Pharmacokinetics modeling for molecular radiotherapy

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Overview

• **Models:**
  - Role of PK modeling in dosimetry
  - Different types of models
  - Advantages using PBPK modeling
  - Model development

• **Fitting and model selection:**
  - Data weighting
  - Model selection
  - Quality control

• **Application/Example:**
  - RIT with $^{90}$Y labelled anti-CD66 antibody
Role of PK modeling in dosimetry

Dosimetry/Treatment planning:
Accurate estimation and/or prediction of
time-integrated activity coefficients
(Lea-Catcheside factor for BED)

Added value:
Help to improve the therapeutic index
(special role of PBPK models)
Role of PK modeling in dosimetry

\[ D(r_T) = A_0 \cdot \sum_{r_S} \tilde{a}(r_S) \cdot S(r_T \leftarrow r_S) \]

Absorbed dose

Admin. activity

S value

Target organ

Source organ

Time-integrated activity coefficient
(outdated: residence time)

\[ \tilde{a}(r_S) = \frac{1}{A_0} \int_0^\infty A(r_S, t) dt \]

Activity in source region

Absorbed dose

MIRD Pamphlet No. 21
From imaging to time activity data

Injection

Calibration

ROI-drawing...

Activity in organ i [MBq]

Time [h]
From time activity data to time-integrated activity coefficients

\[ \text{Activity in organ } i \ [\text{MBq}] \]

\[ \text{Time } [\text{h}] \]

PK-Modeling

\[ \tilde{\alpha}_i \]

\[ \text{Fraction of injected activity } [\text{]} \]

\[ \text{Time } [\text{h}] \]
Different types of pharmacokinetic models

- Empirical models
- PBPK models (hybrid)
- Whole body PBPK models

“physiological reality”
Empirical models

\[ f_1(t) = A_1 e^{-\lambda_{\text{phys}} t} \]
\[ f_2(t) = A_1 e^{-(\lambda_1 + \lambda_{\text{phys}}) t} \]
\[ f_3(t) = A_1 e^{-(\lambda_1 + \lambda_{\text{phys}}) t} + A_2 e^{-\lambda_{\text{phys}} t} \]
\[ f_4(t) = A_1 e^{-(\lambda_1 + \lambda_{\text{phys}}) t} + A_2 e^{-(\lambda_1 + \lambda_{\text{phys}}) t} \]
\[ f_{4A}(t) = A_1 e^{-(\lambda_1 + \lambda_{\text{phys}}) t} - A_1 e^{-(\lambda_2 + \lambda_{\text{phys}}) t} = A_1 \left[ e^{-\lambda_1 t} - e^{-\lambda_2 t} \right] e^{-\lambda_{\text{phys}} t} \quad ; \quad \lambda_2 > \lambda_1 \]
(predominantly) Empirical model

Model structure simple
Parameters represent effective or “apparent” values

More physiological information

$^{64}$Cu-DOTA-RGD Kinetics

Ferl et al. JNM 2009
(rather physiological based) PK models

Kletting et al JNM 2011
General structure whole body PBPK model

Shah et al. J Pharmacokinet Pharmacodyn 2012
PBPK model organ level for antibodies

Shah et al. J Pharmacokinet Pharmacody 2012
Advantages of PBPK 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

• Better identifiably and validation of fitted parameters
• Less measurements necessary
Development steps

- Definition of the modelling purpose
- Specification of the general structure of global model
- Definition of the structure for each organ
- Implementation using adequate software
- Inclusion of literature values
- Fit model to data, model selection
- Validation
- Refinement
Different needs/limitations

- Calculation of area under the curve
- Predictions for therapy under different conditions (affinity, amount) than pre-therapeutic measurements

- Available measurement techniques
- Number of measurements and data sets
- A priori knowledge of biodistribution and parameters

What kind of model is useful for my purposes?
What is feasible?
Components of whole body PBPK models I

