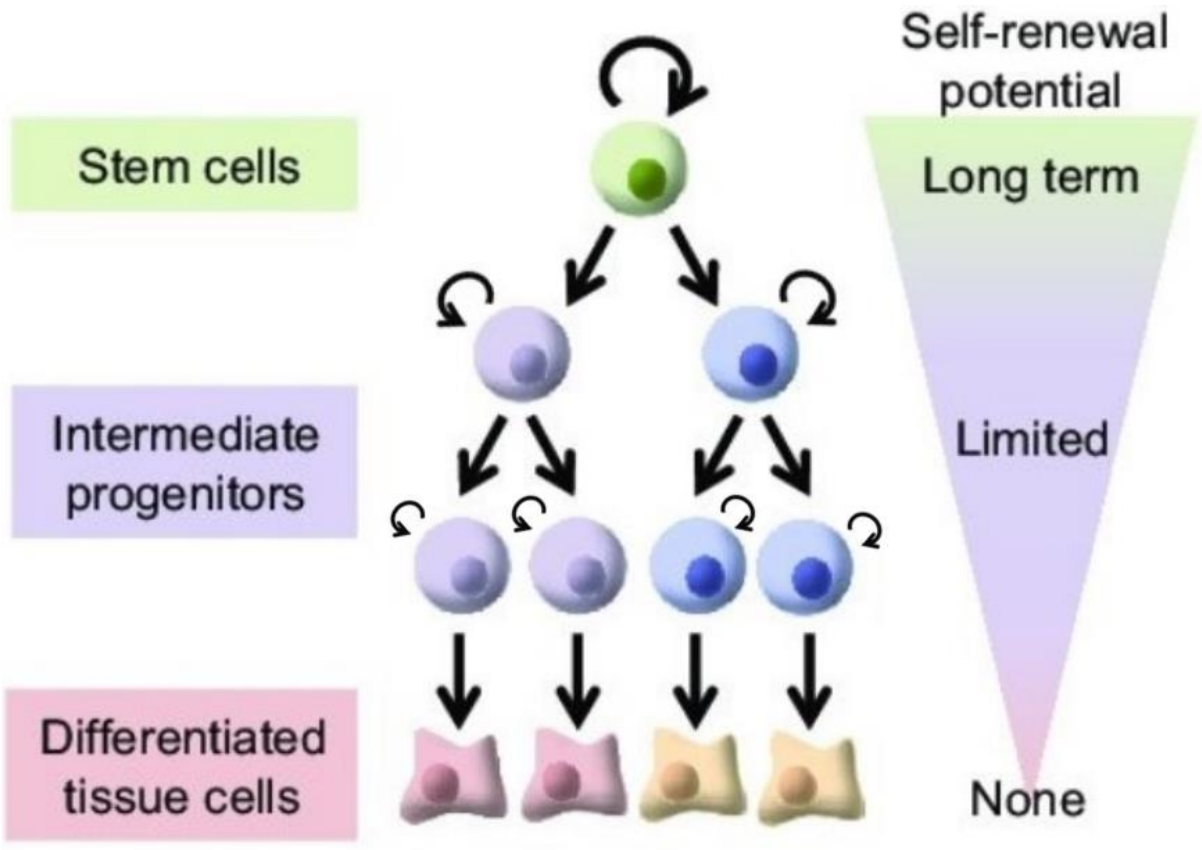
Cells can differentiate depending on which genes are expressed and which proteins are encoded in the expressed genes.



cellular hierarchy of the intestine



Constant size and tissue maintenance are consequences of …



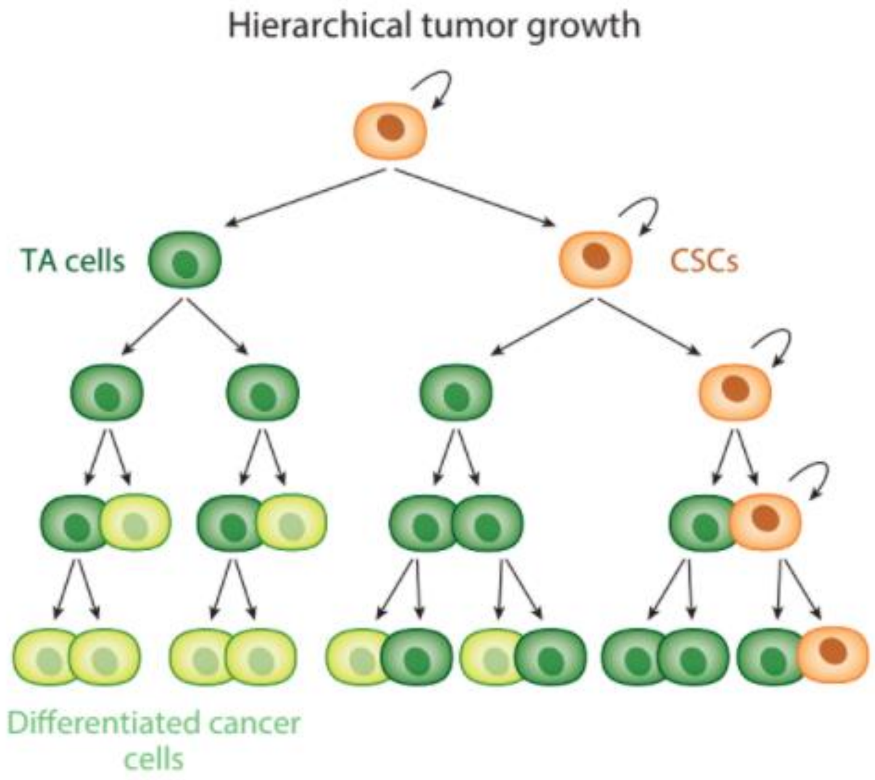
Most of the tissues maintain a constant size, the cells that make up these tissues are constantly turning over → **Control**

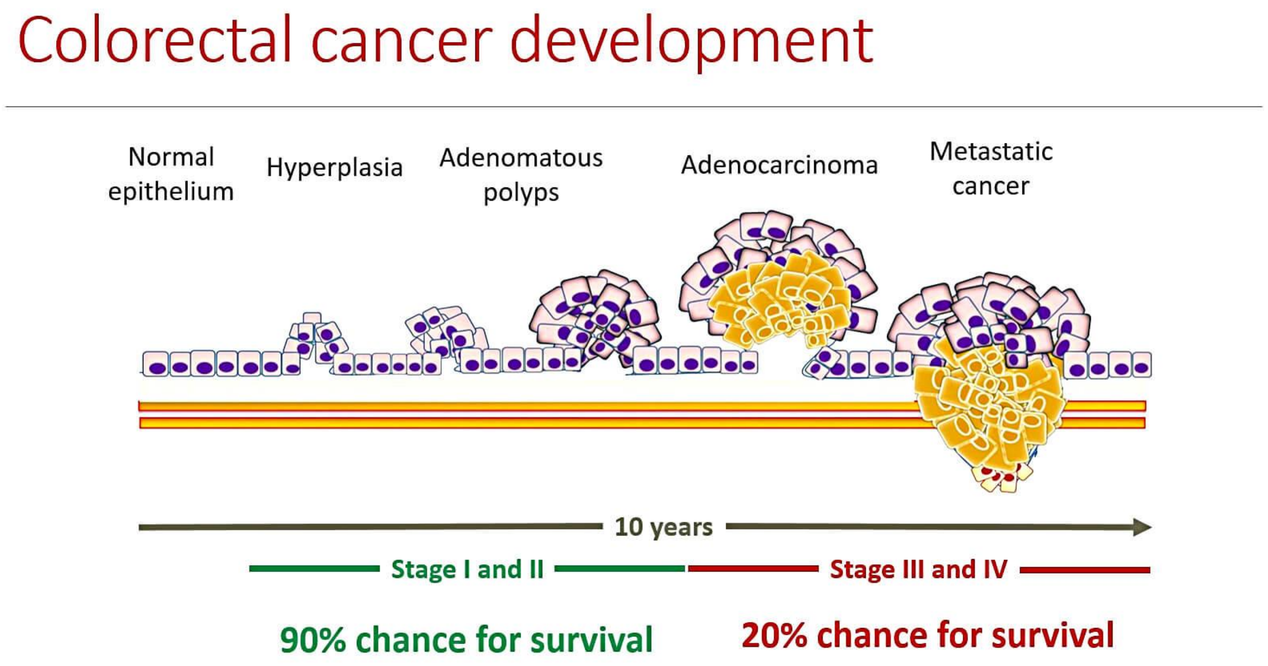
To do so, its rates of cell death, cell division and differentiation must remain in balance.

In order to coordinate their function, organization, and rates of death and division, the cells in a tissue are constantly processing and responding to signals from one another.

proliferation, differentiation and interaction among cell types.

Uncontrolled proliferation is one characteristic of cancer





What is this project about?

