Model-based individual managing of thrombopenia during multi-cyclic chemotherapy

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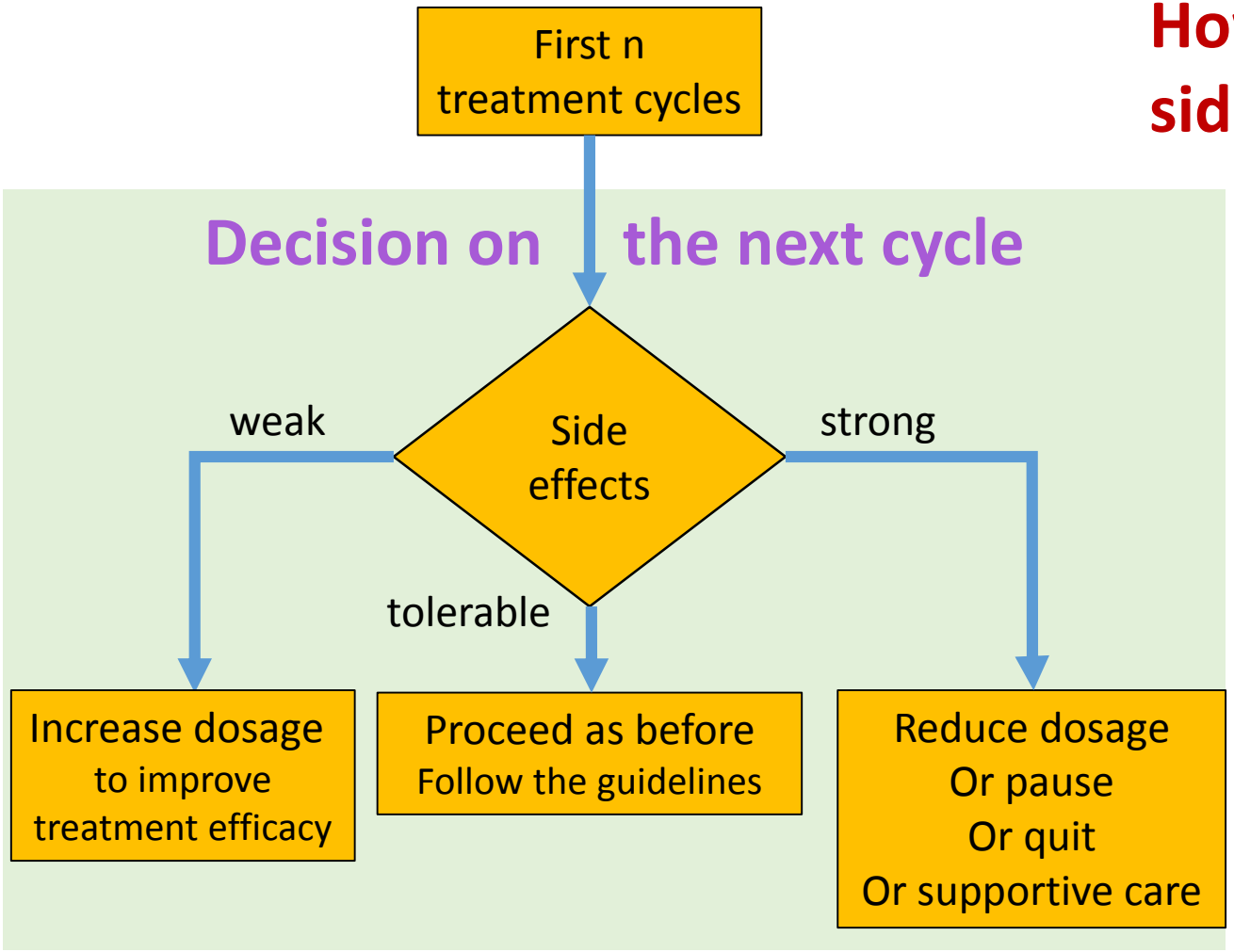
Budapest

The next-cycle managing scheme



How to predict hematological side effects with high precision?

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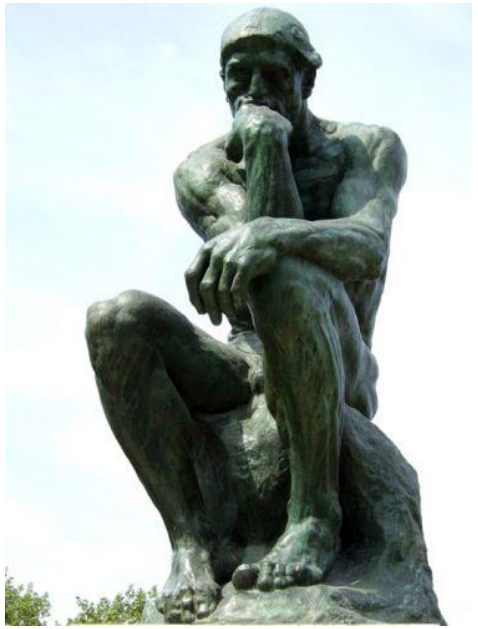


?

How?

Thrombopenia is scarcely predictable
statistical models are imperfect

- A few patients with high toxic response limit therapy intensification for the entire population

Statistical risk score

- Low risk group

Grade (WHO)	0	1	2	3	4
Cycle 1-3	89.2%	5.8%	2.8%	1.6%	0.5%
Cycle 4-6	67.8%	15.1%	9.2%	5.9%	2%

- High risk group

Grade (WHO)	0	1	2	3	4
Cycle 1-3	19.7%	14.4%	24%	26%	16%
Cycle 4-6	7.5%	7.1%	16.8%	31.4%	37.2%

- Tox calculator for calculating thrombopenia prognostic scores
  - CHOP-like regimen
  - Aggressive NHL
- http://www.toxcalculator.com/

