PBPK/PD modeling for predicting tumor response

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Motivation PBPK modeling

- To identify the optimal pre-loading for ^{90}Y labeled anti-CD45 antibody (2009)
- To investigate:
  - saturation effects in radioligand therapy (2012)
  - the possibility to predict therapy biokinetics with the PET/CT (2016)
  - the influence of total tumor volume in ^{177}Lu-PSMA therapy (2018)

PBPK = physiologically based pharmacokinetic

Motivation PBPK/PD modeling

- To link the pharmacokinetics with the pharmacodynamics within one model
- To estimate effective radiobiological parameters
- To predict tumor response based on one PET/CT measurement

PBPK/PD = physiologically based pharmacokinetic/pharmacodynamic

Motivation PBPK/PD modeling

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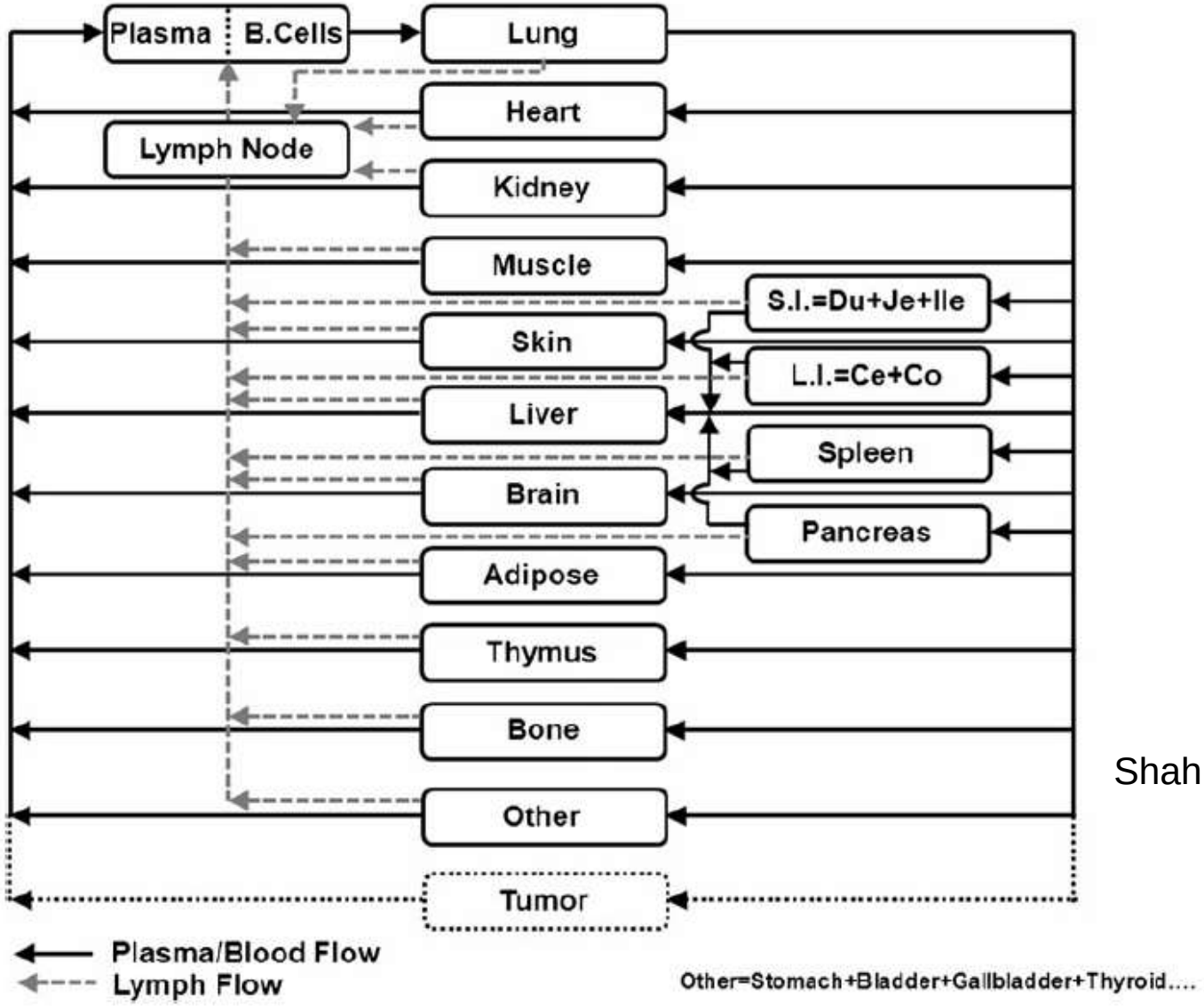
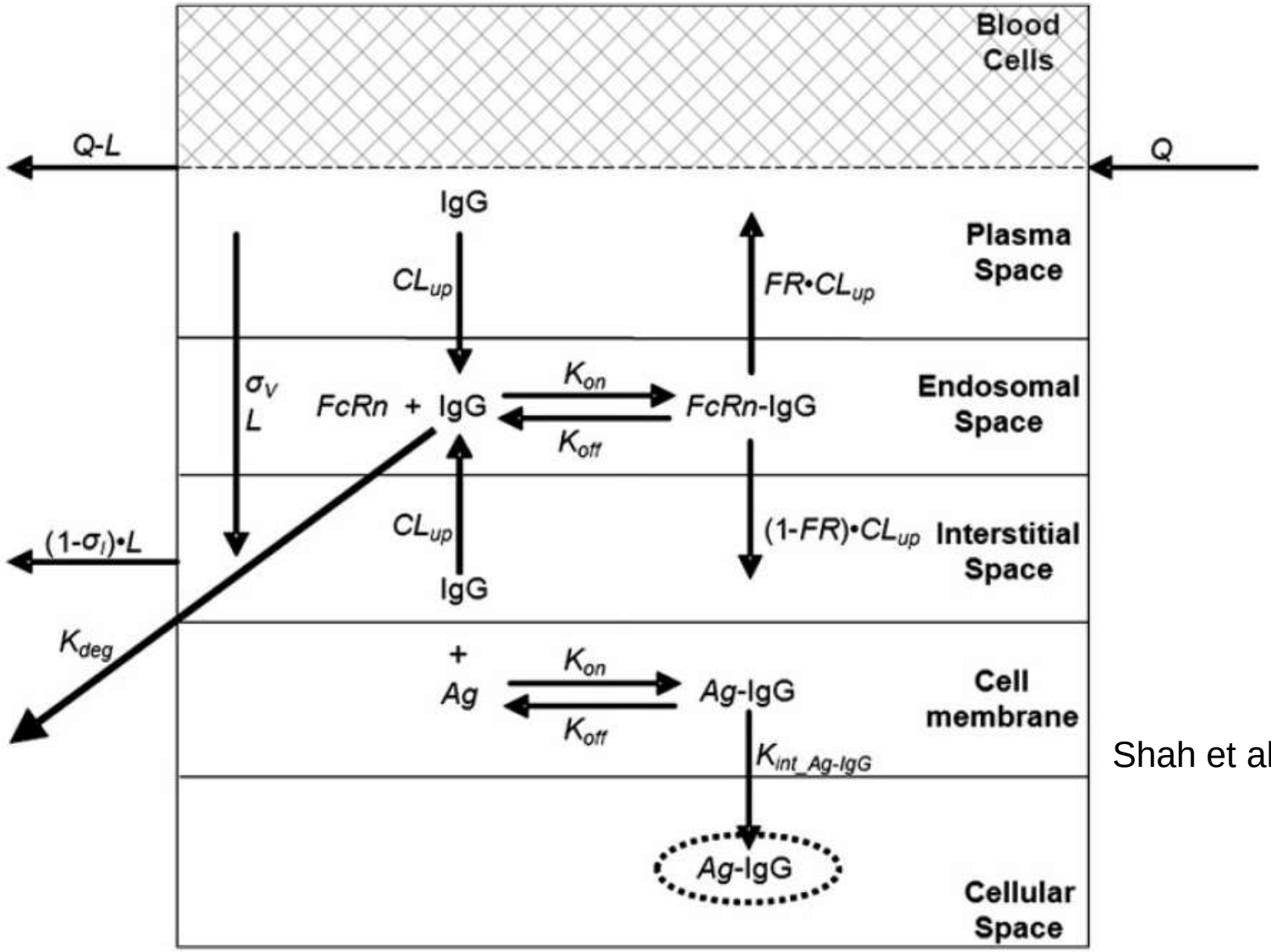
⟶ Big step towards treatment planning

