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Rasmus Kristoffer
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# Mathematical Modelling of Myeloproliferative Neoplasms and Hematopoietic Stem Cells

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

Rasmus Kristoffer Pedersen

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Roskilde University, Denmark

2<sup>nd</sup> Nordic Biomathematics Days
May 10<sup>th</sup>, 2022

# Introduction

▶ Who am I?

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    - ▶ Postdoc at the PandemiX Research Center, working on COVID-19 and historical epidemics.

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  - ▶ Illustration of how mathematical modelling could contribute to clinical practice in 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.

# Our purpose and goal

- **Myeloproliferative Neoplasms (MPNs):** Group of diseases characterized by overproduction of blood cells.

# Our purpose and goal

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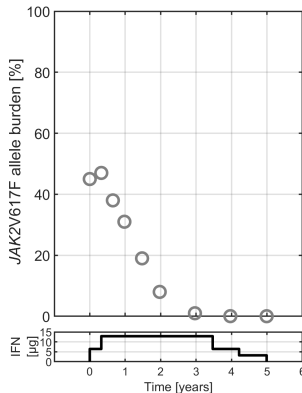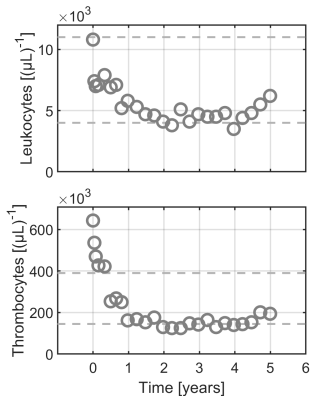Model behaviour
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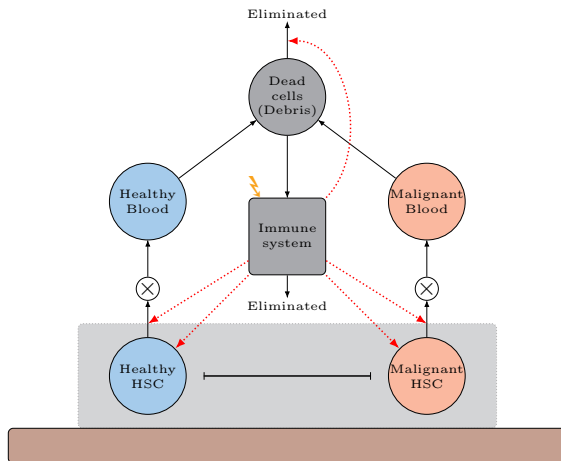Population modelling
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▶ **Myeloproliferative Neoplasms (MPNs):** Group of diseases characterized by overproduction of blood cells. Believed to arise from mutations occuring in hematopoietic stem cells (HSC)

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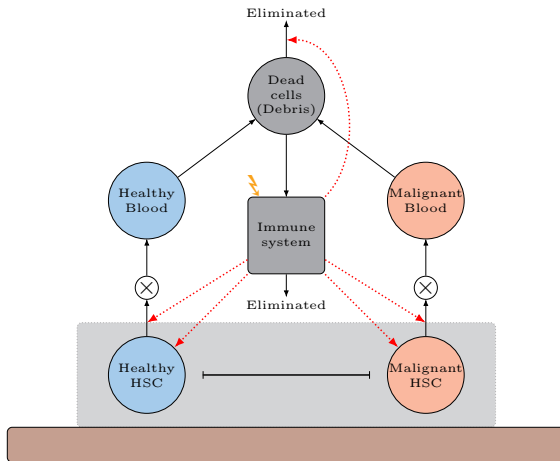Relating to clinical data
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▶ **Myeloproliferative Neoplasms (MPNs):** Group of diseases characterized by overproduction of blood cells. Believed to arise from mutations occuring in hematopoietic stem cells (HSC)

▶ **Clinicians from Zealand University Hospital:** MPN-patients treated with pegylated interferon-$\alpha$ obtain long-term normalization of cell-counts.

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- **Clinicians from Zealand University Hospital:** MPN-patients treated with pegylated interferon-$\alpha$ obtain long-term normalization of cell-counts.

- **Data:** Clinical trial with patients treated with interferon-$\alpha$.

- **Goal:** Can the effects of interferon-$\alpha$ 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).

# Model dynamics

▶ System of 6 ODEs, with about 16 parameters.

