Centre for Process Systems Engineering

Imperial College London

MOBILE

Modelling, Optimization and mp-MPC of Biomedical Systems

Stratos Pistikopoulos

Outline

- **The MOBILE project**
  - **a brief overview**

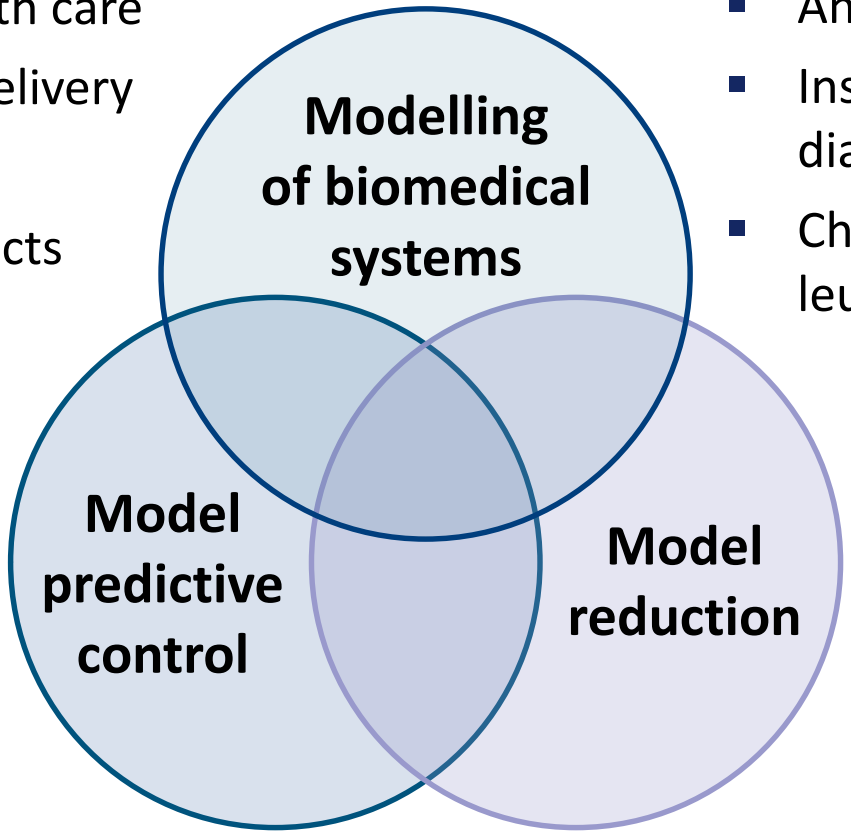
- **Focus on**
  - Leukaemia
  - Anaesthesia

Overview - ERC Advanced Grant MOBILE project

Modelling, Control and Optimisation of Biomedical Systems

Objectives:

- Personalised health care
- Optimised drug delivery
- Patient safety
- Reduced side-effects



Biomedical systems:

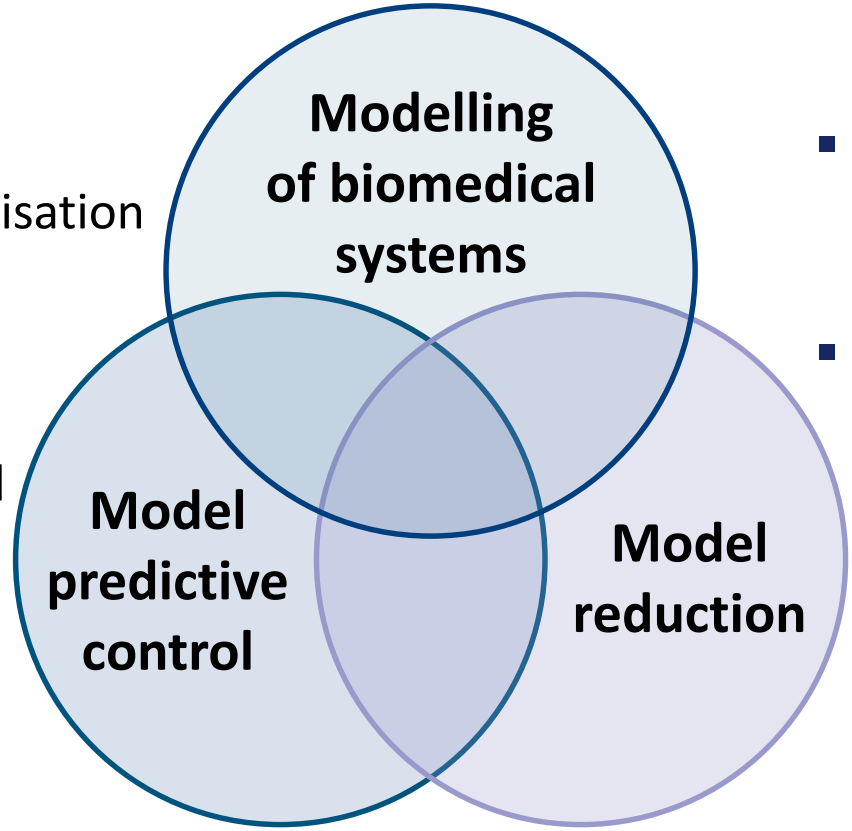
- Anaesthesia
- Insulin delivery for type I diabetes
- Chemotherapy for leukaemia

Overview - ERC Advanced Grant MOBILE project

Modelling, Control and Optimisation of Biomedical Systems

Model predictive control

- Explicit & robust MPC for hybrid systems
  Pedro Rivotti
  Christos Panos
- Mixed Integer optimisation under uncertainty
  Martina Wittmann-Hohlbein
- MPC/Estimation and model reduction
  Romain Lambert
  HJ Chang
  Ioana Nascu



Modelling of biomedical systems

- Anaesthesia
  Alexandra Krieger
  Ioana Nascu
- Insulin delivery for type I diabetes
  Stamatina Zavitsanou
- Chemotherapy for leukaemia
  Eleni Pefani
  Eirini Velliou
  Maria Fuentes Gari
  (MULTIMOD)

Framework towards optimal drug delivery systems

Model Development

Individual Patient

High Fidelity Model

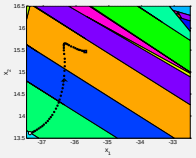
Model Reduction

Model Predictive Control/ Optimisation

Measurement device/ State Estimation

MEASUREMENTS/ STATES

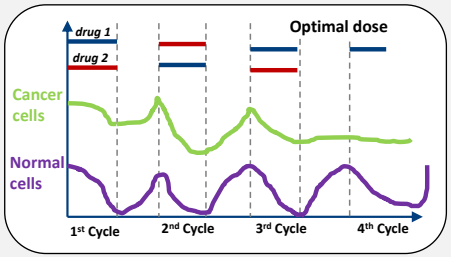
mp-MPC



Optimal control law/ trajectory

mp-MPC on a Chip

Optimal Scheduling



Patient

OPTIMAL DRUG DELIVERY/DOSAGE

Set points

Individual constraints

Disturbances

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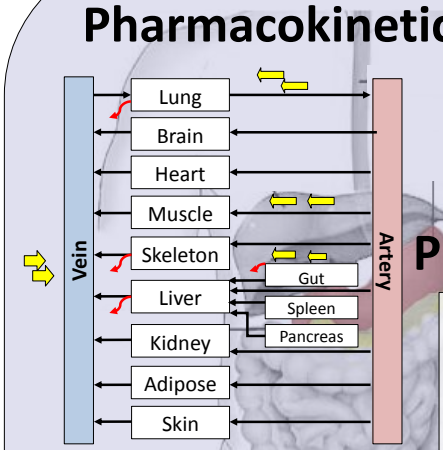
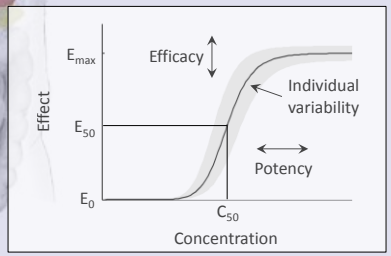
Mathematical Modelling

Model Development
Individual Patient
High Fidelity Model

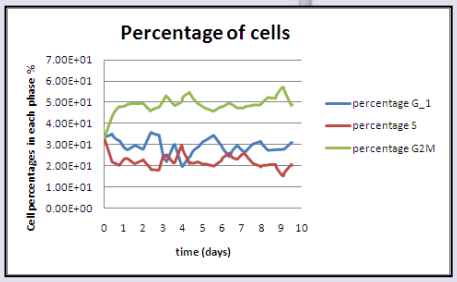
Pharmacokinetics

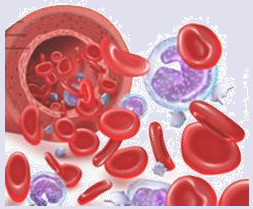


Pharmacodynamics

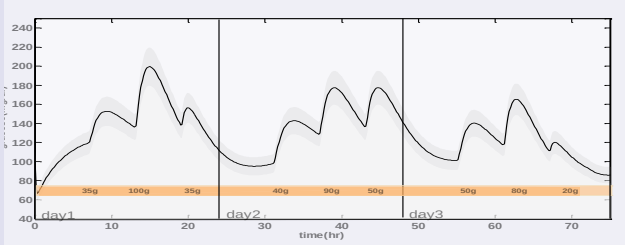


Cell Cycle





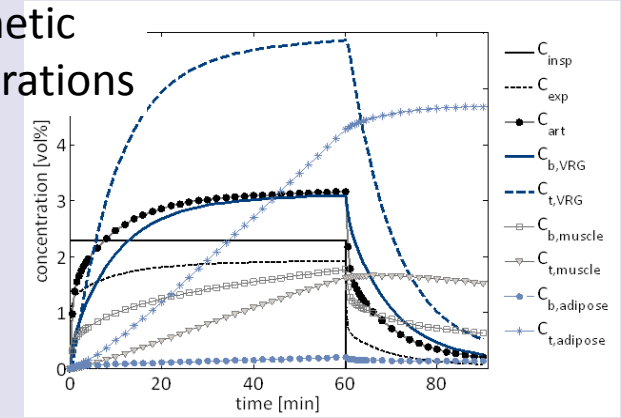
Diabetes Type I



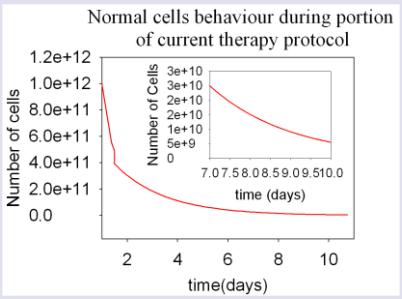
Glucose Profile

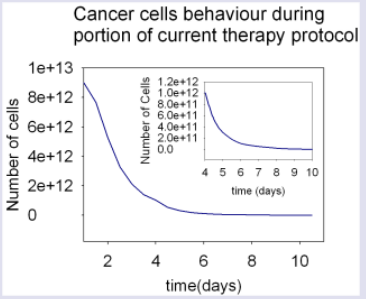
Anaesthesia

Anaesthetic concentrations



Leukaemia





Cell population profiles

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Platform For The Optimal Design Of Personalised Chemotherapy Protocols

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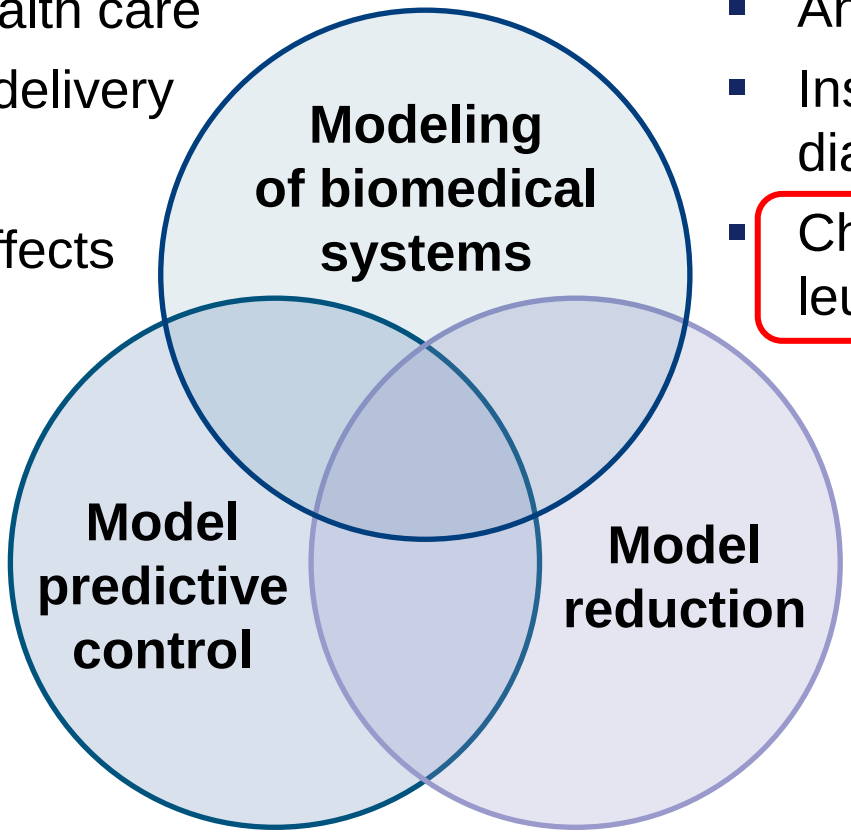
MULTISCALE COMPUTATIONAL MODELING OF CHEMICAL AND BIOCHEMICAL SYSTEMS
MULTIMOD ITN

Overview - ERC Advanced Grant MOBILE project

Modeling, Control and Optimization of Biomedical Systems

Objectives:

- Personalised health care
- Optimised drug delivery
- Patient safety
- Reduced side-effects



Biomedical systems:

- Anesthesia
- Insulin delivery for type I diabetes
- Chemotherapy for leukemia

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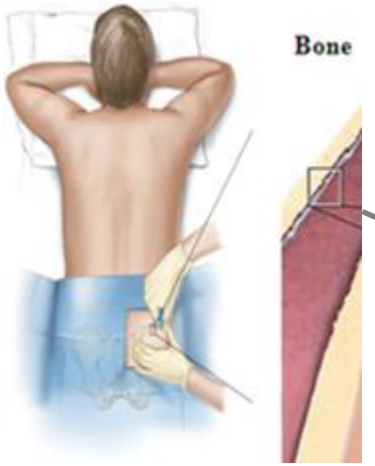
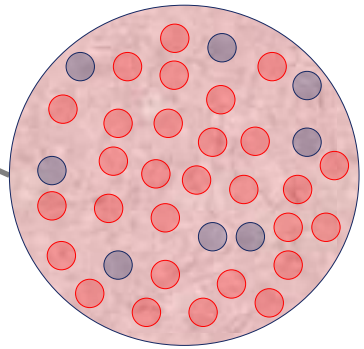
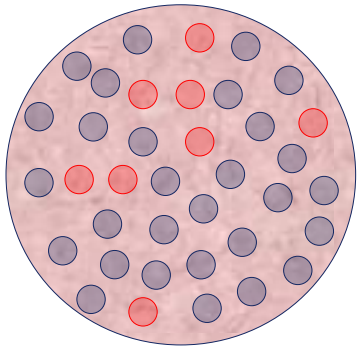
Platform for optimal personalised chemotherapy protocols
Focus on AML Disease

