Mathematical Modelling of Myeloproliferative Neoplasms and Hematopoietic Stem Cells

An overview of our recent work and a look to the future

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Mathematical Modelling of MPNs and HSC

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Introduction
Background
Purpose

The model
Description
Model behaviour

Relating to clinical data
Fitting to data
Hypothetical scenarios
Population modelling

Discussion
Our results
The future

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Introduction
Background
Purpose
The model
Description
Model behaviour
Relating to clinical data
Fitting to data
Hypothetical scenarios
Population modelling
Discussion
Our results
The future

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Introduction
Background
Purpose
The model
Description
Model behaviour
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Fitting to data
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Population modelling
Discussion
Our results
The future

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- This talk:
  - Illustration of how mathematical modelling could contribute to clinical practice in the future.
  - Focus on general aspects of mathematical modelling rather than mathematical details.

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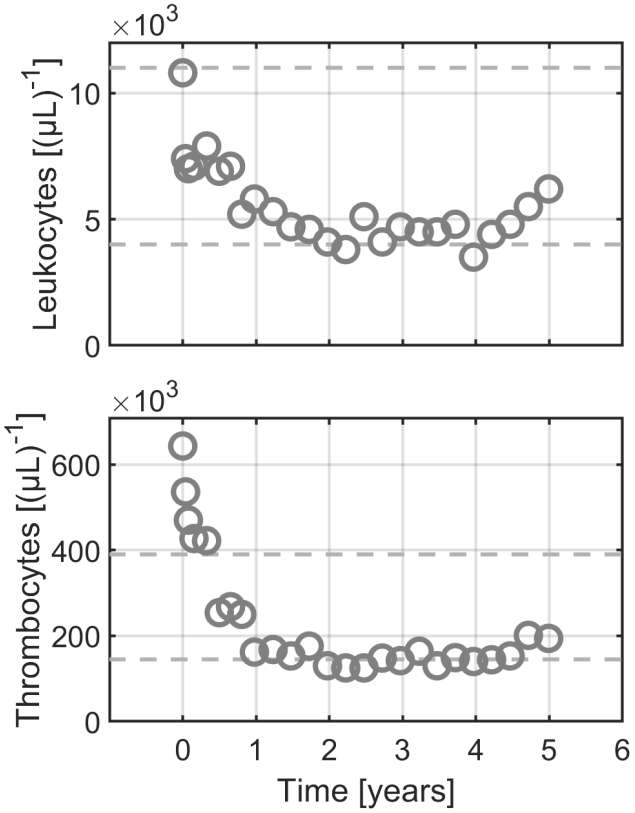

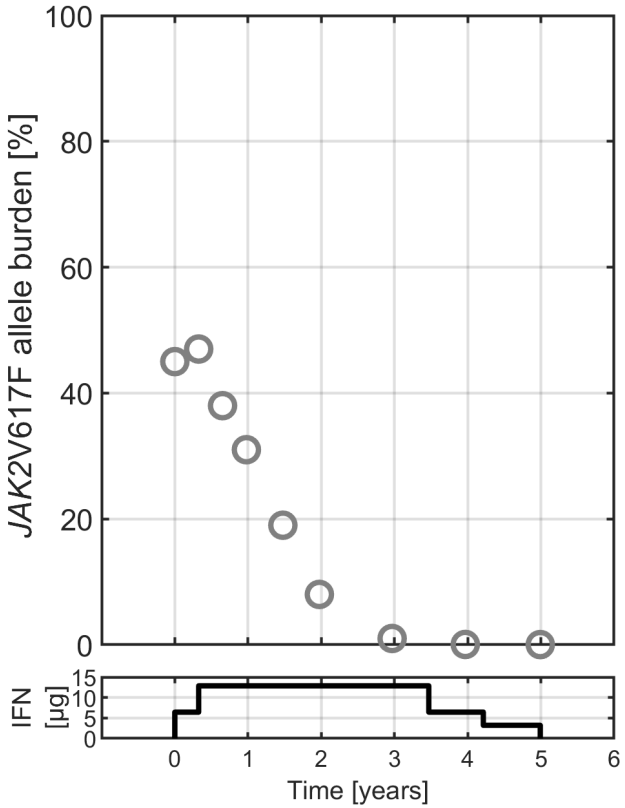

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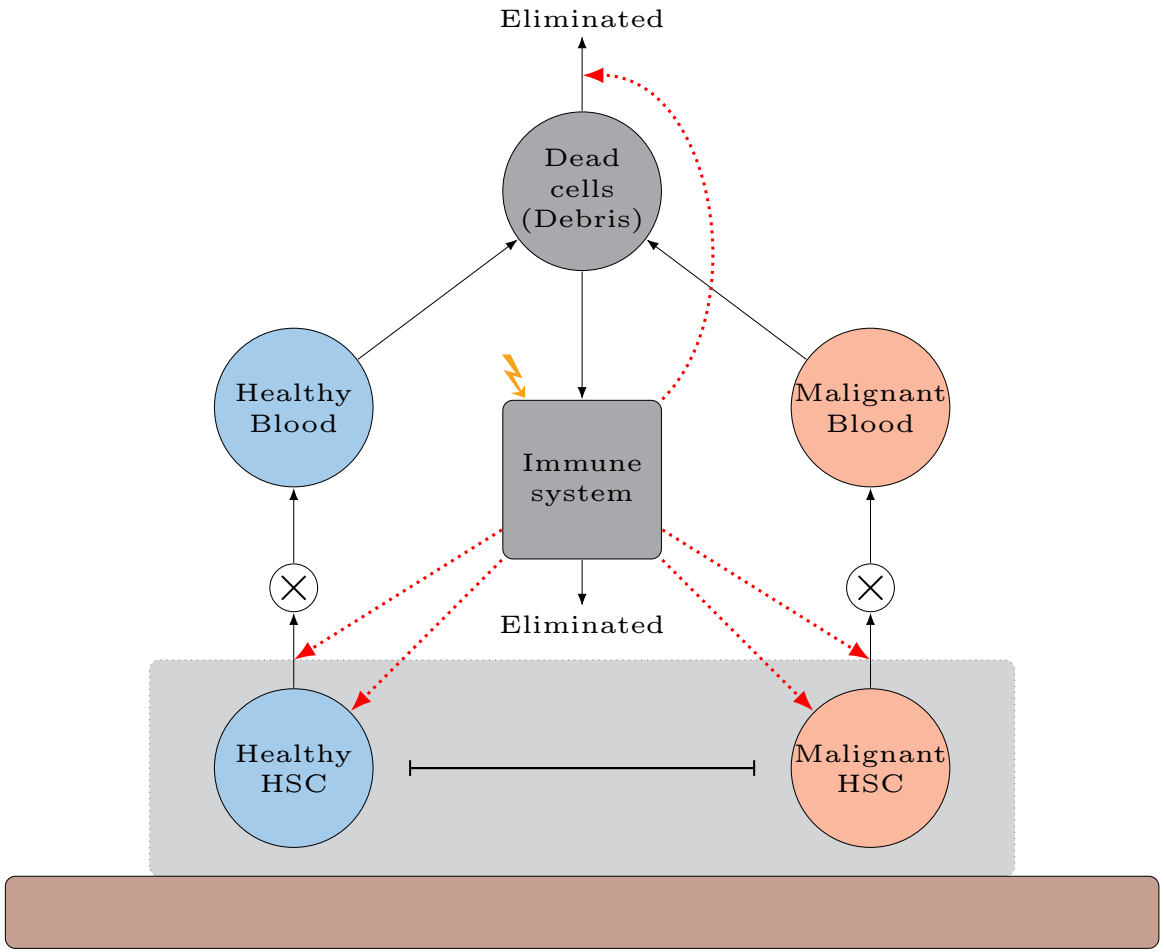
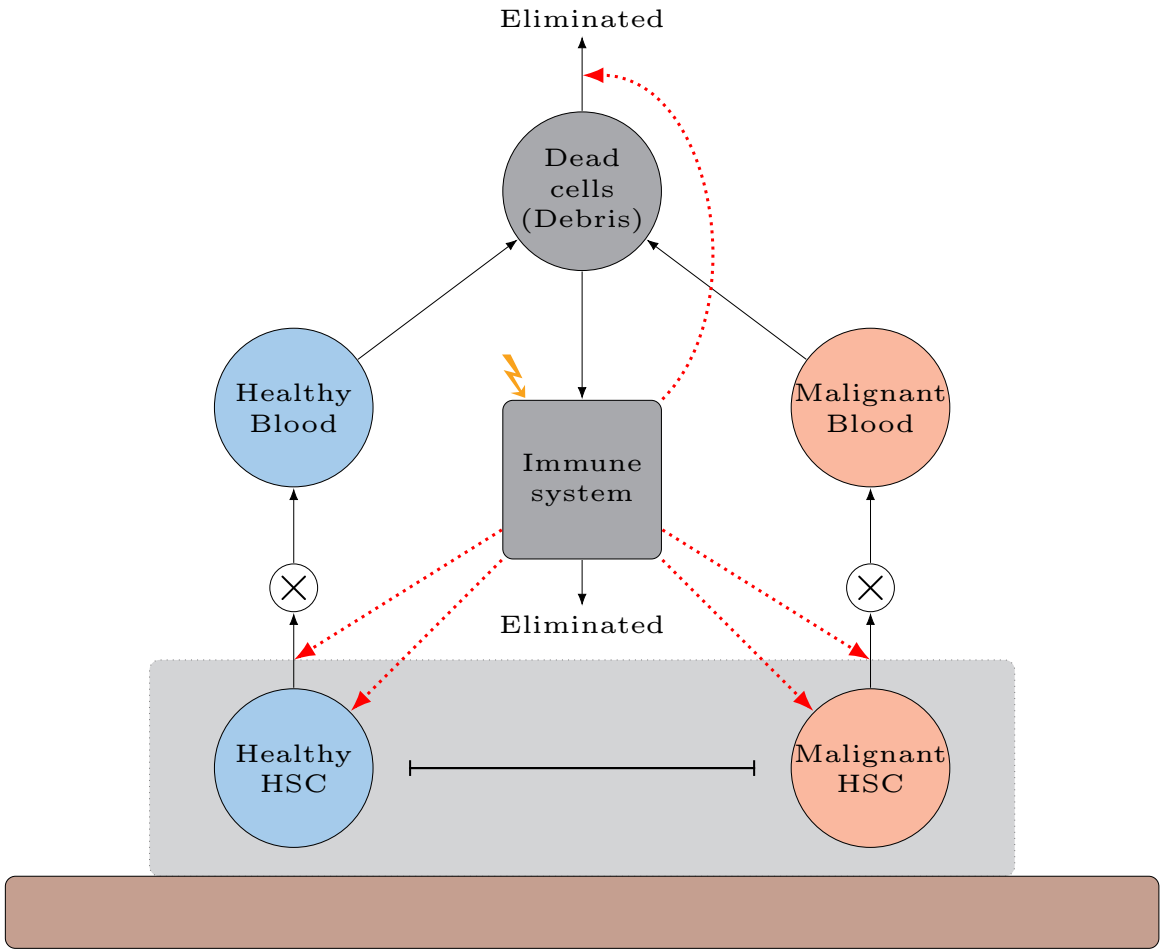
- **Clinicians from Zealand University Hospital:** MPN-patients treated with pegylated interferon-α obtain long-term normalization of cell-counts.
- **Data:** Clinical trial with patients treated with interferon-α.
- **Goal:** Can the effects of interferon-α be accurately described by a mathematical model?