• General structure:
  - blood flows (Leggett 1995 or Shah 2012)
  - blood volumes (Leggett 1995 or Shah 2012)
  - interstitial volumes (Shah 2012)
  - fraction of distribution in interstitium (Schmidt 2009)

• Transport into and in interstitial spaces:
  - convection (Rippe 1994 or Chauhan 2011)
  - diffusion (Thurber 2011)
  - lymphatic flow (Rippe 1994 or Jain 1987)

• Receptor-Ligand interactions:
  - specific binding, $k_{on}$, $k_{off}$ (Graff 2003)
  - monovalent or bivalent (Kaufman 1992)
  - internalisation/recycling (Graff 2003 or Kletting 2012)
  - degradation and release (Velikyan 2010 or Kletting 2012)
Components of whole body PBPK models II

• Unspecific uptake and metabolism
  - FCRn specific (for antibodies) (Garg 2007 or Shah 2012)
  - endocytosis (for nanoparticles) (Tran 2013)

• Distribution of metabolites or non immunoreactive fraction
  - free nuclide
  - labelled fragments (Eger 1987)
  - labelled non immunoreactive antibody (Kletting 2015)

• Renal clearance (Schmidt 2009 or Kletting 2010)
The art of simplification

Why is it important to use an explicit structure?
• To increase prediction accuracy and understanding of your biological system
• Reduce number of required measurements (if structure and parameters all well known)

Why is it important to simplify your model structure?
• Decrease development and computation time
• Avoid inaccuracies if the physiological structure or mechanism with the pertaining parameter value is unknown (e.g. internalisation model)

When is it recommended to simplify your model structure?
• Sampling times do not allow the identification of a certain structure and parameter
• Certain extrapolation scenarios can be excluded (e.g. used amounts)
• Used substance has no access to certain tissue (blood-brain barrier)
  → Lumping should not affect kinetics of organs of interest
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  - Model development
• Fitting and model selection:
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  - Model selection
  - Quality control
• Applications/Examples:
  - RIT with $^{90}$Y labelled anti-CD66 antibody
  - PRRT with $^{90}$Y labelled DOTATATE
Things to consider before fitting

Mulitmodel approach is highly recommended!

Kletting et al. Med Phys 2013
Data error model/Data weighting

\[ \sigma_i^2 = \nu \cdot (A + B \cdot y_i^C) \]

\[ \frac{(y_i - f(x_i))^2}{\sigma_i^2} \]

A, B and C are defined by the user.

Prefactor \( \nu \): Fixed (absolute weighting) or calculated

Example: known relative error of 10% \( \rightarrow \) \( \nu = 1; A=0; B=0.1^2; C=2 \)

Muzic et al. Med Phys 2006
The art of fixing or fitting parameter (with Bayesian Information)

Fix:
Parameter which are not sensitive and/or are accurately known (CT-measured volumes)

Fit with Bayes:
Sensitive and individually varying parameters, with a priori known population distribution

Fit without Bayes:
Sensitive and individually varying parameter, with a priori unknown population distribution
Objective Function (Sums of Squares)

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

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

Measured data point and error

Population mean value and standard deviation included as Bayesian information
Fitting your model/function

\[ f_1(t) = A_1 \cdot e^{-(\lambda_{\text{phys}} + \lambda_1) t} + A_2 \cdot e^{-(\lambda_{\text{phys}} + \lambda_2) t} \]

\[ f_2(t) = A_1 \left( e^{-(\lambda_{\text{phys}} + \lambda_1) t} - e^{-(\lambda_{\text{phys}} + \lambda_2) t} \right) \]
Example: Fitted Curves

\[ f_1(t) = A_1 \cdot e^{-(\frac{\lambda_{phys}}{\lambda_1})t} + A_2 \cdot e^{-(\frac{\lambda_{phys}}{\lambda_2})t} \]

\[ f_2(t) = A_1 \cdot \left( e^{-(\frac{\lambda_{phys}}{\lambda_1})t} - e^{-(\frac{\lambda_{phys}}{\lambda_2})t} \right) \]