We studied two scenarios of cell proliferation

Normal tissue growth

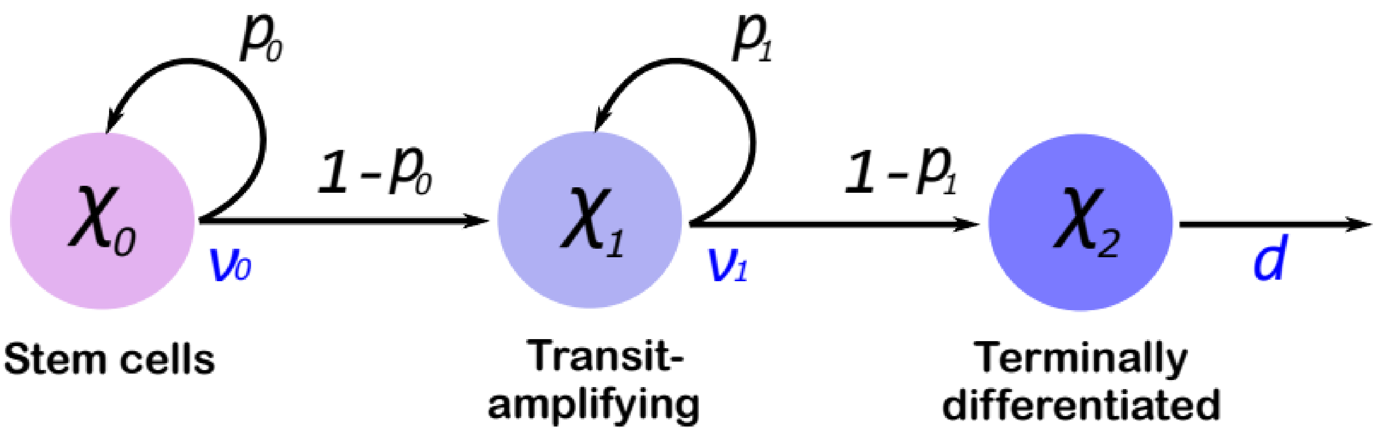
A review of the work of Lander et al.[1] on the different feedback control strategies on a three stages cell lineage model.

Control of tumor growth

Find the optimal drug treatment that targets the specific cell types in the lineage and controls cancer cells' proliferation.

[1] A. D. Lander et al. Cell lineages and the logic of proliferative control. PLOS Biology, 7:1–1, 01 2009

Cell lineage as a model for tissue growth



$$\dot{\chi}_0(t) = (2p_0 - 1)v_0\chi_0(t)$$
$$\dot{\chi}_1(t) = 2(1 - p_0)v_0\chi_0(t) + (2p_1 - 1)v_1\chi_1(t)$$
$$\dot{\chi}_2(t) = 2(1 - p_1)v_1\chi_1(t) - d\,\chi_2(t)$$

The open-loop system can achieve steady- state

A quickly inspection:

$$\dot{\chi}_0(t) = (2p_0 - 1)v_0\chi_0(t)$$

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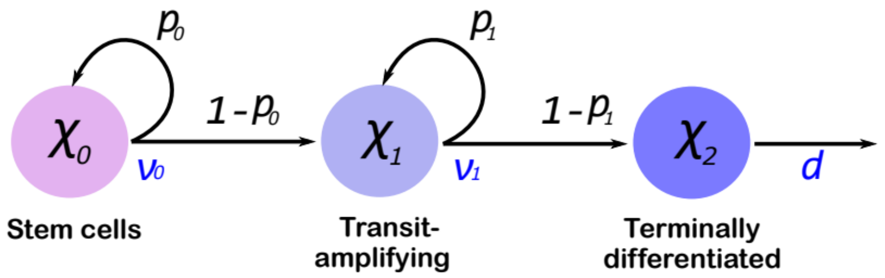

- If $p_i > 0.5$ for any i: $\chi_2 \to \infty$

- If $p_i < 0.5\ \forall\ i$: when $d = 0$ then $\chi_0, \chi_1 \to 0$ and χ_2 fixed value.

  When $d \neq 0$ then $\chi_0, \chi_1, \chi_2 \to 0$

- If $p_0 < 0.5$ and $p_1 = 0.5$: $\chi_0 \to 0$

  when $d = 0$, $\chi_2 \to \infty$.
  when $d \neq 0$ and d sufficiently small.
  The system reaches steady state with 0 Stem cells.

The open-loop system can achieve steady- state

- If $p_0 = 0.5$ and $p_1 < 0.5$: $\chi_0 \to \chi_0(0) = \chi_0^*$

when $d = 0$, $\chi_2 \to \infty$.
when $d \neq 0$ and d sufficiently small.
The system reaches steady state.

A quickly inspection:

$$\dot{\chi}_0(t) = (2p_0 - 1)v_0\chi_0(t)$$

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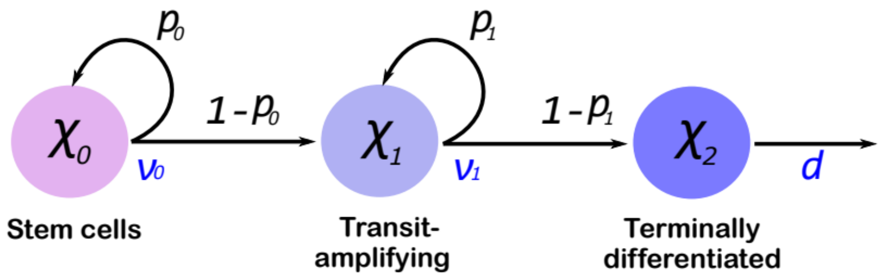
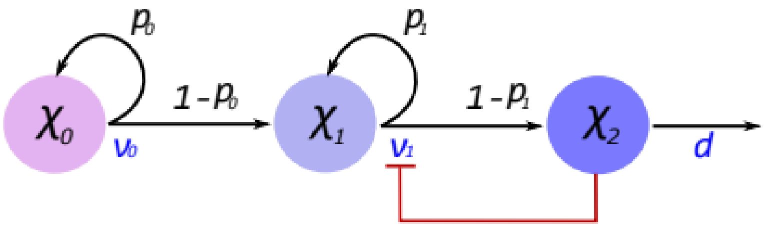
$$\dot{\chi}_2(t) = 2(1 - p_1)v_1\chi_1(t) - d\,\chi_2(t)$$

$$\chi_{1S} = \frac{\xi}{1 - 2p_1}\chi_0^* \qquad \chi_{2S} = \frac{2\xi}{\delta}\frac{1 - p_1}{1 - 2p_1}\chi_0^*$$

$$\xi = \frac{v_0}{v_1} \qquad \delta = \frac{d}{v_1}$$



One negative feedback loop is not a good control strategy



$$S_{p_1} = \frac{p_1}{\chi_2}\frac{d\chi_2}{dp_1} \geq 1,\ p_1 \in \left[1-\frac{1}{\sqrt{2}}, 0.5\right) \qquad S_{v_0} = 1$$

The dynamics needs to be under control!

$$v_1 \to \frac{v_1}{1+h\chi_2}$$

$$\tau = v_1 t$$

$$\dot{\chi}_0(\tau) = 0 \ \to \dot{\chi}_0(\tau) = \ \chi_0^*$$

$$\dot{\chi}_1(\tau) = \xi\chi_0^* + (2p_1 - 1)\frac{1}{1+h\chi_2}\chi_1(\tau)$$

$$\dot{\chi}_2(\tau) = 2(1-p_1)\frac{1}{1+h\chi_2}\chi_1(\tau) - \delta\,\chi_2(\tau)$$

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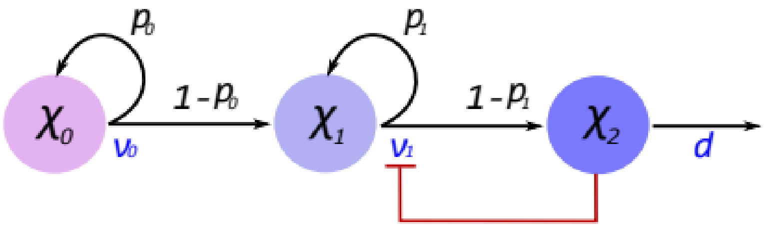