Model description



(Pedersen et al, 2021)

Model description



(Pedersen et al, 2021)
Based on previous model of Andersen et al (2017), combined with a model of HSC developed together with Thomas Stiehl (Roskilde University & RWTH Aachen).

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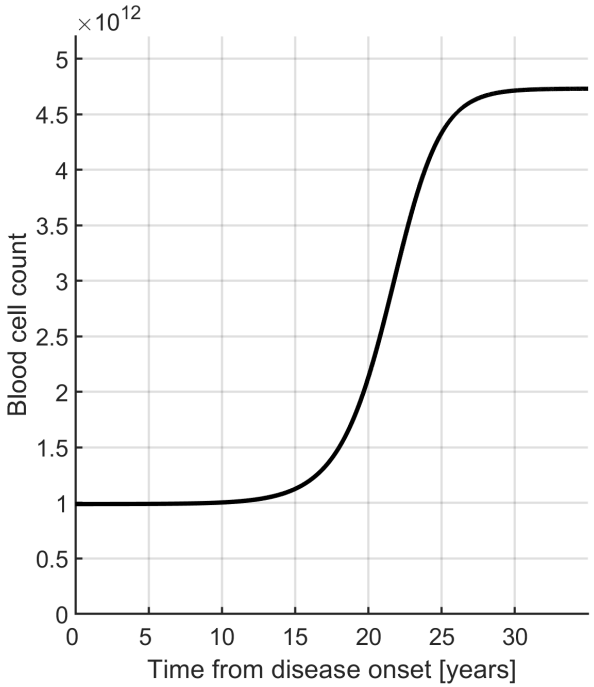
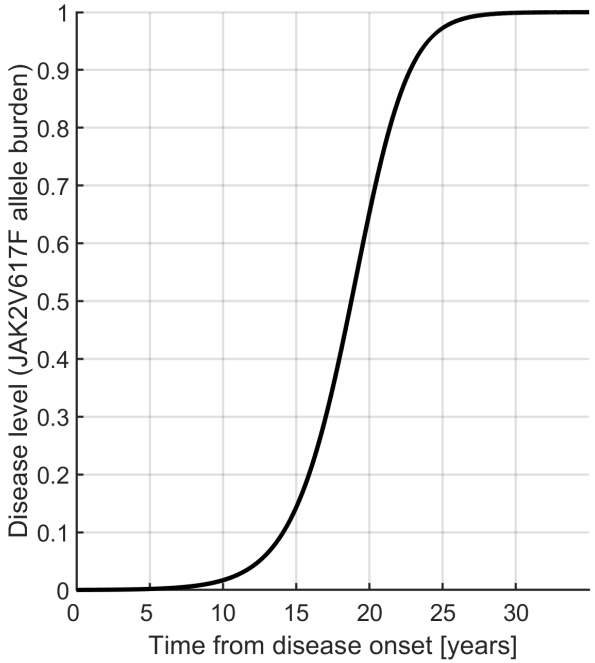
  - No mutations $\rightarrow$ long-term health.
  - Disease progression over a long period (15+ years).
  - Chronic inflammation leads to faster disease progression.
- We can perturb specific model-parameters that relate to the biological effect of interferon-α treatment.

Treatment-specific perturbations





Typical disease progression in the model.

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Introduction
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Purpose
The model
Description
Model behaviour
Relating to clinical data
Fitting to data
Hypothetical scenarios
Population modelling
Discussion
Our results
The future

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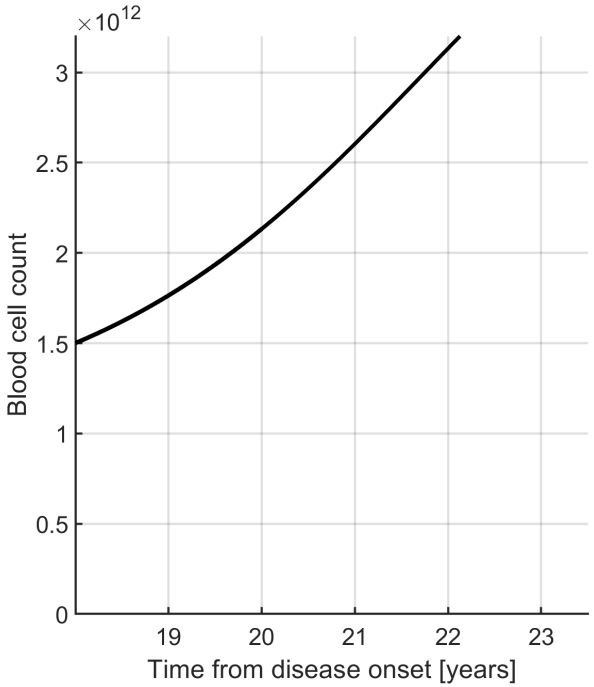
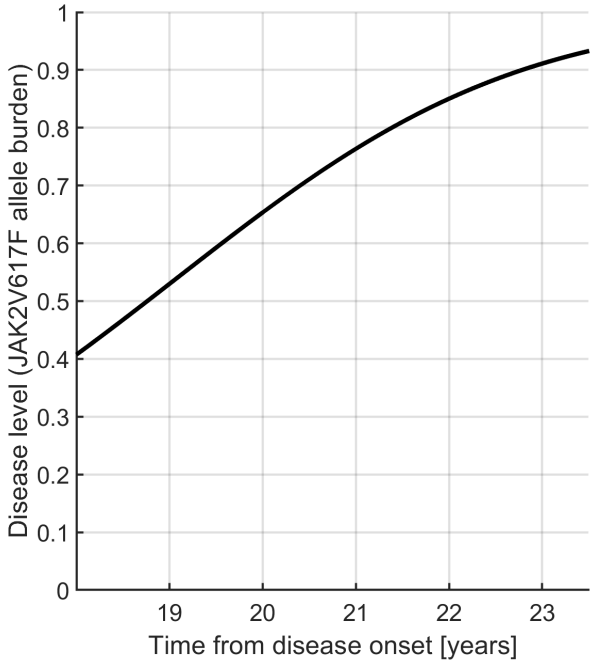
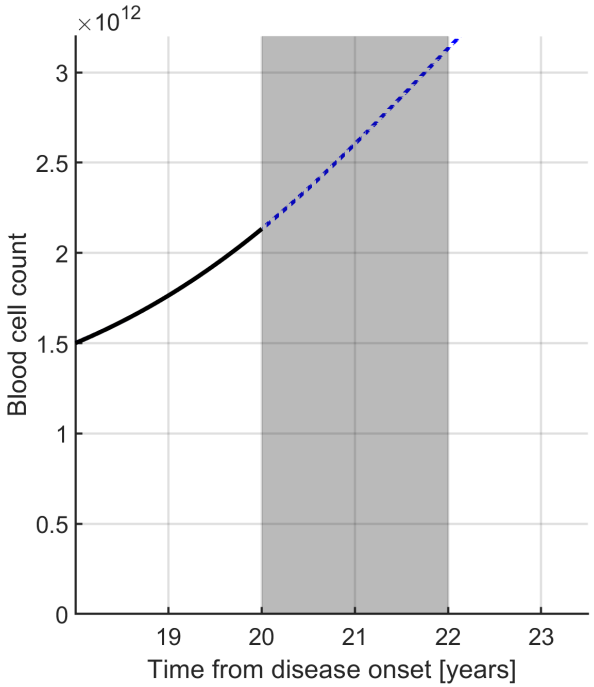
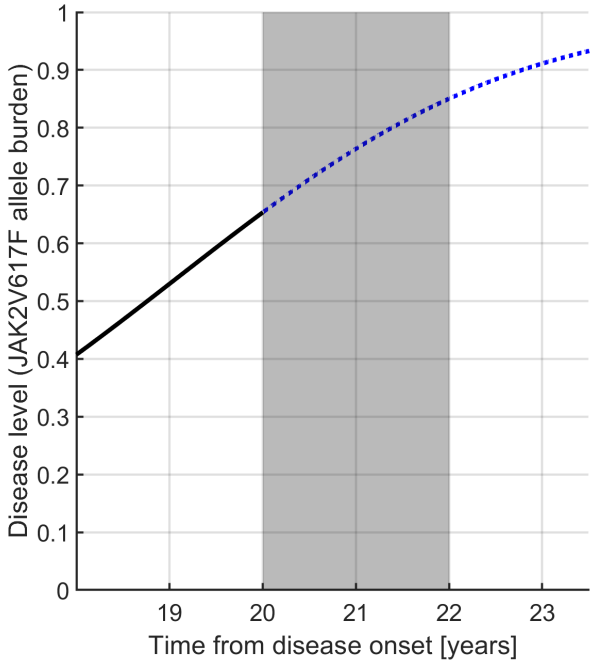