1. **AML:** aggressive blood cancer characterised by a weak immune system
2. **Diagnosis of bone marrow:** cancer cells more than normal
3. **Chemotherapy purpose**
   - Eradicate as many cancer cells as possible
   - Objective after 1st cycle - Bone Marrow with more normal than cancer cells
   - By treatment completion fully eradicate AML blasts

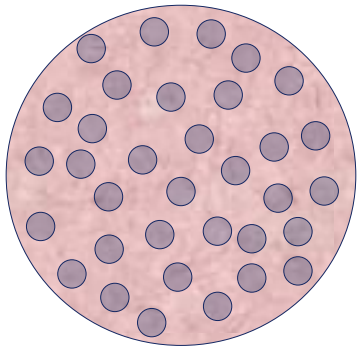




AML blasts
Normal cells



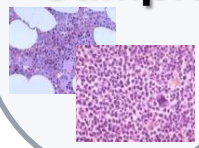
1st chemotherapy cycle



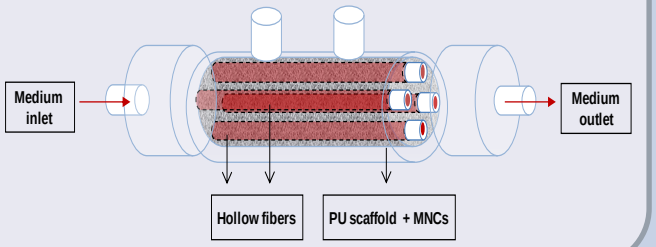
Treatment completion

Platform for optimal personalised chemotherapy protocols

Patient Sample



In Vitro Platform



- Bioreactor design for the culture of primary leukaemia in-vitro
- Experiments realisation for the characterisation and modelling of normal and cancer cell cycle based on patient-specific and disease-specific information

(Prof. Mantalaris group, Dr. N. Panoskaltsis)

Automated Treatment Design

- Validation of high-fidelity model for the simulation of disease behaviour under treatment
- Design optimal treatment protocols based on patient and disease specific information

(Prof. Pistikopoulos group, Dr. N. Panoskaltsis)

Optimal protocols validation

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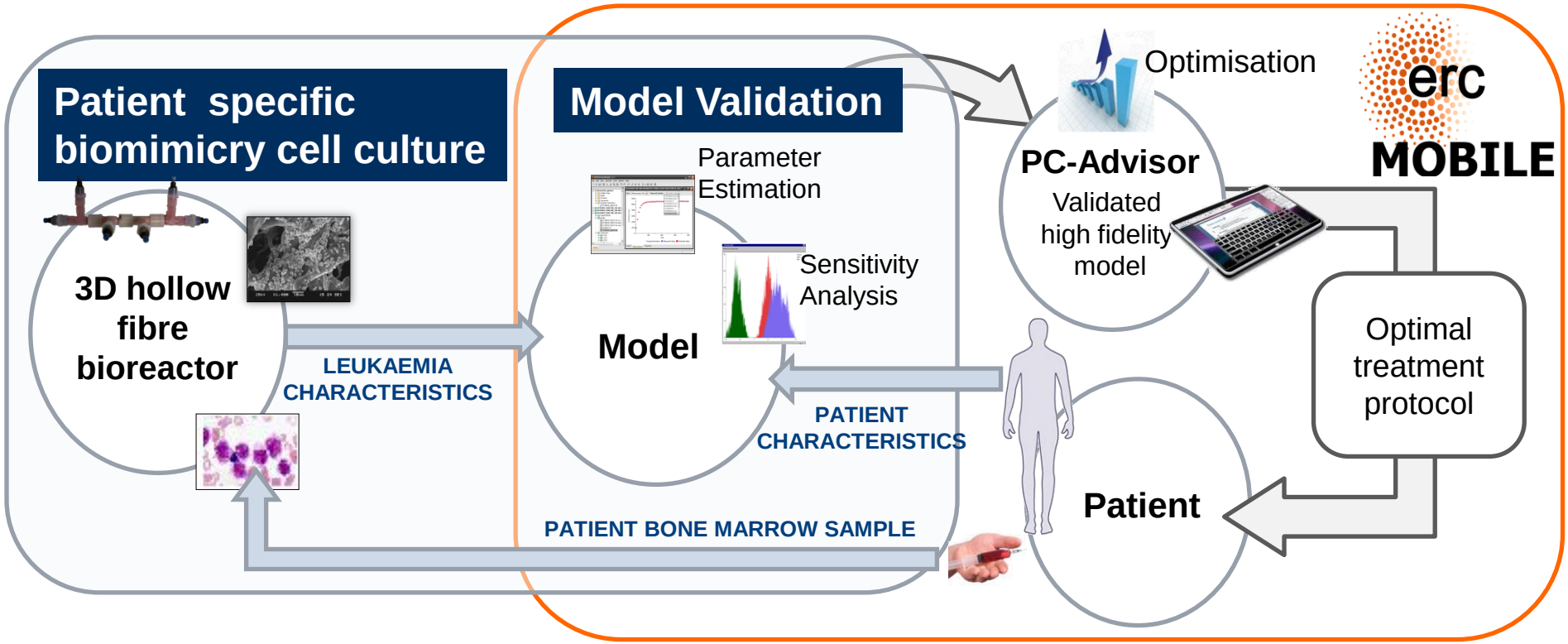
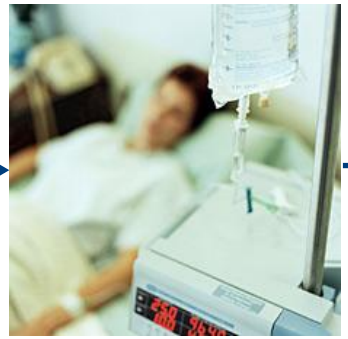
Platform for optimal personalised chemotherapy protocols



Platform for optimal personalised chemotherapy protocols



Patient

- sex
- age
- height
- weight
- BSA

Measurement

- Tumour biopsy
- Karyotype analysis
- % of Cancer cells
- % of Normal cells
- Haematology test
- Cardiac function
- Kidney function
- Liver function

Personalised optimal protocol

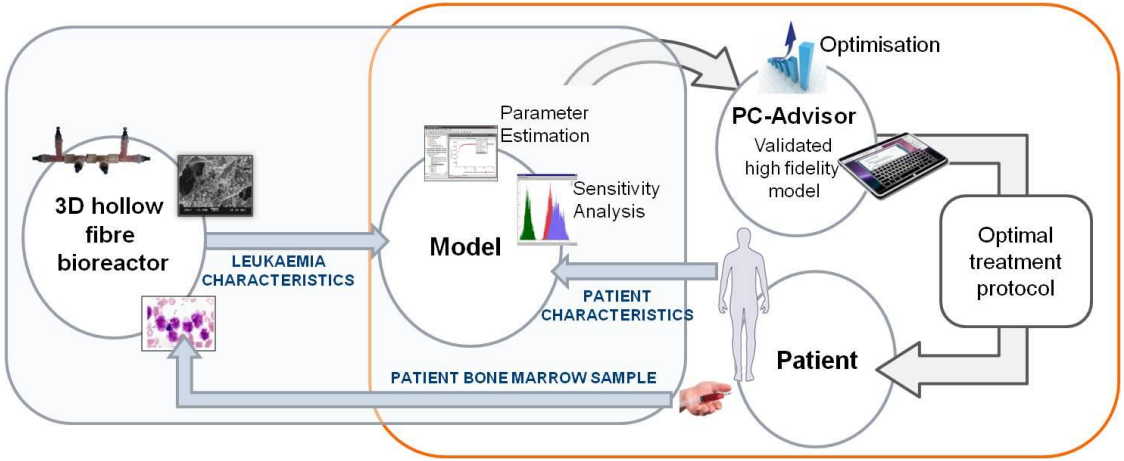
Optimal chemotherapy scheduling

Platform for optimal personalised chemotherapy protocols
The Research Team

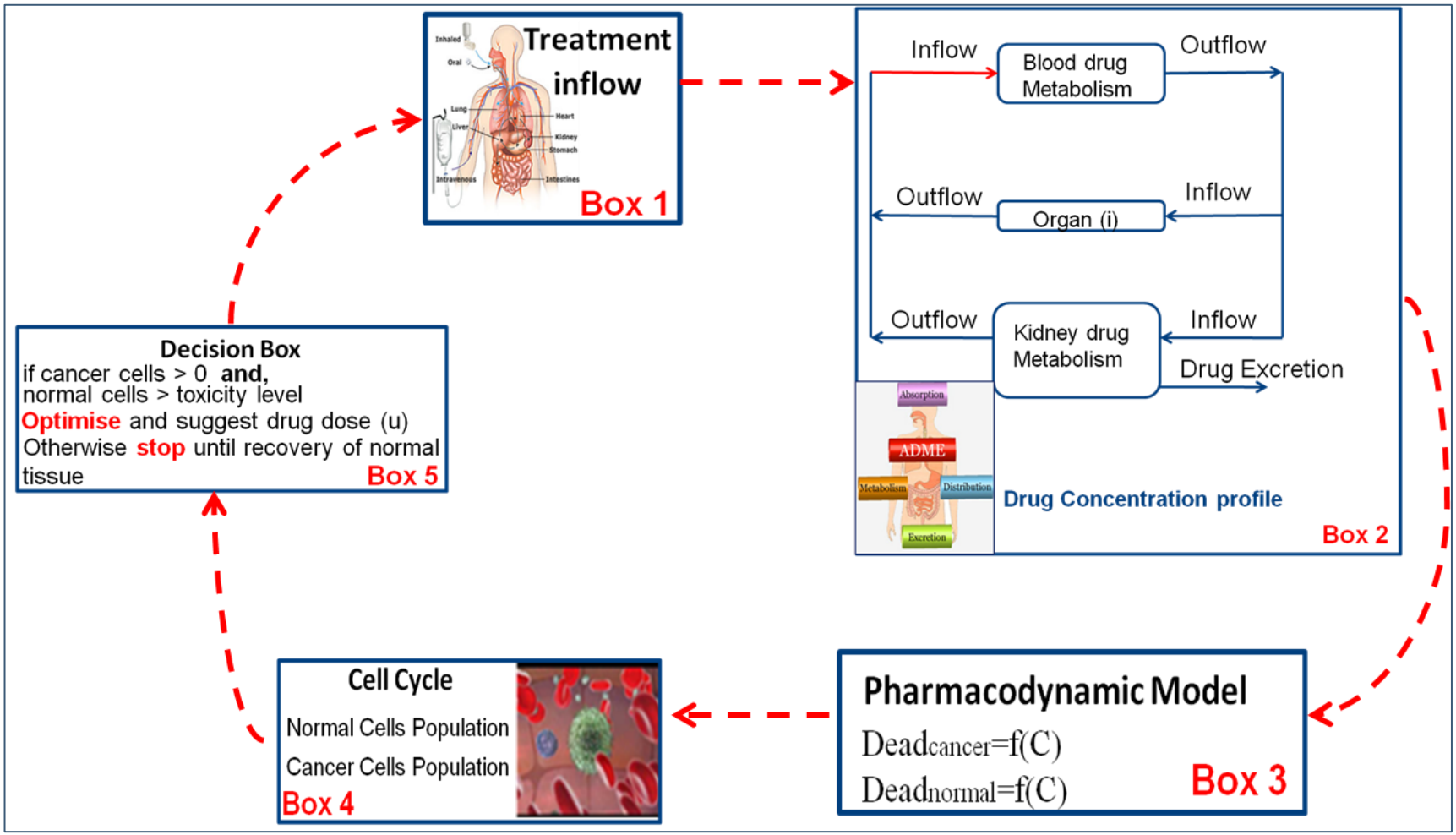
Dr. N. Panoskaltsis
Prof. A. Mantalaris
Prof. E. Pistikopoulos

Dr. R. Misener
Dr. M. Rende
Dr. E. Velliou

E. Pefani (PhD student)
M. Fuentes (PhD student)



Framework for the Design of optimal chemotherapy protocols



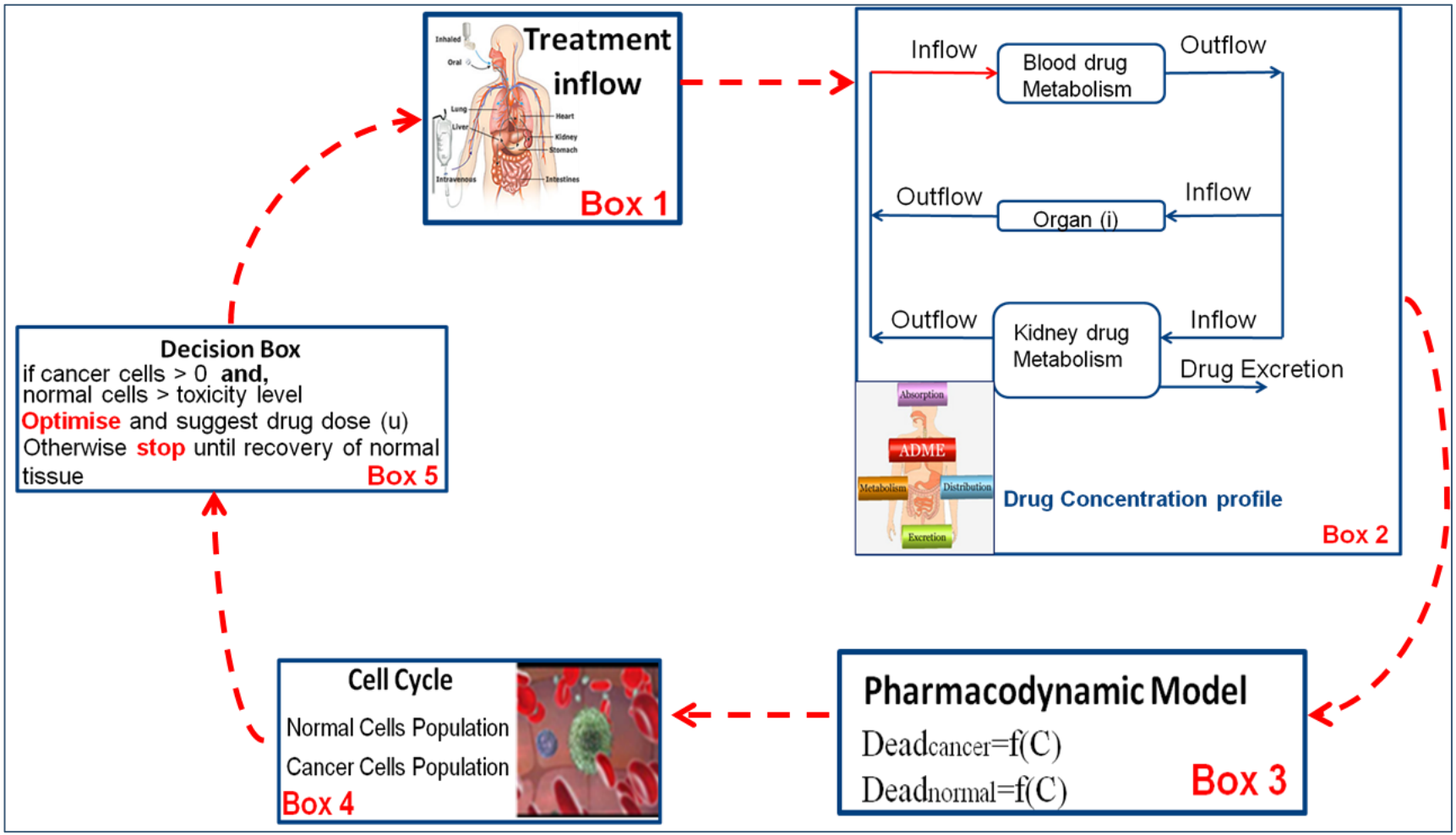
Framework for the Design of optimal chemotherapy protocols

