"Mathematical Modelling of Myeloproliferative Neoplasms and Hematopoietic Stem Cells"

Ph.D.-defense

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Section 1

Introduction

Introduction and overview

Overall plan: Guided tour of the thesis

- Background on mathematical modelling and blood cancers

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  - The combined "HSC-Niche + Cancitis" model

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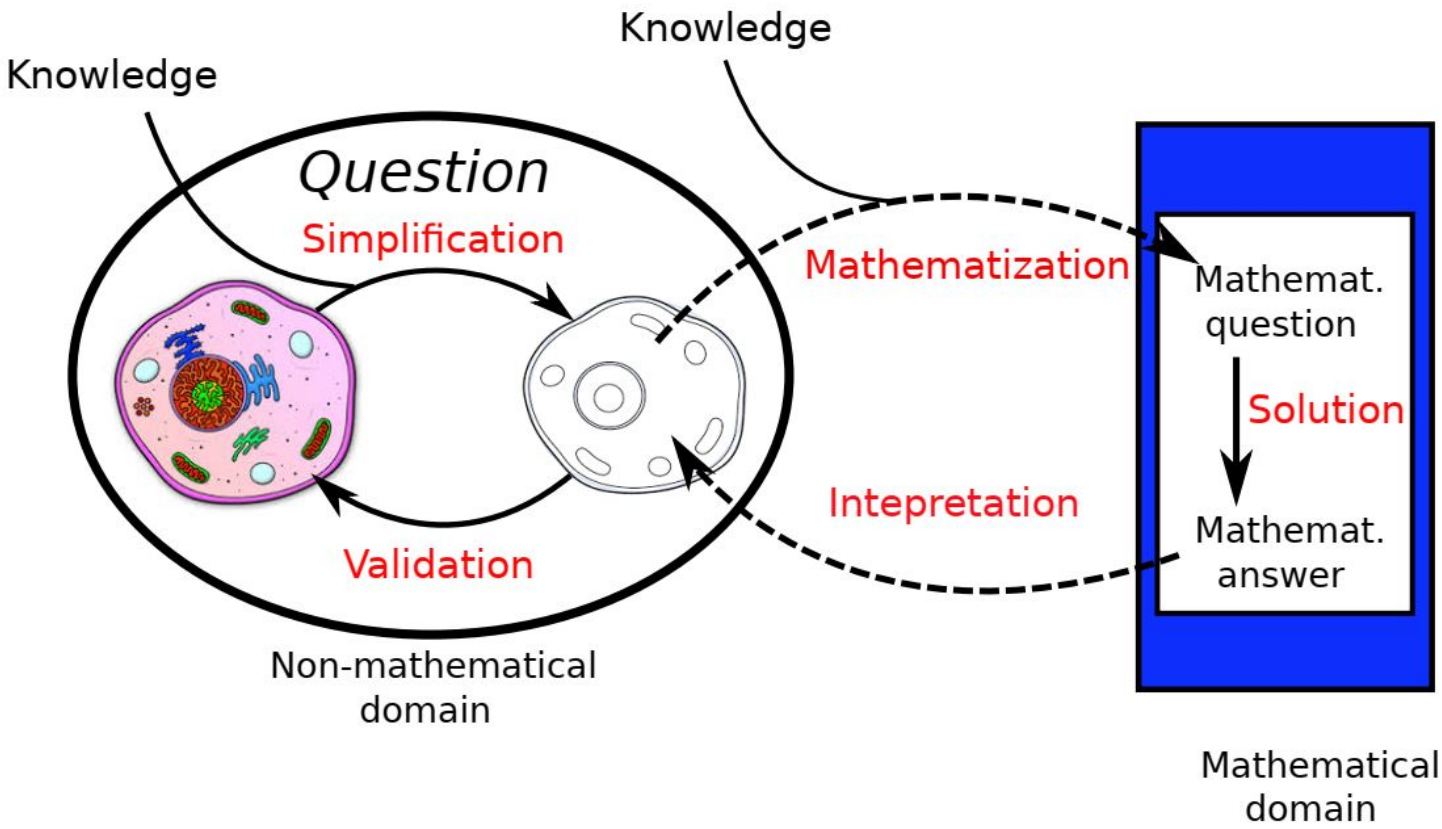
  - The combined "HSC-Niche + Cancitis" model
- Comments about mathematical modelling of blood cancers

Section 2

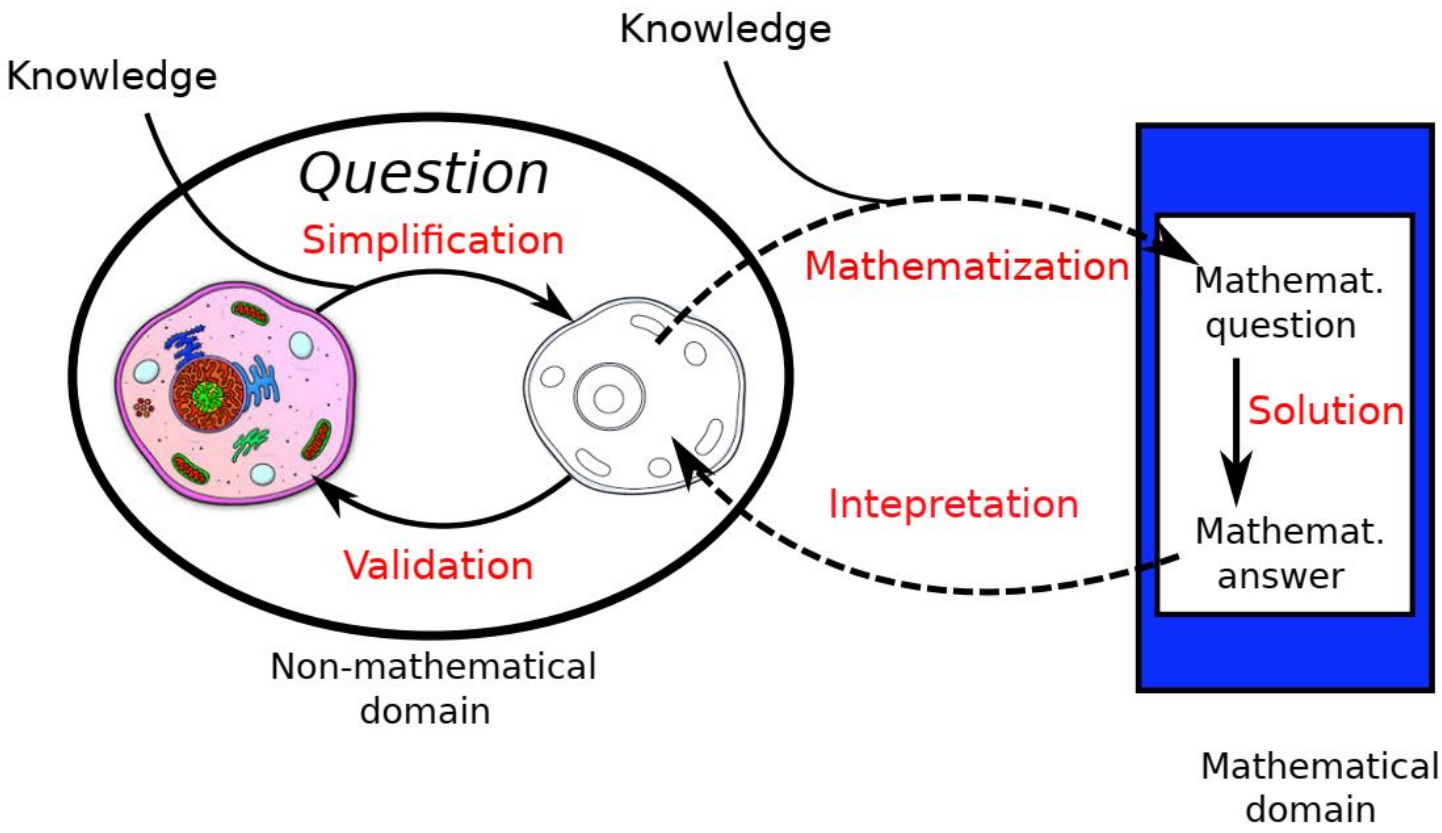
Setting the stage

Mathematical Modelling



The modelling cycle, taken from (Hansen & Ottesen, 2020)

Mathematical Modelling



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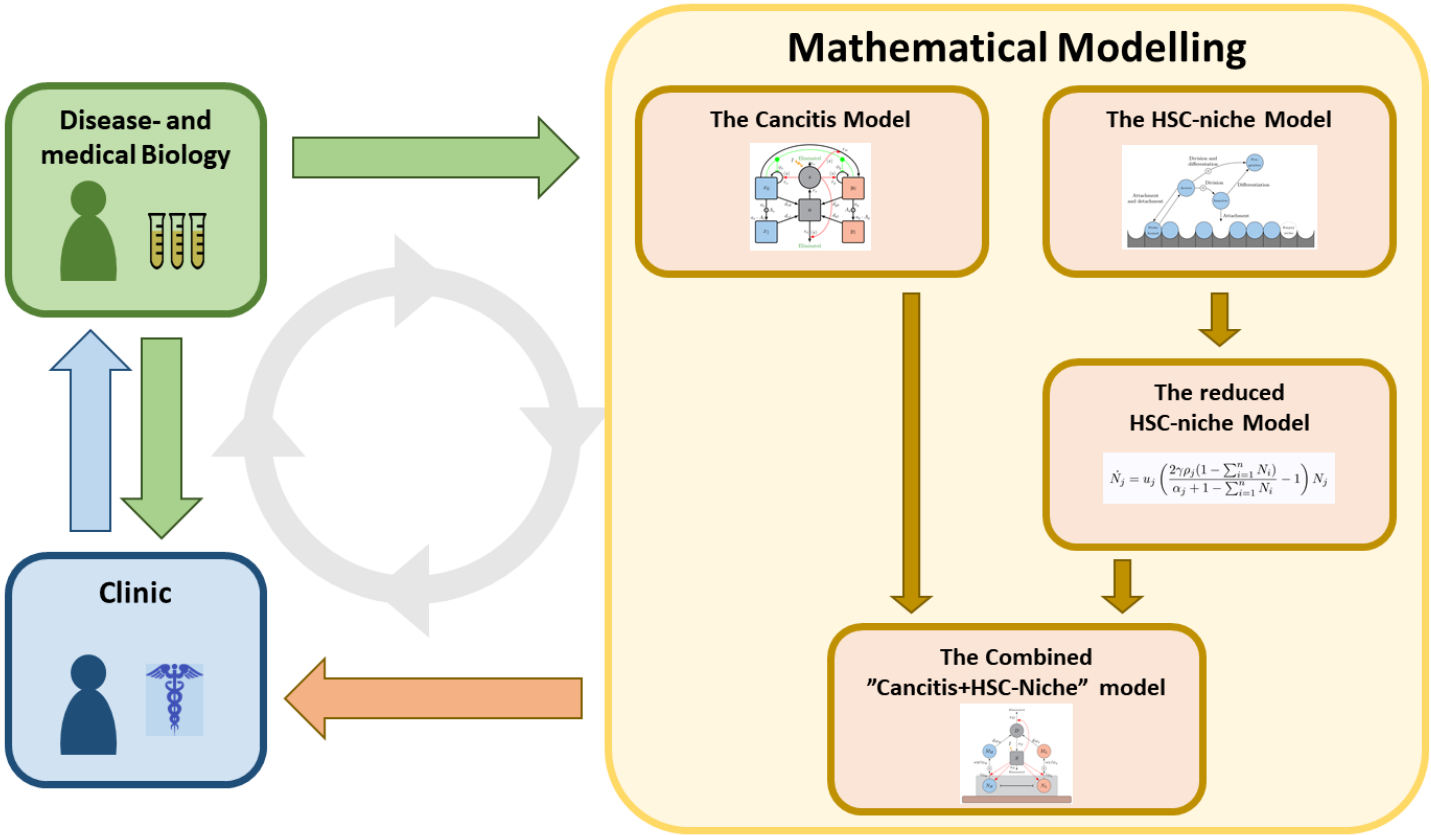
"If you want to be successful, pick a cancer and work on that"
- Doron Levy (University of Maryland), CIRM Math-Cancer workshop, summer 2018

Mathematical Modelling



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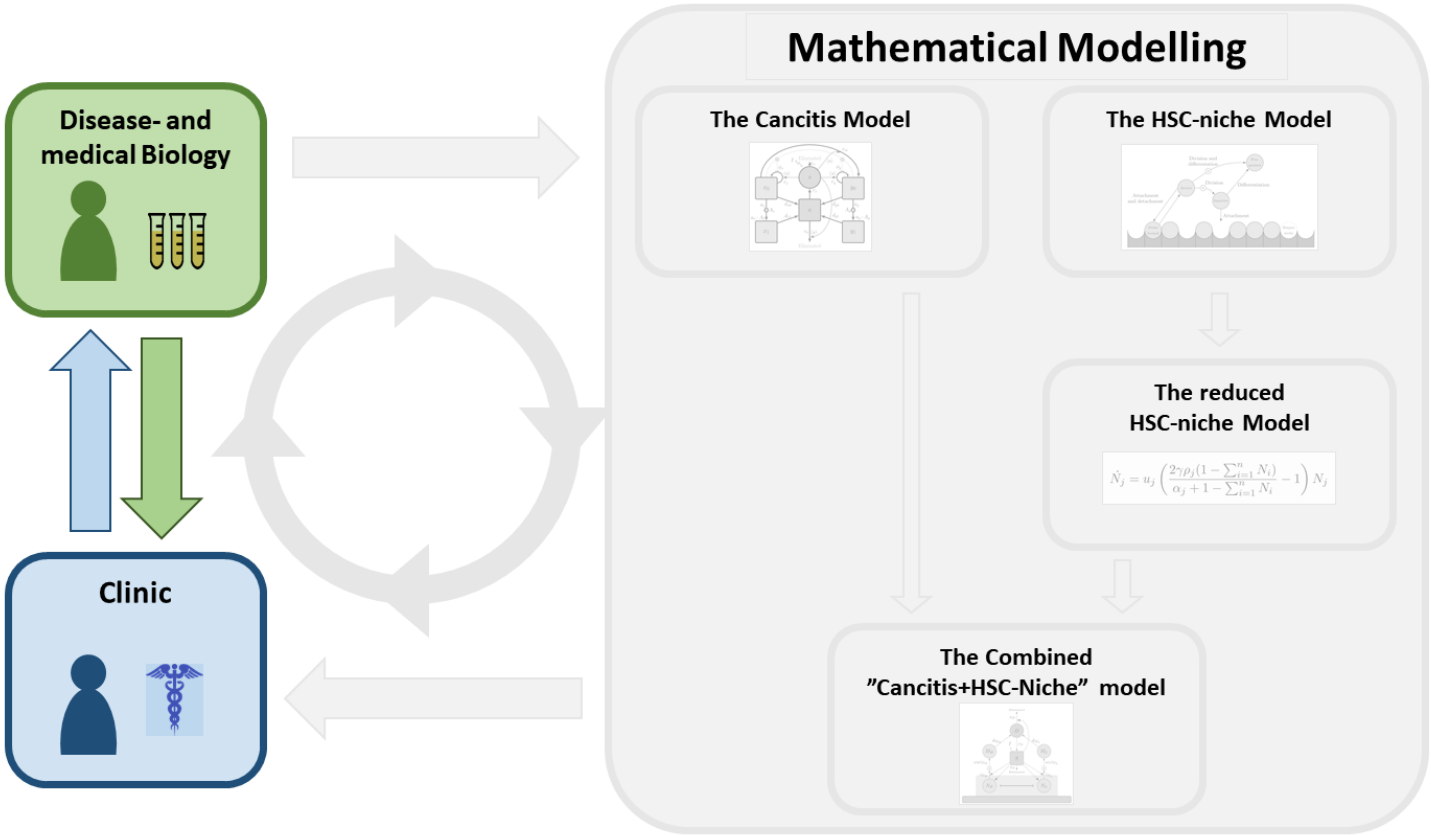
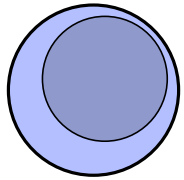


The blood system and MPNs

- **HSC:** Hematopoietic Stem Cells. Produces progenitor cells.



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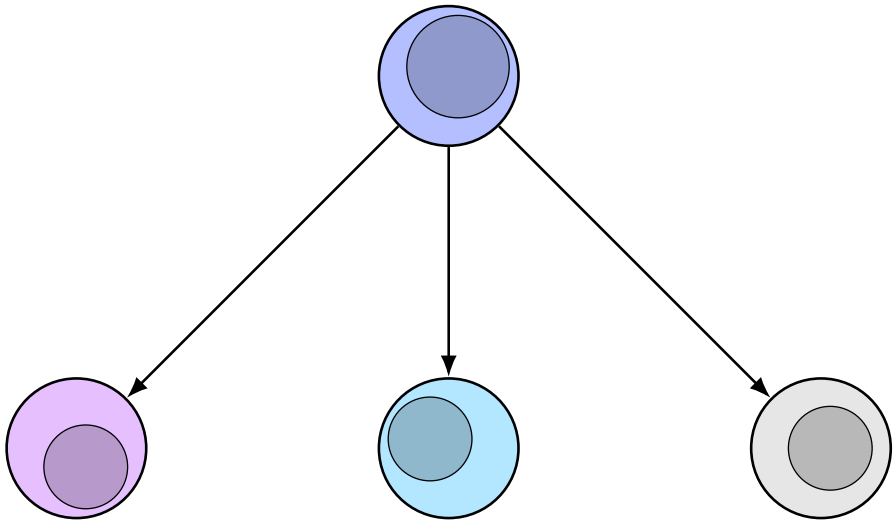

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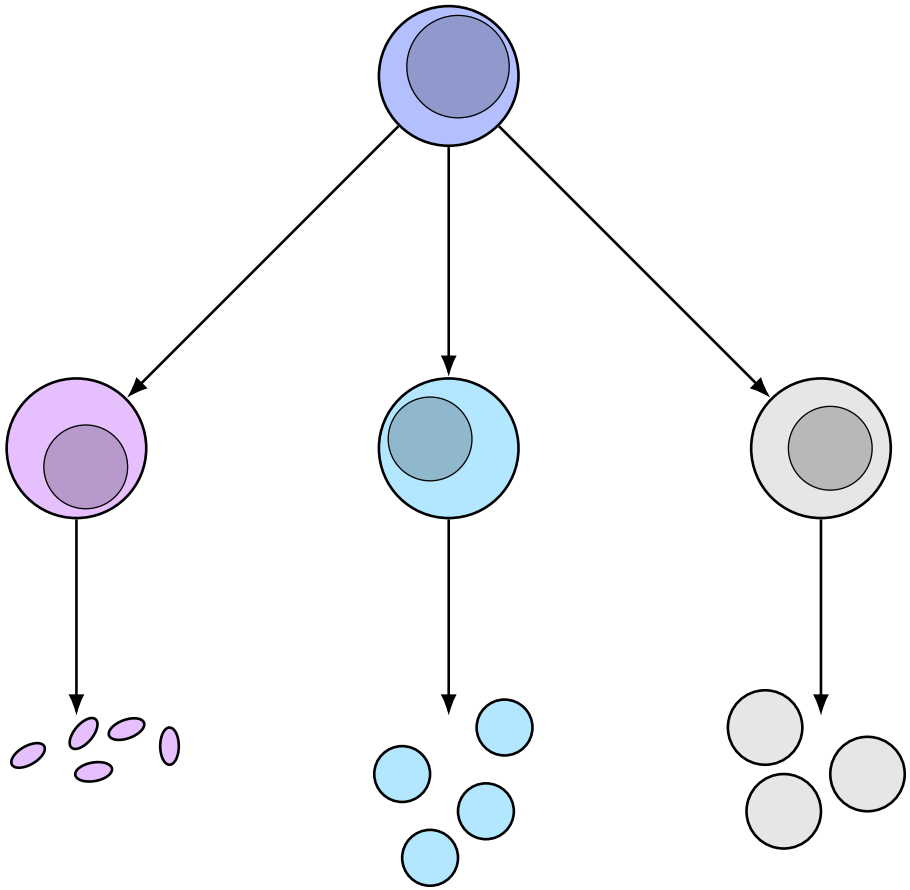

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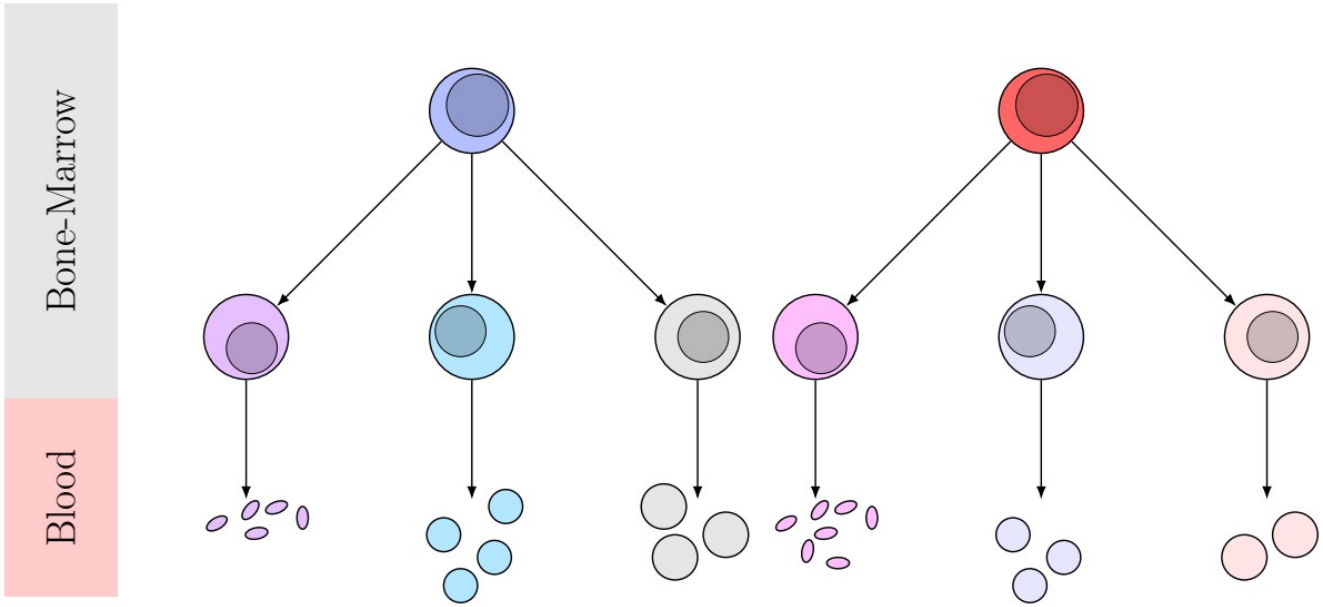

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  Group of diagnoses, e.g.
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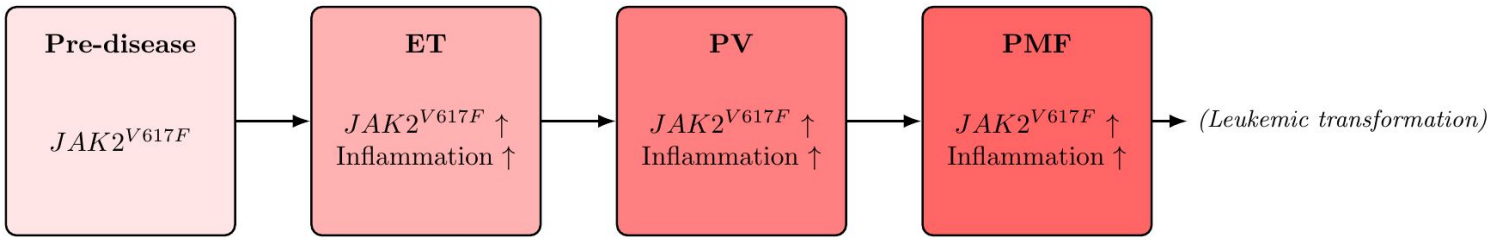

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(Note: We do not consider CML, and focus only on the Philadelphia-chromosome-negative MPNs)

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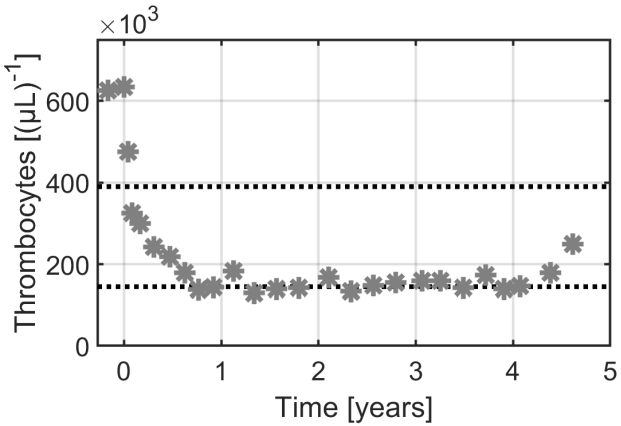
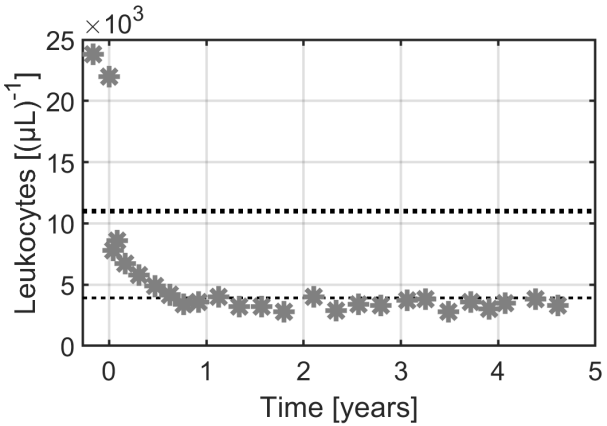
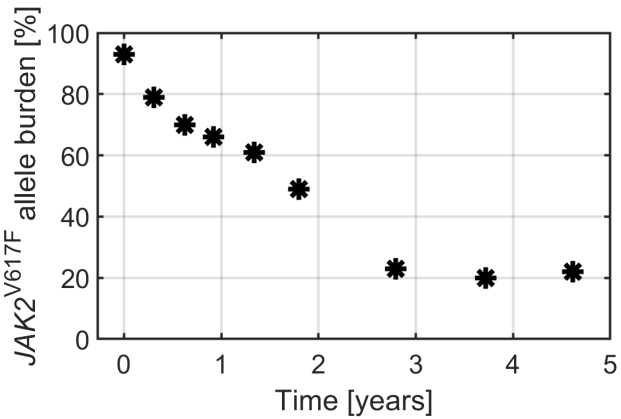
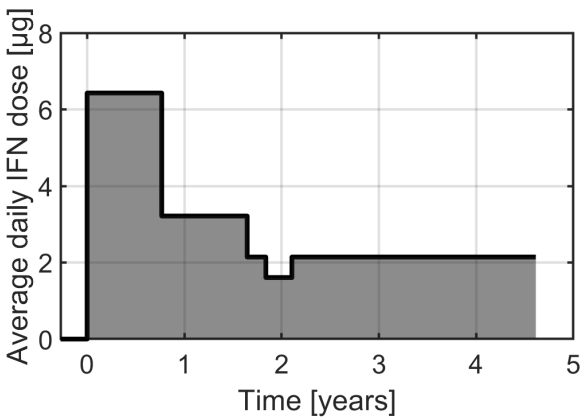


