# Modelling Hematopoietic Stem Cells

## and their Interaction with the Bone Marrow Microenvironment.

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Statistics and Biomathematics Seminar
~~Chalmers University of Technology, Gothenburg, Sweden~~
Online, from my living room
April 21$^{st}$, 2020

# Brief outline

- Background for the work

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- A combination of two models and fit to patient data

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- Part of a larger Danish collaboration.
  Direct work with clinicians from Zealand University Hospital, Roskilde.


- Monthly meetings for discussion and sharing of knowledge.

# Myeloproliferative Neoplasms and Hematopoietic Stem Cells

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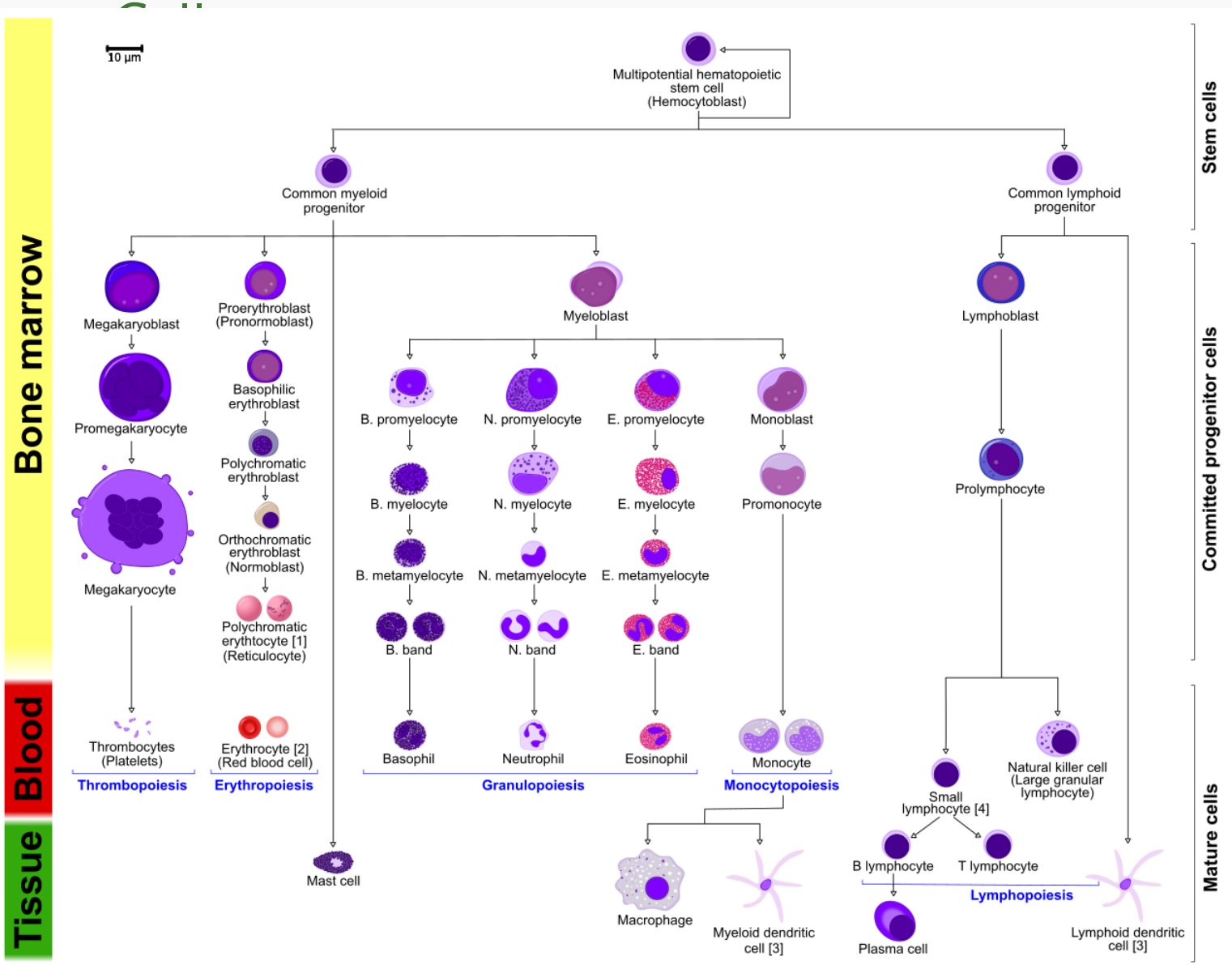

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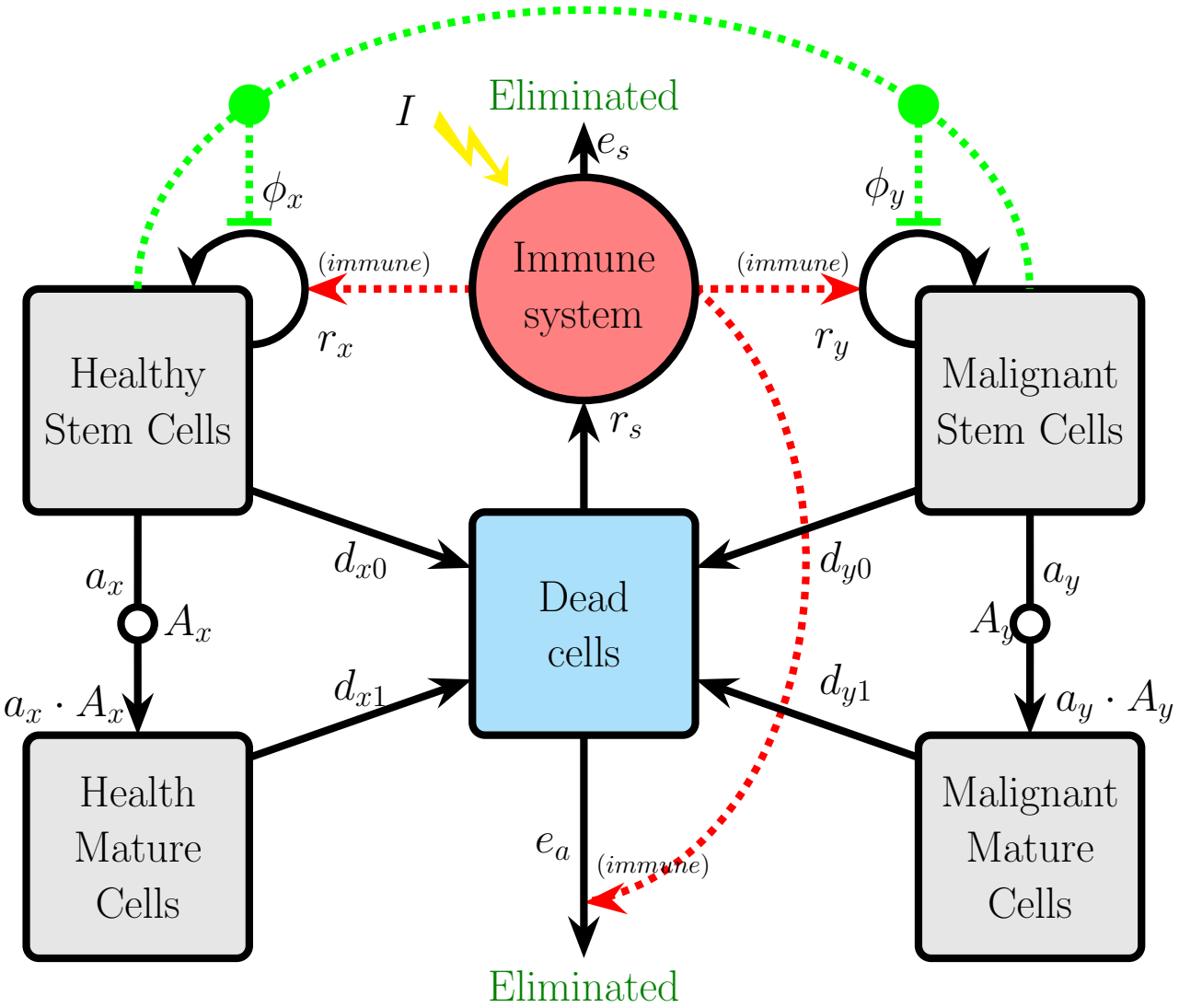
  - Stem cells and mature blood cells.
  - Feedback from the blood through the immune system and inflammation.

# The "Cancitis" Model



# The "Cancitis" Model

System of 6 ODEs, with 17 parameters.

$$\dot{x_0} = (r_x \phi_x s - d_{x_0} - a_x) x_0 \tag{1a}$$
$$\dot{x_1} = a_x A_x x_0 - d_{x_1} x_1 \tag{1b}$$
$$\dot{y_0} = (r_y \phi_y s - d_{y_0} - a_y) y_0 \tag{1c}$$
$$\dot{y_1} = a_y A_y y_0 - d_{y_1} y_1 \tag{1d}$$
$$\dot{a} = d_{x_0} x_0 + d_{y_0} y_0 + d_{x_1} x_1 + d_{y_1} y_1 - e_a a s \tag{1e}$$
$$\dot{s} = r_s a - e_s s + I \tag{1f}$$
$$\phi_x = \phi_x(x_0, y_0) = \frac{1}{1 + (c_{xx} x_0 + c_{xy} y_0)} \tag{1g}$$
$$\phi_y = \phi_y(x_0, y_0) = \frac{1}{1 + (c_{yx} x_0 + c_{yy} y_0)} \tag{1h}$$

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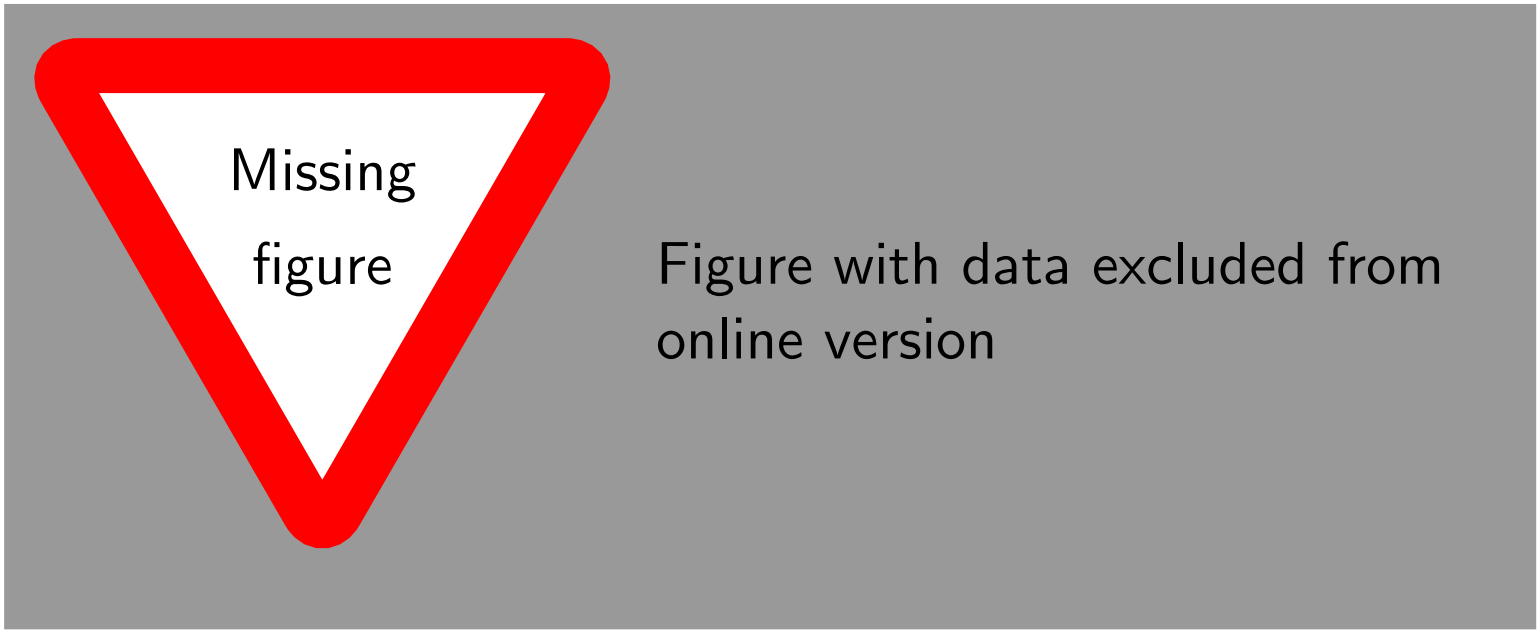



