

Integral individualized mechanistic model of hematopoiesis

explains and predicts joint dynamics of thrombocytes, granulocytes and lymphocytes under different chemotherapeutic and adjuvant treatments scenarios

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Background

- Leukopenia and thrombocytopenia frequently result from **chemotherapy-induced bone marrow damage**
- Maturation of different blood cell lines are interdependent branching processes and influenced from stem-cells-niches supporting osteoblasts
- Understanding of entire **hematopoiesis** during chemotherapy is crucial for the control of thrombocytes nadir by dose adjustments and supportive treatments (**platelet transfusion**, stimulating treatment using growth factors such as **thrombopoietin (TPO)** or **granulocyte-colony stimulating factor G-CSF (filgrastim)** with an option of pegylation)

Objectives

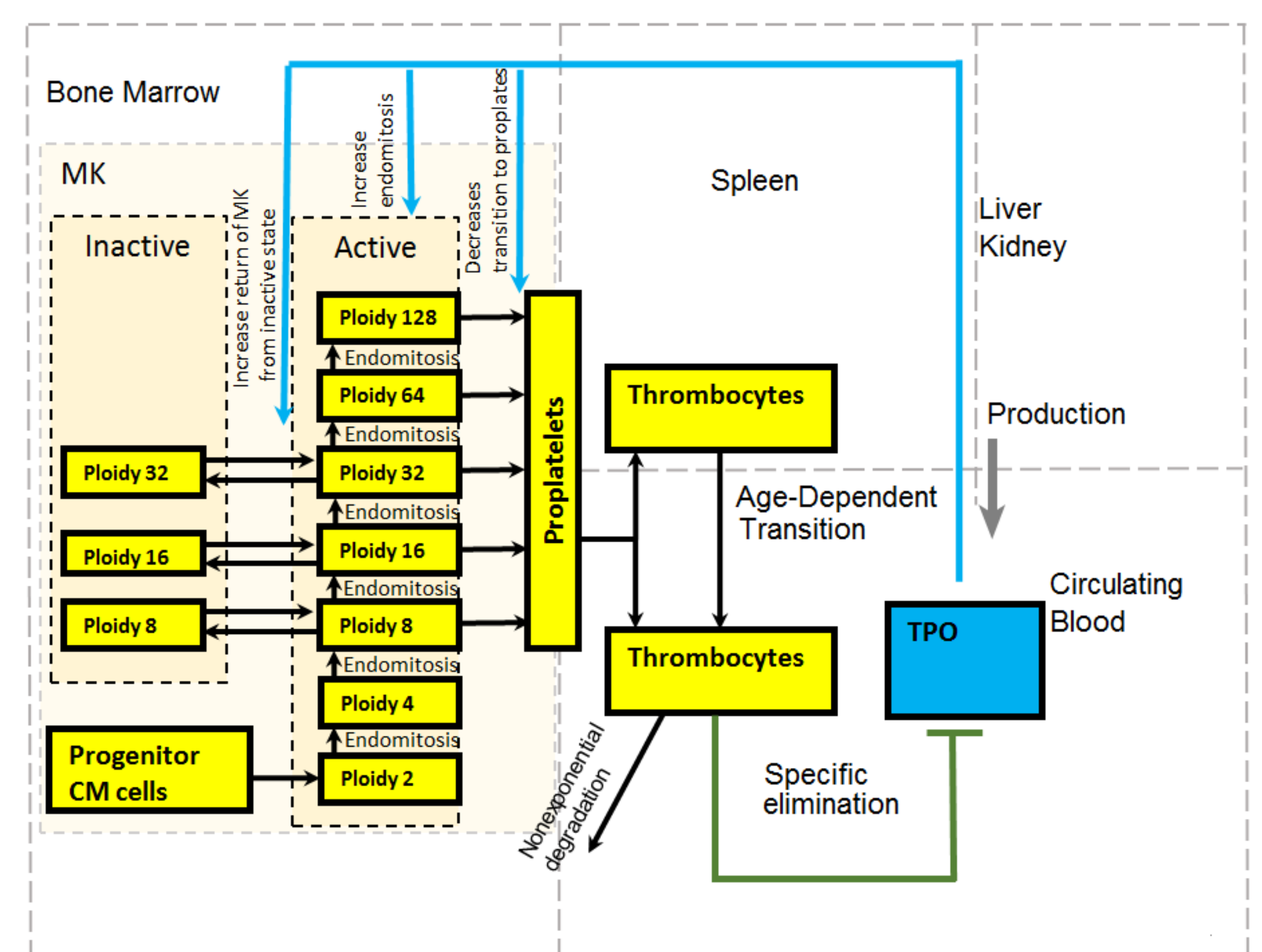
- Revision and fusion of our former single-lines hematopoiesis models with osteoblasts/osteoclasts dynamics (Komarova et al model¹)
 - Granulopoiesis model under chemotherapy² and G-CSF derivatives³
 - Individualized thrombopoiesis model under chemotherapy⁴
 - Modeling the **long-term effects** of multi-cyclic chemotherapies by means of osteoblasts loss
- Development of a novel lymphopoiesis model taking into account chemotherapy influence on the lymphocytes recirculation
- Simultaneous estimation of the parameters** for individual patient data and averaged data of other studies