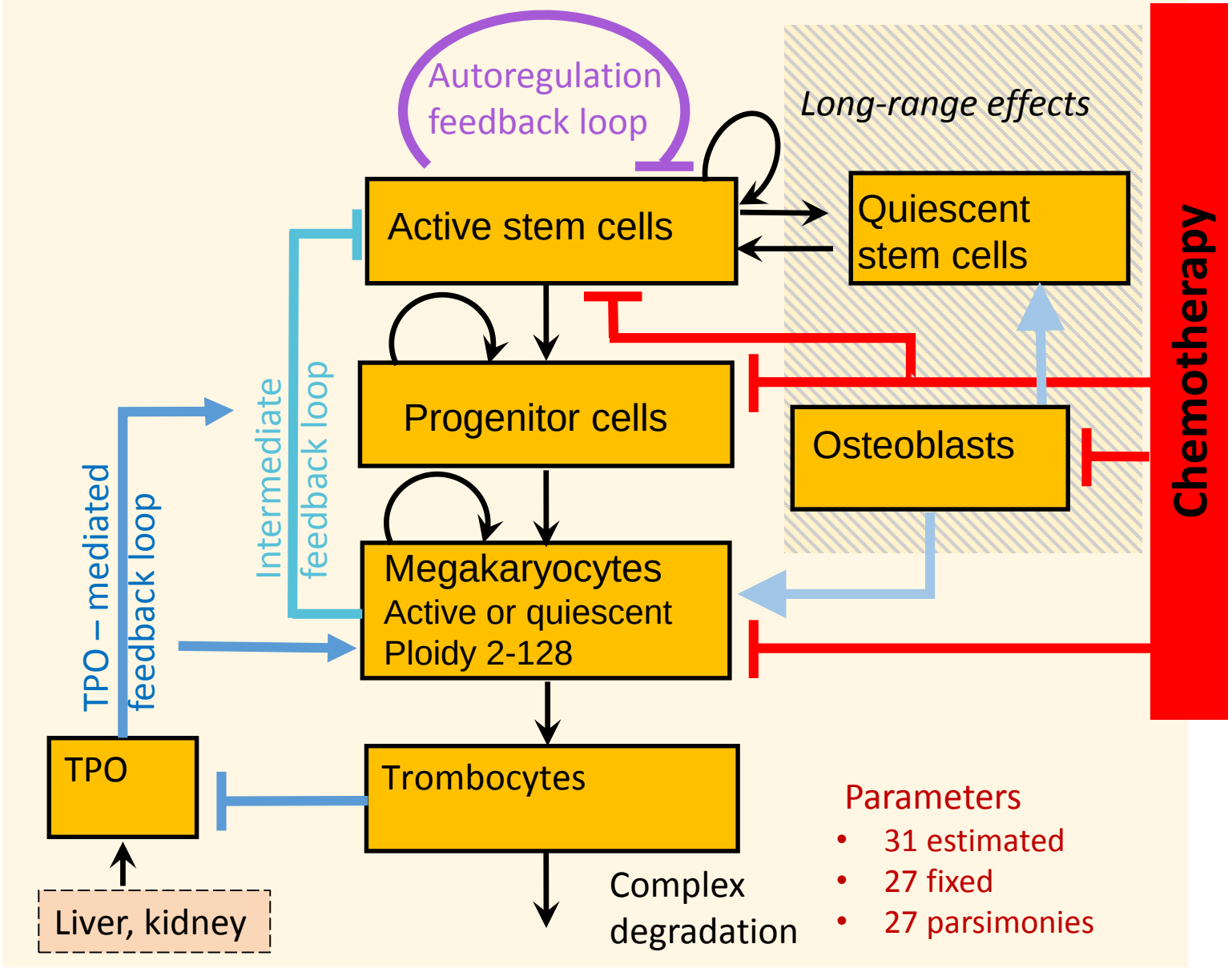
IOV of blood cells response to multi-cyclic chemotherapy

- IOV, a current approach:
  - Considered as ***random effects by current mixed effects models***
  - A tool for neutrophil guided dose adaptation in chemotherapy
    - Wallin et al (2009), Friberg et al (2002)
- Mechanistic reasons for IOV
  - Accumulating injury in the bone marrow
  - Different timescales of biological processes
  - Several levels of feedbacks in hematopoiesis

The former basic human model of thrombopoiesis

- "A biomathematical model of human thrombopoiesis under chemotherapy", Scholz et al (2010), *Journal of Theoretical Biology*
  - ODE mechanistic model
  - Explains
    - Multi-cyclic poly-chemotherapy
    - Different biological experiments
- Challenges
  - The human model to be updated
  - Individualization of parameters and treatments
    - Highly heterogeneous platelets responses to the same chemotherapy regimens
    - Individual changes in treatment plans
- Aim
  - Individualized model-based treatment plans for multi-cyclic chemotherapy and auxiliary treatments

Our updated mechanistic model



Our approach of data integration

Individualized model should be consistent with other studies

Clinical individual data
i-th patient

Treatment condition
- Chemotherapy
- Supportive treatments

Observed dynamics
- Palelets
- (TPO)

Virtual participation

As if an i-th patient took part **also** in every biological experiment

Biological experiments

Treatment condition
- TPO injection
- Chemotherapy
- Platelets transfusion

Observed avereaged data
- Palelets
- TPO
- Megakaryocytes
- Osteoblasts

- i-th parameters set is used for simulation
  - **Extended individual data**
    - Real individual clinical data
    - Simulation of biological experiments
  - i-th goal function
    - penalizes deviations of
    - simulated from observed data

- **Simultaneous** data fitting
  - Individual and population parameters
  - Summation of individual goal functions
    - For all patients together

Individual clinical data used for modelling

- BEACOPP Chemotherapy
  - Treats Hodgkin‘s lymphoma
  - 6-8 cycles, 14 or 21 days each
- CHOP-Like chemotherapies
  - Treats Non-Hodgkin lymphoma
  - 6 cycles, 14 or 21 days each

Drug	BEACOPP	CHOP	CHOEP	Cycle Day	Mode
Cyclophosphamide	650 mg/m^2	750 mg/m^2	750 mg/m^2	1	IV
Doxorubicin	25 mg/m^2	50 mg/m^2	50 mg/m^2	1	IV
Etoposide	100 mg/m^2	-	100 mg/m^2	1-3	IV
Oncovin	1.4 mg/m^2	1.4 mg/m^2	1.4 mg/m^2	1 or 8 (BEACOPP)	IV
Prednisone	40 mg/m^2	40 mg/m^2	40 mg/m^2	1-5 or 1-14 (BEACOPP)	PO
Procarbazine	100 mg/m^2	-	-	1-7	PO
Bleomycin	10 mg/m^2	-	-	8	IV