Zooming in on year 20 after original mutation.

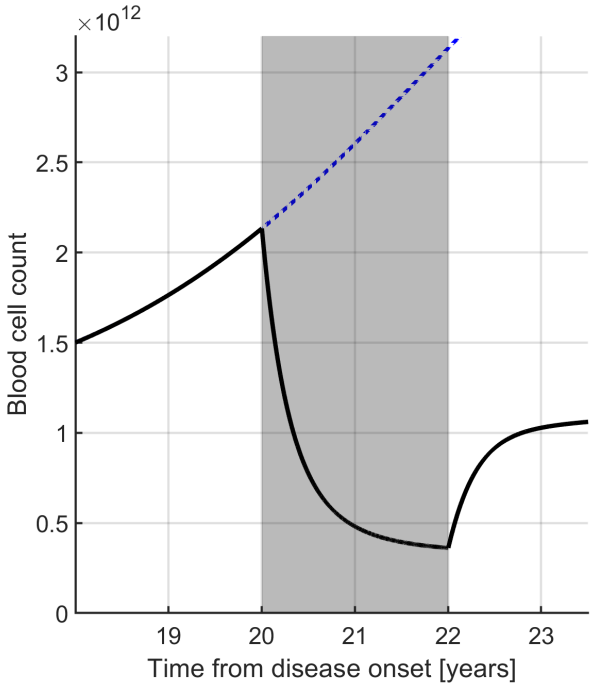
Treatment-specific perturbations

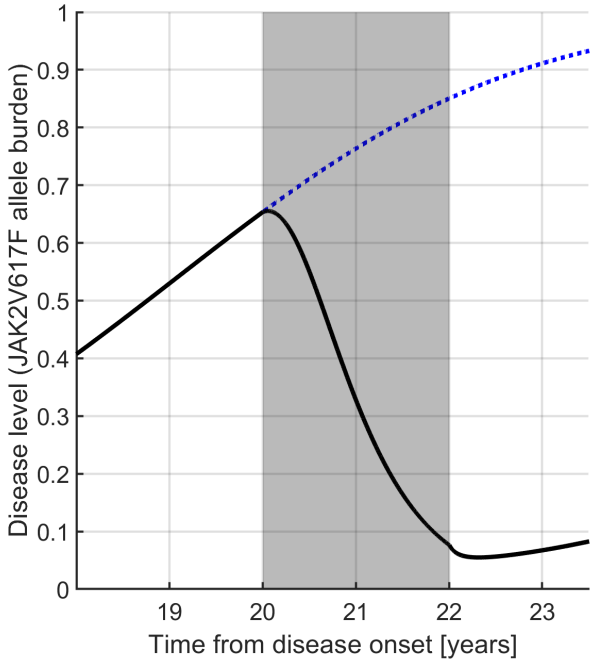




Considering two years of treatment.

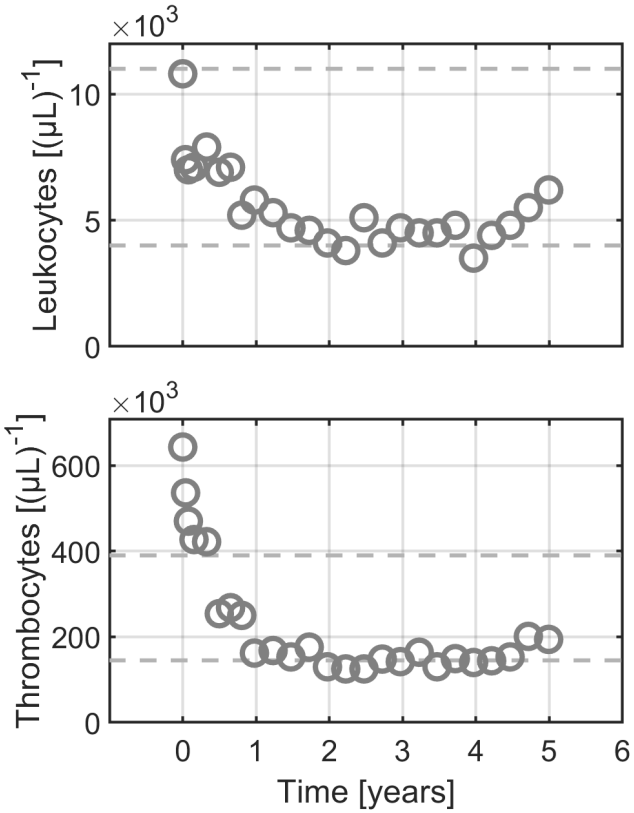
Treatment-specific perturbations

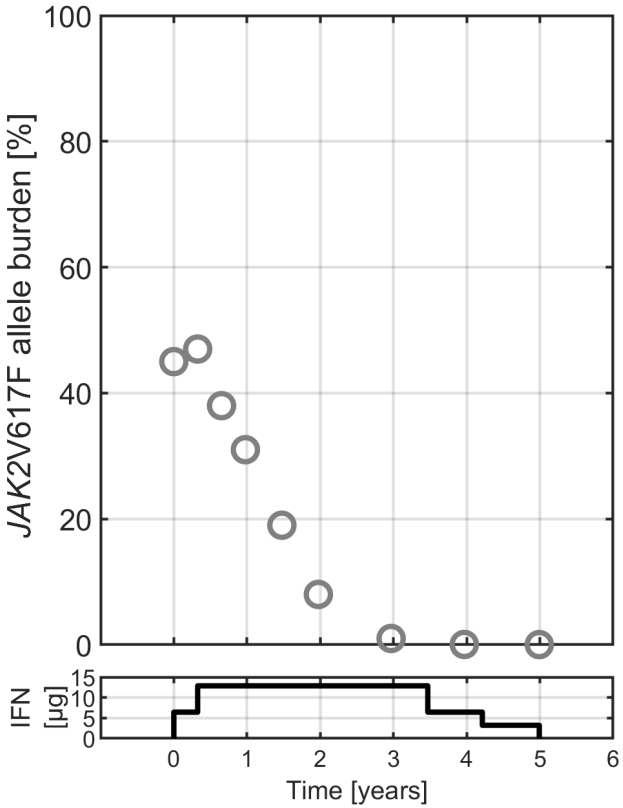




Considering two years of treatment.
Perturbing model-parameters related to treatment.