Patient-data from Interferon-$\alpha$ treated patients

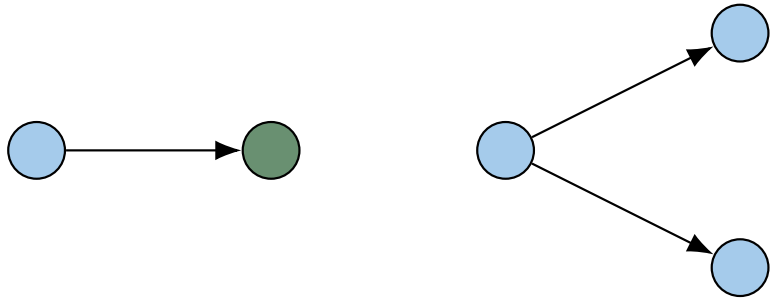
# The "Cancitis" Model

- A lot of parameters, but most are described in the literature.
- Dynamics of model can be related to data from clinics.
- Agreement with a large subset of patient-data.
- However, what about the mechanistic interpretation of parameter-changes?

# Modelling: Biological assumptions

We wish to include the most important features of HSC.

- Characterised by *multi-potent differentiation* and *self-renewal*.



where ● are stem cells and ● is a differentiated/progenitor cell.

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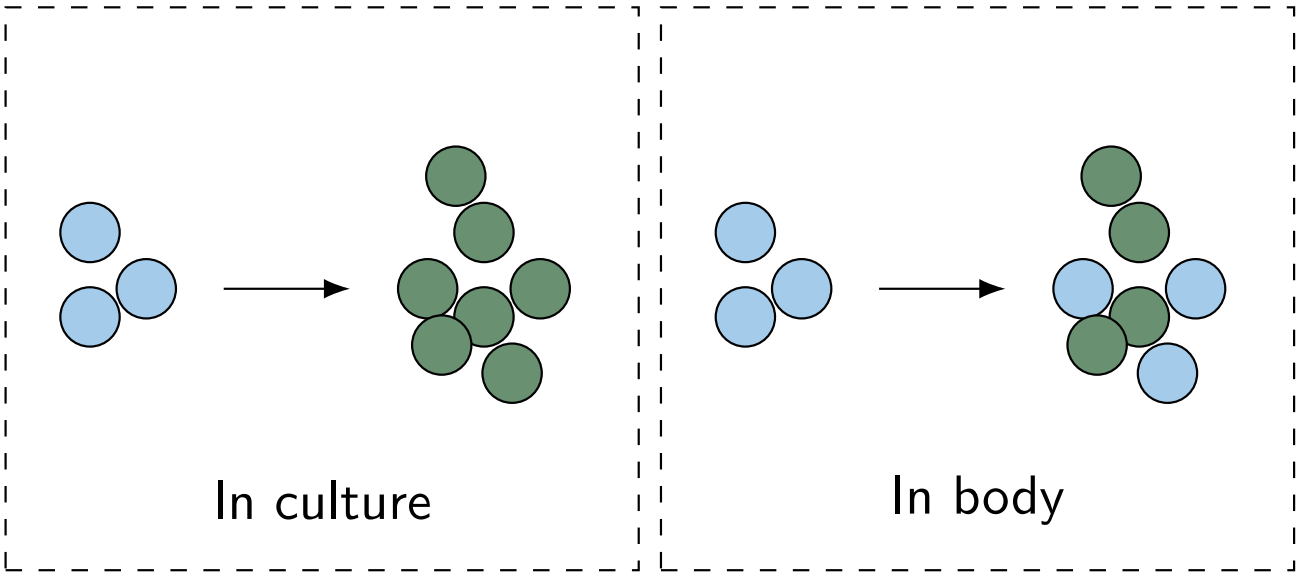

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- Lack of self-renewal in culture
- Bone-marrow "niches" interact with HSC in a yet unspecified way.
  Previous mathematical models of HSC behaviour: (Ashcroft et al., 2017), (Wang, Stiehl et al. 2017), (Becker et al., 2019), (Wilson and Trumpp, 2006).

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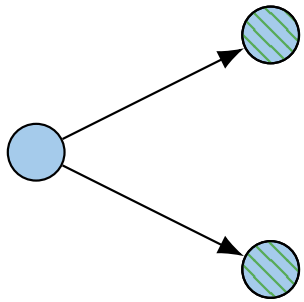

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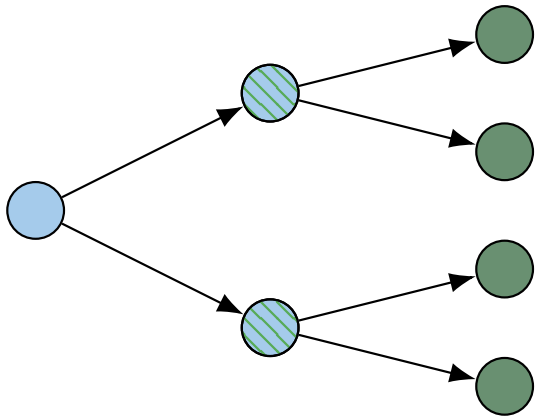

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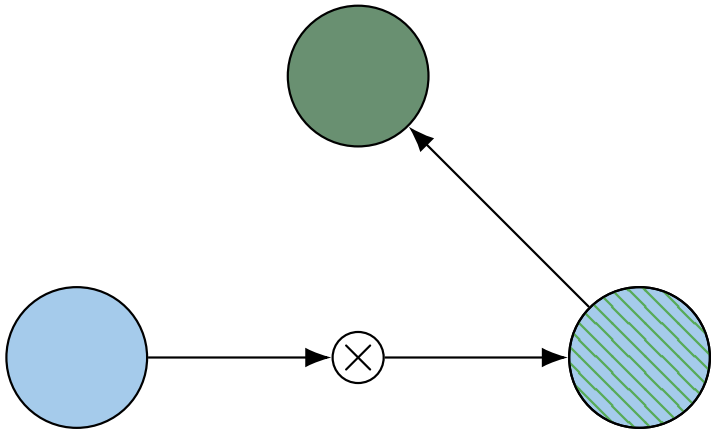

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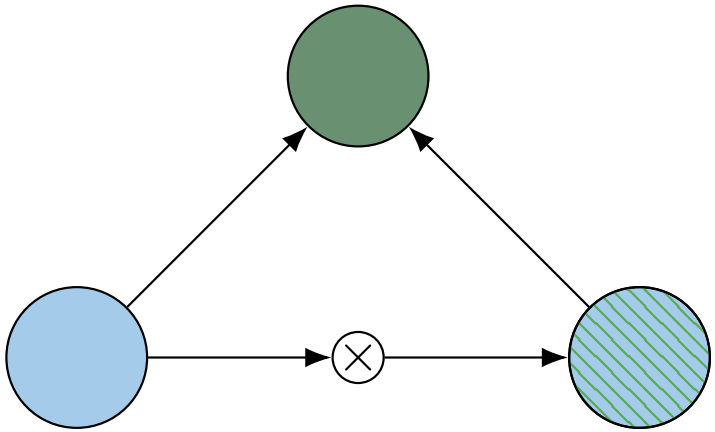

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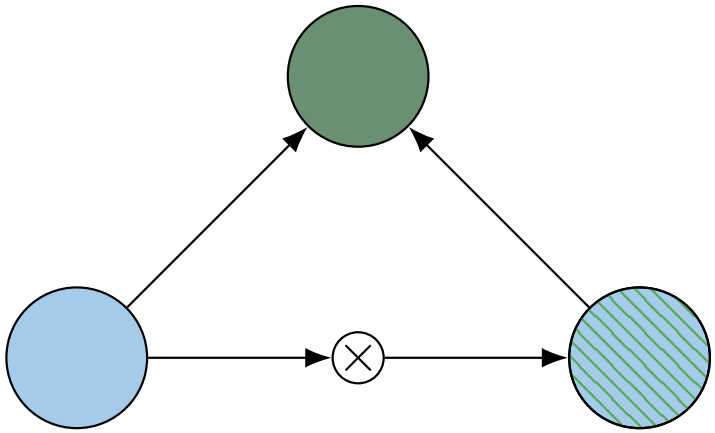

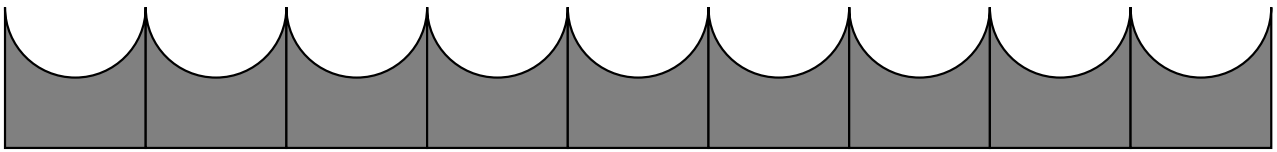

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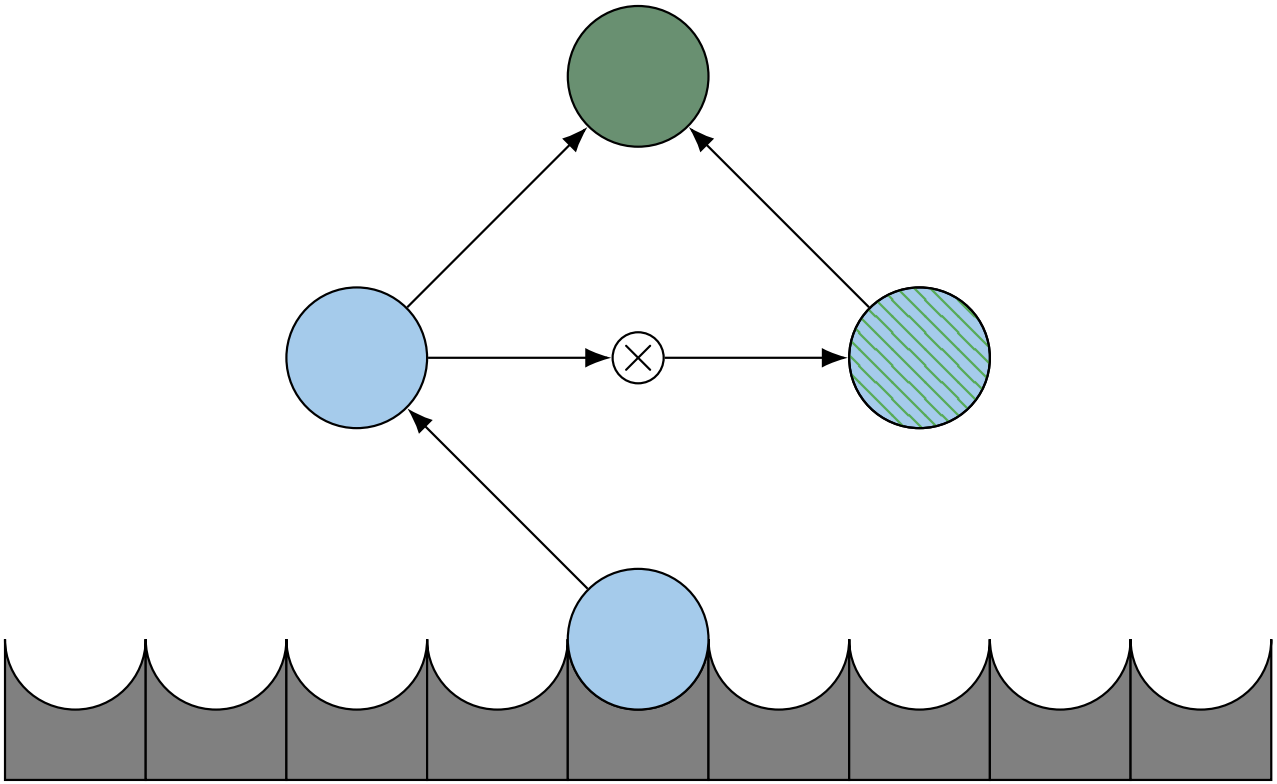

