Pharmacokinetic modeling

methods, potentials and perspectives

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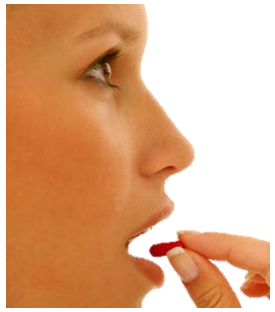
Main goals

- Forecast the concentration profile of drugs in blood and tissues.
- Determine patient individual pharmacokinetics (PK), in order to reduce unpredictability due to inter-individual variability.
- Predict drug response in terms of pharmacodynamic features.

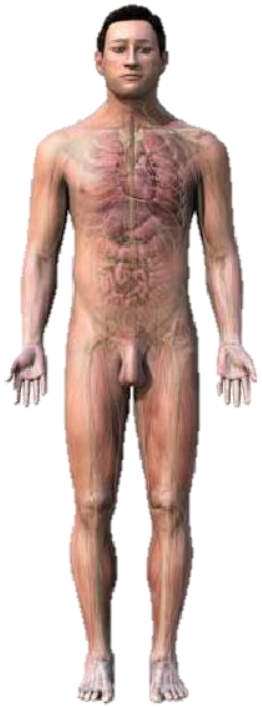
Method

Administration



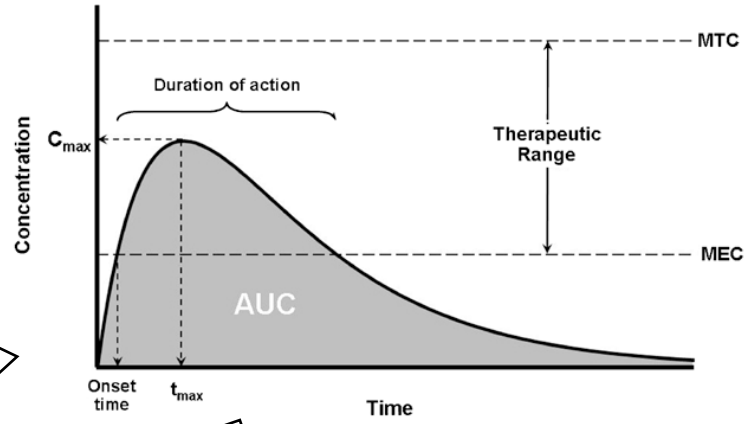
Oral

Endovenous

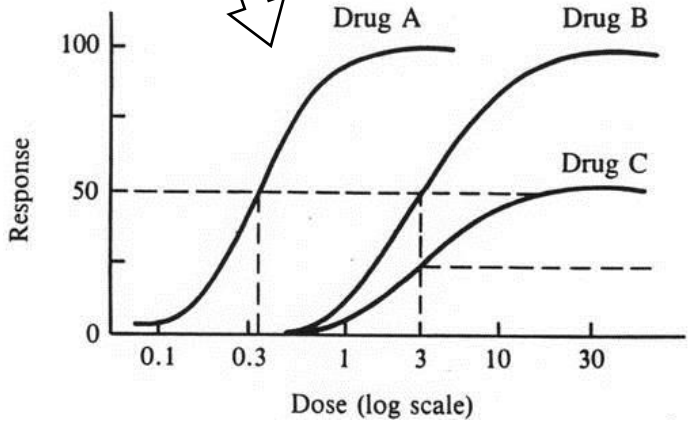


ADME

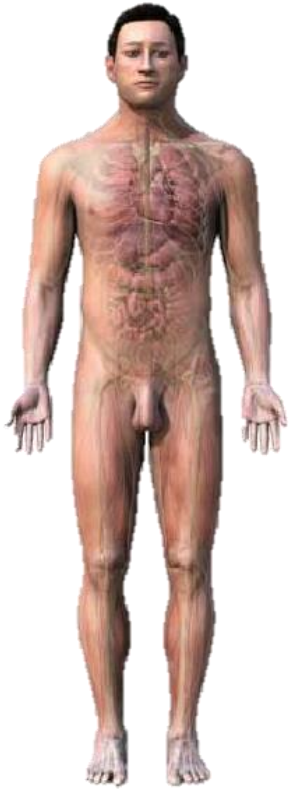
PK

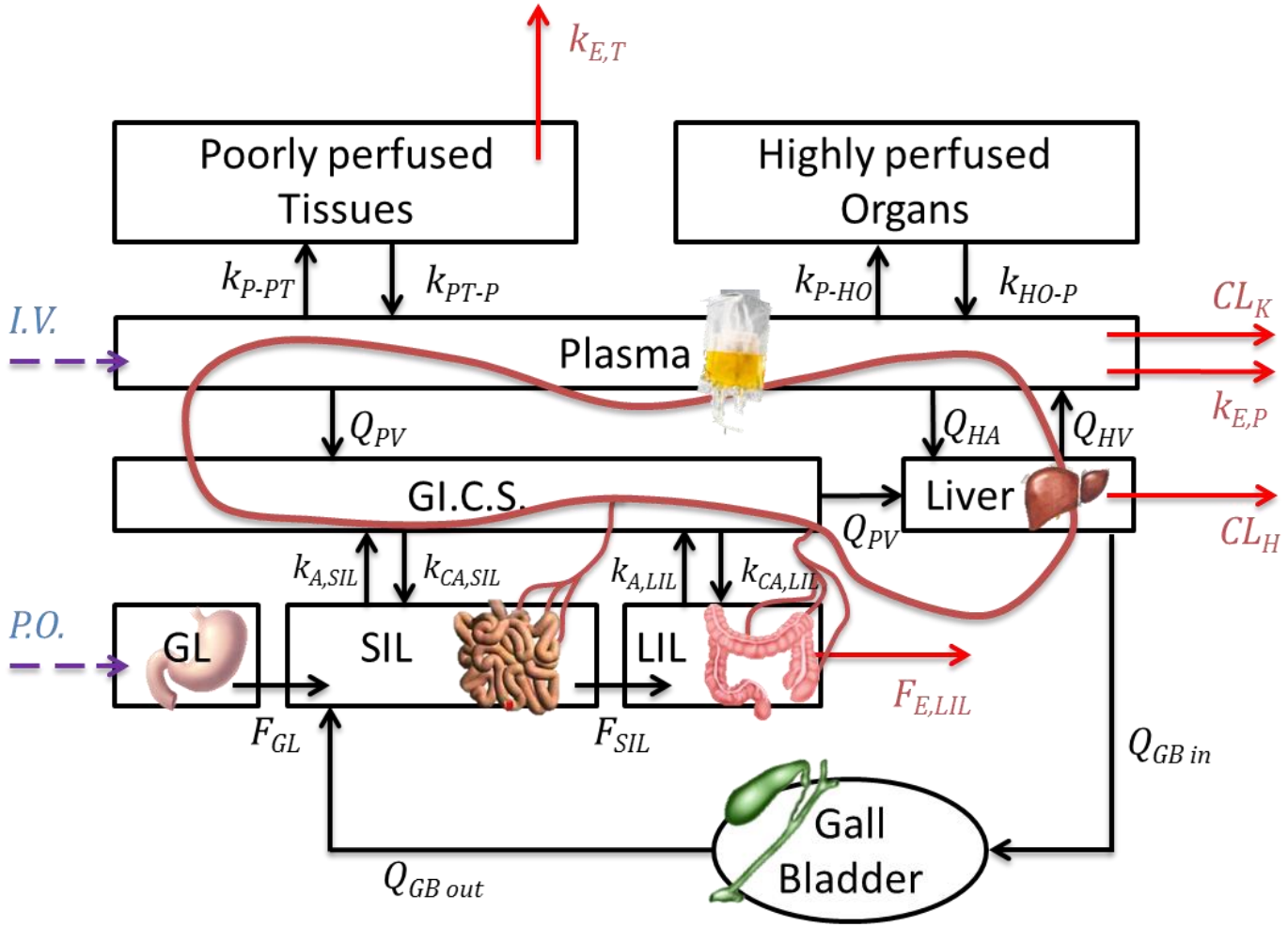


PD



Compartmental model structure





$$\begin{cases} \dfrac{d\boldsymbol{y}}{dt} = f(\boldsymbol{y}, t) \\ \boldsymbol{y}(0) = \boldsymbol{y_0} \end{cases}$$

Model outlook