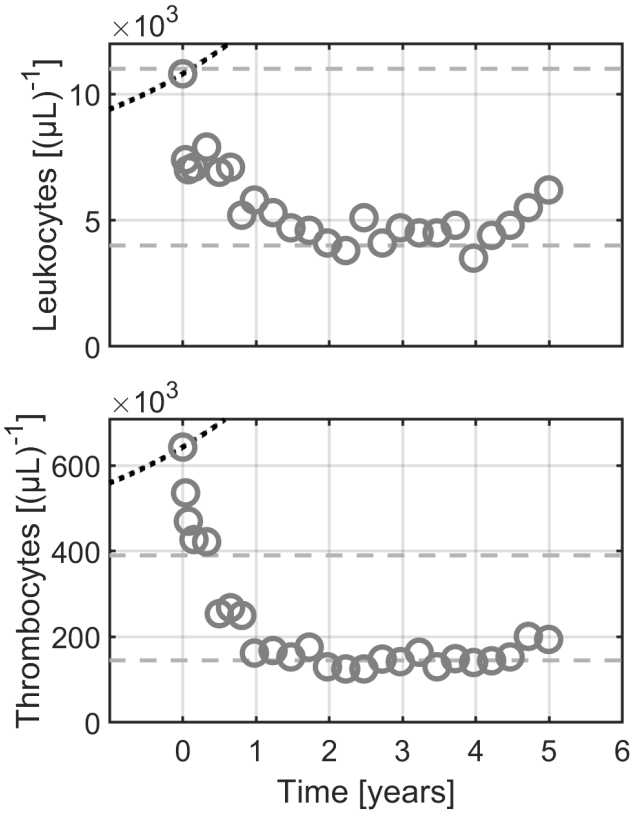
Fitting to data

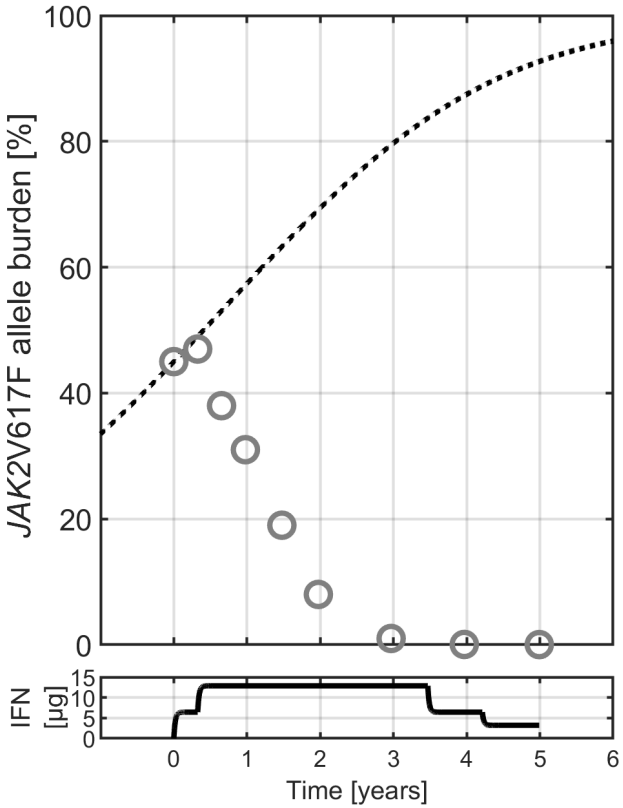




Raw data

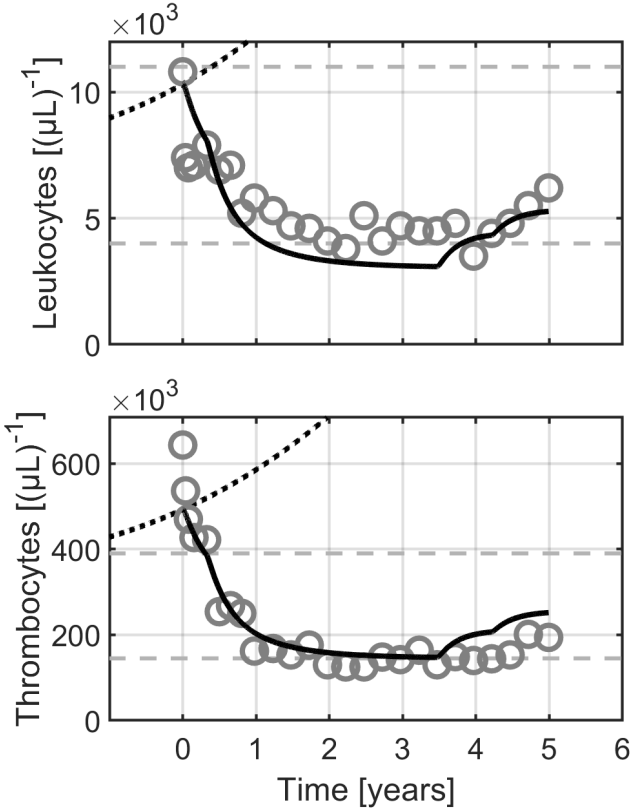
Fitting to data

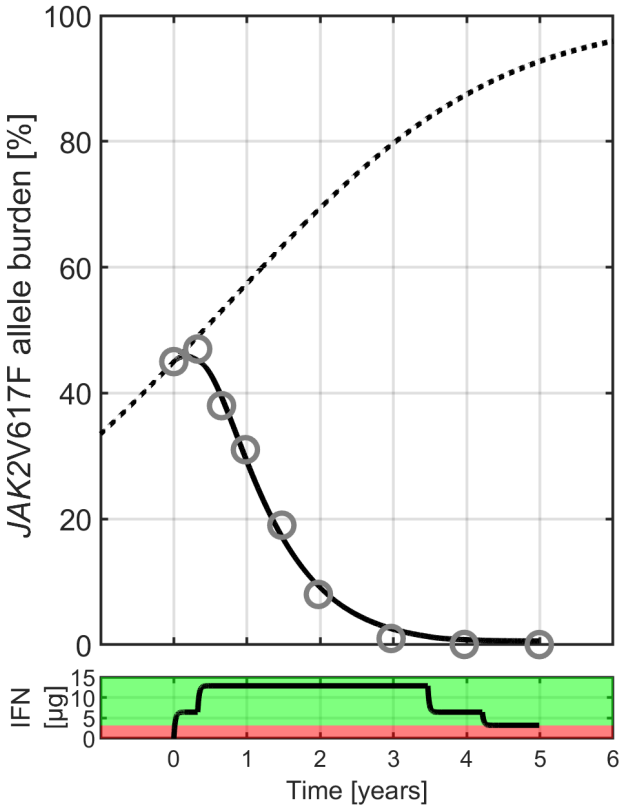




Adding modelled scenario without treatment, time-shifted to agree with baseline data (and PK/PD-modelling of treatment)

Fitting to data

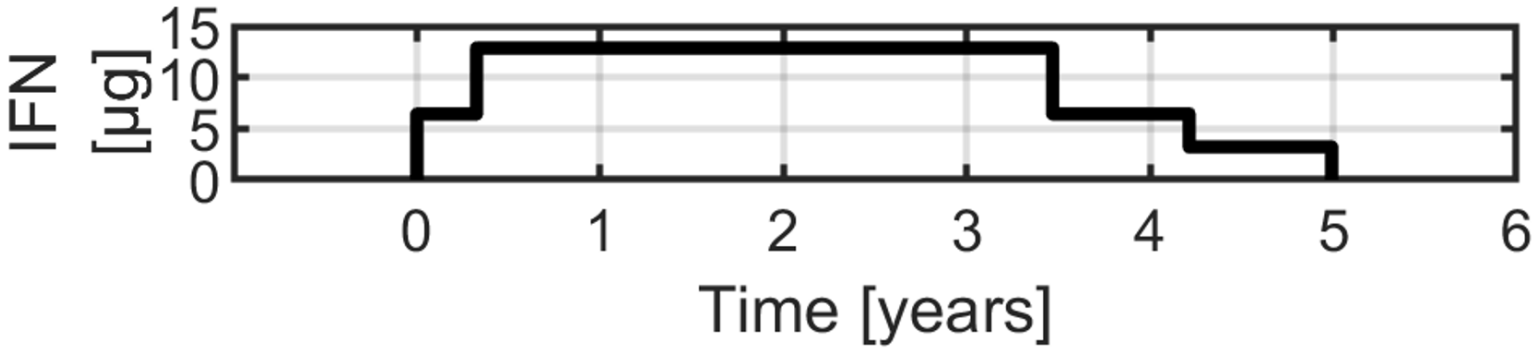




Dose-dependent fitting of model-parameters

Halting treatment

Actual treatment:



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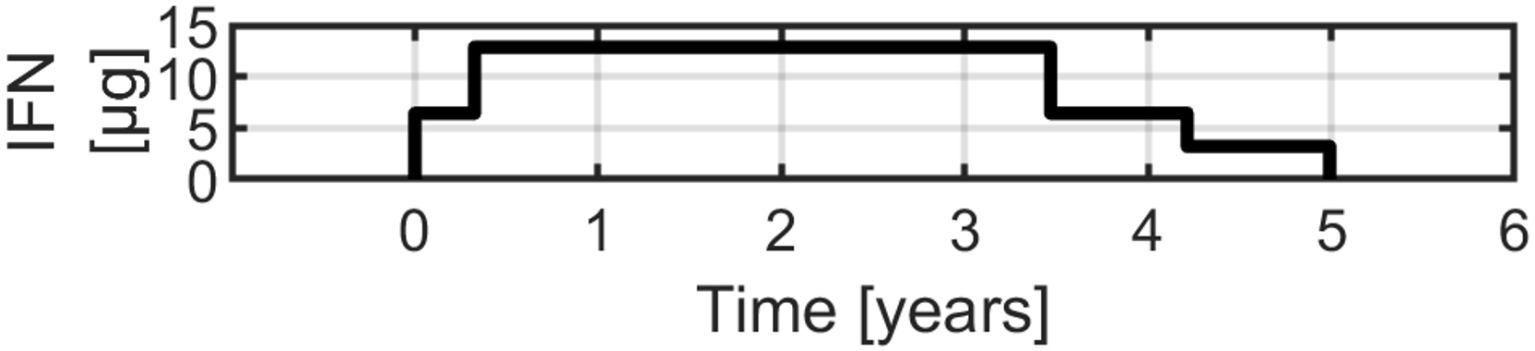
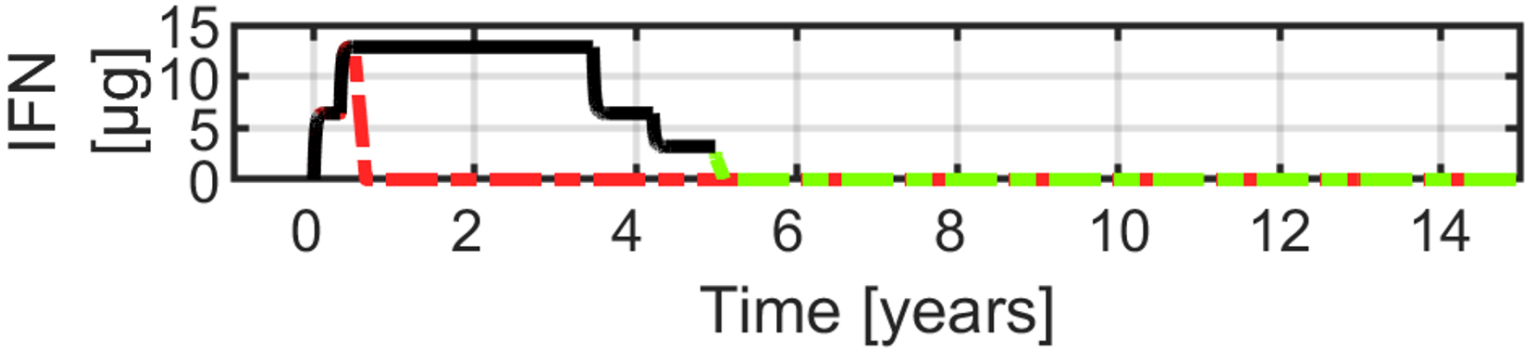


Hypothetical treatment:



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The model
Description
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Discussion
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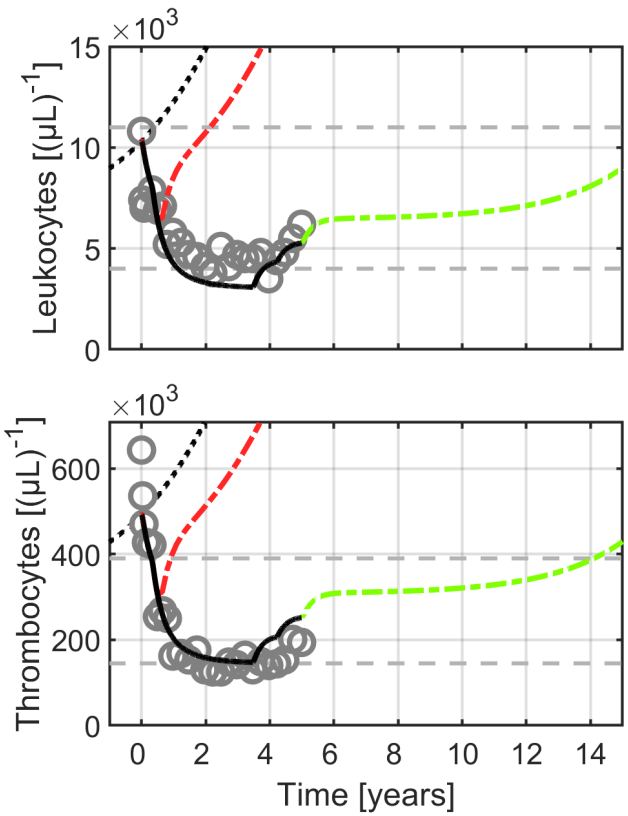
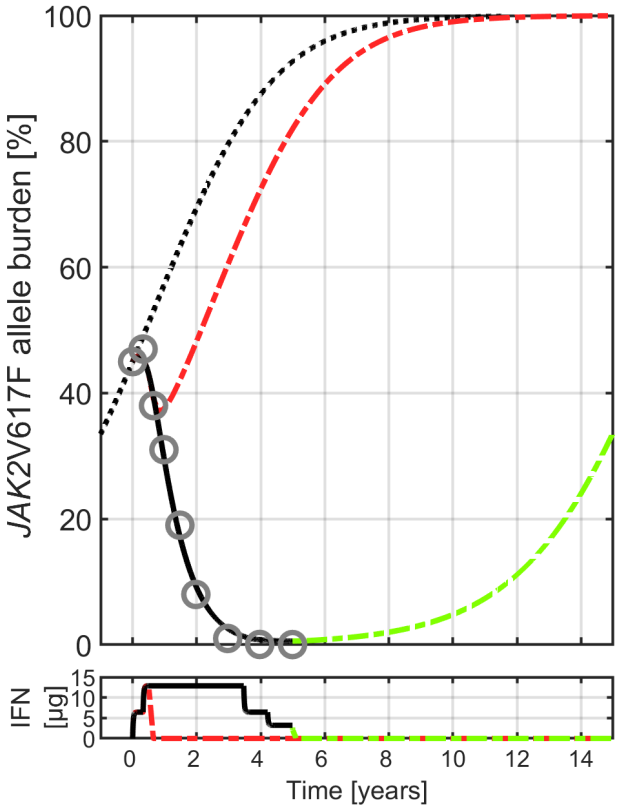
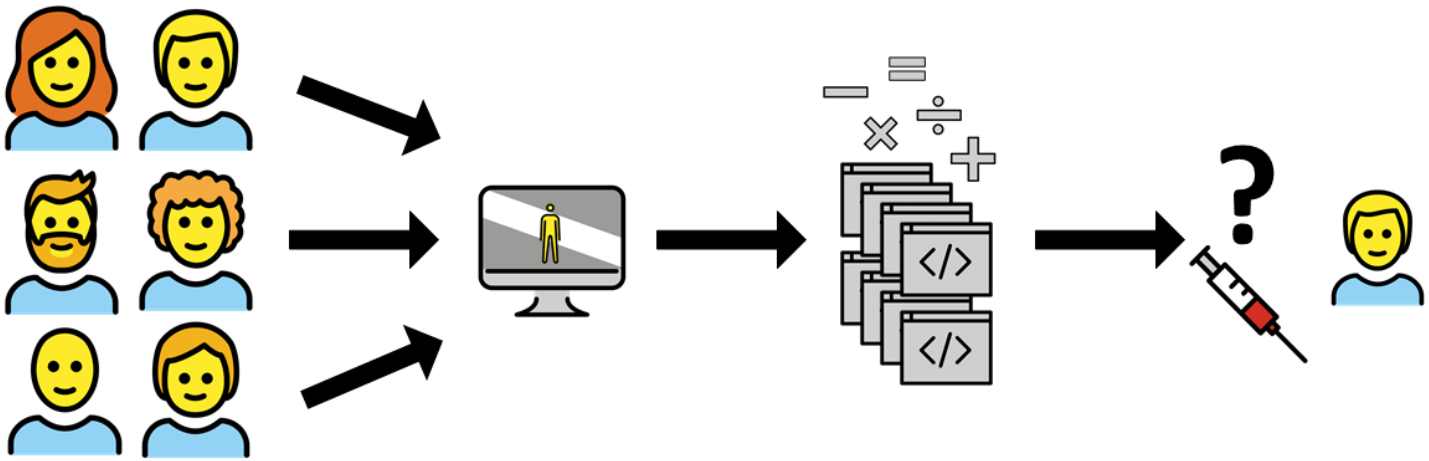




Population modelling



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Background
Purpose
The model
Description
Model behaviour
Relating to clinical data
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Hypothetical scenarios
Population modelling
Discussion
Our results
The future