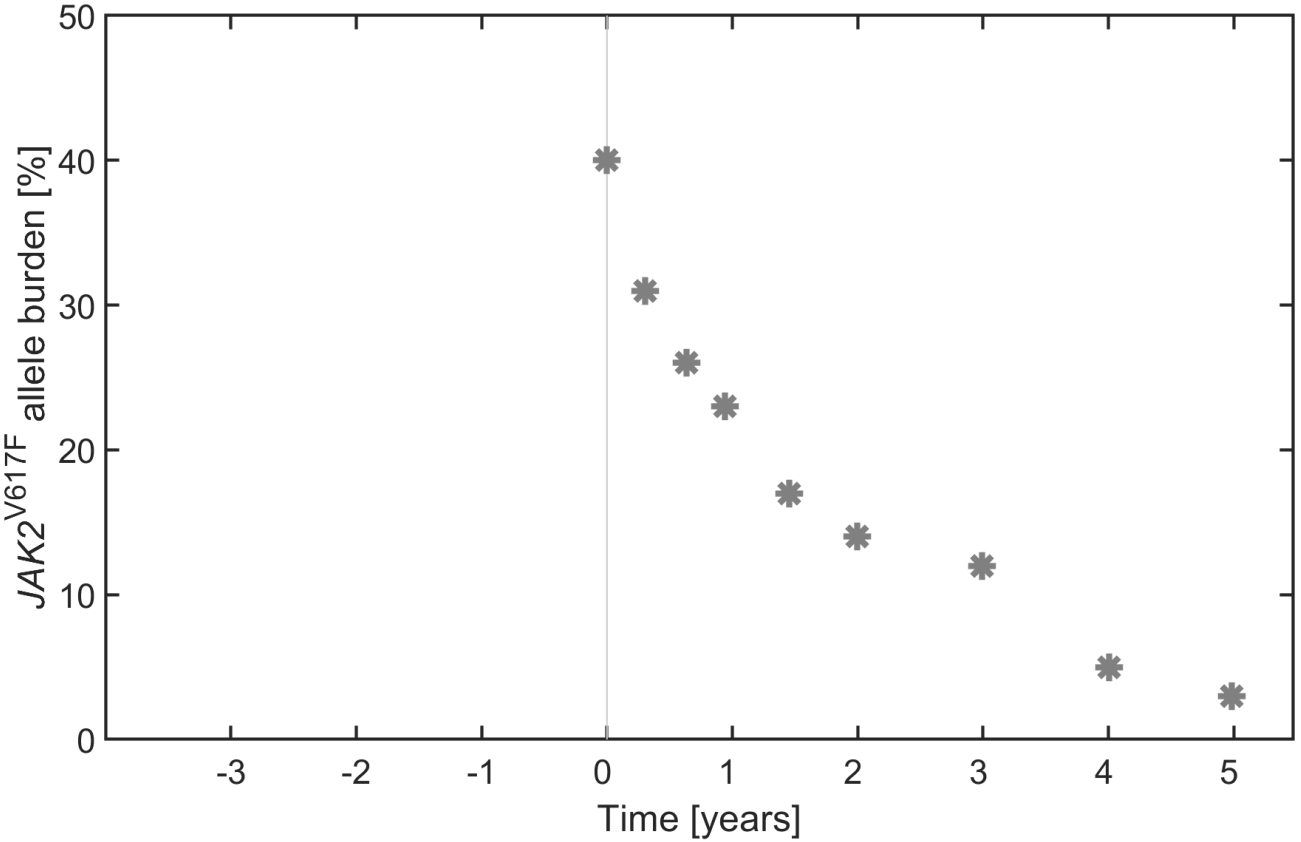






Patient P075

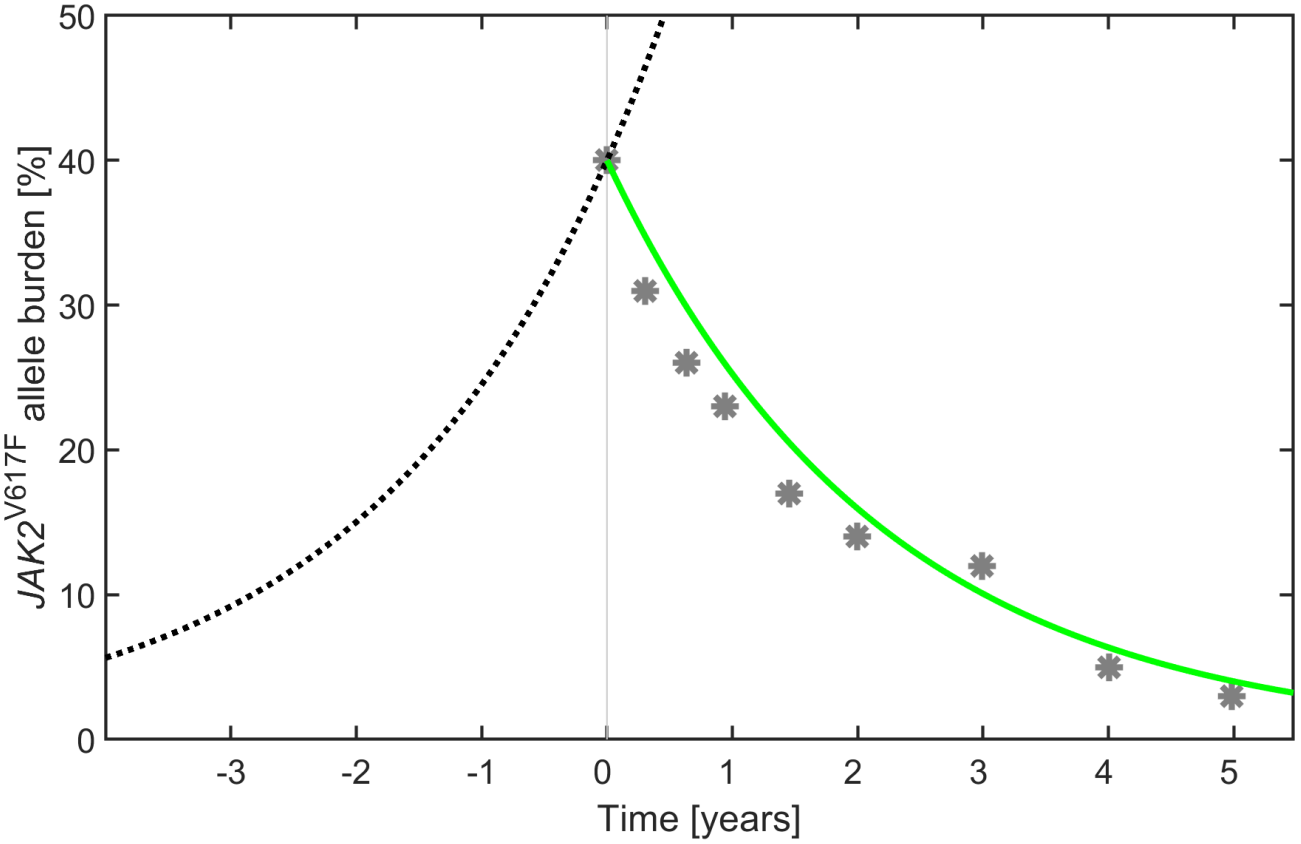
The DALIAH trial, empirical modelling



Patient P016

For details, see chapter 3 or Pedersen et al (2020)

The DALIAH trial, empirical modelling



Patient P016

For details, see chapter 3 or Pedersen et al (2020)

Comments on empirical approach

- The “what”, not the “why”

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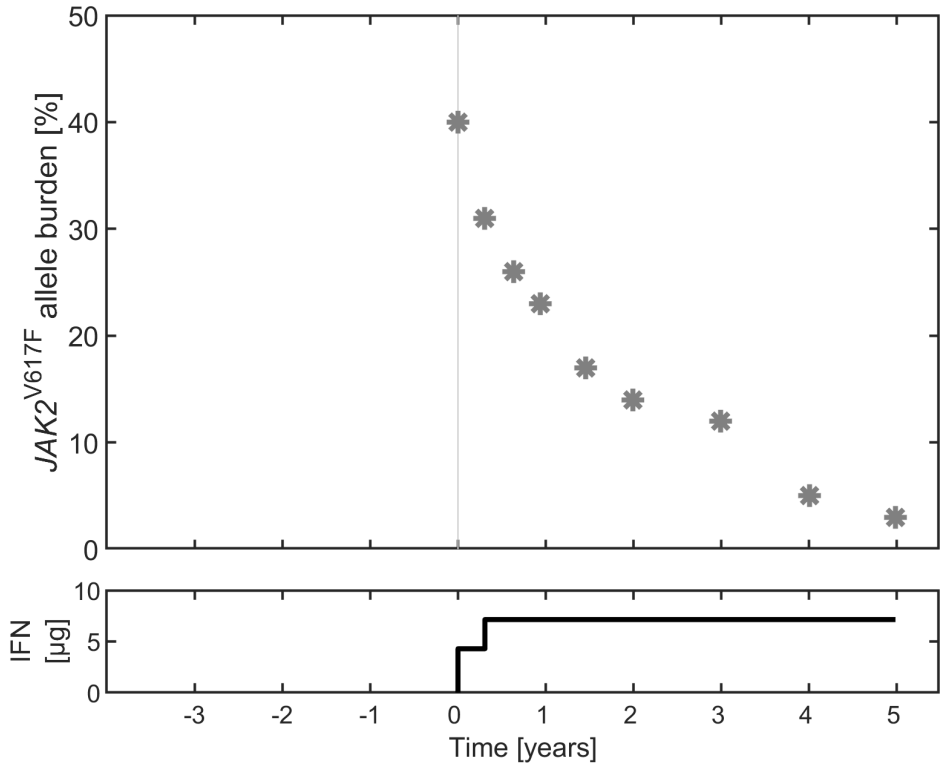
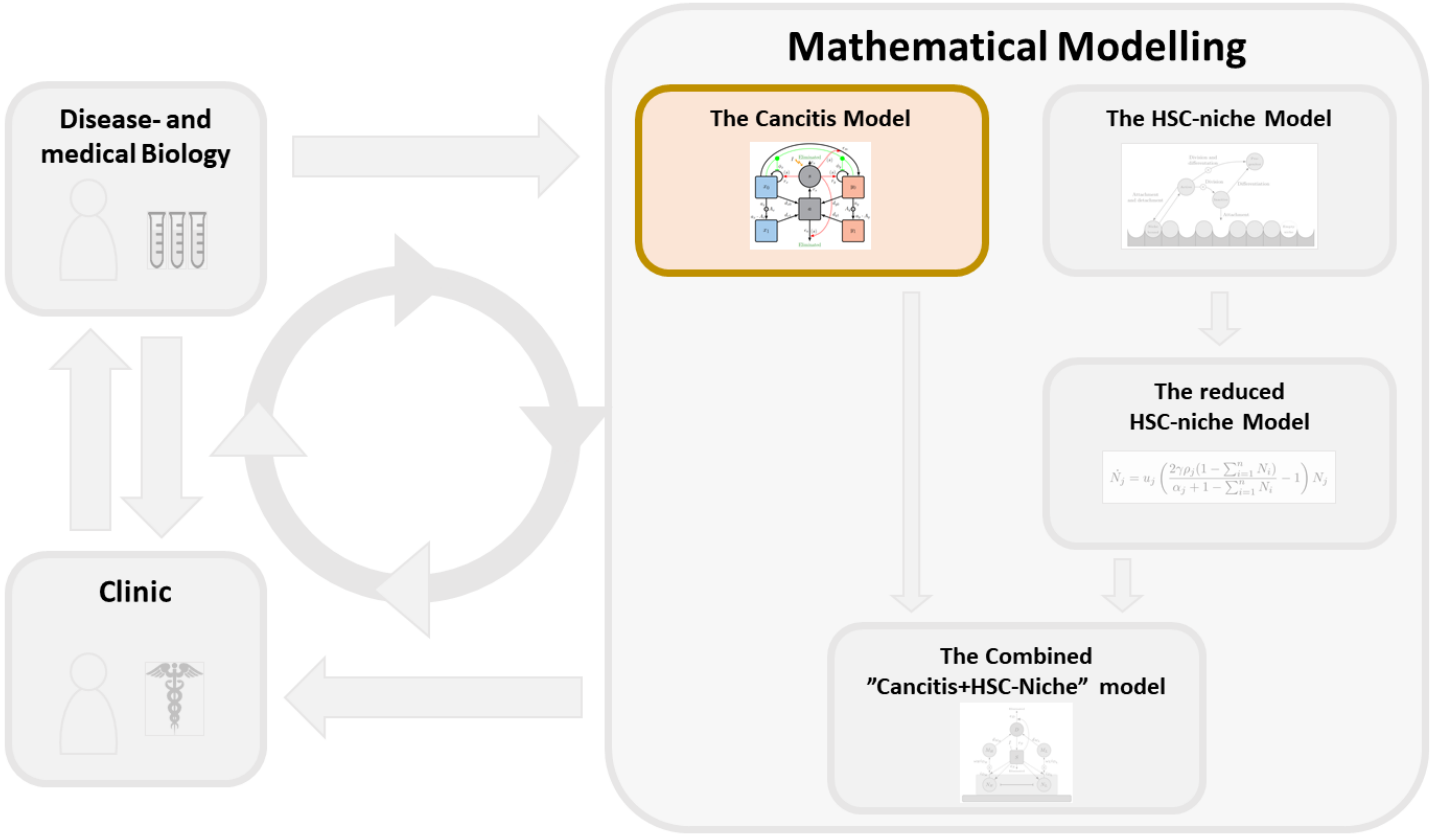
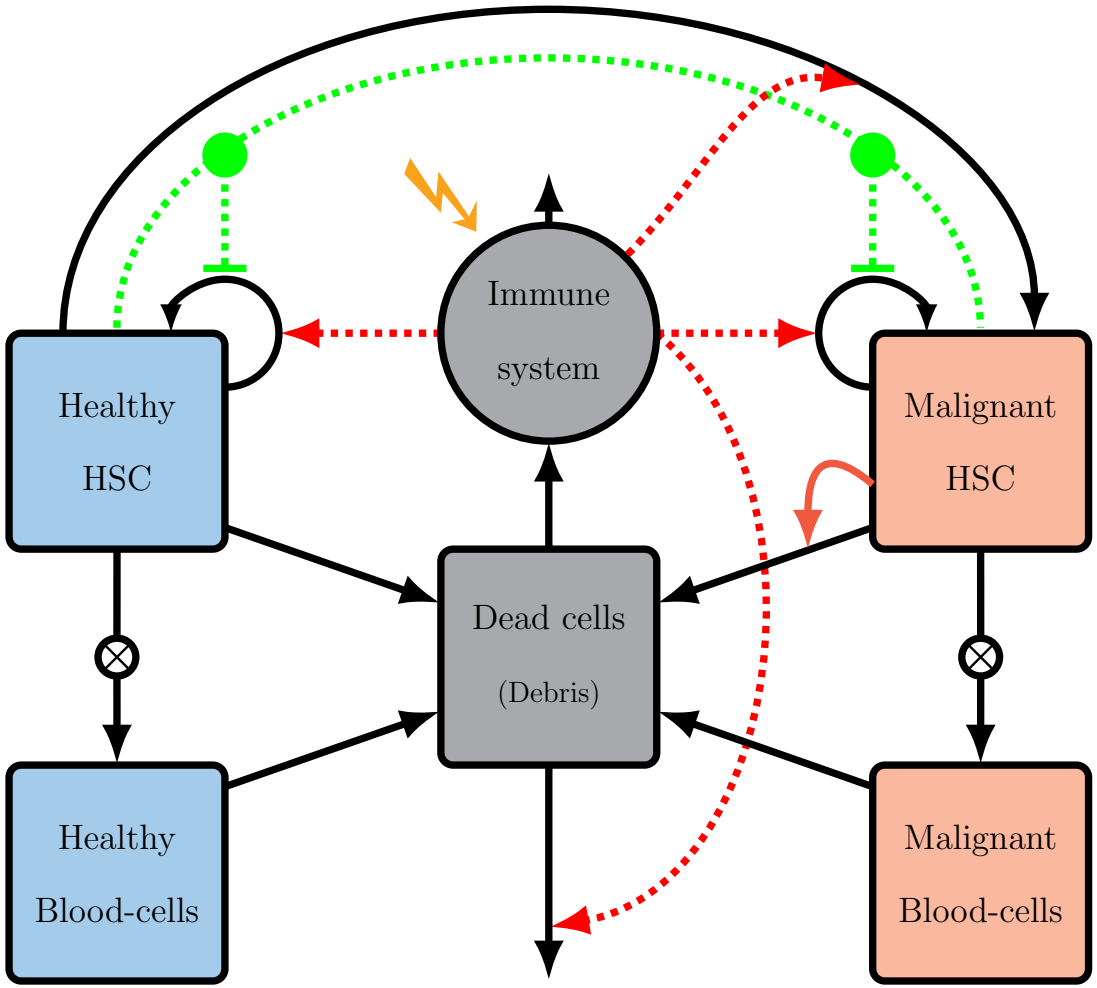


Patient P016

Section 3
The Cancitis model



The Cancitis Model, model description



For details, see chapter 5, figure 5.1 or Andersen et al (2017)

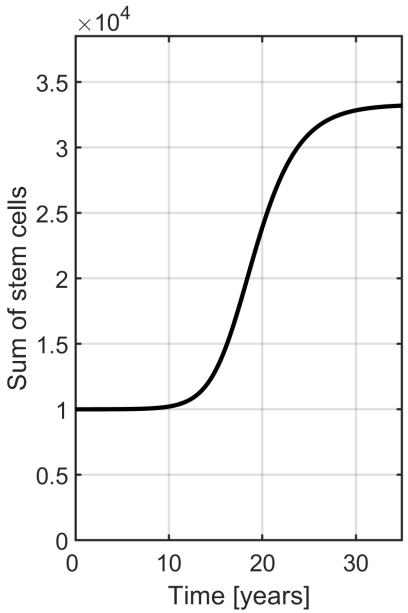
The Cancitis Model, equations and example

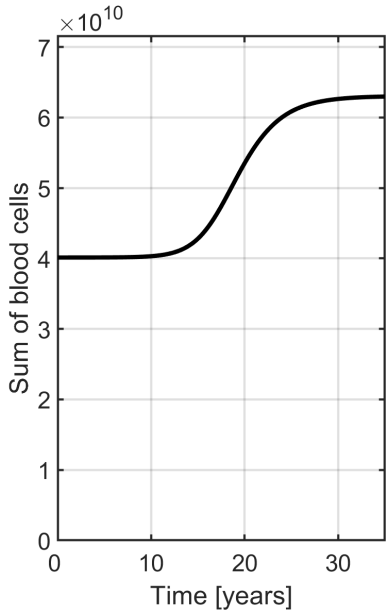
$$\dot{x_0} = \left(r_x \phi_x(x_0, y_0) s - d_{x_0} - a_x\right) x_0 - r_m s x_0$$
$$\dot{y_0} = \left(r_y \phi_y(x_0, y_0) s - \hat{d}_{y_0} - \tilde{d}_{y_0} y_0 - a_y\right) y_0 + r_m s x_0$$
$$\dot{x_1} = a_x A_x x_0 - d_{x_1} x_1$$
$$\dot{y_1} = a_y A_y y_0 - d_{y_1} y_1$$
$$\dot{a} = d_{x_0} x_0 + d_{x_1} x_1 + \left(\hat{d}_{y_0} + \tilde{d}_{y_0} y_0\right) y_0 + d_{y_1} y_1 - e_a a s$$
$$\dot{s} = r_s a - e_s s + I$$

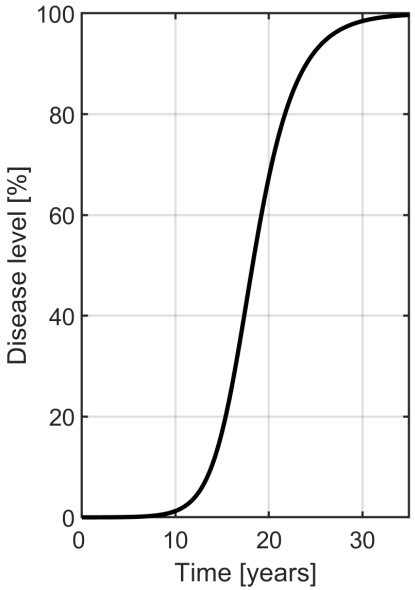
where $\dot{}$ denotes the time-derivative. The functions $\phi_x(x_0, y_0)$ and $\phi_y(x_0, y_0)$ are defined as:

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

The Cancitis Model, equations and example

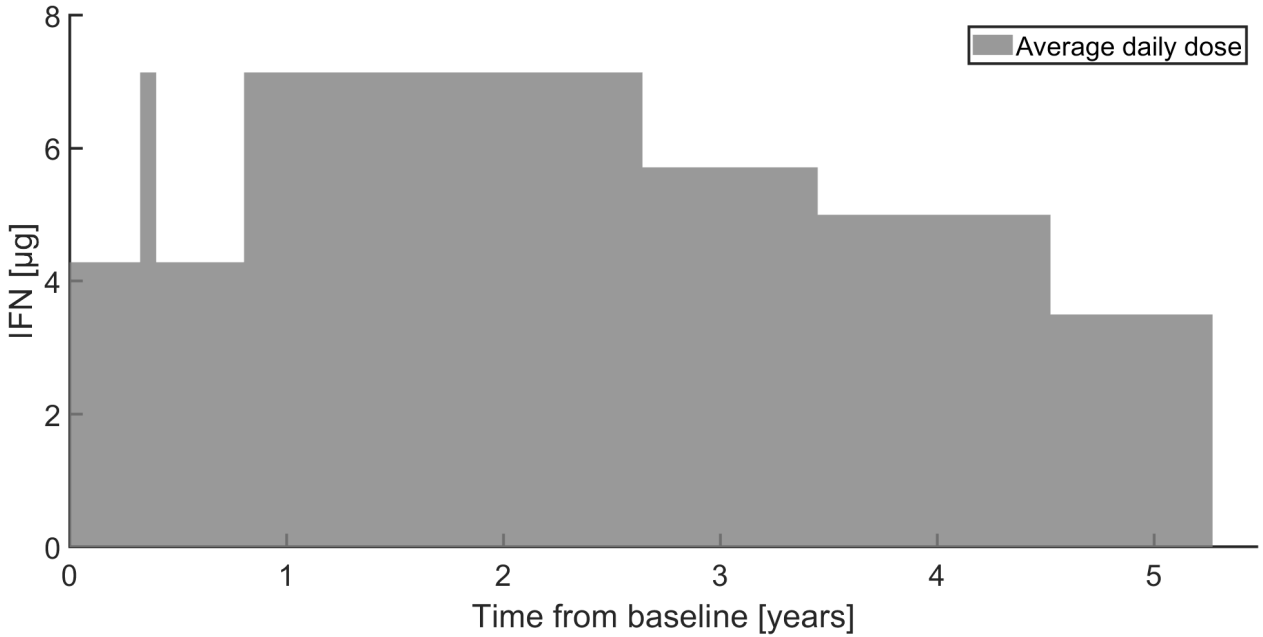






The Cancitis Model, IFN-treatment

What happens when the drug is injected?