Treatment inflow in blood compartment as a function of:

- administration route
- drug dose
- Injection rate
- Duration of drug administration

Box 1

Framework for the Design of optimal chemotherapy protocols



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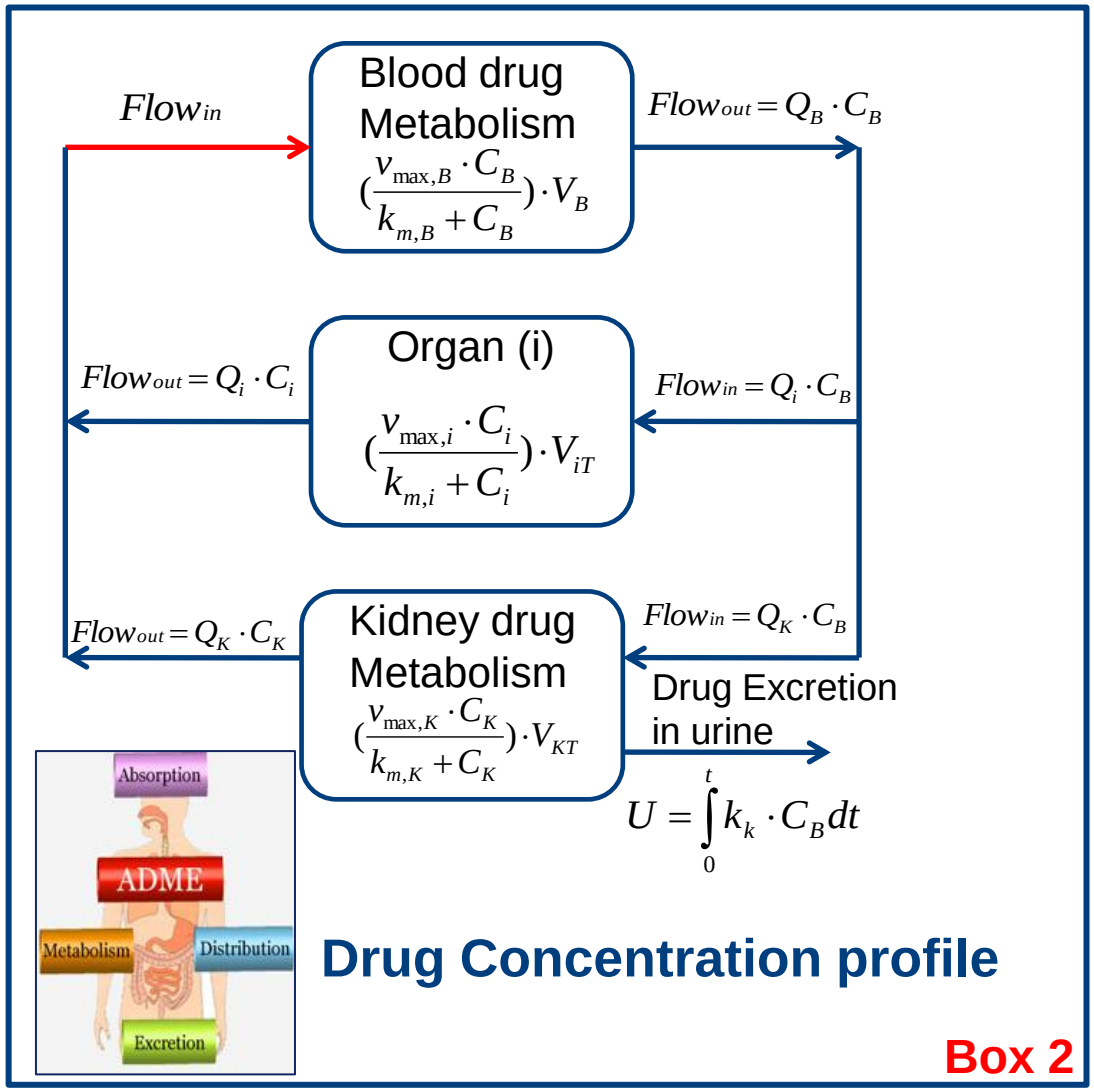
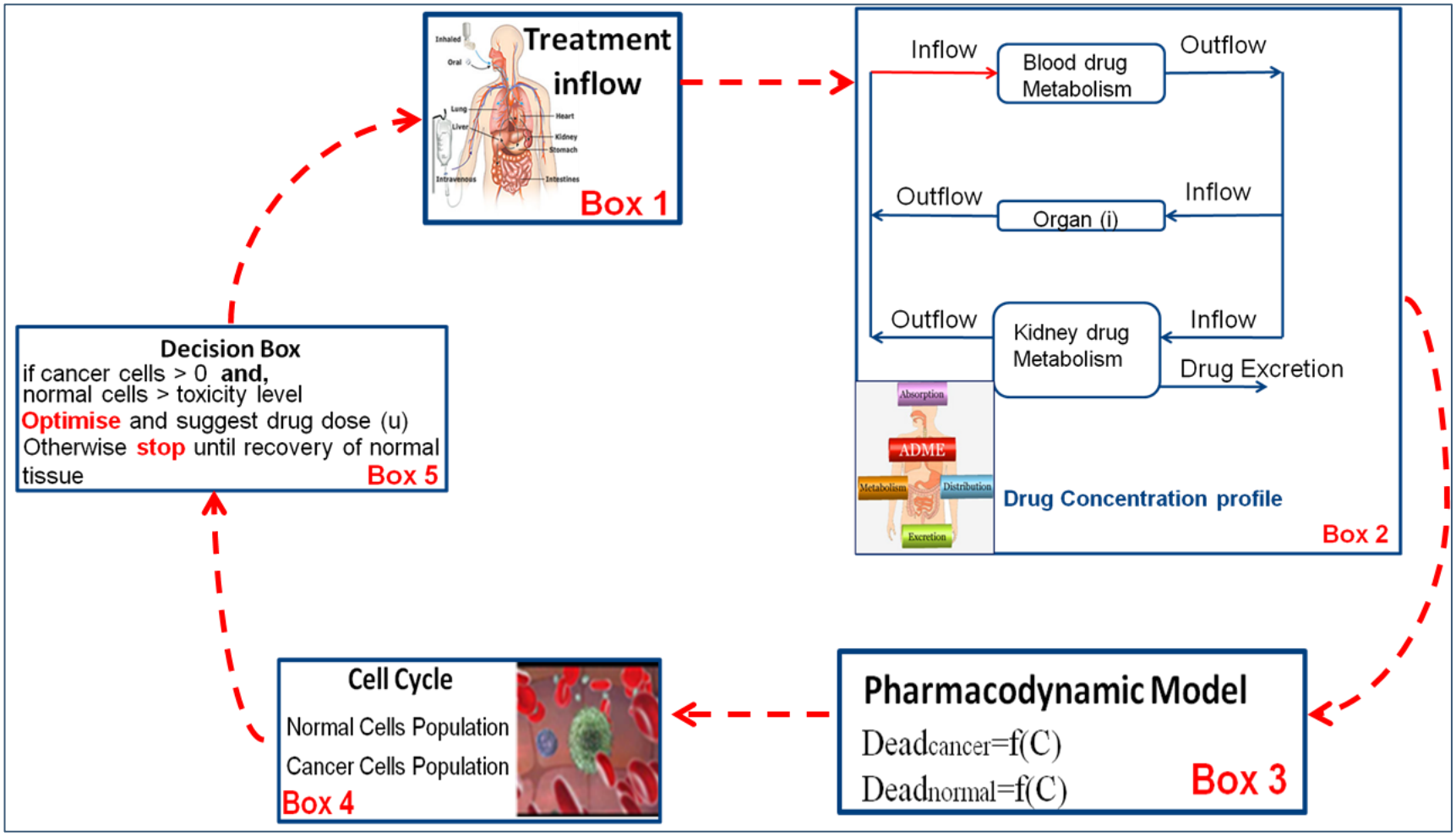


Framework for the Design of optimal chemotherapy protocols



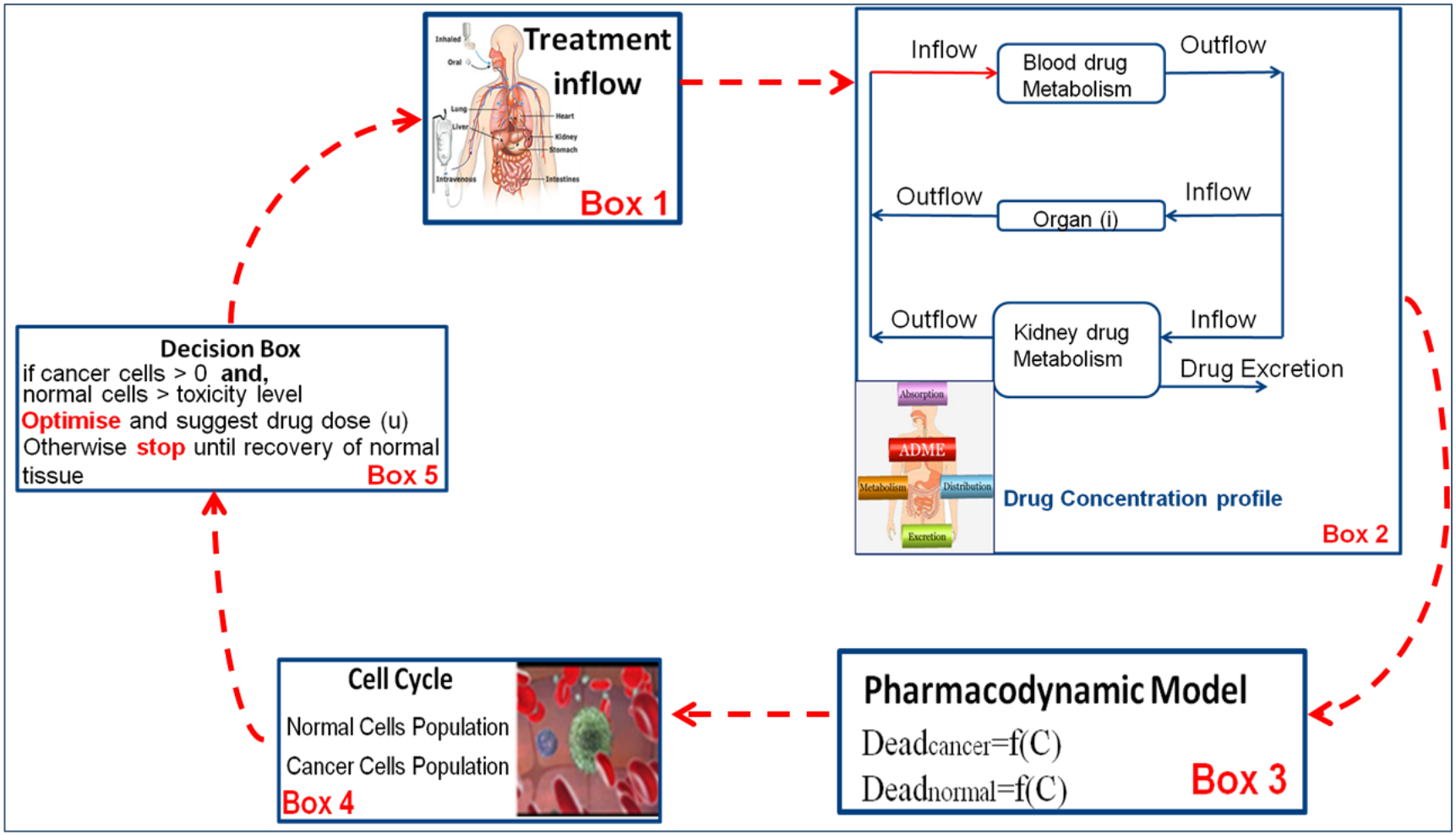
Framework for the Design of optimal chemotherapy protocols

Pharmacodynamic Model

$$effect_j = \frac{E_{\max,j} \cdot C_{M,j}^{slope,j}}{E_{50,j} + C_{M,j}^{slope,j}}$$

Box 3

Framework for the Design of optimal chemotherapy protocols



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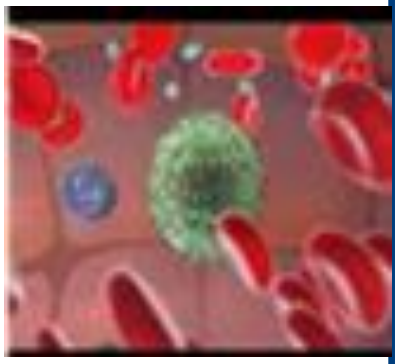
Framework for the Design of optimal chemotherapy protocols

Normal & Cancer Cells

$$\frac{dG_1}{dt} = 2 \cdot b \cdot G_2M - k_1 \cdot G_1 - effect_j \cdot G_1$$

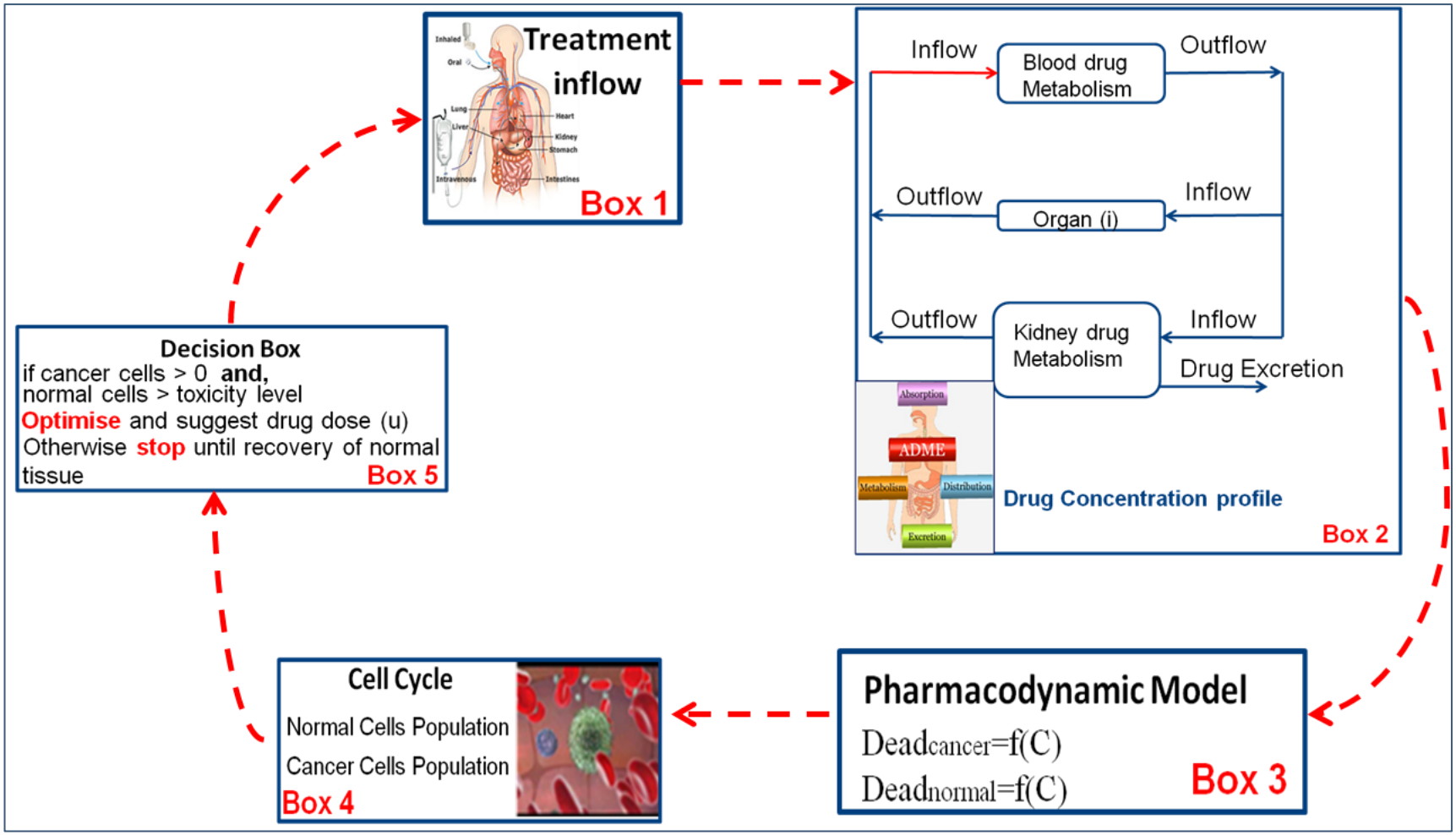
$$\frac{dG_2M}{dt} = k_2 \cdot S - b \cdot G_2M - effect_j \cdot G_2M$$

$$\frac{dS}{dt} = k_1 \cdot G_1 - k_2 \cdot S - effect_j \cdot S$$



Box 4

Framework for the Design of optimal chemotherapy protocols



Framework for the Design of optimal chemotherapy protocols

Check level of cancer cells

If cancer cells = 0 **stop**

Else if cancer cells > 0 **then,**
Check level of normal cells

If normal cells < toxicity level, **stop**
until recovery of normal tissue

Else if normal cells > toxicity level
Optimise and suggest drug dose (u)

