Deutsche
Gesellschaft
für Nuklearmedizin
e.V.

Translational Research in Molecular Imaging and Radionuclid Therapy

August 31 – September 2, 2017

Kinetic Modelling and Quantitative Imaging

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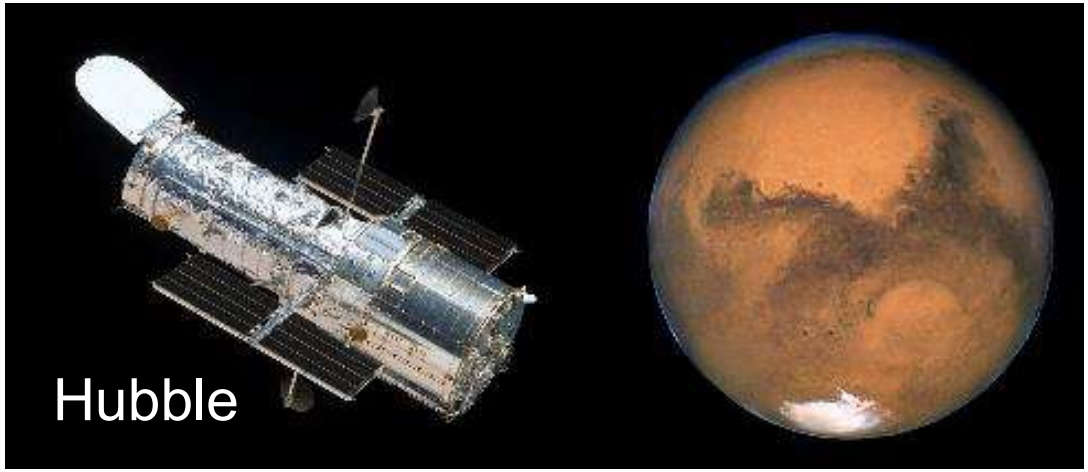
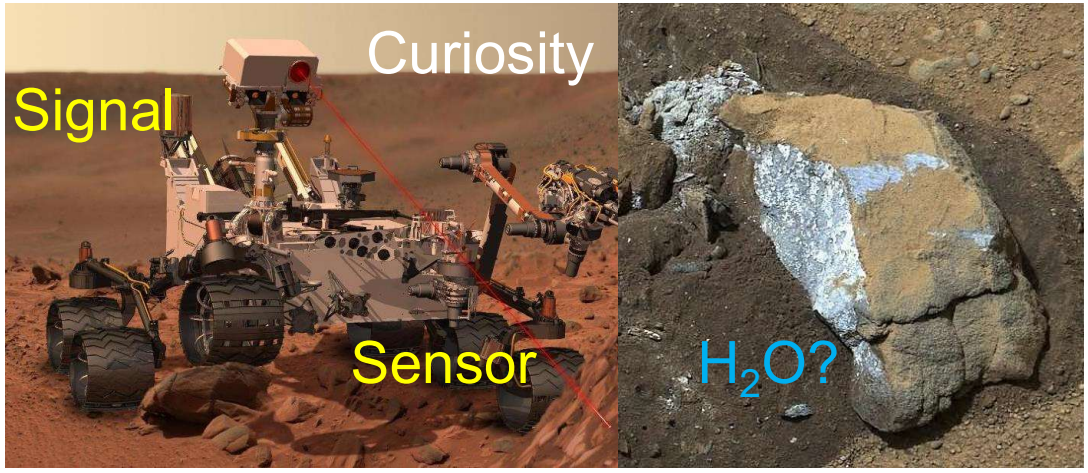
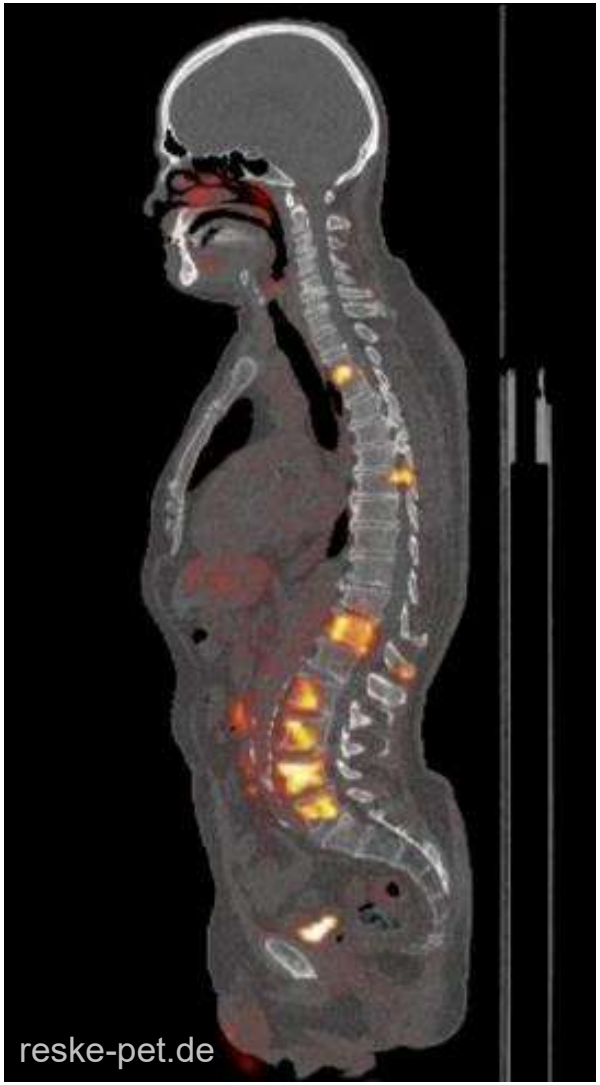
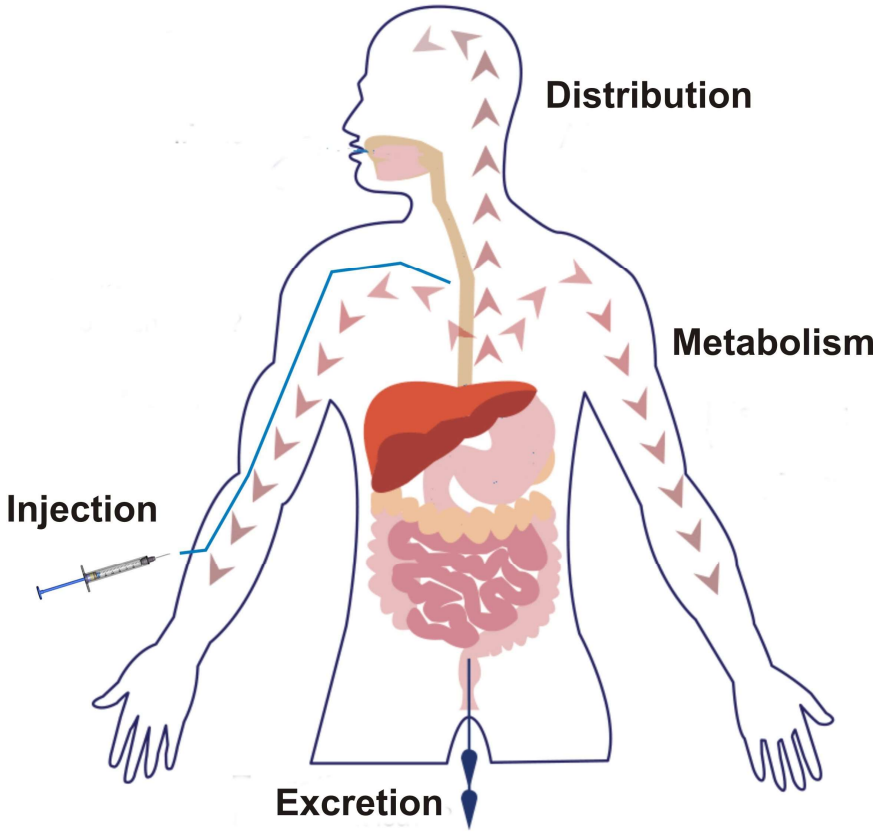
Molecular Imaging





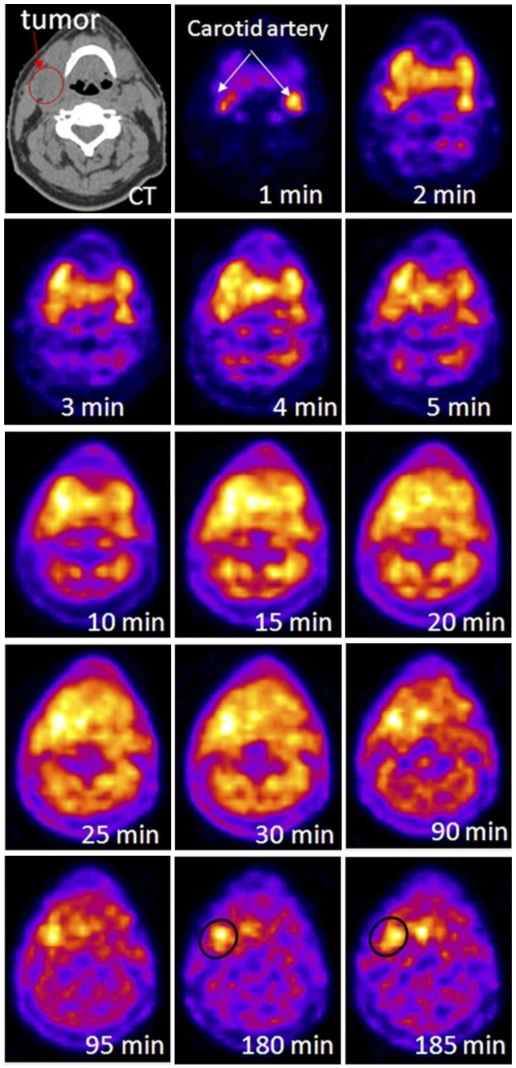


Challenges of Molecular Imaging Quantification



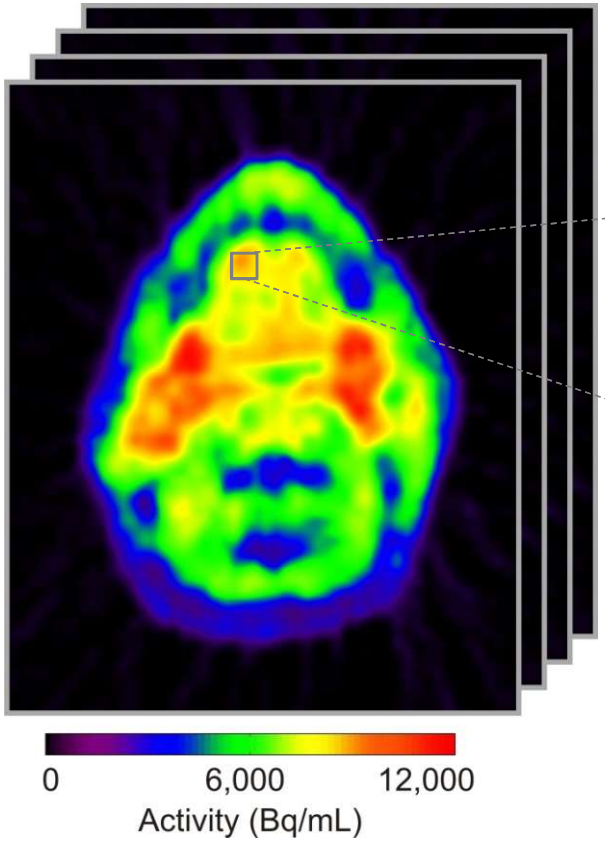
Dynamic imaging signal

Confounding factors



[Carlin & Humm, J Nucl Med 2012]