Biological data

- Single dose's pegylated TPO effect on dynamics of
  - Platelets and megakaryocytes counts
  - Megakaryocytes fractions of different ploidies
  - Total TPO concentration
- Non-exponential degradation of transfused labeled platelets
  - Platelets transit time depends strongly on the initial platelets count
    - Nearly 2-fold shorter for patients with severe thrombopenia
- Long-range effects of chemotherapy
  - Osteoblasts count decrease
  - Destruction of hematopoietic stem cell niches

Harker et al (2000), Hanson and Slichter study (1985), Li et al (2015)

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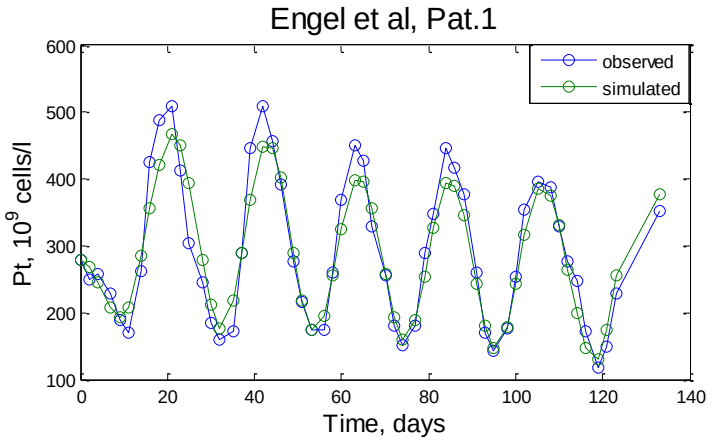
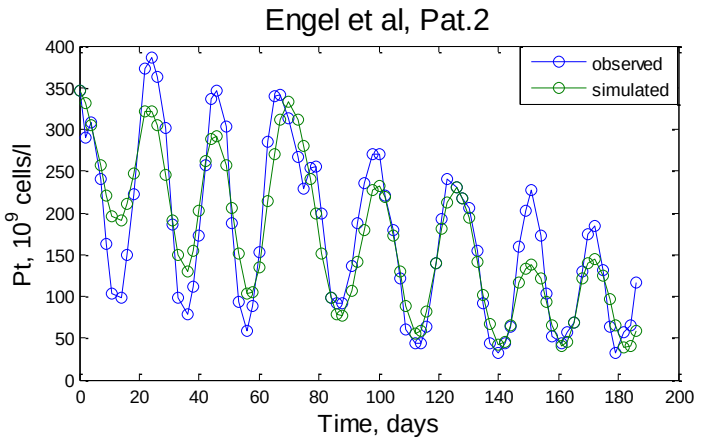
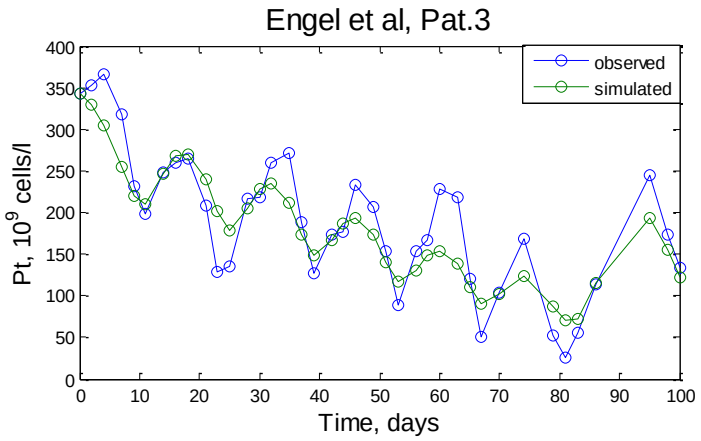
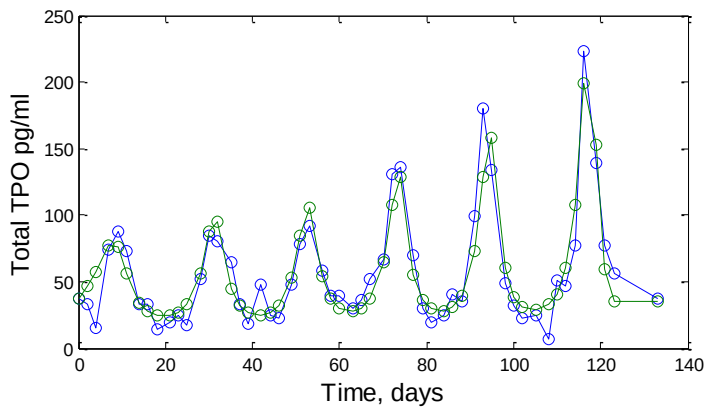
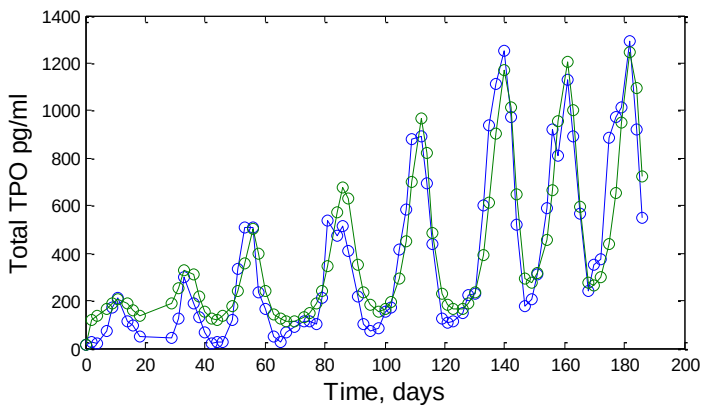
Fitting of platelets and TPO dynamics of the patients from Engel et al study