In its complete formulation, the model comprises a system of 15 ordinary differential equations (ODE), including 33 parameters that need to be assigned/determined.

$$\frac{dA_{gl}(t)}{dt} = PO - F_{GL}$$

$$\frac{dA_{sil}(t)}{dt} = -A_{sil}(t) * k_{ASIL} + F_{GL} - F_{SIL} + \frac{C_{gics}(t) * k_{CA\,SIL} * V_{SIL}}{R_{GICS}}$$

$$\frac{dA_{lil}(t)}{dt} = -A_{lil}(t) * k_{ALIL} - F_{ELIL} + F_{SIL} + \frac{C_{gics}(t) * k_{CA\,LIL} * V_{LIL}}{R_{GICS}}$$

$$V_P \frac{dC_p(t)}{dt} = -C_p(t) * (k_{PT} * V_P + k_{PHP} * V_P + Q_{HA} + Q_{PV}) + C_t(t) * k_{TP} * V_T + C_l(t) * Q_{HV} + C_{hp}(t) * k_{HPP} * V_{HP} + IR - C_p^{\alpha}(t) * CL_K - C_p(t) * k_{E\,P} * V_P$$

Degree of Freedom

Variable

Patient Individual Parameter

$$V_T \frac{dC_t(t)}{dt} = -C_t(t) * k_{TP} * V_T + C_p(t) * k_{PT} * V_P$$