Basic structure of a whole-body PBPK model



Shah et al. J Pharmacokinet Pharmacodyn 2012

PBPK model organ level for antibodies



Shah et al. J Pharmacokinet Pharmacodyn 2012

General and individual information

Organism properties

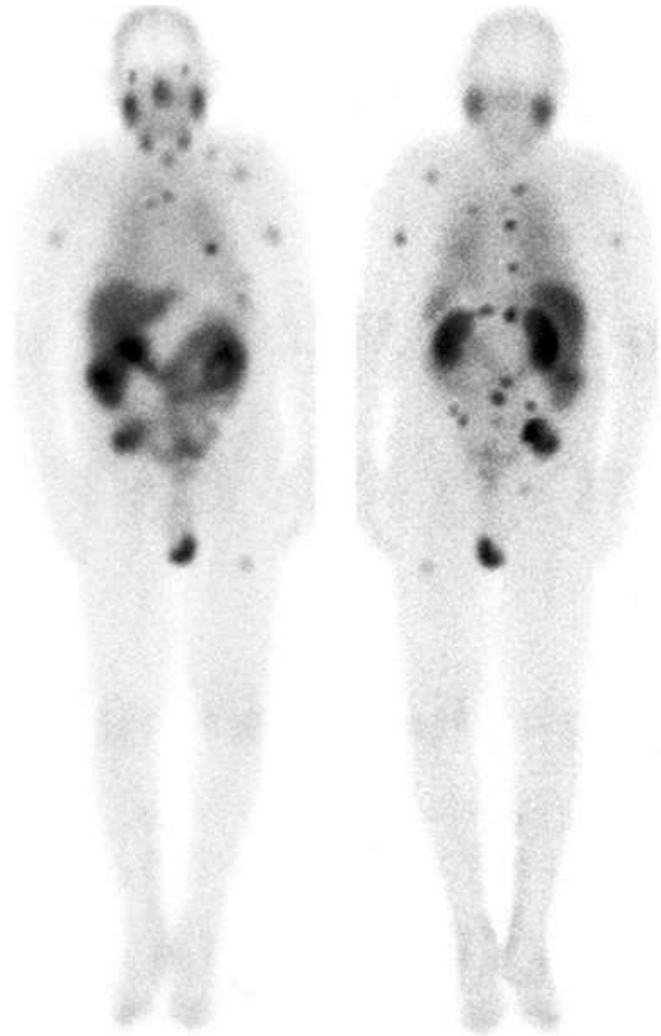
Drug properties

Anatomy and physiology
- Organ volumes
- Surface areas
- Tissue composition
- Blood flow rates
- Expression levels

Physico-chemical properties
- Lipophilicity (logP, logD, logMA)
- Molecular Weight
- pKa/pKb

Drug biological properties
- Fu
- Partition coefficients
- Permeability
- active processes (Km, Vmax, Kd)