# Model dynamics

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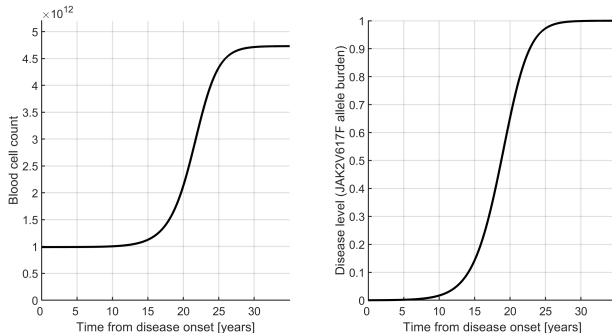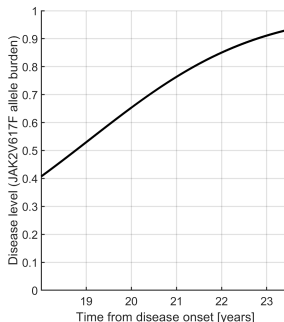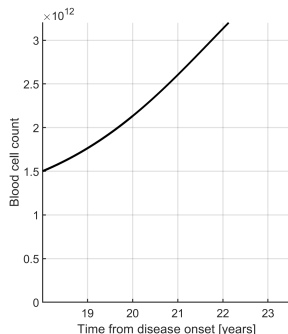Model behaviour

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- System of 6 ODEs, with about 16 parameters.
- Most parameters determined from the literature.

# Model dynamics

▶ System of 6 ODEs, with about 16 parameters.

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▶ General model behaviour in agreement with clinical intuition.

# Model dynamics

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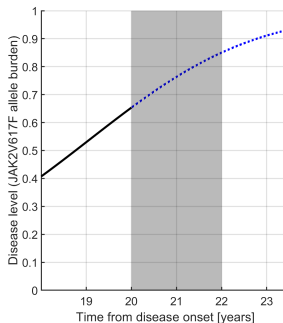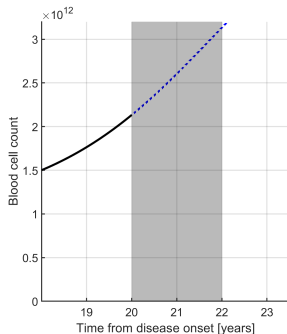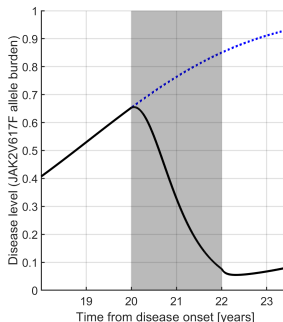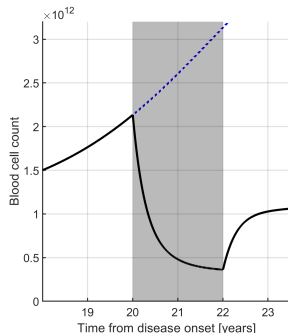
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- System of 6 ODEs, with about 16 parameters.
- Most parameters determined from the literature.
- General model behaviour in agreement with clinical intuition.
    - No mutations $\rightarrow$ long-term health.

# Model dynamics

- ▶ System of 6 ODEs, with about 16 parameters.
- ▶ Most parameters determined from the literature.
- ▶ General model behaviour in agreement with clinical intuition.
    - ▶ No mutations → long-term health.
    - ▶ Disease progression over a long period (15+ years).

# Model dynamics

- System of 6 ODEs, with about 16 parameters.
- Most parameters determined from the literature.
- General model behaviour in agreement with clinical intuition.
    - No mutations → long-term health.
    - Disease progression over a long period (15+ years).
    - Chronic inflammation leads to faster disease progression.

# Model dynamics

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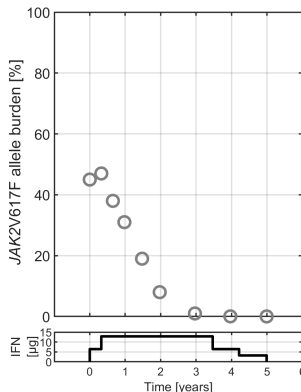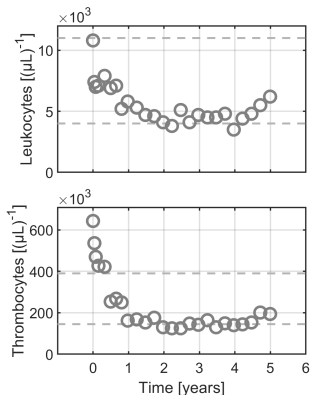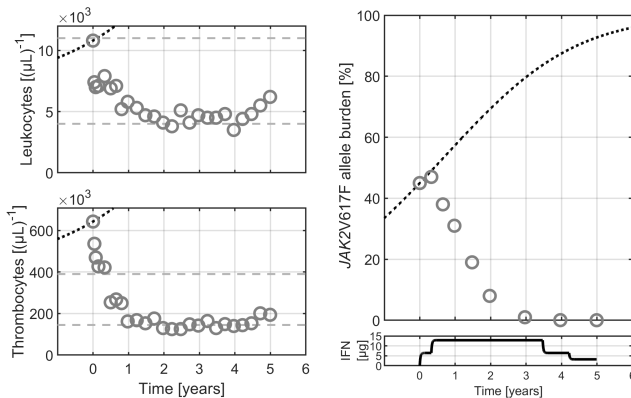Relating to clinical data