$$V_{GICS} \frac{dC_{gics}(t)}{dt} = A_{sil}(t) * k_{ASIL} + A_{lil}(t) * k_{ALIL} + C_p(t) * \frac{Q_{PV}}{R_{GICS}} - C_{gics}(t) * \left(Q_{PV} + \frac{V_{SIL} * k_{CA\,SIL}}{R_{GICS}} + \frac{V_{LIL} * k_{CA\,LIL}}{R_{GICS}}\right)$$

$$V_L \frac{dC_l(t)}{dt} = C_p(t) * Q_{HA} + C_{gics}(t) * Q_{PV} - C_l(t) * (Q_{HV} + CL_H)$$

$$V_{HP} \frac{dC_{hp}}{dt} = C_p(t) * k_{PHP} * V_P - C_{hp}(t) * k_{HPP} * V_{HP}$$

The PBPK model requires several parameters, which can be split into three categories:

1. **Individualized** (*e.g.*, compartment volumes, blood fluxes)

   parameters are specific for each patient depending on some correlations

   available in the literature and a few basic patient information (sex, body mass)

2. **Assigned** (*e.g.*, drug fraction bound to proteins)

   parameters are assumed as constant values for every patient

3. **Degrees of Freedom** (*e.g.*, mass transfer coefficients)