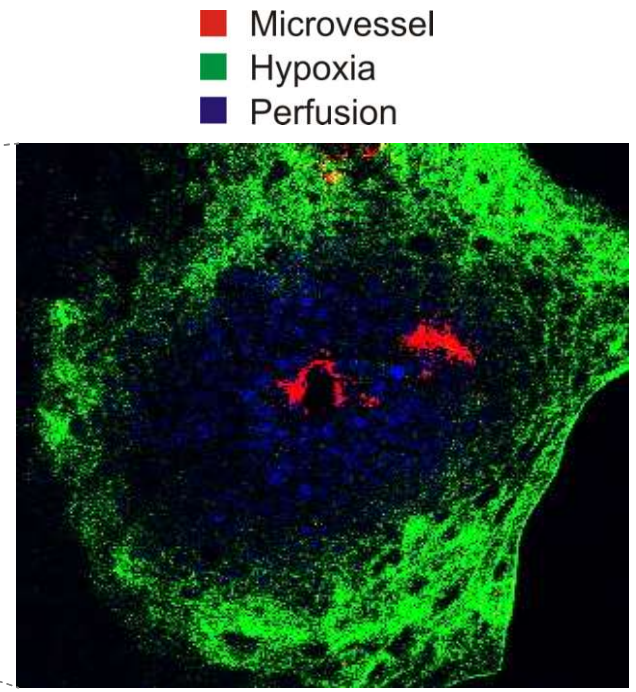
Quantification of Molecular Imaging



PET images: ^{18}F-Fmiso

Static Analysis

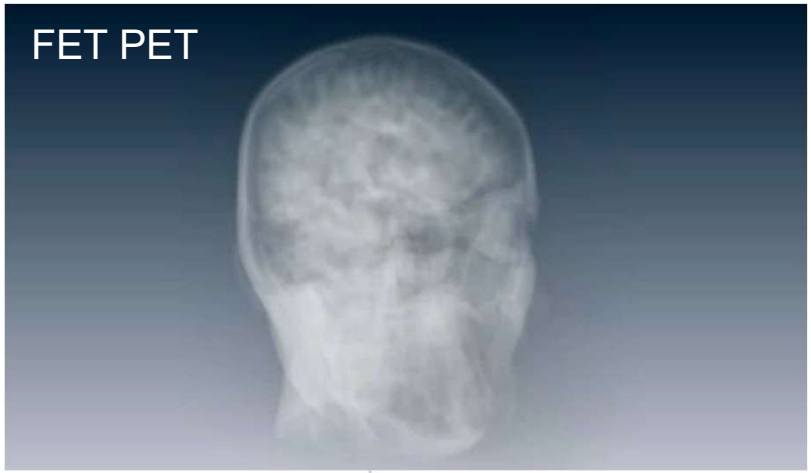
Dynamic Analysis

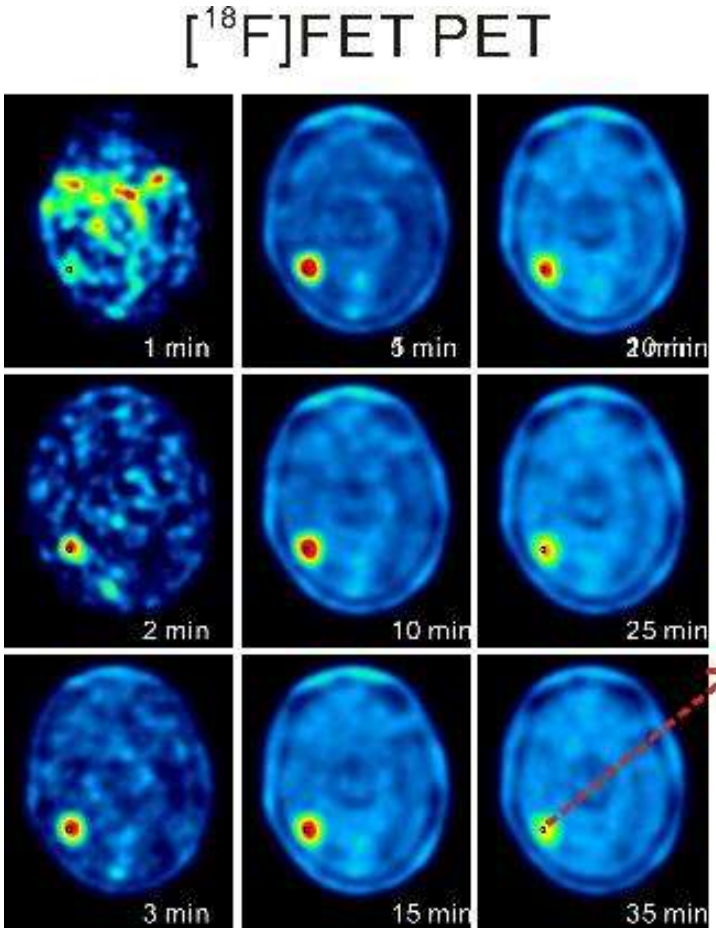


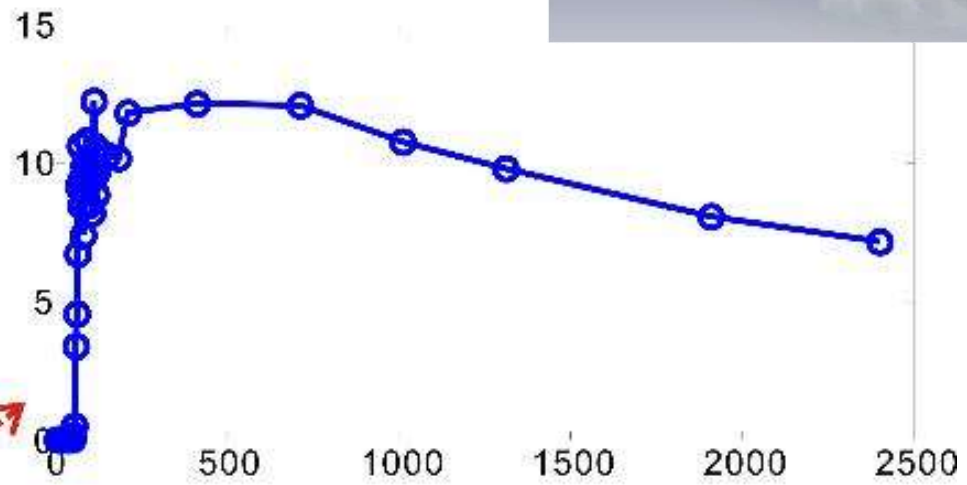
Tumor microenvironment (immunohistochemistry)

- ❑ Qualitative
- ❑ Semi-quantitative
- ❑ Quantitative

Quantitative Analysis: Dynamic PET & Time-Activity Curve (TAC)

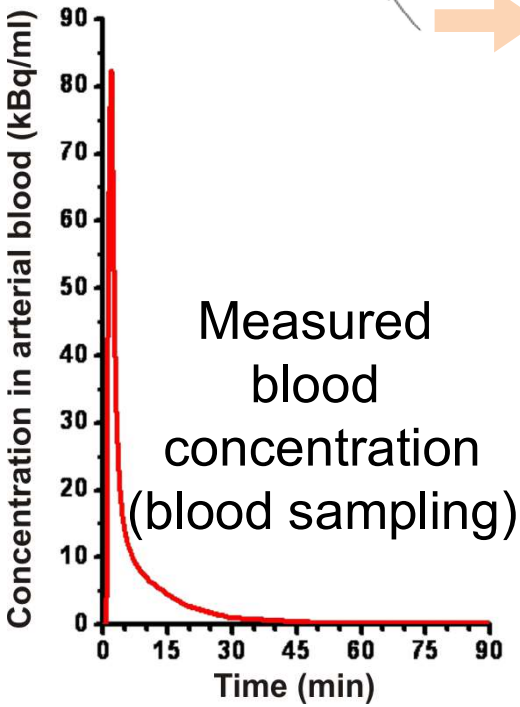






Quantitative Analysis: Pharmacokinetic Modeling

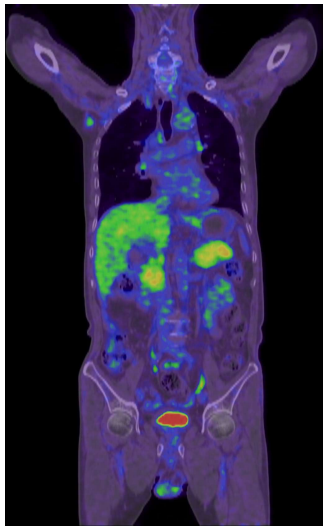
Tracer injection

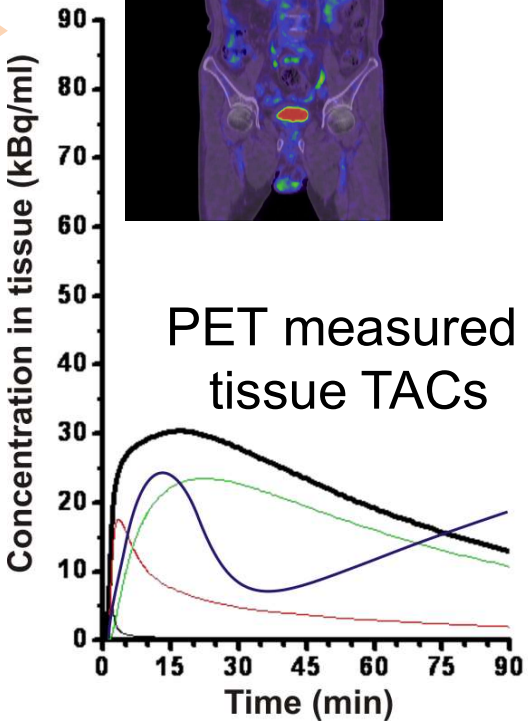


Measured blood concentration (blood sampling)

Pharmaco-kinetics

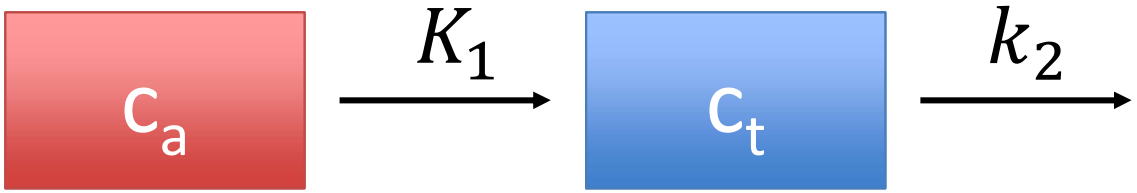
Tissue response





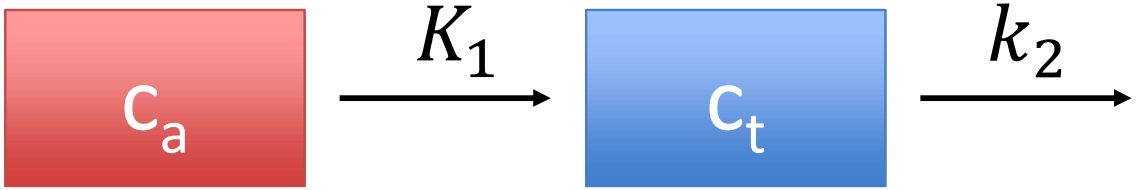
PET measured tissue TACs

Compartmental Model



- Compartment: a theoretical volume for tracer
- Instant homogeneous distribution within entire compartment
- Steady-state: constant physiological processes & molecular interactions
- Transport between compartments: pure diffusion
- Linear interconnections among compartments