Box 5

A Quick Guide to The Proposed Model

$$\inf low_j = \frac{u_j \cdot \sqrt{\frac{height \cdot weight}{3600}}}{duration_j}$$, j:anti-leukemic drug

Drug schedule (decision variable)

$$V_B \cdot \frac{dC_{B,j}}{dt} = \sum_{i:H,Li,M,Le,K} Q_i \cdot C_{i,j} - Q_B \cdot C_{B,j} + \inf low_j$$

$$V_i \cdot \frac{dC_{i,j}}{dt} = Q_i \cdot C_{B,j} - Q_i \cdot C_{i,j} - k_{k,j} \cdot C_{B,j} - \left(\frac{v_{\max,i,j} \cdot C_{i,j}}{K_{m,i,j} + C_{i,j}}\right) \cdot V_{iT}$$

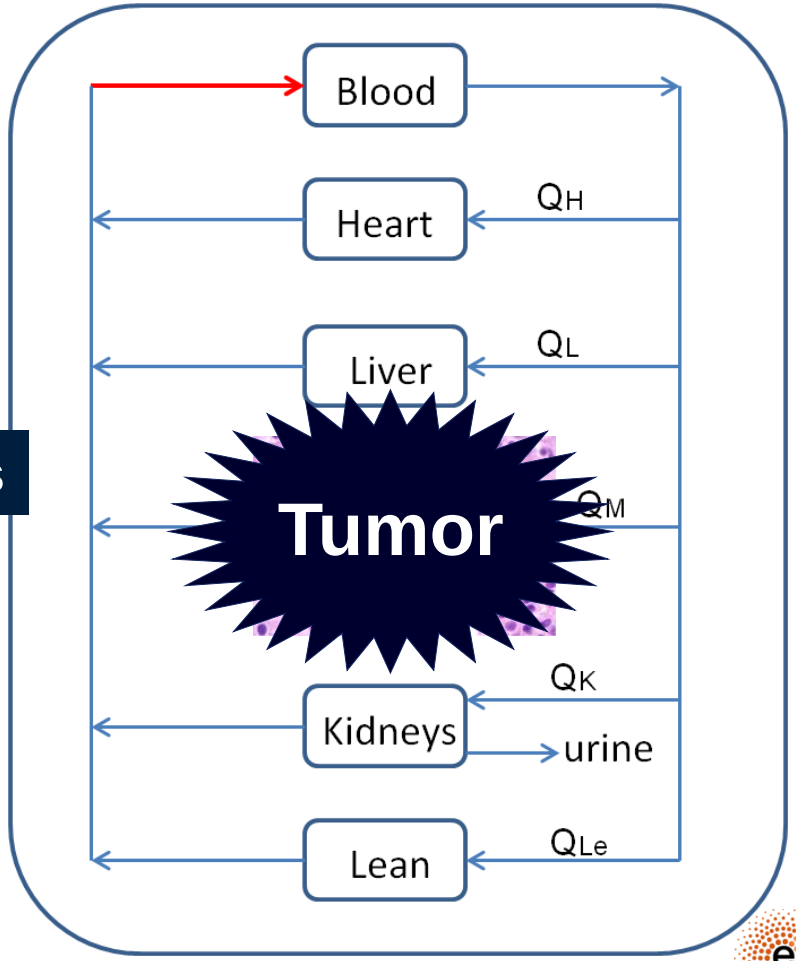
$$effect_j = \frac{E_{\max,j} \cdot C_{M,j}^{slope,j}}{E_{50,j} + C_{M,j}^{slope,j}}$$

Drug effectiveness

$$\frac{dP_y}{dt} = k_{y-1} \cdot P_{y-1} - k_y \cdot P_y - effect_j \cdot P_y$$

y:cell cycle phase

Percentage of sensitive cells



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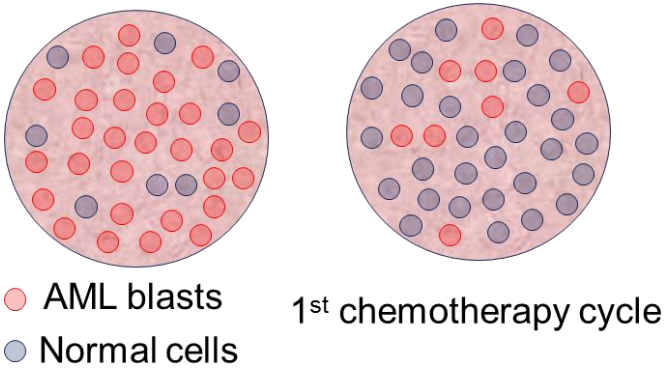
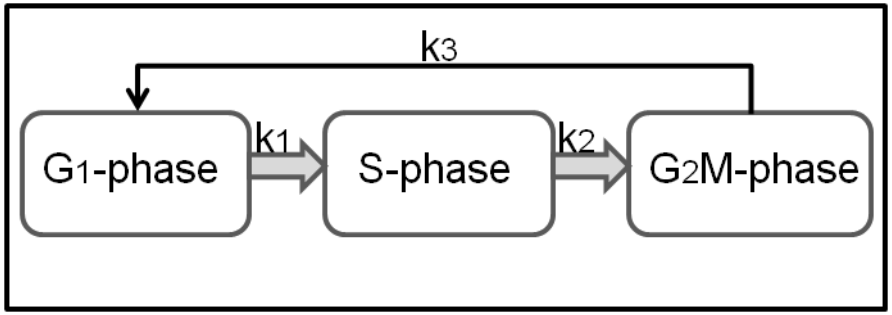
Closer look at the cell cycle

1. Distinguish between normal and AML cells

2. Cell states: **proliferation** or **dormancy**



AML cell cycle model

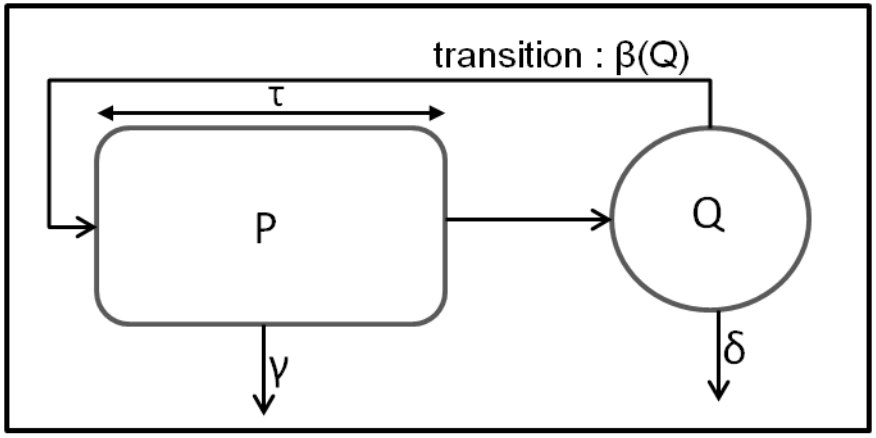


$$\frac{dG_1}{dt} = 2 \cdot k_3 \cdot G_2M - k_1 \cdot G_1 - effect_j \cdot G_1$$

$$\frac{dS}{dt} = k_1 \cdot G_1 - k_2 \cdot S - effect_j \cdot S$$

$$\frac{dG_2M}{dt} = k_2 \cdot S - k_3 \cdot G_2M - effect_j \cdot G_2M$$

Normal cell cycle model



$$\frac{dQ}{dt} = -\delta \cdot Q - \beta(Q) \cdot Q + 2 \cdot e^{-\gamma \cdot \tau} \cdot \beta(Q) \cdot Q$$

$$\frac{dP}{dt} = -\gamma \cdot P + \beta(Q) \cdot Q - e^{-\gamma \cdot \tau} \cdot \beta(Q) \cdot Q - effect_j \cdot P$$

$$\beta(Q) = \beta_o \cdot \frac{\theta^n}{\theta^n + Q^n}$$

Simulation results for one patient case study

Physiological patient characteristics

Sex: Male Age: adult Weight: 70 kg Height: 1.80 m

	Organ Volume (lt)	Organ blood flow (lt/min)
Blood	2.67	4.04
Kidney	1.06	1.24
Kidney tissue	0.3	-
Heart	0.448	0.24
Liver	1.7	1.45
Liver tissue	1.6101	-
Bone Marrow	2	0.18
Lean Tissue	27	0.93

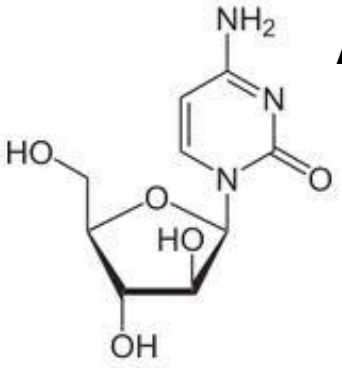
Disease characteristics

AML cells: $2.6 \cdot 10^9$ cells / kg Normal Cells: $3.57 \cdot 10^8$ cells/kg

AML Cells		
G_1-phase duration (hrs)	S-phase duration (hrs)	G_2M-phase duration (hrs)
61	19	3.62

Simulation results for one patient case study

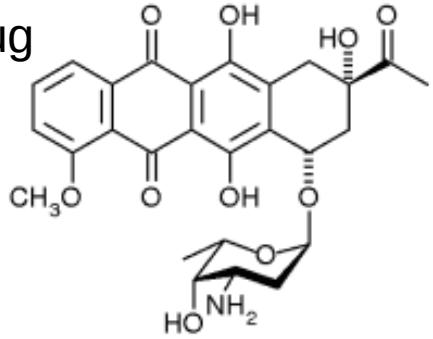
Drugs and chemotherapy protocol



Ara-C: anti-neoplastic drug

block DNA expression

S phase specific



DNR: anthracycline drug

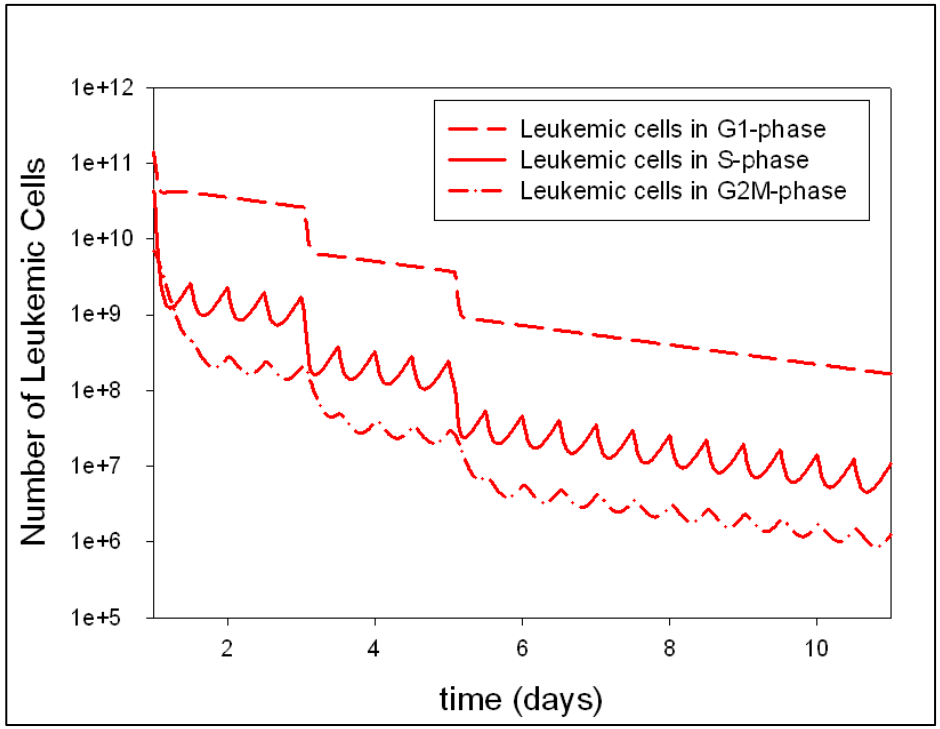
prevent DNA and RNA formation

G_1 and S phase specific

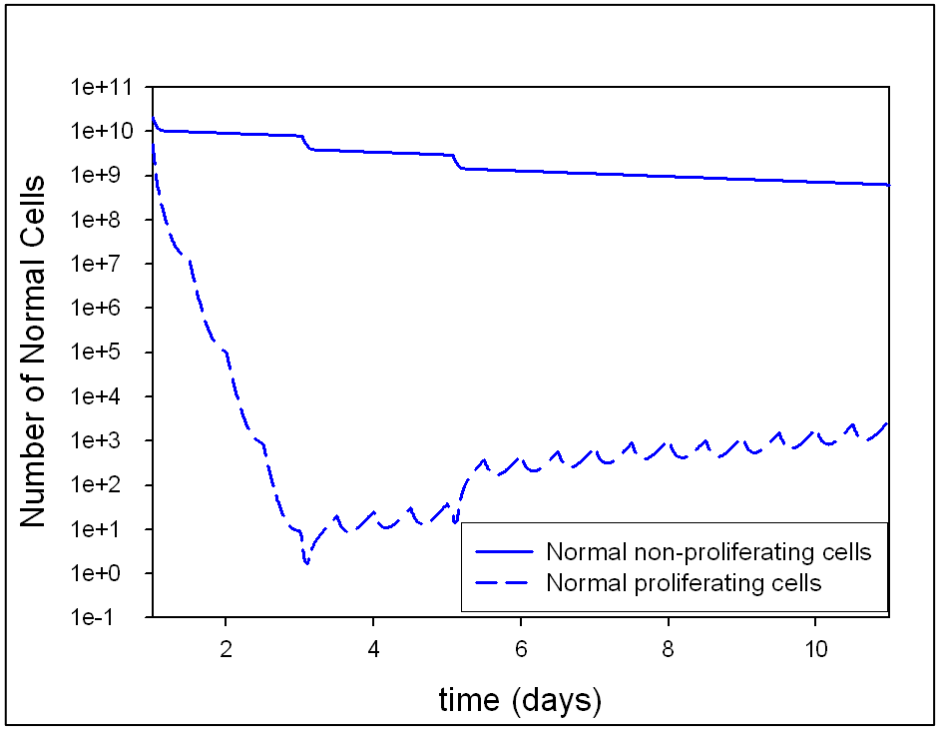
Protocol	Dose	Application duration	Application Schedule
Mix of DNR & Ara-C			
DNR	60 mg/m^2	1 hr iv application	1 daily application for days 1,3,5 of treatment
Ara-C	100 mg/m^2	push	Two daily applications, every 12 hours, for days 1-10