<table>
<thead>
<tr>
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\[ f_1(t) = A_1 \cdot e^{-(\lambda_{phys} + \lambda_1)t} + A_2 \cdot e^{-(\lambda_{phys} + \lambda_2)t} \]

\[ f_2(t) = A_1 \cdot \left( e^{-(\lambda_{phys} + \lambda_1)t} - e^{-(\lambda_{phys} + \lambda_2)t} \right) \]

Which function is most supported by the data?
Model Selection: Akaike Information Criterion (AIC)

Objective function

\[
AICc = -2 \ln(P) + 2K + \frac{2K(K+1)}{N-K-1}
\]

or in least square case:

\[
AICc = -N \ln\left(\frac{SS}{N}\right) + 2K + \frac{2K(K+1)}{N-K-1}
\]

\[
\Delta_i = AICc_i - AICc_{\text{min}}
\]

\[
\omega_i = \frac{e^{-\Delta_i/2}}{\sum_{i=1}^{R} e^{-\Delta_i/2}}
\]

- \(N\) ... measurements
- \(K\) ... adjustable parameters
  (+1 if \(v\) is estimated)
- \(SS\) ... sum of squared residuals
- \(R\) ... number of models
- \(\omega\) ... Akaike weight
  (probability)
Example: Fitted Curves

\[
f_1(t) = A_1 \cdot e^{-(\lambda_{phys} + \lambda_1)t} + A_2 \cdot e^{-(\lambda_{phys} + \lambda_2)t}
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<tr>
<th>SS</th>
<th>R²</th>
<th>ν</th>
<th>AIC</th>
<th>AICc</th>
<th>Δi</th>
<th>w</th>
<th>Rang</th>
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<tbody>
<tr>
<td>sum 2 exp A2=-A1</td>
<td>29.4257</td>
<td>0.9852</td>
<td>1</td>
<td>32.8692</td>
<td>44.8692</td>
<td>0</td>
<td>1</td>
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<td>sum 2 exp</td>
<td>0.8586</td>
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<td>1</td>
<td>33.9063</td>
<td>73.9063</td>
<td>29.0370</td>
<td>0</td>
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</table>

AUC = (46.7 ± 2.4) h
## Goodness of Fit + Model Selection

**TABLE I. Quality control of fits.**

<table>
<thead>
<tr>
<th>Results</th>
<th>Condition</th>
<th>Quality control</th>
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<tbody>
<tr>
<td>Plot</td>
<td>...</td>
<td>Visual inspection</td>
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<tr>
<td>$R^2^a$</td>
<td>...</td>
<td>Close to 1</td>
</tr>
<tr>
<td>AIC$^b$</td>
<td>...</td>
<td>Compare with values of other functions</td>
</tr>
<tr>
<td>AICc$^c$</td>
<td>$J^d + 2 \leq N^e$</td>
<td>Compare with values of other functions</td>
</tr>
<tr>
<td>$w_{\text{AICc}}^f$</td>
<td>All functions $J + 2 \leq N$</td>
<td>If $w_{\text{AIC}} &gt; 0.01$ function is used for inference</td>
</tr>
<tr>
<td>Parameter</td>
<td>$J \leq N$</td>
<td>Plausible values</td>
</tr>
<tr>
<td>Parameter SE</td>
<td>$J + 1 \leq N$</td>
<td>CV $&lt; 25%$ precise$^g$; CV $&lt; 50%$ acceptable$^h$</td>
</tr>
<tr>
<td>Correlation matrix</td>
<td>$J + 1 \leq N$</td>
<td>$-0.8 &lt;$ each element $&lt; 0.8^i$</td>
</tr>
<tr>
<td>Weighted residuals</td>
<td>...</td>
<td>Random distribution</td>
</tr>
</tbody>
</table>

---

$a$: Coefficient of determination.

$b$: Akaike information criterion.

$c$: Corrected Akaike information criterion.

$d$: For absolute weighting $J = K = \text{number of adjustable parameters}$ for relative weighting $J = K + 1$.

$e$: Number of data points.