\+ Age, BSA, Creatinine… +



Kuepfer et al. 2016

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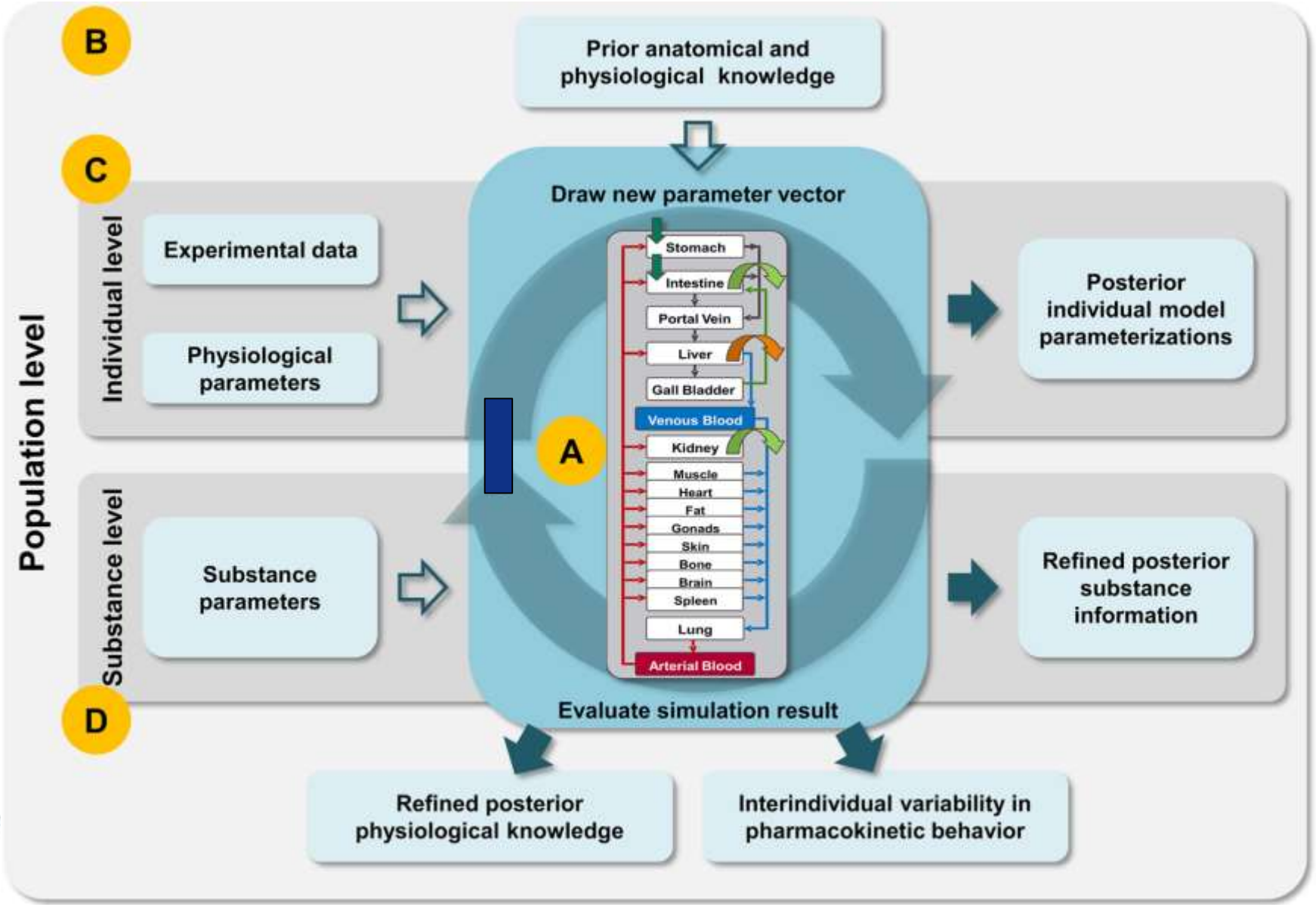
Integrating information in a Bayesian Framework



Krauss et al. 2015

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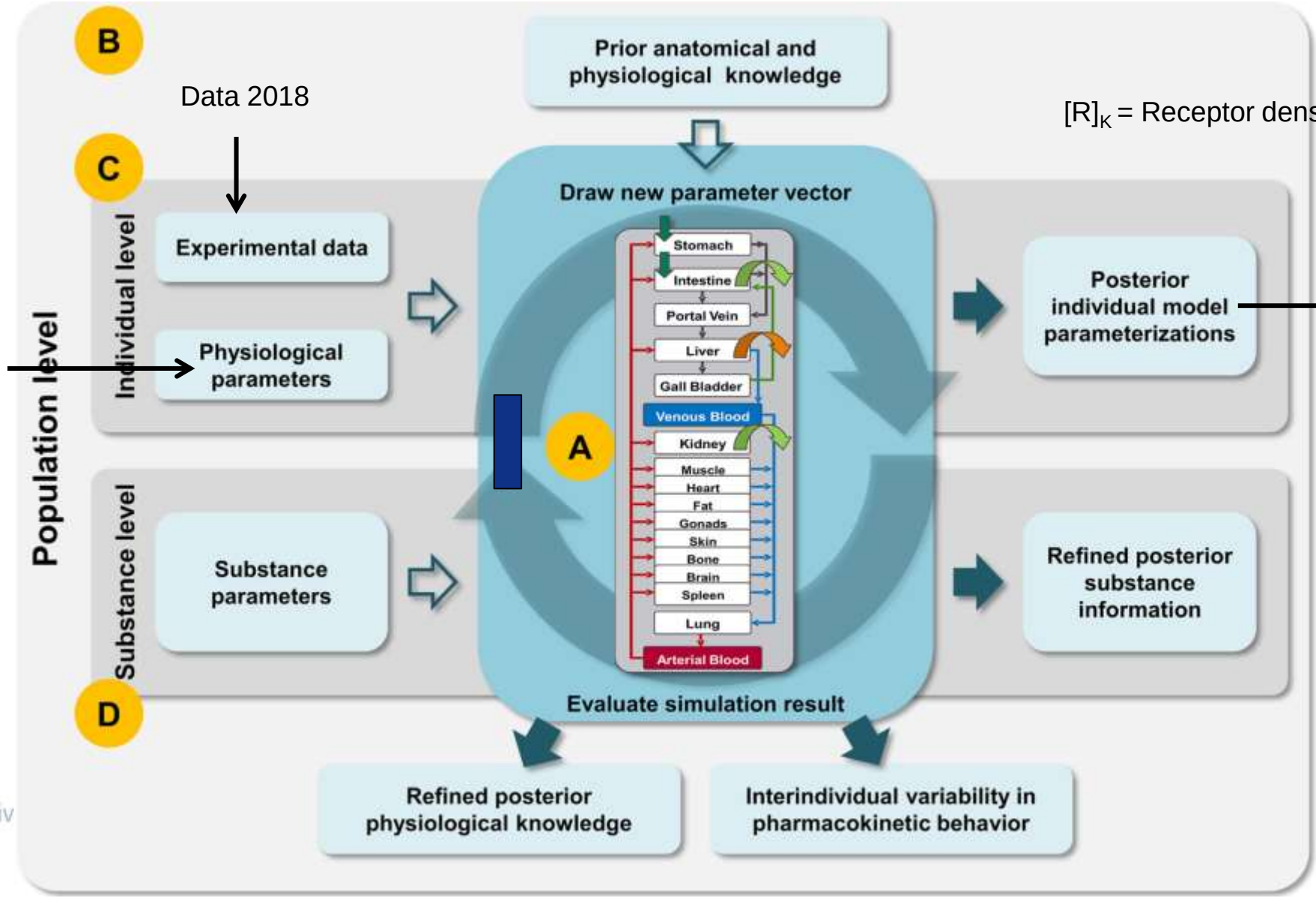