Compartmental Model



$$\frac{dc_t}{dt} = K_1 c_a - k_2 c_t$$

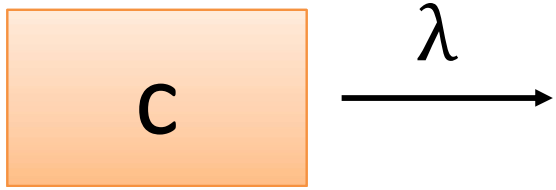
$$c_t = K_1 e^{-k_2 t} \otimes c_a$$

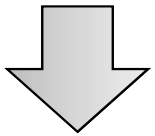
Compartmental Model

- Radioactive decay

$$\frac{dc}{dt} = -\lambda c$$

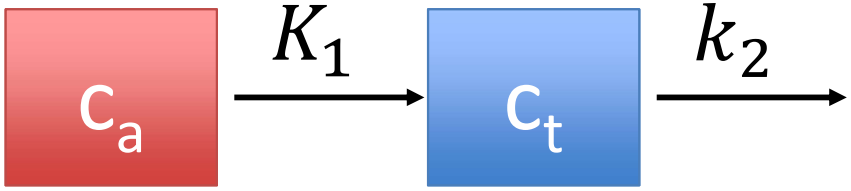
- Compartmental representation





$$c = c_0 e^{-\lambda t}$$

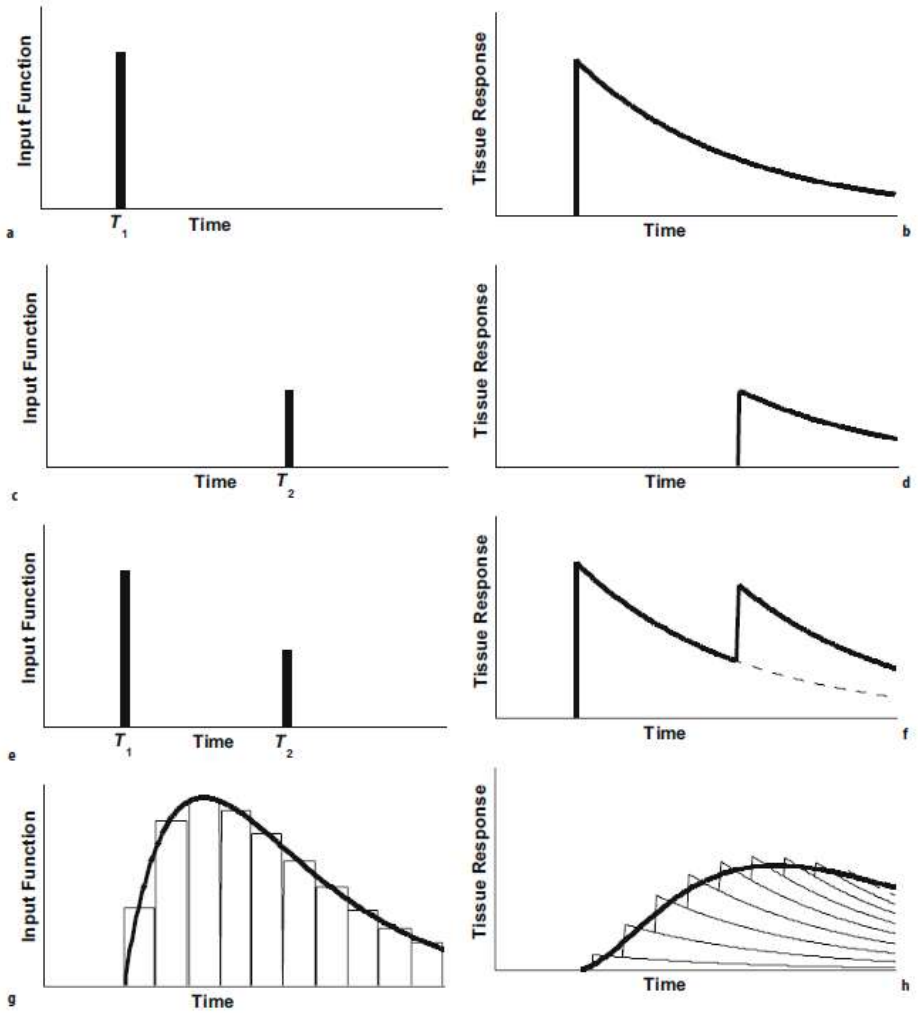
Compartmental Model



$$c_t = K_1 e^{-k_2 t} \otimes c_a$$

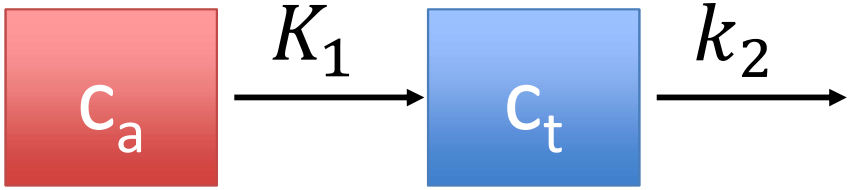
$$c_t(t) = K_1 \int_0^t e^{-k_2 (t-\tau)} c_a(\tau) d\tau$$

Convolution: sum of system responses



[Carson 2003]

Curve Fitting



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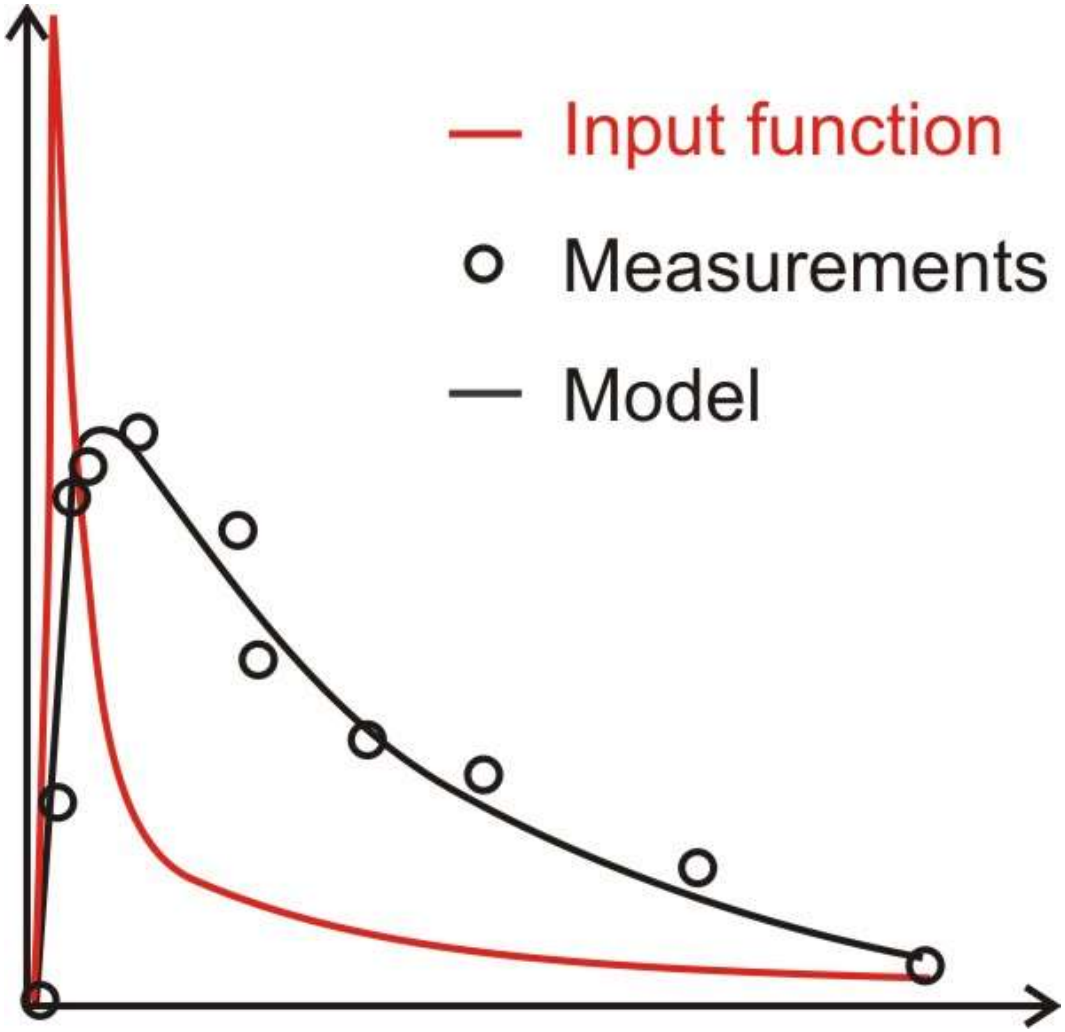
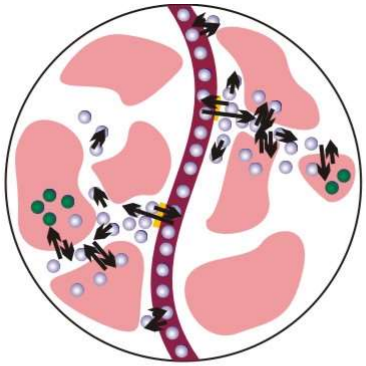


Two Tissue Compartment Model

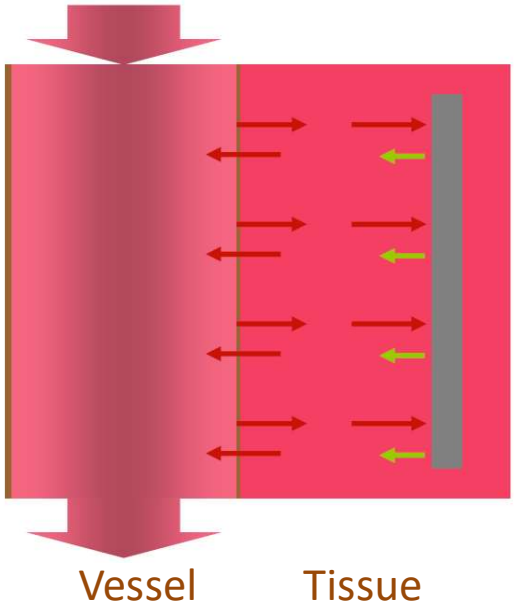
- Physiological process
  - Free ligand in plasma
  - Permeation through endothelium
  - Free ligand in tissue
  - A fraction binds to receptor
  - A fraction dissociates again
  - Diffusion back to plasma
- Model
  - Physical / Chemical states