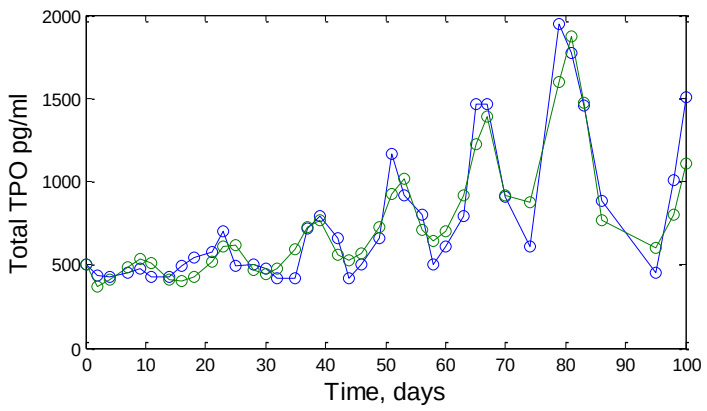






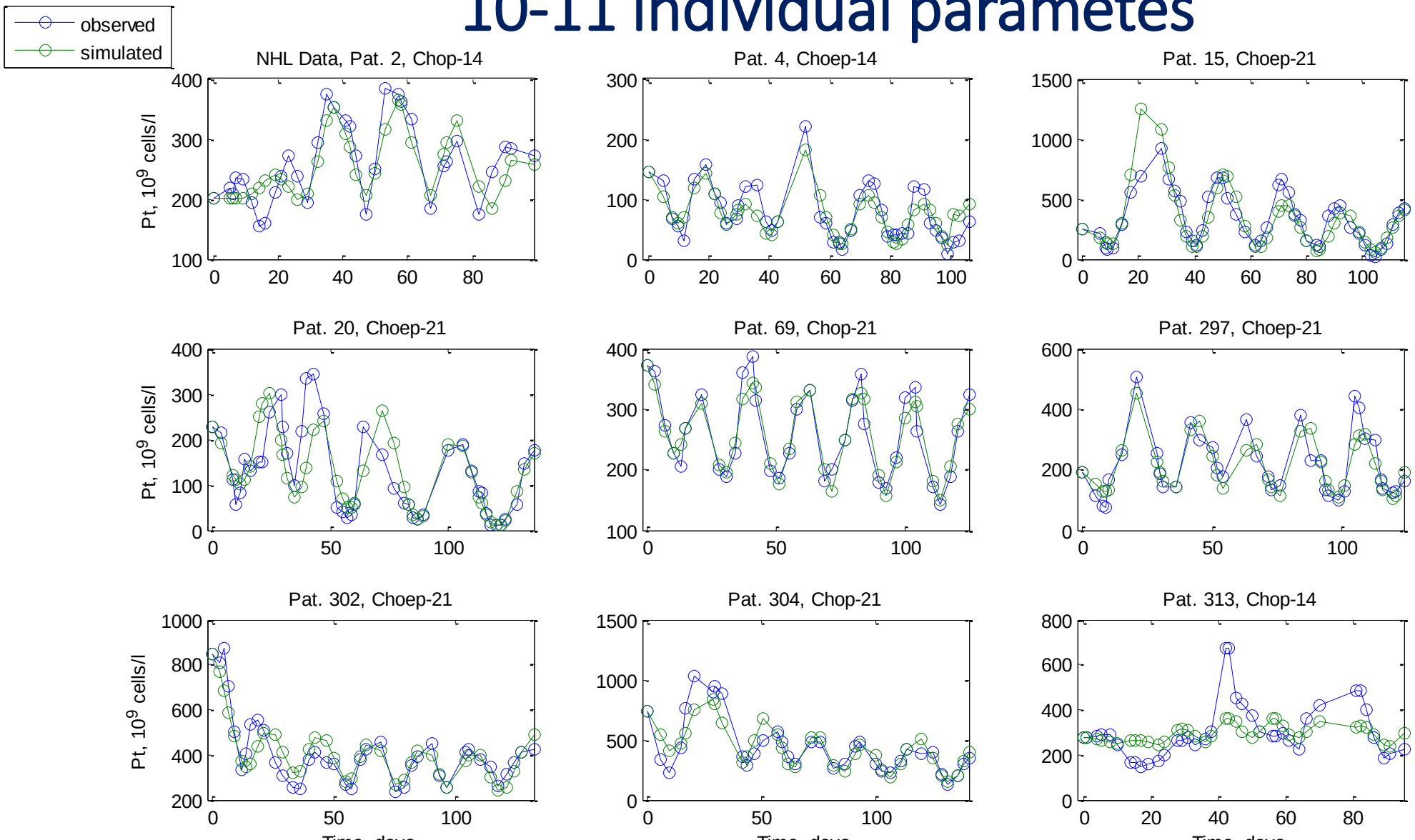






CHOEP Clinical data: individual fits

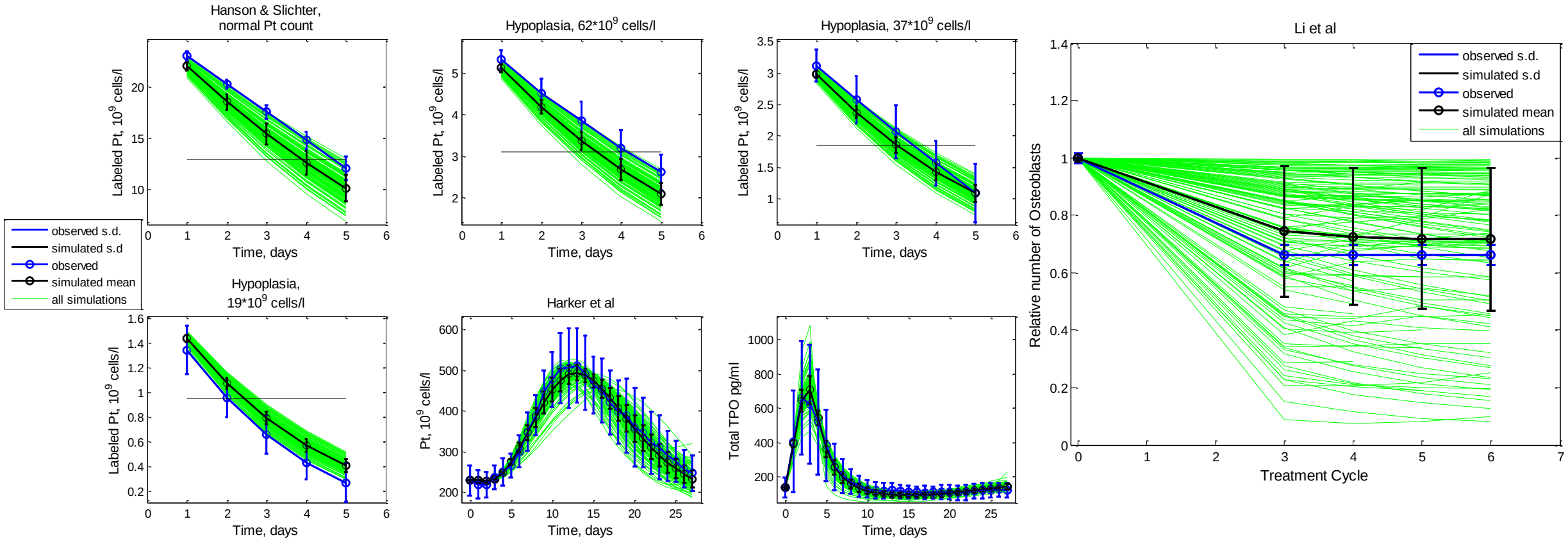
10-11 individual parametes



Simulations of the 135 CHOEP data patients

conditions of biological data, virtual participation

Hanson, Slichter (1985); Harker et al (2000), Li et al (2015)