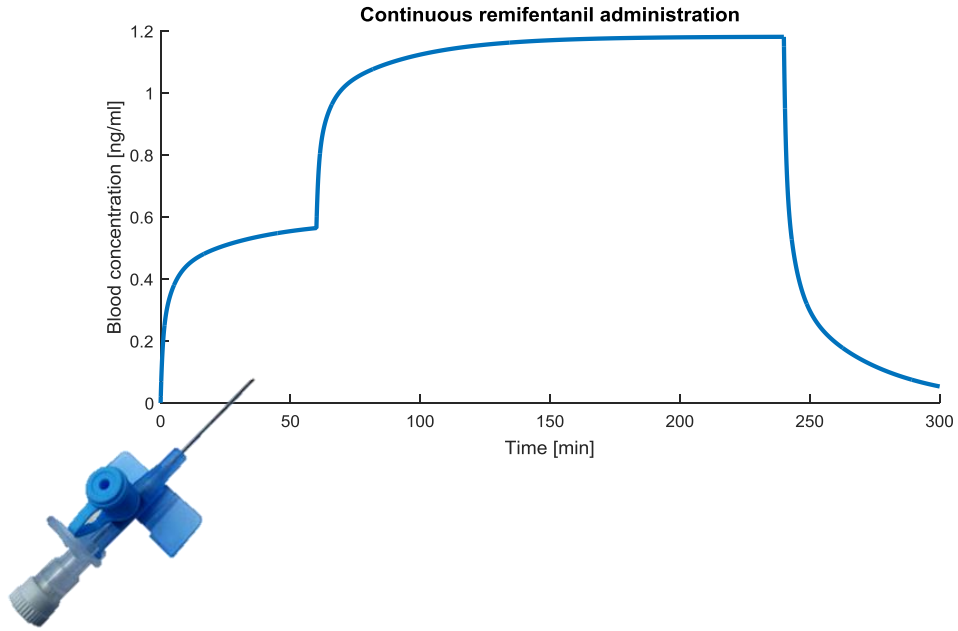
   parameters are unknown and are determined with a nonlinear regression

   procedure respect to experimental data

How does the model work?
1. Data acquisition

Input information:

- Administration (type, dosage, duration)
- Patient characteristics
- Drug molecule features



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Mammals:

Humans:

- Sex
- Age
- Body weight
- Height
- Fat/Lean body mass
- Specific organ impairment
- …

How does the model work?
1. Data acquisition

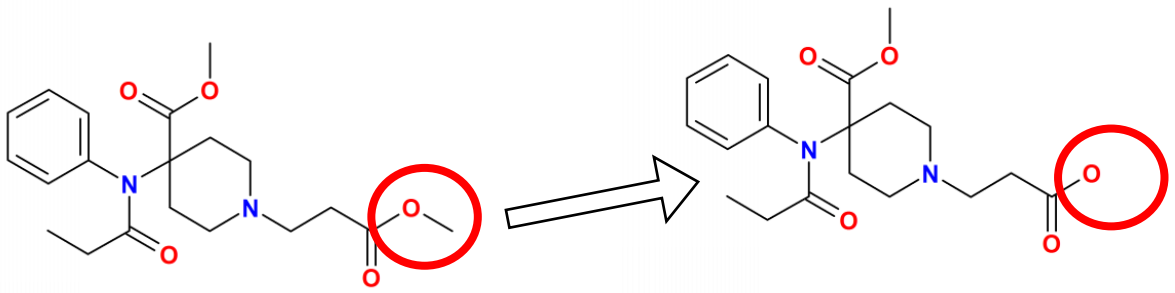
Input information:

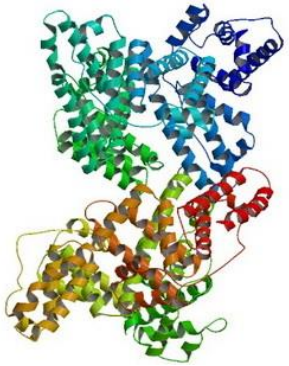
Administration (type, dosage, duration)

Patient characteristics

Drug molecule features

- Metabolism pathways (reactions)
- Plasma protein binding
- Lipophilicity
- pK_a
- …