    => Compartments
    - well mixed homogenous material
    - **Not** physical volume



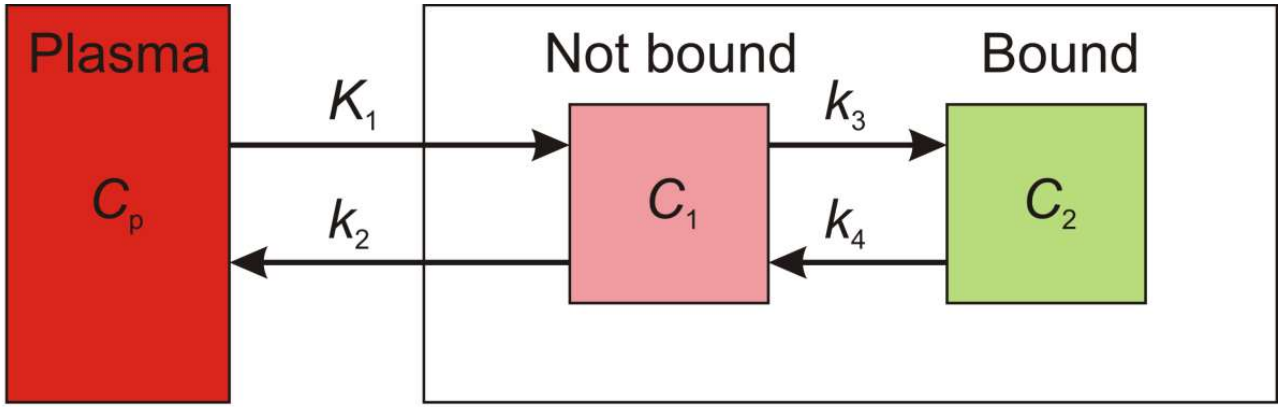
Interstitial+intracellular transport

+metabolism



Two Tissue Compartment Model

- Fixed number of compartments
- Transport between compartments: pure diffusion
- Linear interconnections among compartments
- First-order process: transfer proportional concentration
- Constant-coefficient, ODE
- Curve fitting of TAC



[Watabe H. *et. al. Annals of Nuclear Medicine* 2006]

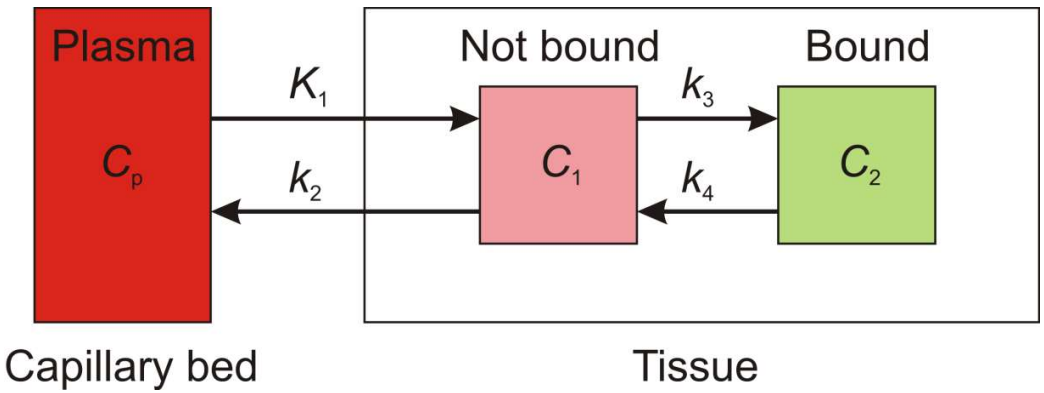
[Gunn R. N. *et. al. J Cereb Blood Flow Metab* 2001]

Two Tissue Compartment Model

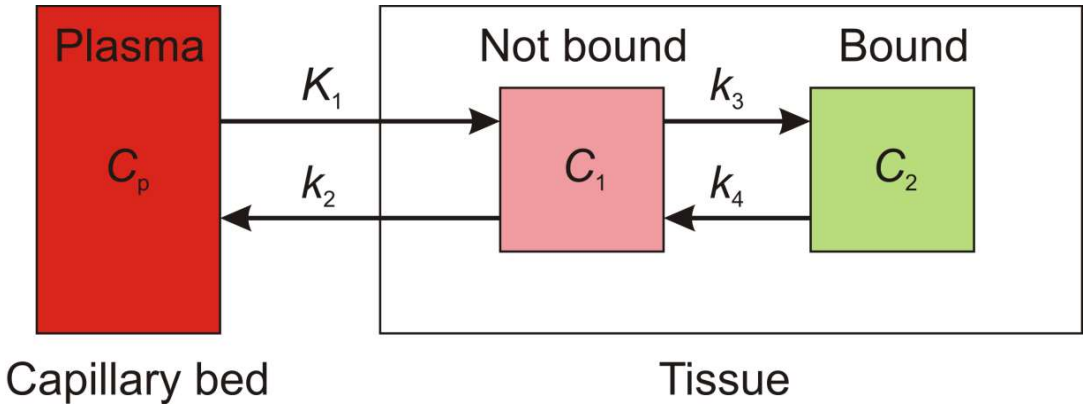
- Arterial concentration $C_p(t)$: measured
- Concentration in tissue compartments:
  - $C_1(t)$: free tracer
  - $C_2(t)$: specifically bound tracer
- Concentration change:

$$\frac{dC_1(t)}{dt} = K_1 C_p(t) - k_2 C_1(t) - k_3 C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$



Two Tissue Compartment Model



$$C_{tissue}(t) = C_1(t) + C_2(t)$$

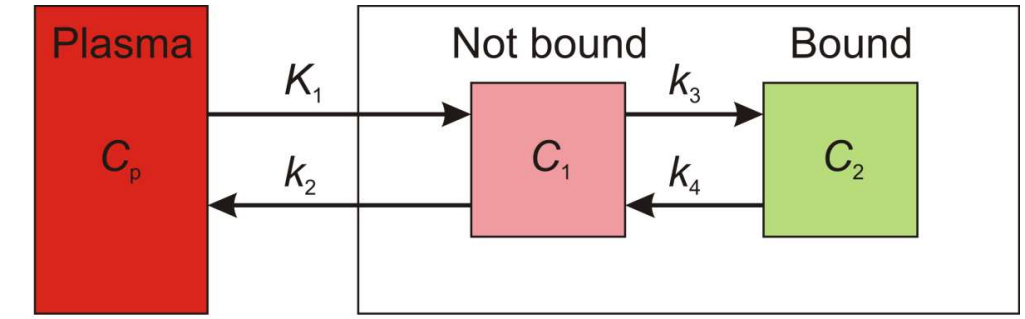
$$\frac{dC_1(t)}{dt} = K_1 C_p(t) - k_2 C_1(t) - k_3 C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

$$C_1(t) = IRF_1\,(K_1, k_2, k_3, k_4, t) \otimes C_p(t)$$

$$C_2(t) = IRF_2\,(K_1, k_2, k_3, k_4, t) \otimes C_p(t)$$

Two Tissue Compartment Model



$$C_{tissue}(t) = C_1(t) + C_2(t)$$

$$C_1(t) = IRF_1\,(K_1, k_2, k_3, k_4, t) \otimes C_p(t)$$
$$C_2(t) = IRF_2\,(K_1, k_2, k_3, k_4, t) \otimes C_p(t)$$

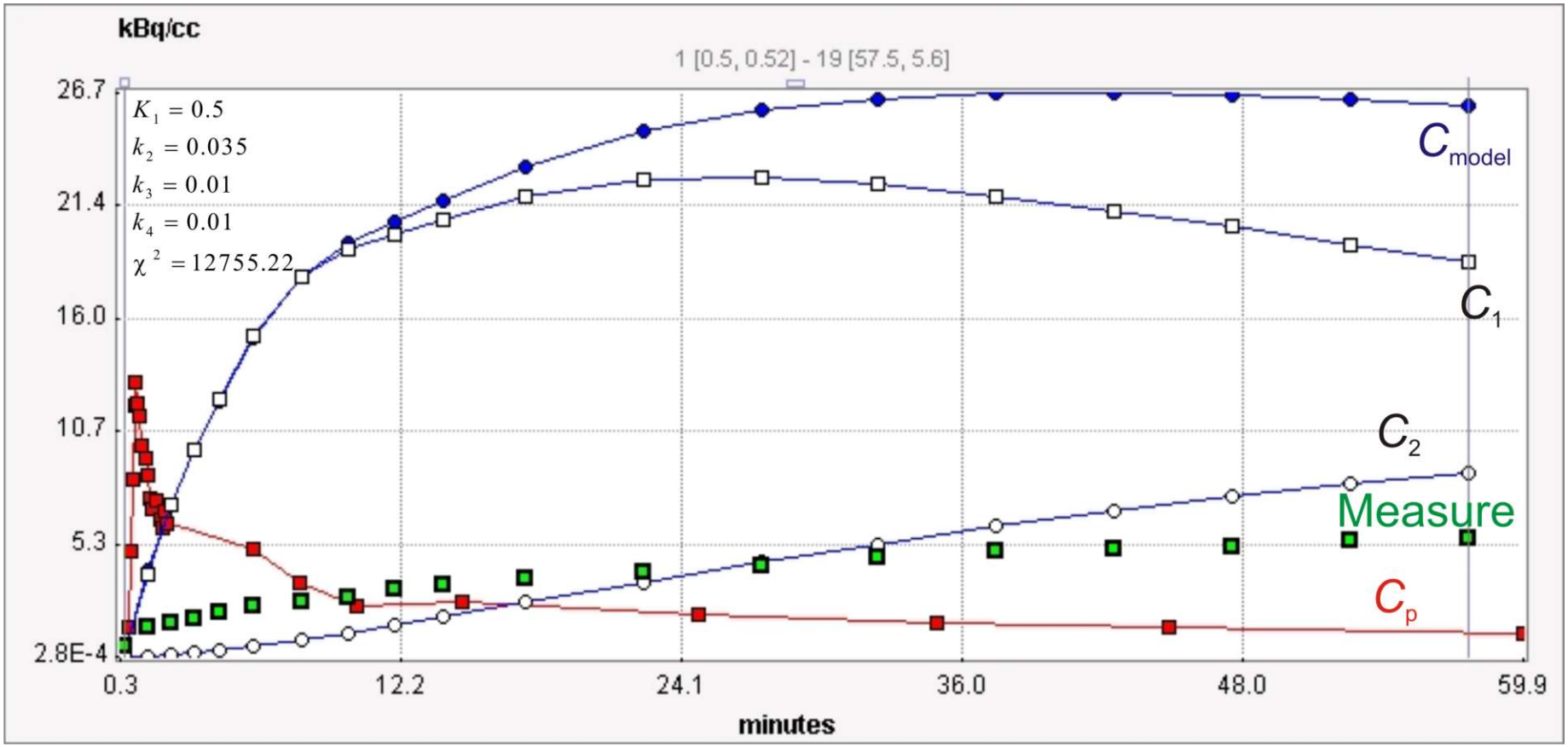
$$IRF_1\,(K_1, k_2, k_3, k_4, t) = \frac{K_1}{(\alpha_2 - \alpha_1)}\left[(k_4 - \alpha_1)e^{-\alpha_1 t} + (\alpha_2 - k_4)\,e^{-\alpha_2 t}\right]$$
$$IRF_2\,(K_1, k_2, k_3, k_4, t) = \frac{K_1 k_3}{(\alpha_2 - \alpha_1)}\left[e^{-\alpha_1 t} + e^{-\alpha_2 t}\right]$$

$$\alpha_1 = \frac{(k_2 + k_3 + k_4) - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}}{2} \qquad \alpha_2 = \frac{(k_2 + k_3 + k_4) + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}}{2}$$