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▶ System of 6 ODEs, with about 16 parameters.

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▶ General model behaviour in agreement with clinical intuition.
  ▶ 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-$\alpha$ treatment.

# Treatment-specific perturbations

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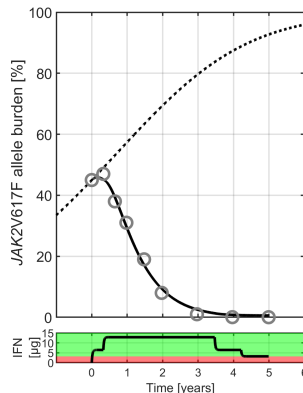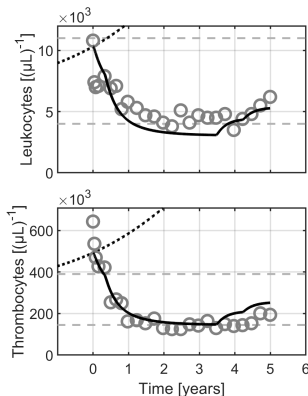Model behaviour

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Typical disease progression in the model.

# Treatment-specific perturbations

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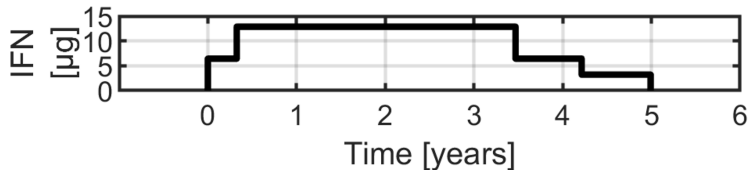Fitting to data
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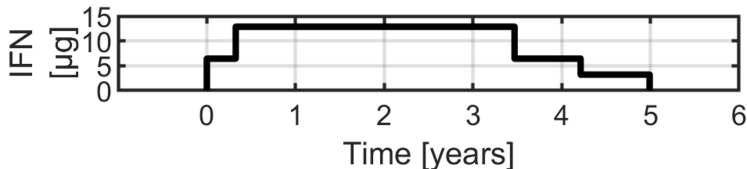Population modelling
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Zooming in on year 20 after original mutation.

# Treatment-specific perturbations

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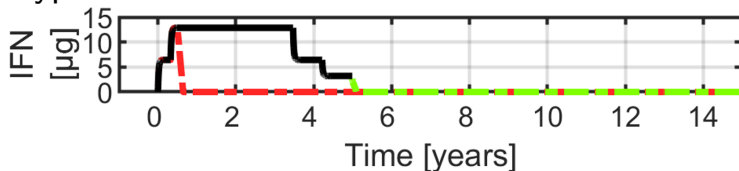
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Considering two years of treatment.

# Treatment-specific perturbations

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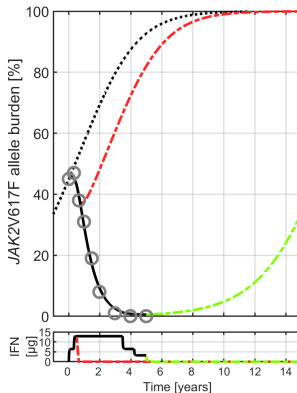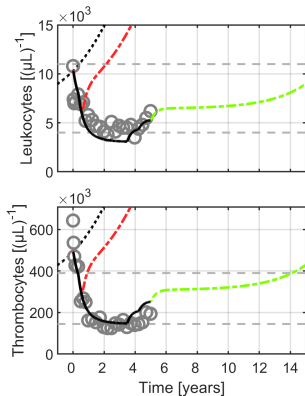Background
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Considering two years of treatment.
Perturbing model-parameters related to treatment.