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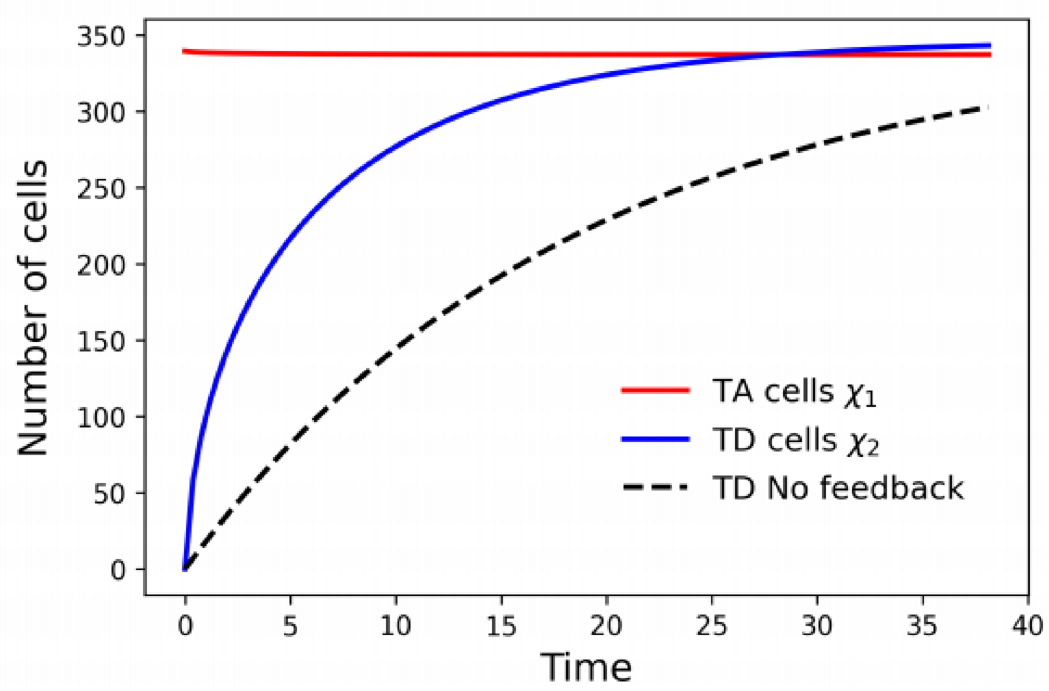

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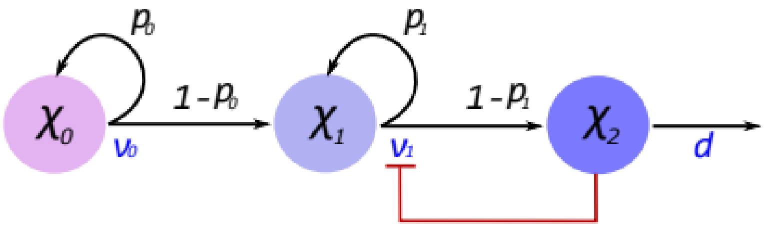

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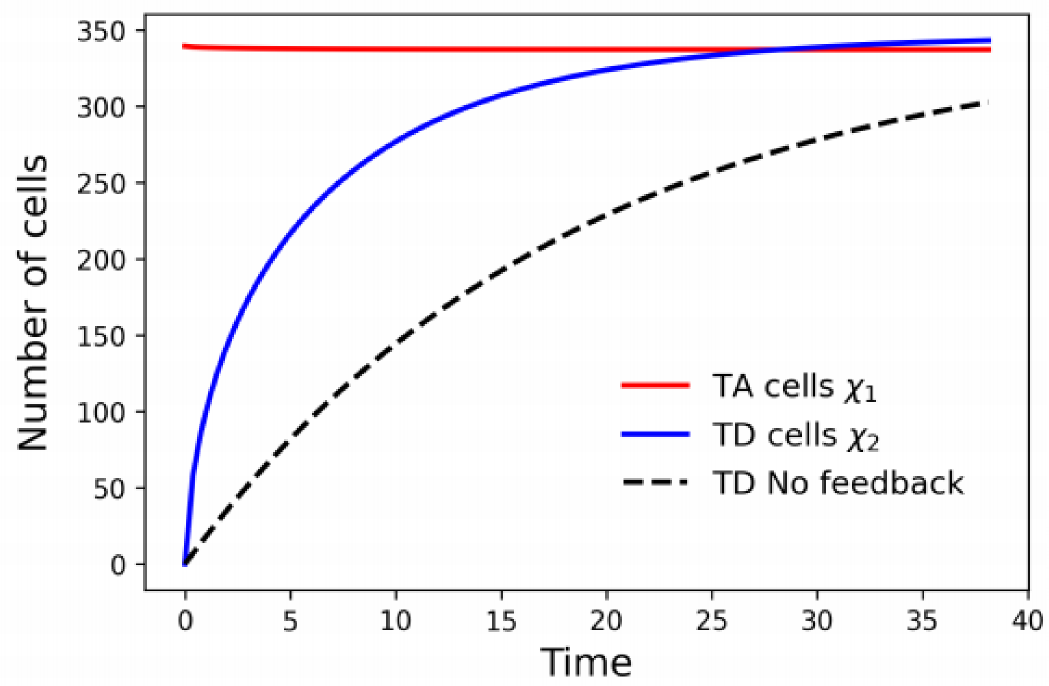
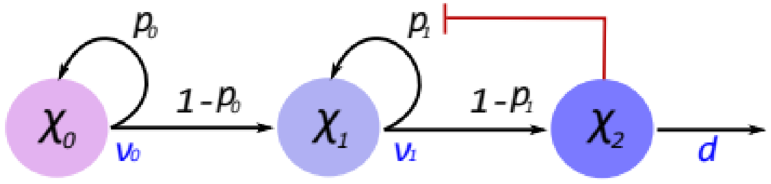