Simulation results for one patient case study

- **AML Blasts**



- **Normal Cells**



- **<u>3-log reduction</u>**: $1.92 \cdot 10^{11}$ to $1.77 \cdot 10^{8}$ cells
- Cells in the three phases are decreasing
- Highly concentrated in G1-phase (phase with higher duration)

- **<u>2-log reduction :</u>** $2.64 \cdot 10^{10}$ to $6.25 \cdot 10^{8}$ cells
- Proliferating are steeply decreasing
- Non-proliferating cells act as “reservoir” and protect the cell population

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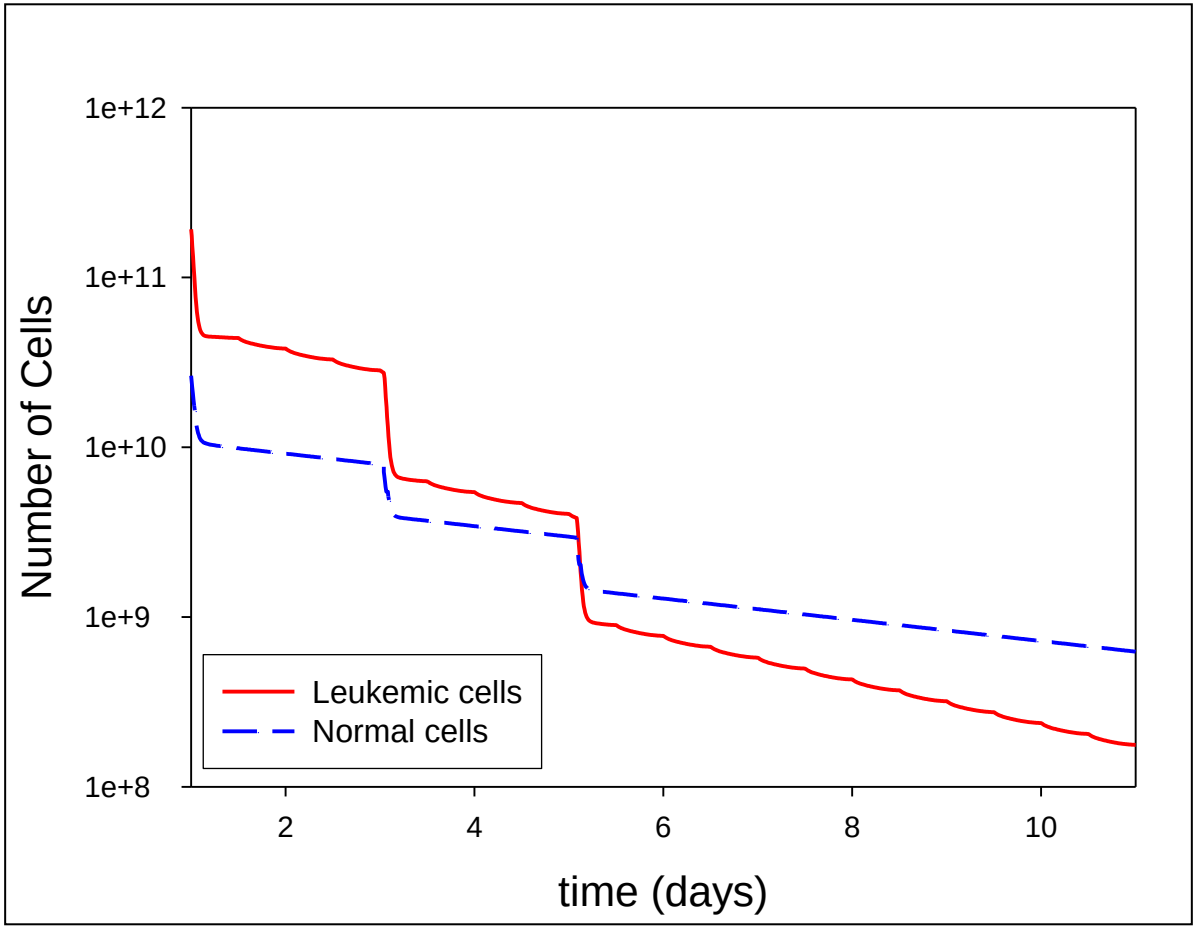
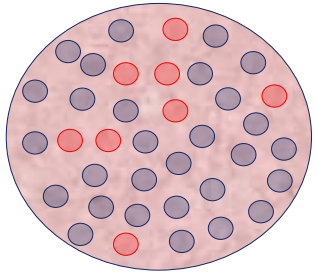
Simulation results for one patient case study





AML blasts
Normal cells

- **<u>Cycle completion</u>**: Normal cells ($6.25 \cdot 10^8$ cells) > leukemic cells ($1.77 \cdot 10^8$ cells)
- 1st chemotherapy objective received from the **<u>5th day of treatment</u>**

The optimization problem

$$\min_{t_{n,j},j,u_{n,j}} Cells_{leuk}$$

$$s.t$$

$$Cells_{nor,n,j} = f(effect_{n,j})$$

$$Cells_{leuk,n,j} = f(effect_{n,j})$$

$$effect_{n,j} = f(C_{M,n,j})$$

$$C_{M,n,j} = f(\inf low_{n,j})$$

$$Inflow_{n,j} = \sum_{n=1}^{n=NA} \frac{dose_{n,j}}{duration_{n,j}} \cdot (t_{n,j} - t_{AD})$$

$$Cells_{nor}\big|_{n=NA} \geq Cells_{leuk}\big|_{n=NA}$$

Objective: minimize the number of cancer cells
while keeping normal cells above a certain level & higher than AML cells

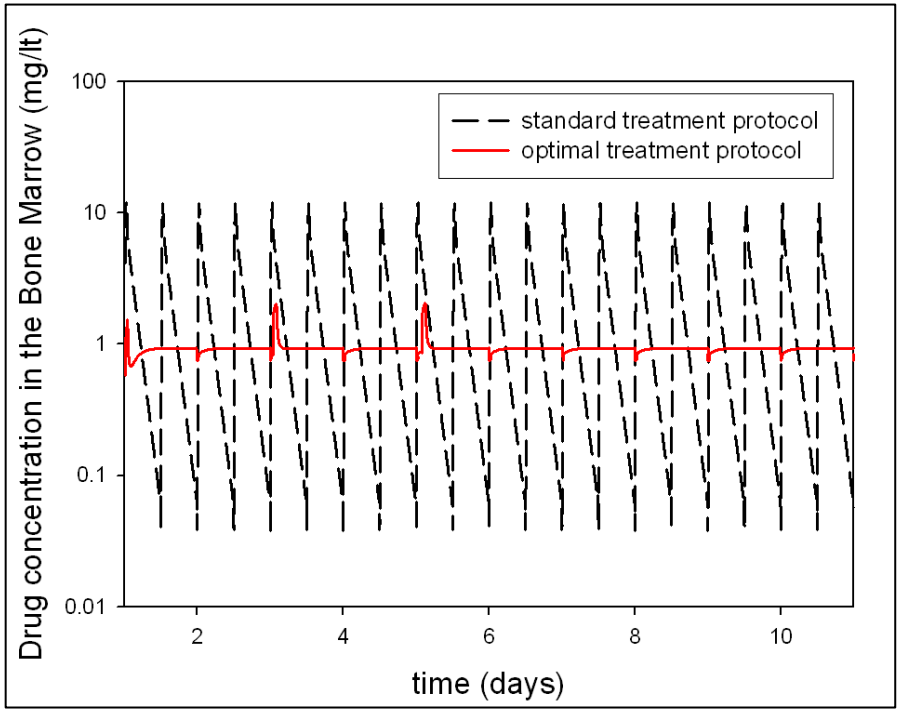
Decision variables:

- Choice of drugs
- Dose load
- Dose duration
- Number of treatment applications
- Interval period between applications

Optimization results for one patient case study

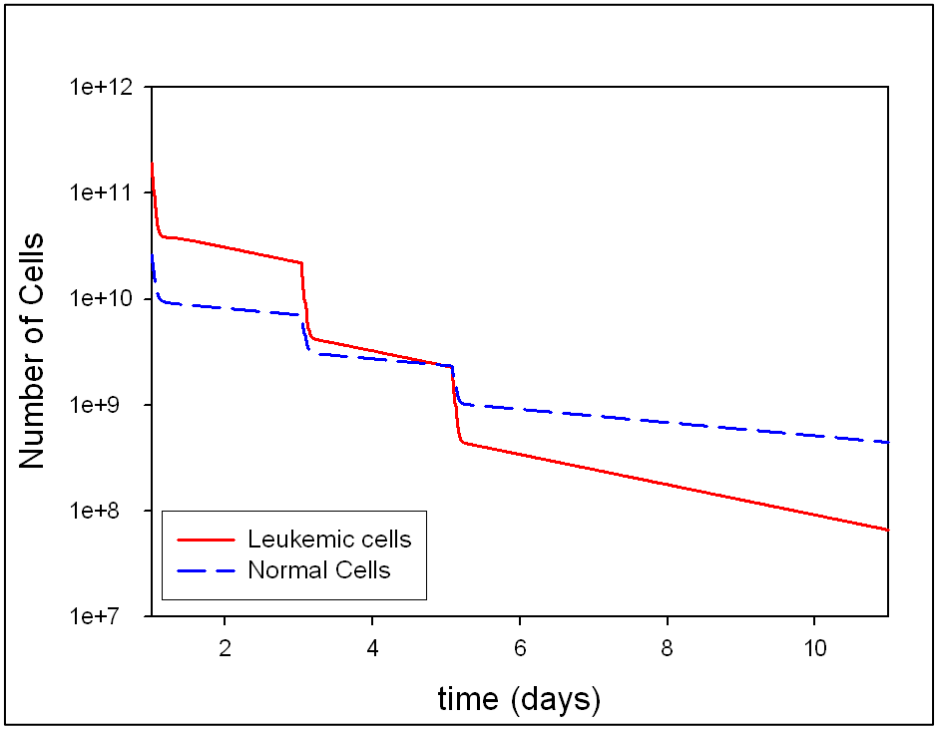
Optimal Suggested Protocol (gOPT / gPROMS)

Protocol	Dose	Application duration	Application Schedule
DNR (40<u_dnr<90)	90 mg/m^2	1 hr iv application	1 daily application for days 1,3,5 of treatment
Ara-C (100<u_araC<1000)	200 mg/m^2	24-hrs	for days 1-10



Optimization results for one patient case study

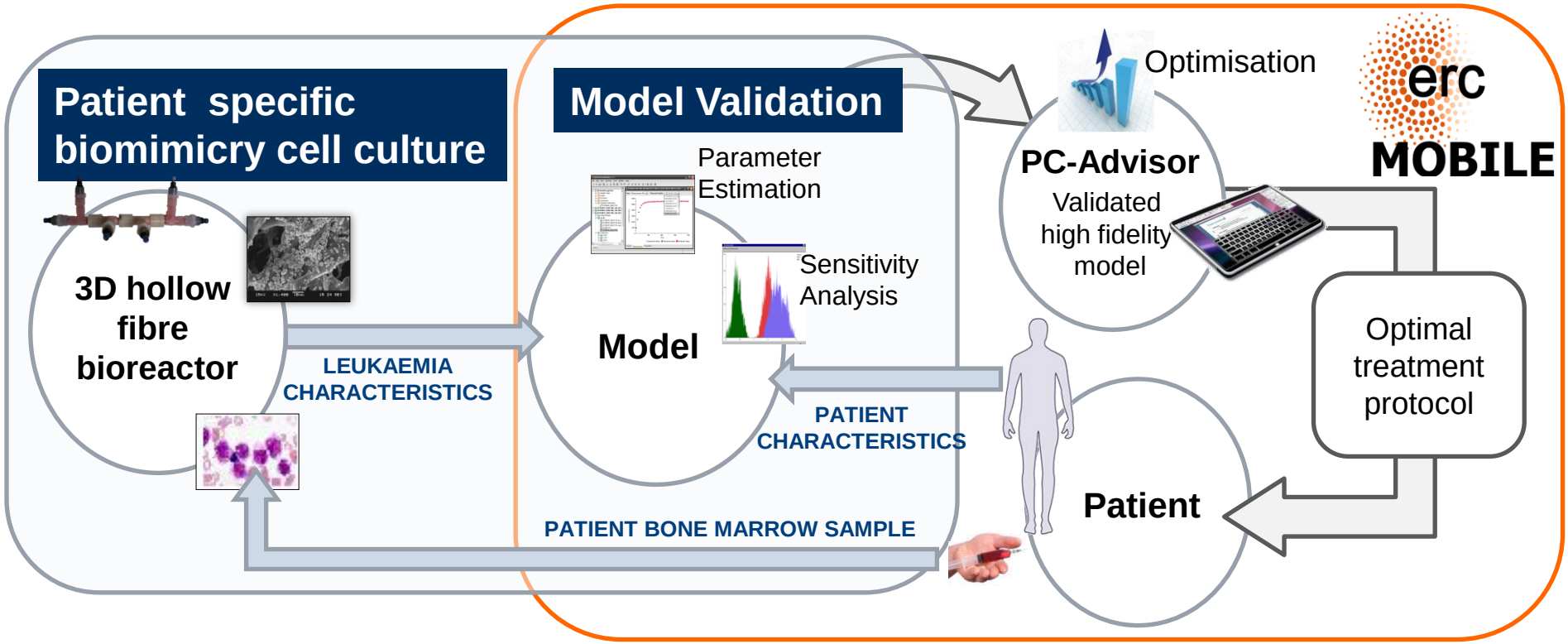
Cell numbers	Standard	Optimal
Leukemic Cells (cells)	**$1.77 \cdot 10^8$**	**$6.62 \cdot 10^7$**
Cells in RNA-synthesis phase	$1.65 \cdot 10^8$	$6.43 \cdot 10^7$
Cells in DNA-synthesis phase	$1.06 \cdot 10^7$	$1.5 \cdot 10^6$
Cells in mitosis phase	$1.2 \cdot 10^6$	$2.6 \cdot 10^5$
Normal Cells (cells)	**$6.25 \cdot 10^8$**	**$4.44 \cdot 10^8$**
Non-Proliferating Cells	$6.25 \cdot 10^8$	$4.44 \cdot 10^8$
Proliferating Cells	2949	3215



