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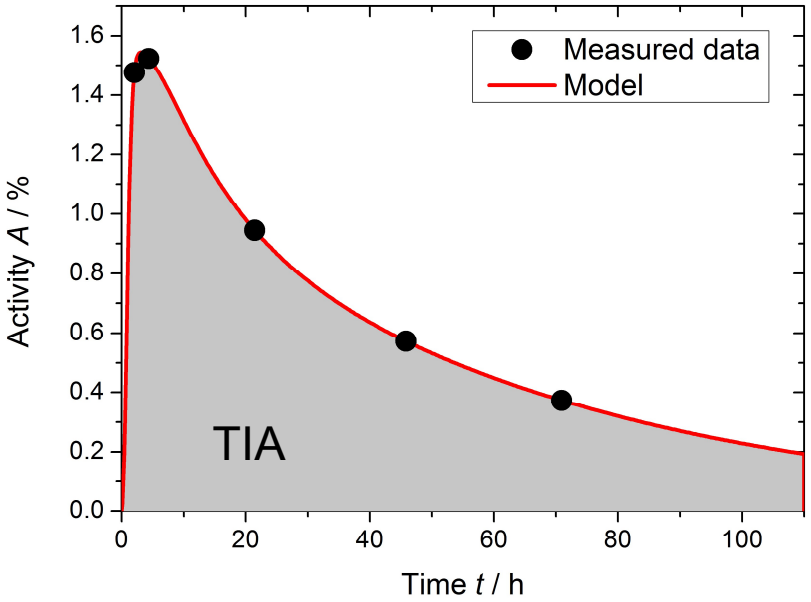
Reconstructing Organ Pharmacokinetics

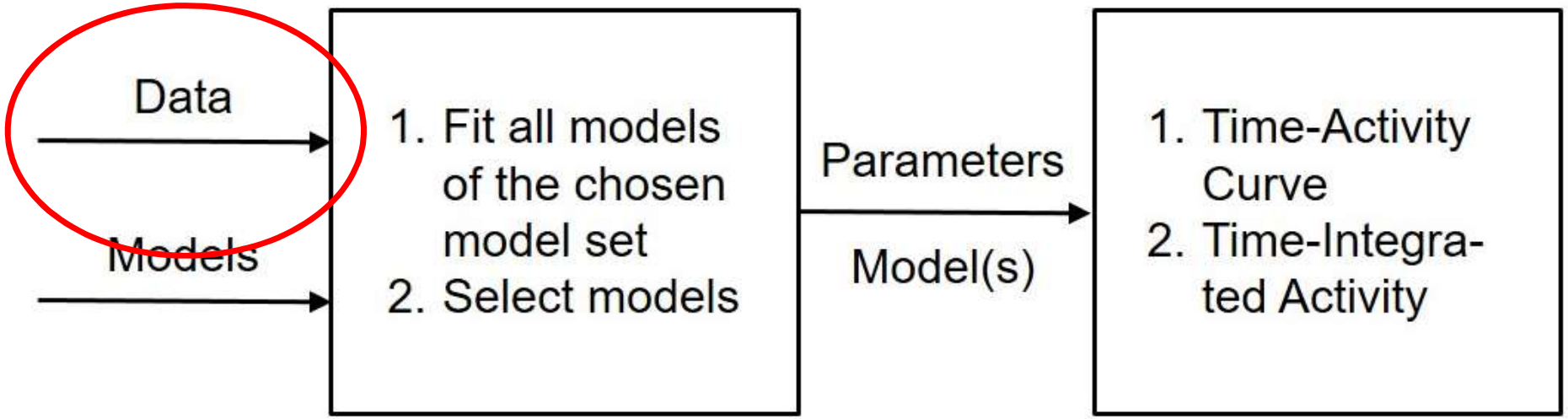
Reconstructing Organ Pharmacokinetics



TIA = Time-integrated activity

- Accurate and precise calculation of time-integrated activity,
- as a prerequisite for dosimetry,
- which is in turn a prerequisite for developing optimal treatment planning.