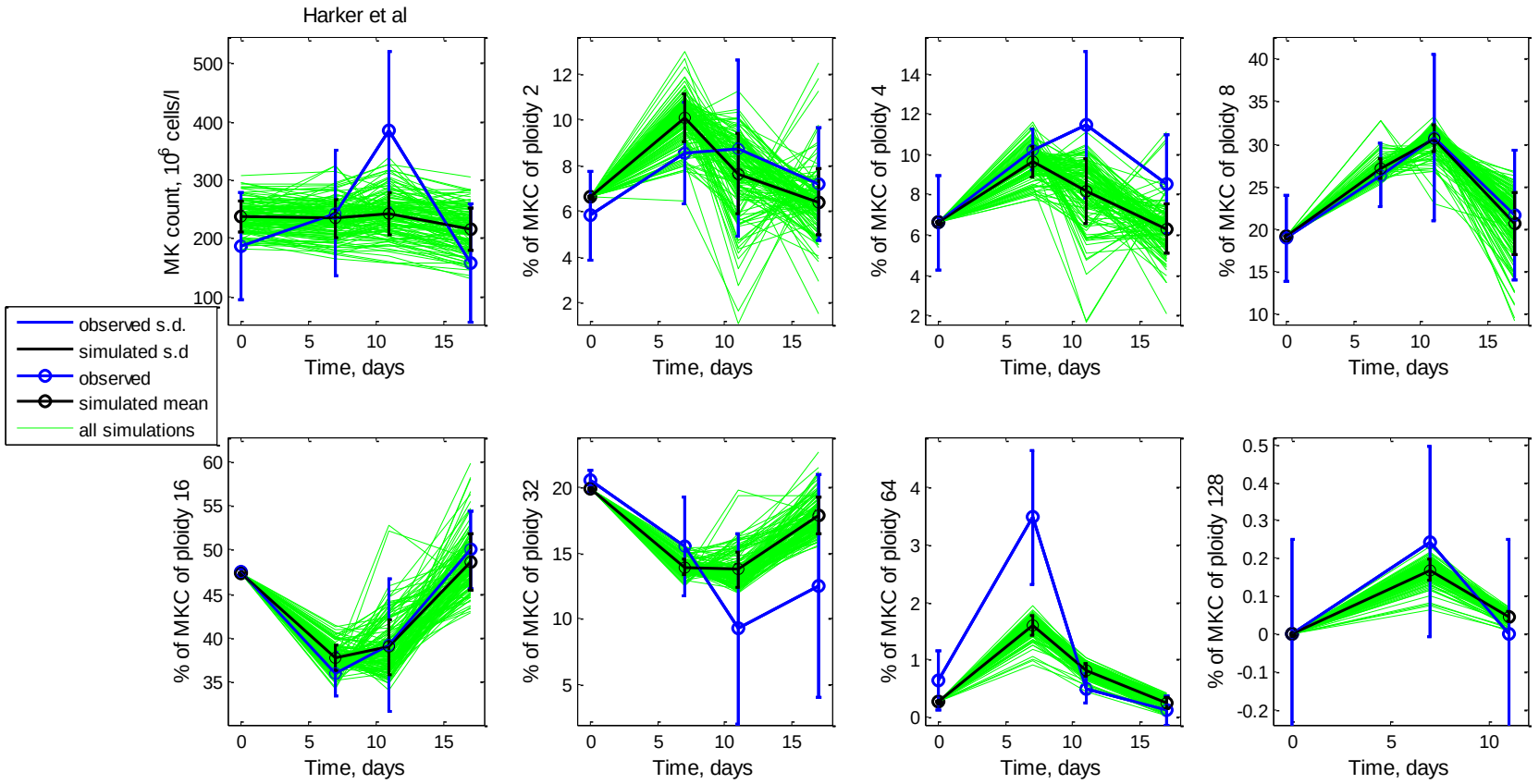


- The black horizontal line shows a half value of labeled platelets in Hanson et al experiment injected at the day 0