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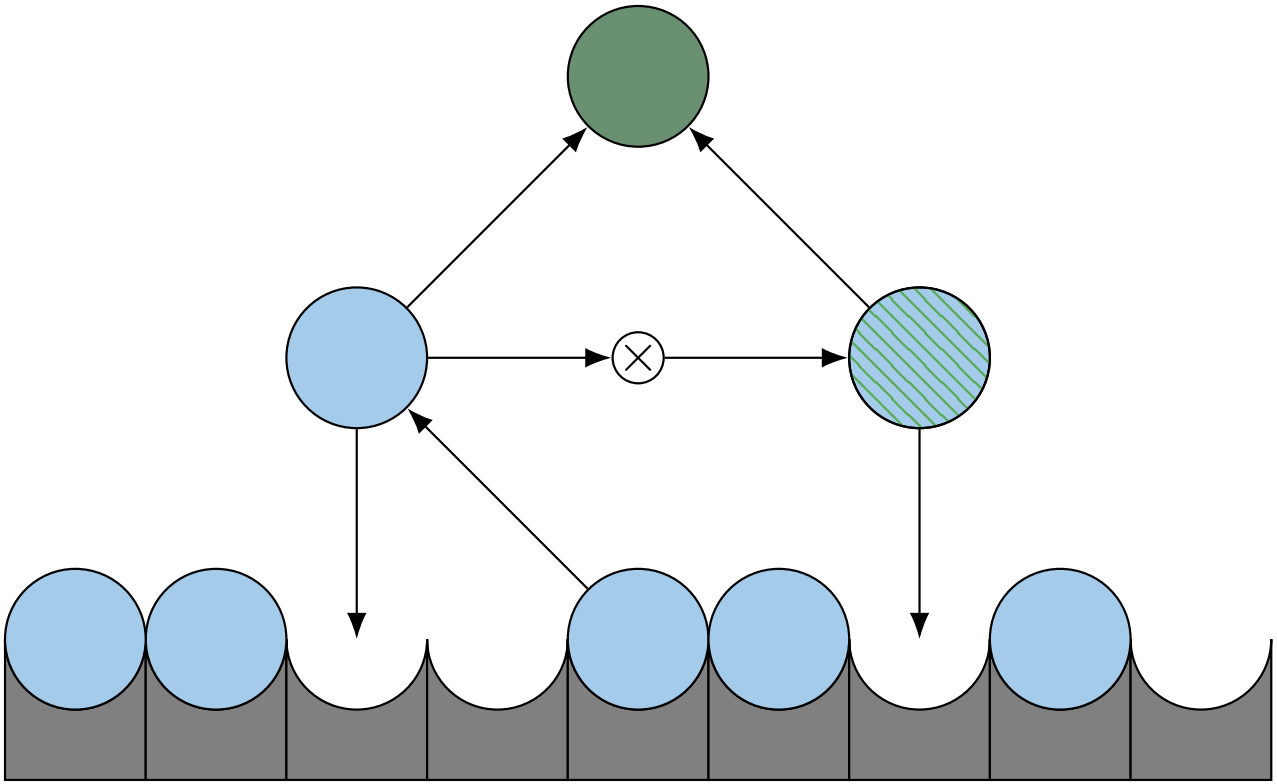

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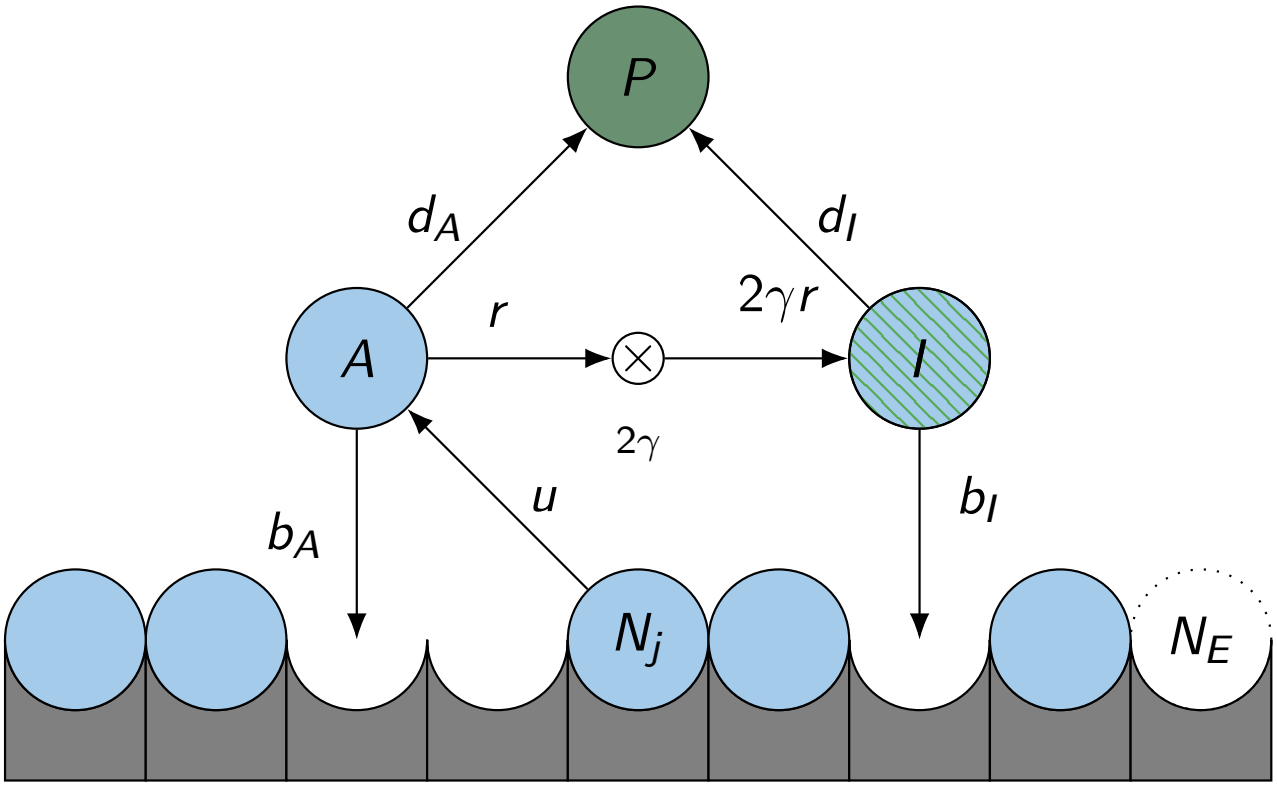


$N_j$: Niche-bound, $A$: Active, $I$: Inactive, $N_E$: Empty niches

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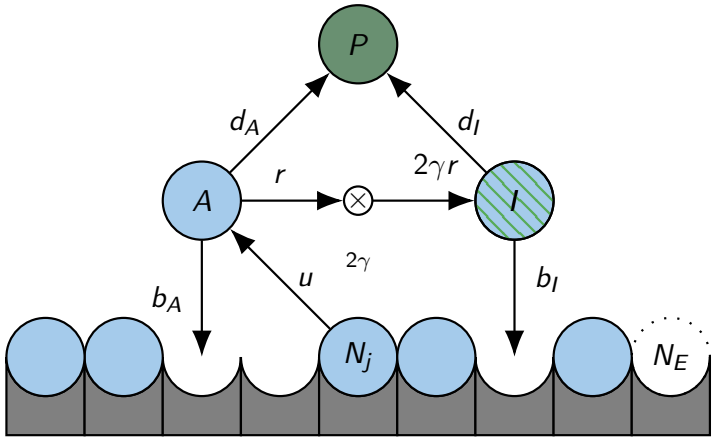
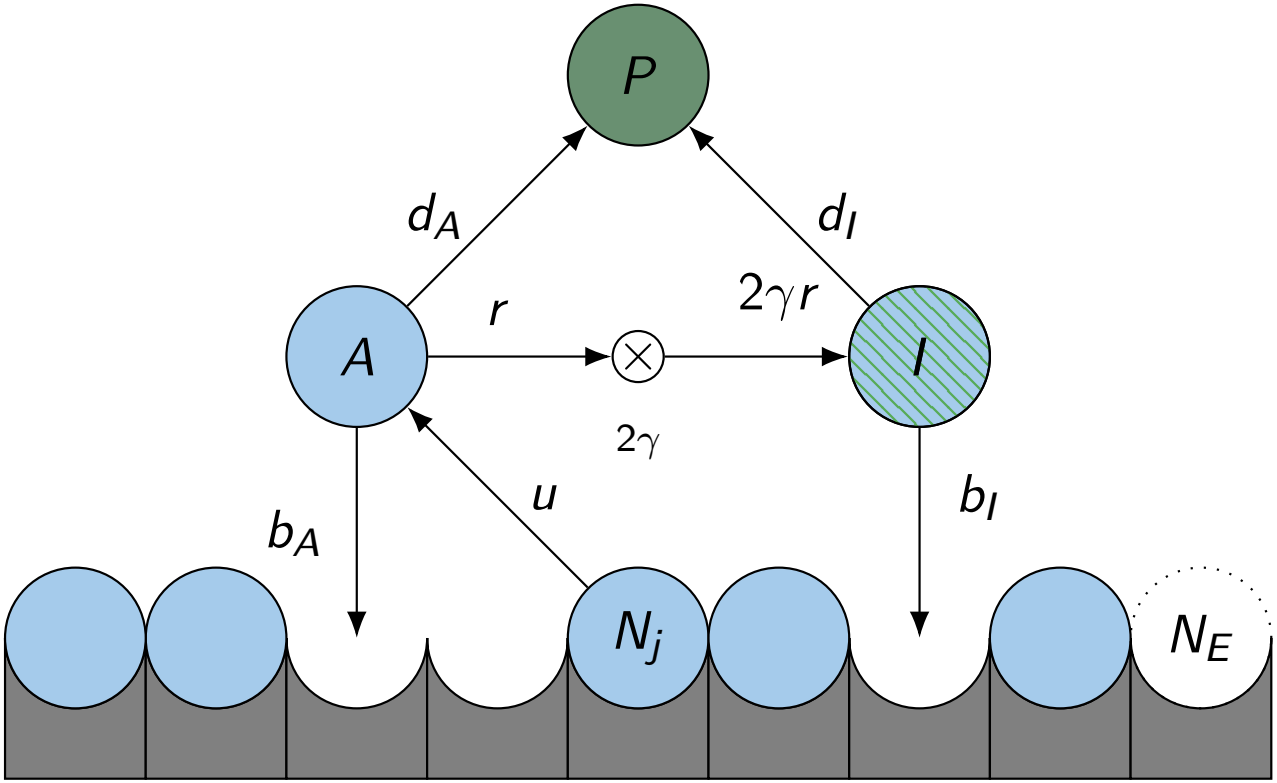



$$\frac{dN_E}{dt} = -b_I N_E I - b_A N_E A + uN_j$$
$$\frac{dN_j}{dt} = b_I N_E I + b_A N_E A - uN_j$$
$$\frac{dI}{dt} = 2\gamma rA - b_I N_E I - d_I I$$
$$\frac{dA}{dt} = uN_j - b_A N_E A - rA - d_A A$$

# Competition for niche-space




$N_j$: Niche-bound, $A$: Active, $I$: Inactive, $N_E$: Empty niches

Considering multiple subpopulations of stem cells:
Work of Thomas Stiehl $\Rightarrow$ Healthy and malignant cells compete for a shared niche.