Model structure

- Multi-compartment ODE system
- The stem cells either mature to progenitor cells or to lymphoid precursors
- Both stem and progenitor cells can be active or quiescent
- Megakaryocytes can be active or quiescent
- Activation of quiescent cells
 - TPO activates directly the quiescent cells in a long-ranged fashion
 - Osteoblasts support quiescence
 - G-CSF eliminate osteoblasts in a short-ranged fashion
- Granulopoietic precursors differentiate to early banded (CBC) and later segmented neutrophils (CSC) sequestered in bone marrow

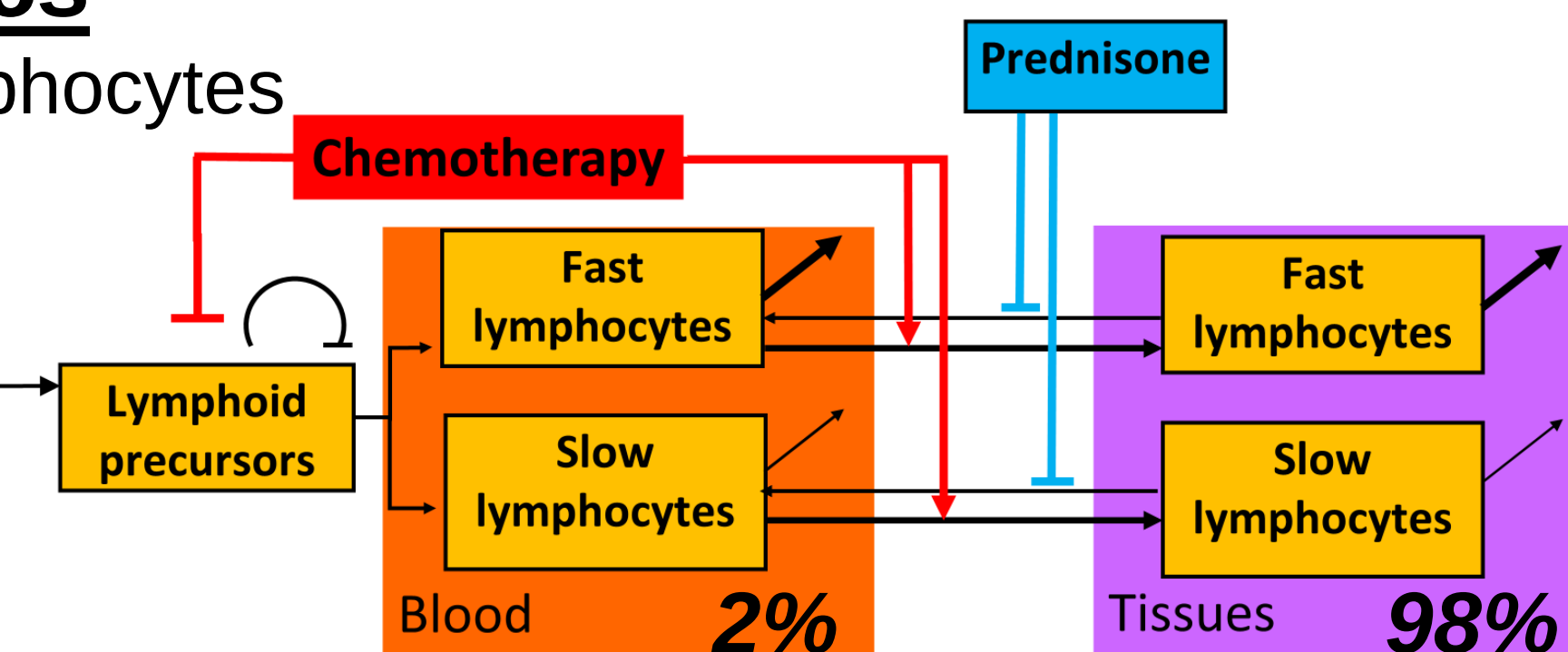
- Branching processes
 - Maturing progenitors can differentiate either to granulocytes or to megakaryocytes depending on concurrence between TPO and G-CSF
 - Megakaryocytes of ploidies 8-128 can create proplatelets
 - G-CSF stimulates release of banded and segmented neutrophils to a blood
- Chemotherapies eliminate
 - all active precursors (short-ranged effect)
 - osteoblasts inducing long-ranged decrease of platelets and granulocytes