Two Tissue Compartment Model

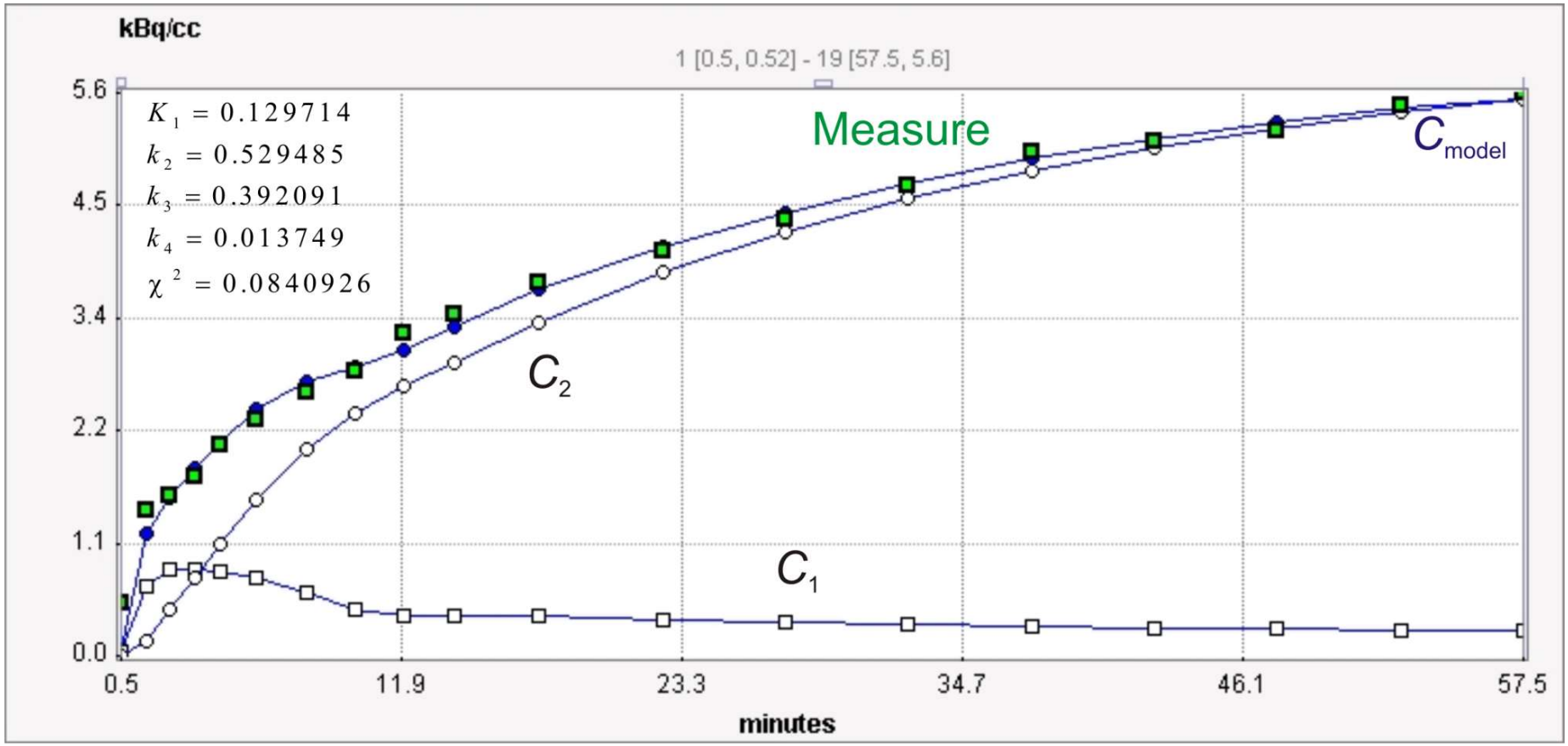
- Given K_1, k_2, k_3, k_4 and $C_p(t)$
- Calculate $C_{model}(t)$

PMOD

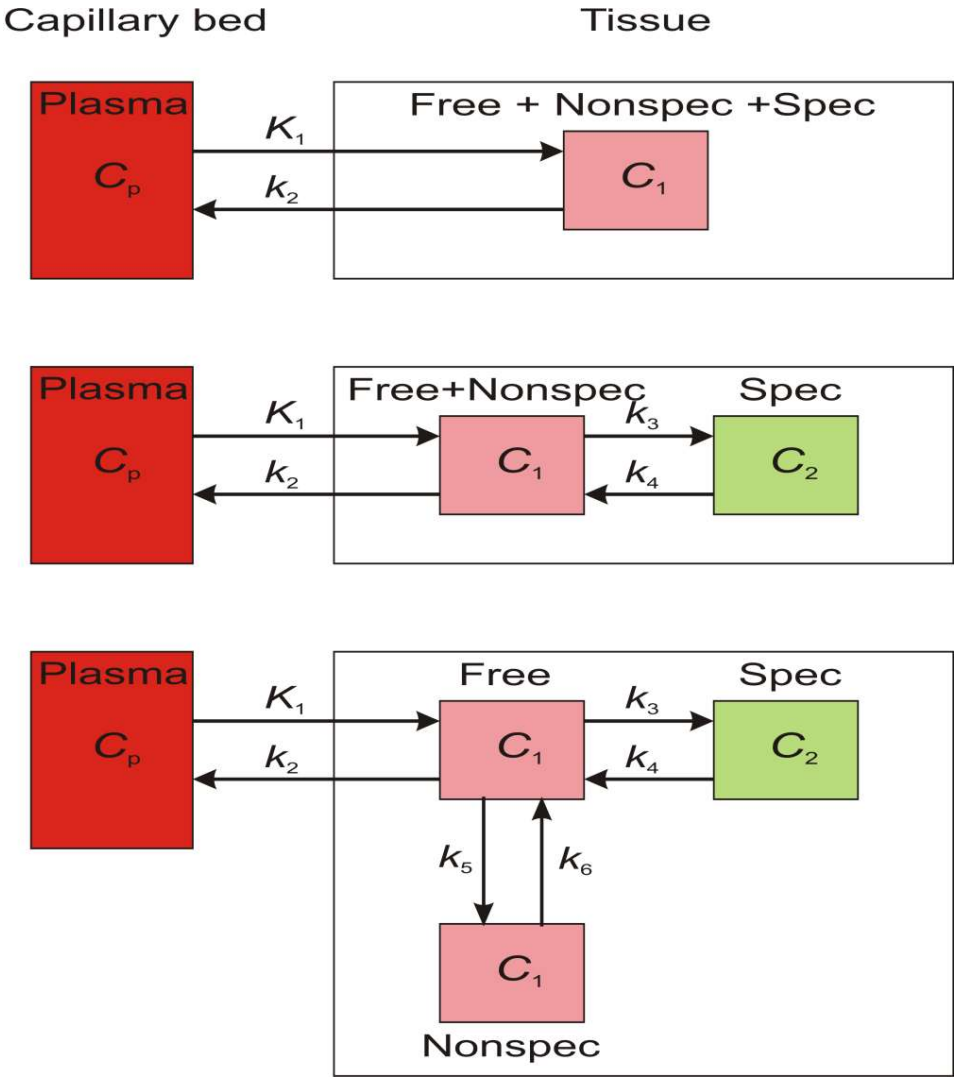


Two Tissue Compartment Model

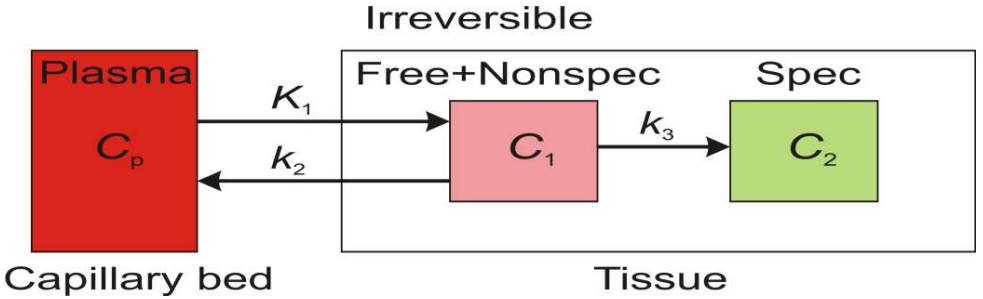
- Criteria of difference between $C_{measure}(t)$ and $C_{model}(t)$: χ^2
- Optimization algorithm: modify K_1, k_2, k_3, k_4 to minimize χ^2



Compartmental Model

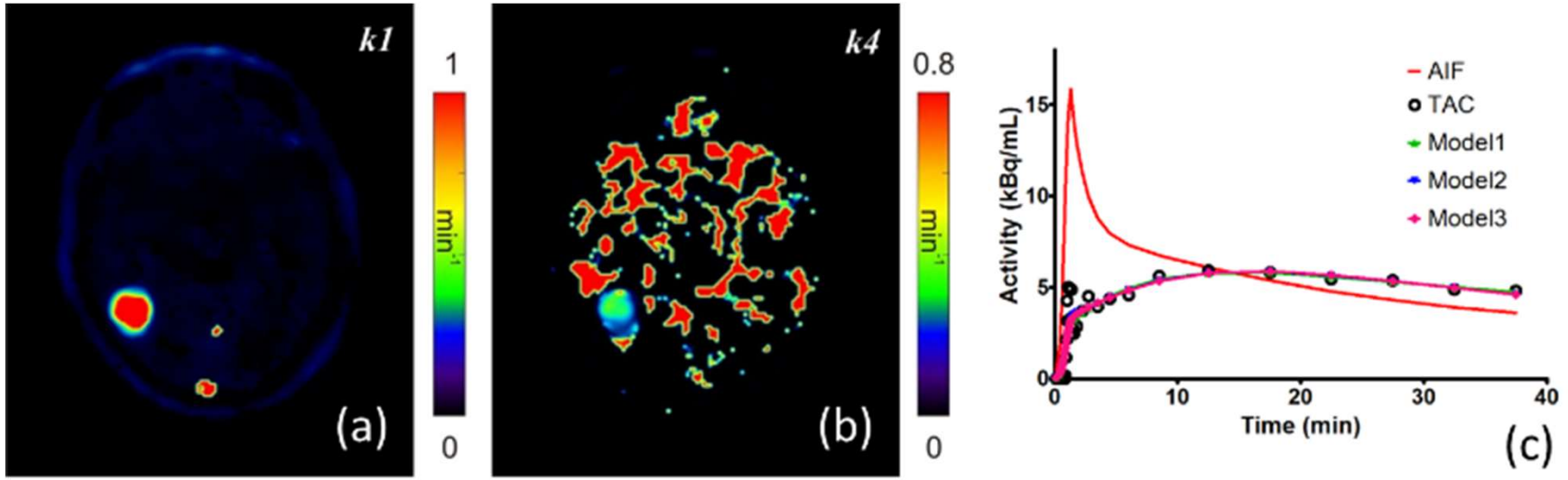


- One compartment
  - $[^{15}O]H_2O$
- Two compartment
  - $[^{18}F]FDG$
  - $[^{18}F]FMISO$
- Three compartment
- Irreversible model