Reduction of $4 \cdot 10^8$ AML cells

Cost of less $1 \cdot 10^8$ normal cells

Platform for optimal personalised chemotherapy protocols



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Individualised physiologically based modelling and model predictive control of volatile anaesthesia

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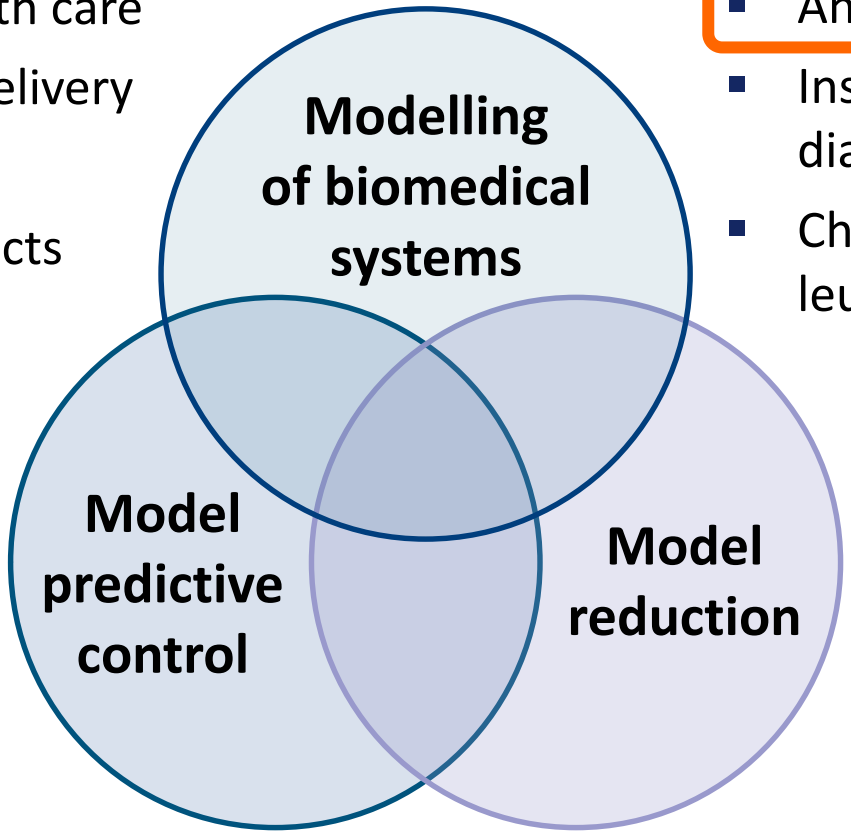
Overview - ERC Advanced Grant MOBILE project

Modelling, Control and Optimisation of Biomedical Systems

Objectives:

- Personalised health care
- Optimised drug delivery
- Patient safety
- Reduced side-effects



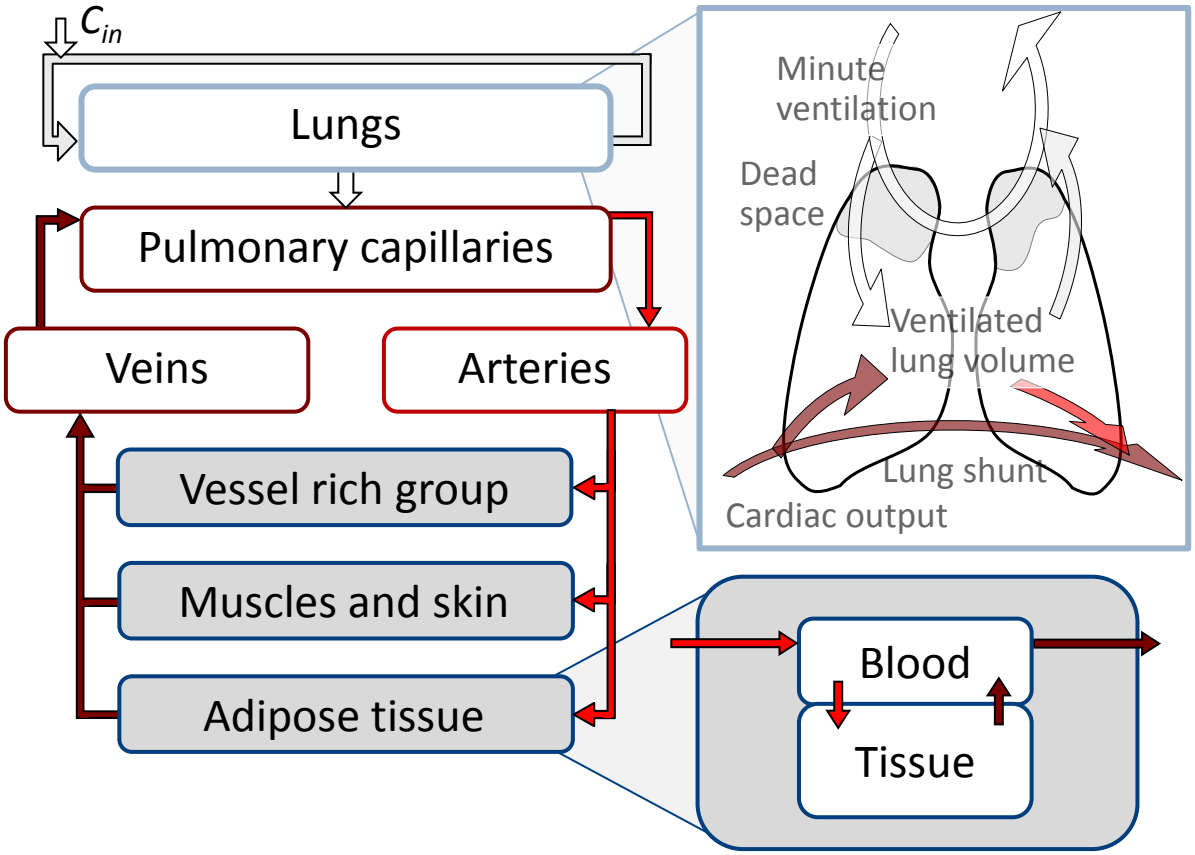
Biomedical systems:

- Anaesthesia
- Insulin delivery for type I diabetes
- Chemotherapy for leukaemia

Mathematical Pharmacokinetic Model for Anaesthesia

Drug distribution

Physiologically based compartmental pharmacokinetic model for volatile anaesthesia



Individually adapted model variables and parameters

- to the patient
- to the properties of the volatile anaesthetic agent

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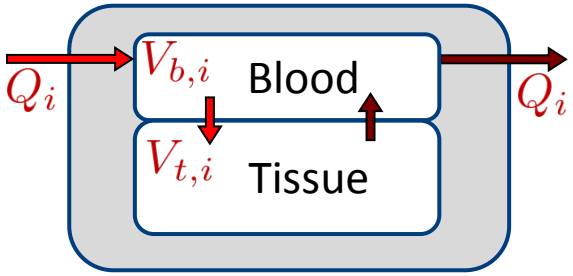
Mathematical Pharmacokinetic Model for Anaesthesia

Body compartment

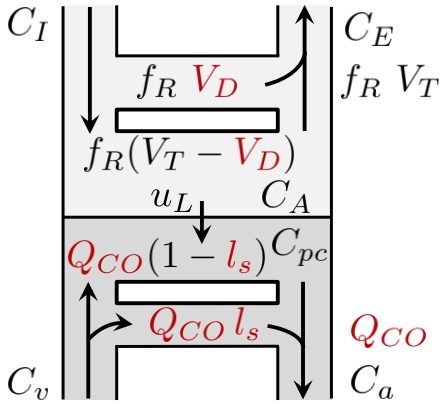
$$V_{b,i}\frac{dC_{b,i}}{dt} = Q_i(C_a - C_{b,i}) - Q_i(\lambda_i C_{b,i} - C_{t,i})$$

$$V_{t,i}\frac{dC_{t,i}}{dt} = Q_i(\lambda_i C_{b,i} - C_{t,i}) \Leftarrow u_{t,i}$$



$$C_{t,i}\,|_{eq} = \lambda_i C_{b,i}$$

Lungs



$$V_L\frac{dC_A}{dt} = f_R(V_T - V_D)(C_I - C_A) - Q_{CO}(1-l_s)(\lambda C_A - C_v)$$

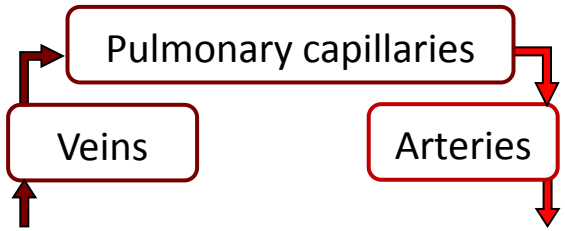
$$\Uparrow u_L$$

$$V_L = 11.97 \cdot \exp(-0.097 \cdot \mathrm{BMI}) + 0.46$$

Blood pools

$$C_a\,Q_{CO} = C_{pc}\,Q_{CO}\,(1-l_s) + C_v\,Q_{CO}\,l_s$$

$$C_v = \frac{\sum_i Q_i\,C_{b,i}}{Q_{CO}}$$



[1] Krieger, A., et al. (2011). 21st European Symposium on Computer Aided Process Engineering, volume 29, 1495-1499. Elsevier.

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Pharmacodynamic Modeling

Hypnotic effect of the anesthetic agent

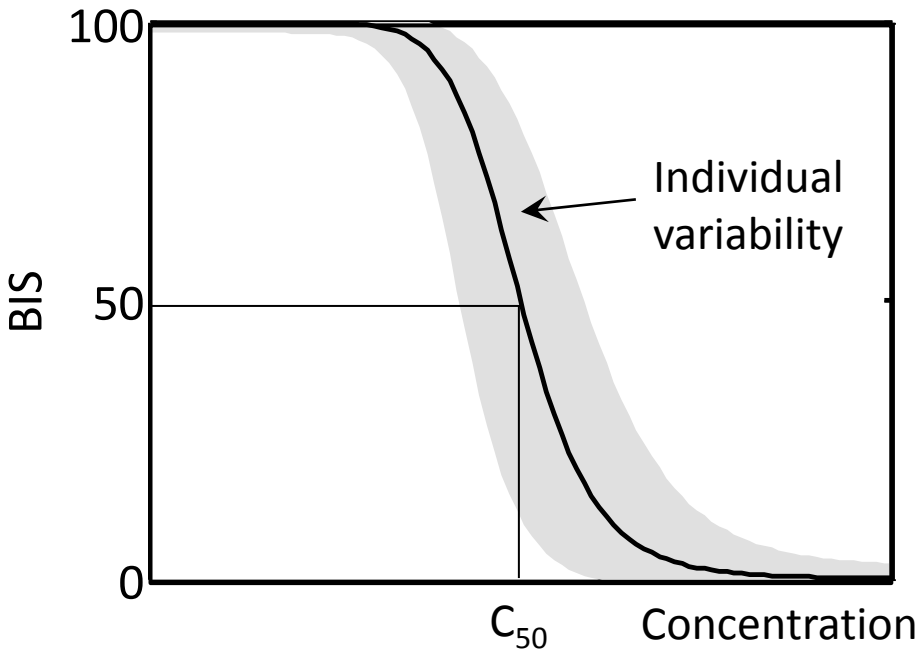
measured by the Bispectral Index (BIS)

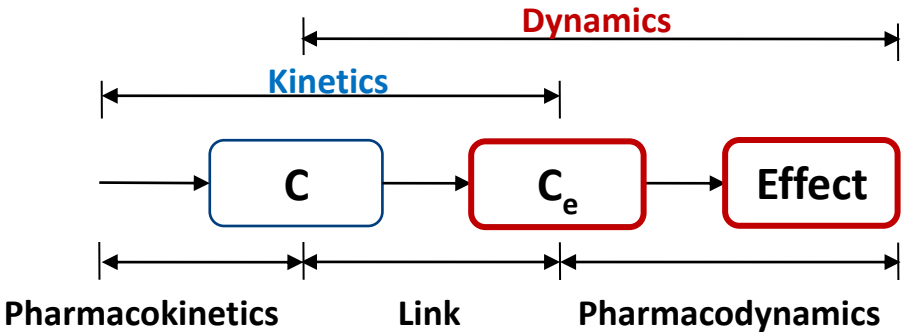
$$\frac{dC_e}{dt} = k_{e0}(C - C_e)$$

$$BIS = BIS_0 + (BIS_{max} - BIS_0)\frac{C_e^{\gamma}}{C_e^{\gamma} + C_{50}{}^{\gamma}}$$

Individual parameters:

k_{e0}	Delay of effect
C_{50}	Concentration at 50% effect
γ	Sensitivity to drug





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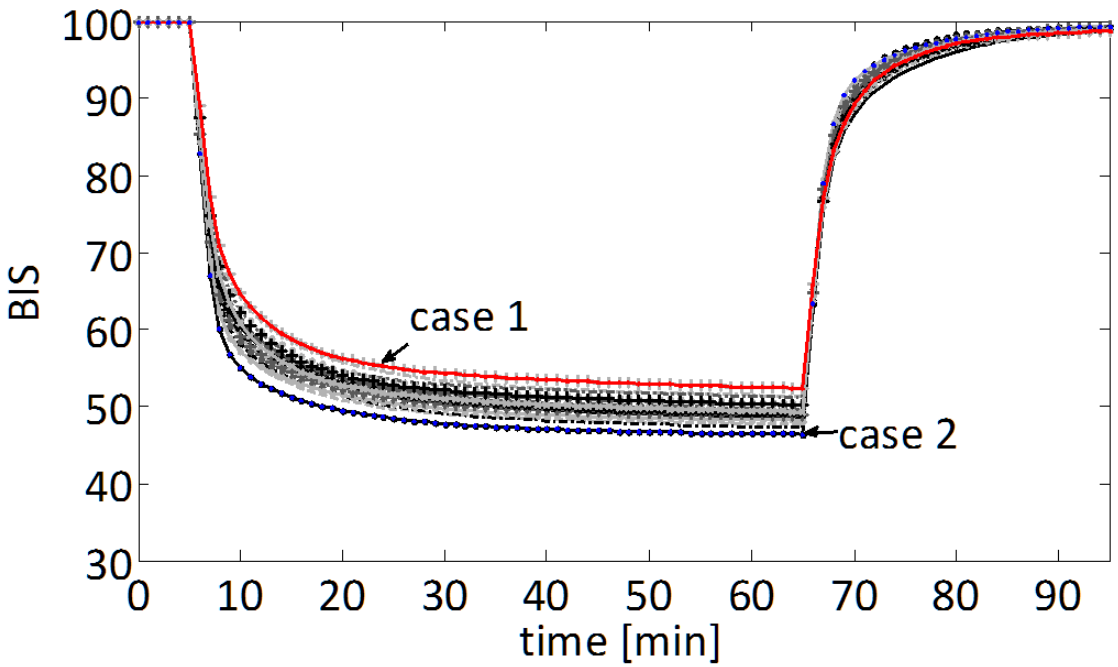
Model Analysis – Pharmacokinetic Parameters

Drug distribution

Hypnotic level (BIS) for variation in PK



Variable	Value	Deviation	Ref
λ	1.4	1.38 – 1.46	[3]
λ_{VRG}	1.65	1.45 – 1.86	[3]
λ_{M}	2.57	1.44 – 3.19	[3]
λ_{F}	50	43.84 – 55.8	[3]
$r_{CO,VRG}$	0.75	0.75 – 0.85	[4]
$r_{CO,M}$	0.181	0.1 – 0.181	[4]
$r_{CO,F}$	0.054	0.045 – 0.054	[4]
$V_{t,VRG}$	6 000	5 400 – 6 600 mL	[4]
$V_{t,M}$	14 500	11 600 – 17 400 mL	[4]
$V_{t,F}$	33 000	26 400 – 39 600 mL	[4]
Q_{CO}	5 000	3 000 – 7 000 mL	[1]
V_{DS}	30% V_T	20% – 45% V_T	[1]

[1] Krieger, A., et al. (2011). 21st European Symposium on Computer Aided Process Engineering, volume 29, 1495-1499. Elsevier.