How does the model work?
2. Simulation

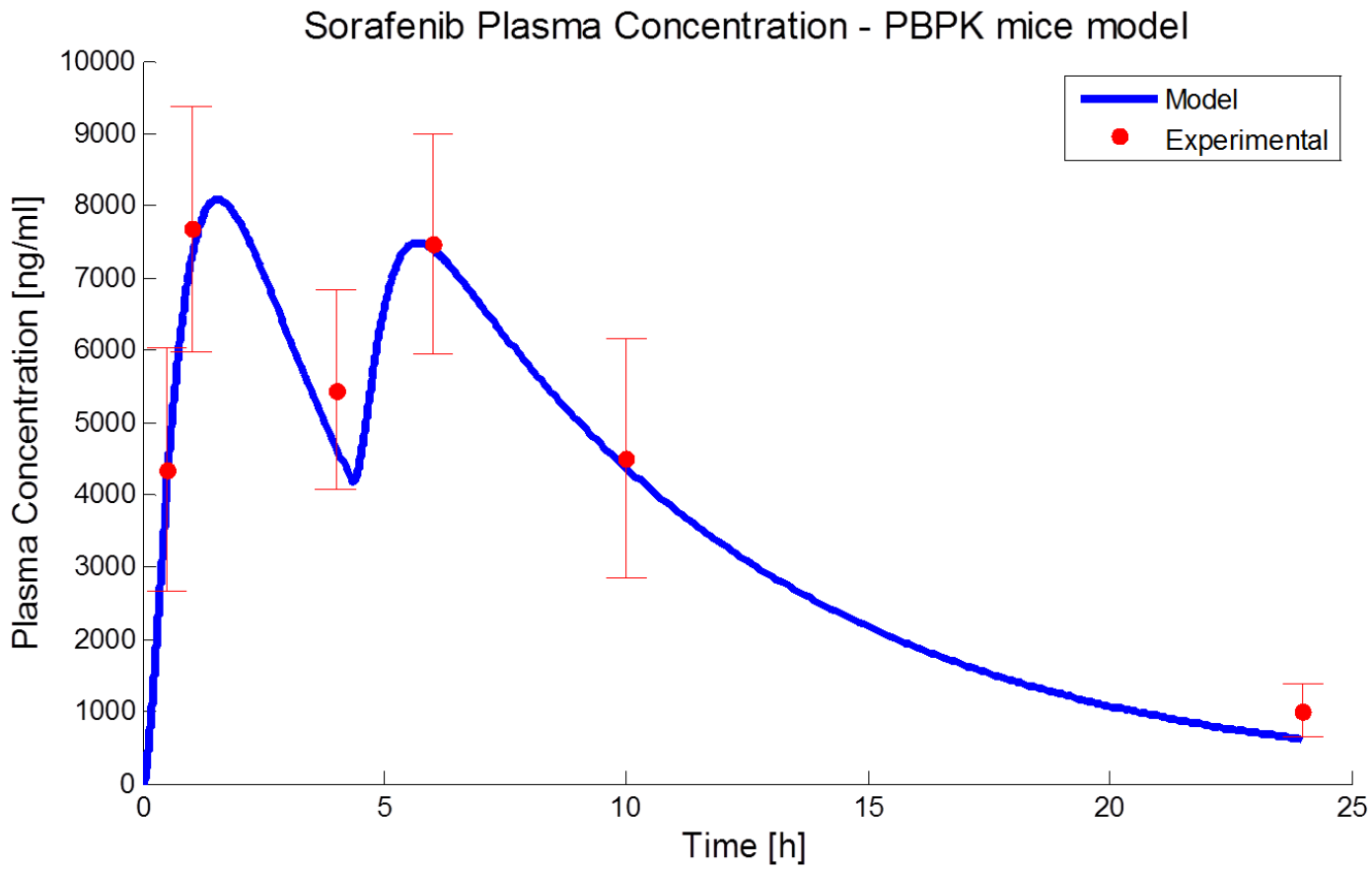
Input information:

- Administration (type, dosage, duration)
- Patient characteristics
- Drug molecule features