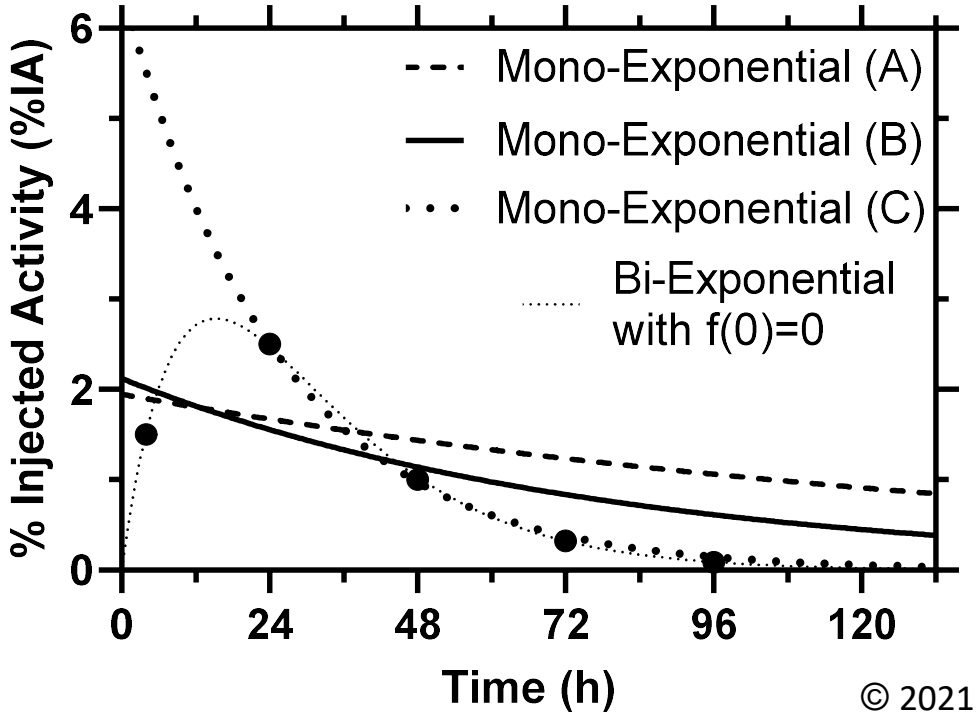
Time-Integrated Activity (Coefficients)



Glatting, G. „Data, Models, Curve Fitting and Model Selection.” *Handbook of Nuclear Medicine and Molecular Imaging for Physicists, Modelling, Dosimetry and Radiation Protection, Volume II*, edited by Michael Ljungberg, CRC Press, 2022

Example: Different Temporal Samplings

- number of data
- optimal time sampling
- uncertainty calculation



Mono-exponential fitted to 3 data points:

(A)	(4, 24, 48) h	TIA = 308 %IA h
(B)	(4, 24, 72) h	TIA = 164 %IA h
(C)	(24, 48, 96) h	TIA = 163 %IA h

Underlying truth:
Bi-exponential with TIA = 116 %IA h

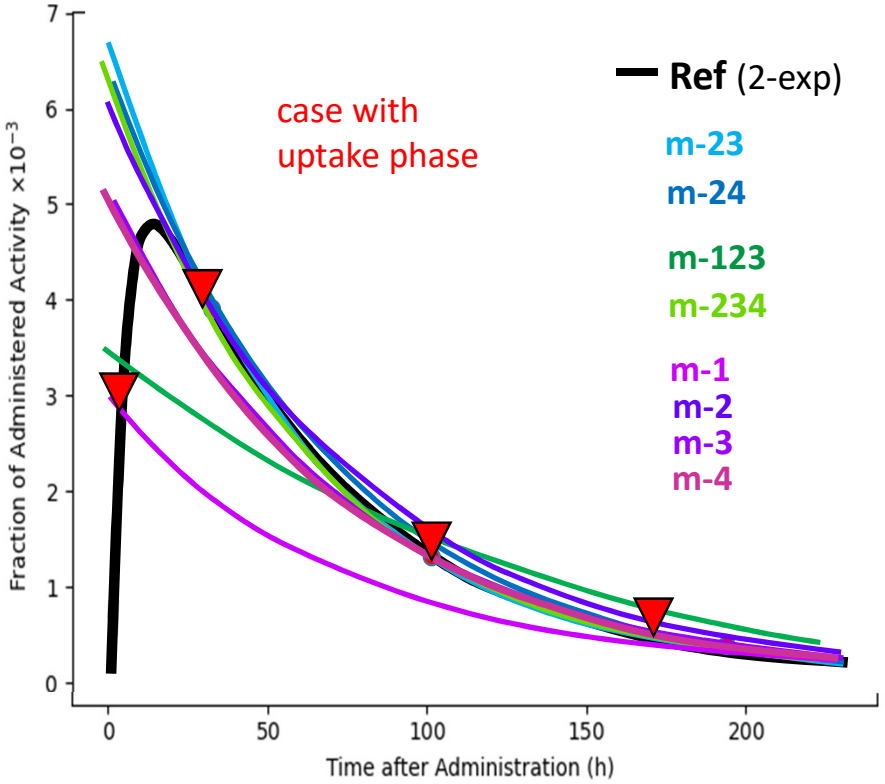
Large differences for assumed noise-free measurements!