$f$: Akaike weights.

$g$: Definition of precise coefficient of variation according to Ref. 5.

$h$: Definition of acceptable coefficient of variation (Ref. 27).

$i$: Acceptable range according to Wastney et al. (Ref. 27).
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Model for $^{111}$In/$^{90}$Y labelled anti-CD66 antibody

Kletting et al. JNM 2010

Problem: Different pre-therapeutic and therapeutic serum measurements → Red marrow kinetics also different
If pre-therapeutic and therapeutic biodistribution are not equal, sums of exponentials are not adequate.

PBPK model was developed to:

Predict therapy based on pre-therapeutic measurements considering different amounts of antibody (0.5±0.1 mg and 1.3±0.5 mg).
General structure: Explicitly modelled organs/lumping

**Explicit:**
Critical organs

→ Organs containing a large number of granulocytes

**Lumping:**
Remaining tissue:
Low and similar activity concentration

→ Muscle, fat etc.

\[ {^{111}}\text{In-anti-CD66 44.4 h p.i.} \]
Transport from the vascular to the interstitial space

Jain et al. 1989
Two pore model of transvascular flux

Davda et al. International Immunopharmacology 2008
Transport from the vascular to the interstitial space

\[
\frac{(1-\sigma_L)(J_{iso} + \alpha_L L) + (1-\sigma_S)\alpha_L L + PS_L + PS_S}{v_{vas}}
\]

\[
(1-\sigma_S) \cdot J_{iso} + PS_L + PS_S
\]

\[
\frac{(1-\sigma_{sym}) \cdot L}{v_{int} \cdot a}
\]

\[
a = \frac{\varepsilon_{Ligand}}{\varepsilon_{invin}}
\]
Transport from the vascular to the interstitial space

Rippe and Haraldsson, Acta Physiol Scand 1987 (two pore model):

- Diffusion dominant for molecule radius \( r_m < 3 \text{ nm} \)
- Convection becomes increasingly important for \( r_m > 3 \text{ nm} \)
- Convection dominant for \( r_m > 4-6 \text{ nm} \) (small pore radius)

**DOTATATE:** \( r_m \approx 1 \text{ nm} \) → diffusion most important for all tissues

**IgG:** \( r_m \approx 5 \text{ nm} \) → convection most important for most tissues

Liver, spleen, red marrow: larger gaps and pores → increased diffusion (convection)

Solid tumour: 1. low lymph flow, high interstitial pressure → low convection
   2. larger gaps and pores → increased diffusion
Transport from the vascular to the interstitial space

\[
\frac{(1 - \sigma_L)(J_{iso} + \alpha_L L) + (1 - \sigma_S)\alpha_L L + PS_L + PS_S}{v_{vas}} \rightarrow 10 \text{ min}^{-1}
\]

For liver, spleen and RM:

\[
\frac{(1 - \sigma_L)(J_{iso} + \alpha_L L) + (1 - \sigma_S)\alpha_L L + PS_L + PS_S}{v_{int} \cdot \alpha} \rightarrow k_{on,non}
\]

\[
\frac{(1 - \sigma_{syn}) \cdot L}{v_{int} \cdot \alpha} = \frac{\varepsilon_{Ligand}}{\varepsilon_{indin}}
\]
Specific binding

Mono/bivalent or effective

Immunoreactivity $r = 1 \rightarrow$ fully intact antibody

Nonlinear binding because we assumed saturation effects
Internalization and degradation

\[ \text{Ab}_{\text{interstitial}} \xrightarrow{F/V_{\text{art}}} \text{AbAg} \xrightarrow{k_{\text{on,non}}} \text{Ab}_{\text{internal}} \xrightarrow{\lambda_{\text{release}}} \text{Ab}_{\text{interstitial}} \]

\[ \text{Ab}_{\text{interstitial}} \xrightarrow{F/V_{\text{art}}} \text{AbAg} \xrightarrow{k_{\text{on,non}}} \text{Ab}_{\text{interstitial}} \xrightarrow{\lambda_{\text{degradation}}} \]
Unspecific (FcRn) binding and metabolism

\[ [\text{FcRn}] >> [\text{Ab}] \]