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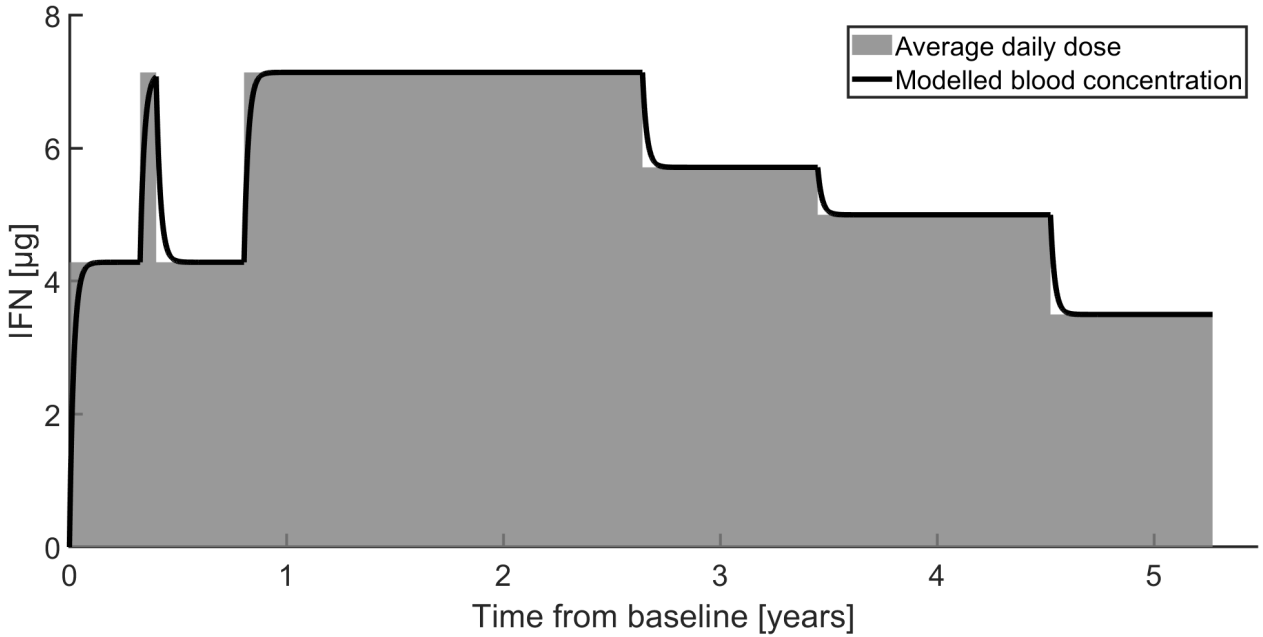

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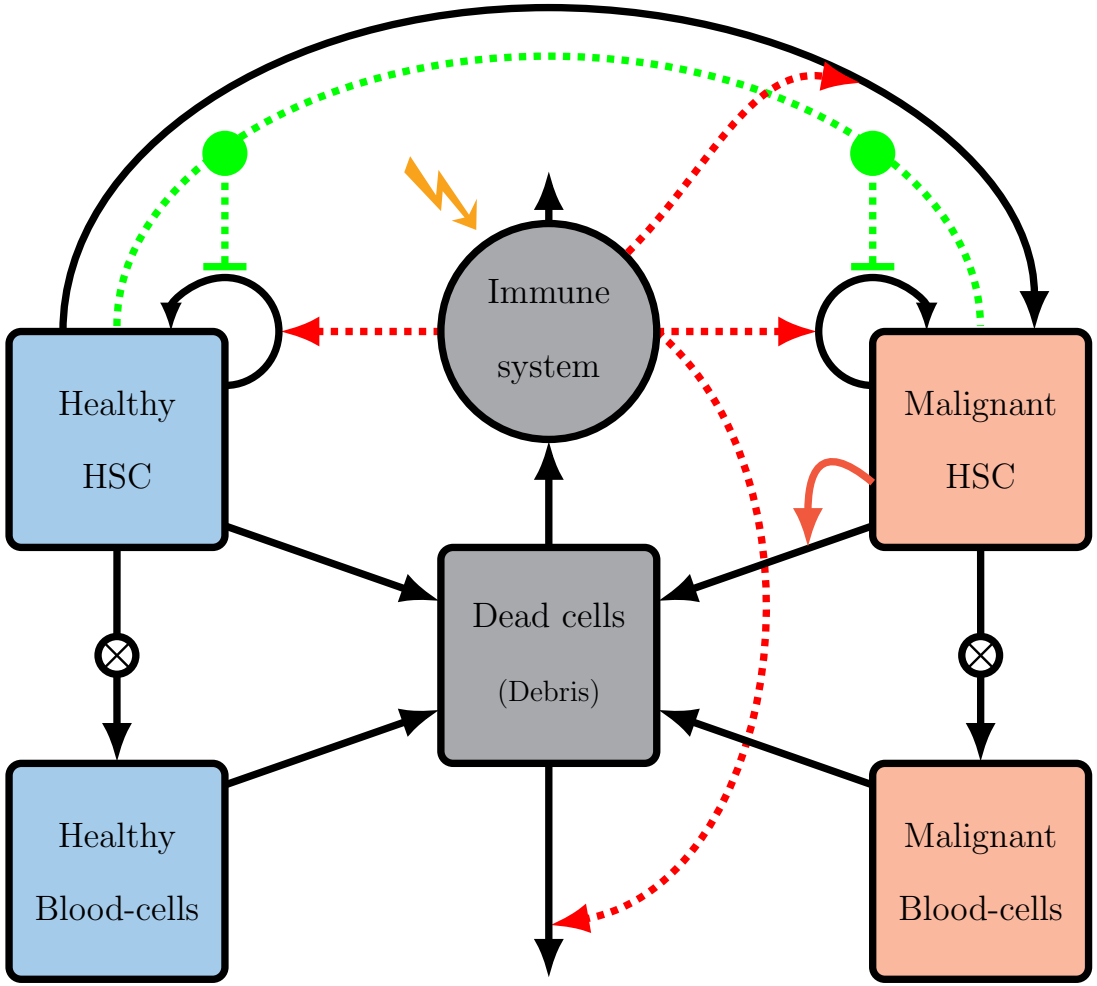

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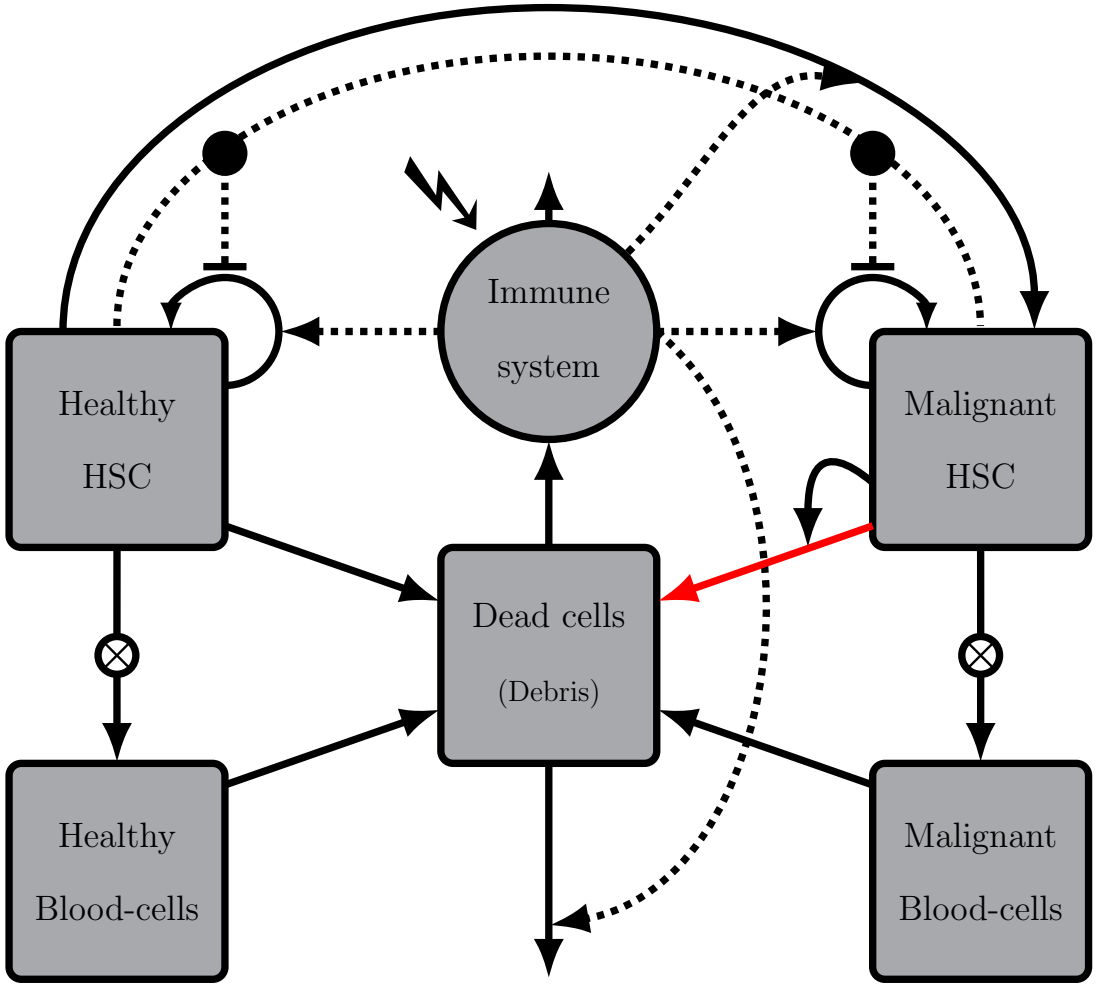

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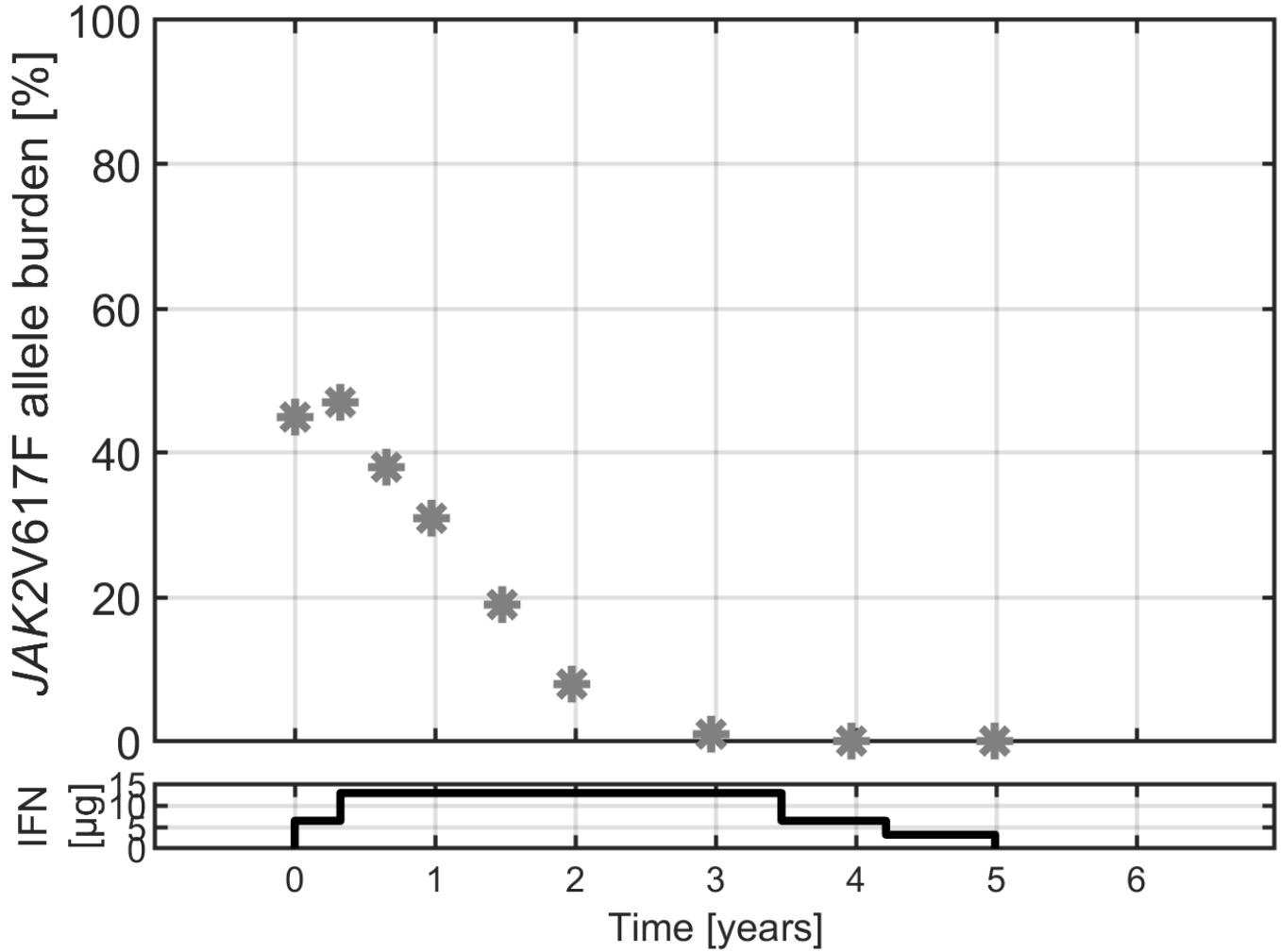
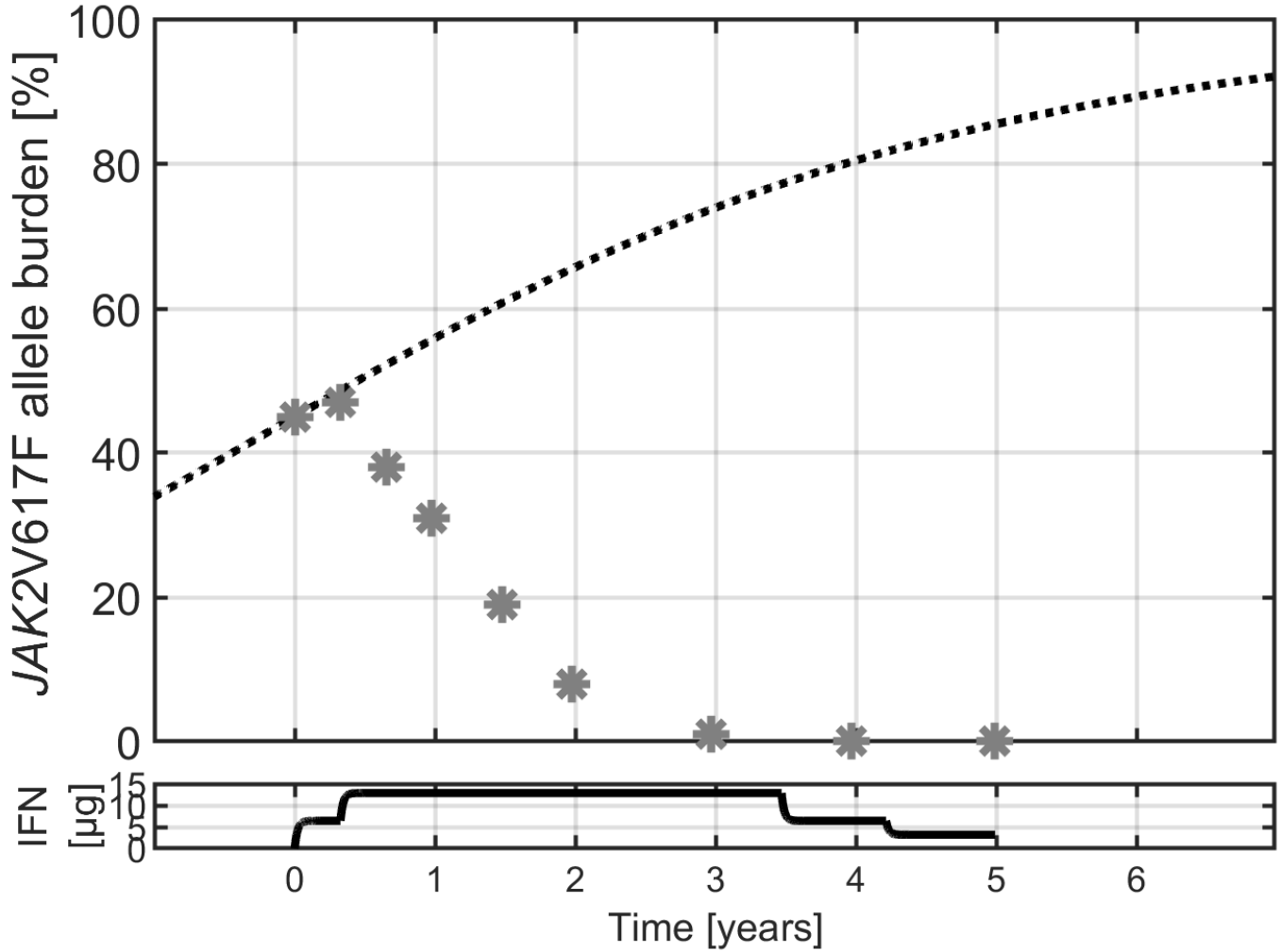


Patient P198

The Cancitis Model, IFN-treatment



Patient P198

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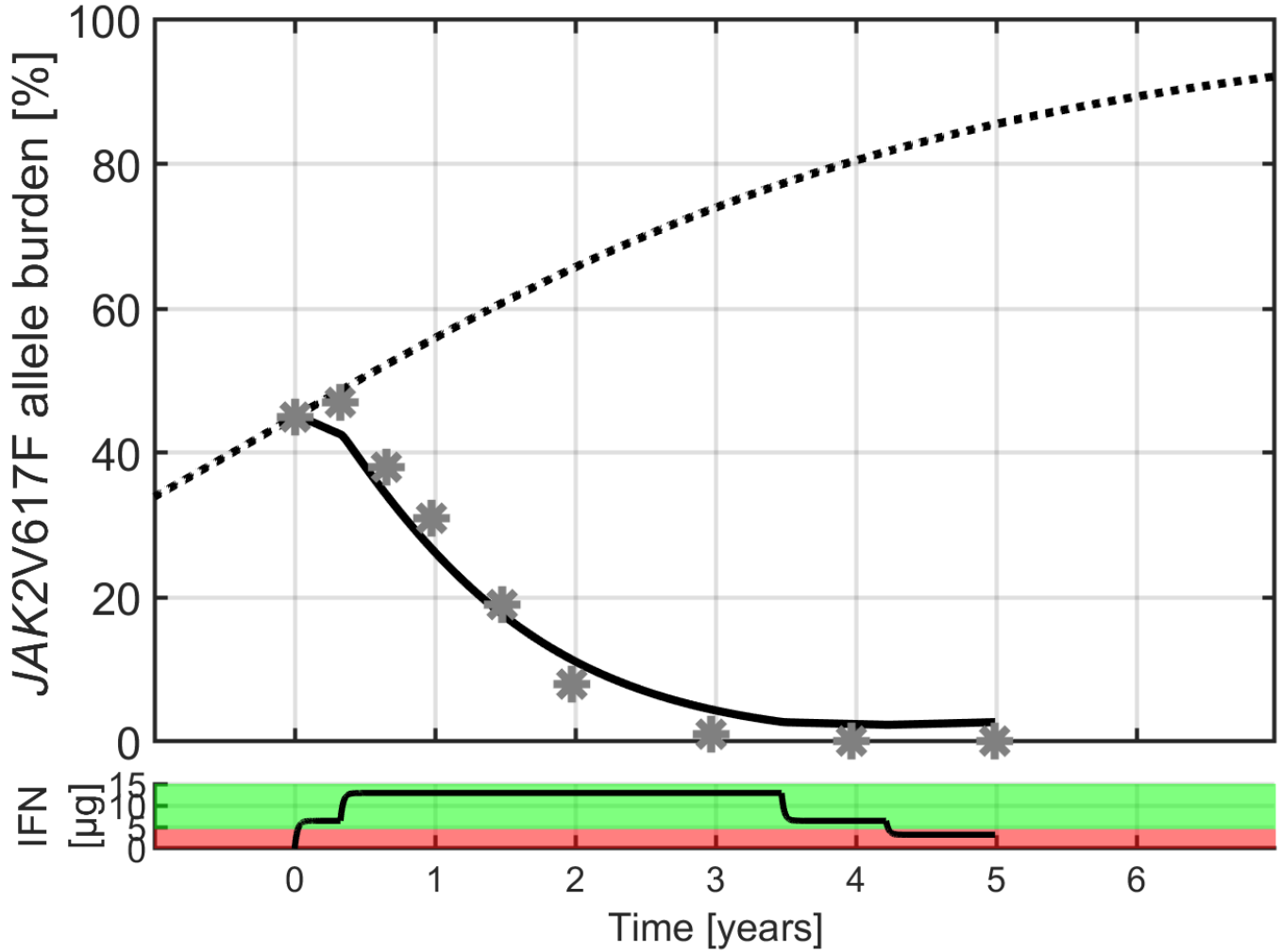

Patient P198

The Cancitis Model, findings so far

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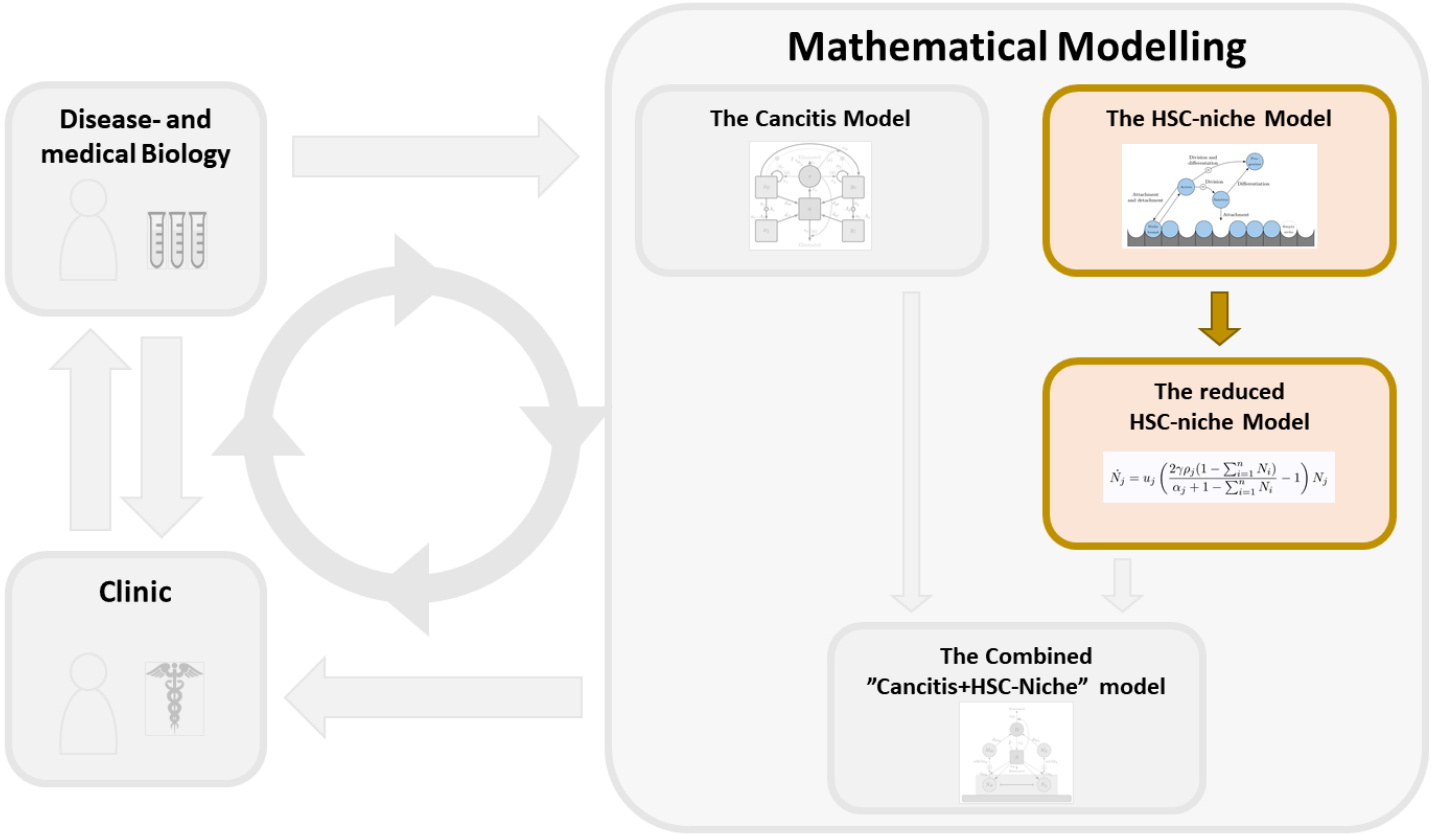
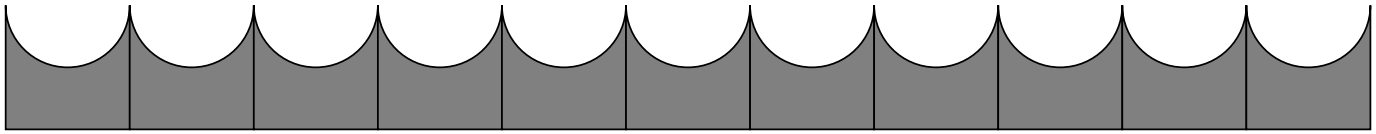
- 80% increased death of malignant stem cells causes steady state stability to change, leading to long-term healthy of the patient.
- For many of the DALIAH patients, this was attained with $5\mu g$ IFN daily ($35\mu g$ weekly)

Section 4
The HSC niche model



The HSC niche Model, description



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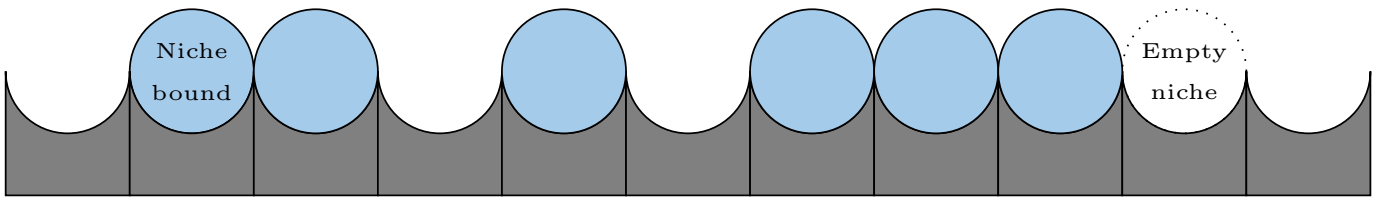

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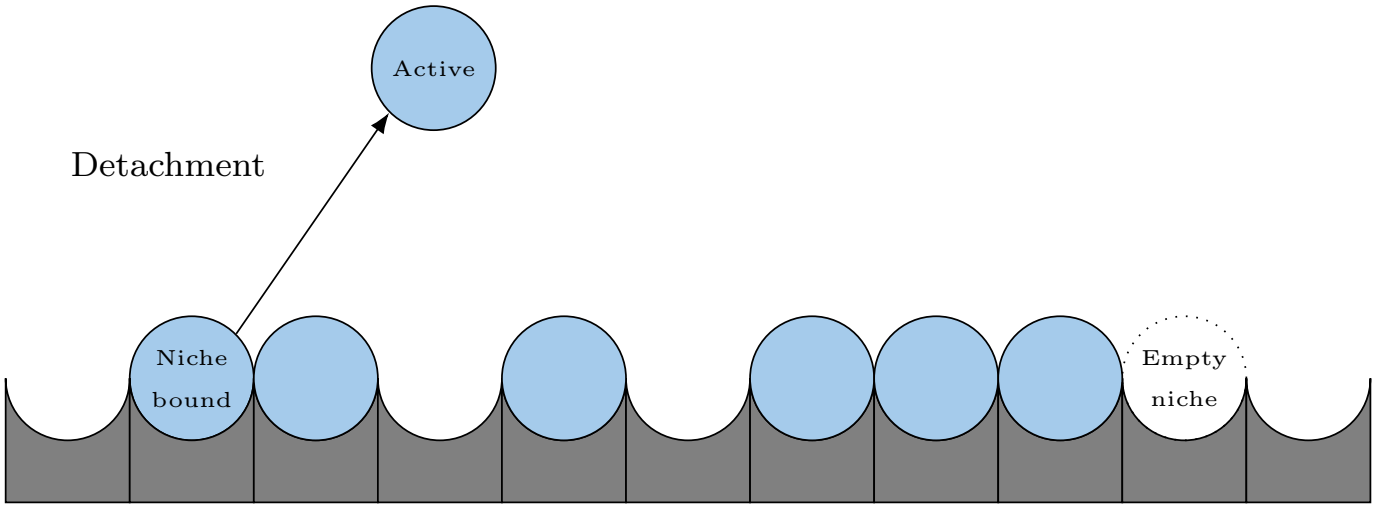

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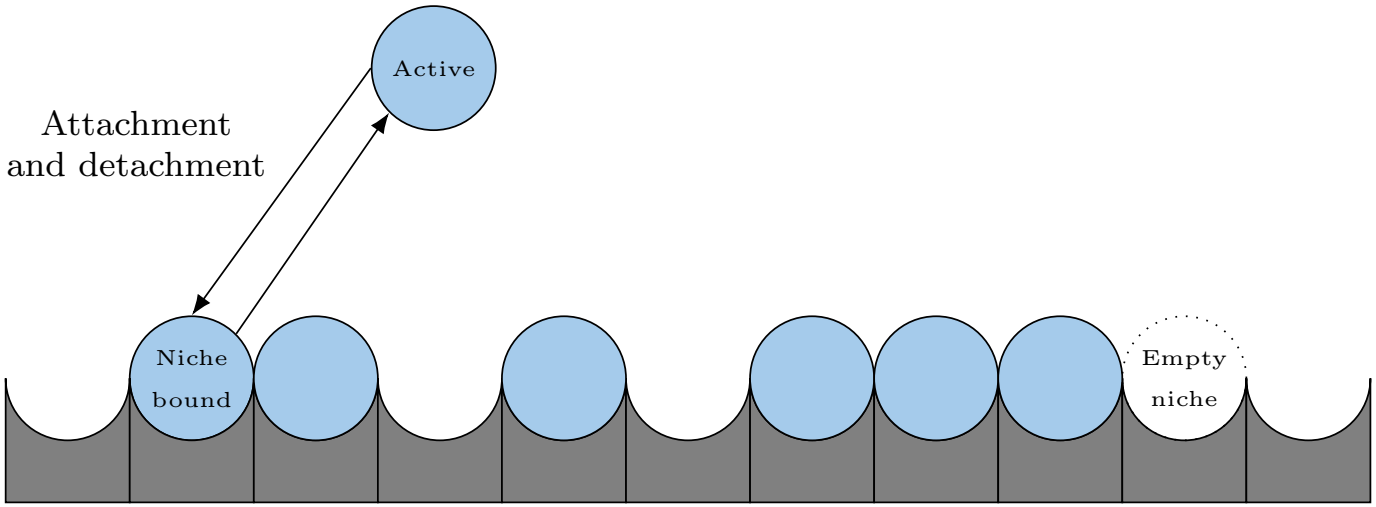