TIA = Time-Integrated Activity

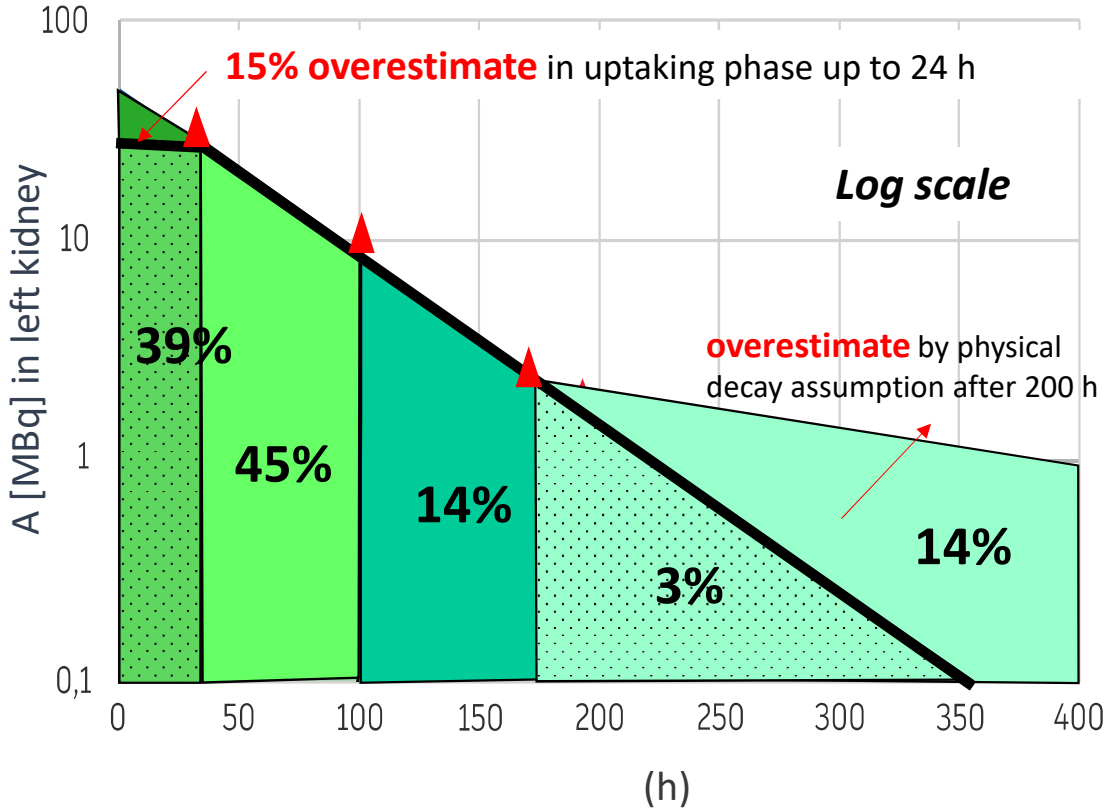
Different monoexp fits for kidney A(t) in a patient

experimental data IEO - TP @ 6, 30, 96 and 170 h

Monoexp fits, different time points (L kidney)



% of TIA, effective curve (L kidney)

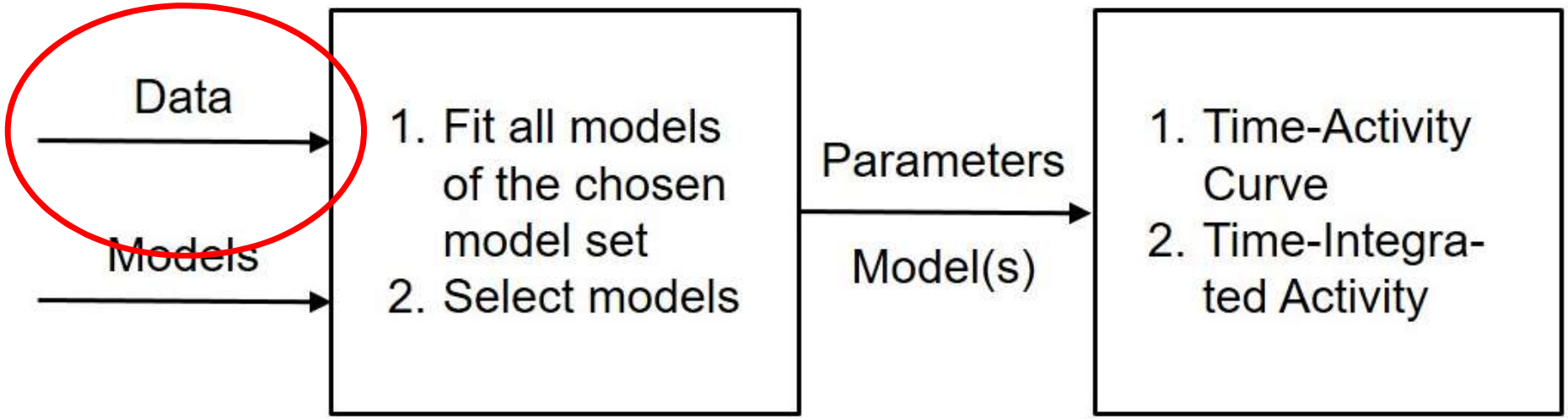


Courtesy of Rachele Danieli, Master Thesis 2021

Time-Integrated Activity (Coefficients)