# 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:

# Halting treatment

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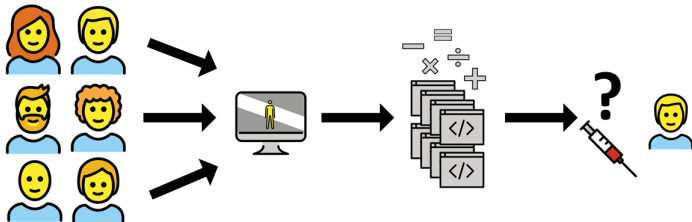Relating to clinical
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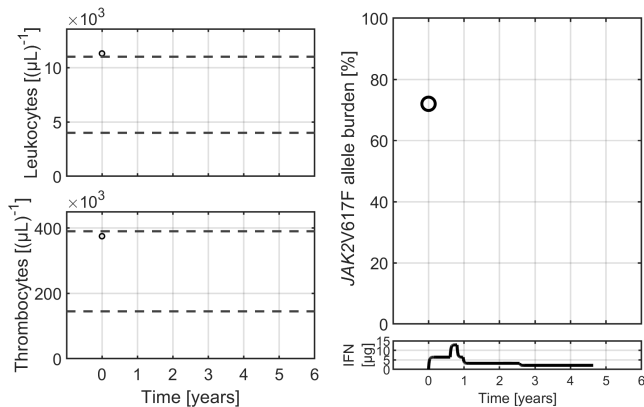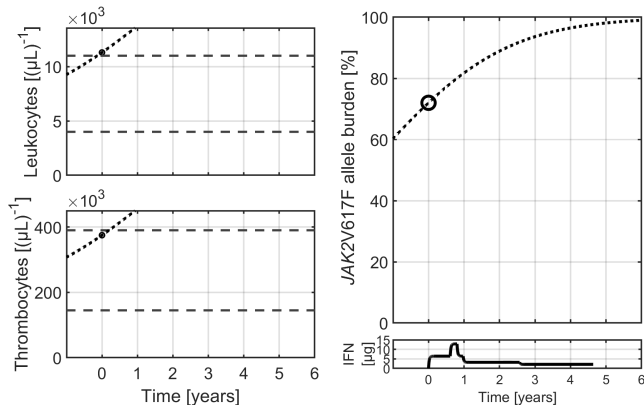
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Actual treatment:



Hypothetical treatment:

# Halting treatment

# Population modelling

# Population modelling

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

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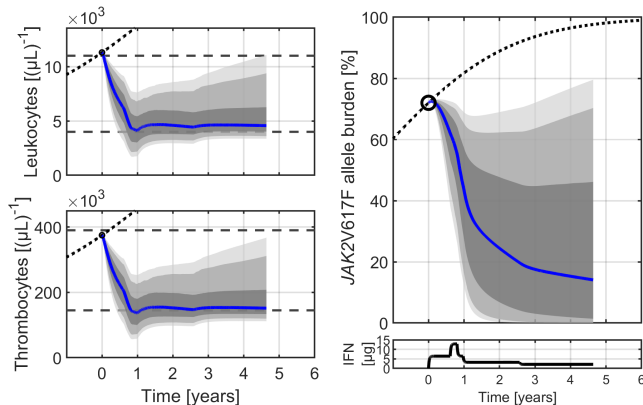Pedersen

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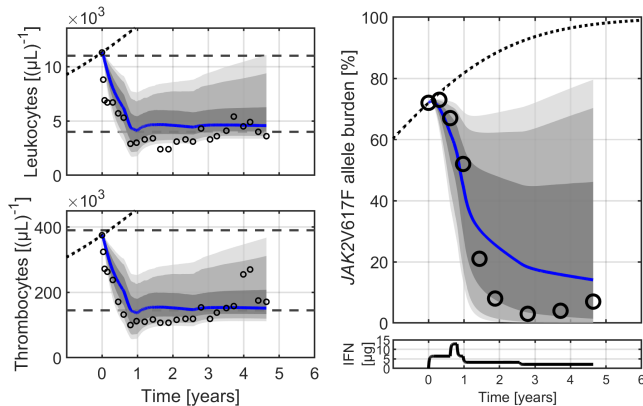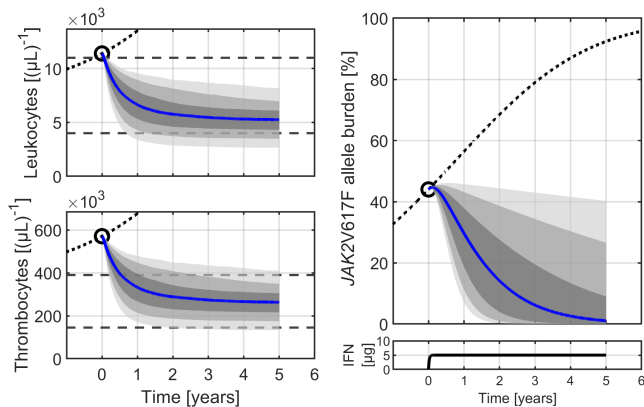Population modelling

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Completely hypothetical patient: Baseline data from mean of cohort.