$[R]_K$ = Receptor density kidneys

$[R]_K$= 27±12 nmol/l

from data 2016

$[R]_K$= 16±4 nmol/l

Krauss et al. 2015

Bayesian Framework: Used Objective Function (Sums of Squares)

observation

prior

$$P(\vec{p} \mid y_i, Gaussian) = \prod_{i=1}^{N} \frac{1}{\sqrt{2\pi\sigma_i^2}} \exp\left\{-\frac{(y_i - f(x_i \mid \vec{p}))^2}{2\sigma_i^2}\right\} \cdot \prod_{j=1}^{K} \frac{1}{\sqrt{2\pi\omega_j^2}} \exp\left\{-\frac{(p_j - \bar{p}_j)^2}{2\omega_j^2}\right\}$$

$$-2\ln(P) = \sum_{i=1}^{N}\left\{\ln(2\pi\sigma_i^2) + \frac{(y_i - f(x_i))^2}{\sigma_i^2}\right\} + \sum_{j=1}^{K}\left\{\ln(2\pi\omega_j^2) + \frac{(p_j - \bar{p}_j)^2}{\omega_j^2}\right\}$$

Measured data point and error

Population mean value
and standard deviation included
as Bayesian information

Muzic et al. Med Phys 2006

Advantages of PBPK/PD models

- Simulation of different scenarios using the same basic structure:
  - different amounts of substance
  - different affinities of ligands
- Inclusion of parameters from other experiments/studies:
  - in vitro binding studies and internalisation studies
  - in vivo animal studies → scale up from mouse to human easier
  - physiological and tumour parameters
  - population parameters for a certain patient group
- Less measurements necessary for equal accuracy

Example radioligand therapy using ^{177}Lu-PSMA I&T

Aim: To develop a method that allows predicting PSMA–positive tumor volume after RLT based on:

- pre-therapeutic PET/CT measurement
- PBPK/PD modeling

Patient data

For 13 patients with metastatic castration resistant prostate cancer:

- PET/CT before and after therapy (% injected activity and volumes)
- Planar imaging during therapy
- Time activity data: kidneys, total body, total tumor, 2 tumor lesions per patient
- Basic data (age, activities, amount of peptide,…)

Time line

22±14 d

41±1 d

Measurements:

- tumor volume 1
- % injected activity

% injected activity

tumor volume 2

^{68}Ga-PSMA-HBED-CC

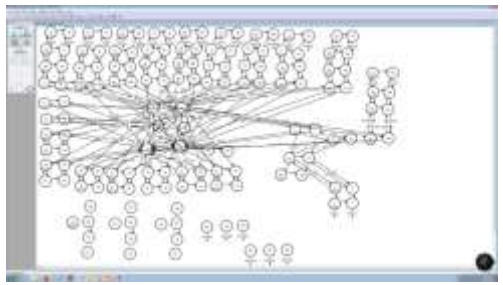
^{177}Lu-PSMA-I&T

Injections:

PET/CT Injection:
- Amount
- Affinity
- Activity
- Molecular size
- Half-life

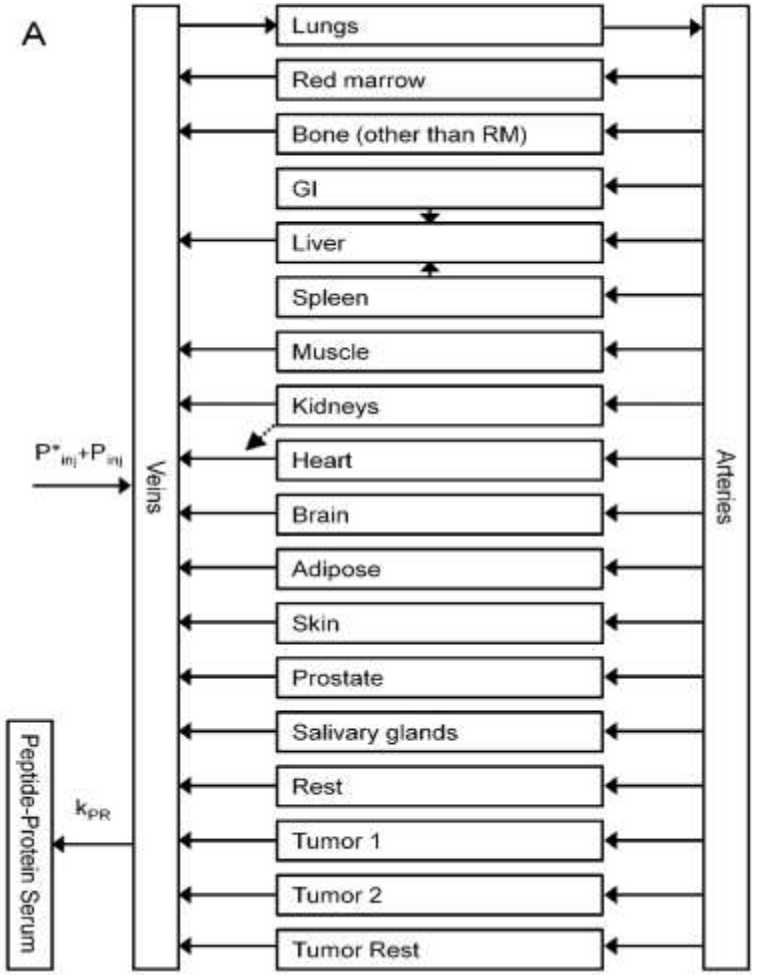
Therapy Injection:
- Amount
- Affinity
- Activity
- Molecular size
- Half-life