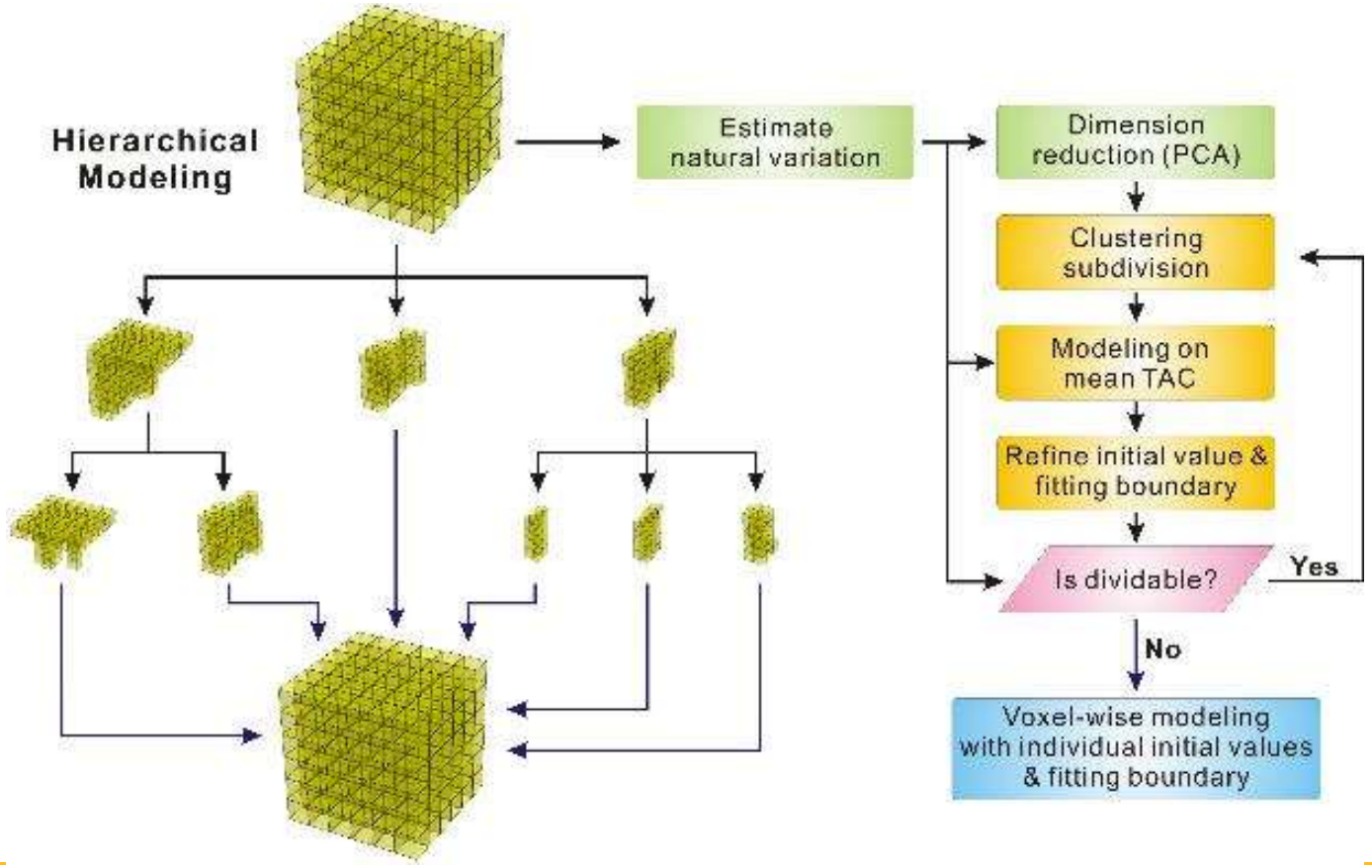
Local Minima of Nonlinear Fitting

- a) & b): parametric images (k1 & k4) using direct voxel-wise modeling (PMOD) for a slice of Patient #1;
- c): an example TAC and the three resulting modeling curves fitted using three different sets of initial values:
  - Model1: χ^2 =0.723; k1=0.10, k2=0.12, k3=0.01, k4=0, VB=0.14
  - Model2: χ^2 =0.749; k1=0.81, k2=5.42, k3=0.64, k4=0.11, VB=0.05
  - Model3: χ^2 =0.754; k1=0.15, k2=0.66, k3=0.63, k4=0.20, VB=0.13

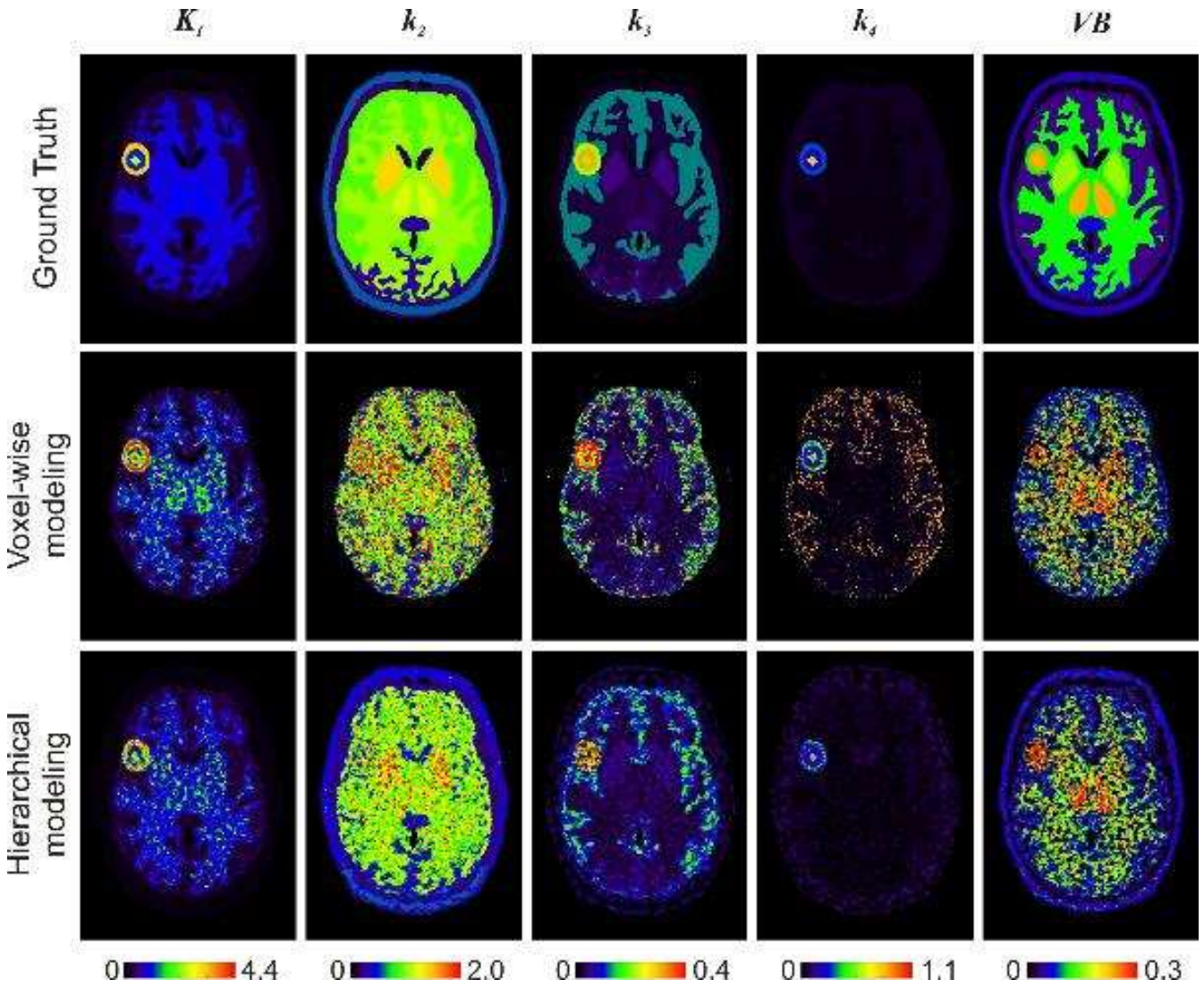


Hierarchical Pharmacokinetic Modeling

- Assumption: Similar TACs has similar kinetic parameters
- Clustering the TACs according to their similarities
- Gradually refining the initial values and fitting boundaries