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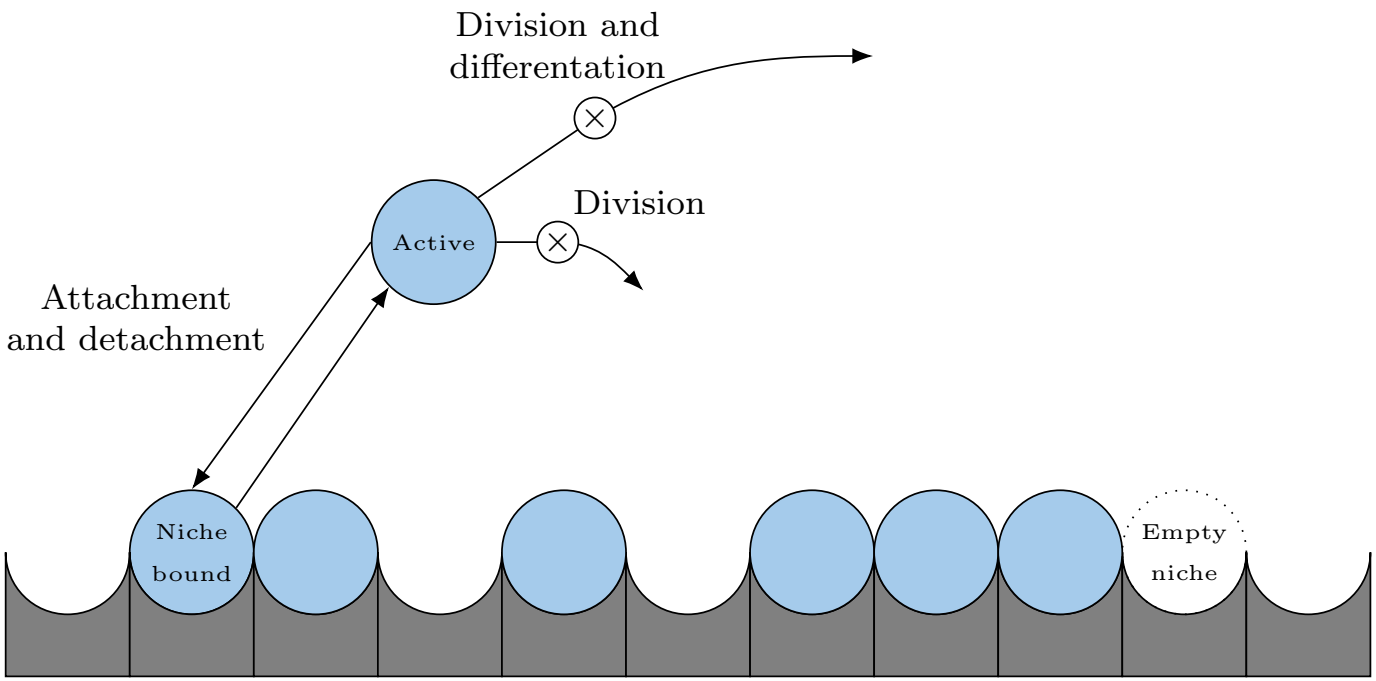

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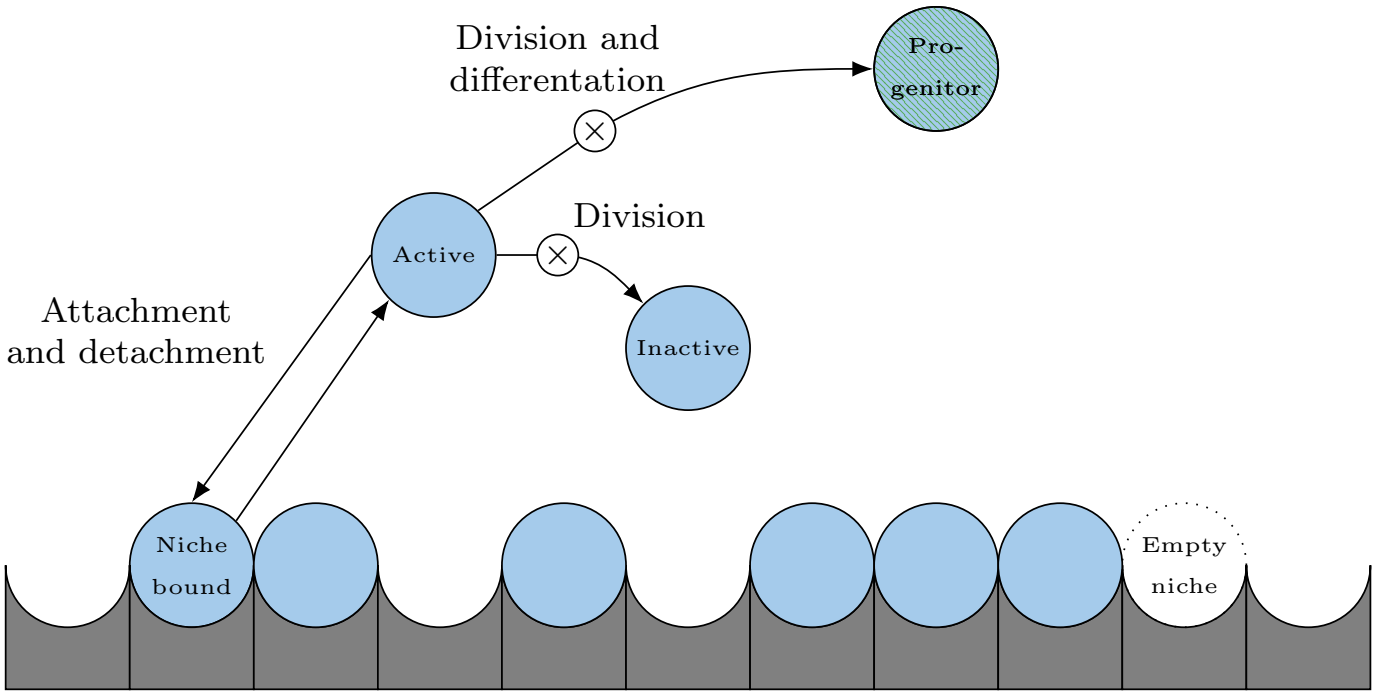

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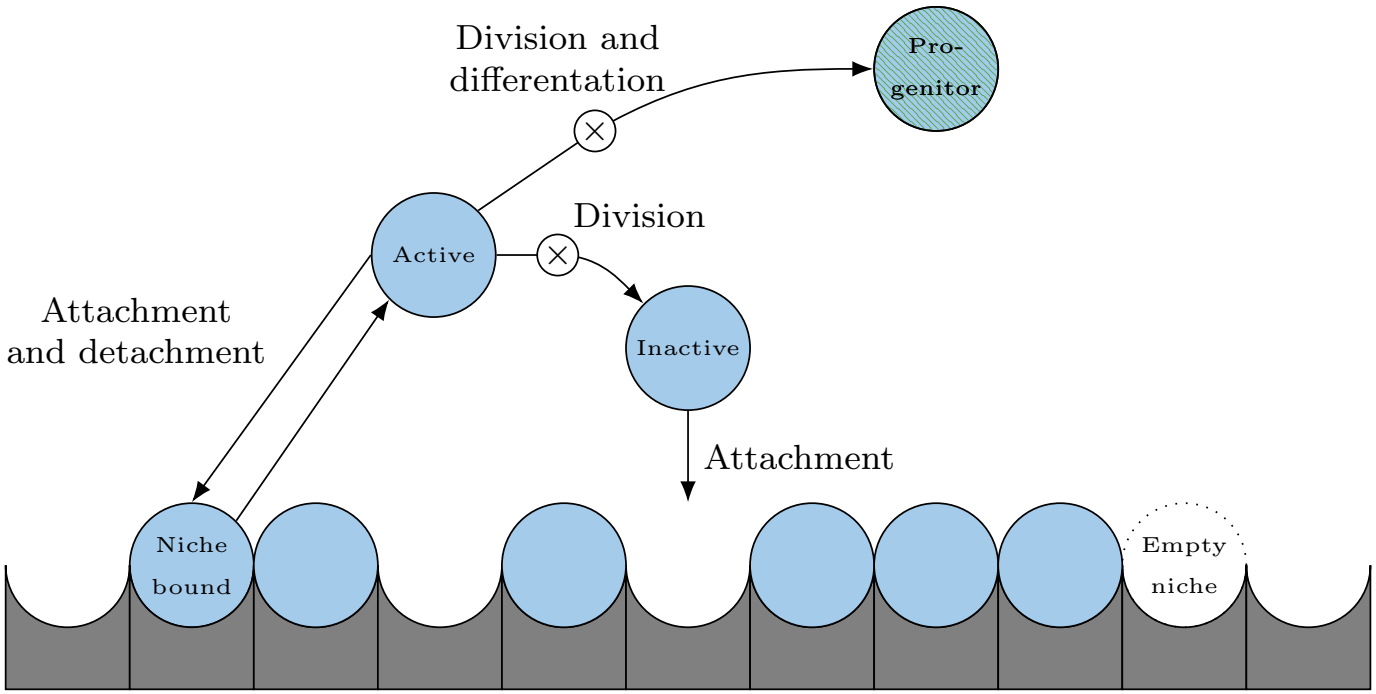

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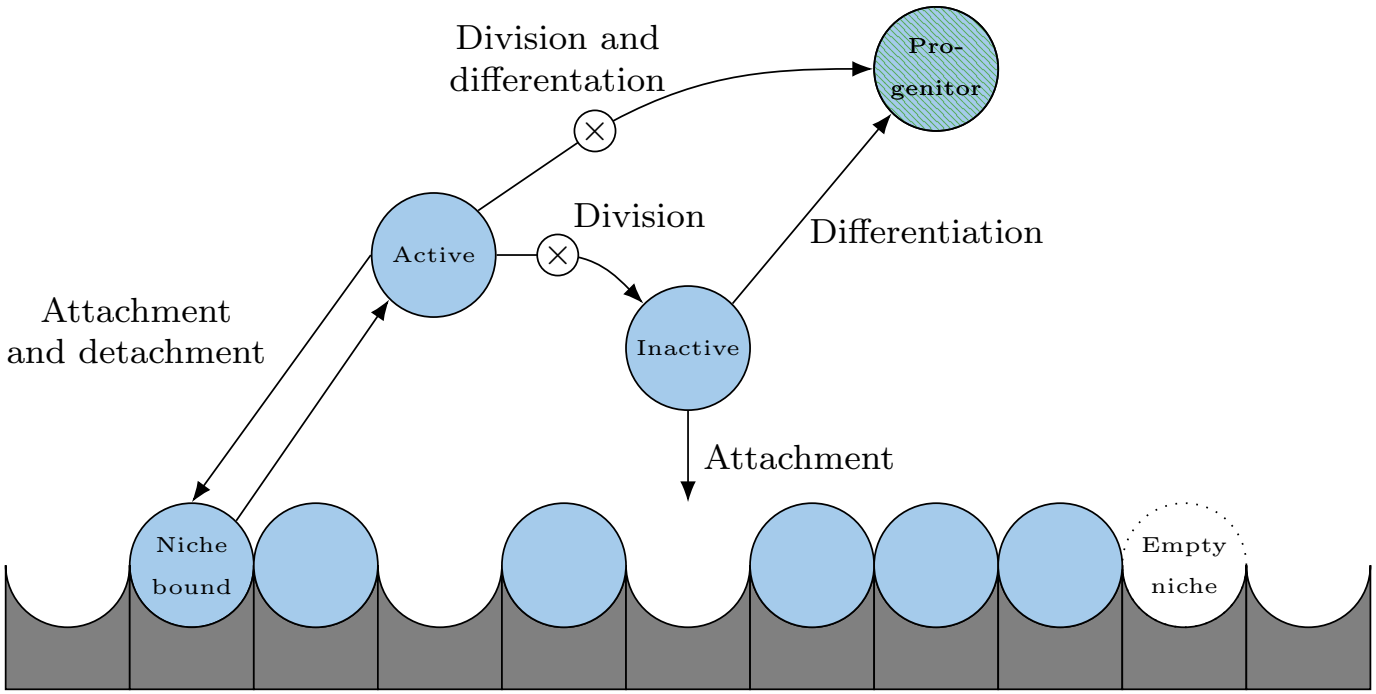

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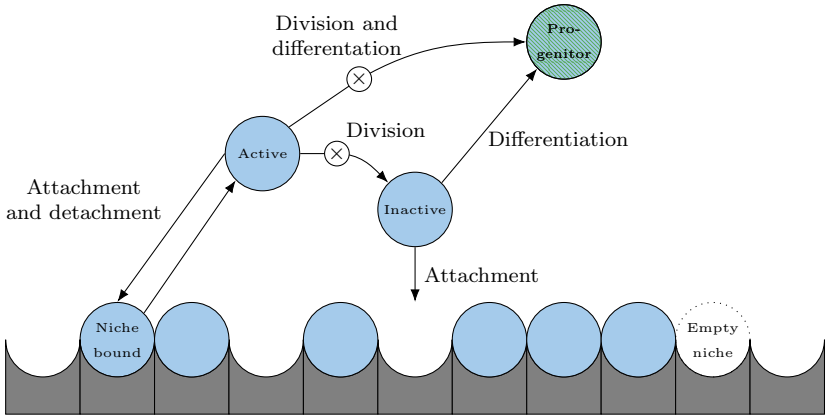

$$\dot{N} = b_I(K - N)I + b_A(K - N)A - uN$$
$$\dot{I} = 2\gamma rA - b_I(K - N)I - d_I I$$
$$\dot{A} = uN - b_A(K - N)A - rA - d_A A$$
$$N_E = K - N$$

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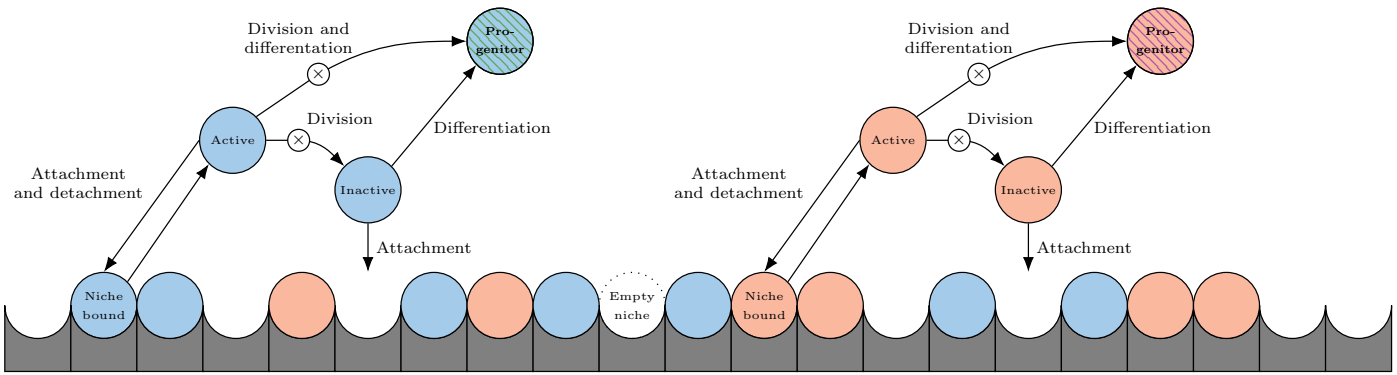


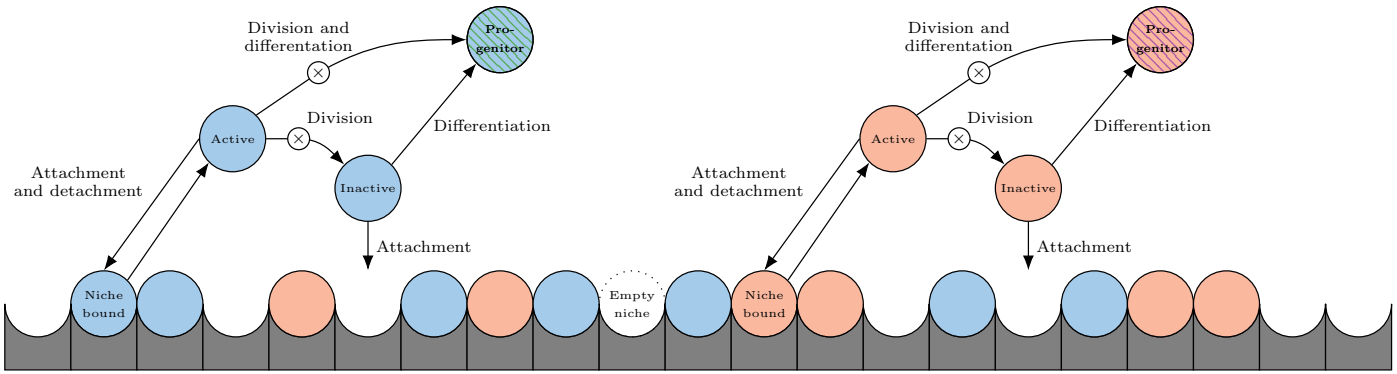
$$\dot{N}_j = b_{I_j}\left(K - \sum_{i=1}^{n} N_i\right) I_j + b_{A_j}\left(K - \sum_{i=1}^{n} N_i\right) A_j - u_j N_j$$

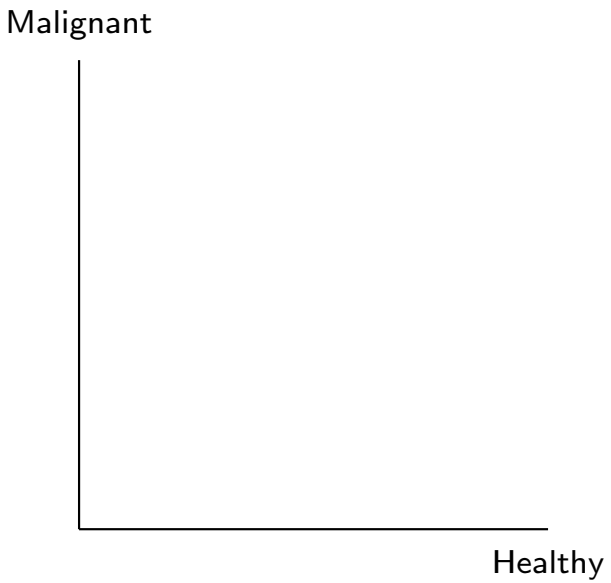
$$\dot{I}_j = 2\gamma r_j A_j - b_{jI}\left(K - \sum_{i=1}^{n} N_i\right) I_j - d_{I_j} I_j$$

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

$$N_E = K - \sum_{i=1}^{n} N_i$$

The HSC niche Model, immediate results





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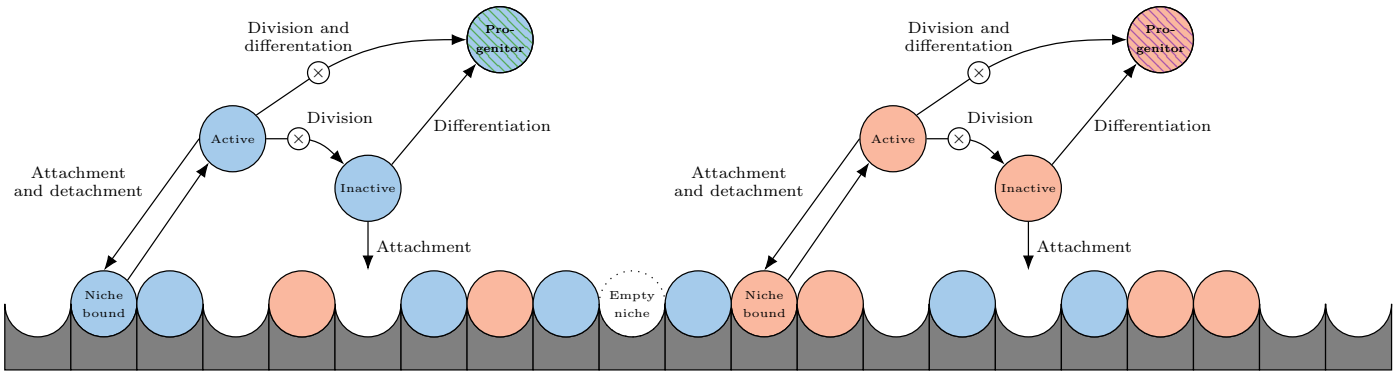
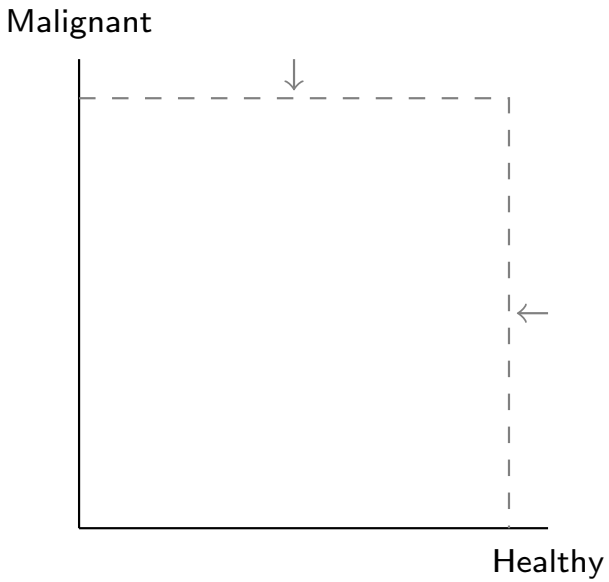


- Attractive trapping region



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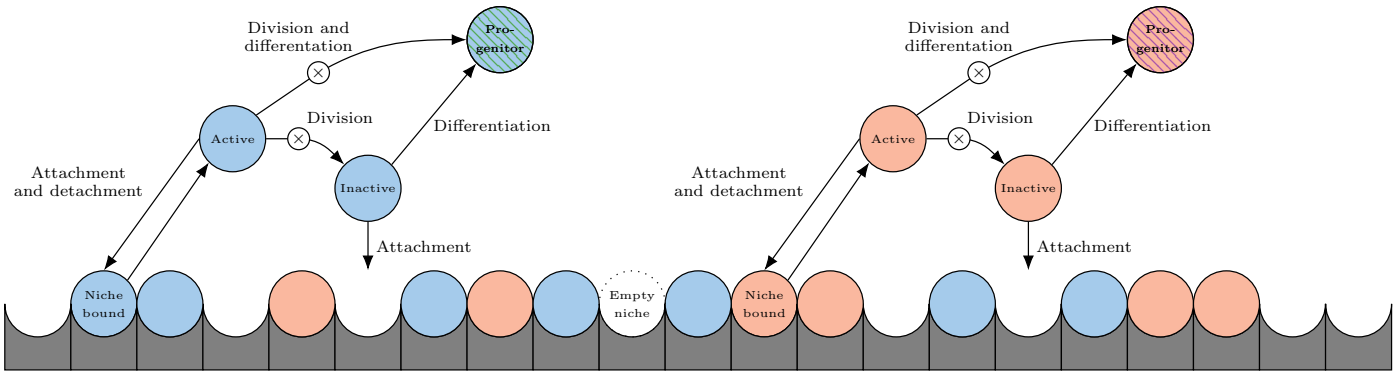
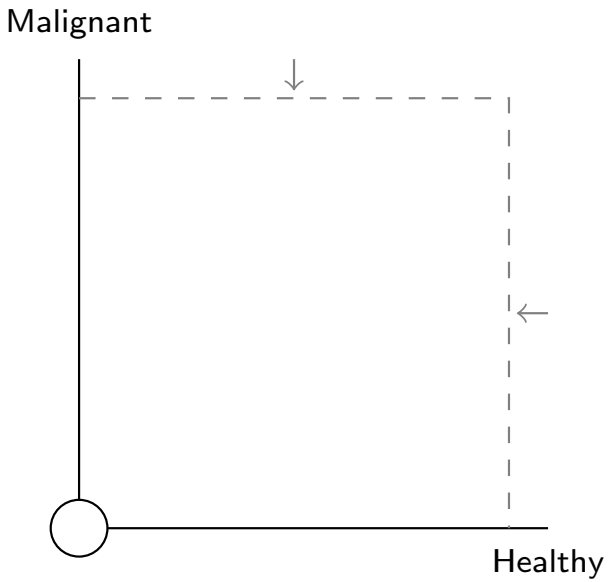


- Attractive trapping region
- Steady states:
  - No cells (Exhaustion)



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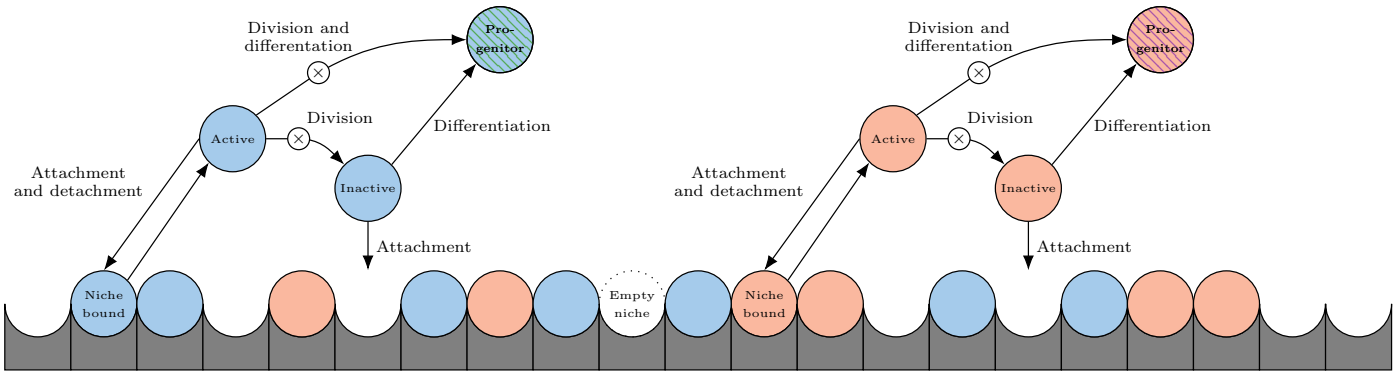