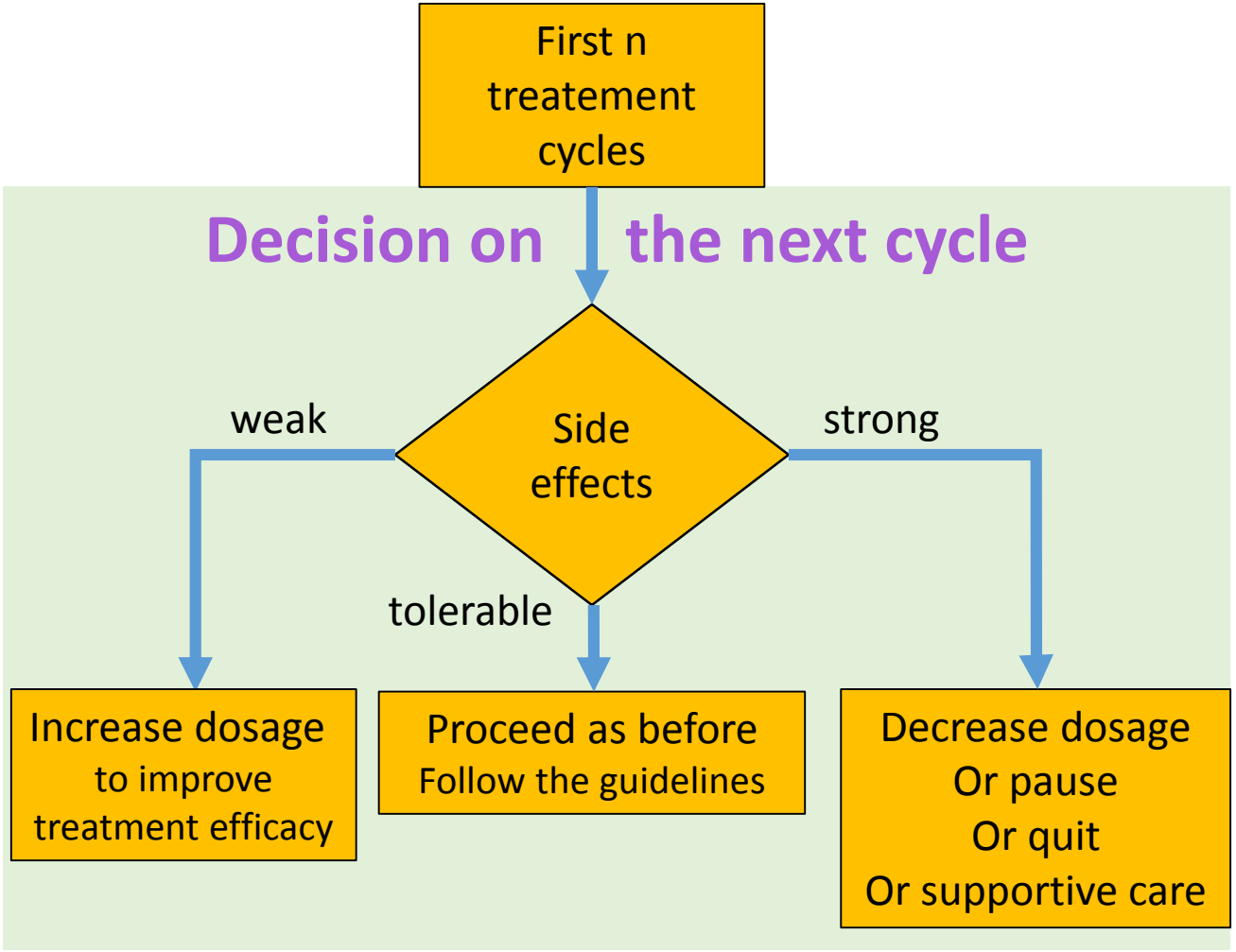
Simulations of the 135 NHL Study patients

conditions of biological data, virtual participation

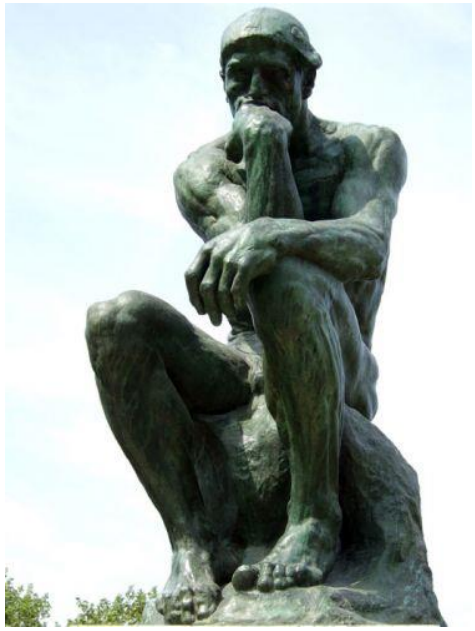
Hanson, Slichter (1985); Harker et al (2000)



The next-cycle managing scheme



How to predict the toxicity precisely in advance?

!  !

Use our model!

Use our tool!

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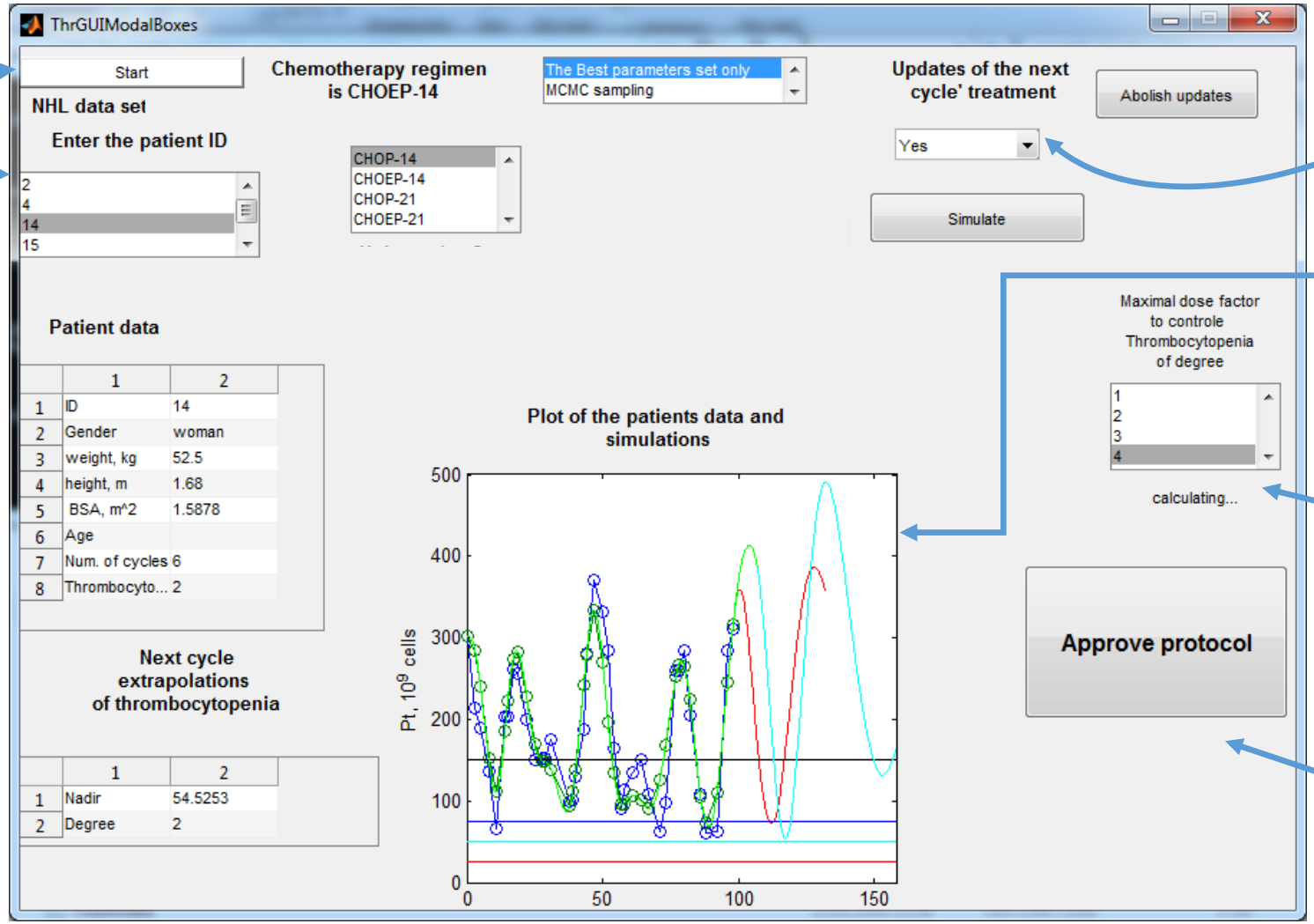
The medical next-cycle managing tool