Test on Simulation Phantom



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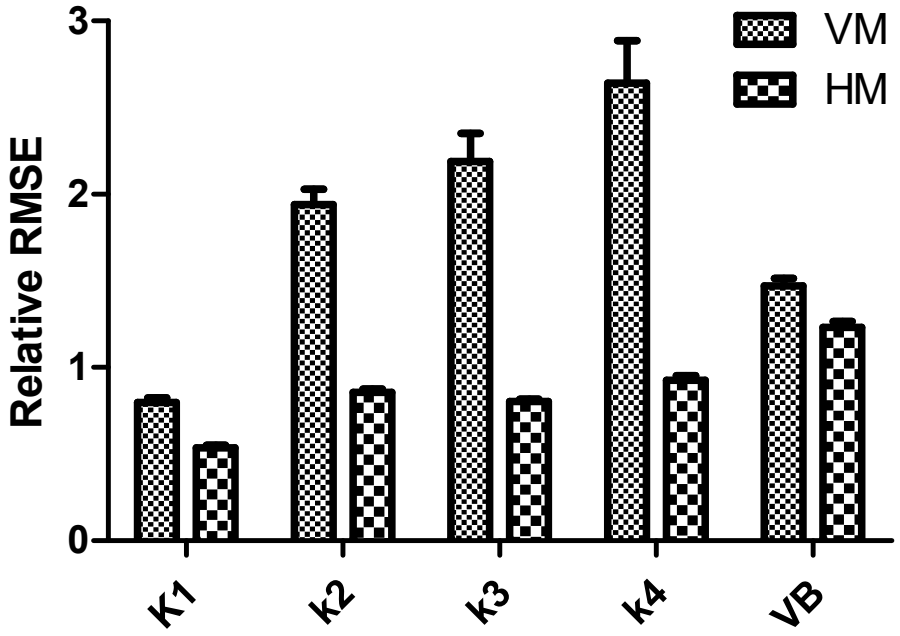
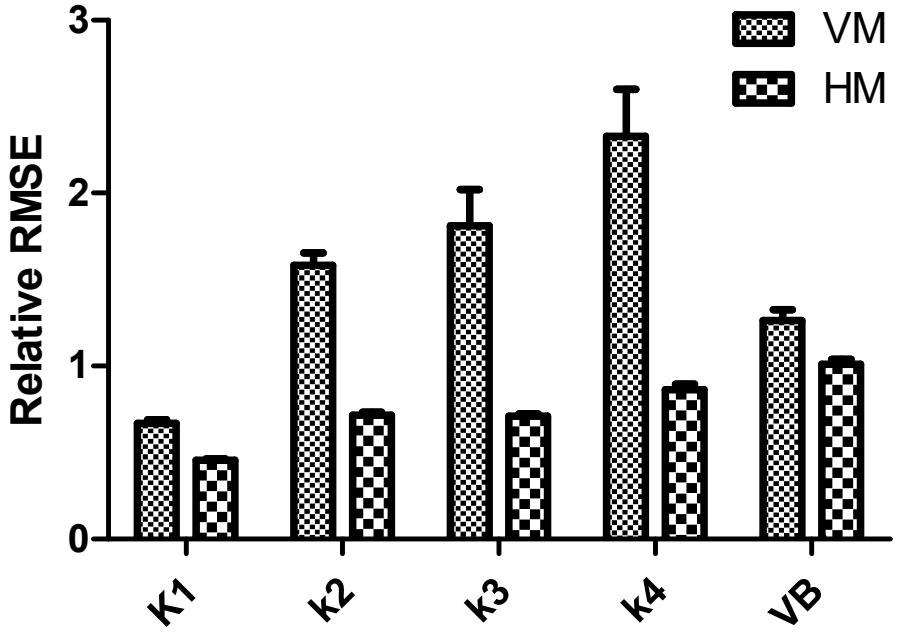
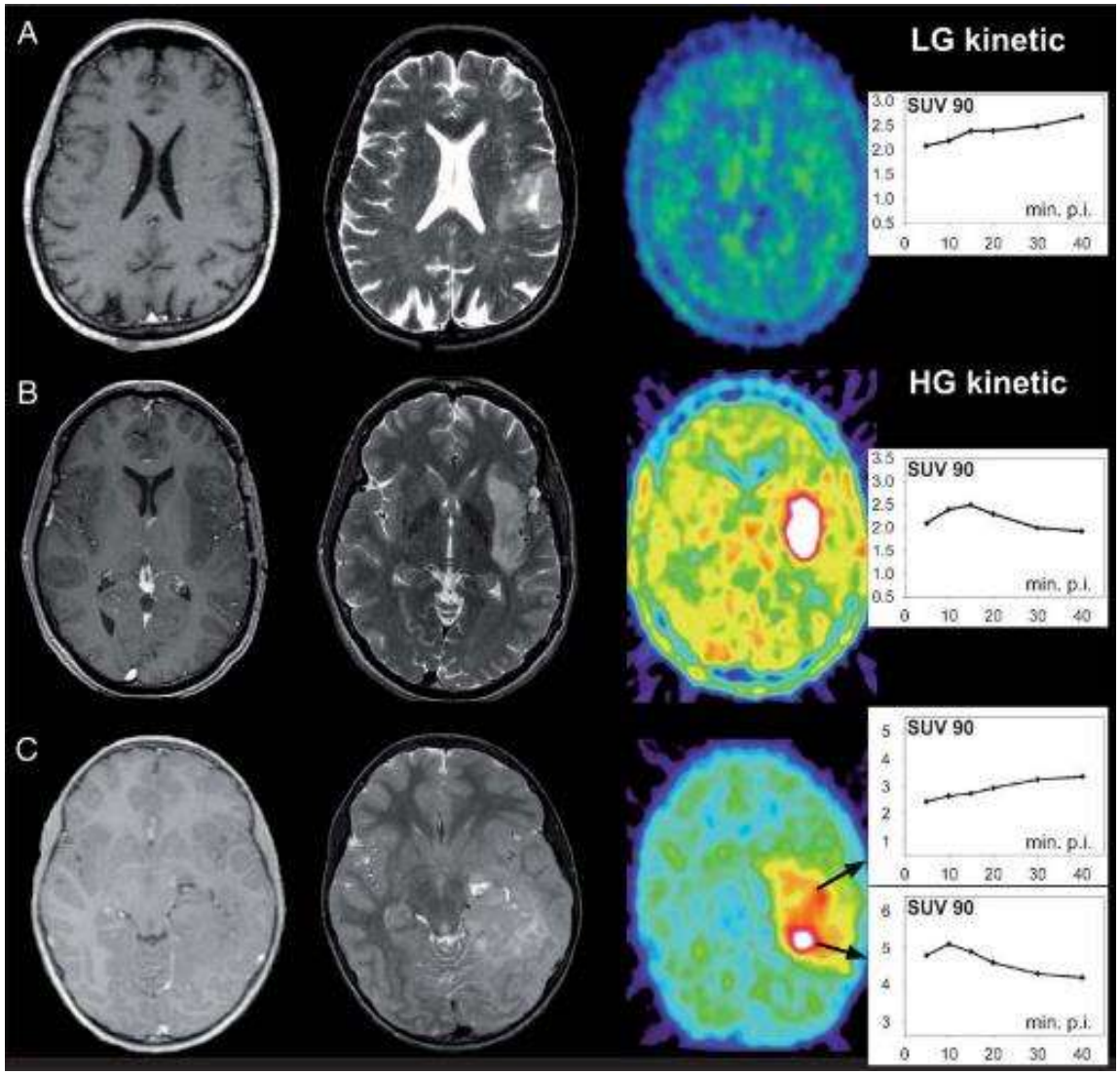




Example Application of Pharmacokinetic Modeling

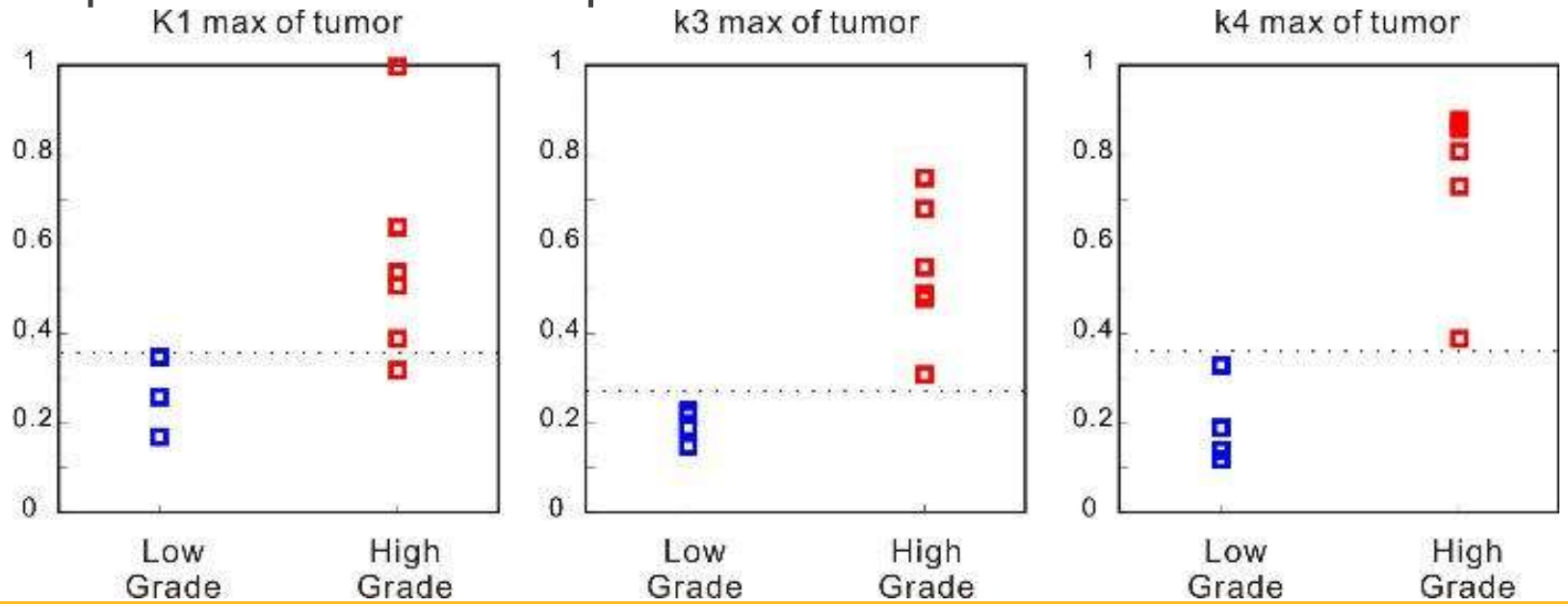
[^{18}F]FET



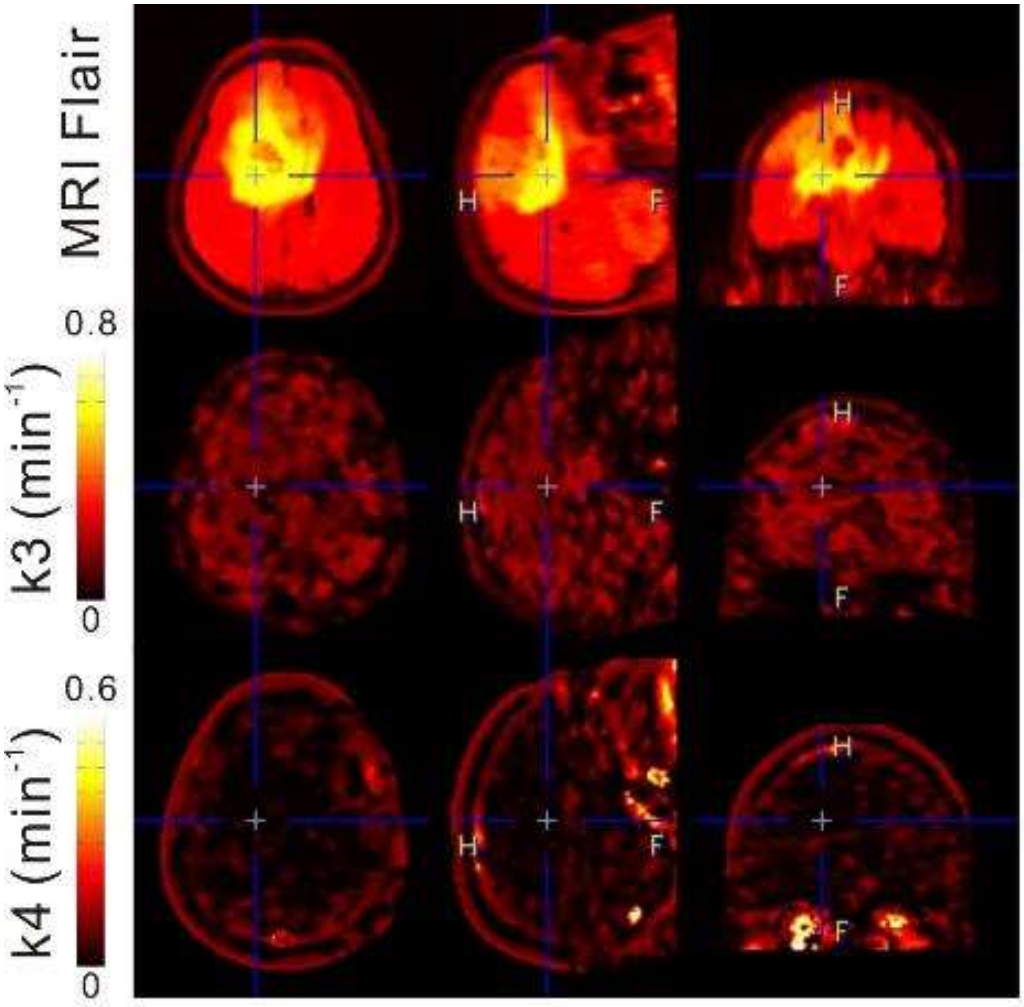
[Kunz et al Neuro Oncol 2011]