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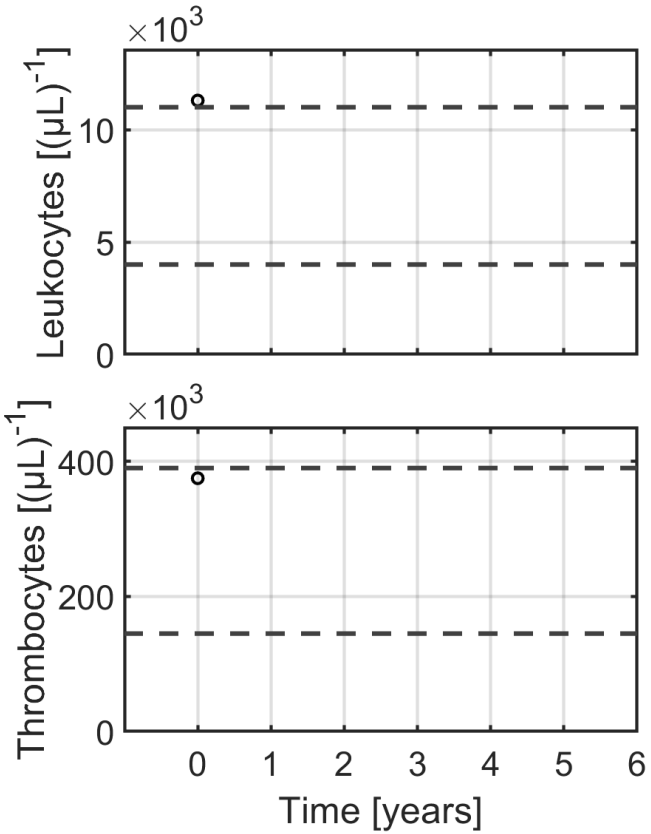
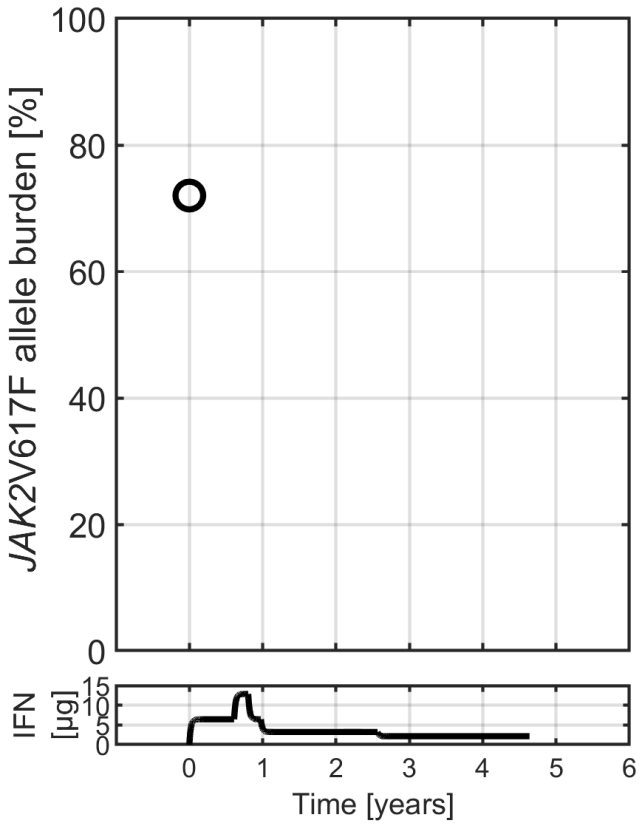
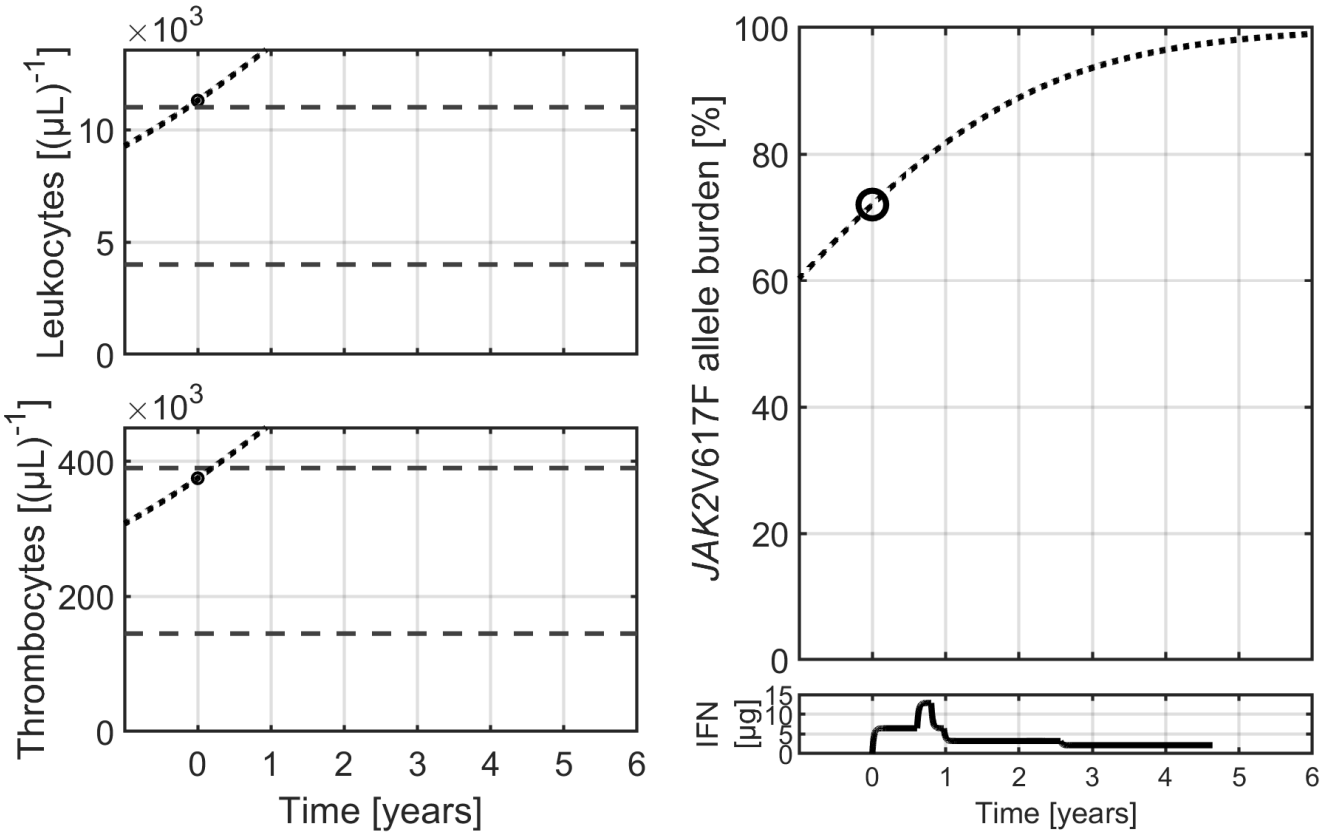