# Summary and discussion

▶ Mathematical modelling can relate mechanistic
understanding of treatment to clinical measures.

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- ▶ Individual patients' response to treatment can be captured by the model.

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- ▶ Combining the response of multiple patients could make forecasting possible.

# Summary and discussion

- ▶ 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

- ▶ Highly complex diseases affecting the entire body can be modelled succesfully.

# Comments on the future

▶ Highly complex diseases affecting the entire body can
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▶ Mathematical models as expert-assistance tool.

# 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.

# Comments on the future

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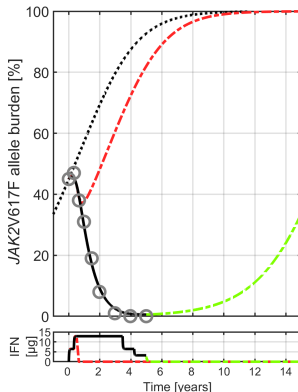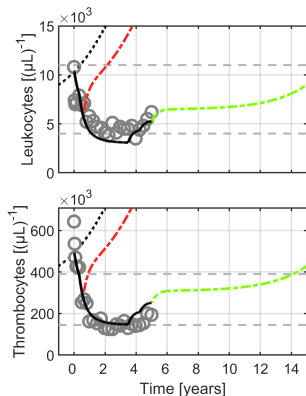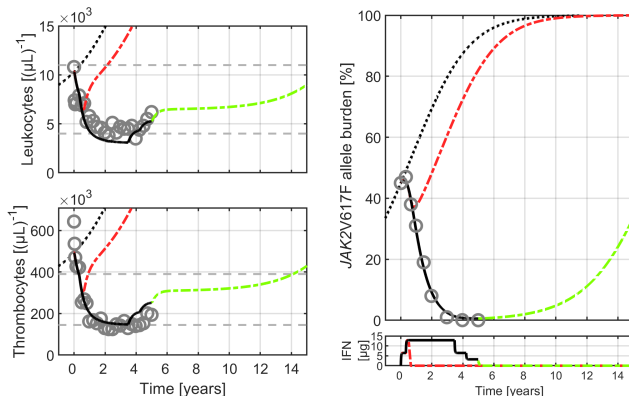Population modelling

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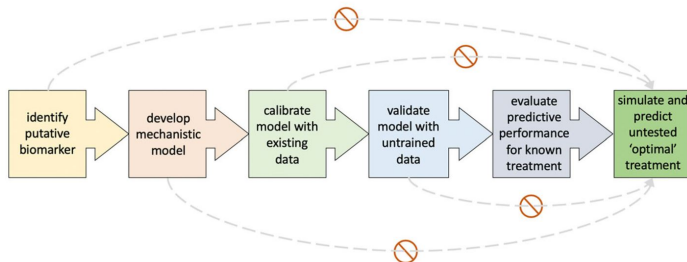
▶ Mathematical models as expert-assistance tool.

▶ 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

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▶ Pedersen RK, et al (2021), Dose-dependent mathematical modeling of interferon-$\alpha$-treatment for personalized treatment of myeloproliferative neoplasms. *Comp. Sys. Onco.*; 1:e1030. https://doi.org/10.1002/cso2.1030

▶ Pedersen RK, et al (2021), Mathematical modelling of the hematopoietic stem cell-niche system: Clonal dominance based on stem cell fitness. *Journal of Theoretical Biology*, Volume 518, 110620, https://doi.org/10.1016/j.jtbi.2021.110620

▶ Ottesen JT, Pedersen RK, et al (2020), Mathematical Modeling of MPNs Offers Understanding and Decision Support for Personalized Treatment. *Cancers*; 12(8):2119. https://doi.org/10.3390/cancers12082119

▶ Andersen M, Sajid Z, Pedersen RK, et al (2017), Mathematical modelling as a proof of concept for MPNs as a human inflammation model for cancer development. *PLoS ONE* 12(8): e0183620. https://doi.org/10.1371/journal.pone.0183620

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