Gear JI *et al.* EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations. *Eur J Nucl Med Mol Imag* **2018**;45:2456-74

Remark: The uncertainty of your data are also input data.



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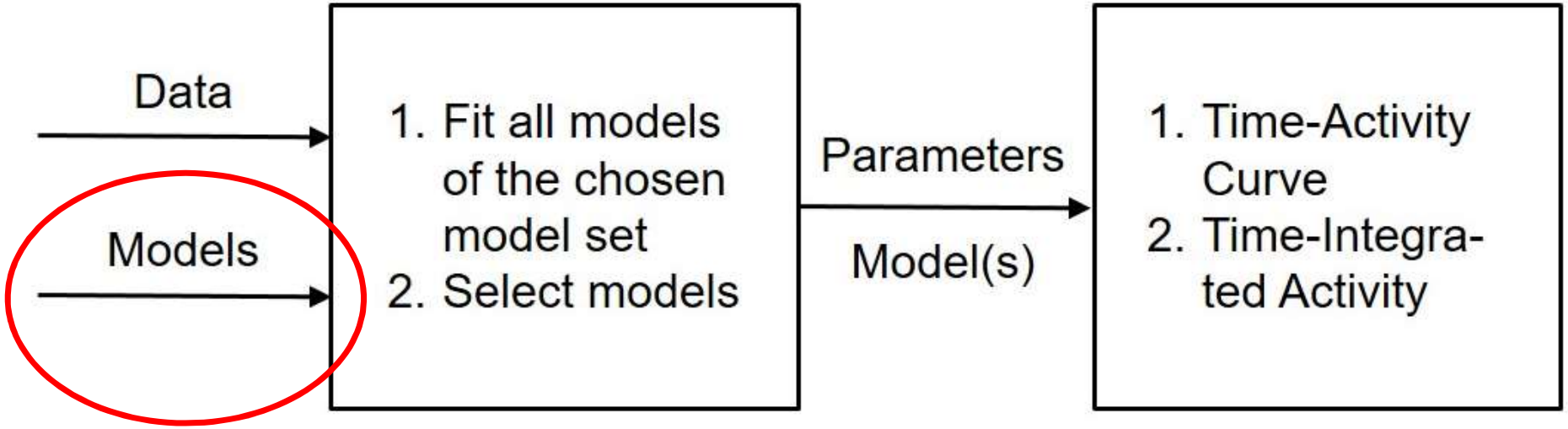
Time-Integrated Activity (Coefficients)



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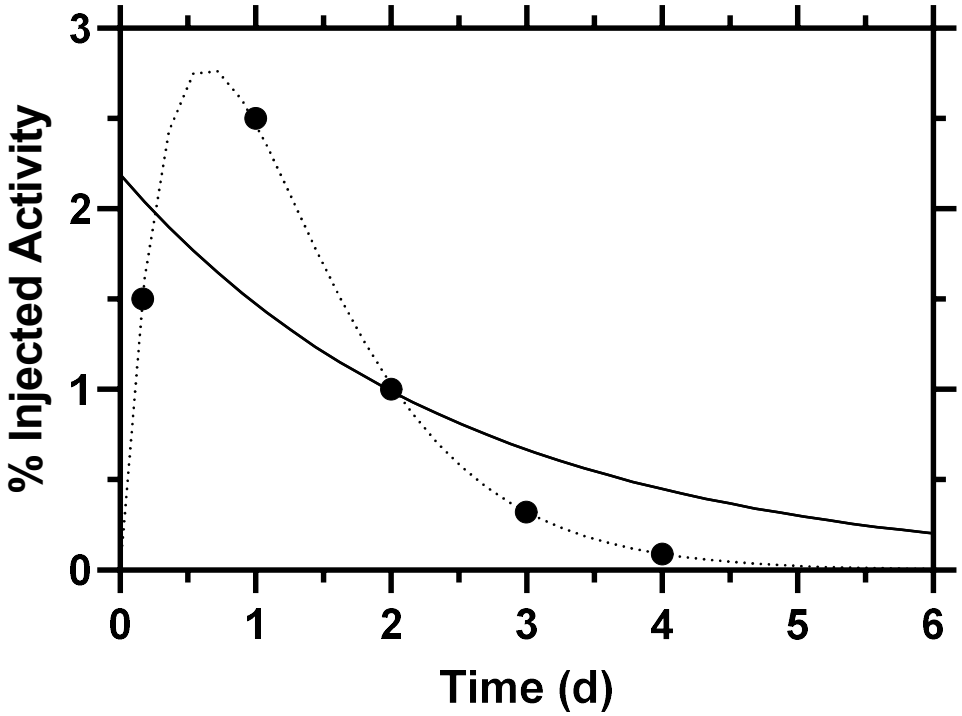
Input: Mathematical Models = *a priori* Information