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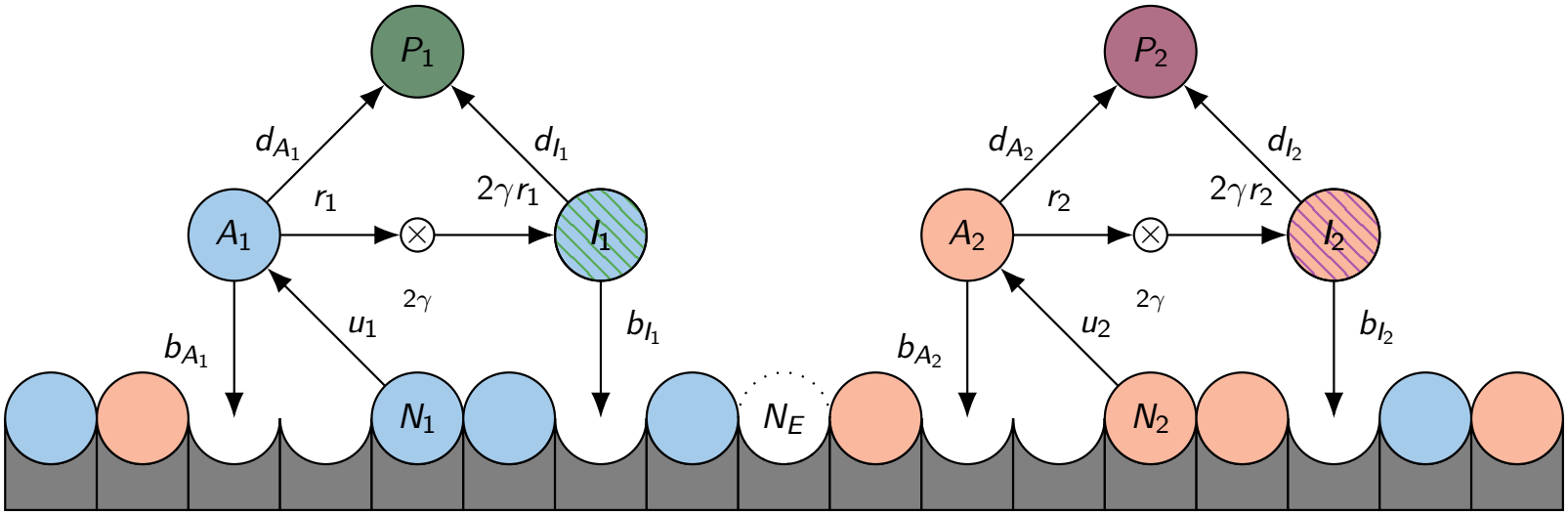


$N_1$: Niche-bound clone 1 $A_1$: Active clone 1 $I_1$: Inactive clone 1

$N_2$: Niche-bound clone 2 $A_2$: Active clone 2 $I_2$: Inactive clone 2

$N_E$: Empty niches

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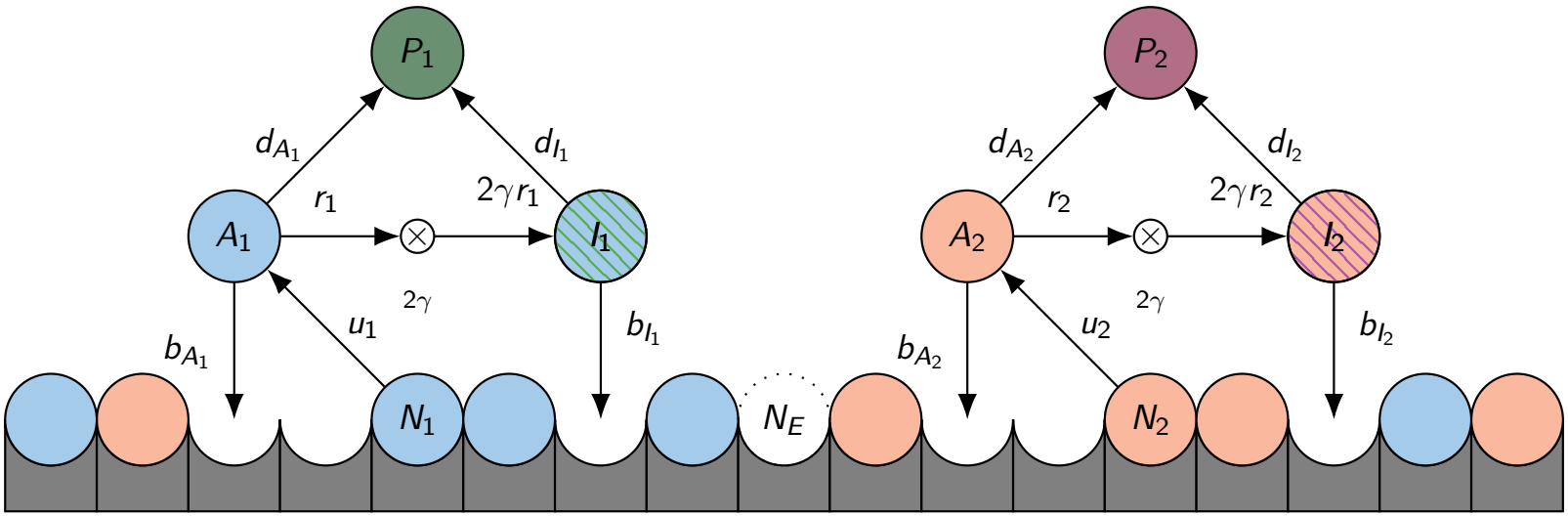


$$\frac{dN_E}{dt} = u_1 N_1 + u_2 N_2 - N_E \left( b_{I_1} I_1 + b_{A_1} A_1 + b_{I_2} I_2 + b_{A_2} A_2 \right)$$

$$\frac{dN_1}{dt} = b_{I_1} N_E I_1 + b_{A_1} N_E A_1 - u_1 N_1 \qquad \frac{dN_2}{dt} = b_{I_2} N_E I_2 + b_{A_2} N_E A_2 - u_2 N_2$$

$$\frac{dI_1}{dt} = 2\gamma r_1 A_1 - b_{I_1} N_E I_1 - d_{I_1} I_1 \qquad \frac{dI_2}{dt} = 2\gamma r_2 A_2 - b_{I_2} N_E I_2 - d_{I_2} I_2$$

$$\frac{dA_1}{dt} = u_1 N_1 - (b_{A_1} N_E + r_1 + d_{A_1}) A_1 \qquad \frac{dA_2}{dt} = u_2 N_2 - (b_{A_2} N_E + r_2 + d_{A_2}) A_2$$

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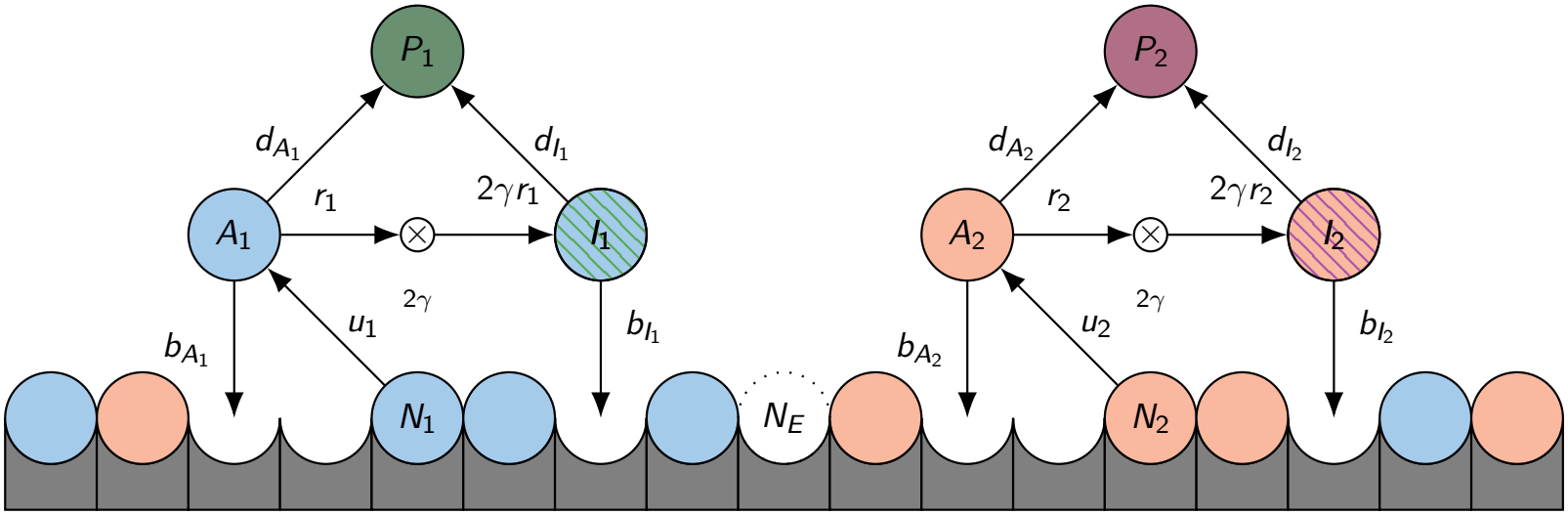


$$\frac{dN_E}{dt} = \sum_{i=1}^{n} u_i N_i - N_E \sum_{i=1}^{n} (b_{I_i} I_i + b_{A_i} A_i)$$

$$\frac{dN_j}{dt} = b_{I_j} N_E I_j + b_{A_j} N_E A_j - u_j N_j$$

$$\frac{dI_j}{dt} = 2\gamma r_j A_j - b_{I_j} N_E I_j - d_{I_j} I_j$$

$$\frac{dA_j}{dt} = u_j N_j - b_{A_j} N_E A_j - r_j A_j - d_{A_j} A_j$$

for $j$ from 1 to $n$, where $n$ is the number of distinct clones.