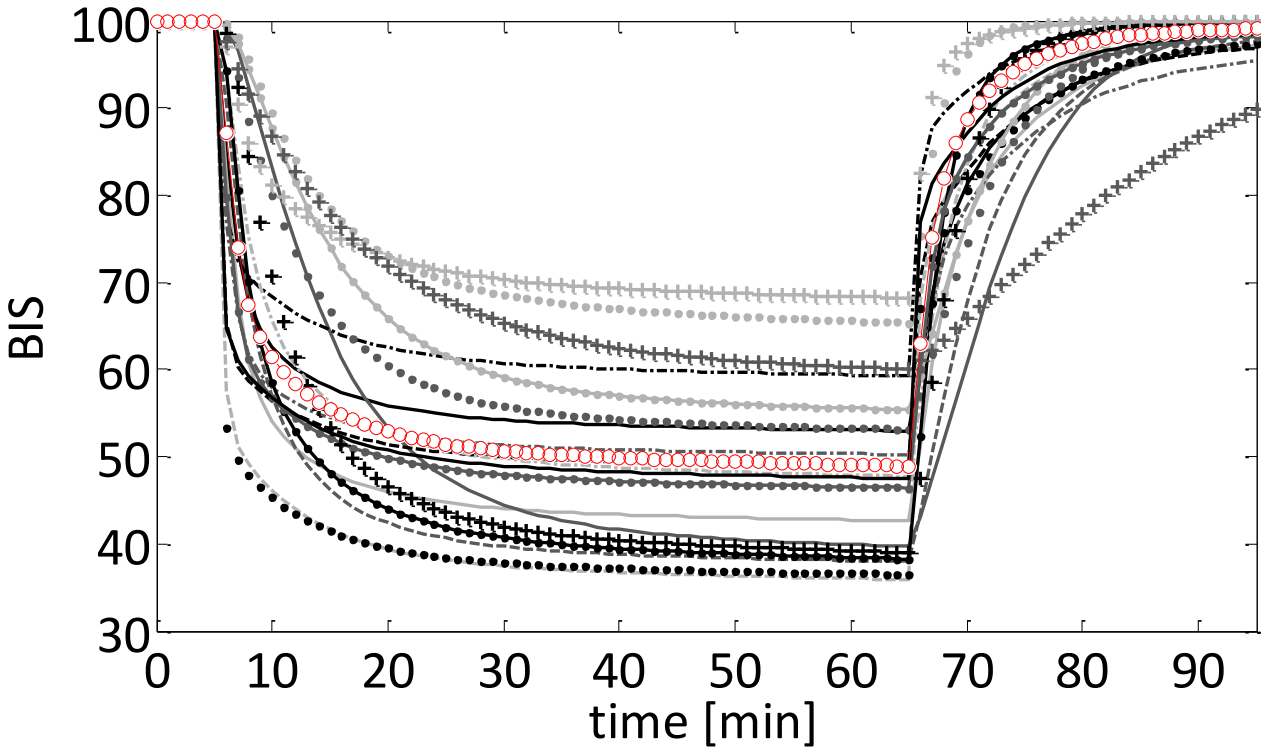
[3] Eger, E.I., Eisenkraft, J.B., and Weiskopf, R.B. (2002). The Pharmacology of Inhaled Anesthetics. Dannemiller Memorial Educational Foundation, 1st edition.

[4] Eger, E.I. (1974). Anesthetic Uptake and Action. Baltimore: Williams & Wilkins.

Model Analysis – Pharmacodynamic Parameters

Drug effect

Hypnotic level of 20 patients with individually estimated PD parameters C_{50}, k_{e0} and γ reported by Gentilini [2]

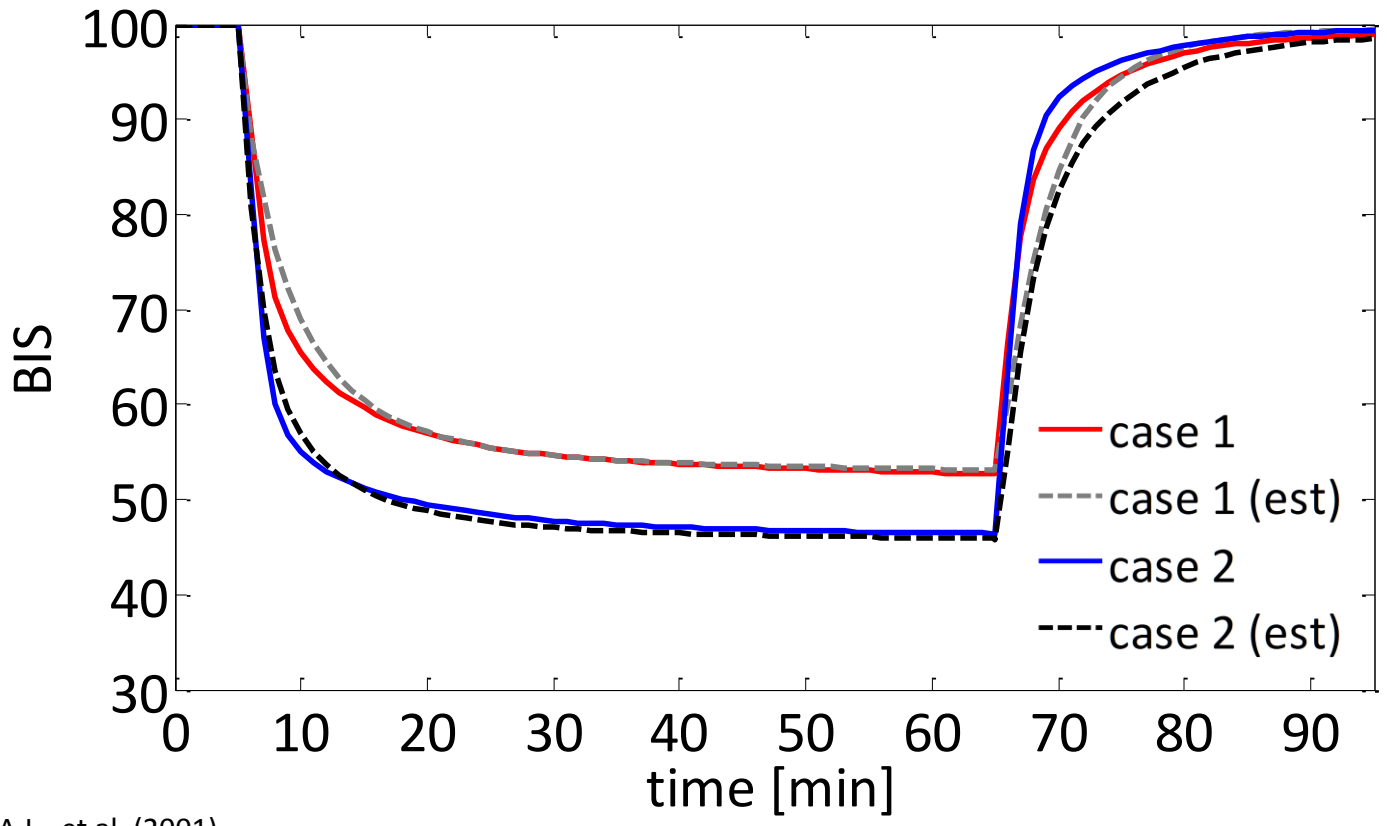


[2] Gentilini, A.L., et al. (2001). Modeling and closed-loop control of hypnosis by means of Bispectral index (BIS) with isoflurane. IEEE Transactions on Biomedical Engineering, 48(8), 874-889.

Model Analysis – Pharmacodynamic Parameters

Estimation of PD parameters to fit case 1 and case 2

Parameter	case 1	case 2	Ref [2]
k_{e0}	0.372	0.585	0.385
C_{50}	0.766	0.630	0.748
γ	1.633	1.387	1.534



[2] Gentilini, A.L., et al. (2001).

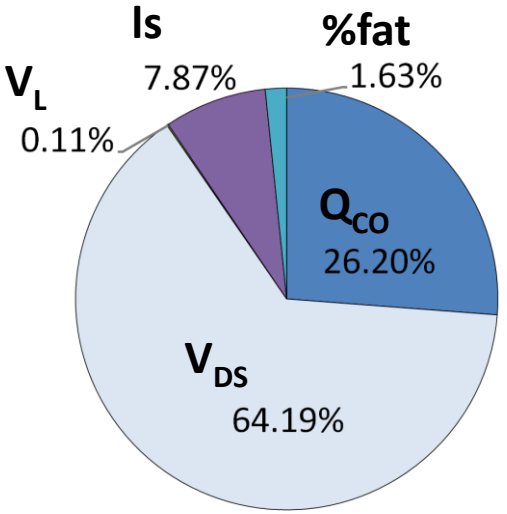
Model Analysis – PD and PK Parameters

Add PK parameter V_{DS} with the highest sensitivity [1] to the PD parameters in order to fit case 1 and 2

Estimation results

Parameter	Optimal Estimate	Standard Deviation
case 1		
k_{e0}	0.427	0.060
C_{50}	0.761	0.038
γ	1.382	0.061
V_{DS}	0.389	0.110
case 2		
k_{e0}	0.607	0.065
C_{50}	0.607	0.019
γ	1.610	0.052
V_{DS}	0.437	0.063

Sensitivity analysis of PK variables



[1] Krieger, A., et al. (2011)

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Model Analysis – PD and PK Parameters

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case 2		
k_{e0}	0.607	0.065
C_{50}	0.607	0.019
γ	1.610	0.052
V_{DS}	0.437	0.063

Correlation matrix

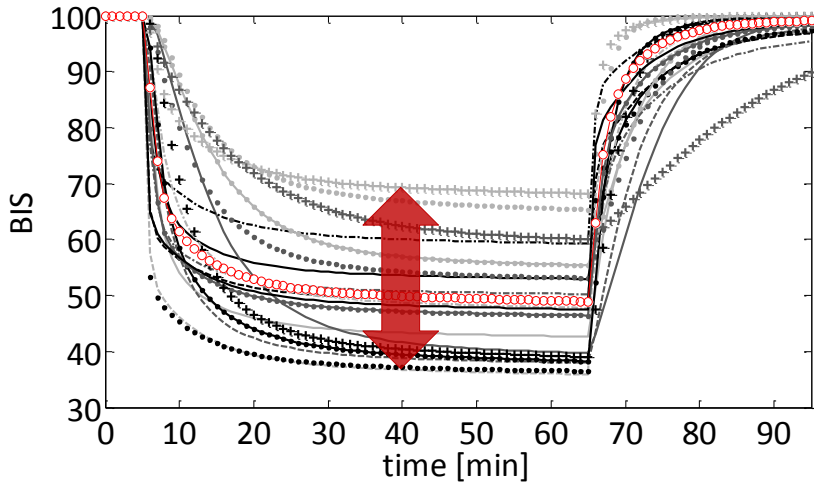
	k_{e0}	C_{50}	γ	V_{DS}
k_{e0}	1	-0.81	0.26	0.85
C_{50}	-0.81	1	-0.61	-0.98
γ	0.10	-0.27	1	0.50
V_{DS}	0.82	-0.99	0.29	1

[1] Krieger, A., et al. (2011)

Model Analysis – PD and PK Parameters

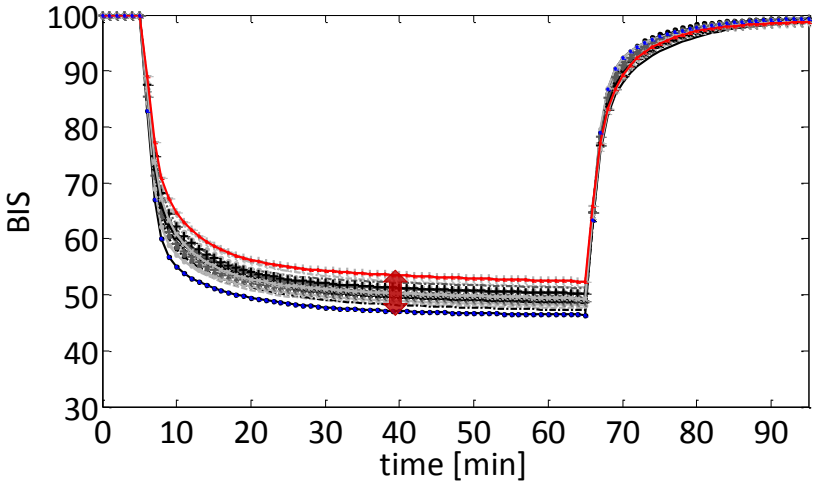
High variability for pharmacodynamics

Study by Gentilini et al. 2001 for 20 patients



Lower variability for pharmacokinetics

Variation for PK parameters



- Influence of PD parameters on the output variability is more profound than influence of PK parameters
- PK variability can be captured by adjusting PD parameters

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Results – Validation PK/PD Model