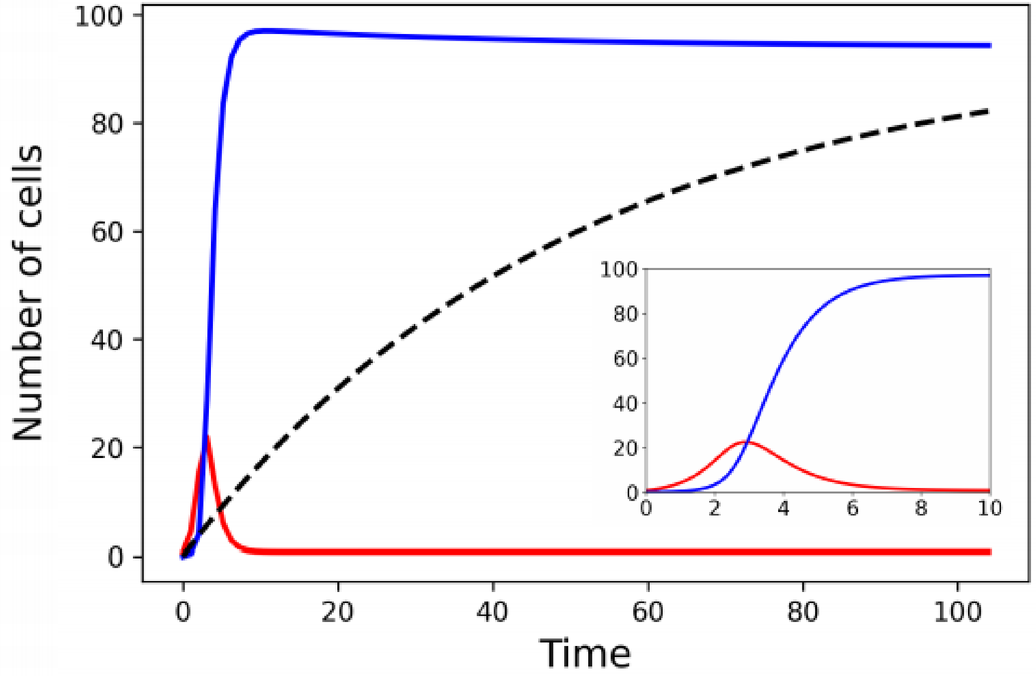
Fast regeneration

High values of progenitors: $x_1 \approx \chi_2$

One negative feedback loop is not a good control strategy



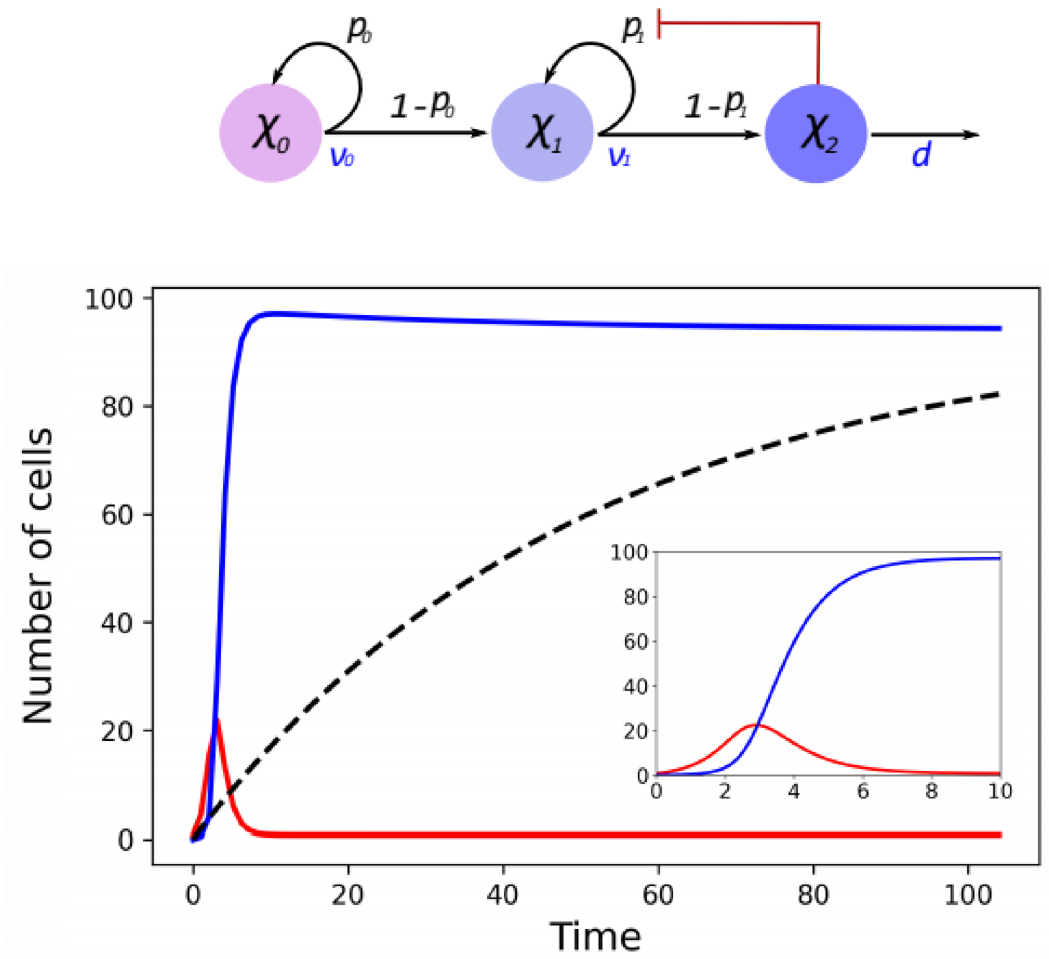
$$p_1 \to \frac{p_1}{1 + g\chi_2}$$

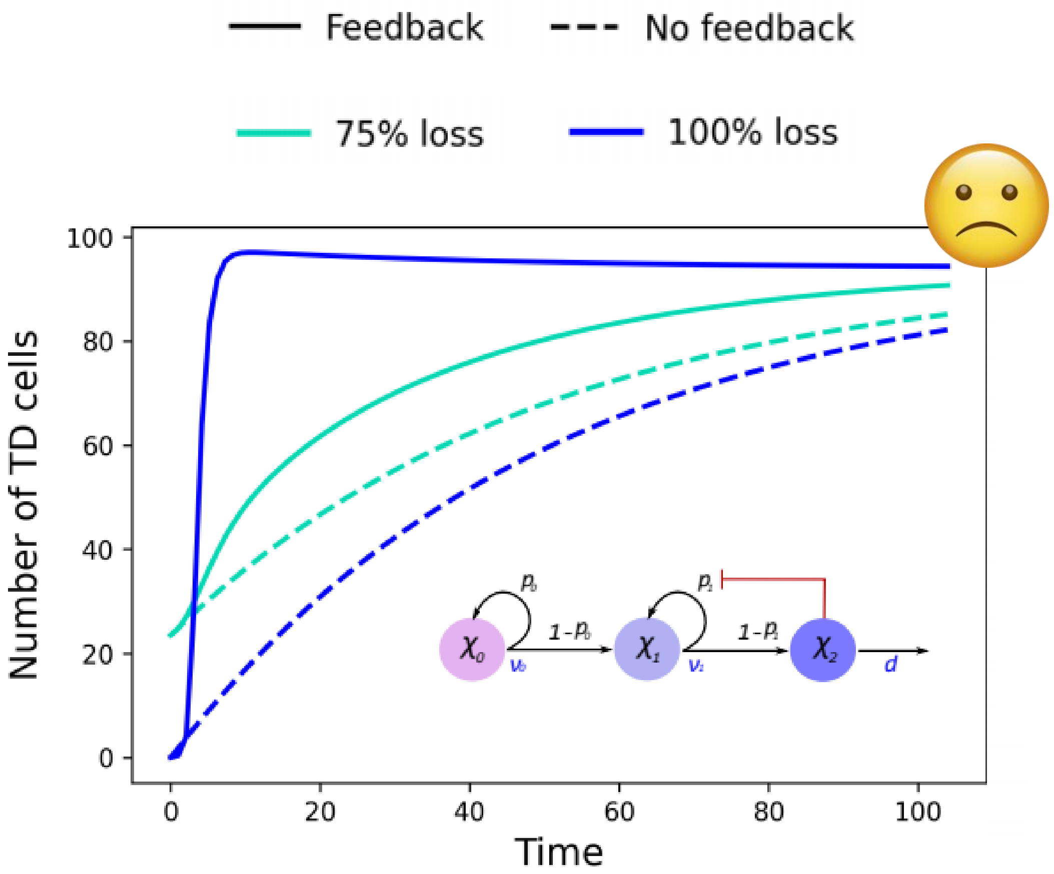


Fast regeneration

Significantly low progenitor loads

One negative feedback loop is not a good control strategy

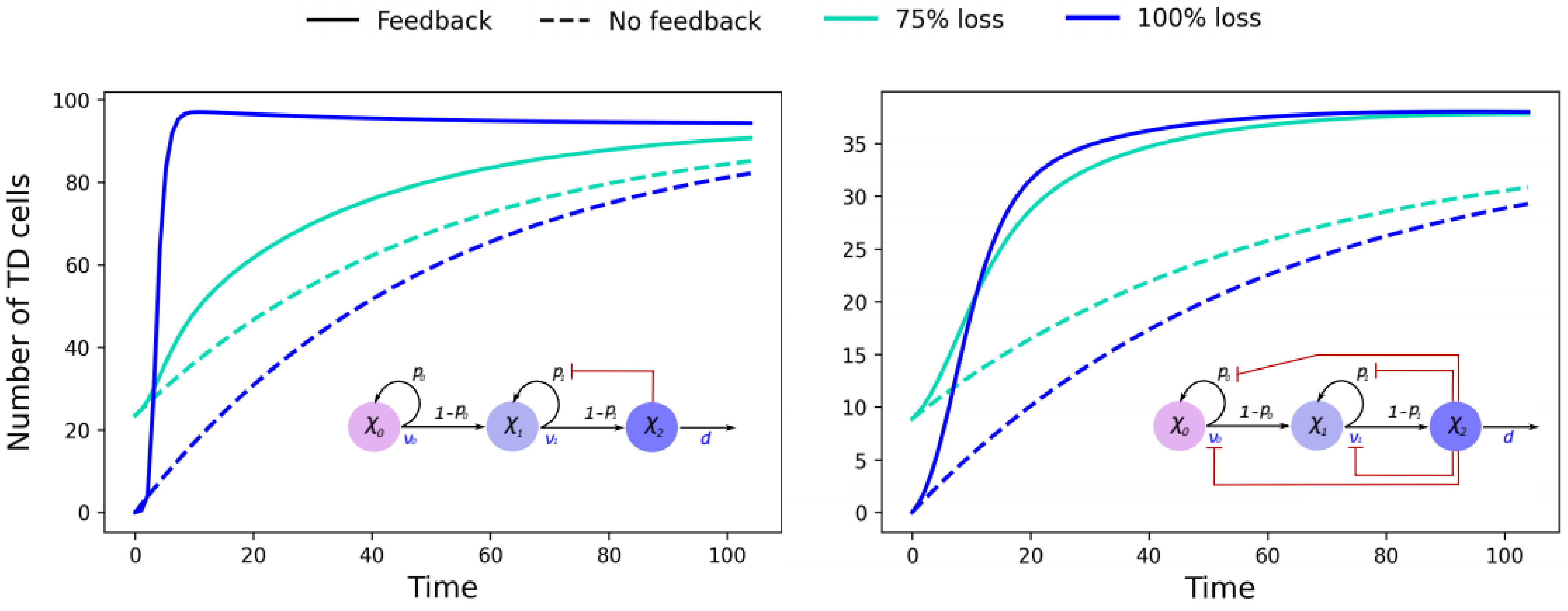




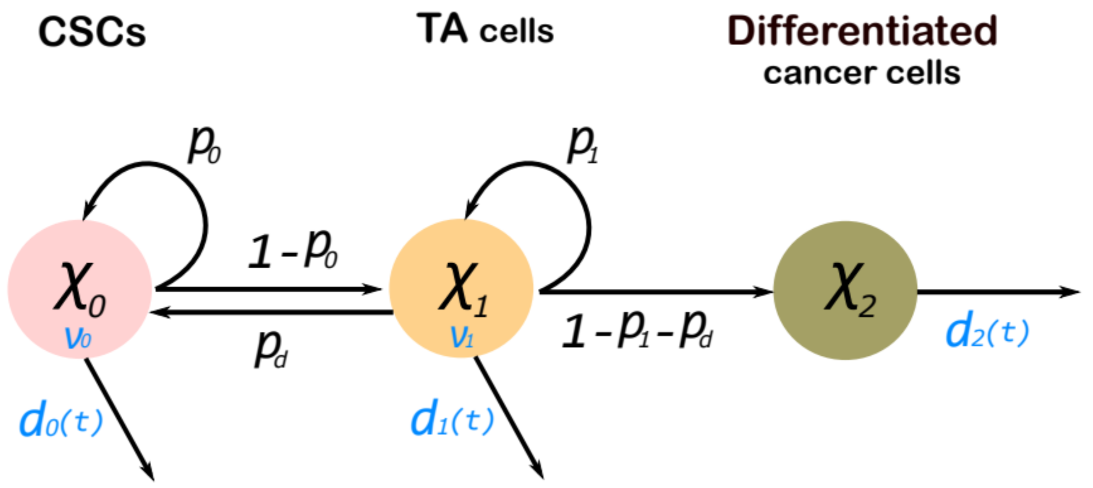
Negative feedback in all parameters improve the drawbacks of previous strategies