- Attractive trapping region
- Steady states:
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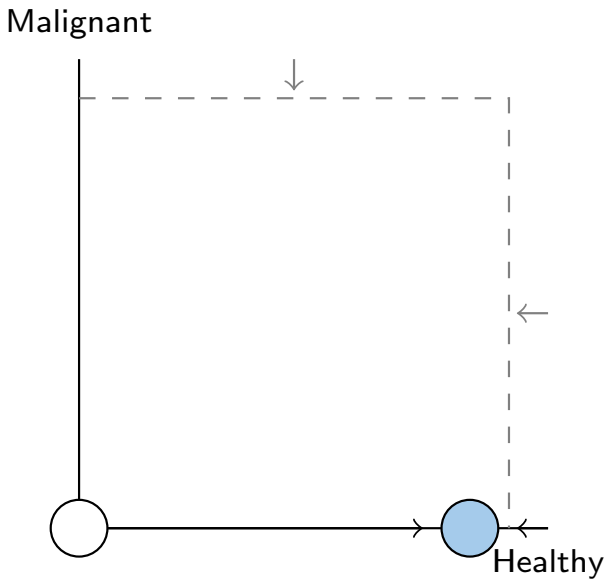
  - Only healthy



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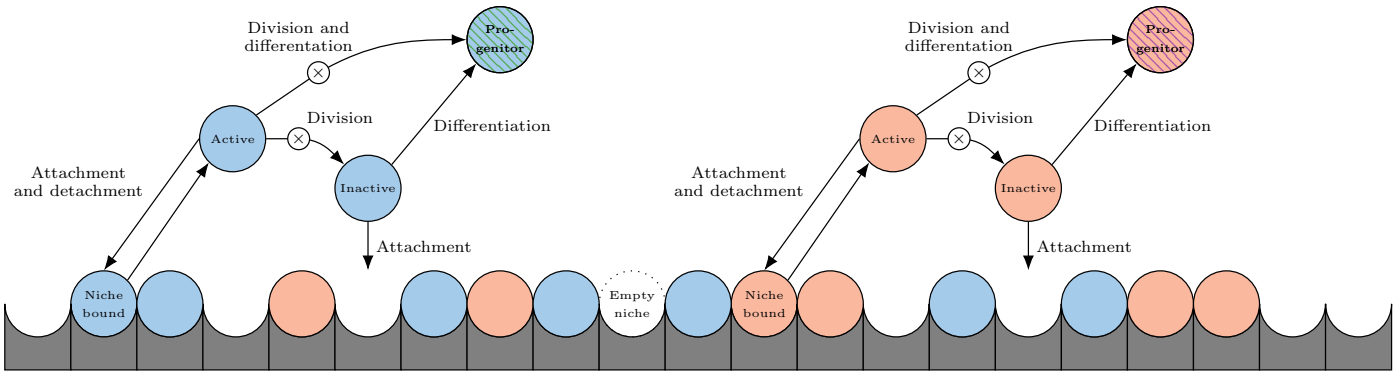

- Attractive trapping region
- Steady states:
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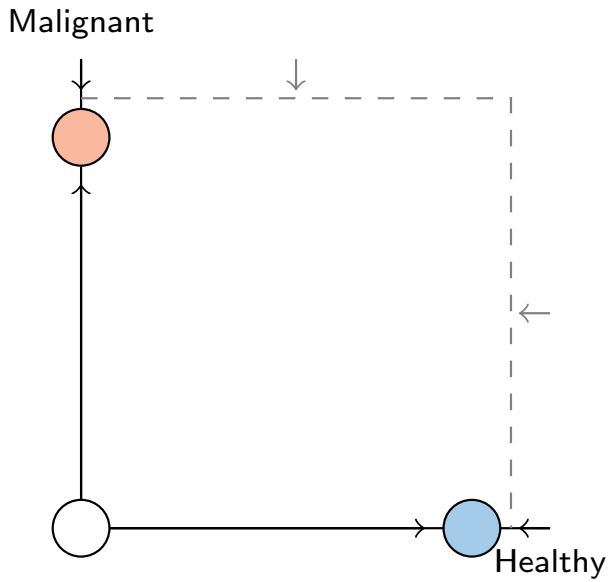
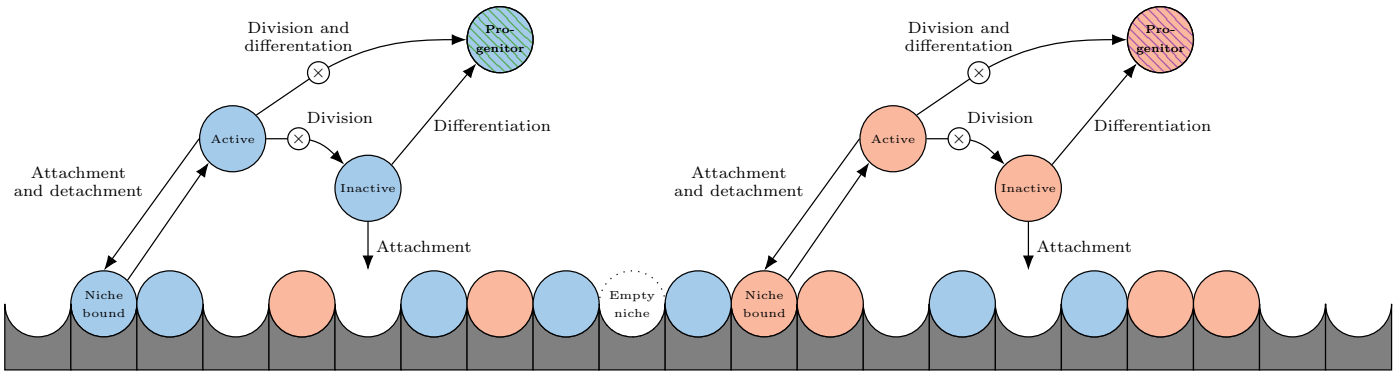
  - Only malignant



The HSC niche Model, immediate results



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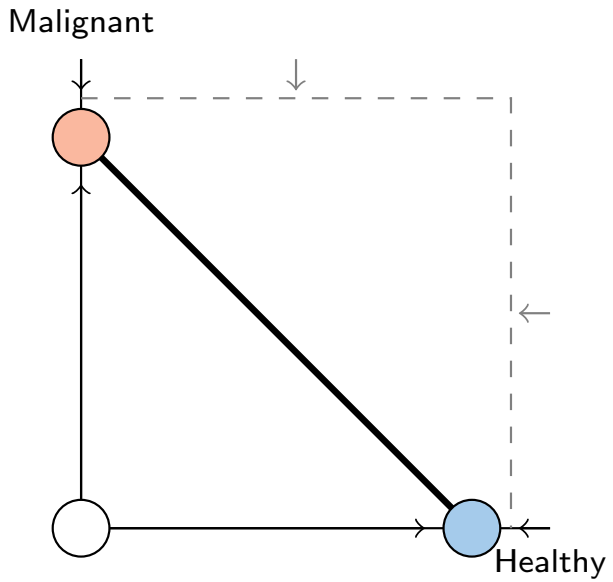

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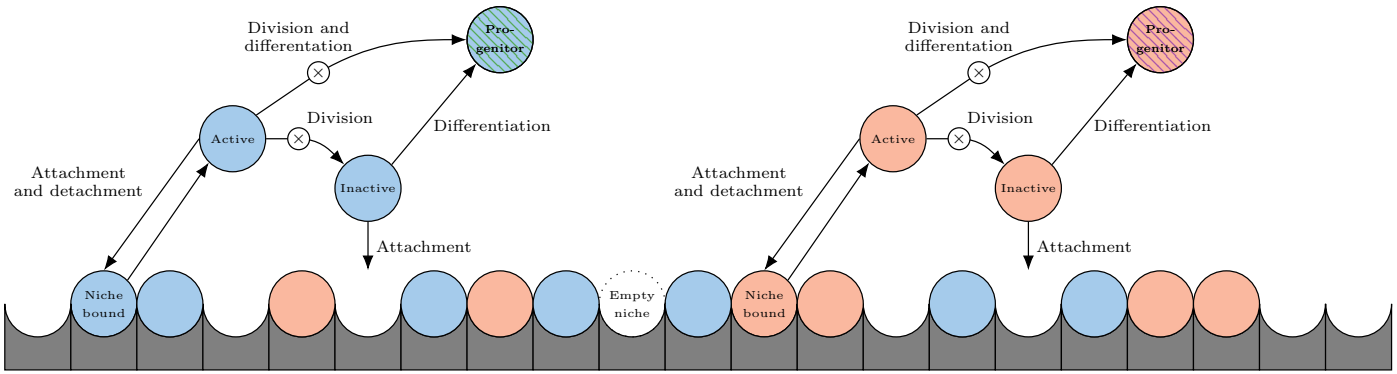

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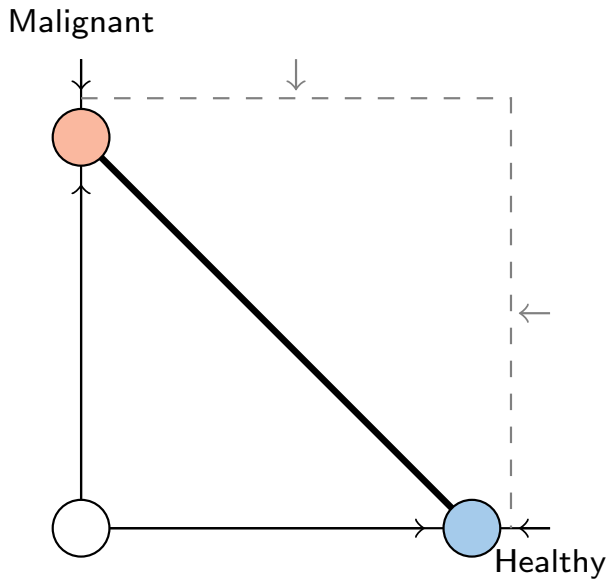
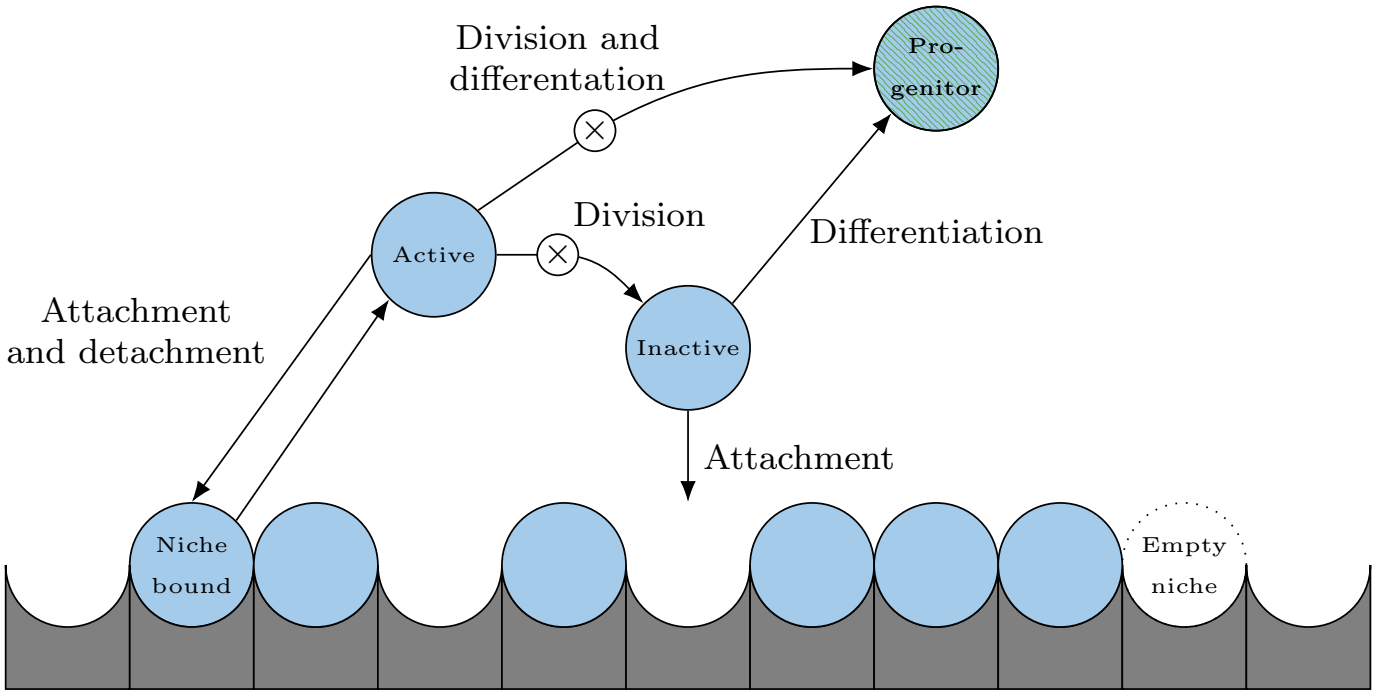
  - Only malignant
  - Co-existence
- HSC fitness:

$$F_j = \frac{b_{I_j}\left((2\gamma - 1)r_j - d_{A_j}\right)}{d_{I_j}(r_j + d_{A_j})}$$



The HSC niche Model, reduction



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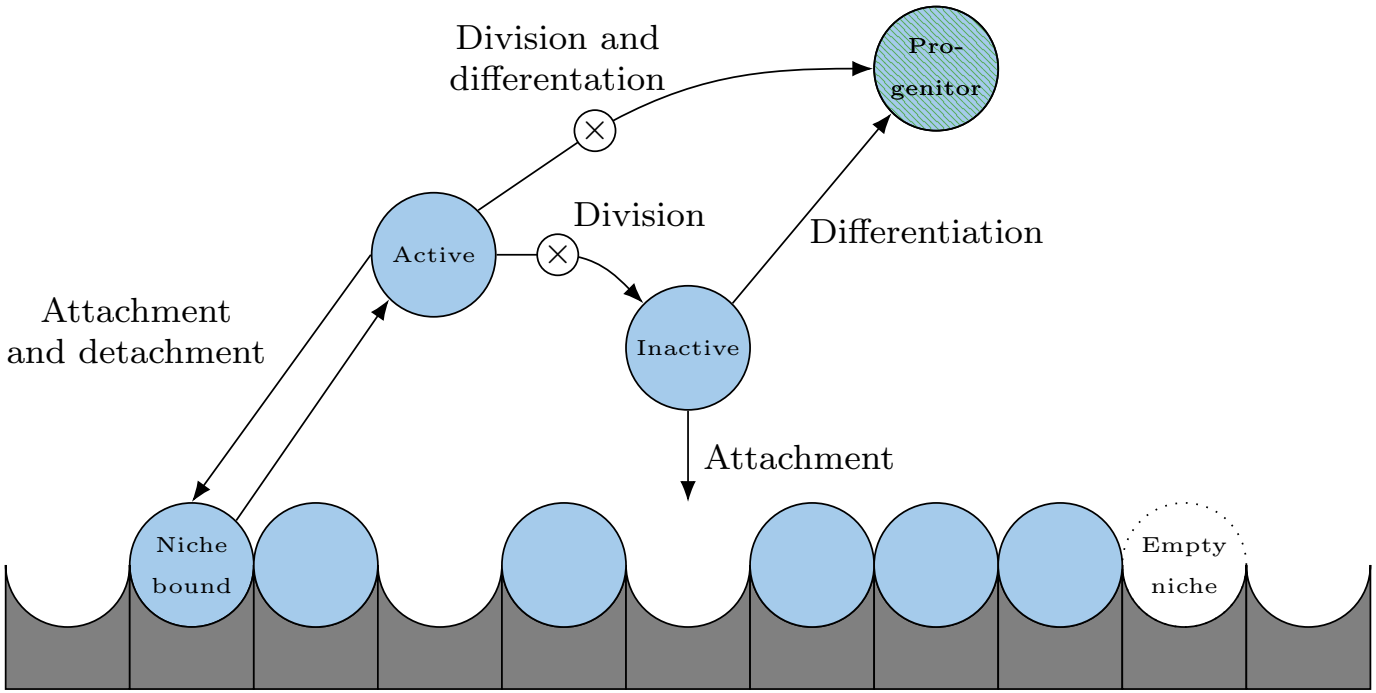

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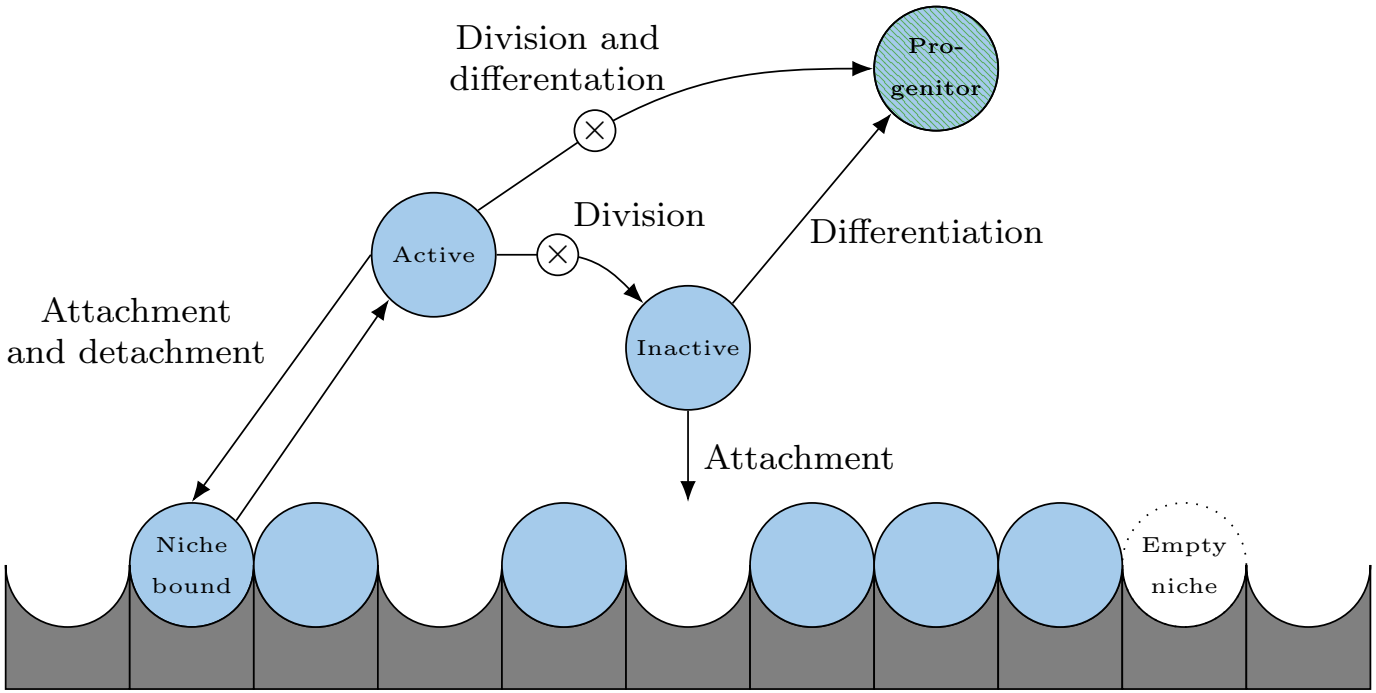
The HSC niche Model, reduction



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

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  where $\rho_j = \frac{r_j}{r_j + d_{A_j}}$ and $\alpha_j = \frac{d_{I_j}}{b_{I_j} K}$.
- Only minor changes to dynamics.
- *Importantly, concept of HSC fitness still exists:*

$$f_j = \frac{2\gamma\rho_j - 1}{\alpha_j}$$

The HSC niche Model, (even more) reduction

If there are only two types of HSC, and they are very similar ($f_1 \approx f_2$), we can reduce further.

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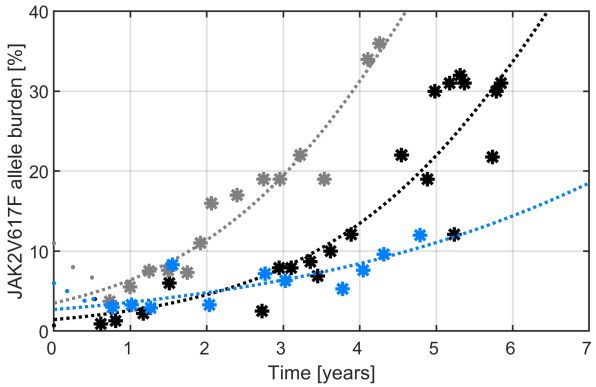
$$\dot{C} = \phi(1 - C)C \tag{1}$$

where $\phi = g_2(T_1^*) = u_2 \frac{\alpha_2}{\alpha_2 + f_1^{-1}} \left(\frac{f_2}{f_1} - 1 \right)$.

The HSC niche Model, (even more) reduction

$$\dot{C} = \phi(1 - C)C \tag{1}$$



(a)

$\phi > 0$

$f_1 < f_2$

The HSC niche Model, (even more) reduction

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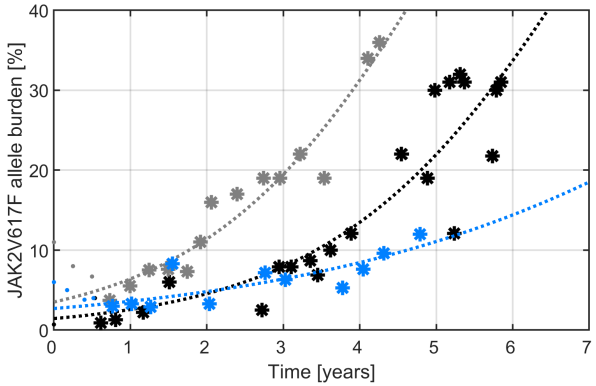

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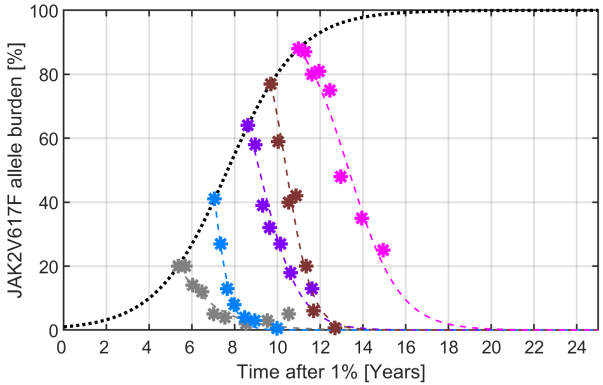

(b)

$\phi < 0$

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The HSC niche model, summing it up

- A detailed description of an experimentally inaccessible system

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The HSC niche model, summing it up

- A detailed description of an experimentally inaccessible system
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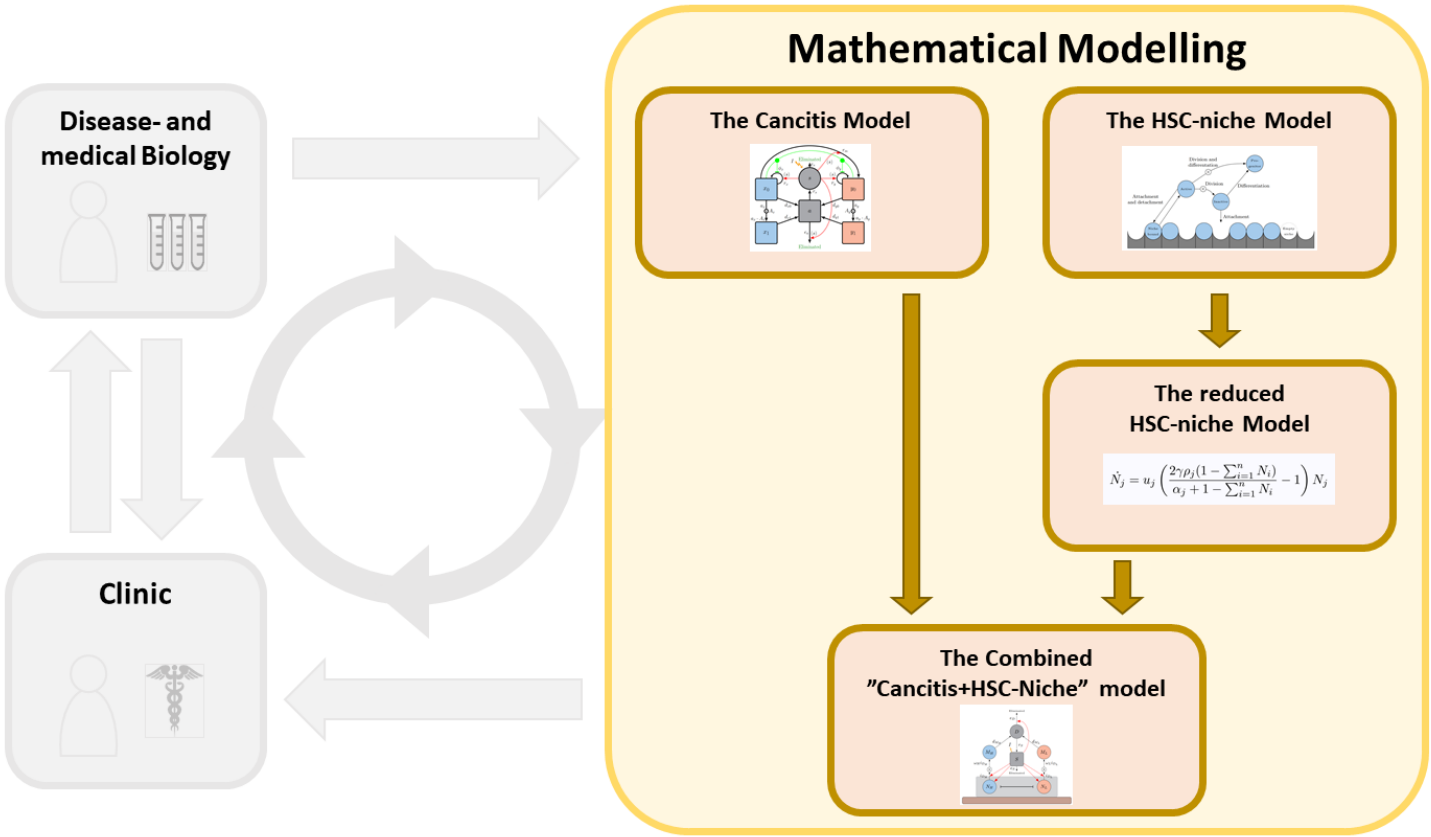
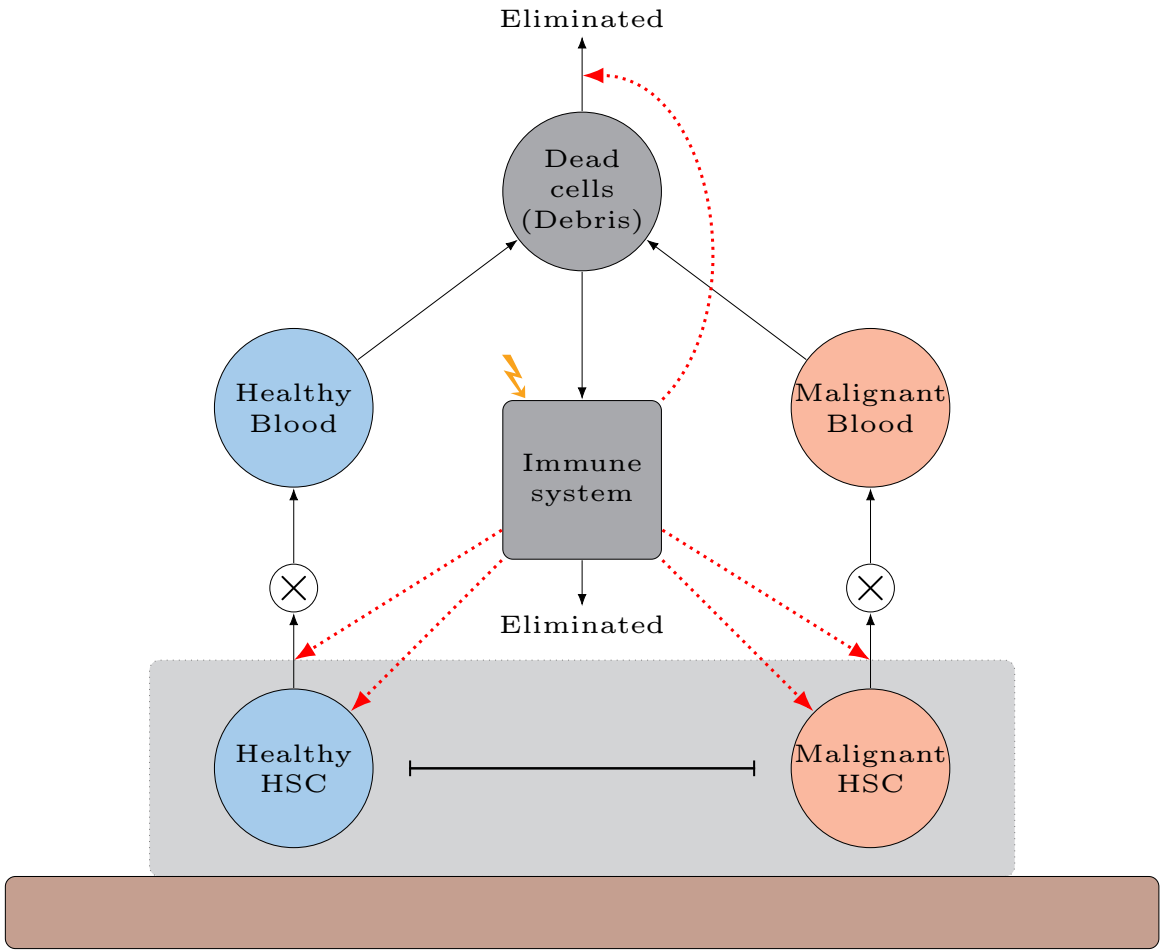
  Similar to the empirical modelling of the DALIAH trial data!
- Possible explanation for *why* data looks the way it does