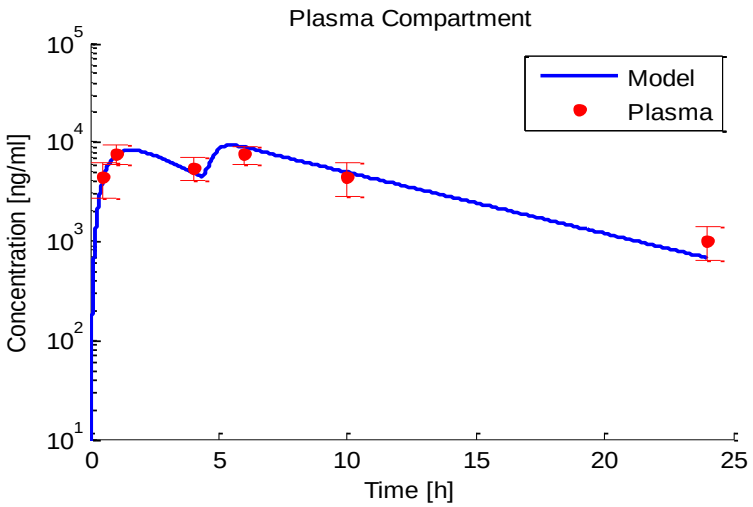
Mathematical Model

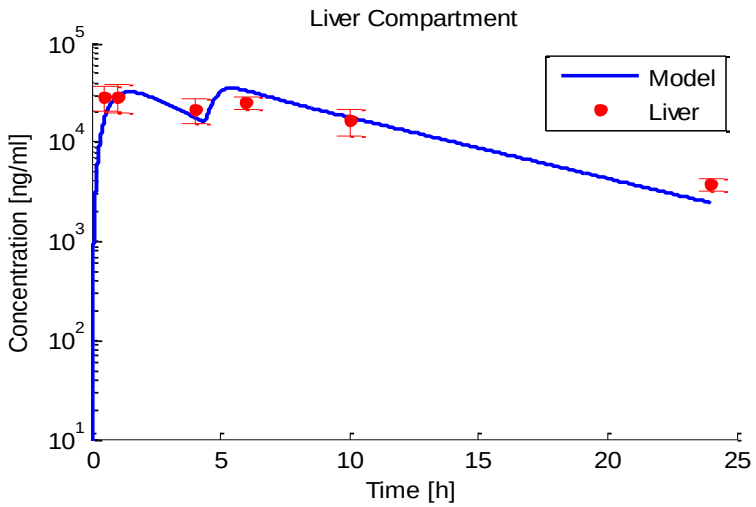
$$\begin{cases} \frac{d\boldsymbol{y}}{dt} = f(\boldsymbol{y}, t) \\ \boldsymbol{y}(0) = \boldsymbol{y_0} \end{cases}$$

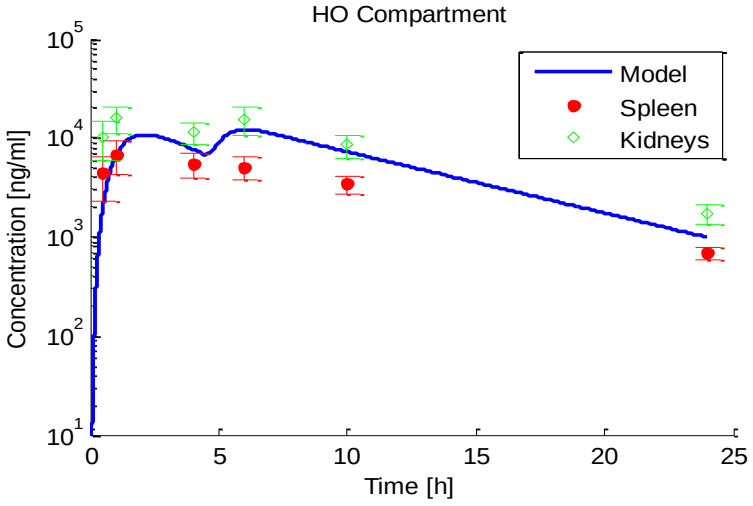
How does the model work?
3. Model output