Switch of related parameters in PBPK/PD model

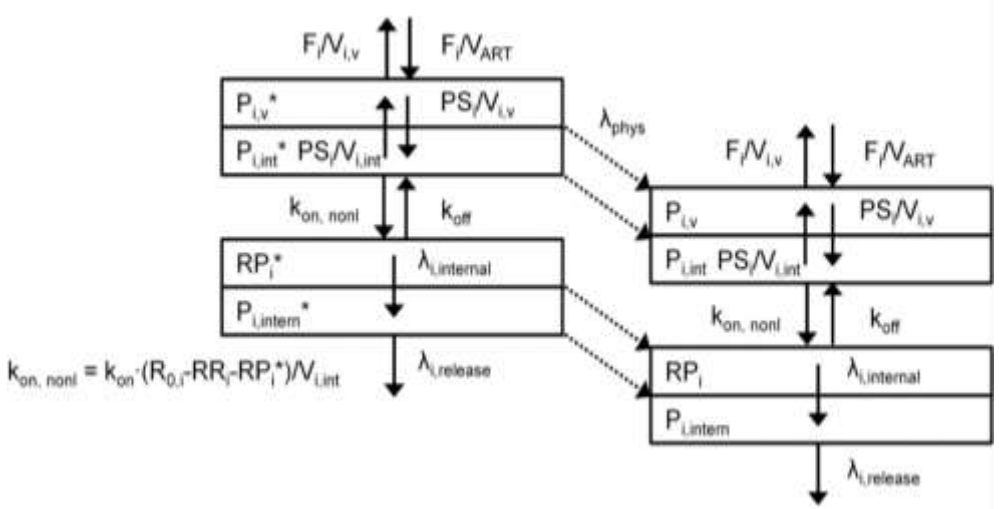


Physiologically Based Pharmacokinetic (PBPK) Model

Global structure



Organ-Level



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Tumor growth and dose effect model

$$V_{TU,total}(t) = V_{TU,total,0} \times e^{(\lambda_g \times t - \alpha_{TU} \times BED_{TU})} \quad \text{Eq. 1}$$

$$BED_{TU} = D_{TU} \times \left(1 + \frac{G_{TU}}{\alpha_{TU}/\beta_{TU}} \times D_{TU}\right) \quad \text{Eq. 2}$$

$$G_{TU}(T) = \frac{2}{D_{TU}^2} \times \int_0^T \dot{D}_{TU}(t)dt \times \int_0^t \dot{D}_{TU}(\omega) \times e^{-\mu_{TU}(t-\omega)}d\omega. \quad \text{Eq. 3}$$

For the calculation of the absorbed dose, only the self-dose was considered:

λ_g bone lesions: $5.1 \cdot 10^{-6}$ min^{-1};
λ_g soft-tissue lesions: $3.8 \cdot 10^{-6}$ min^{-1}

Berges et al.1995

α_{TU}/β_{TU} =1.49 Gy
μ_{TU} = 0.0061 min^{-1}

Fowler et al. 2001

Algorithm

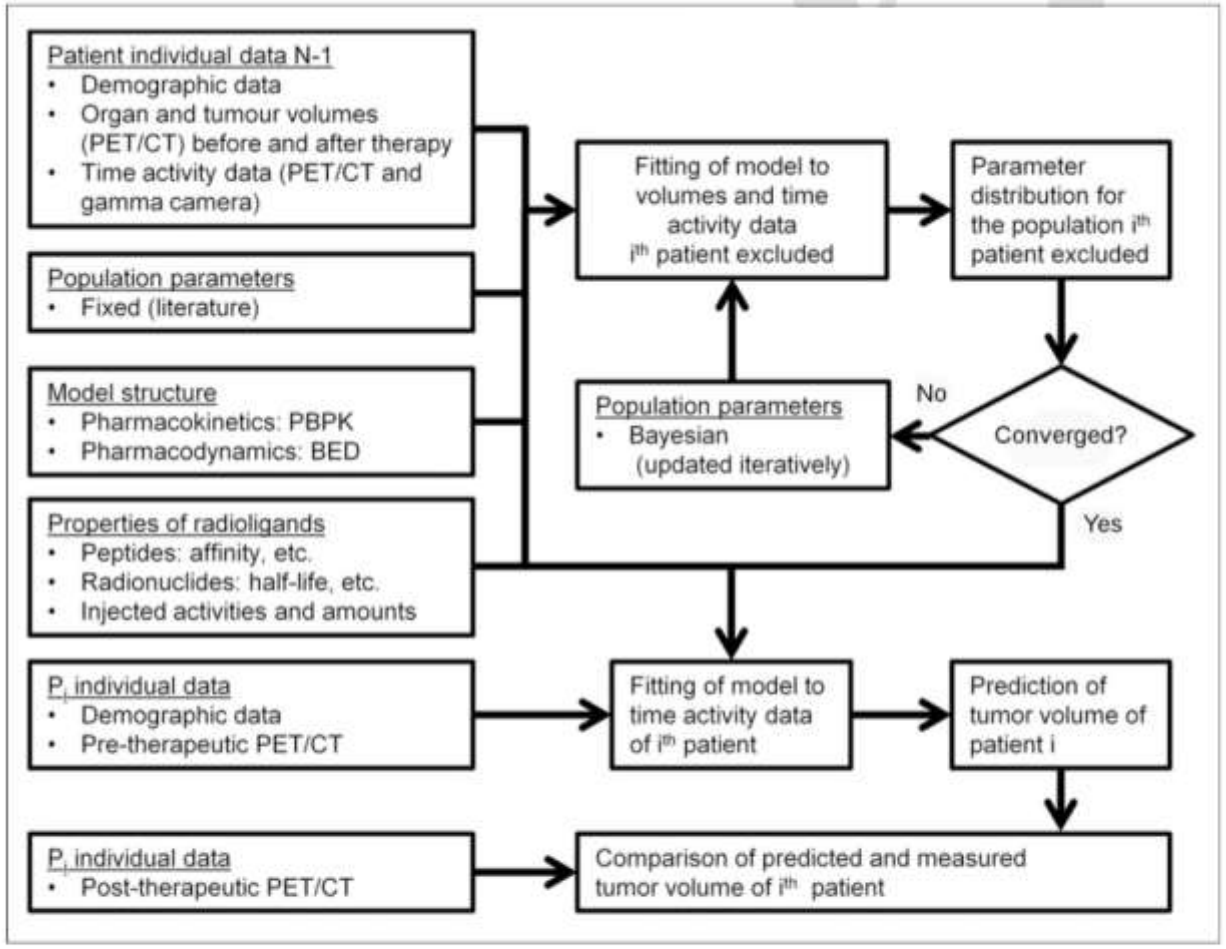

FIGURE 1. Model fitting and prediction of tumor volume after treatment. Iterative fitting approach was used to determine Bayesian parameters for investigated population. On the basis of the PBPK model, population parameters (as fixed or Bayesian information) and pretherapeutic PET of excluded patient, volume after treatment was predicted and compared with measured values. This was conducted for all (n = 13) patients.