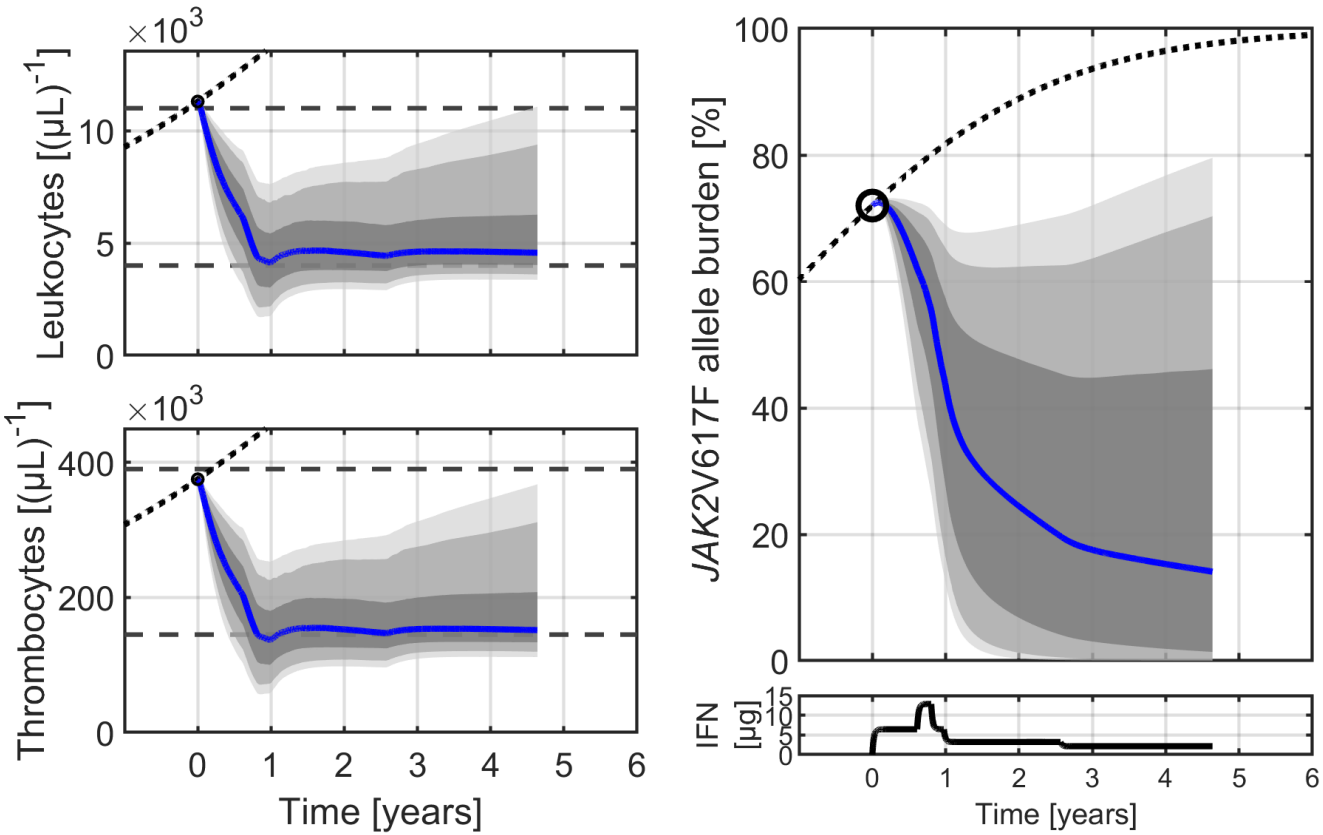
Baseline data

Population modelling



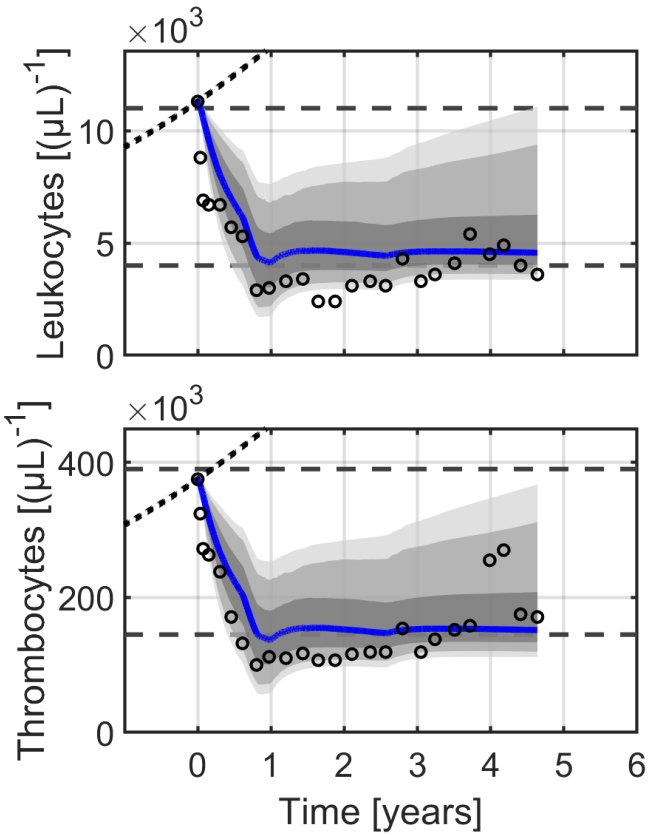
Estimating stage of disease progression and prediction in absence of treatment.

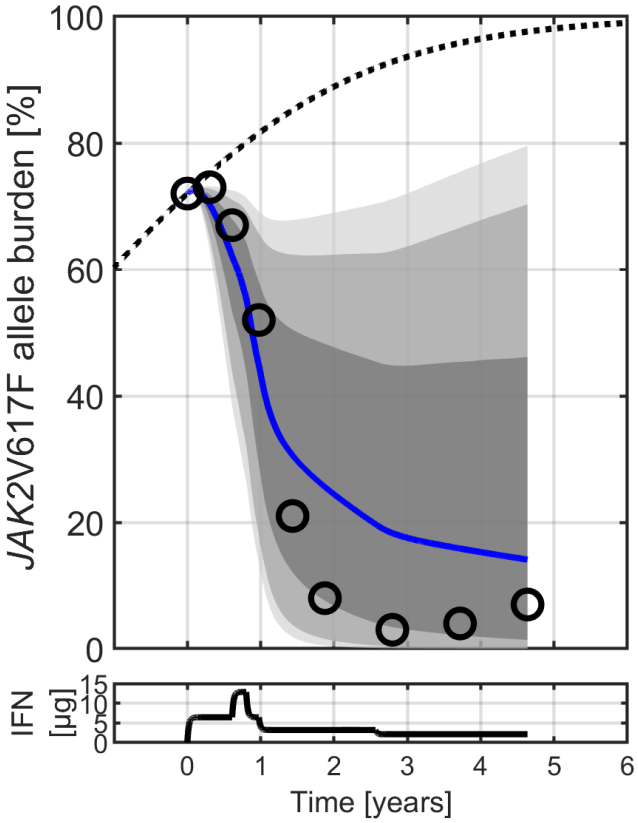
Population modelling



Simulation 1000 virtual patients with same treatment-plan.

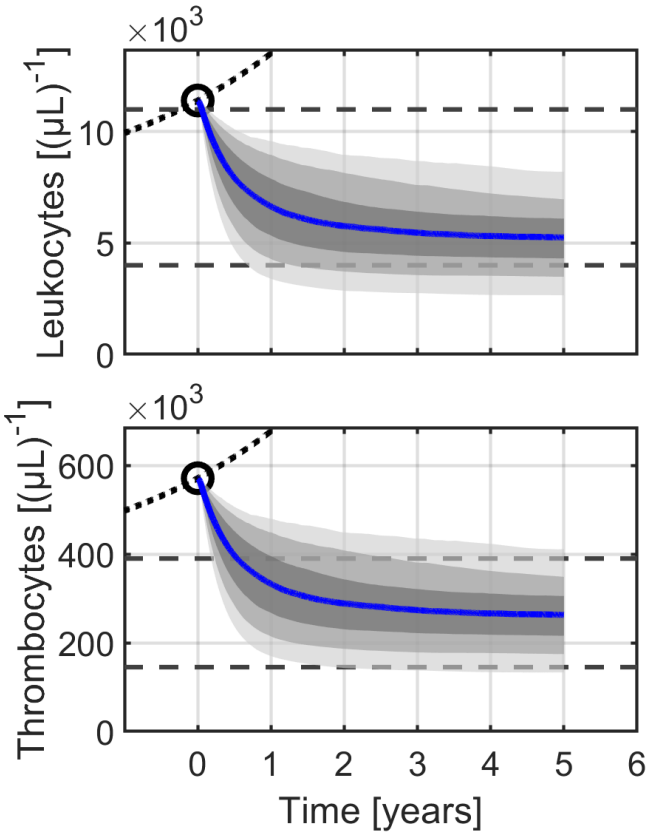
Population modelling

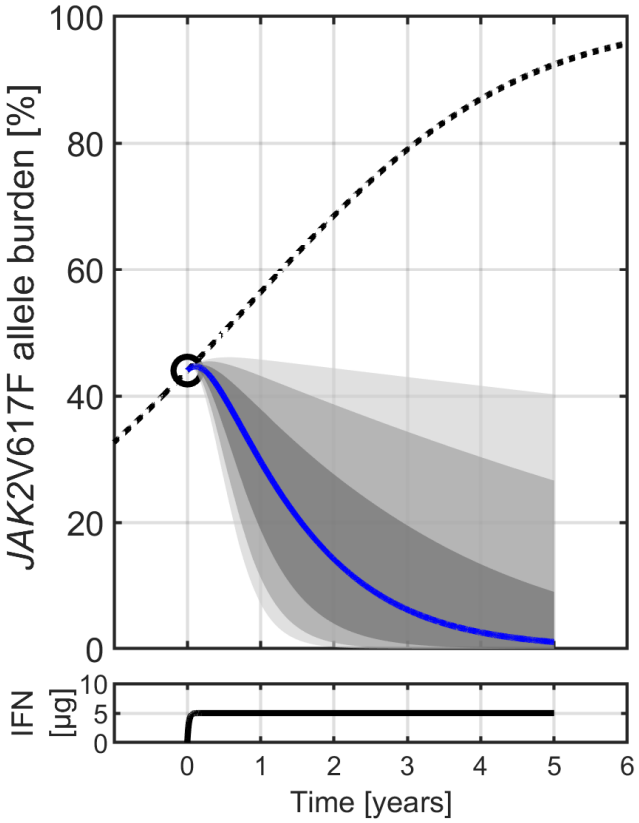




Comparing to actual patient data

Population modelling





Completely hypothetical patient: Baseline data from mean of cohort.

Summary and discussion

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- Mathematical modelling can relate mechanistic understanding of treatment to clinical measures.
- Individual patients' response to treatment can be captured by the model.
- Combining the response of multiple patients could make forecasting possible.
- However, further validation is required before predictions can be used in the clinic.