Chose study / treatment
Chose patient



Manual adjustment of the next-cycle dose

Calls a special pop up menu

Visualization of predicted

- Course of platelets
- Thrombopenia grades
- **Different treatment scenarios**

Model-based prediction to find minimal dose for the next cycle that control thrombocytopenia of prescribed degree

Approve and save the final protocol for the next cycle

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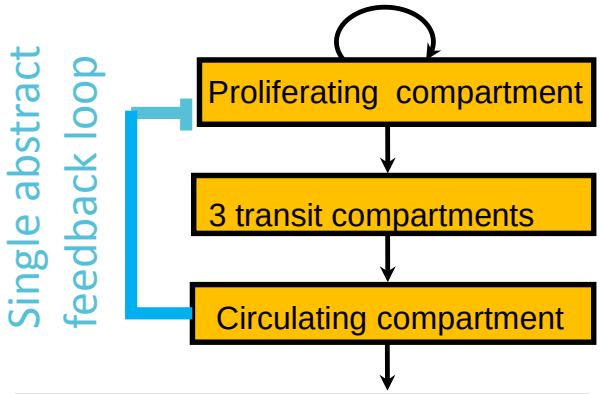
Next-cycle predictability
thrombopenia grades

Models validation and comparison
Based on the clinically important outcome



Parameters estimation
- For each patient
- Using platelets dynamics during the first k cycles

Simulation
- Conditions of all the next k+1, k+2,…, N cycles

Predictions for the cycles k+1, k+2,…, N
- Platelets nadirs
- **Thrombocytopenia grades (G)**
- **Grades difference (GD): observed and predicted**

M
- Our mechanistic model
  - 3 feedbacks
  - Active and quiescent cells
  - Osteoblasts

S
- Semi-mechanistic model
  - Friberg et al (2002)
  - 1 abstract feedback
  - 5 compartments
    - 1 proliferating
    - 3 transit
    - 1 circulating

GD (M) — **GD** (S)

GD Relation comparison Sk/Mk

Comparison of next-cycle predictions mechanistic and simplistic empiric models

- GD relations between simplistic and mechanistic models

Cycle	S2/M2	S3/M2	S4/M2	S5/M2
3	1.09			
4	1.13	1.07		
5	1.64	1.58	1.38	
6	1.48	1.35	1.11	0.98

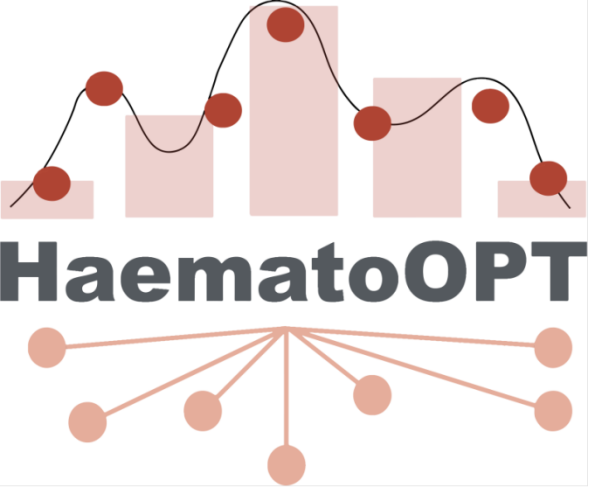
Cycle	S3/M3	S4/M3	S5/M3
4	1.55		
5	1.82	1.59	
6	1.72	1.42	1.25

Cycle	S4/M4	S5/M4
5	2.44	
6	1.8	1.59

- Mi and Si are the respective GD for mechanistic and semi-mechanistic models
  - Calibration during cycles 0,…, i
- Colors
  - Blue : GD-relations of the next cycle prediction of semi-mechanistic to predictions of the mechanistic model
  - Yellow : GD-relations of long-ranged predictions of semi-mechanistic and mechanistic models
  - **M needs 2-cycles less information than S for giving better predictions**

Conclusions

- More detailed mechanistic modeling of thrombopoiesis
  - Quiescent stem cells and megakaryocytes
  - Complex dynamics of megakaryocytes of different ploidies
  - Bone-marrow- supporting osteoblast
  - Long-term influence of multi-cyclic chemotherapies
  - Non-exponential platelets degradation
- Novel approach to combine clinical individual data with population averaged data
- Good individual fits for clinical data
- Stand-alone GUI tools for medical predictions
- Higher predictive power of our mechanistic model compared to semi-mechanistic model
  - Regarding degrees of thrombopenia



HaematoOpt Project

- Model-based optimisation and individualisation of treatment strategies in haematology
  - Erythropoiesis
  - Granulocytopoiesis
  - Thrompopoiesis
  - Regulation by growth factors
  - Haematopoietic stem cells
    - Normal and blood cancer cases
  - The models have been developed and consolidated in cooperation with basic research partners and clinical trial groups over the last 10 years
- Prof. Dr. Ingo Röder
  - The project coordinator
  - Technical University of Dresden
    - Institute for Medical Informatics and Biometry (IMB)

Acknowledgements

- HaematoOPT - Federal Ministry of Education and Research
- Technical University of Dresden (Bornhäuser, Röder)
- German Hodgkin‘s Lymphoma Study Group (Engert)
- German Study Group of High-grade Non-Hodgkin Lymphoma (Pfreundschuh)

Thank You!