Eger et al. 1987

\[ \lambda_{\text{uptake unspecific}} \]

\[ \lambda_{\text{deg unspecific}} \]

\[ \text{Ex}_{\text{delay}} \]

\[ \text{Ab}_{\text{Main vascular}} \]
Labelled antibody fragments and clearance

Eger et al. Cancer Research 1987
Assigning data to the model compartments

\[ r = 1 \]

\[
\begin{bmatrix}
\text{AgAb}_l \\
\text{AgAb}_s \\
\text{Ab}_c \\
\text{Ab}_G \\
\text{Ab}_p \\
\text{Ab}_{RM} \\
\text{Ab}_{RM} \\
\text{Ex} \\
\text{Meta}_{ex1} \\
\text{Meta}_{ex2} \\
\text{Meta} \\
\text{Marrow} \\
\text{Veins/Arteries}
\end{bmatrix}
\]

\[
\text{bound and free antibody in red marrow} + \text{fraction of bound antibody in blood} + \text{fraction of antibody fragments in blood} + \text{fraction of antibody underlying veins/arteries}
\]

Kletting et al. JNM 2010
Model refinement 1: $r$ is not $\sim 1$

- **Fully intact**
  - Diagram A

- **Half intact**
  - Diagram B

- **Non binding**
  - Diagram C

$r = 0.8$

Kletting Plos One 2015
**Validation of parameter values**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fitted values mean ± SD</th>
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<tr>
<td></td>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
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<tr>
<td>$A_{\text{RM}}$ [nmol] †</td>
<td>21±14</td>
<td>17±13</td>
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<tr>
<td>$A_{\text{B}}$ [nmol] †</td>
<td>0.58±0.39</td>
<td>0.50±0.38</td>
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<tr>
<td>$A_{\text{L}}$ [nmol] †</td>
<td>0.31±0.26</td>
<td>0.33±0.27</td>
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</tr>
<tr>
<td>$A_{\text{S}}$ [nmol] †</td>
<td>0.22±0.19</td>
<td>0.25±0.30</td>
<td></td>
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<tr>
<td>$\text{ex}_1$ [unity] ‡</td>
<td>0.235±0.089</td>
<td>0.226±0.091</td>
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<tr>
<td>$\text{ex}_a$ [unity] ‡</td>
<td>0.107±0.048</td>
<td>0.098±0.038</td>
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</tr>
<tr>
<td>$f_{\text{RM}}$ [%] †</td>
<td>0.67±0.21</td>
<td>0.73±0.24</td>
<td></td>
</tr>
<tr>
<td>$c_{\text{RM}}$ [unity] ‖</td>
<td>1.22±0.33</td>
<td>1.20±0.34</td>
<td></td>
</tr>
<tr>
<td>$\lambda_{\text{db}}$ [1/min 10^{-5}] §</td>
<td>6.8±1.7</td>
<td>6.8±1.7</td>
<td></td>
</tr>
<tr>
<td>$r_{\text{im}}$ [unity] ‡‡</td>
<td>0.801±0.090</td>
<td>0.806±0.098</td>
<td></td>
</tr>
<tr>
<td>$V_{\text{Serum}}$ [l] ‡‡</td>
<td>2.99±0.62</td>
<td>3.00±0.63</td>
<td></td>
</tr>
</tbody>
</table>

- $10^4$ / cell
- 4 times lower than normal
- Overestimation of red marrow
- Equal to Press et al 1996
- Typical but far from 1

Kletting Plos One 2015
Validation measurements versus prediction

% administered activity / l

Relative Deviation RD

$^{111}$In anti-CD66 Ab fitted
$^{90}$Y anti-CD66 Ab predicted
$^{90}$Y anti-CD66 Ab measured