1. Estimation of population values excluding i^{th} patient
2. Fitting with only PET/CT data + Bayesian info
3. Simulation of tumour volumes 6 weeks p.i.
4. Comparison of simulated and measured volumes

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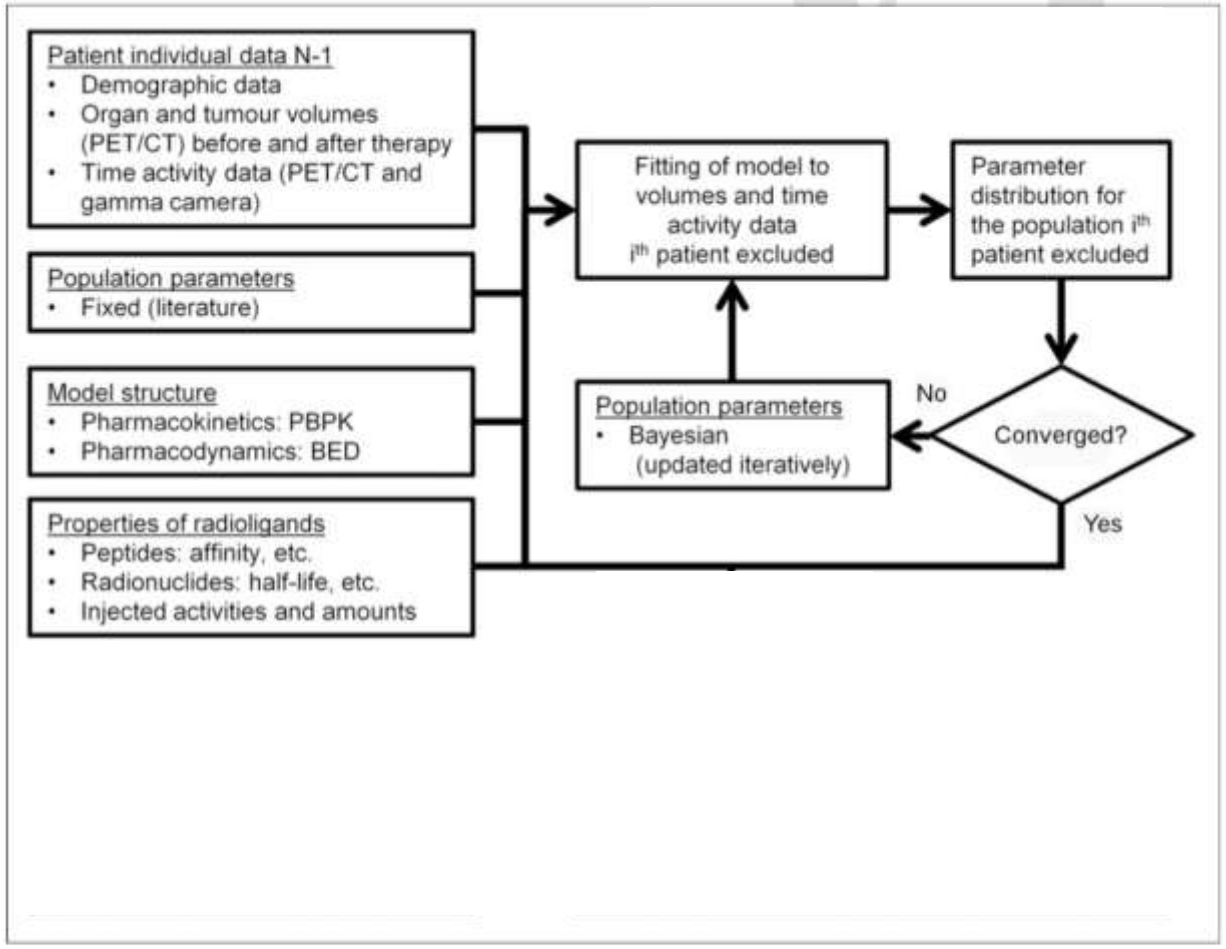
1. Estimation of populations values



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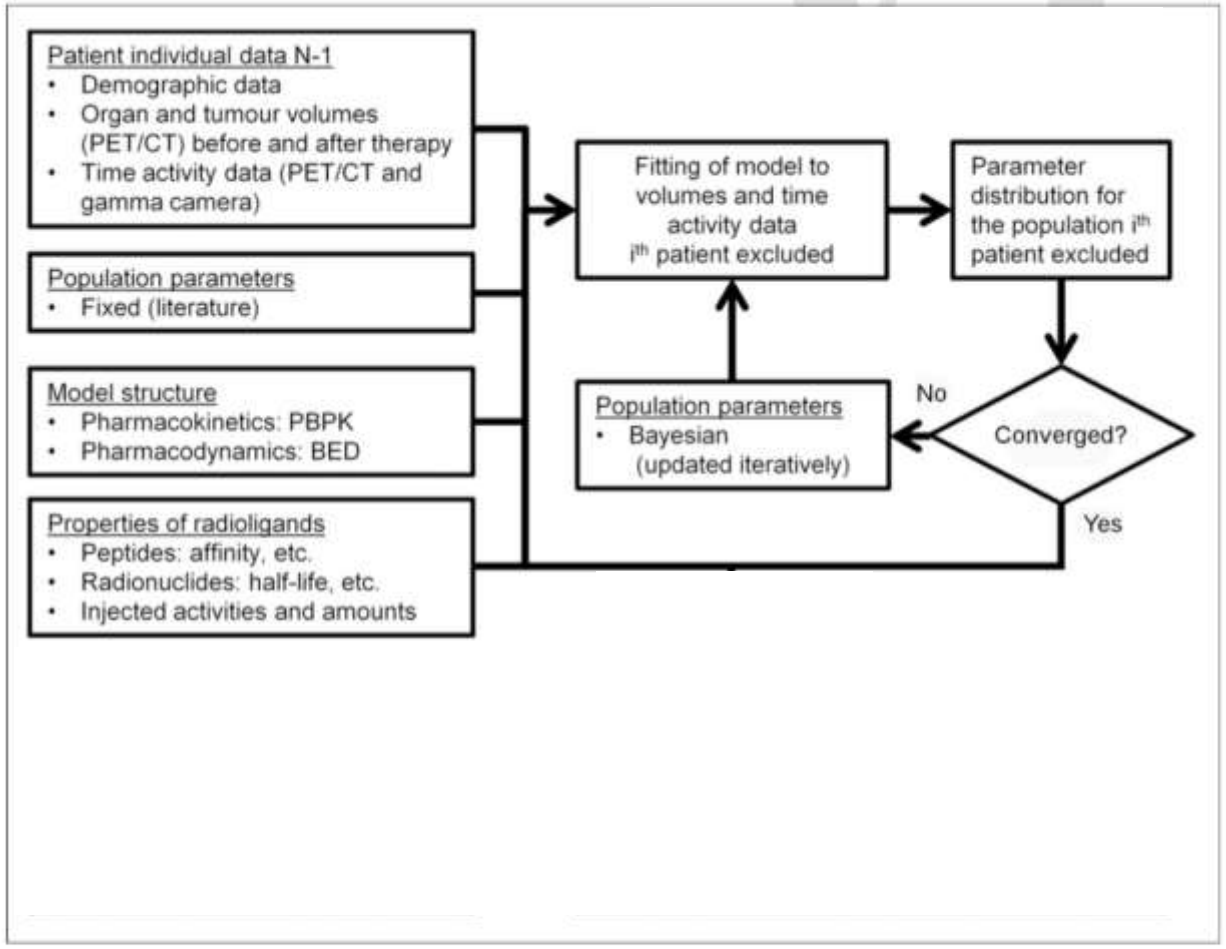
For each patient:
Estimation of population values
leaving out the data of just this patient