BACK UP

A sequence of parameters estimations
Bayesian approach

Parameters estimation
- 9 individual parameters
- 22 population parameters

Prior or fixed values

Informative clinical data
Engel et al (1999)
- 3 patients
- BEACOPP or CHOEP treatment
- TPO and platelets measurements
  - At least 50 measured points pro entity

Biological data
- Harker et al (2000)
- Hanson et al (1985)
- Li et al (2015)

Parameters estimation
- 10-11 individual parameters

Less informative clinical data
German non-Hodgkin's lymphoma trial group
- More than 1500 patients treated with CHO(E)P-14 or CHO(E)P-21
  - *135 patients were included*
    - *At least 4 cyclest with at least 5 platelets measurments per cycle*

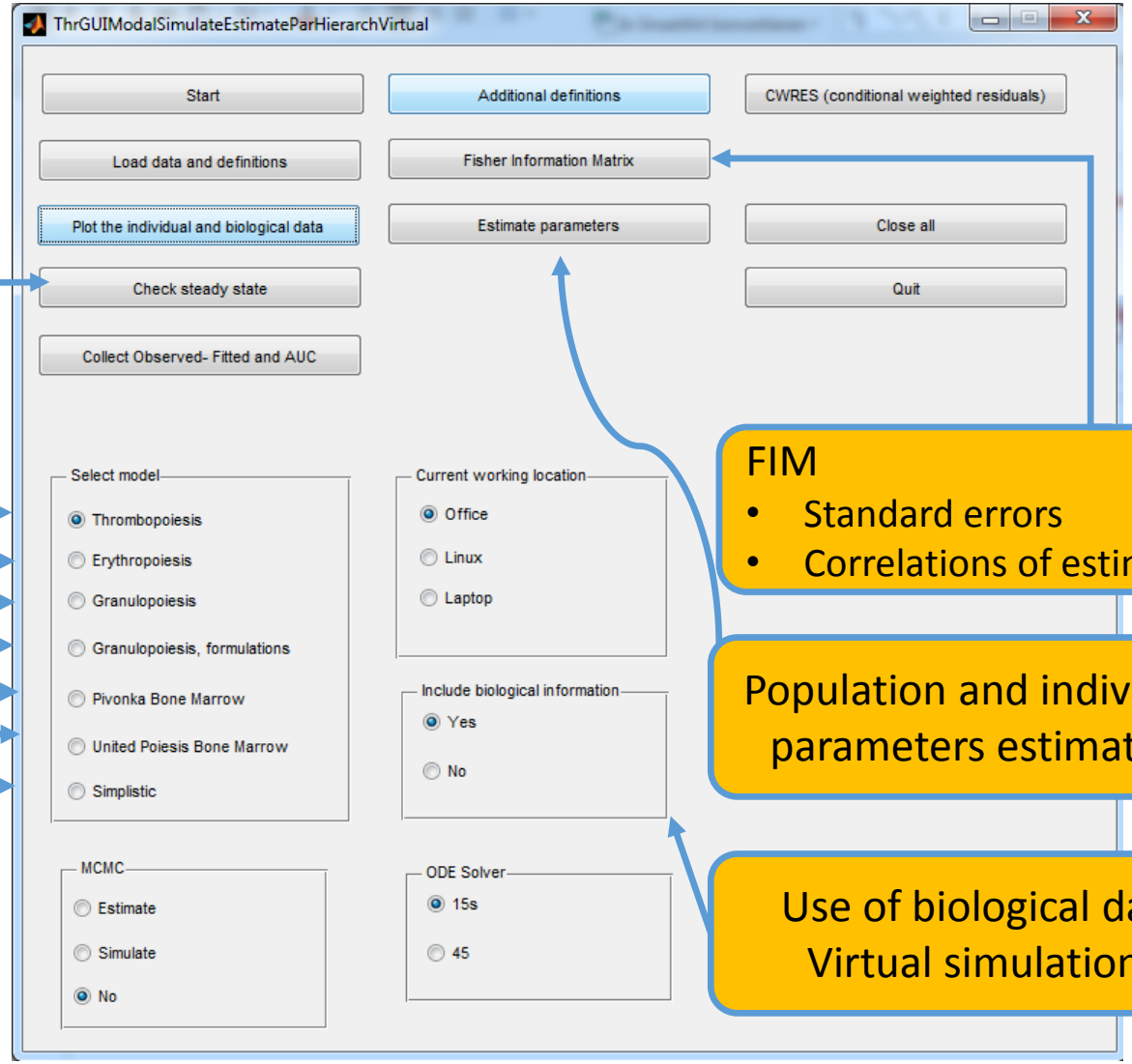
Biological data
- Harker et al (2000)
- Hanson et al (1985)

The scientific tool

haematoxicity research and prediction

- Stability study
- Proof of steady state

Models
- Complex hematopoietic
- Bone-remodeling
- Semi-mechanistic



FIM
- Standard errors
- Correlations of estimates

Population and individual parameters estimation

Use of biological data
Virtual simulations

History

2 major approaches to computational treatment optimization

- Virtual computer simulation of treatment plans
  - The expert assessment of the goodness of treatment
    - Bentley et al (1966), Holmes et al (1966)
- Minimization (maximization) of certain objective (a target function)
  - quantifies a trade-off between quantitated efficacy and drawbacks
    - Hope et al (1967), King PH et al (1969),
    - Wolbarst et al (1980), Wolbarst et al (1982)

History

- More than 40 years of model-based planning of cancer treatment
  - Bahrami and M. Kim (1975)
  - Rubinow and Lebowitz (1976)
  - Swan et al (1977 a,b)
  - Kondradov et al (1978 a,b)
- An objective function design and the ways of application of optimal control theory
  - Swan (1990)
  - Murray (1990)

History
Hematopoiesis

- The first comprehensive mathematical models
  - Dynamical behavior of mature and precursor blood cells
    - Stem cells, single compartment
  - negative feedbacks from mature to stem cells
  - Granulopoiesis
    - King S and Morley (1967)
  - Erythropoiesis
    - Detailed factor-mediated feedback mechanism
    - Kirk et al (1968)
      - delayed differential equations in order to approximate this multi-compartment differentiation process
    - Mylrea et al (1971)
  - First multi-compartment model
    - Duechting W (1973)

History
universal prototype model

- A combination of multi-compartment maturing sequence with elaborate factor-mediated feedbacks on early maturating compartments
  - (Wichmann et al 1976)
  - Very detailed summary for granulopoiesis and erythropoiesis Wichmann et al (1985)
  - Thrombopoiesis Wichmann et al (1979)
  - Neutropoiesis Rubinow and Lebowitz (1975)
    - Cancer treatment optimization of blood cancer treatment
      - Rubinow and Lebowitz (1976)