Kletting Plos One 2015
Further refinement 2: Including population values

Maaß et al. CBR 2015
Summary example RIT with anti-CD66 antibody

Before: Only data driven, AUC of pre-therapeutic measurements

<table>
<thead>
<tr>
<th>Additional knowledge</th>
<th>Assumption</th>
<th>Additional benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiology: Human</td>
<td>r = 1</td>
<td>Prediction of therapeutic biodistribution</td>
</tr>
<tr>
<td>Compound: anti CD66 antibody</td>
<td></td>
<td>Correction for red marrow scaling</td>
</tr>
<tr>
<td>Ratio for numbers of granulocytes in RM, L, S</td>
<td>r ≠ 1</td>
<td>Higher mean prediction accuracy</td>
</tr>
<tr>
<td>Population parameters from 27 AML patients</td>
<td>r ≠ 1</td>
<td>Higher individual prediction accuracy</td>
</tr>
</tbody>
</table>

r = immunoreactivity
Summary

- PK modeling plays an important role in molecular radiotherapy
- Define the modeling purpose
- Include as much information as possible
- Simplification are important but be careful
- Modeling is science and art (and sometimes fun)
Transport from the vascular to the interstitial space for solid tumours

No lymph flow

\[
\frac{(1 - \delta_L) \cdot J_{iso} + PS_L + PS_S}{v_{vax}} \quad \text{Ab}_{\text{vascular}} \\
\frac{(1 - \delta_S) \cdot J_{iso} + PS_L + PS_S}{v_{int} \cdot a} \quad \text{Ab}_{\text{intersitial}}
\]
Transport of antibody from the vascular to the interstitial space of a solid tumour

<table>
<thead>
<tr>
<th>Model</th>
<th>Extravasation rate [day$^{-1}$]</th>
<th>Convection assumed?</th>
<th>Diffusion assumed?</th>
<th>Lymphatic flow [ml/g/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sung et. al 1990</td>
<td>0.187</td>
<td>yes</td>
<td>no</td>
<td>$8 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>Baxter et. al 1994</td>
<td>0.191</td>
<td>yes</td>
<td>yes</td>
<td>$1.4 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>Ferl et. al 2005</td>
<td>0.730</td>
<td>yes</td>
<td>yes</td>
<td>assumed 0</td>
</tr>
<tr>
<td>Thurber et al 2012</td>
<td>0.737</td>
<td>no</td>
<td>yes</td>
<td>assumed 0</td>
</tr>
</tbody>
</table>
Whole body PBPK model for peptides

sst2 positive organs:

\[ k_{\text{on, nonl}} = k_{\text{on}} \cdot \frac{(R_{0,i} - RR_i - RP_i^*)}{V_{i,\text{int}}} \]

Developed using SAAM 2

Kletting et al. 2015 JNM
Different maximal activity for different ligand amounts

\[
BED_i = D_i \cdot \left(1 + \frac{G_i}{\alpha_i / \beta_i} \cdot D_i\right)
\]

Simulated

\[
A_{inj,j} = \frac{-\tilde{a}_{K,j}(T) + \sqrt{\tilde{a}_{K,j}(T)^2 + \frac{8\int_0^T a_{K,j}(t)dt \cdot \int_0^t a_{K,j}(\omega) \cdot e^{-\mu_K(t-\omega)} d\omega \cdot BED_{K, fixed}}{\alpha_K / \beta_K}}}{4 \cdot S_{K\leftarrow K} \int_0^T a_{K,j}(t)dt \cdot \int_0^t a_{K,j}(\omega) \cdot e^{-\mu_K(t-\omega)} d\omega}
\]

→ Iso dose curve for kidney
Explicit modelling of labelled and unlabelled fraction

...is required:

• if data is not decay corrected
• if binding rates are different
• for optimal preload determination

Kletting et al. JNM 2009
Optimal combination of amount and activity
Further issues

Voxel based dosimetry and PK modelling?
Pharmacokinetic $\rightarrow$ Pharmacodynamic $\rightarrow$ modelling the effect
Scaling mouse to men
Monte-Carlo simulations for error analysis
??