$$v_0 \to \frac{v_0}{1 + j\chi_2} \qquad v_1 \to \frac{v_1}{1 + h\chi_2} \qquad p_0 \to \frac{p_0}{1 + k\chi_2} \qquad p_1 \to \frac{p_1}{1 + g\chi_2}$$

$$\boxed{\frac{2p_0 - 1}{k} > \frac{2p_1 - 1}{g}}$$



A model for control of tumor growth



$$\dot{\chi}_0 = (2p_0 - 1)\xi\chi_0 + 2\,p_d\chi_1 - u_0\chi_0 = f_0$$
$$\dot{\chi}_1 = 2(1 - p_0)\xi\chi_0 + (2p_1 - 1)\chi_1 - u_1\chi_1 = f_1$$
$$\dot{\chi}_2 = 2(1 - p_1 - p_d)\chi_1 - u_2\chi_2 = f_2$$

$$x(0) = (\chi_0(0), \chi_1(0), \chi_2(0)) \qquad u_i(\tau) = \frac{d_i\,(\tau)}{v_1}$$

$$J = \int_0^T \left[(\chi_0 + \chi_1 + \chi_2) + \frac{\gamma}{2}(u_0^2 + u_1^2 + u_2^2) \right] dt$$

Total amount of cancer cells

Weight

Drug side effects

We applied optimal control theory

$$J = \int_0^T \underbrace{\left[(\chi_0 + \chi_1 + \chi_2) + \frac{\gamma}{2}(u_0^2 + u_1^2 + u_2^2)\right]}_{C(x,u)} dt$$

$$u^*(\tau) = (u_0^*(\tau), u_1^*(\tau), u_2^*(\tau))$$

$$\mathcal{H} = C(x,u) + \lambda(t)^\intercal f(x,u)$$

Sufficient conditions: $i = 0,1,2$

$$\dot{x}_i = \frac{\partial \mathcal{H}}{\partial \lambda_i}$$

Forward-Backward Sweep Method

$$\dot{\lambda}_i = -\frac{\partial \mathcal{H}}{\partial x_i}$$

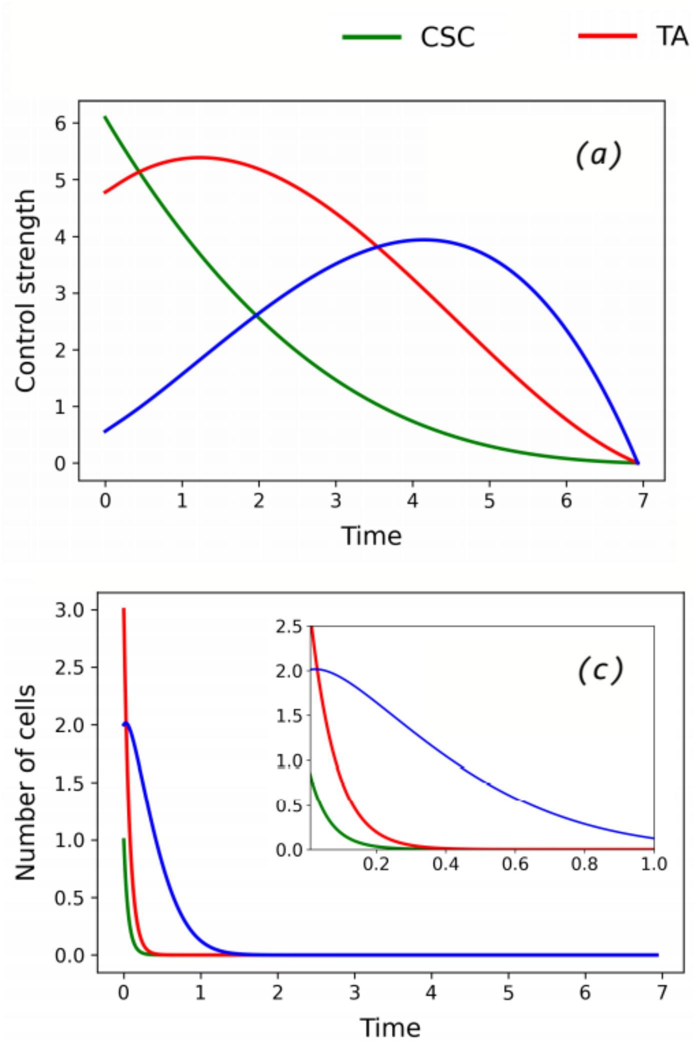
$$\dot{\chi}_0 = (2p_0 - 1)\xi\chi_0 + 2\, p_d\chi_1 - u_0\chi_0$$
$$\dot{\chi}_1 = 2(1 - p_0)\xi\chi_0 + (2p_1 - 1)\chi_1 - u_1\chi_1$$
$$\dot{\chi}_2 = 2(1 - p_1 - p_d)\chi_1 - u_2\chi_2$$

$$\dot{\lambda}_0 = -1 - [(2p_0 - 1)\xi - u_0]\lambda_0 - 2(1 - p_0)\xi\lambda_1$$
$$\dot{\lambda}_1 = -1 - 2p_d\lambda_0 - (2p_1 - 1 - u_1)\lambda_1 - 2(1 - p_1 - p_d)\lambda_2$$
$$\dot{\lambda}_2 = -1 + u_2\lambda_2$$

$$\frac{\partial \mathcal{H}}{\partial u_i} = 0 \qquad u_i = \frac{\lambda_i\chi_i}{\gamma}$$

Boundary conditions: $x_i(0) = \chi_i(0)$ $\quad \lambda_i(T) = \left.\frac{\partial \phi}{\partial x_i}\right|_{t=T} = 0$

Optimal control strategy for $p_d = 0$



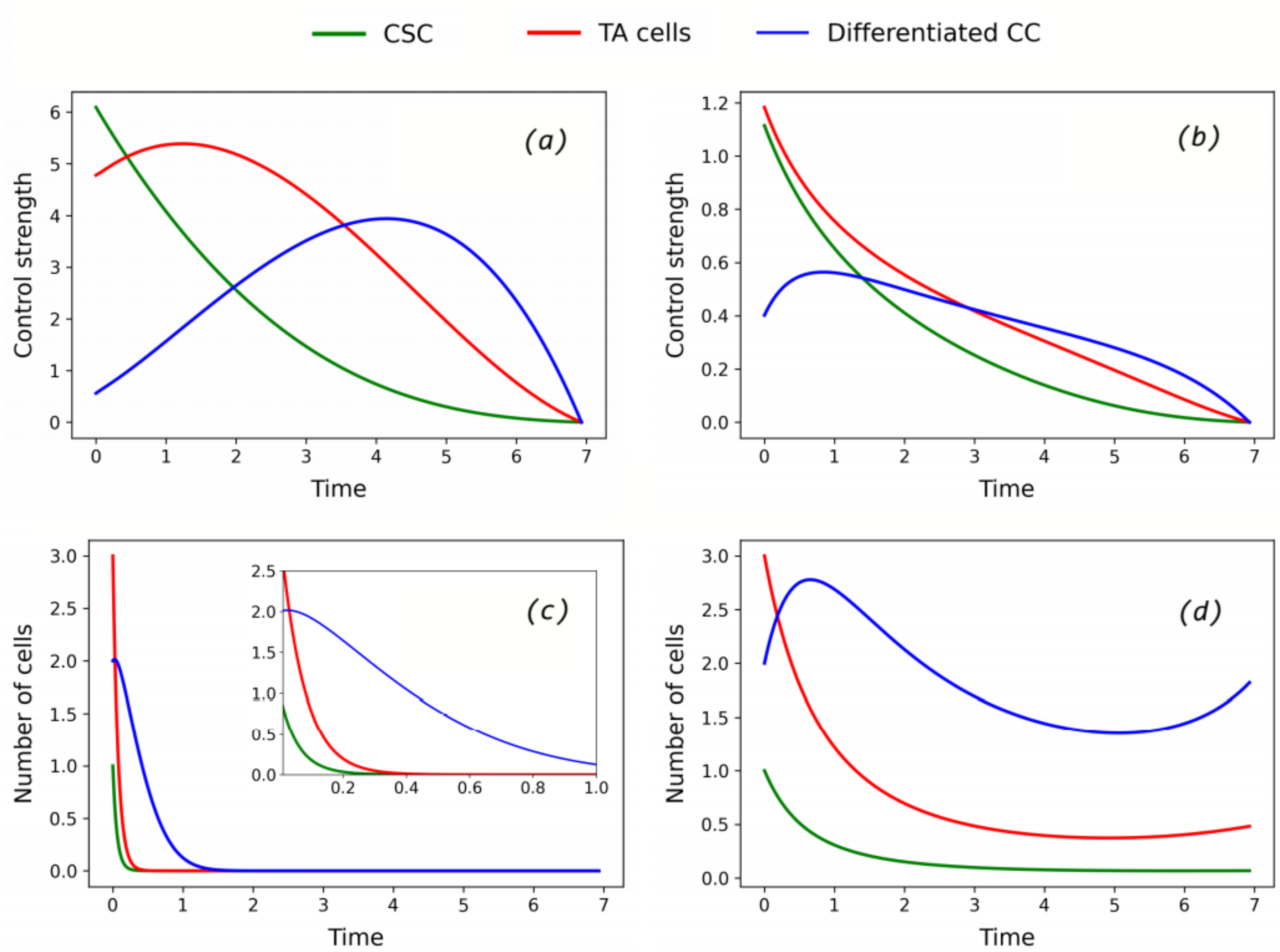
Parameters:

$$p_0 = p_1 = 0.51$$
$$p_d = 0$$
$$\xi = 1$$
$$\gamma = 10$$

Initial conditions:

$$\chi_0 = 1$$
$$\chi_1 = 3$$
$$\chi_2 = 2$$

Optimal control strategy for $p_d = 0$



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Initial conditions:

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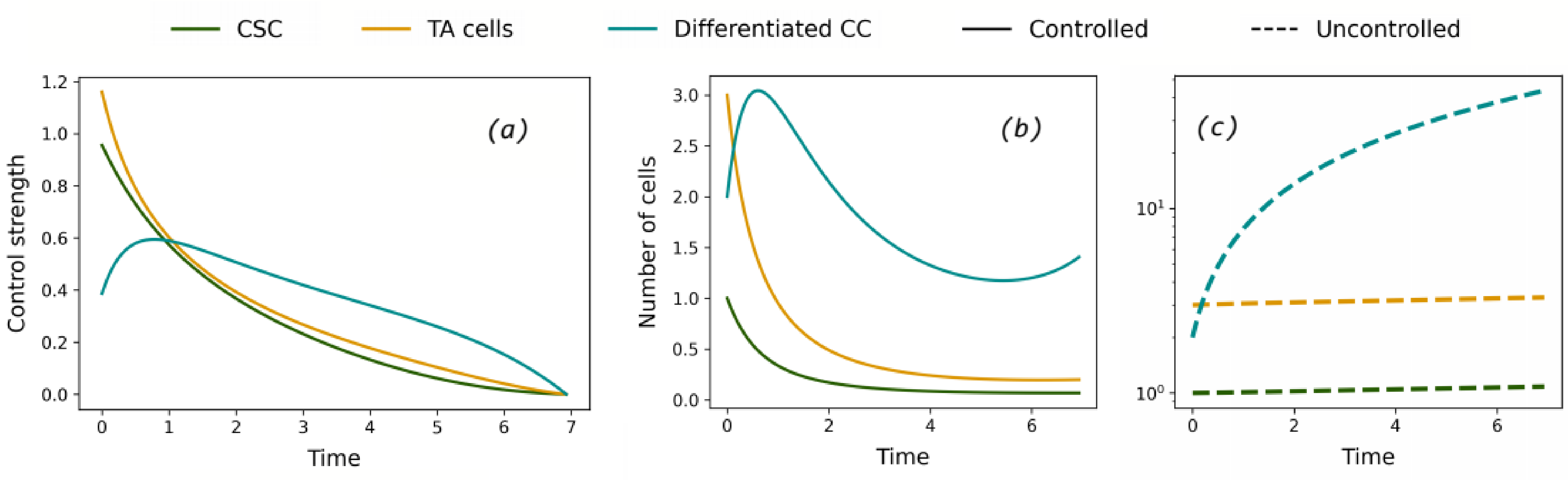
$$\chi_1 = 3$$
$$\chi_2 = 2$$

Optimal control strategy for $p_d \neq 0$

Parameters:

$p_0 = 0.41$
$p_1 = 0.31$
$p_d = 0.031$
$\xi = 1$
$\gamma = 10$



Initial conditions:

Figures (a), (b) and (c)

$\chi_0 = 1, \chi_1 = 3, \chi_2 = 2$

Figures (d), (e) and (f)

$\chi_0 = 1, \chi_1 = 10, \chi_2 = 250$

Optimal control strategy for $p_d \neq 0$

Parameters:

$p_0 = 0.41$
$p_1 = 0.31$
$p_d = 0.031$
$\xi = 1$
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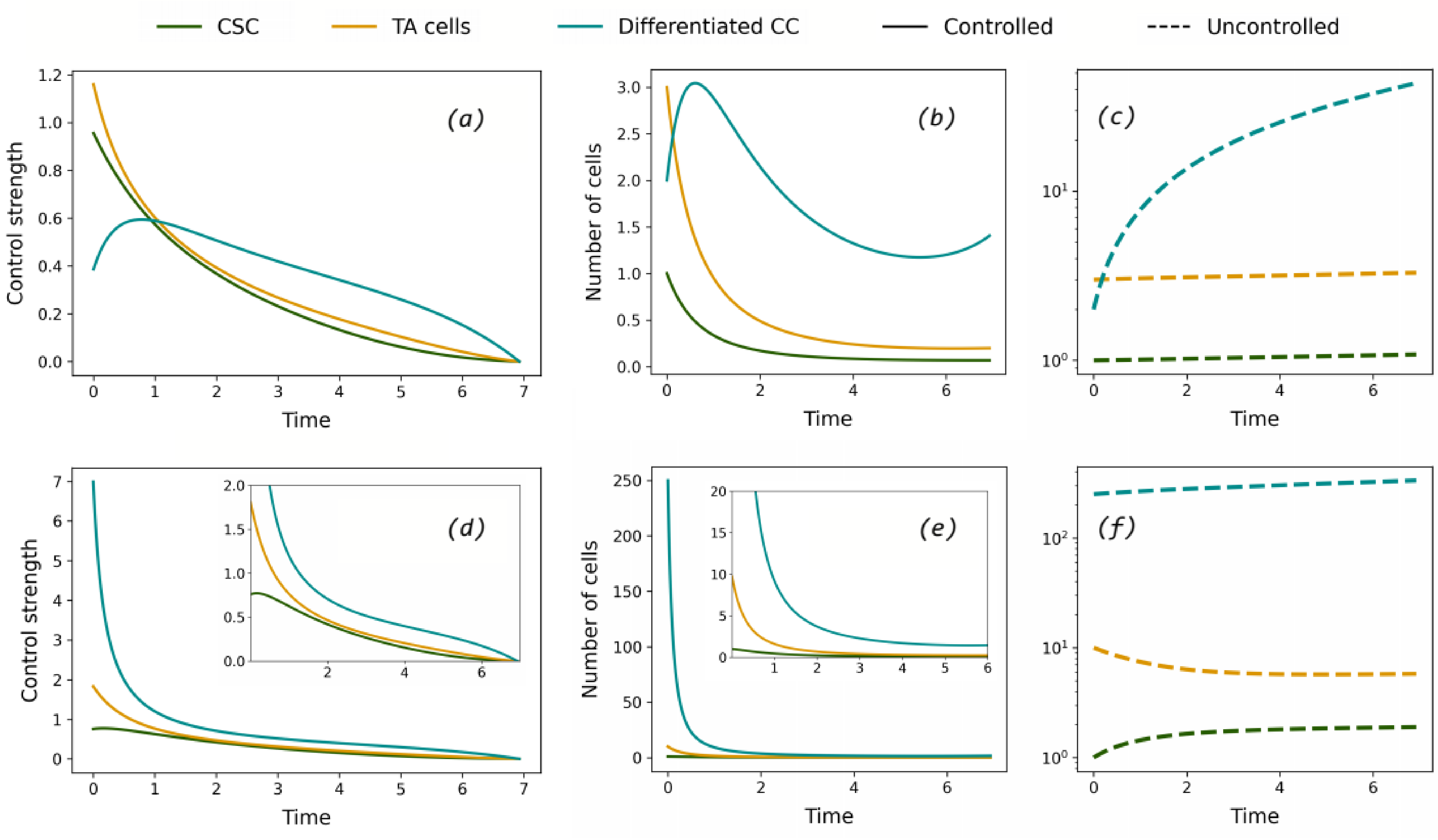
Initial conditions:

Figures (a), (b) and (c)

$\chi_0 = 1,\ \chi_1 = 3,\ \chi_2 = 2$

Figures (d), (e) and (f)

$\chi_0 = 1,\ \chi_1 = 10,\ \chi_2 = 250$



In summary…

- We reviewed the dynamics of a three stages cell lineage as a model of normal tissue growth:

  The best control strategy for this model was applying negative feedback to all parameters of the model.