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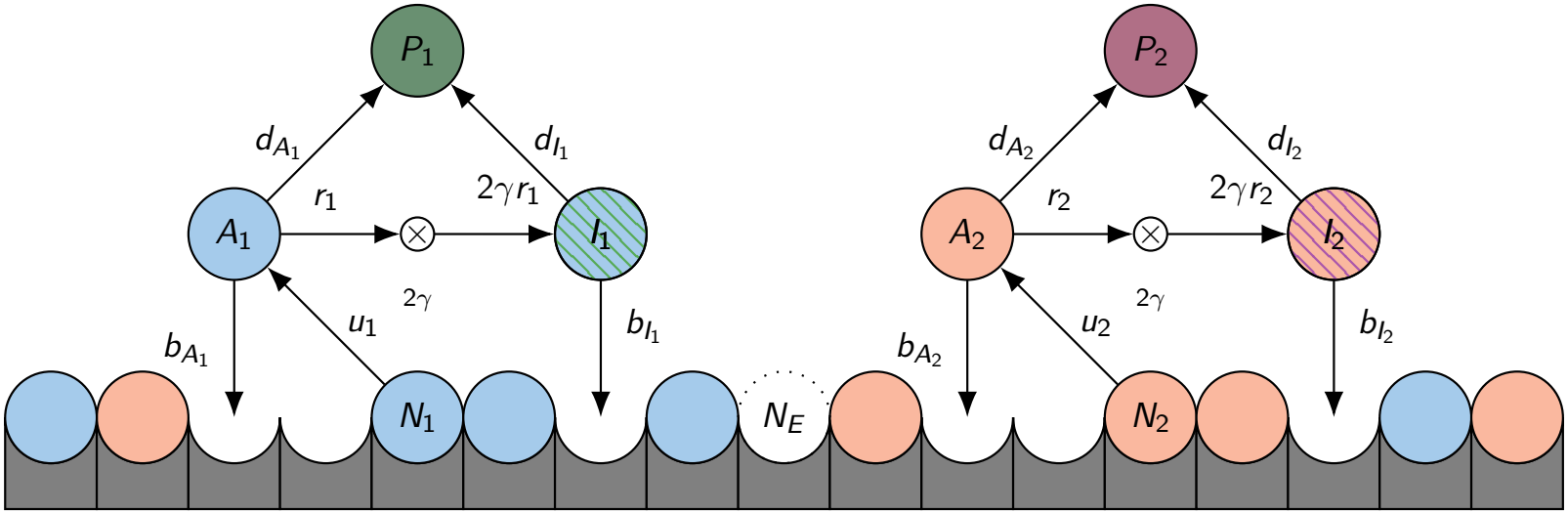
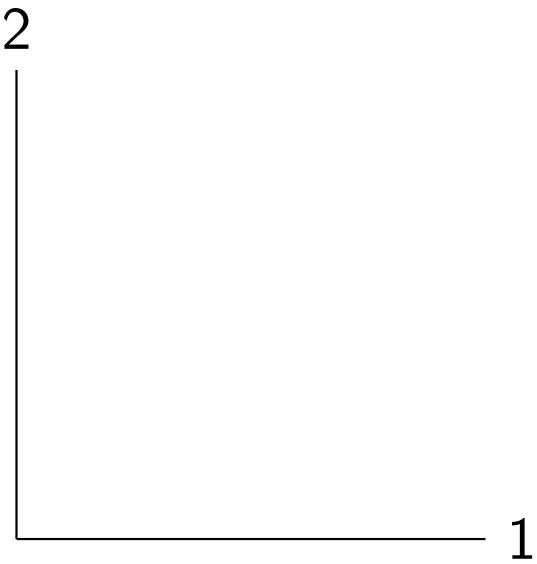



Steady states:



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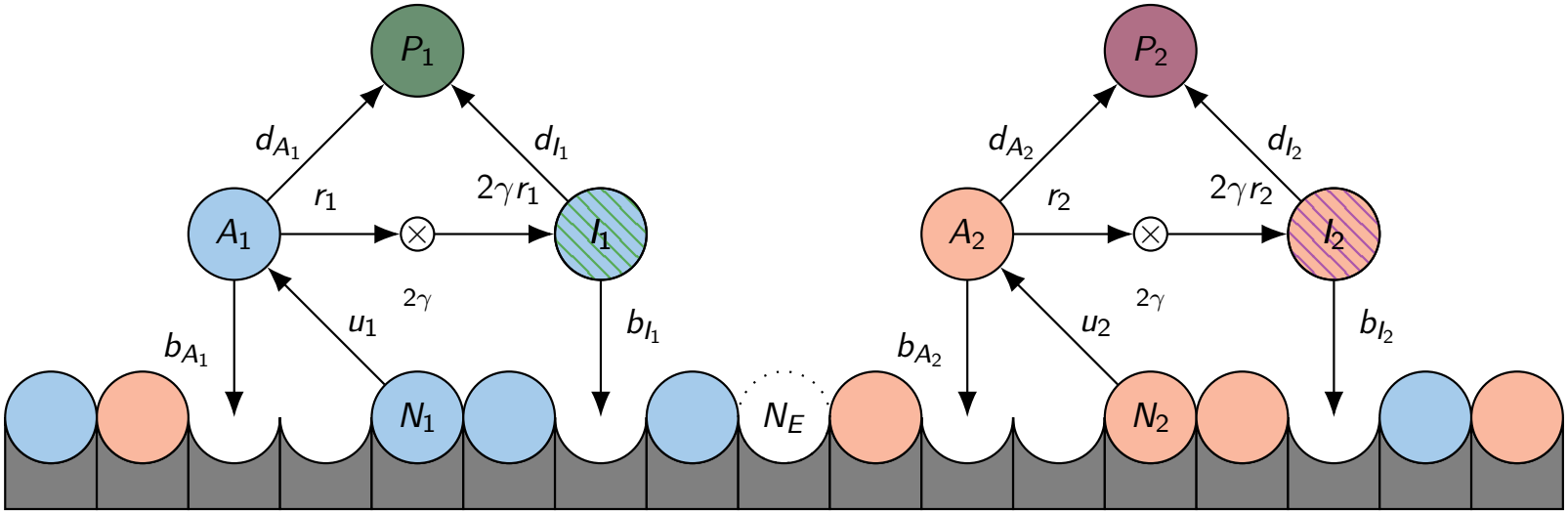
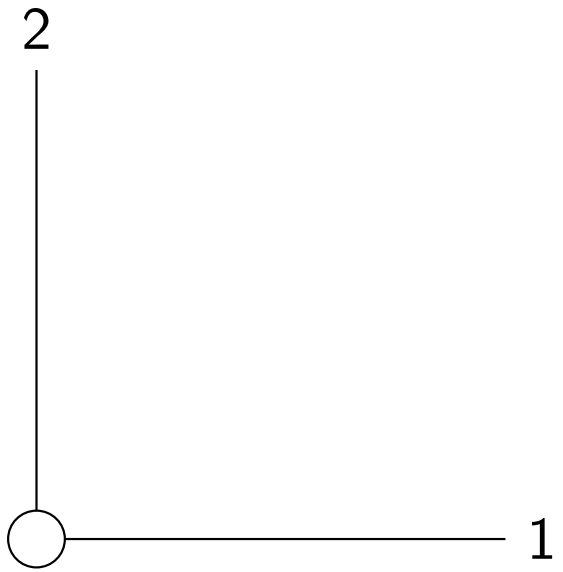



Steady states:

- No cells (Exhaustion)



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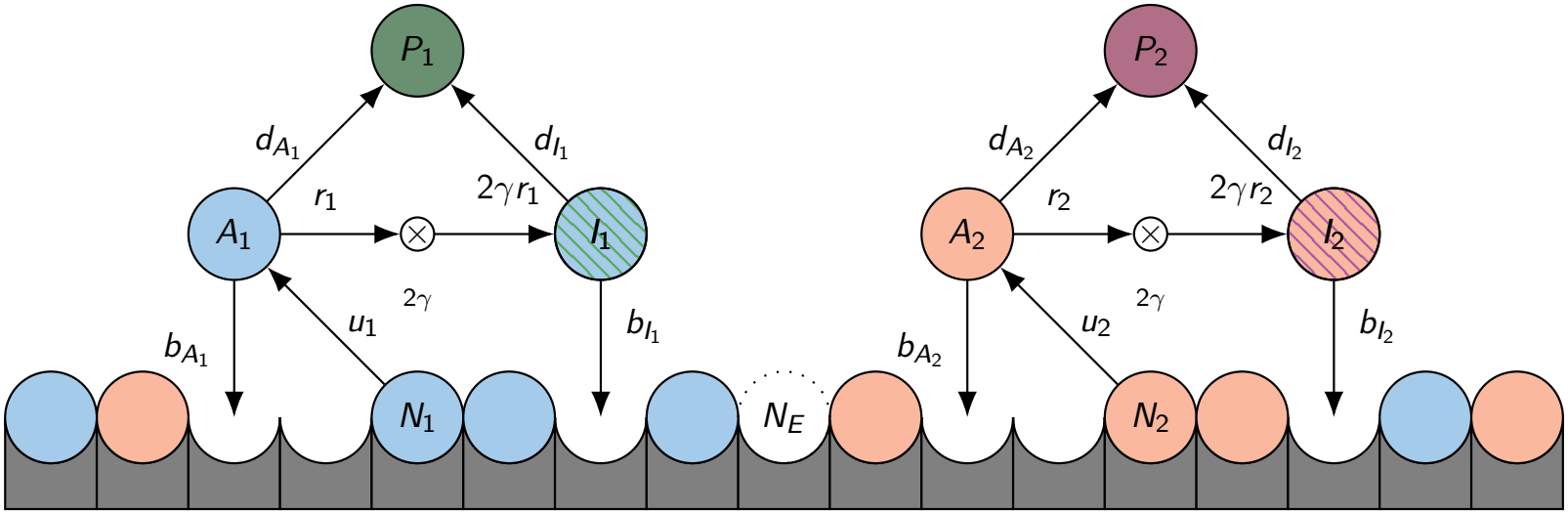
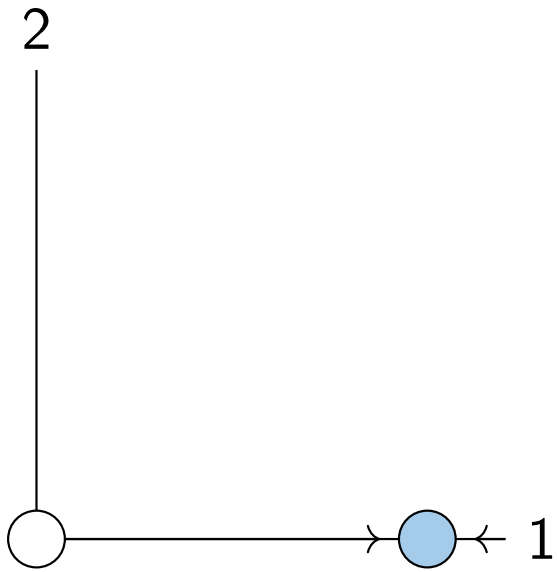



Steady states:

- No cells (Exhaustion)
- Only clone 1 (Health)