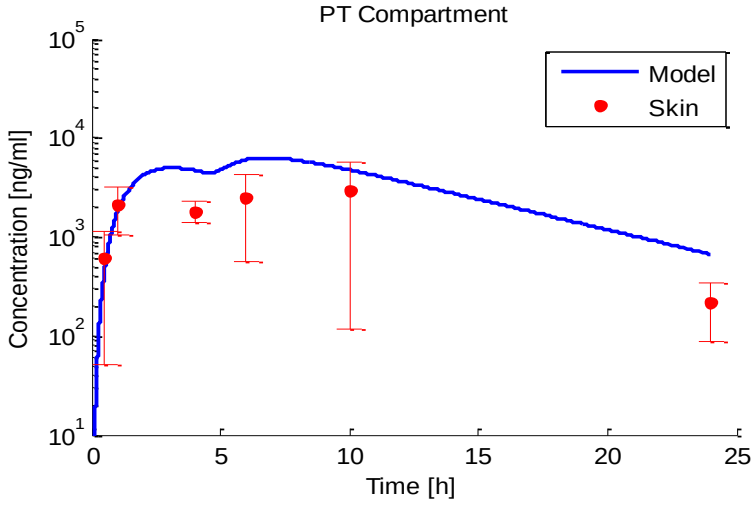


Advantages of physiologically based modeling





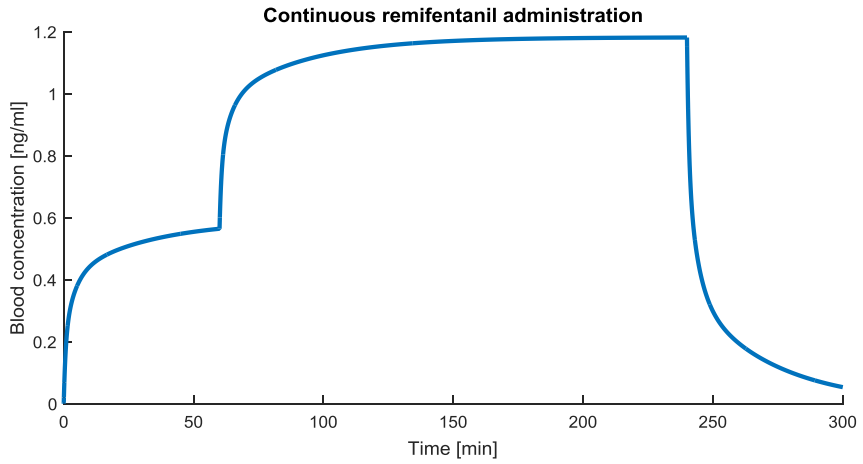


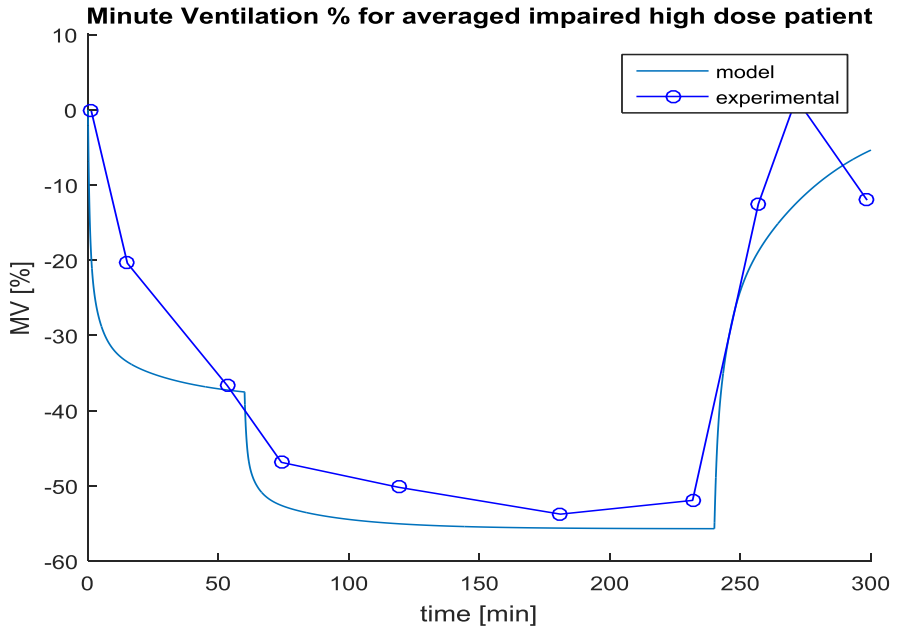


Studies

Three different active principles have been studied:

1. Remifentanil (I.V.) in humans (analgesic)
   - Pharmacokinetics and pharmacodynamics





Studies

So far we have studied three different active principles:

1. Remifentanil (I.V.) in humans (analgesic)
   - Pharmacokinetics and Pharmacodynamics

2. Sorafenib (P.O.) in mice (HCC treatment)
   - Pharmacokinetics

3. Alpha-Mangostin (I.V.) and (P.O.) in mice (dietary xanthone)
   - Pharmacokinetics

Model features

Advantages of the reduced physiologically based approach on modeling:

- Applicability to different animal models
- Simulation of different administration route/dosage regimes

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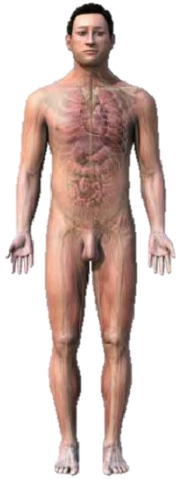

- Injection

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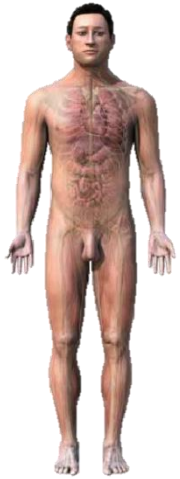

- Injection
- Oral

Model features

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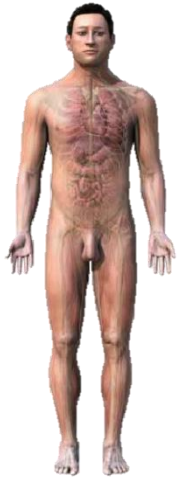

- Injection
- Oral
- Inhalation

Model features