- Optimal control theory allowed us to find the optimal drug treatment for the problem of control of tumor growth.

  The optimal controller was similar in both cases $p_d = 0$ and $p_d \neq 0,$ for the same initial conditions.

  In both cases, for different initial conditions, the optimal controller for CSCs and TA cells corresponds to a treatment where the highest dose of drugs is at the beginning.

What is next?

- Explore different therapeutic strategies; e.g., controlling feedback loops.

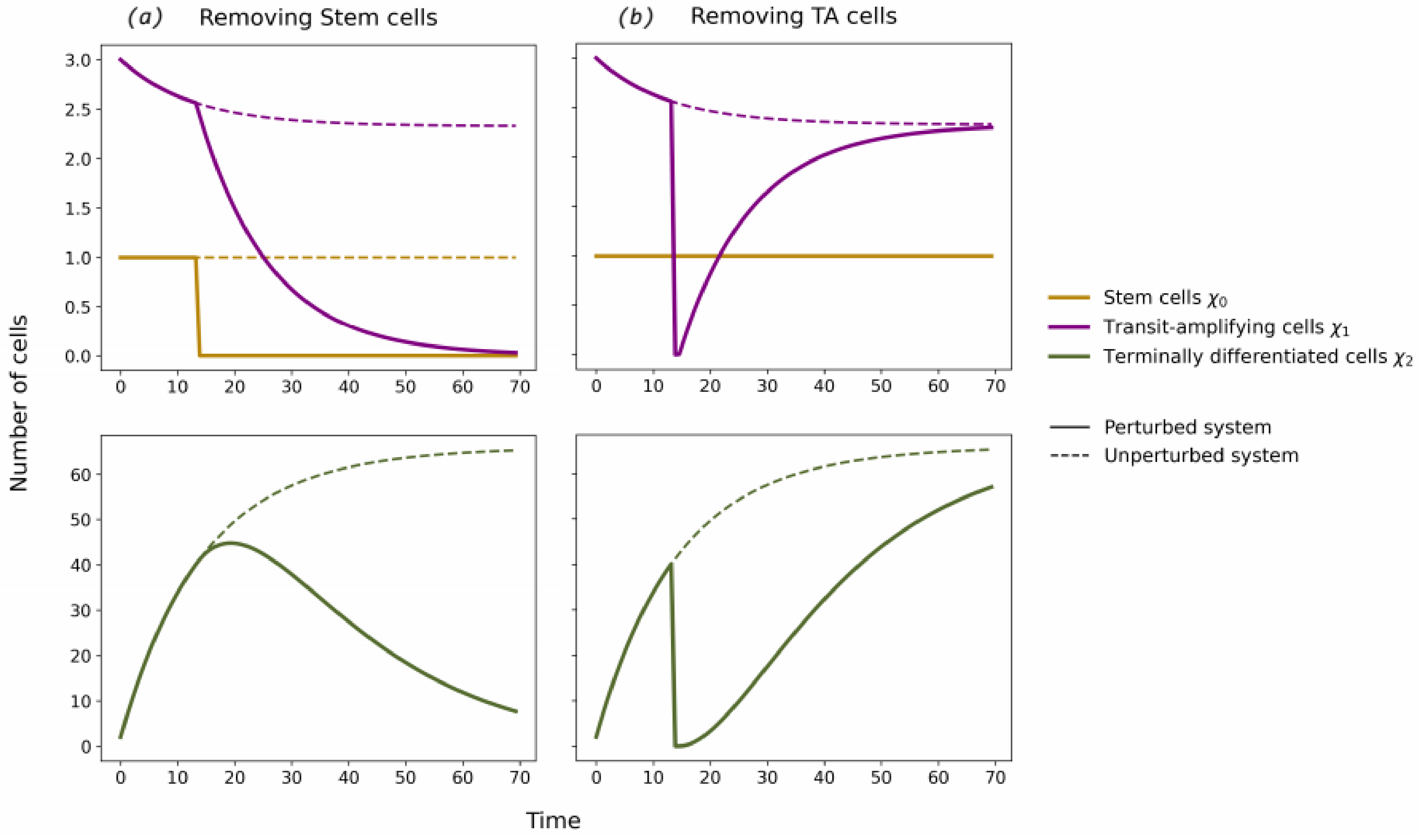
$$\boldsymbol{p_1} \rightarrow \frac{\boldsymbol{p_1}}{\boldsymbol{1} + \boldsymbol{g(t)}\boldsymbol{\chi_2}}$$

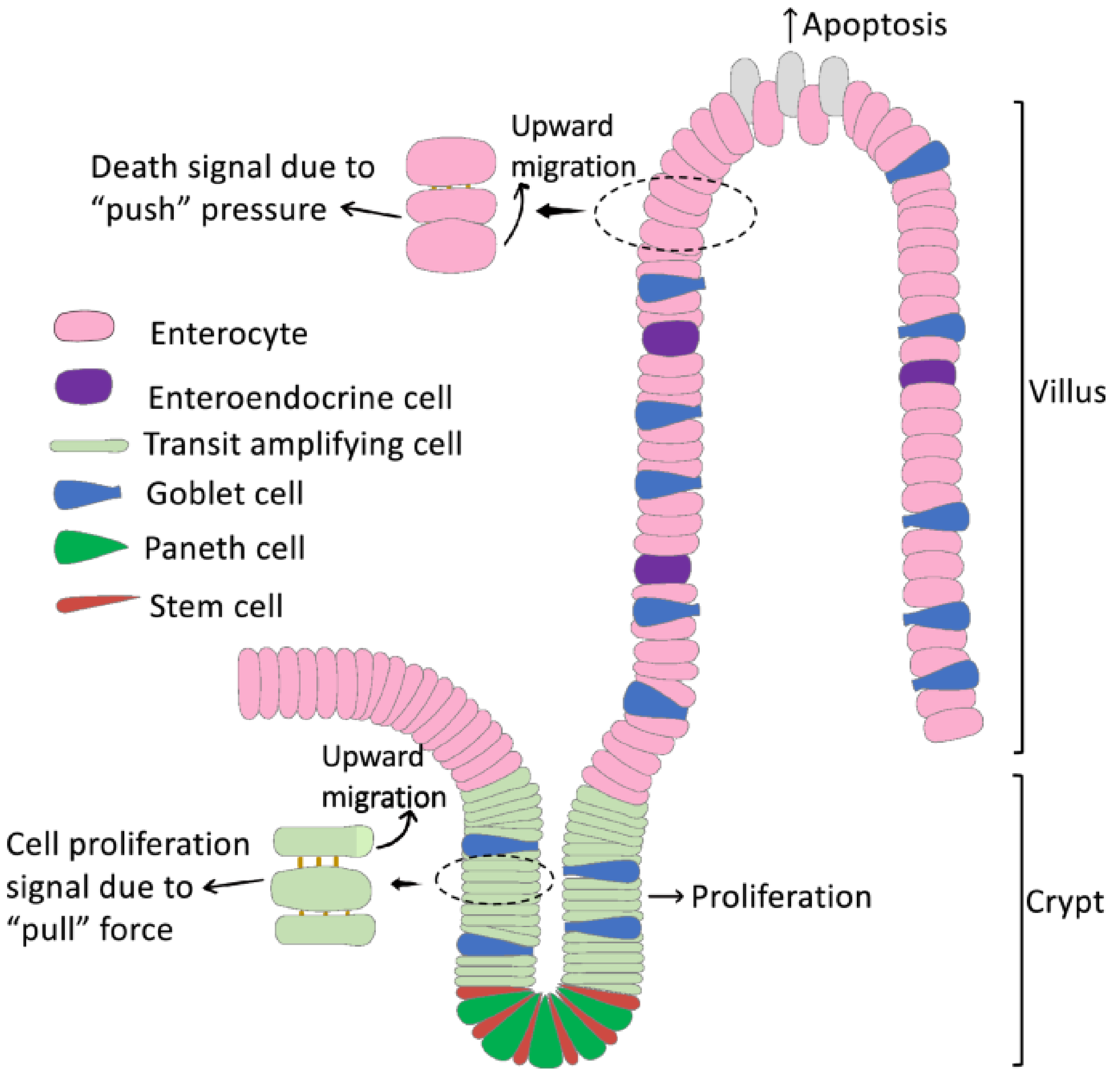
- Study the effects of introducing noise to the model, for which we can apply stochastic optimal control concepts.