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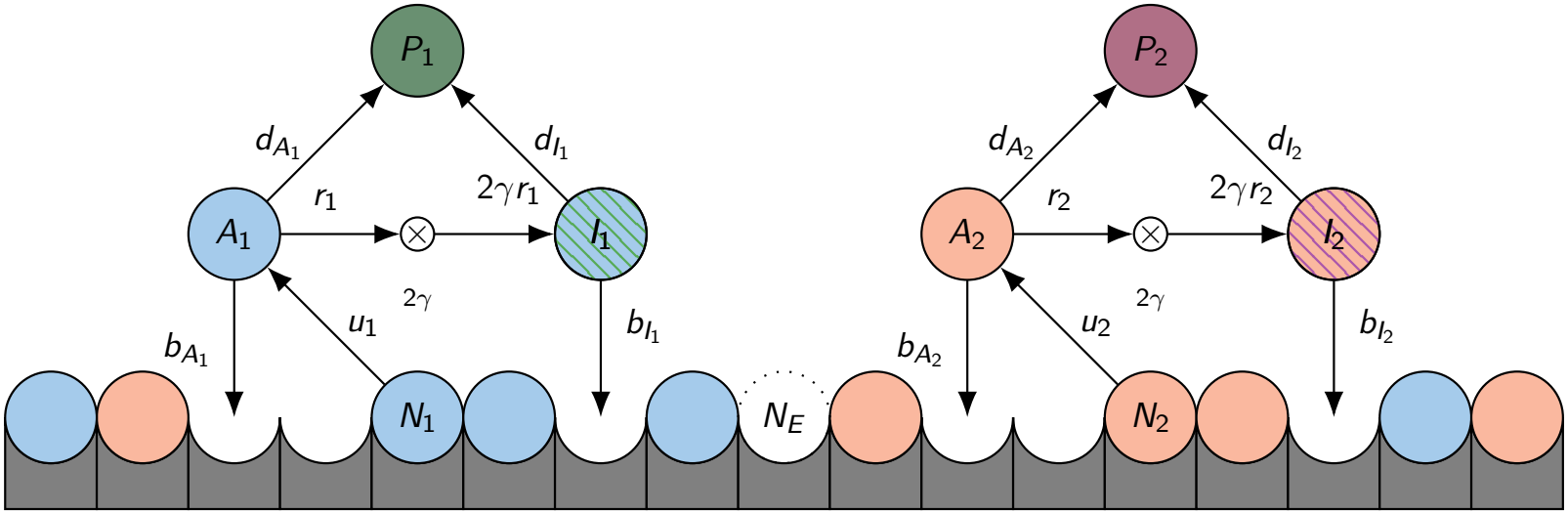


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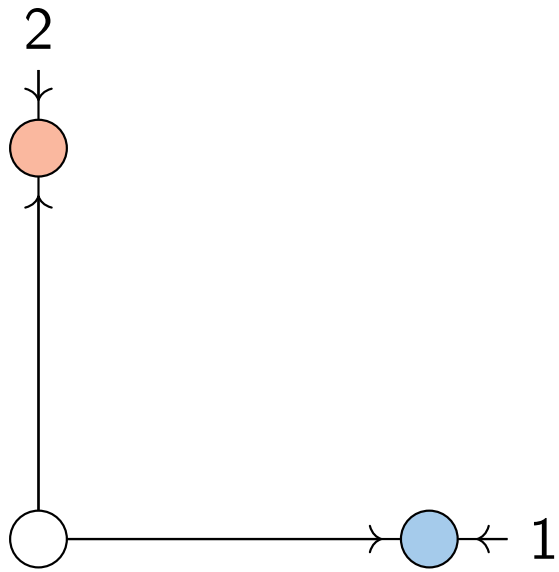

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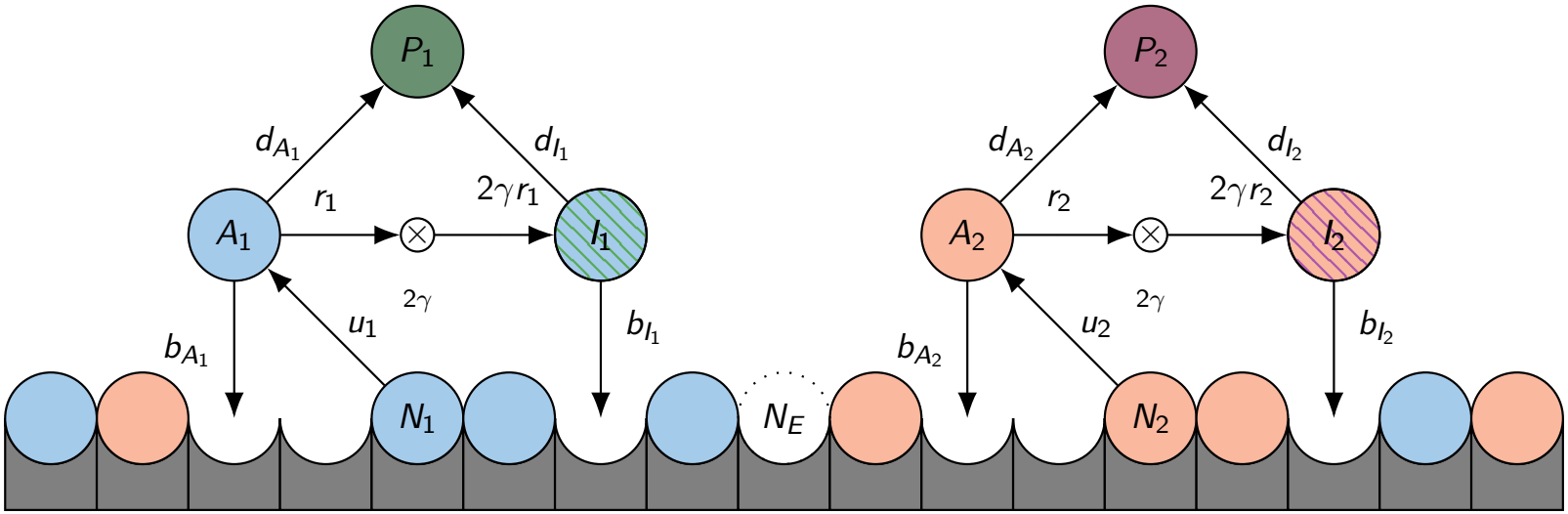


Steady states:

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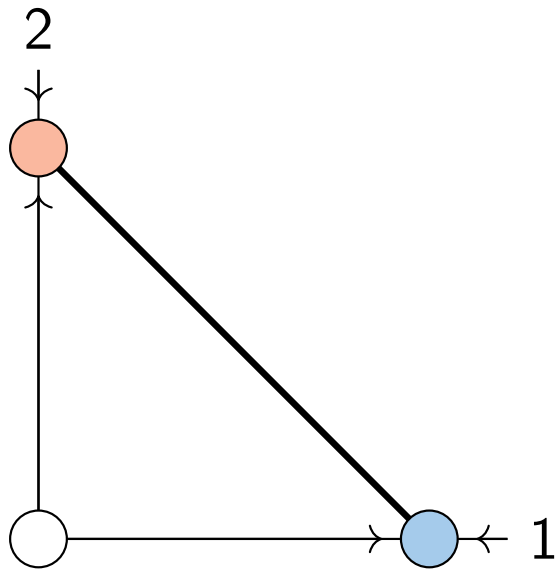
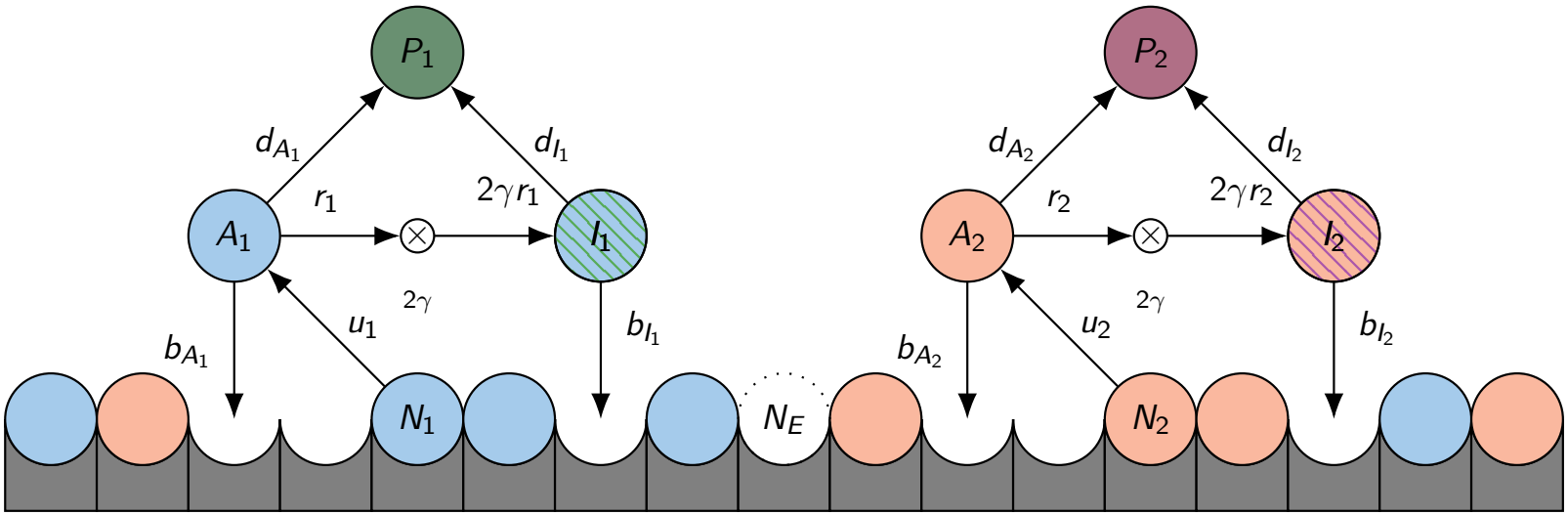
- Only clone 1 (Health)
- Only clone 2 (Disease)
- Co-existence (Suppressed disease?)



# Competition for niche-space - Fitness

Stability of steady states depends on HSC fitness:

$$F_1 = \frac{b_1}{d_{I_1}} \frac{(r_1 - d_{A_1})}{(r_1 + d_{A_1})} \quad \text{and} \quad F_2 = \frac{b_2}{d_{I_2}} \frac{(r_2 - d_{A_2})}{(r_2 + d_{A_2})}$$



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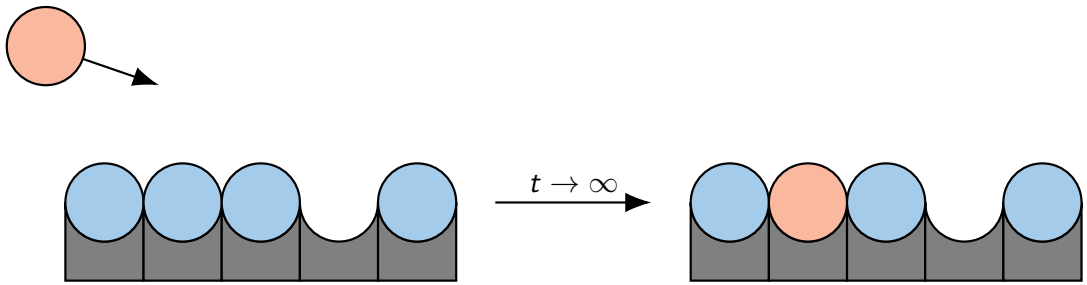
- If $F_1 = F_2$ then coexistence is possible.