Mono-exponential fit all data points:
TIA = 133 %IA h

Underlying truth:
Bi-exponential with TIA = 116 %IA h

Relative deviation = 14 %
Only by chance that low!

Large differences for assumed noise-free measurements!

TIA = Time-Integrated Activity

Biokinetic (or Pharmacokinetic) Modelling

Modelling approaches

1. Model-independent approach
   - purely mathematical; just a function to “fit” the measured data, e.g. trapezoidal rule
2. Compartmental models
   - No strict physiological or anatomical basis
3. Physiological models
   - Identify the compartments with actual body spaces; more complex; actual transfer and flow rates are employed
   - Can be used for simulations and predictions

Model Selection (Choosing an optimal fit function)

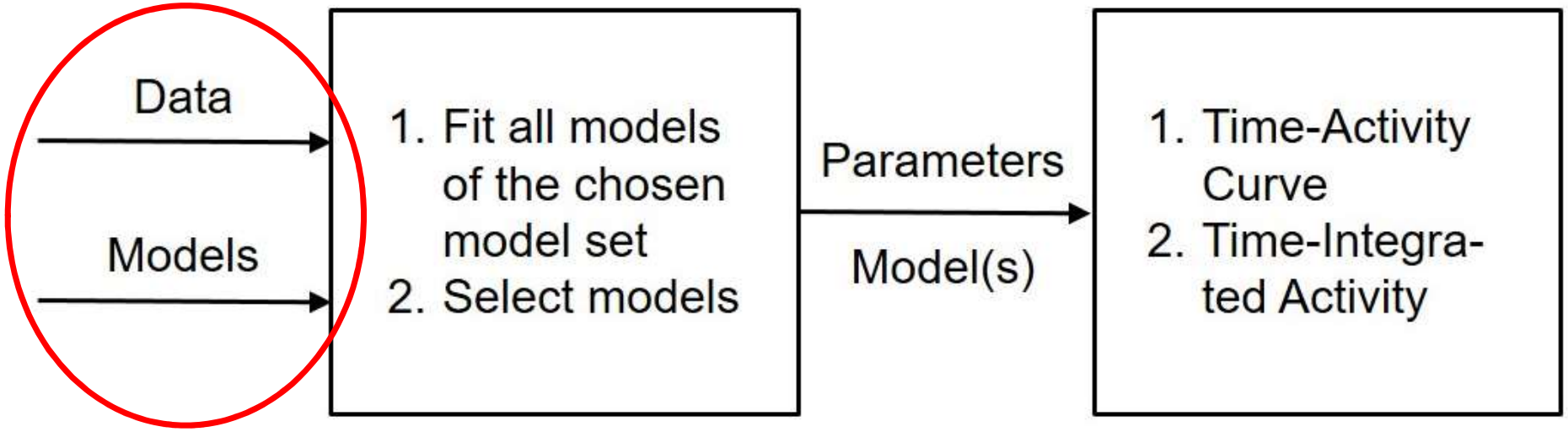
Criteria for choosing a model

- Purpose of the model
  - Just to calculate the area under the curve?
  - To more accurately understand/investigate the biological system?
- Number and precision of obtainable/obtained data points
  - Defines the maximum number of parameters one can determine
- Adequate model known from the literature?
- Is *a priori* knowledge available to be incorporated in a model?
- Parsimony principle

Burnham KP, Anderson DR (2002) Model Selection and Multimodel Interference - A practical Information-theoretic approach. New York: Springer.
Glatting G et al. Choosing the optimal fit function: Comparison of the Akaike information criterion and the F-test. Med Phys 2007;34:4285-92

Time-Integrated Activity (Coefficients)

Why not use the data of a patient population instead of a single patient?



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Population Pharmacokinetic Modelling

(A) PBPK Modelling
(B) NLME Modelling

Advantage?

Much higher ratio of number of data to number of model parameters!