Comments on the future

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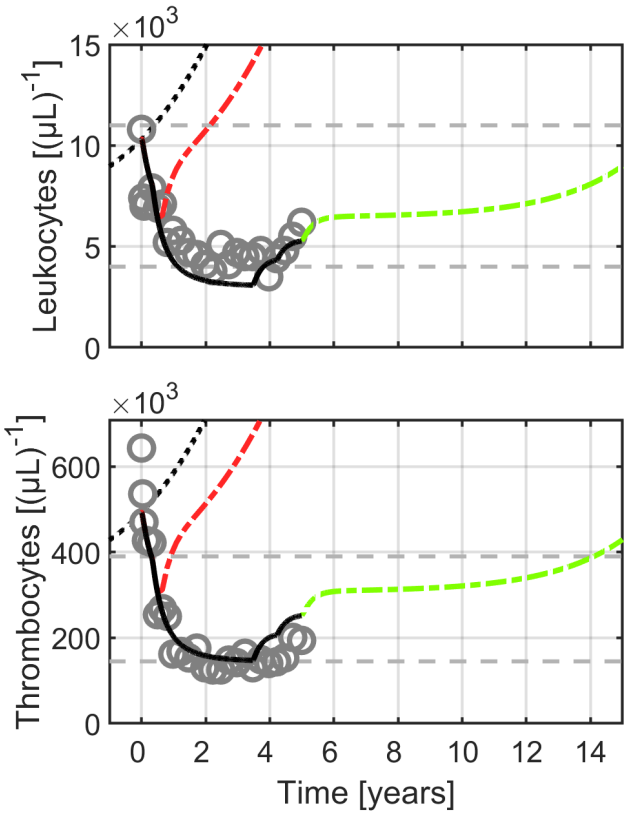
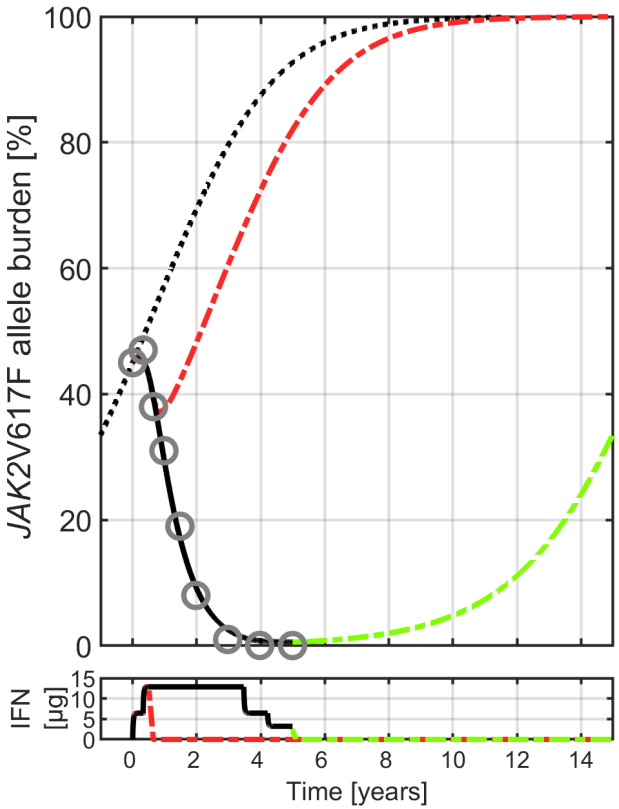
- Mathematical models as expert-assistance tool.





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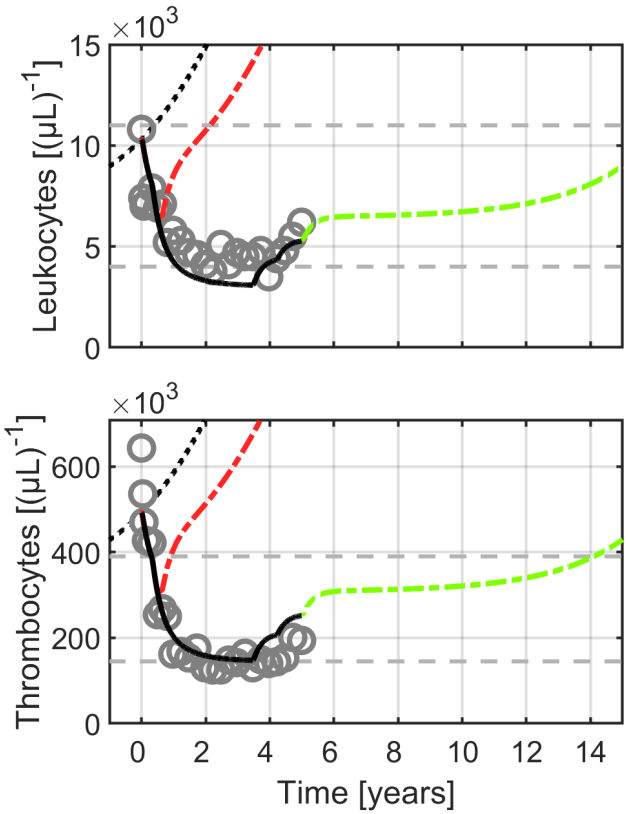
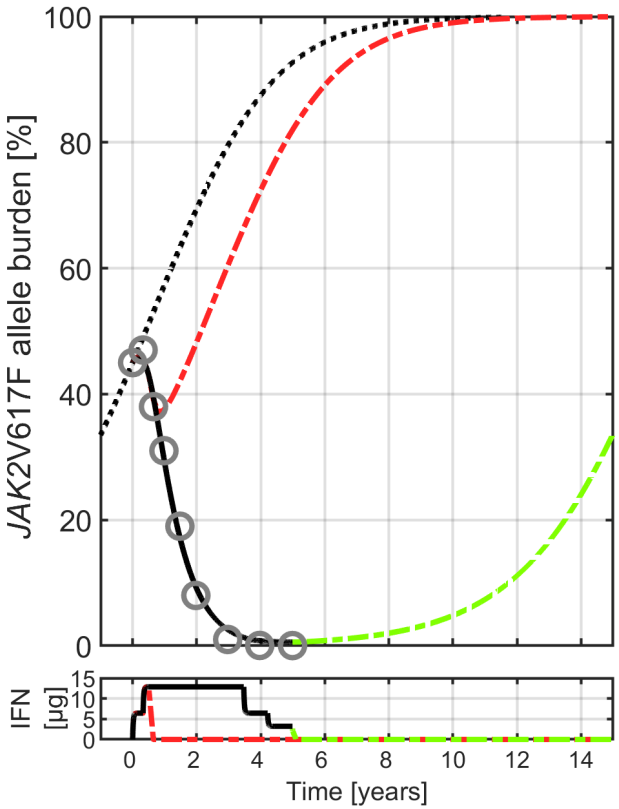
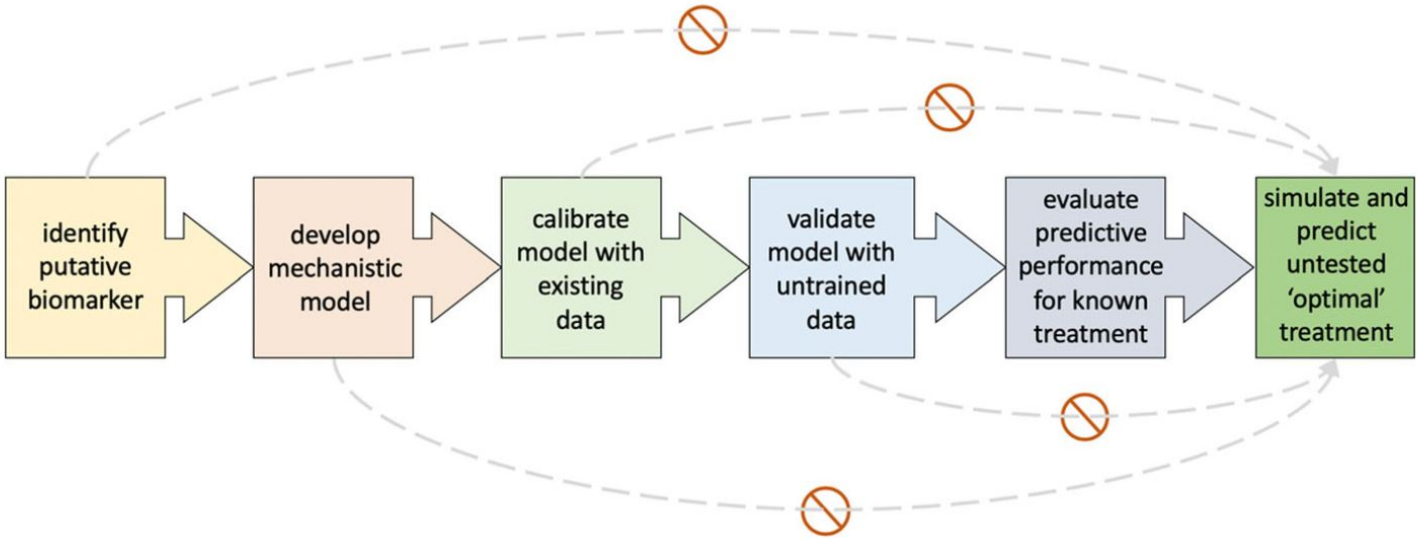
- Highly complex diseases affecting the entire body can be modelled succesfully.
- Mathematical models as expert-assistance tool.
- And as a tool for patient-communication.





Comments on the future

- Highly complex diseases affecting the entire body can be modelled succesfully.
- Mathematical models as expert-assistance tool.
- And as a tool for patient-communication.
- Promising for the future of oncology and heamatology, but careful and thoughtful validation is important.



(Brady & Enderling, 2019)

Thank you for your attention.

Any questions?

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References and related articles

- Pedersen RK, et al (2021), Dose-dependent mathematical modeling of interferon-α-treatment for personalized treatment of myeloproliferative neoplasms. *Comp. Sys. Onco.*; 1:e1030. https://doi.org/10.1002/cso2.1030
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Flowchart for prediction of "optimal" treatment from

- Brady, R., & Enderling, H. (2019). Mathematical Models of Cancer: When to Predict Novel Therapies, and When Not to. *Bulletin of Mathematical Biology*, 81(10), 3722-3731. https://doi.org/10.1007/s11538-019-00640-x