Section 5
The combined model



The combined Cancitis-niche Model



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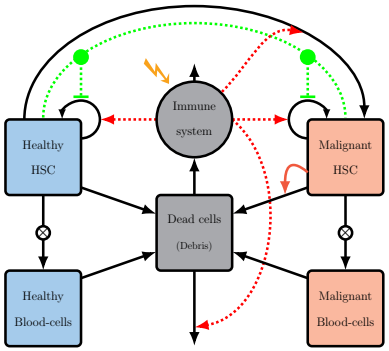
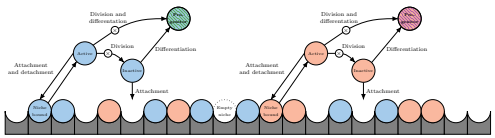


$$\dot{x_0} = (r_x \phi_x(x_0, y_0) s - d_{x_0} - a_x)\, x_0 - r_m s x_0$$
$$\dot{y_0} = \left(r_y \phi_y(x_0, y_0) s - \hat{d}_{y_0} - \tilde{d}_{y_0} y_0 - a_y\right) y_0 + r_m s x_0$$
$$\dot{x_1} = a_x A_x x_0 - d_{x_1} x_1$$
$$\dot{y_1} = a_y A_y y_0 - d_{y_1} y_1$$
$$\dot{a} = d_{x_0} x_0 + d_{x_1} x_1 + \left(\hat{d}_{y_0} + \tilde{d}_{y_0} y_0\right) y_0 + d_{y_1} y_1 - e_a a s$$
$$\dot{s} = r_s a - e_s s + I$$



$$\dot{N}_H = u_H \left(\frac{2\gamma\rho_H(1 - N_H - N_L}{\alpha_H + 1 - N_H - N_L} - 1\right) N_H$$
$$\dot{N}_L = u_L \left(\frac{2\gamma\rho_L(1 - N_H - N_L)}{\alpha_L + 1 - N_H - N_L} - 1\right) N_L$$

The combined Cancitis-niche Model

$$\dot{N}_H = u_H S \left(\frac{2\gamma\rho_H (1 - N_H - N_L)}{\alpha_H + 1 - N_H - N_L} - 1 \right) N_H$$

$$\dot{N}_L = u_L S \left(\frac{2\gamma\rho_L (1 - N_H - N_L)}{\alpha_L + 1 - N_H - N_L} - 1 \right) N_L$$

$$\dot{M}_H = \omega_H i_{D_H} S - d_{M_H} M_H$$

$$\dot{M}_L = \omega_L i_{D_L} S - d_{M_L} M_L$$

$$\dot{D} = d_{M_H} M_H + d_{M_L} M_L - e_D D S$$

$$\dot{S} = r_S D - e_S S + I$$

Purple: Cancitis model, green: HSC-Niche model

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$$\dot{M}_H = \omega_H i_{D_H} S - d_{M_H} M_H$$
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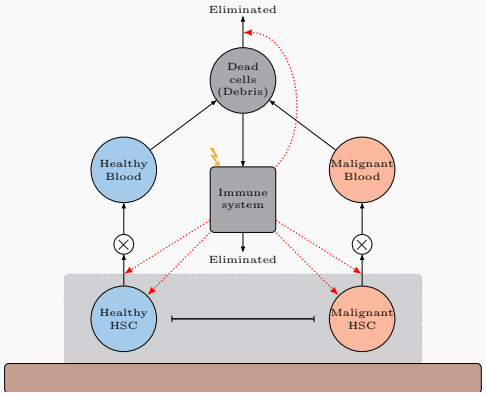
$$\dot{D} = d_{M_H} M_H + d_{M_L} M_L - e_D D S$$
$$\dot{S} = r_S D - e_S S + I$$

where $i_{D_j} = \left(2 - 2\rho_j + \frac{2\gamma\alpha_j\rho_j}{\alpha_j + 1 - N_H - N_L} \right) u_j K N_j$. All parameters are non-negative. In addition, $\rho_j \leq 1$ and $\gamma \geq 1$.

The combined model, brief comments



- Feedback from blood to the HSC system: Increases HSC activation

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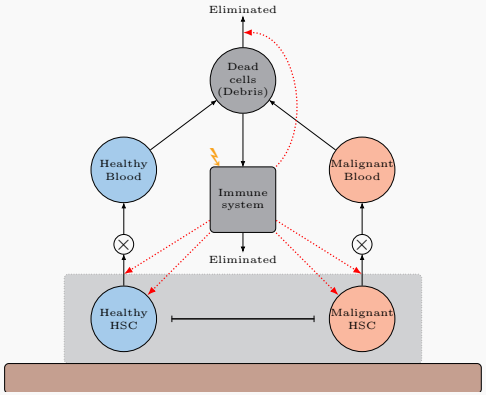
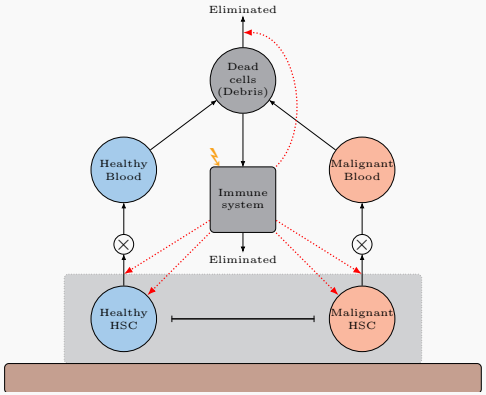


- Feedback from blood to the HSC system: Increases HSC activation
- A refined description of HSC behaviour

The combined model, brief comments



- Feedback from blood to the HSC system: Increases HSC activation
- A refined description of HSC behaviour
- Same steady states as HSC niche model

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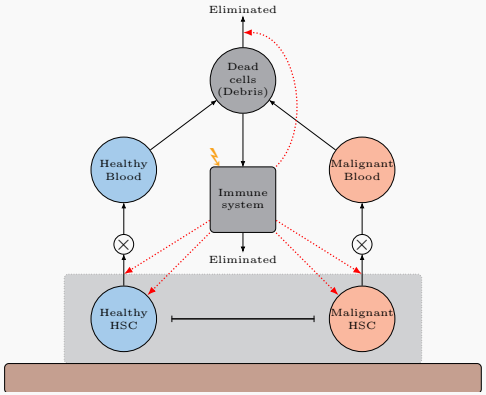

- Feedback from blood to the HSC system: Increases HSC activation
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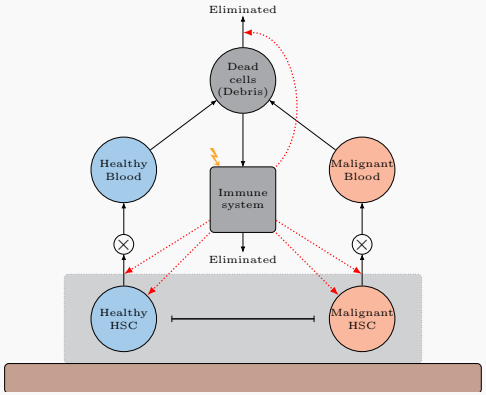

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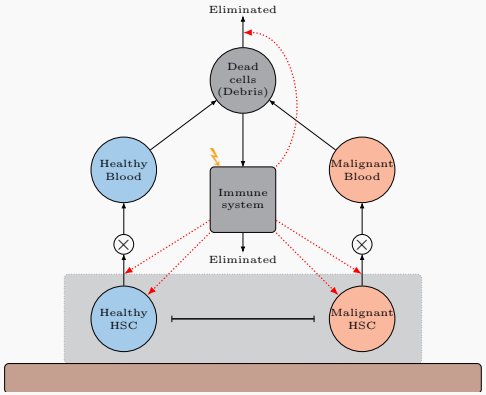

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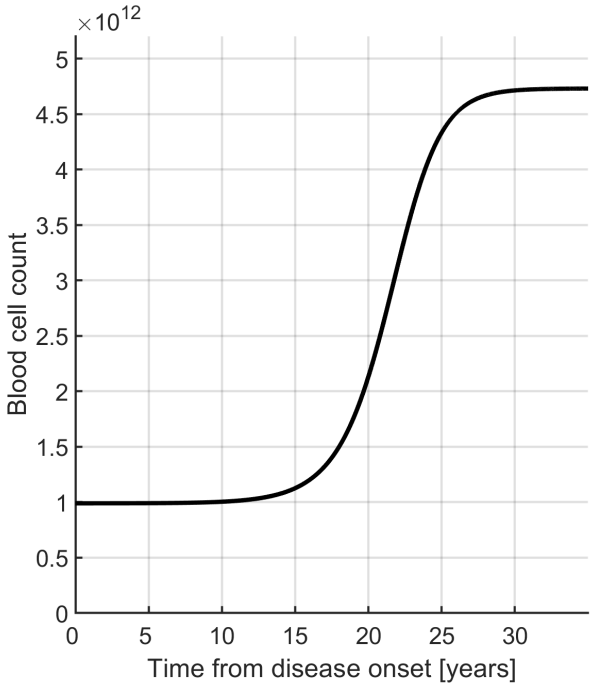
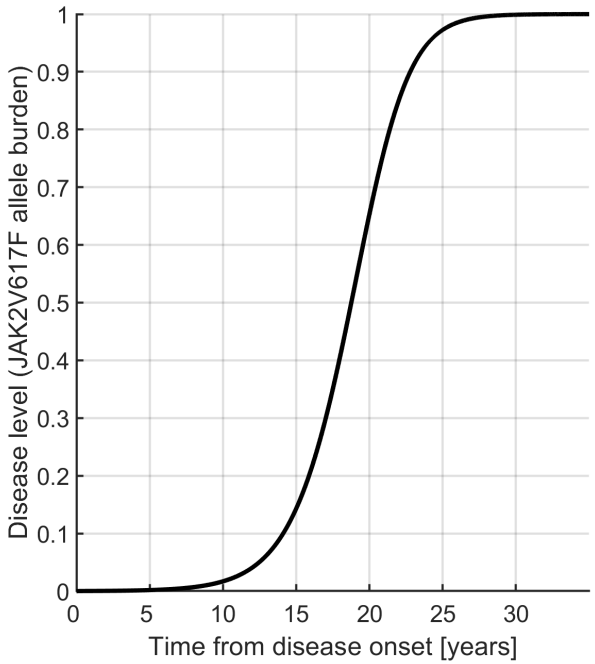
The combined model, the effect of IFN





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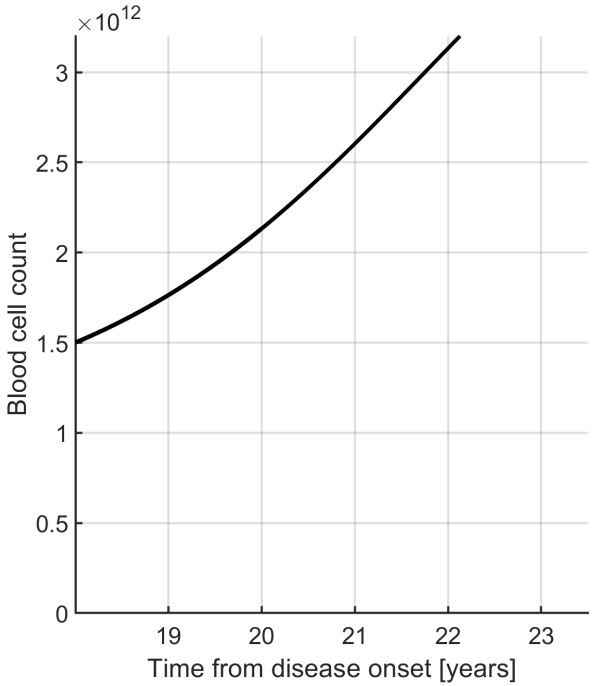

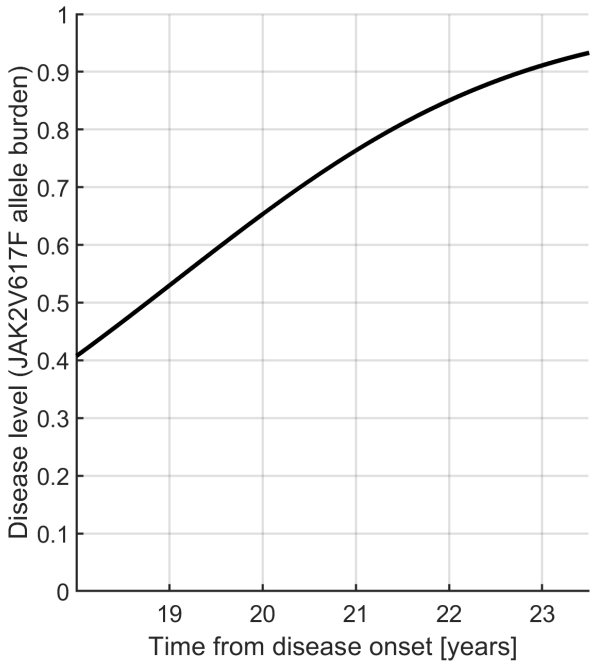

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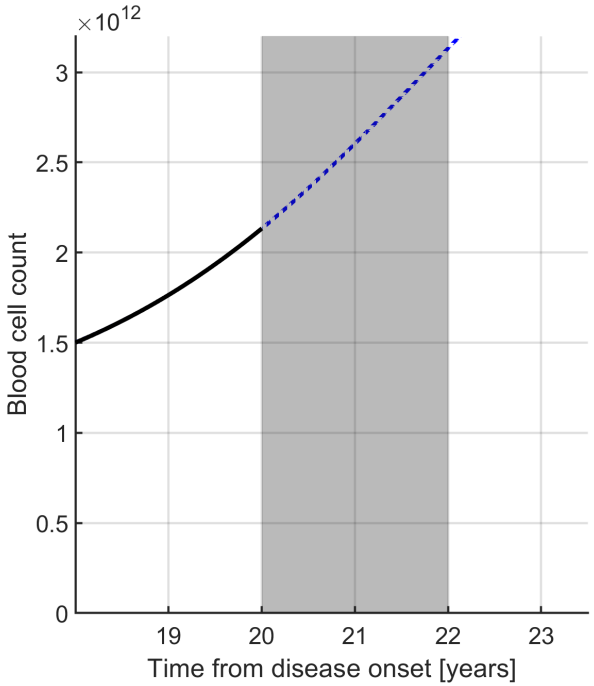

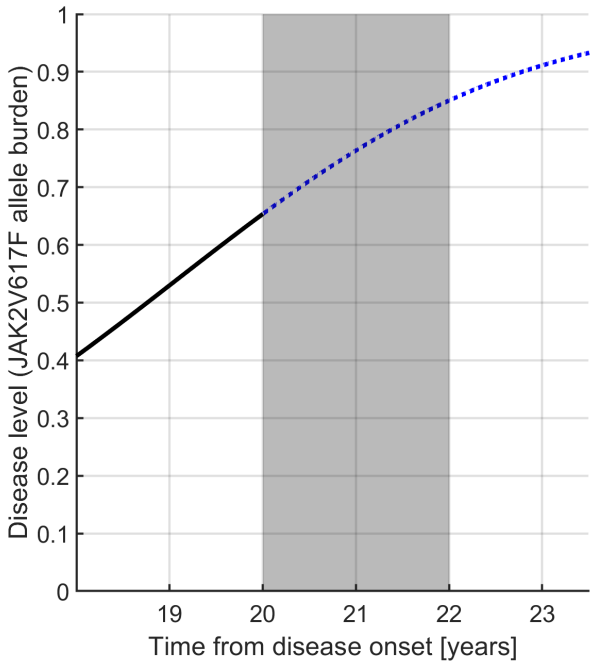

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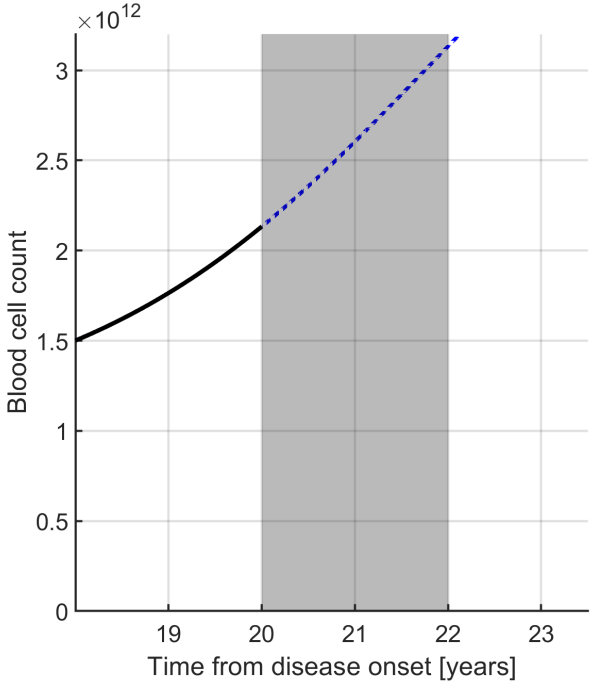
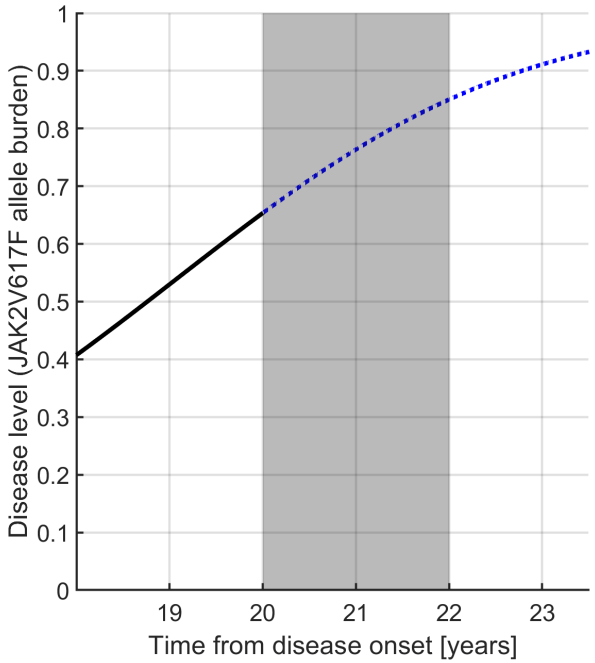
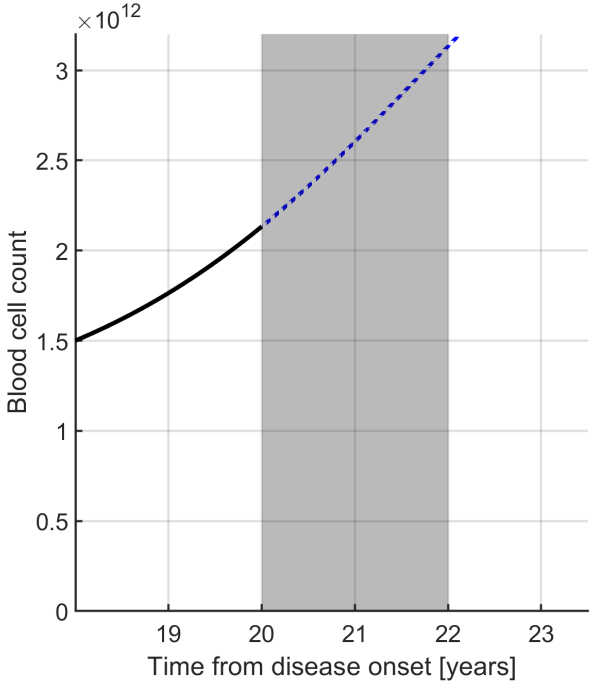
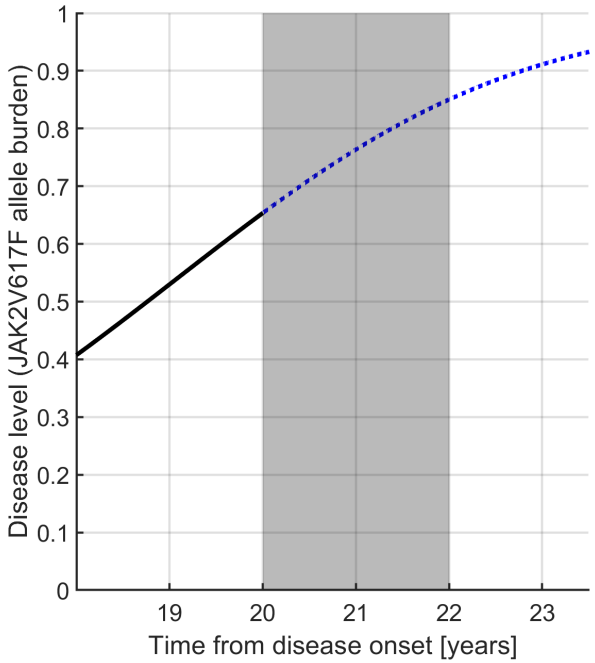




(For the Cancitis model: Death of HSC)

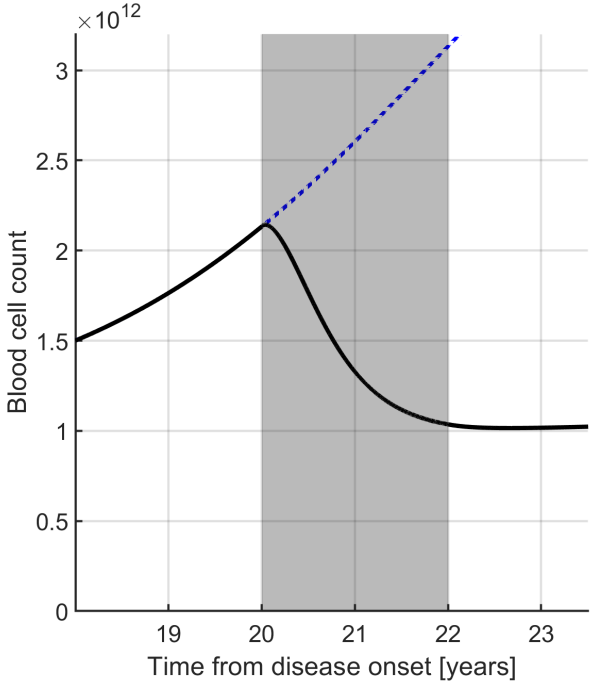
The combined model, the effect of IFN

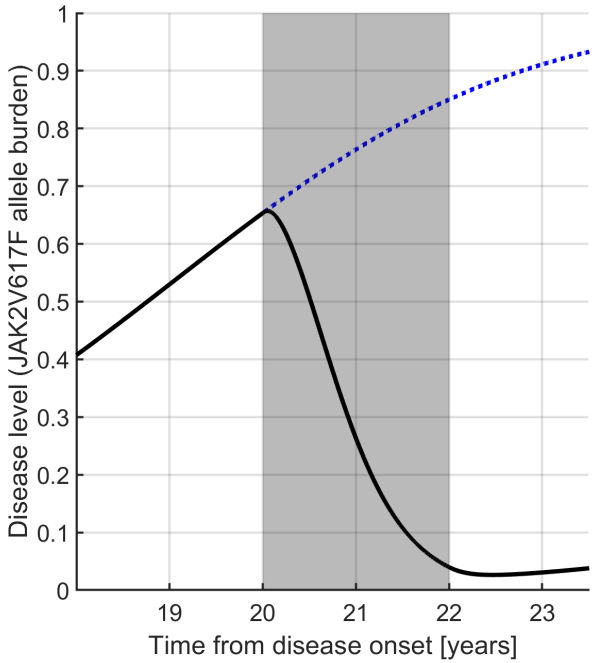




For the combined model:

The combined model, the effect of IFN

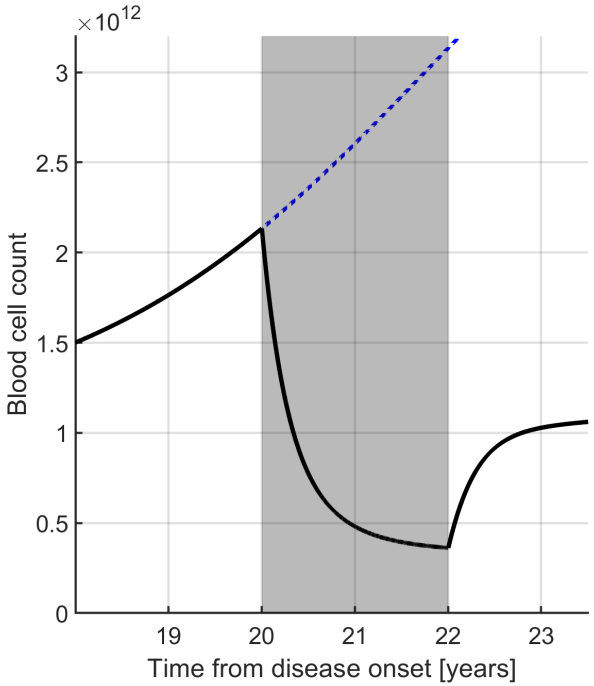


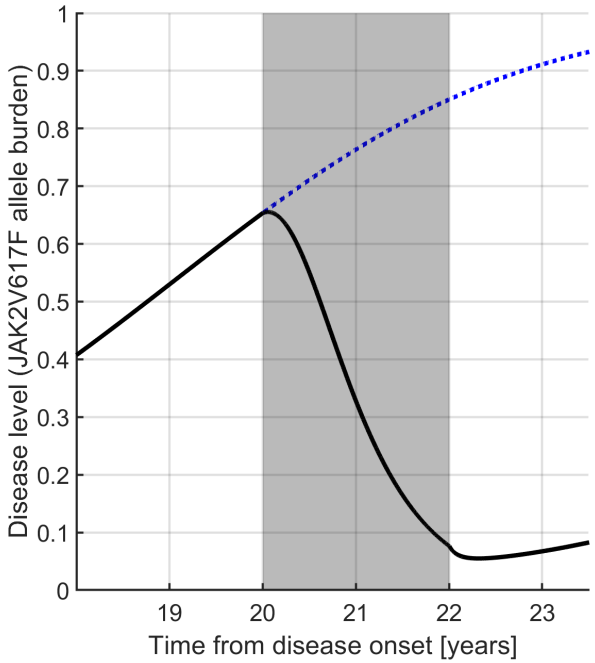


For the combined model:

- Decreased self-renewal of mutated cells, ρ_L

The combined model, the effect of IFN

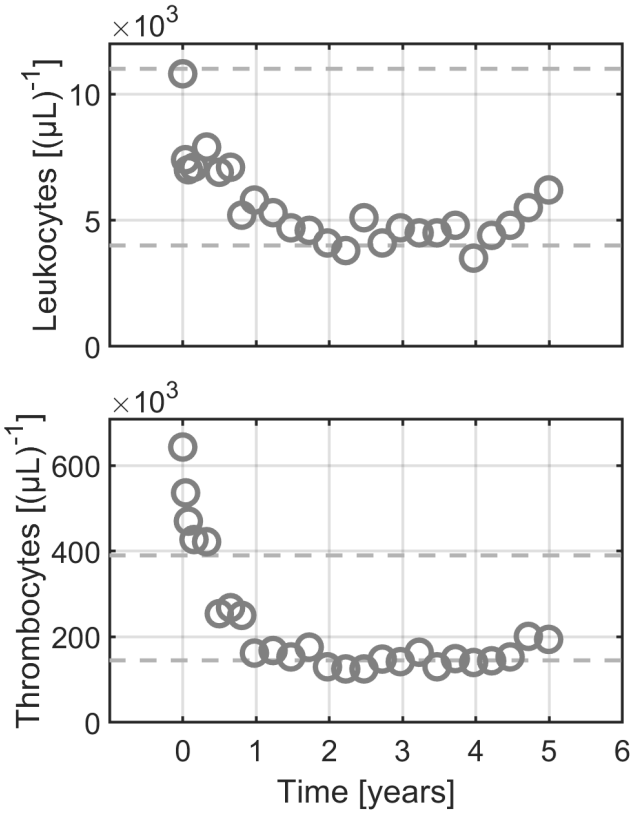


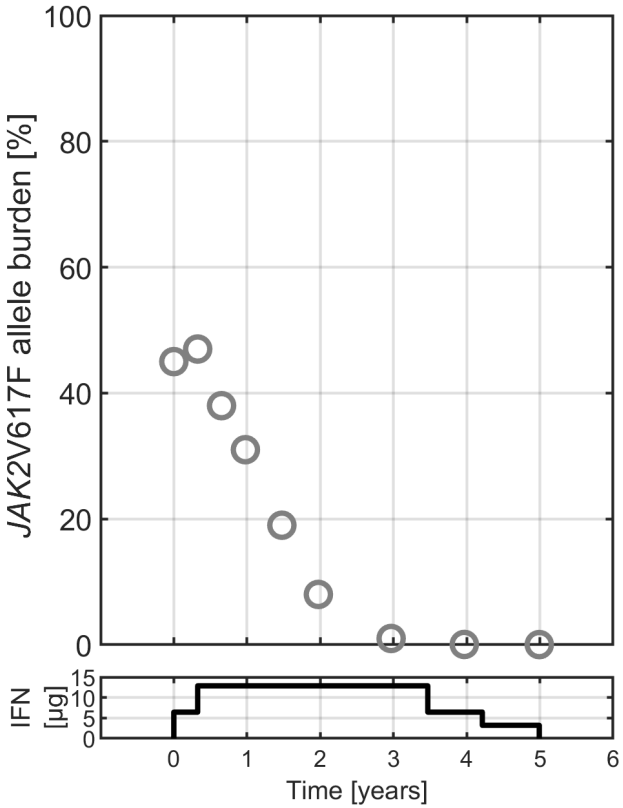


For the combined model:

- Decreased self-renewal of mutated cells, ρ_L
- Death of all actively dividing cells, ω_H and ω_L

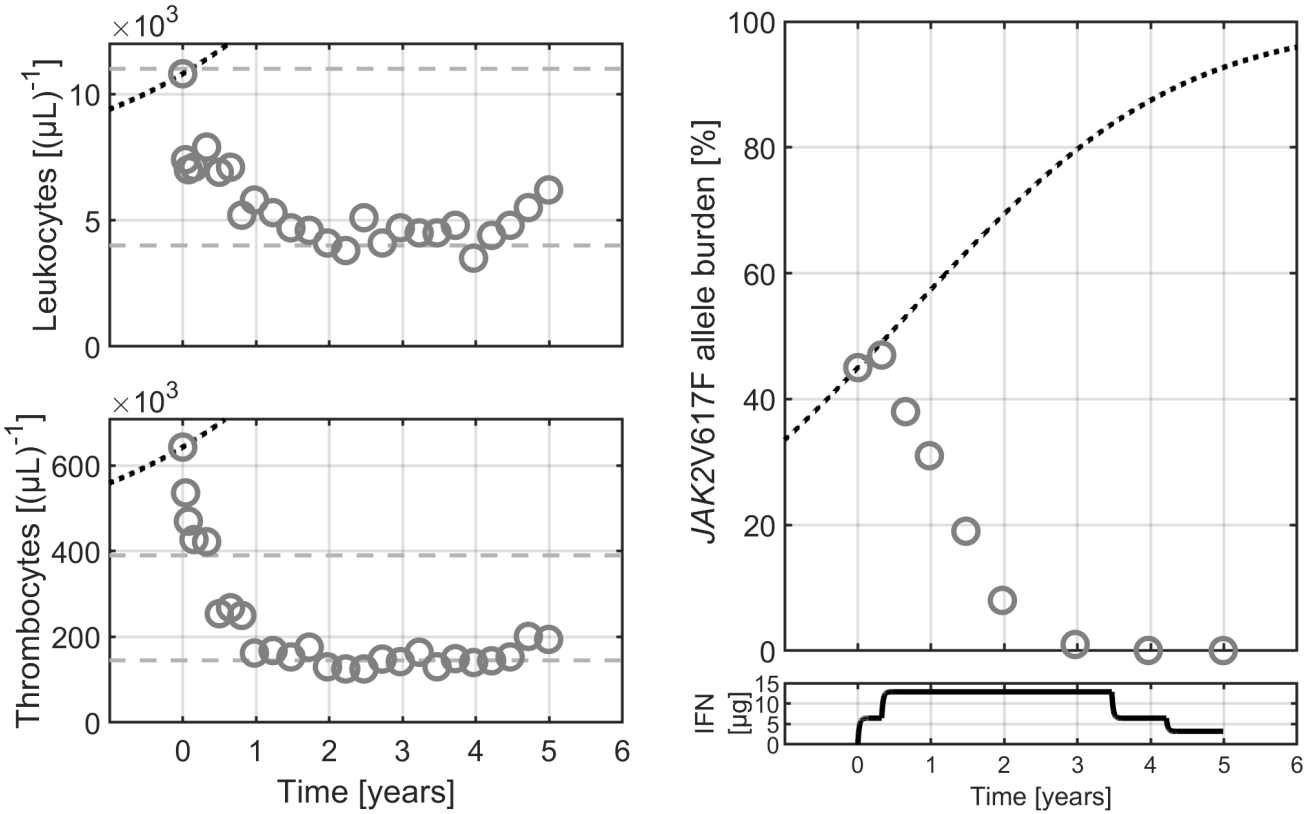
Fitting the combined model to patient data





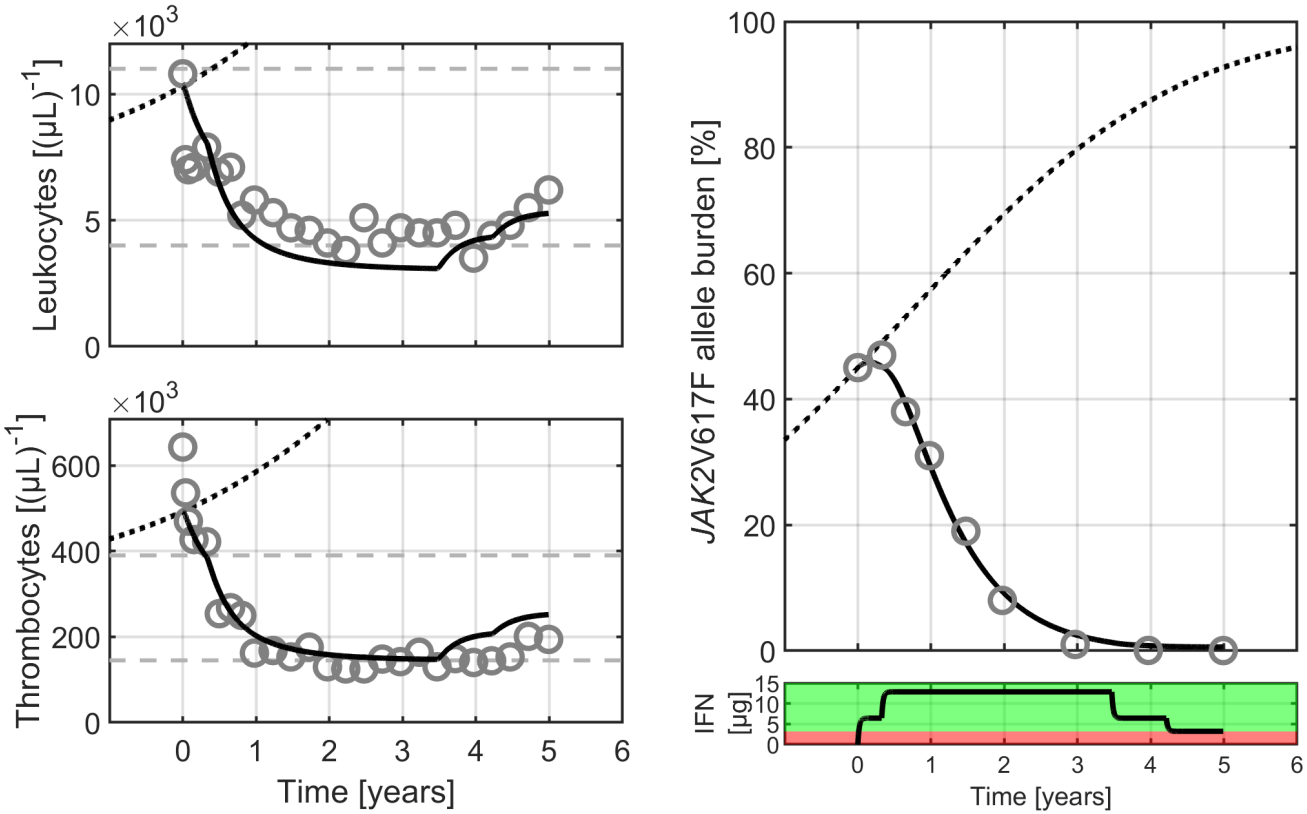
Patient P198, Raw data

Fitting the combined model to patient data



Patient P198, Data, Growth and PK/PD-modelling

Fitting the combined model to patient data



Patient P198, IFN-dose dependent fitting of model-parameters

Fitting the combined model to patient data

Then what?

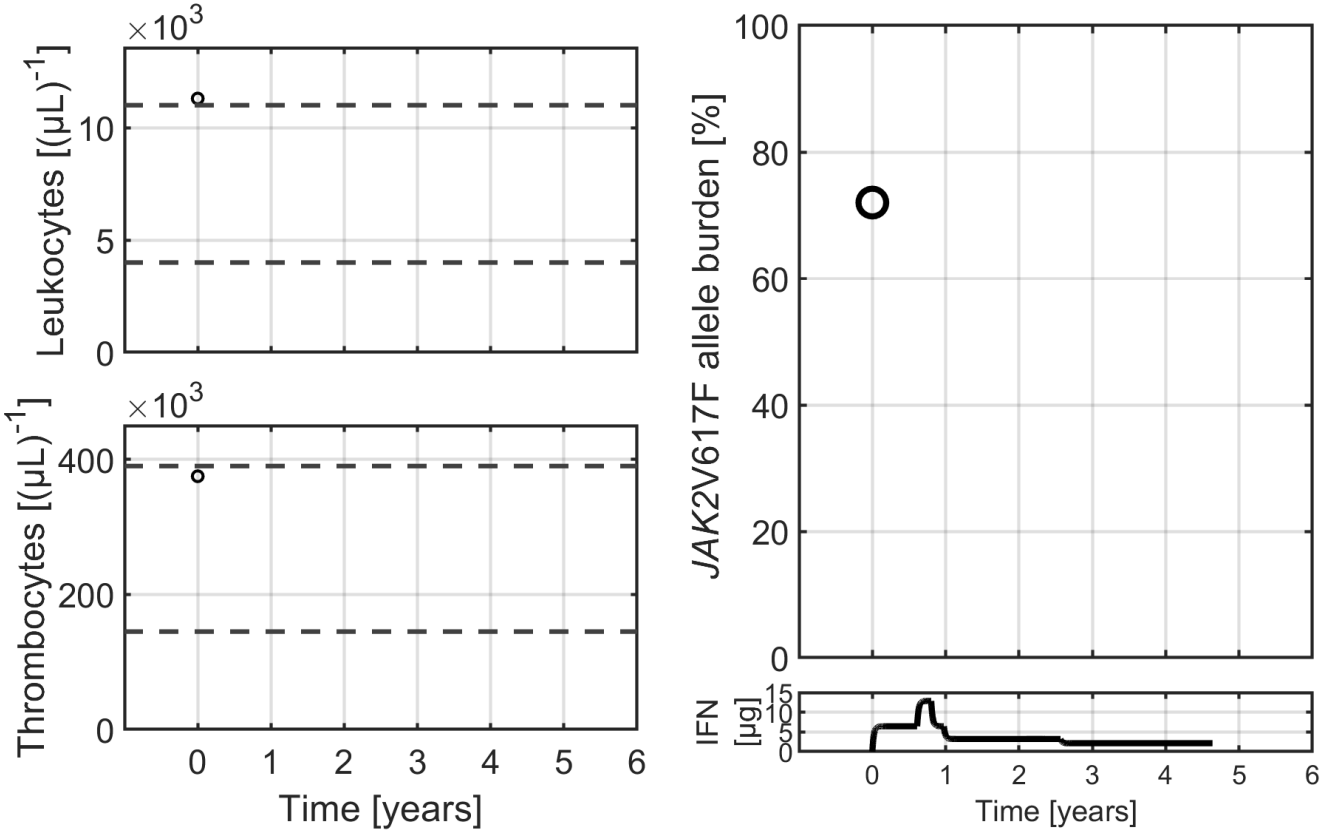
Fitting the combined model to patient data

Then what?
Population modelling!

Fitting the combined model to patient data

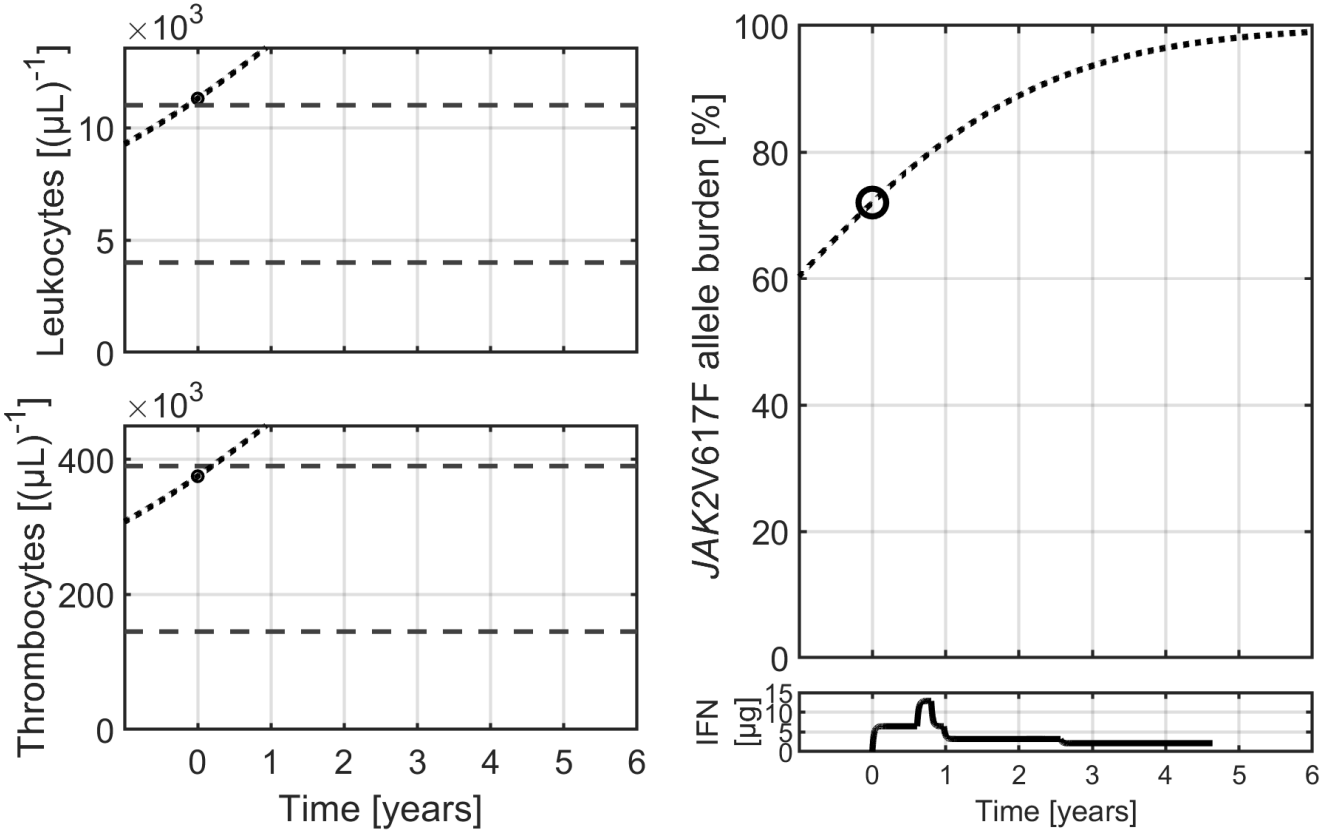
Then what?
Population modelling!
Goal: To describe the effect of IFN on a population level, so expected outcome of treatment can be predicted (with estimated uncertainties of prediction)