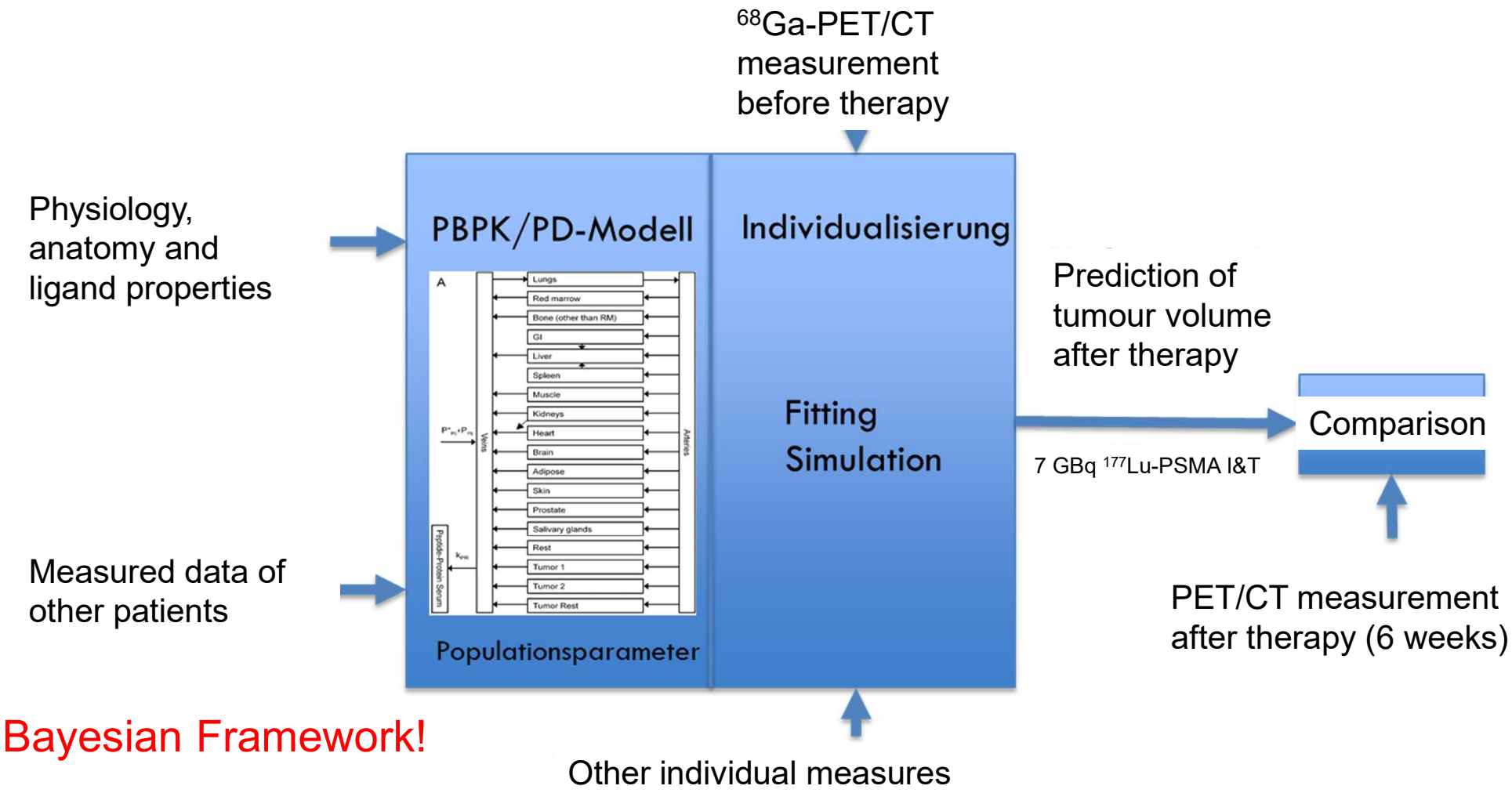
Population Pharmacokinetic Modelling

(A) PBPK Modelling

(B) NLME Modelling

Kletting et al. J Nucl Med 2019

Modelling and Prediction of Tumour Response in RLT



Population Pharmacokinetic Modelling

(A) PBPK Modelling

(B) NLME Modelling

Mould et al. *CPT Pharmacometrics Syst Pharmacol*, 2012

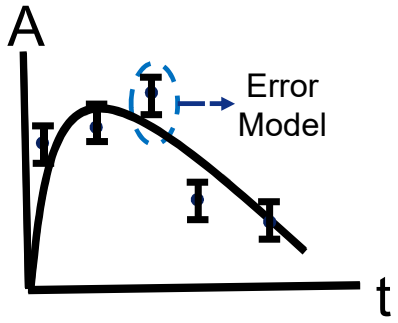
Non-Linear Mixed-Effects (NLME) Modelling

http://clipart-library.com/

Non-Linear Mixed Effects (**NLME**) modeling is a population-based estimation method that can identify drug disposition in terms of **intra-individual** and **inter-individual variability.**