For tumor and kidneys:

- receptor densities
- blood flows per g
- release rates from tissues
- radiosensitivity

1. Estimation of populations values



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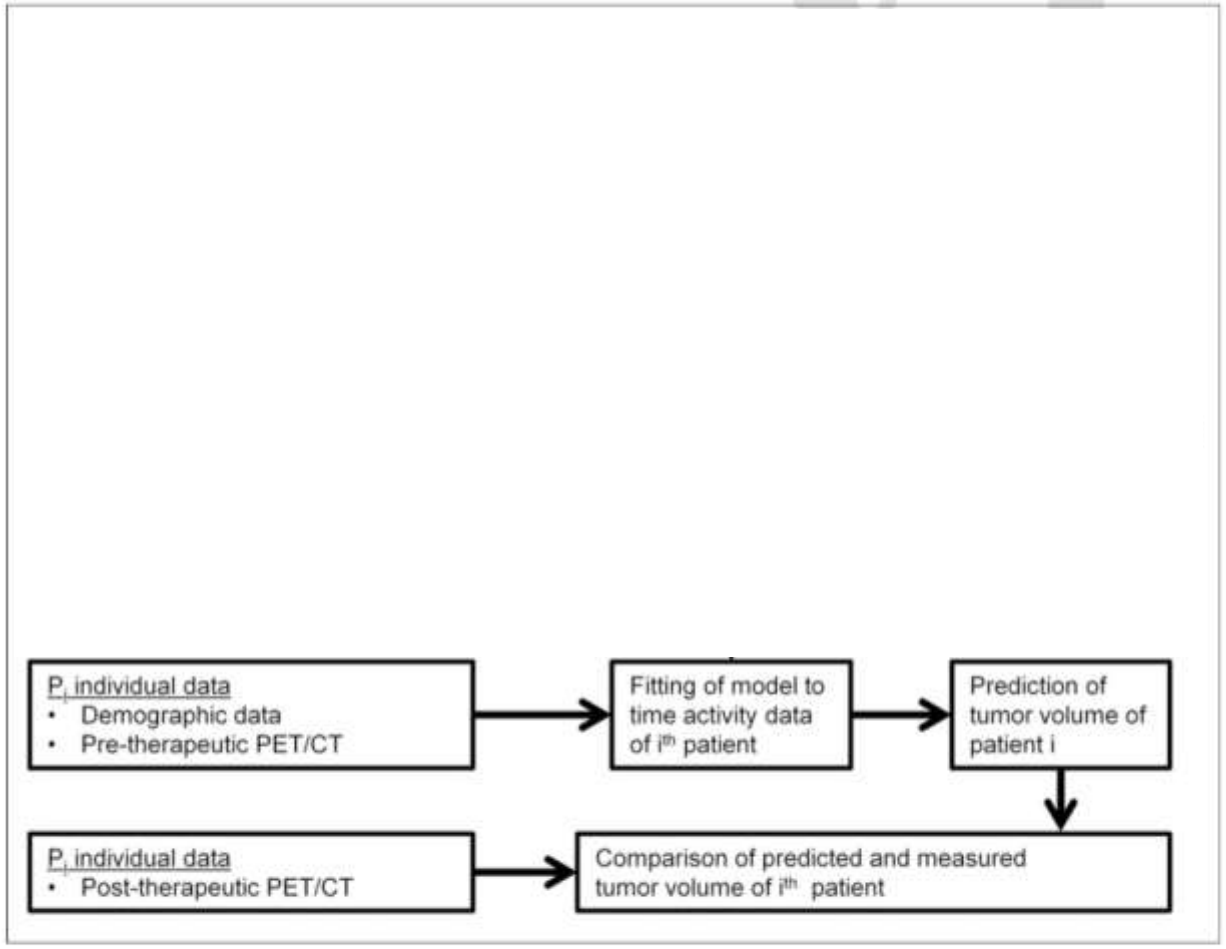
For example:

$\alpha_{TU} = 0.0172 \pm 0.0084\ Gy^{-1}$

2.Fitting with only PET/CT data + Bayes population values



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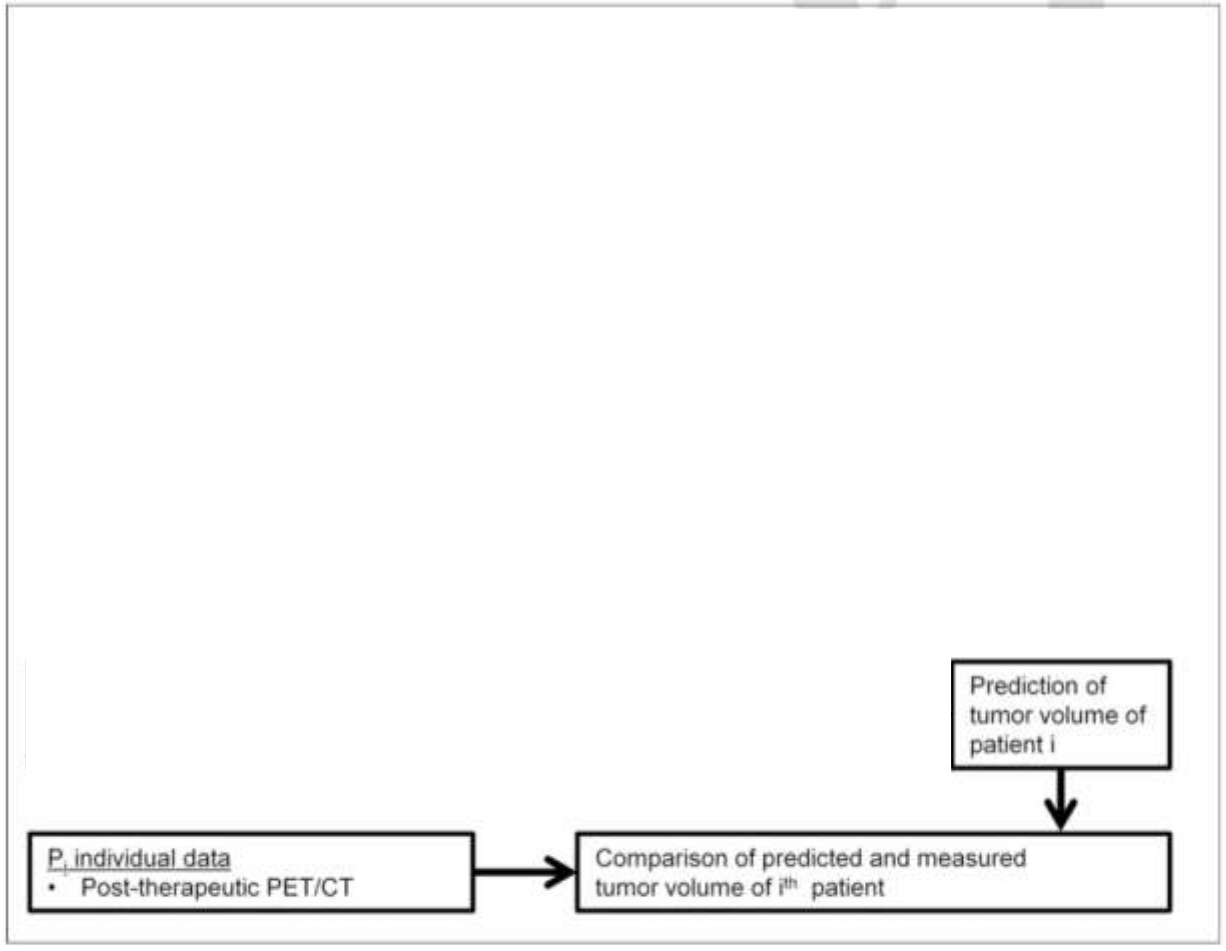
Fixed parameters:
- radiosensitivity
- release rates

Fitted with Bayesian term:
- receptor densities
- blood flows

3.Simulation of therapy and post therapy tumor volumes



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4. Comparions of predicted and measured tumor volumes

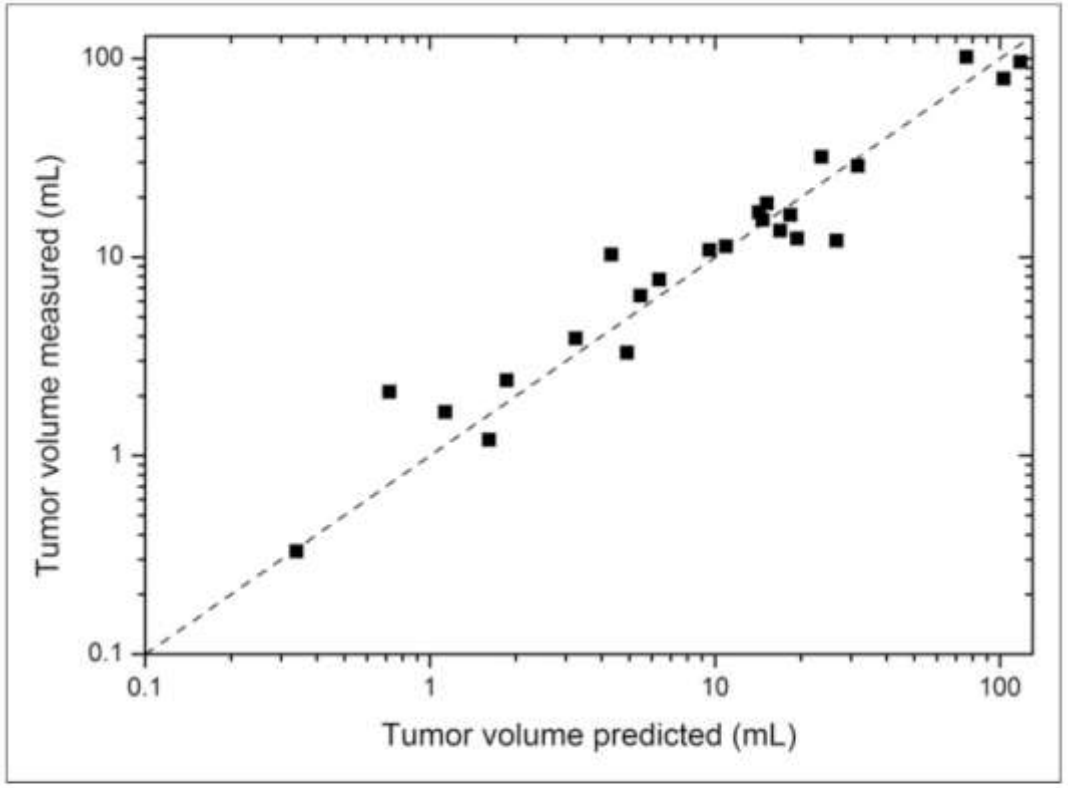

FIGURE 2. Predicted versus measured tumor volume. Prediction is based on PBPK/PD model, pretherapeutic measurement, and population parameters.

$$RD_{\mathrm{TU,volume}} = \frac{V_{\mathrm{TU,total,0}} \times e^{\left(\lambda_g \times t_{\mathrm{PETCT2}} - \alpha_{\mathrm{TU}} \times BED_{\mathrm{TU}}\right)} - V_{\mathrm{TU,total,PETCT2}}}{V_{\mathrm{TU,total,PETCT2}}} \times 100\%. \qquad \text{Eq. 6}$$

$RD_{TU,volume}$ = 1% ± 40%,

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Improvements

Model

- Better tumor growth (power-law) and dose effect model (different states of cells)

Data

- Including SPECT/CT data and more patients
- More accurate and automated estimation of total tumor volume

Methods

- Identification of subpopulations (smaller standard deviations of the Bayesian terms)
- Integration of PSA values as *a priori* information. How?
- Complete uncertainty analysis

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lpdp
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MITIGATE

Probability distributions