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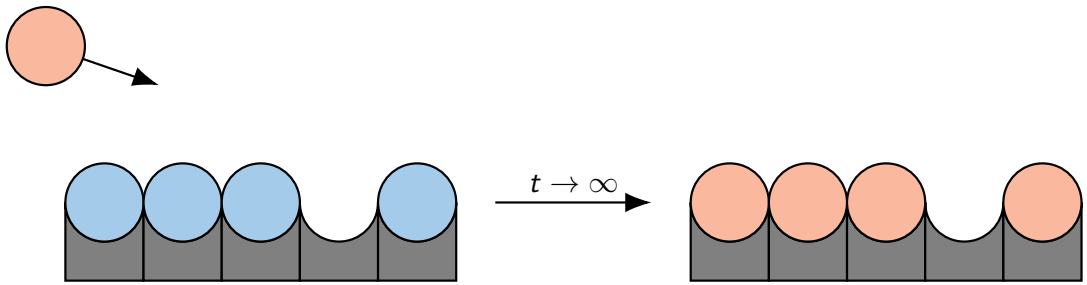
- If $F_1 = F_2$ then coexistence is possible.
- If $F_1 < F_2$ then clone 2 outcompetes clone 1



# Competition for niche-space - Fitness

Stability of steady states depends on HSC fitness:

$$F_1 = \frac{b_1}{d_{l_1}} \frac{(r_1 - d_{A_1})}{(r_1 + d_{A_1})} \quad \text{and} \quad F_2 = \frac{b_2}{d_{l_2}} \frac{(r_2 - d_{A_2})}{(r_2 + d_{A_2})}$$

- If $F_1 = F_2$ then coexistence is possible.
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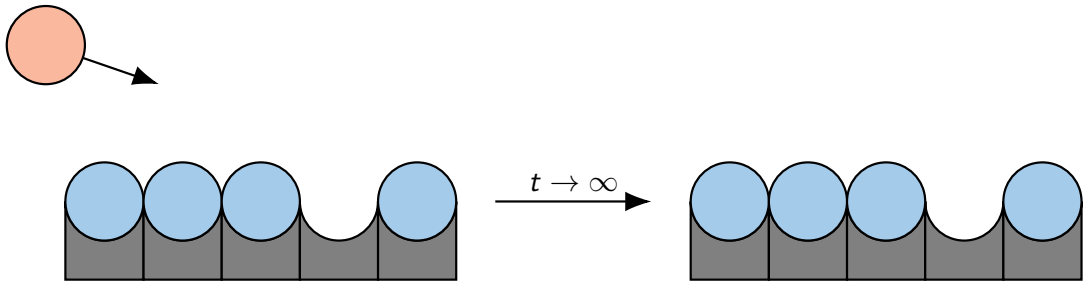

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  *Which is surprisingly similar to fitness as found in ecological systems!*

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*Article draft almost ready for submission!*

# Reducing the model

Under certain (biological) assumptions, we can reduce the model.

$$\dot{N}_E = \sum_{i=1}^{n} u_i N_i - N_E \sum_{i=1}^{n} (b_{I_i} I_i + b_{A_i} A_i)$$
$$\dot{N}_j = b_{I_j} N_E I_j + b_{A_j} N_E A_j - u_j N_j$$
$$\dot{I}_j = 2\gamma r_j A_j - b_{I_j} N_E I_j - d_{I_j} I_j$$
$$\dot{A}_j = u_j N_j - b_{A_j} N_E A_j - r_j A_j - d_{A_j} A_j$$

where $\dot{} = \frac{d}{dt}$ and $j$ from 1 to $n$.

# Reducing the model

Since $\dot{N}_E + \sum_{i=1}^{n} \dot{N}_i = 0$, we set $N_E = K - \sum_{i=1}^{n} N_i$:

$$\dot{N}_j = \left(b_{I_j} I_j + b_{A_j} A_j\right) \left(K - \sum_{i=1}^{n} N_i\right) - u_j N_j$$

$$\dot{I}_j = 2\gamma r_j A_j - \left(b_{I_j} \left(K - \sum_{i=1}^{n} N_i\right) + d_{I_j}\right) I_j$$

$$\dot{A}_j = u_j N_j - \left(b_{A_j} \left(K - \sum_{i=1}^{n} N_i\right) + r_j + d_{A_j}\right) A_j$$

# Reducing the model

Assuming $b_{A_j} = 0$:

$$\dot{N}_j = b_{I_j} I_j \left( K - \sum_{i=1}^{n} N_i \right) - u_j N_j$$

$$\dot{I}_j = 2\gamma r_j A_j - \left( b_{I_j} \left( K - \sum_{i=1}^{n} N_i \right) + d_{I_j} \right) I_j$$

$$\dot{A}_j = u_j N_j - \left( r_j + d_{A_j} \right) A_j$$

# Reducing the model

Scaling variables:

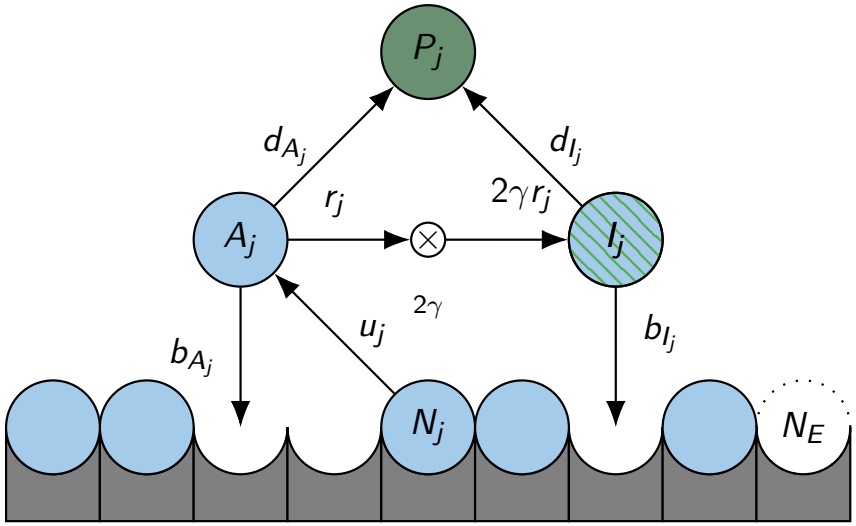
$$\dot{N}_j = u_j \left(1 - \sum_{i=1}^{n} N_i\right) I_j - u_j N_j$$

$$\dot{I}_j = 2\gamma b_{I_j} K A_j - \left(b_{I_j} K \left(1 - \sum_{i=1}^{n} N_i\right) + d_{I_j}\right) I_j$$

$$\dot{A}_j = r_j N_j - \left(r_j + d_{A_j}\right) A_j$$

# Reducing the model

Consequences of biological assumptions:
If $N_j \gg N_E$, then $\dot{I}_j \approx 0$
If $N_j \gg (I_j + A_j)$, then $\dot{A}_j \approx 0$



# Reducing the model

Quasi-steady-state approximation, $\dot{I}_j = 0$ yields:

$$\dot{N}_j = \frac{2\gamma u_j \left(1 - \sum_{i=1}^{n} N_i\right)}{\alpha_j + 1 - \sum_{i=1}^{n} N_i} \left(1 - \sum_{i=1}^{n} N_i\right) A_j - u_j N_j$$

$$\dot{A}_j = r_j N_j - \left(r_j + d_{A_j}\right) A_j$$

where $\alpha_j = \frac{d_{I_j}}{b_{I_j} K}$.

# Reducing the model

Quasi-steady-state approximation, $\dot{A}_j = 0$ yields:

$$\dot{N}_j = u_j \left( \frac{2\gamma\rho_j \left(1 - \sum_{i=1}^{n} N_i\right)}{\alpha_j + 1 - \sum_{i=1}^{n} N_i} - 1 \right) N_j$$

where $\alpha_j = \frac{d_{I_j}}{b_{I_j} K}$ and $\rho_j = \frac{r_j}{r_j + d_{A_j}}$.

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- Possibility for further simplification and simple analysis when $n = 2$

# Putting it all together

## Cancitis model

$$\dot{x_0} = (r_x \phi_x s - d_{x_0} - a_x) x_0$$

$$\dot{x_1} = a_x A_x x_0 - d_{x_1} x_1$$

$$\dot{y_0} = (r_y \phi_y s - d_{y_0} - a_y) y_0$$

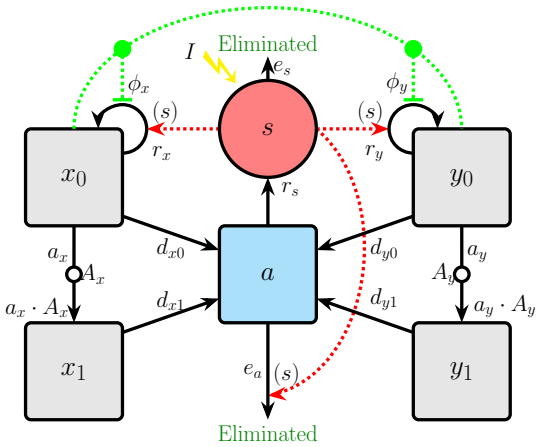
$$\dot{y_1} = a_y A_y y_0 - d_{y_1} y_1$$

$$\dot{a} = d_{x_0} x_0 + d_{y_0} y_0 + d_{x_1} x_1 + d_{y_1} y_1 - e_a a s$$

$$\dot{s} = r_s a - e_s s + I$$

$$\phi_x = \phi_x(x_0, y_0) = \frac{1}{1+(c_{xx} x_0 + c_{xy} y_0)}$$

$$\phi_y = \phi_y(x_0, y_0) = \frac{1}{1+(c_{yx} x_0 + c_{yy} y_0)}$$



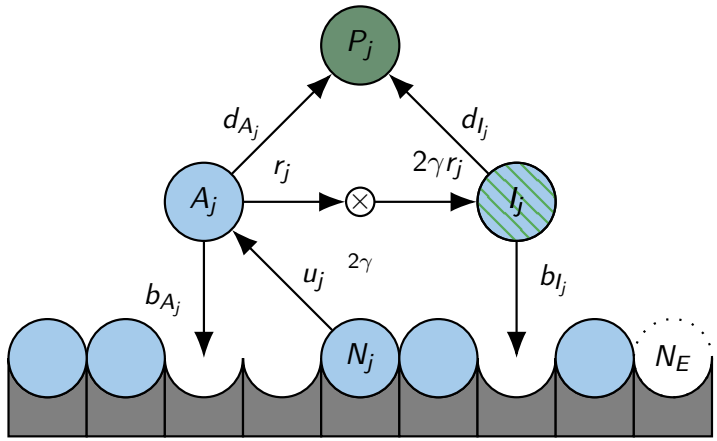

## HSC niche model

$$\dot{N_j} = u_j \left( \frac{2\gamma\rho_j \left(1 - \sum_{i=1}^{n} N_i\right)}{\alpha_j + 1 - \sum_{i=1}^{n} N_i} - 1 \right) N_j$$

where $\alpha_j = \frac{d_{I_j}}{b_{I_j} K}$ and $\rho_j = \frac{r_j}{r_j + d_{A_j}}$.

and production of progenitors:

$$P_j = d_{A_j} A_j + d_{I_j} I_j$$



# Putting it all together

$$\dot{N}_x = u_x s \left( \frac{2\gamma\rho_x (1 - N_x - N_y)}{\alpha_x + 1 - N_x - N_y} - 1 \right) N_x$$

$$\dot{M}_x = A_x P_x - d_{x_1} M_x$$

$$\dot{N}_y = u_y s \left( \frac{2\gamma\rho_y (1 - N_x - N_y)}{\alpha_y + 1 - N_x - N_y} - 1 \right) N_y$$

$$\dot{M}_y = A_y P_y - d_{y_1} M_y$$

$$\dot{a} = d_{x_1} M_x + d_{y_1} M_y - e_a a s$$

$$\dot{s} = r_s a - e_s s + l$$

where $P_j = \left( d_{A_j} + \frac{2\gamma r_j}{1 + d_{I_j}^{-1} b_{I_j} (K - N_x - N_y)} \right) \frac{u_j}{r_j + d_{A_j}} N_j$

# The combined model with patient data

- Perturbation of parameters during treatment

$$\theta(t) = (1 + \delta_\theta D(t))\theta(0) \tag{1}$$

where $D(t)$ is blood-level of drug, and $\delta_\theta$ is patient-specific.