Proof-of-concept population modelling



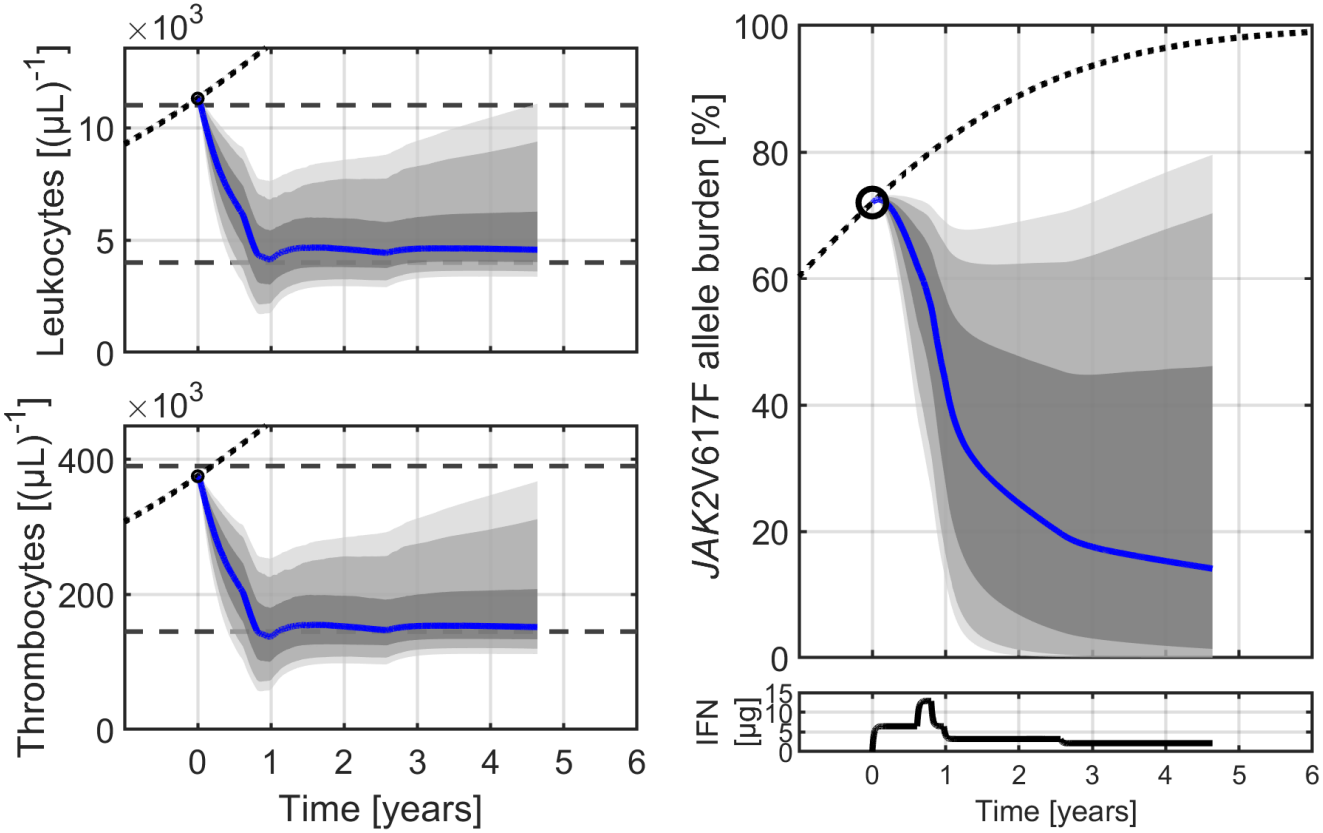
Patient P082

Proof-of-concept population modelling



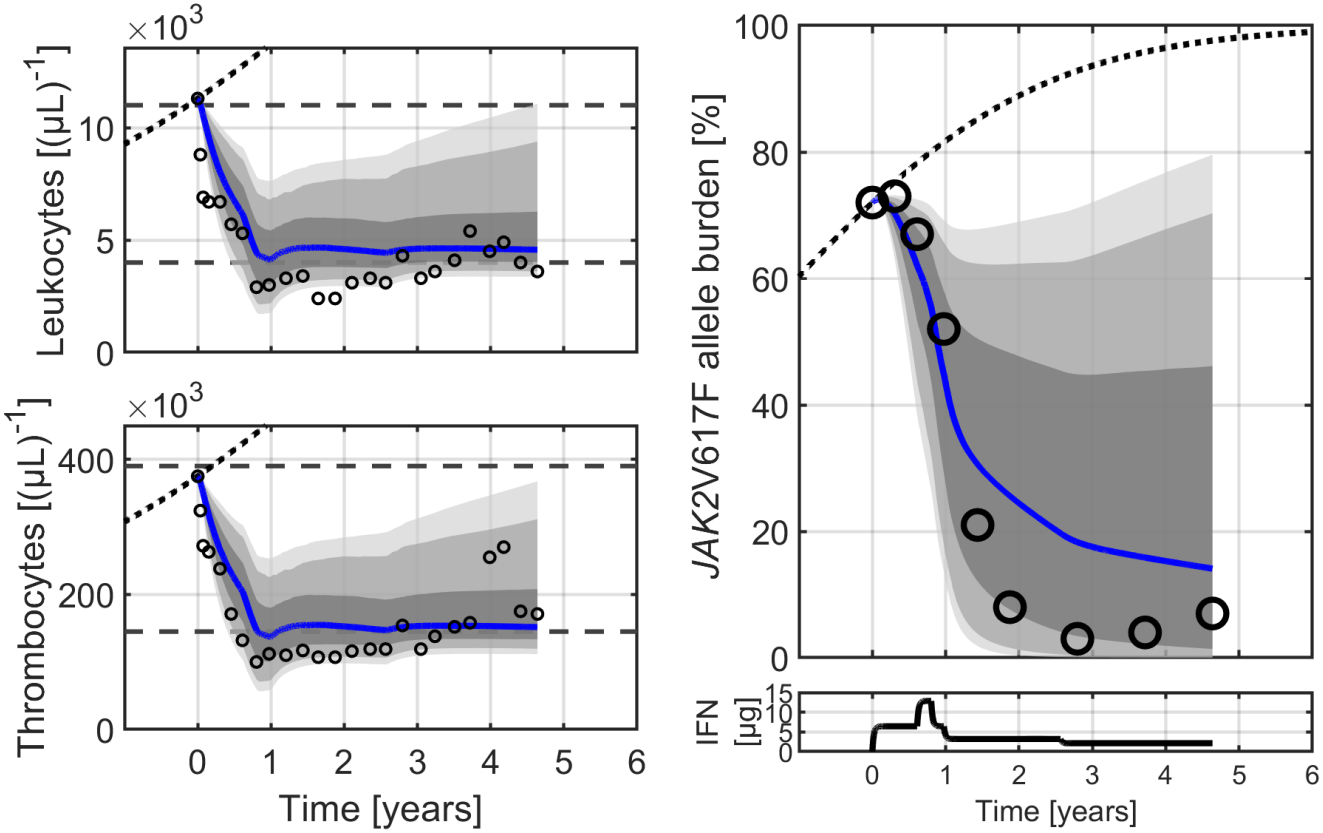
Patient P082

Proof-of-concept population modelling



Patient P082

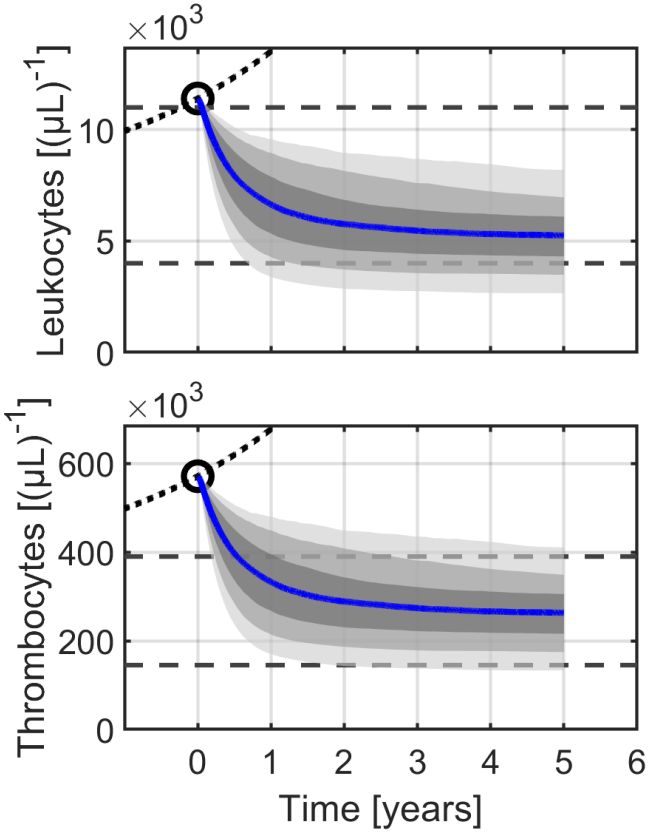
Proof-of-concept population modelling

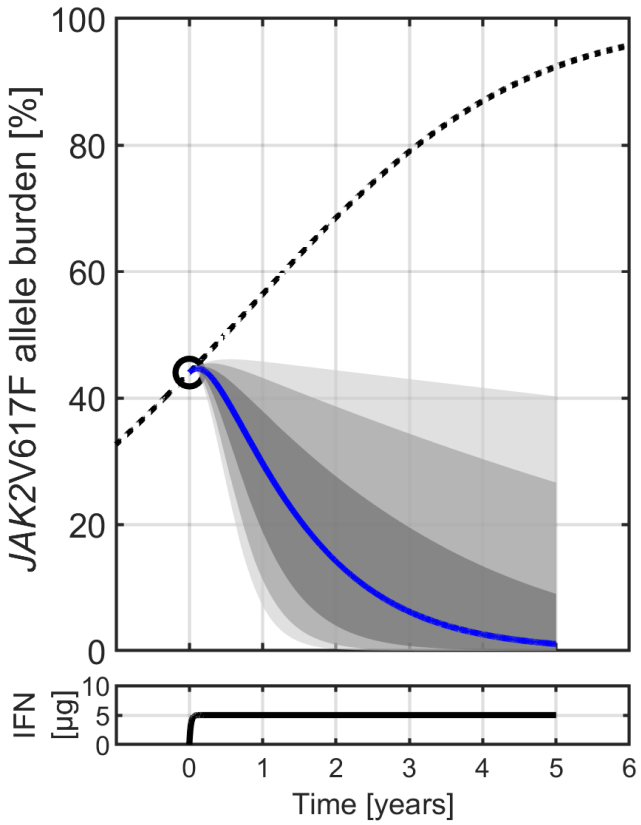


Patient P082

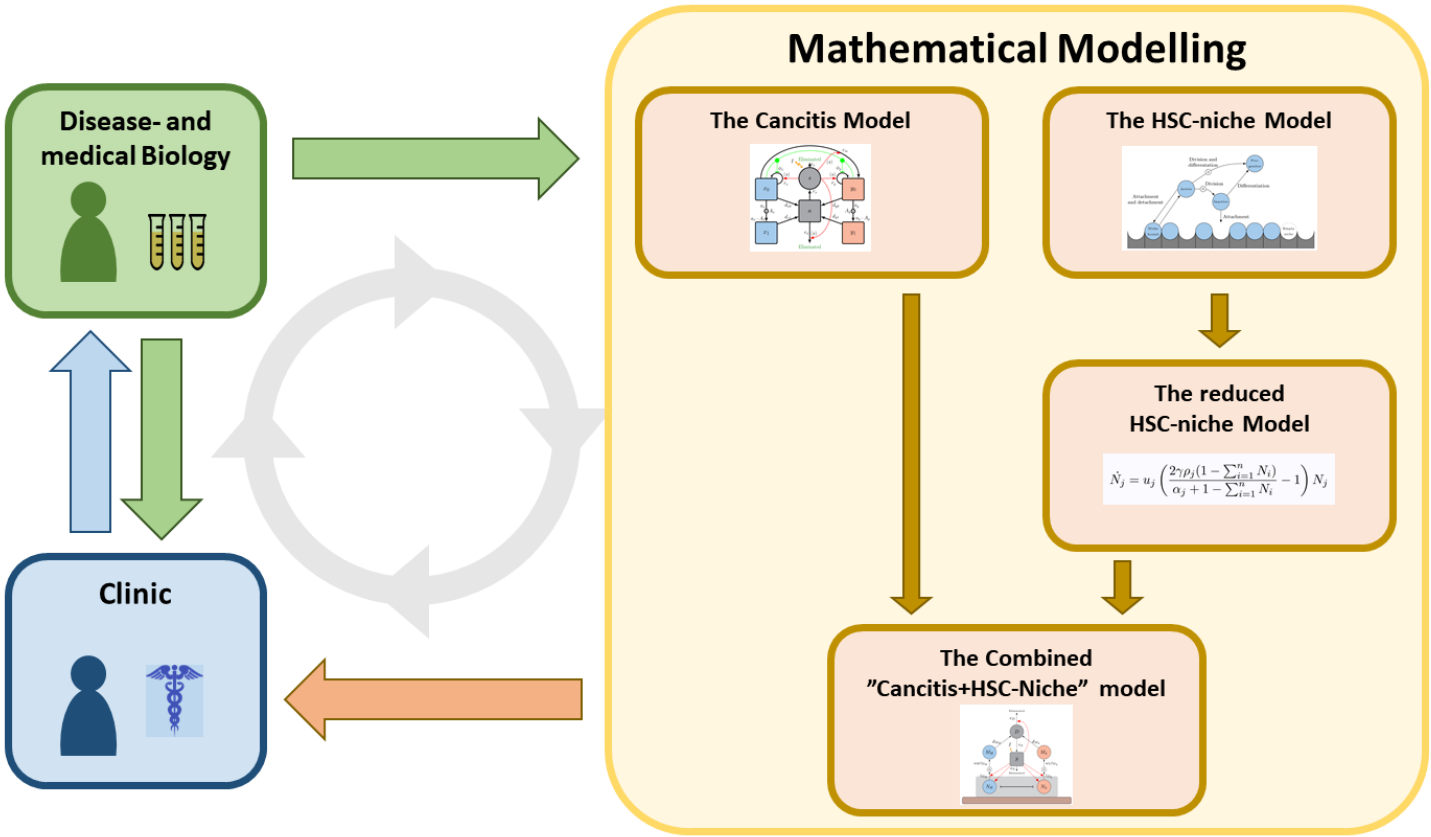
Proof-of-concept population modelling

A hypothetical "typical PV-diagnosed patient"





Section 6
Discussion and conclusion



Summing it up

Through mathematical modelling we have come up with:

- Hypotheses about the behaviour of HSC.

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- Hypotheses about the behaviour of HSC.
- Numerical estimates of efficient HSC treatment requires.
- Biological interpretation of the effect of IFN, on a personalized level.
- Population-level predictions about the expected response of newly diagnosed MPN patients.

Where to go from here?

- Additional model-validation and data-collection.

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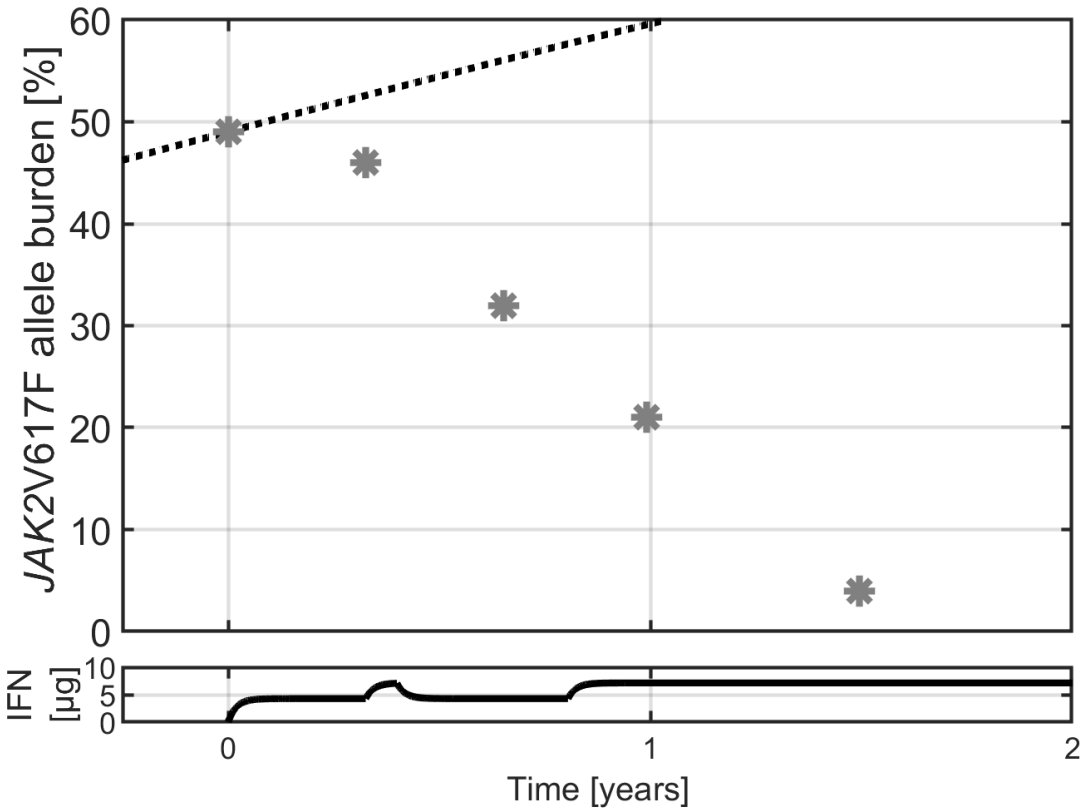
  Particularly for the first year of treatment.

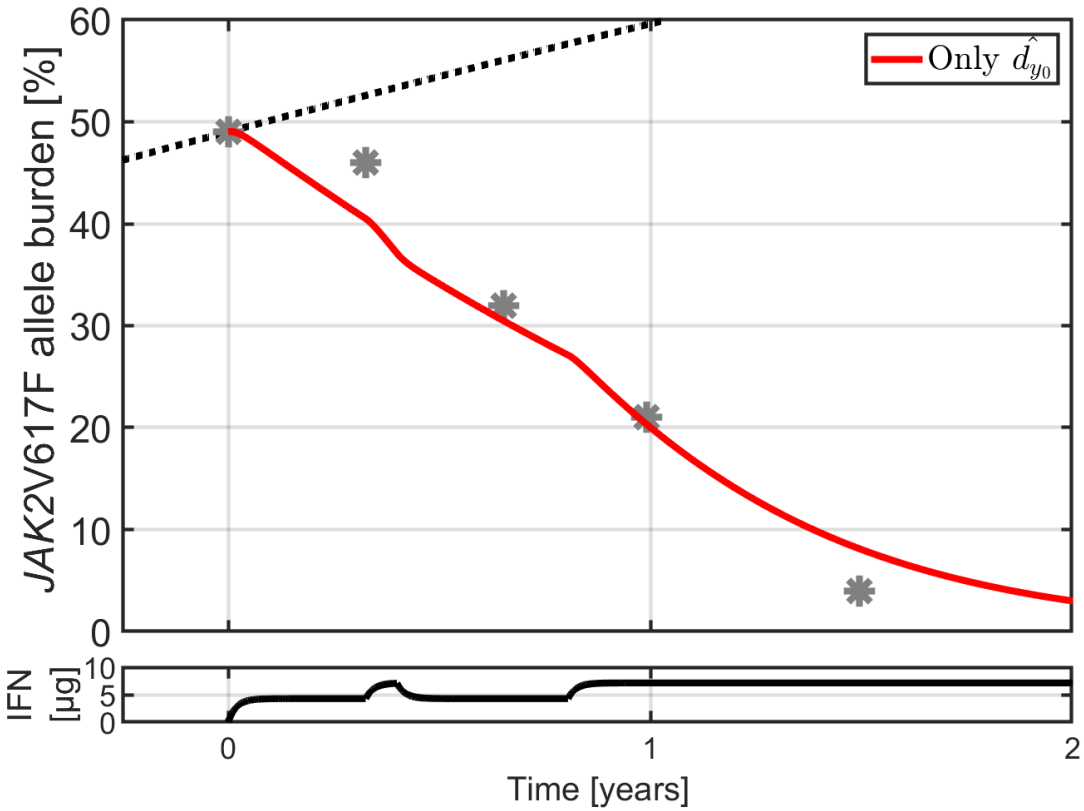


Patient P002

Where to go from here?

- Additional model-validation and data-collection.

  Particularly for the first year of treatment.



Patient P002

Where to go from here?

- Additional model-validation and data-collection.
- Improved identification/stratification of patient sub-diagnoses.

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- Consideration of other drugs (HU, Ruxo, Jakavi, Statins, etc.), and combination treatment.

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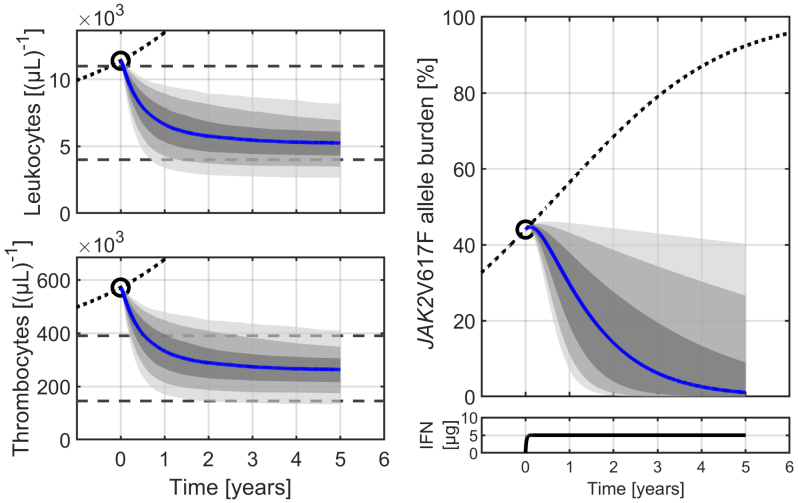
- Additional model-validation and data-collection.
- Improved identification/stratification of patient sub-diagnoses.
- Consideration of other drugs (HU, Ruxo, Jakavi, Statins, etc.), and combination treatment.
- Including additional available data (Cytokine-level, smoking, age, etc.)

Personalized Mathematical Modelling?

Is mathematical modelling the primary clinical tool of tomorrow?



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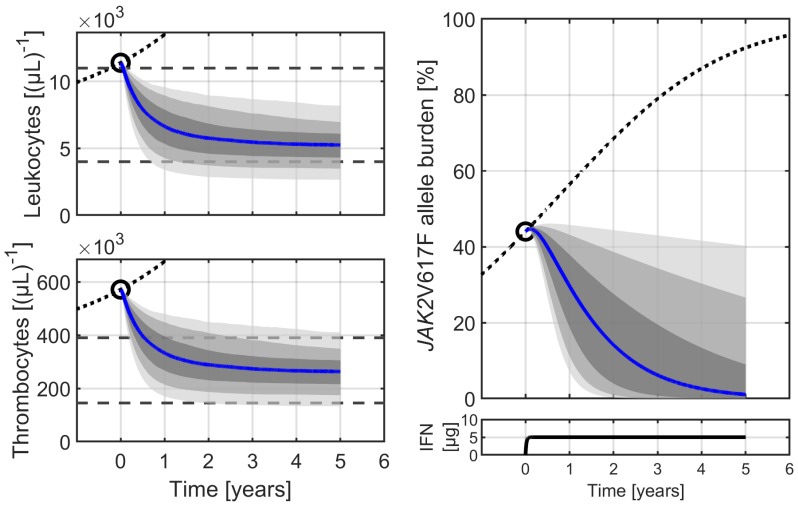

"Completely irresponsible to let mathematical models make decisions..."

Personalized Mathematical Modelling?

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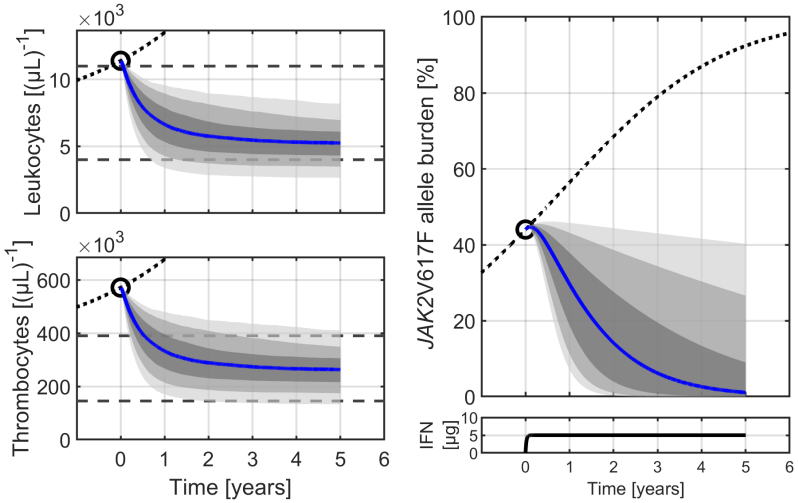

"Completely irresponsible to let mathematical models make decisions, but even worse to ignore them"
- Johnny T. Ottesen

Thank you for your time and attention!

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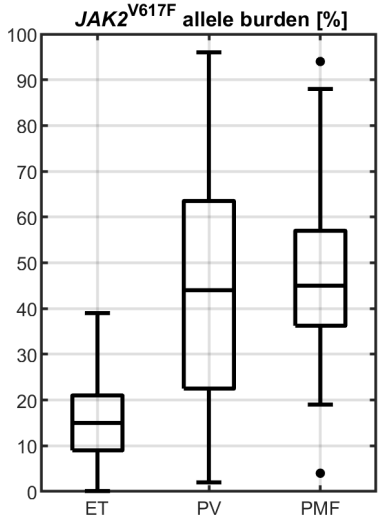
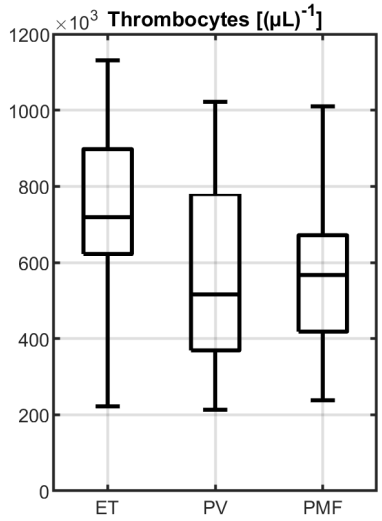
And a big thanks to supervisors and collaborators:

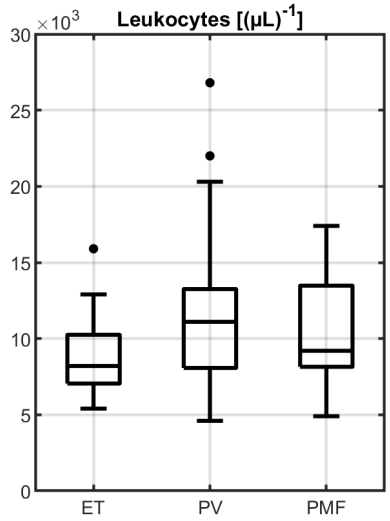
- Johnny Ottesen, Morten Andersen and Hans Hasselbalch
- Thomas Stiehl
- Johanne Gudmand-Høyer, Zamra Sajid and Marc Dam
- Vibe Skov, Lasse Kjær and Trine Knudsen

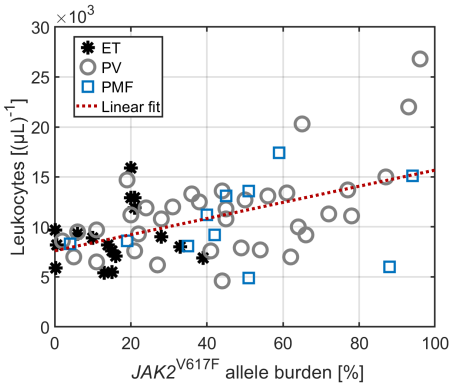
Extra slides and figures

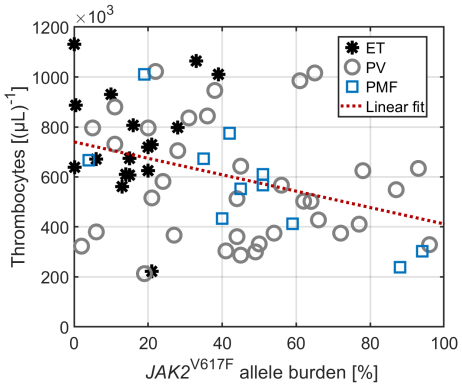
Data

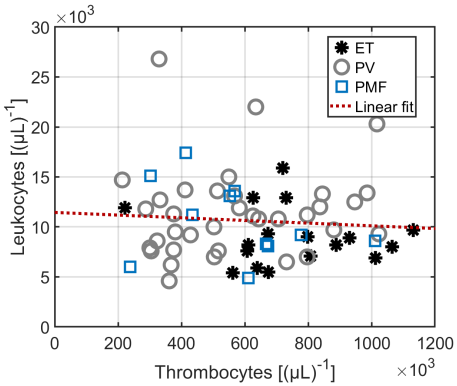












The framework of Brady & Enderling (2019)

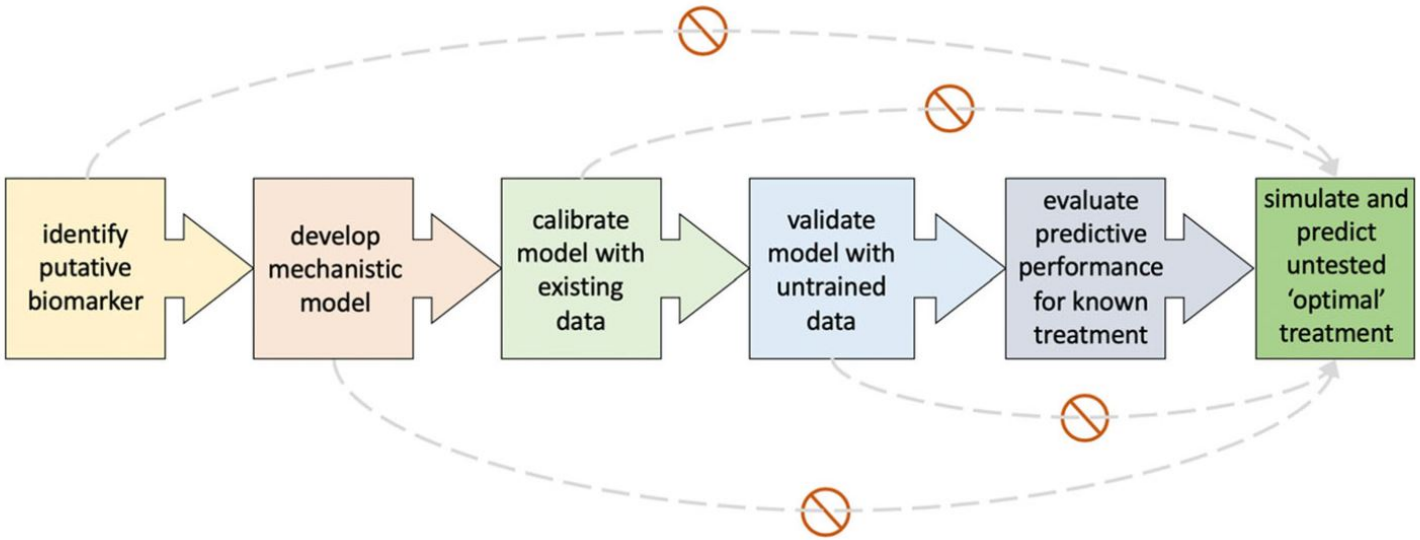


Figure from Brady & Enderling (2019)

The effect of IFN, "hypothetical" consequences

Assuming our guess of the IFN-effect is valid ($\rho_L \downarrow$, $\omega_H \downarrow$ and $\omega_L \downarrow$)
What are the consequences?

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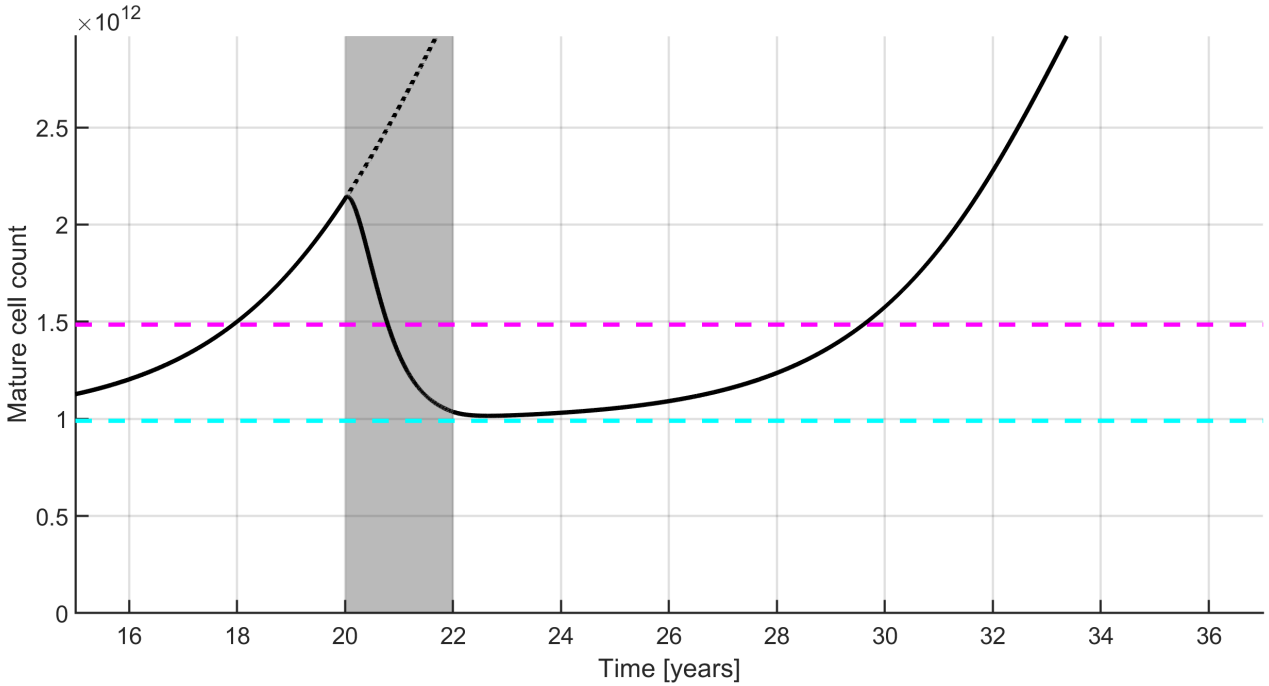

(Here, only ρ_L was decreased)