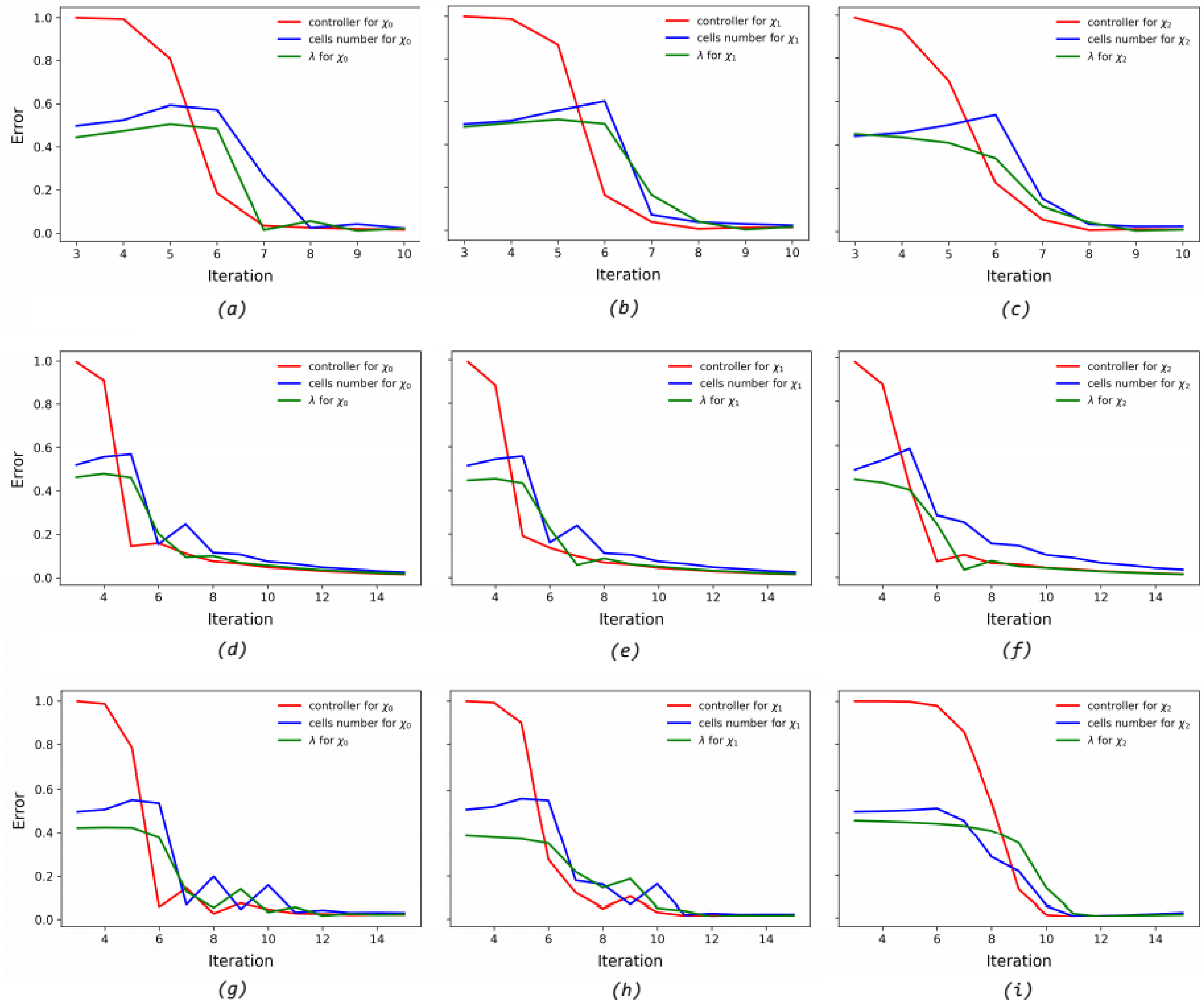
- More complex models can also be done; e.g., Branched cell lineages.

Thank you!

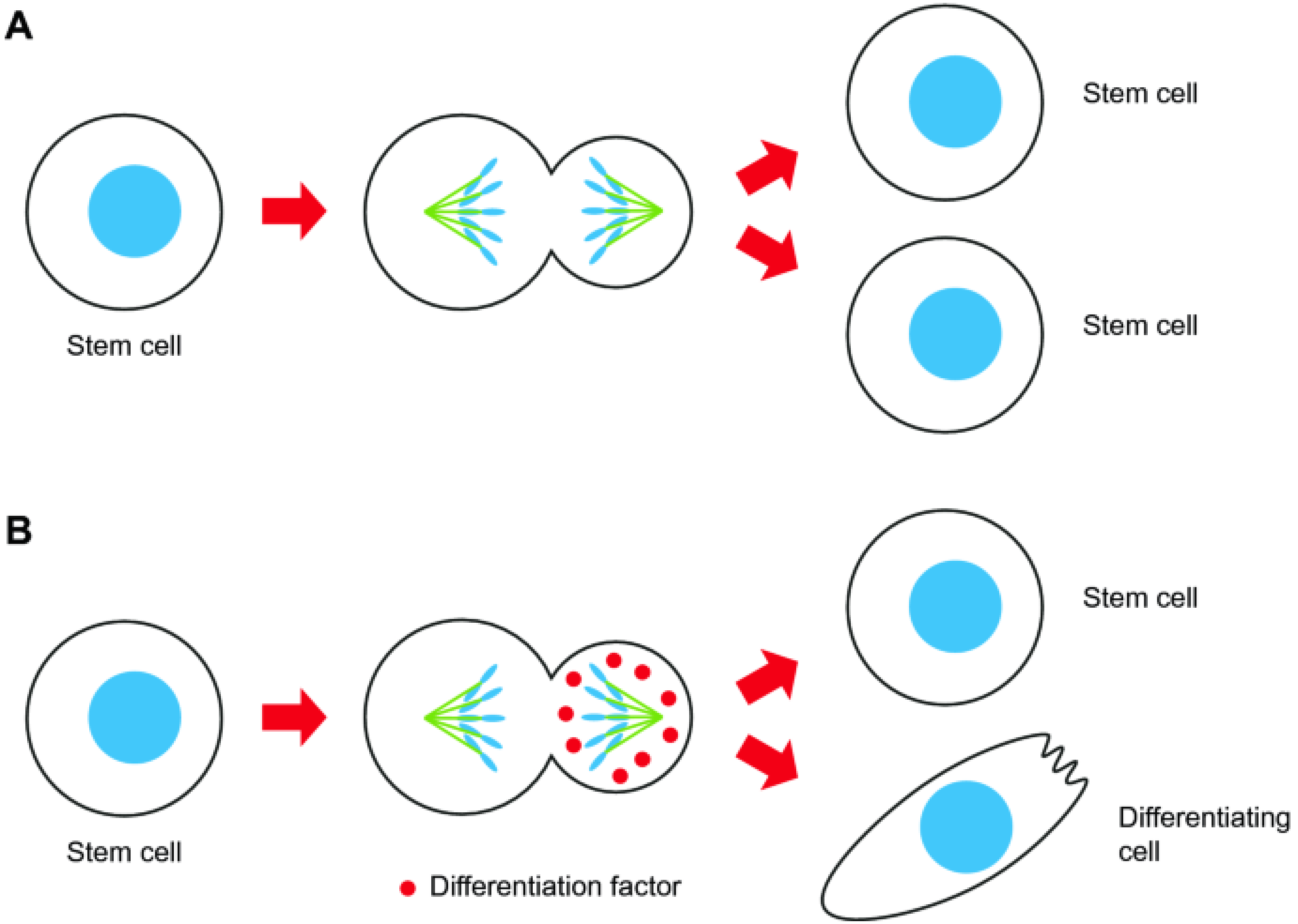
Removing stem cells leads to a complete loss of all cell types




↑Apoptosis
Upward migration
Death signal due to "push" pressure
Enterocyte
Enteroendocrine cell
Transit amplifying cell
Goblet cell
Paneth cell
Stem cell
Villus
Upward migration
Cell proliferation signal due to "pull" force
Proliferation
Crypt



Error
Iteration
controller for χ_0
cells number for χ_0
λ for χ_0
controller for χ_1
cells number for χ_1
λ for χ_1
controller for χ_2
cells number for χ_2
λ for χ_2
(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)
(i)


A
Stem cell
Stem cell
Stem cell
B
Stem cell
Stem cell
Differentiation factor
Differentiating
cell