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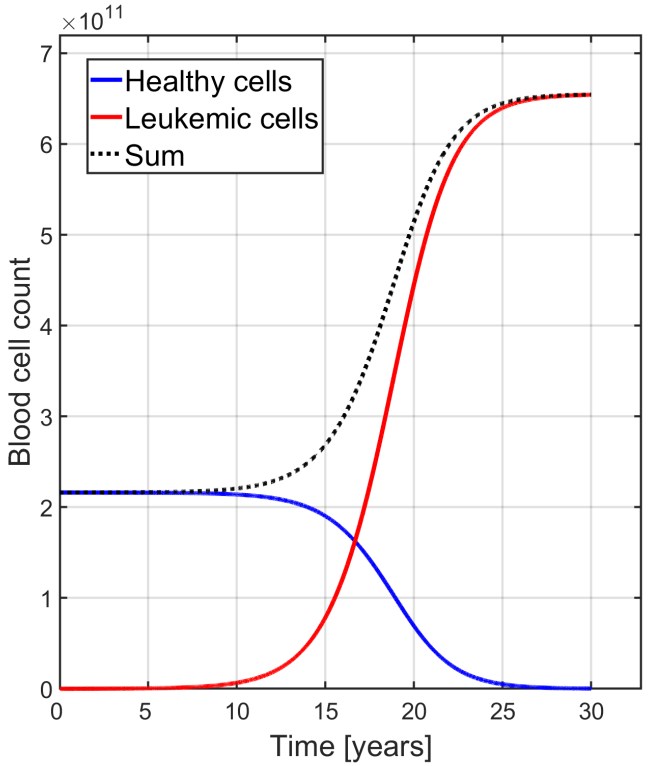
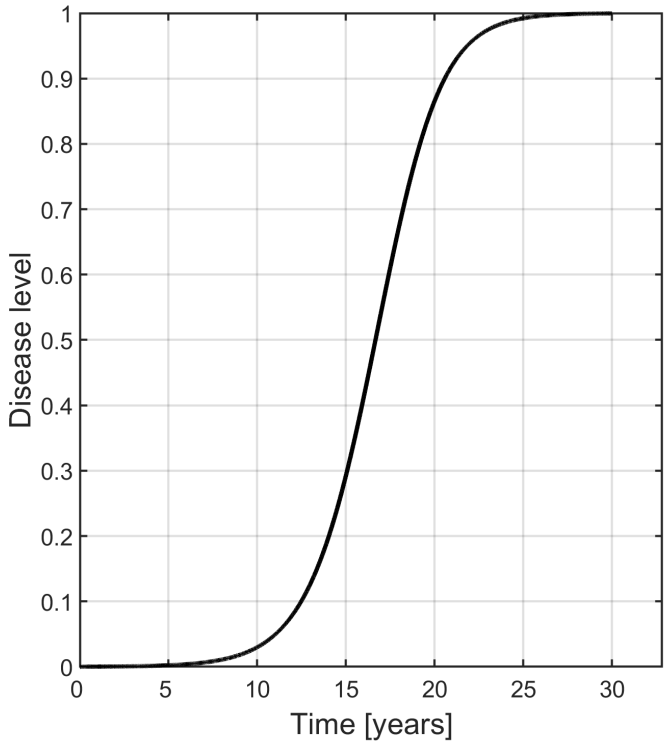
- Relating measurement from blood samples to the model
  - Blood-cell count: $M_x + M_y$ (Thrombocytes or leukocytes)
  - Disease burden in blood: $\frac{M_y}{M_x + M_y}$

# Examples of patient-specific fits

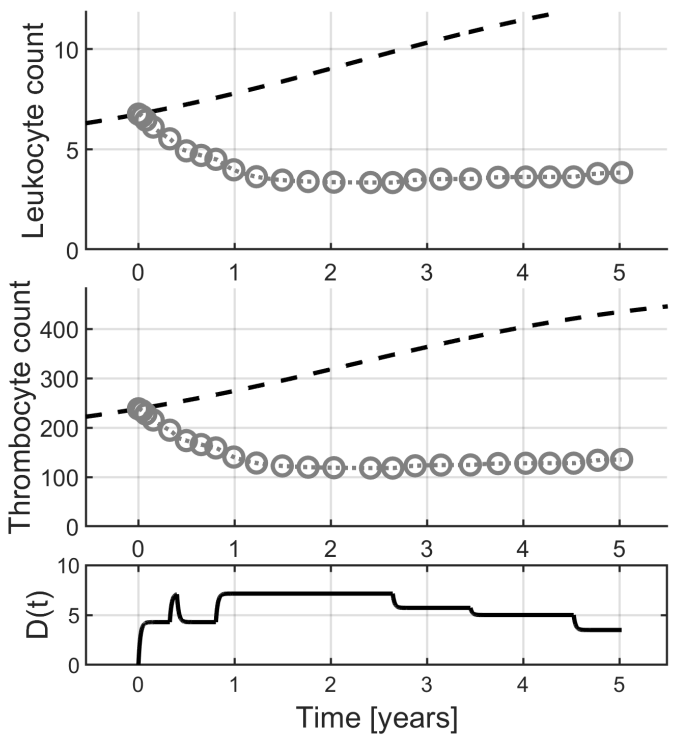
## No treatment

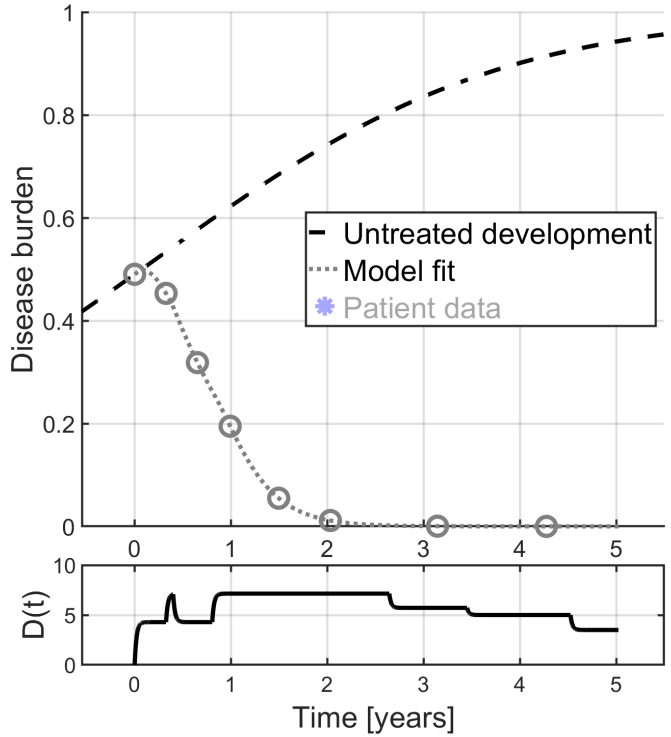


# Examples of patient-specific fits

## Patient 1

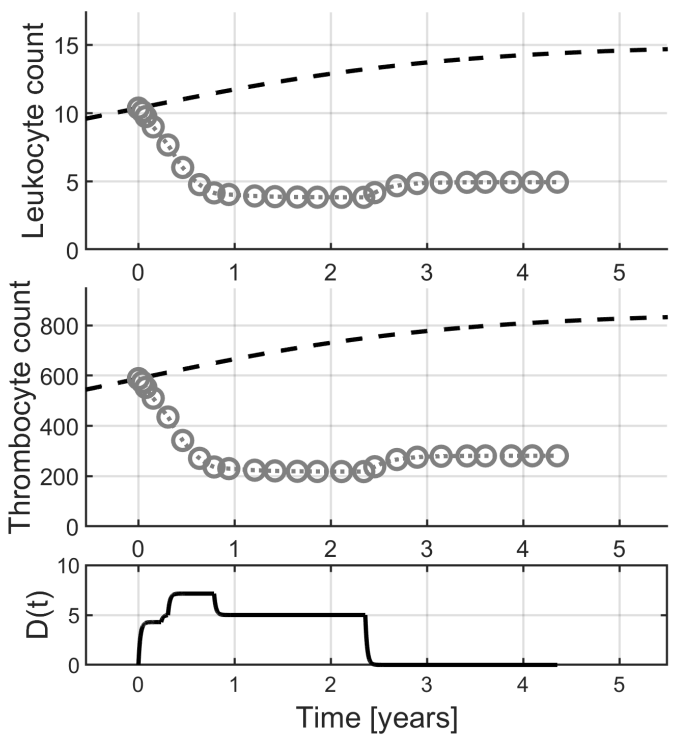


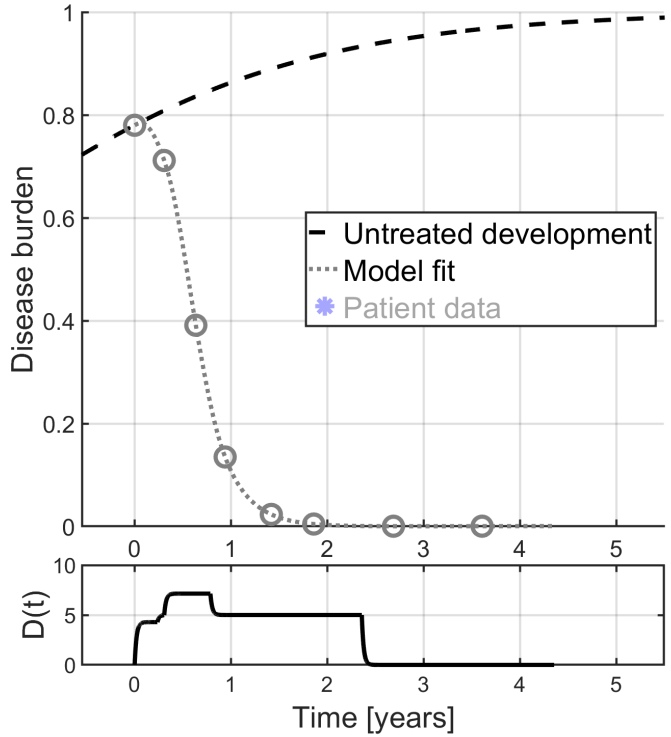




$\theta(t) = (1 + \delta_\theta D(t))\theta(0)$, fitting only the clearing-rates of mature cells ($\delta_{d_{x_1}} = \delta_{d_{y_1}}$) and the differentiation of active HSC ($\delta_{d_{A_y}}$). Data removed in online version.

# Examples of patient-specific fits

## Patient 2

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- The combined model shows great promise for patient-specific predictions based on treatment dosage.

# Thank you for your attention.

## Any questions?

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# References

## Group website: `dirac.ruc.dk/cancitis`


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