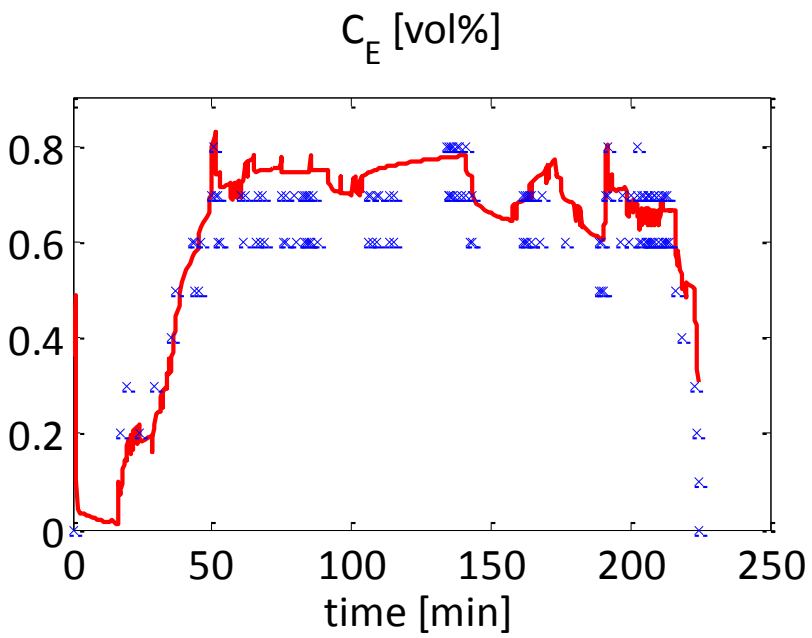
Clinical data

Patient characteristics				
female	66 years	69kg	1.63m	BMI = 26

Parameter		Ref [2]
k_{e0}	0.83	0.385
C_{50}	0.949	0.748
γ	1.9	1.534

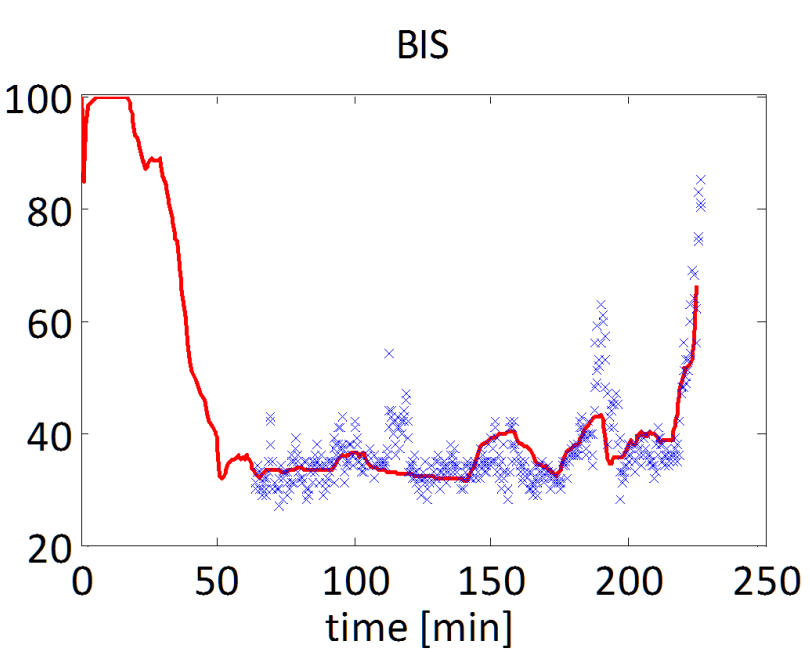
Pharmacokinetic model

Drug distribution



Pharmacodynamic model

Drug effect



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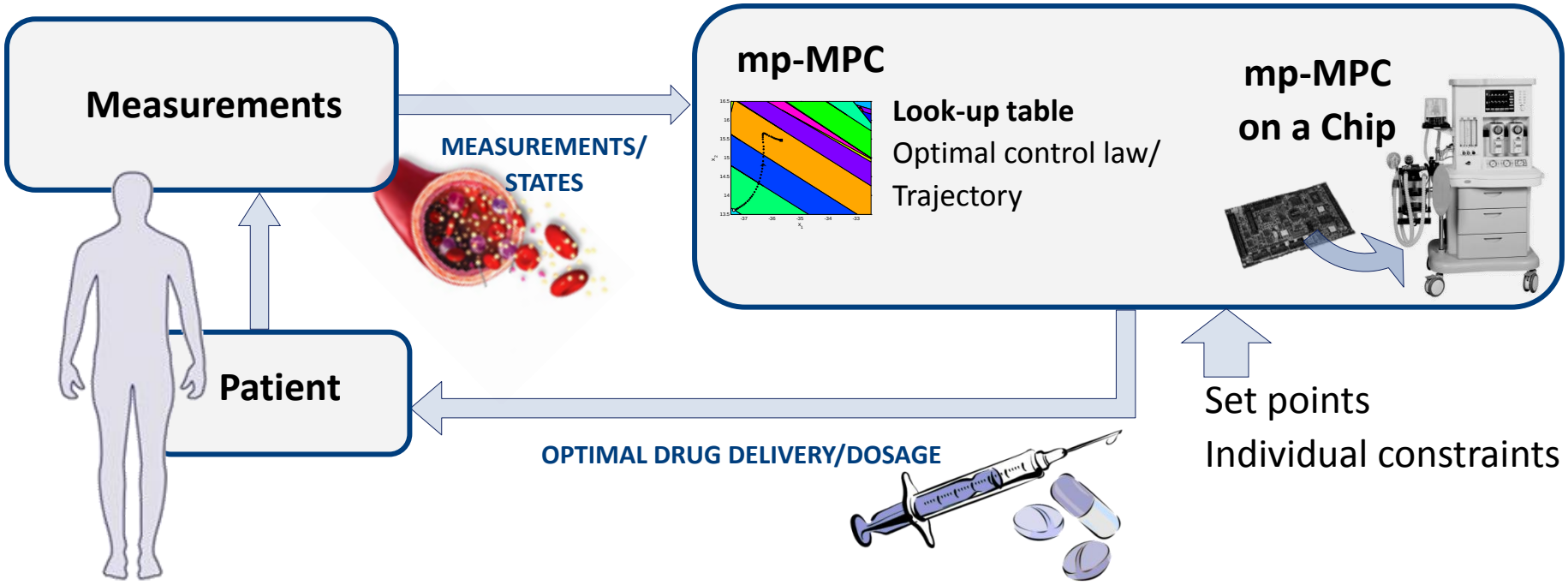
Closing the Loop for Drug Delivery

For the specific patient model



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Closing the Loop for Drug Delivery

Control problem formulation

$$\min_{u_{t+1},,u_{t+N_u}} J = \sum_{i=1}^{N_y} Q(y_i - y_{ref,i})^2 + \sum_{i=0}^{N_u} R(u_i)^2 + \sum_{i=0}^{N_u} R1_i(\Delta u_i)^2$$

$$st. \quad x_{t+1} = Ax_t + Bu_t$$
$$y_t = Cx_t + Du_t$$
$$C_{min} \leq u \leq C_{max}$$
$$C_{e,min} \leq y \leq C_{e,max}$$
$$\Delta u_{min} \leq \Delta u \leq \Delta u_{max}$$

Concentration in the compartments

Hypnotic level given by Ce

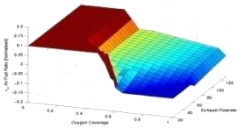
Concentration of inspired volatile anaesthetic agent

Step change in control input

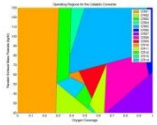
Controller specification:

$N_y = 8$	$N_u = 3$	
$Q = 1000$	$R = 1$	$R1 = 40$
$C \in [0, 3]$	$C_e \in [0, 5]$	$\Delta u \in [-1, 1]$

Optimization problem is reformulated to a mp-QP problem



Online optimisation via offline optimisation MPC on a Chip (Pistikopoulos 2009)



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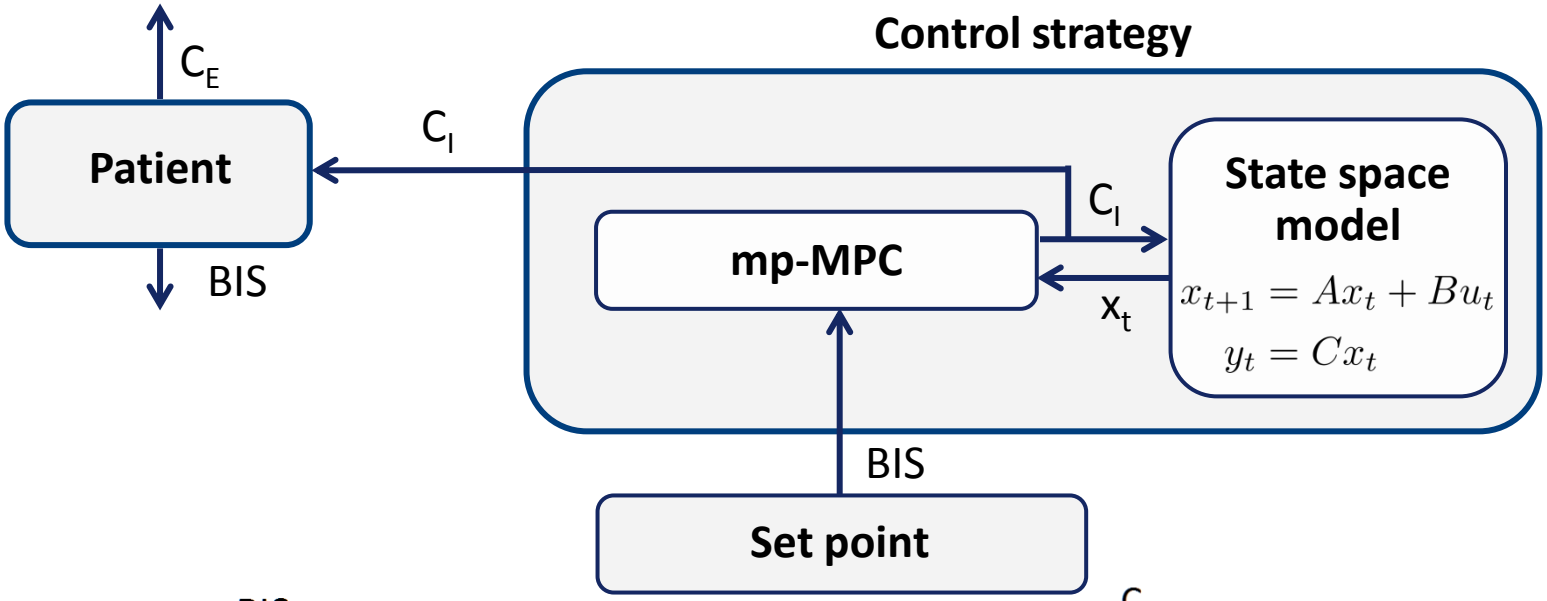
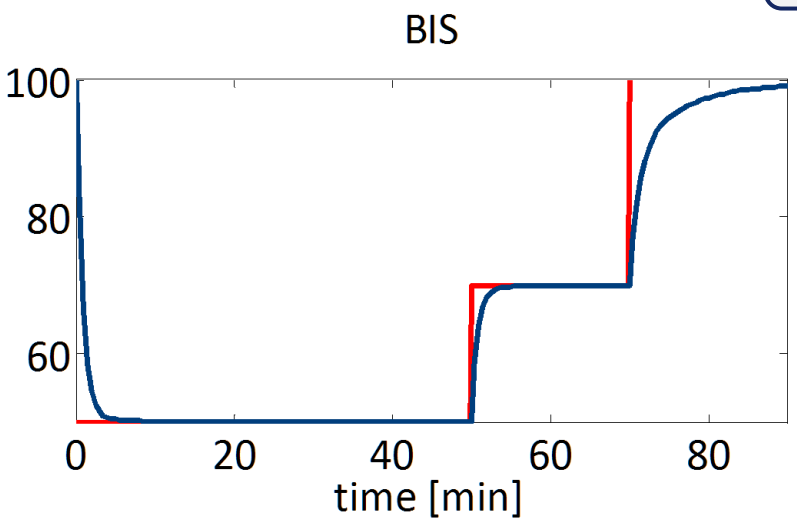
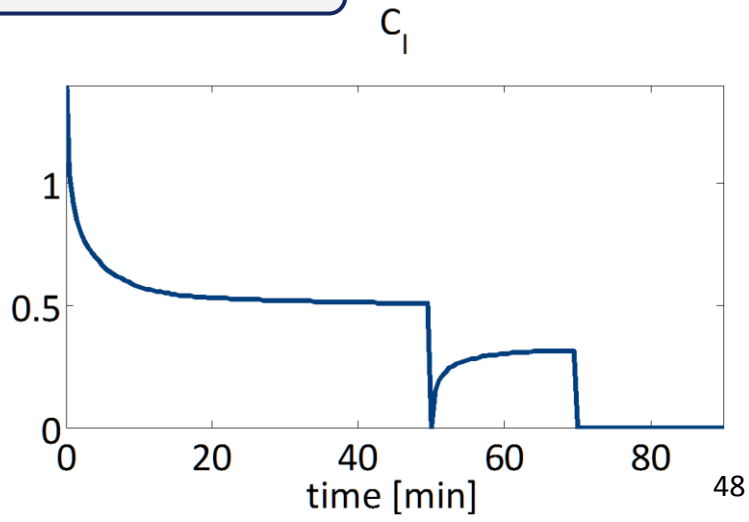
Closing the Loop for Drug Delivery

For the specific patient model







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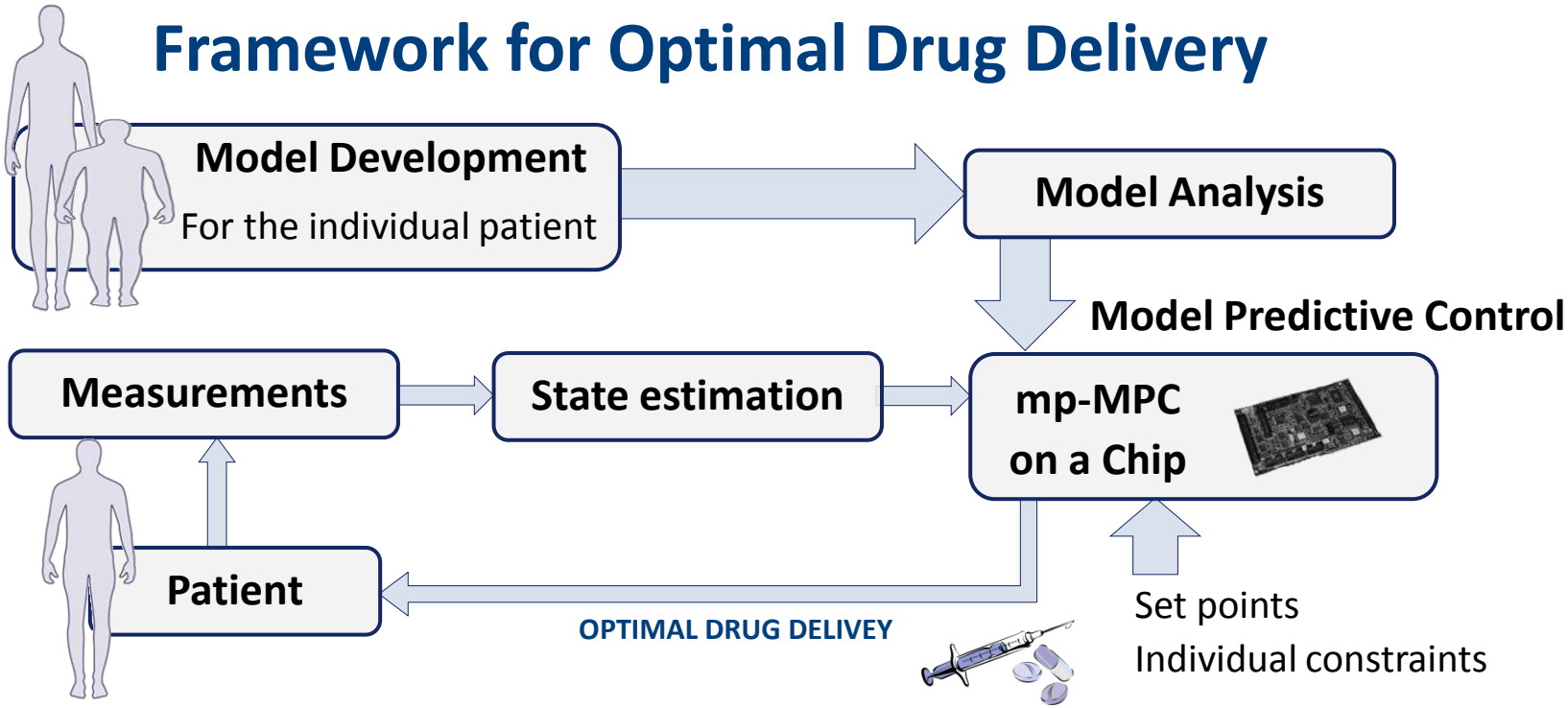
Framework for Optimal Drug Delivery



Ongoing and Future Work

- Design of a control strategy able to cope with the patient variability
- Explore robust control algorithms
- Design of different controllers for patient groups and testing

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Modelling, Optimization and mp-MPC of Biomedical Systems

Stratos Pistikopoulos