Intra-individual variability

Variability of the biokinetic data of radiopharmaceuticals in different organs



Inter-individual variability

Variability of the model parameters, showing the difference between biological parameters from patient to patient

Example: Somatostatin receptor density in kidneys R_k

PATIENT 1 → $R_{k1} \neq R_{k2}$ ← PATIENT 2

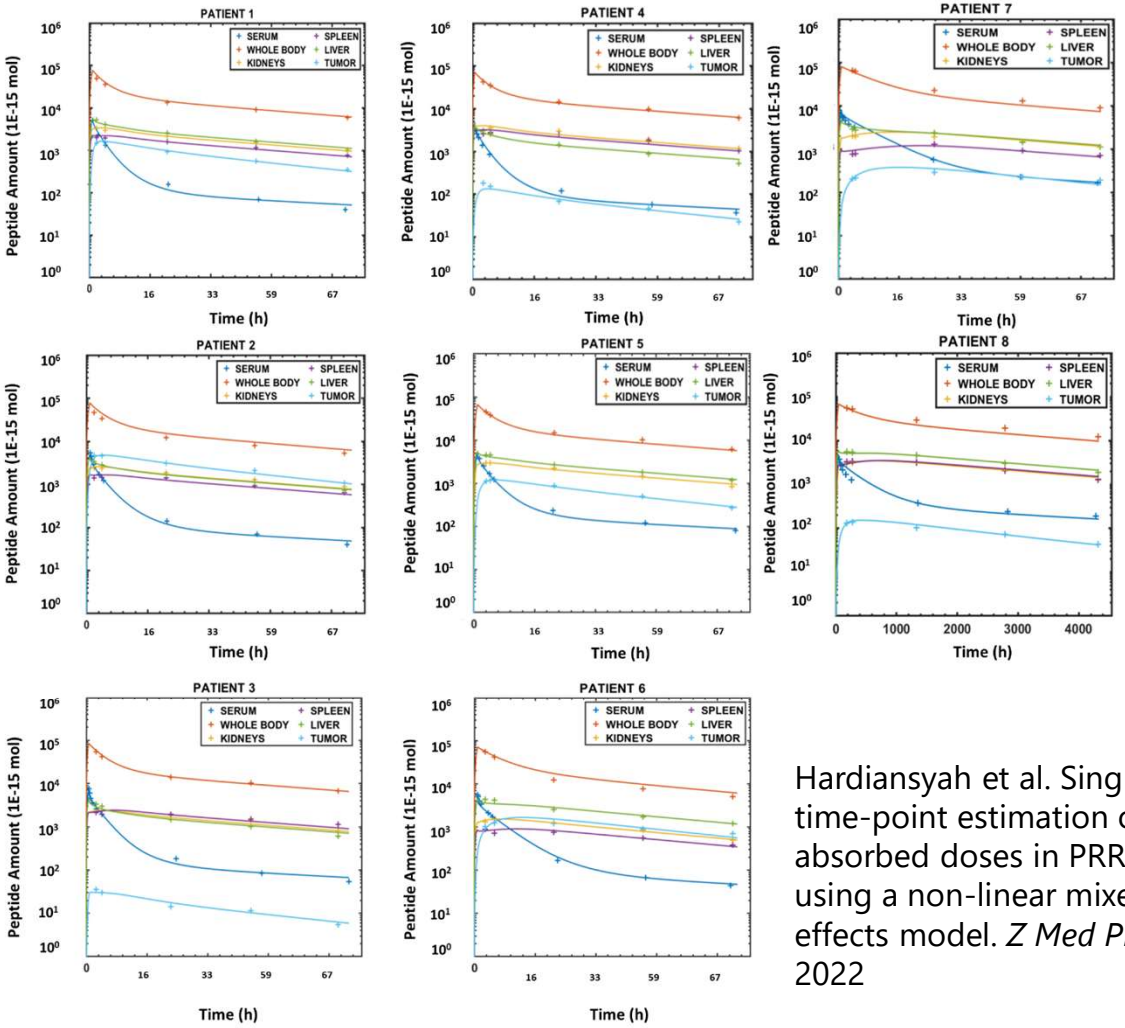
$$R_{k1} = TVR_k \, exp\,(ETA_{R_{k1}})$$

$$R_{k2} = TVR_k \, exp\,(ETA_{R_{k2}})$$

Fixed effect

Random effect

Non-Linear Mixed-Effects (NLME) Modelling



Hardiansyah et al. Single-time-point estimation of absorbed doses in PRRT using a non-linear mixed-effects model. *Z Med Phys* 2022