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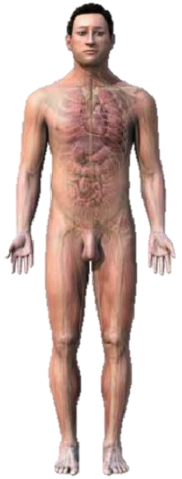

- Injection
- Oral
- Inhalation
- Topical

Model features

Advantages of the reduced physiologically based approach on modeling:

- Applicability to different animal models
- Simulation of different administration route/dosage regimes
- Simplicity, limited experimental information is required
- Assessment of drug concentration in tissues/organs
- Capability to individualize PK predictions

Opportunities and Perspectives

Pharmaceutical companies:

- Early decision in Clinical Trials planning
- Pre-analysis for bioequivalence studies
- First estimate of drugs pharmacokinetic parameters

Clinical applications:

- Knowledge of patient PK profile prior to administration → determination of optimal dosage regime (*e.g.,* analgesic, cancer treatment)
- Prediction of pharmacodynamic effects: **PK**/**PD** modeling

Forthcoming improvements

To achieve a reliable prediction, a good amount of information is required

- Drug physicochemical properties
- Patient individual data (the more detailed, the better prediction)
- Drug PK experimental studies (necessary to fit/optimize the model parameters)

http://pselab.chem.polimi.it