Megakaryocytes dynamics ⁴



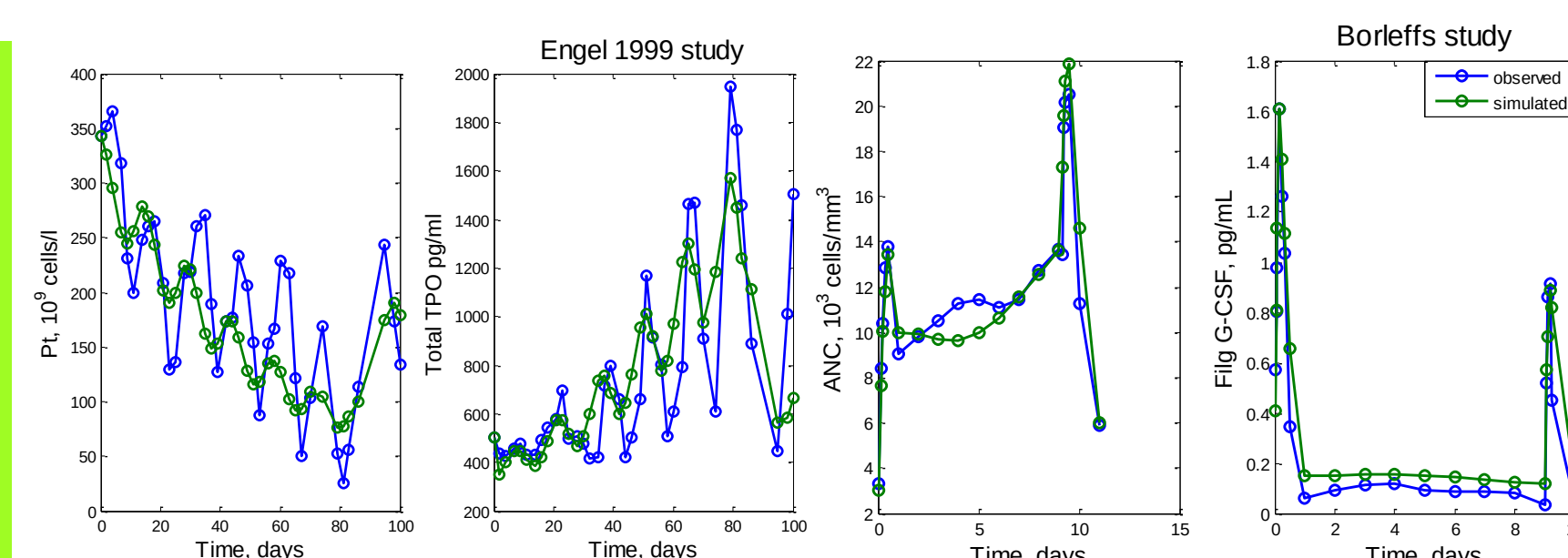
Lymphocytes dynamics

- Chemotherapy induces lymphocytes margination and recirculation

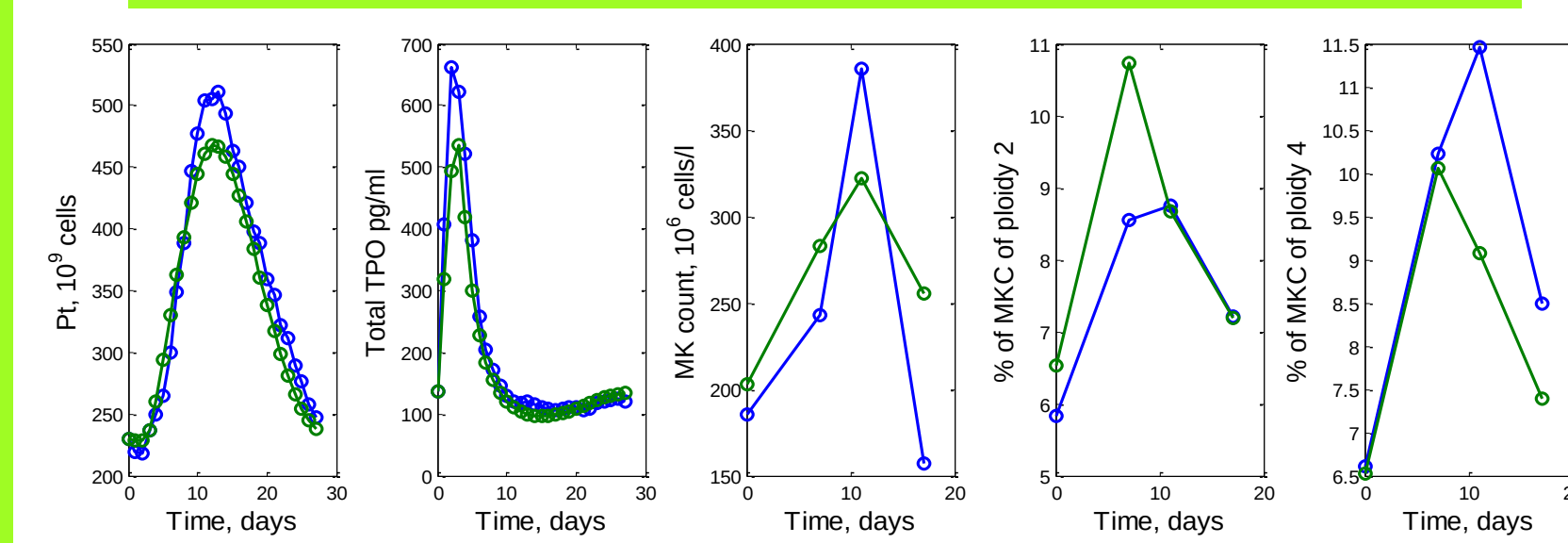


Data and fitting results

- 3 patients were treated with multicyclic CHOEP 21, BEACOPP-21 escalated, BEACOPP-14 poly-chemotherapies combined with filgrastim, Engel et al⁵
- PK/PD effects of dose-escalating subcutaneous peg-filgrastim, Roskos et al⁶
- PK/PD effects of dose-escalating subcutaneous filgrastim, Borleffs et al⁷
- PK/PD effects of recombinant TPO in normal patients, Harker et al⁸
 - Total TPO, megakaryocytes of all ploidies and platelets were monitored



- The green points highlight the model's fits
- The blue points highlight the measured data



- PK/PD effects of filgrastim before and after chemotherapy (carboplatin with paclitaxel), Johnston et al⁹
- PD effect of prednisone on lymphocytes and neutrophils¹⁰
- PD effects of chemotherapy and filgrastim on osteoblasts
- PD effect of filgrastim on proliferative activity of different granulopoietic precursors

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Results and Conclusions

- We successfully established a comprehensive mechanistic model of human hematopoiesis which
 - simulates wide spectrum of chemotherapies as well as supportive treatments
 - simulates different precursor compartments measured in different studies
 - allows simultaneous individual predictions of degrees of thrombopenia, neutropenia and lymphopenia for the first time with superior accuracy compared to statistical or semi-mechanistic competitors
 - has been realized in a tool intended to support real-time individualized decision making and therapy adaptations by physicians during multi-cyclic cancer treatments for the case of thrombopoiesis
- The model development was executed under the **full information concept** by integrating individual patients' data with as much previously known information as possible
- We estimated 74 population and 24 individual parameters