Number of parameters (PRRT-PBPK model)

Inter-individual variability	
- Fixed effect	7
- Random effect	7
Intra-individual variability	
-	1

Number of data	
- Patients	8
- Organs	5
- Time points	5
- Serum data	9

Ratio 267/15 = 17.8

STP-Ratio 243/15 = 16.2

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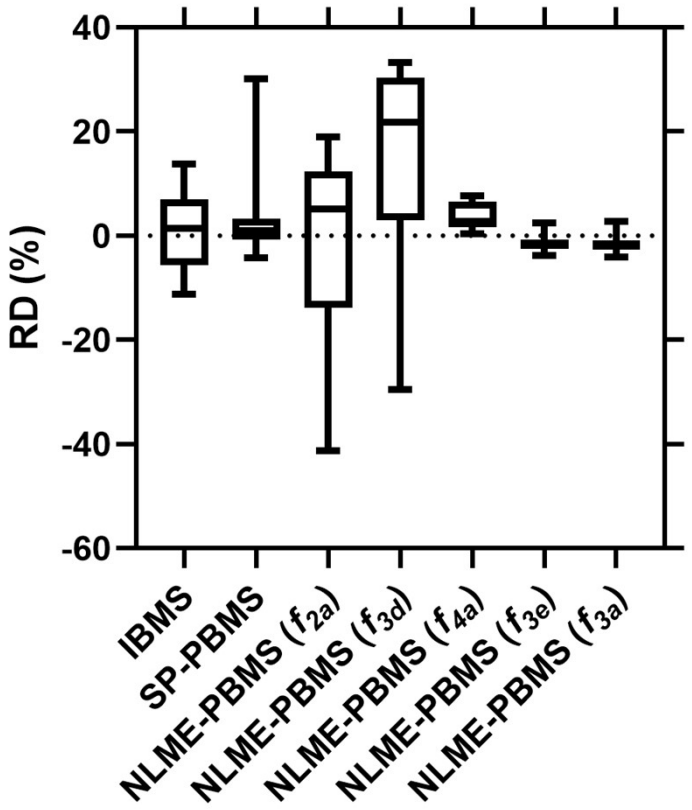
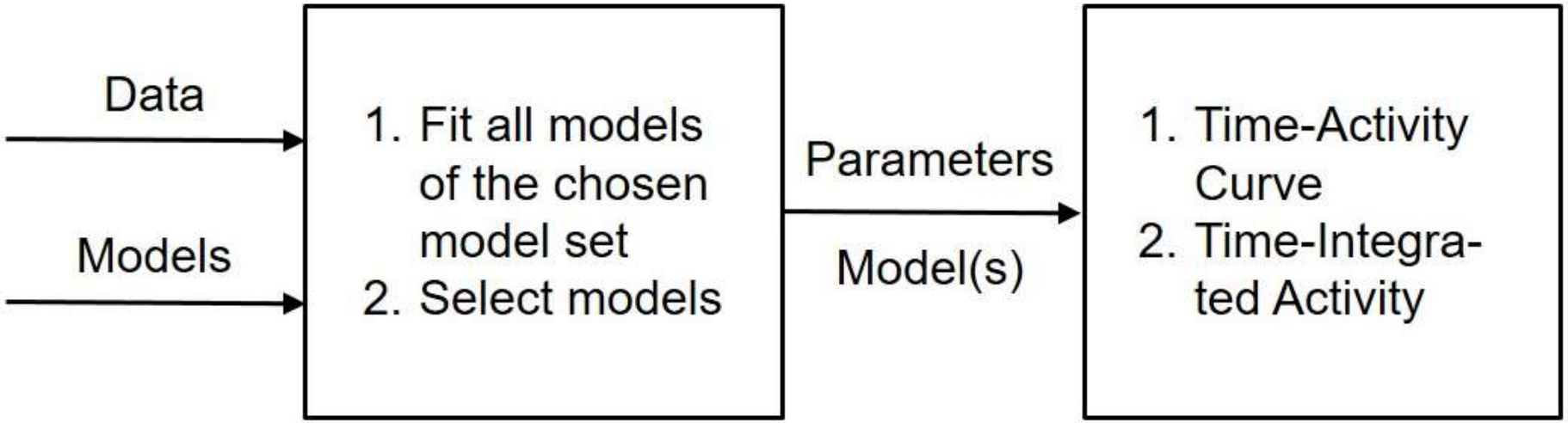
Single-Time-Point: Dependence on Fit Function

[^{177}Lu]Lu-PSMA-I&T



In reviion

Time-Integrated Activity (Coefficients)



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„Garbage in – Garbage out“ paradigm