Example Application of Pharmacokinetic Modeling

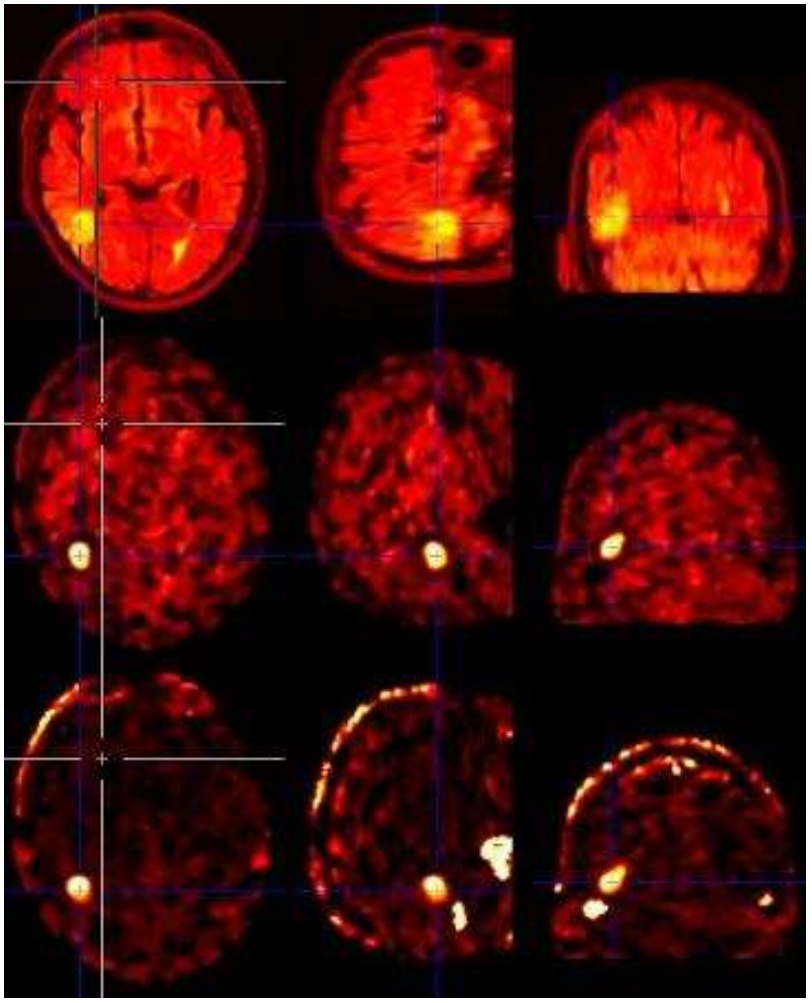
- 10 Patients: 4 Low Grade (WHO II) , 6 High Grade (WHO III &IV)
- Dynamic [^{18}F]FET for 40 min (Siemens mMR)
- OSEM 3D (3 iterations, 21 subsets)
- Tumor delineation on PET + Flair fusion
- Image-derived AIF from internal carotid artery (PET + MPRage)
- Computation < 3 hours / patient



Example Application of Pharmacokinetic Modeling

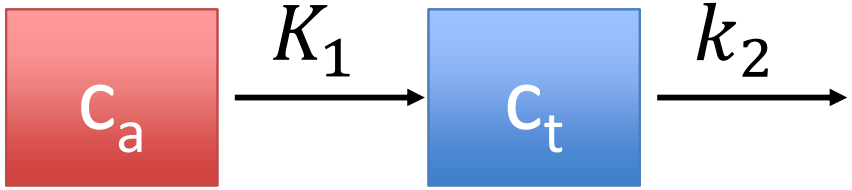


Patient Grade II



Patient Grade IV

Linear Model (Graphical Analysis)



- Compartment model:
  - Non-linear curve fitting
  - Time consuming
  - Not enough robust

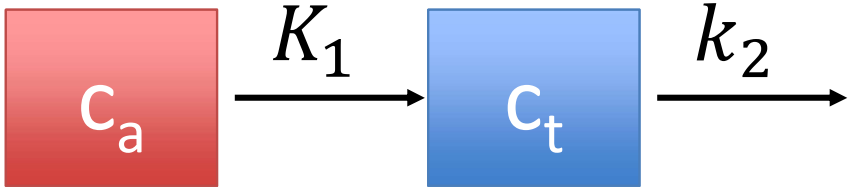
$$\frac{dC_t(t)}{dt} = K_1 C_a(t) - k_2 C_t(t)$$

$$C_t(t) = K_1 \int_0^t C_a(t) - k_2 \int_0^t C_t(t)$$

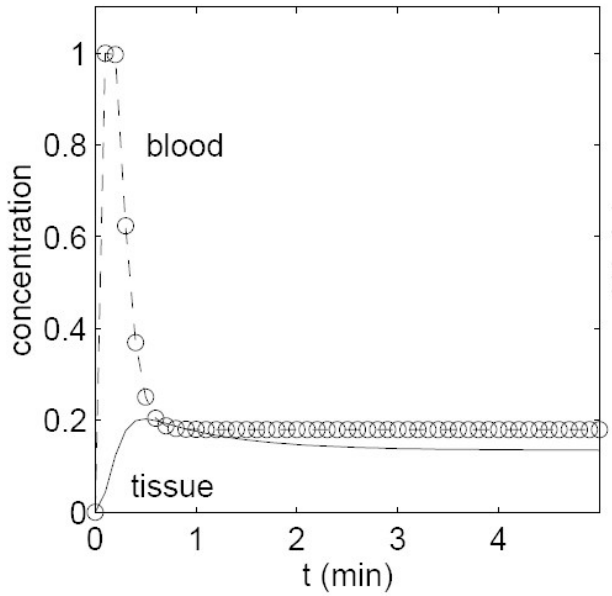
$$c_t = K_1 e^{-k_2 t} \otimes c_a$$

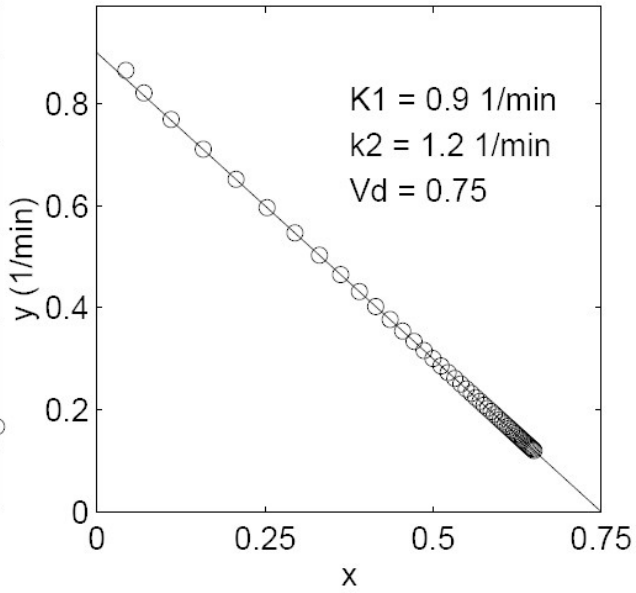
Differential form => integration form
Nonlinear fitting => linear fitting

Linear Model



$$\frac{C_t(t)}{\int_0^t C_a(t)} = K_1 - k_2 \frac{\int_0^t C_t(t)}{\int_0^t C_a(t)}$$





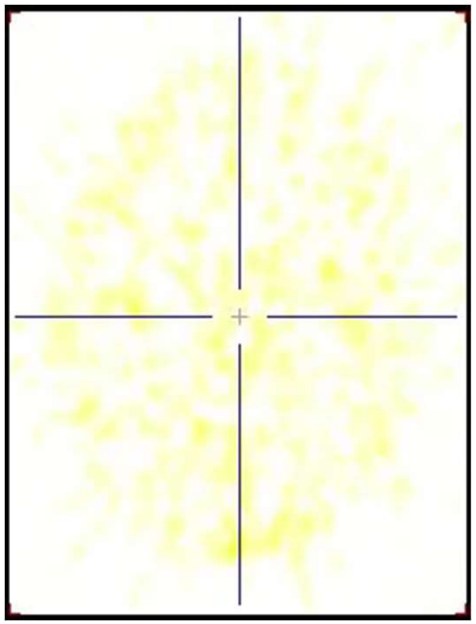
[Maguire R. P. *et. al. PET Pharmacokinetic Course Manual,* 2005]
[van den Hoff J. *et. al. J. Nuclear Medcine,* 1993]

Linear Model

- Compartment model => Graphical model
- Irreversible two compartment model => Patlak Plot
- Reversible two compartment model => Logan Plot

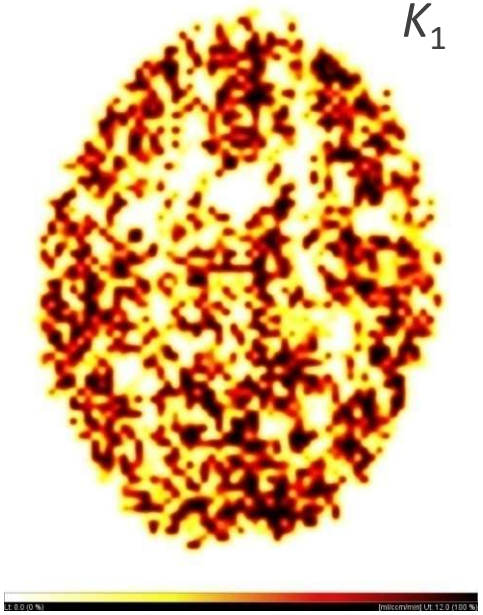
Linear Model

Dynamic PET (1 Slice)

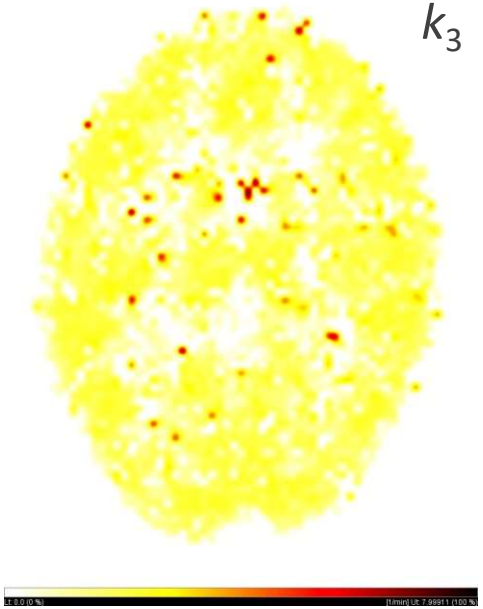


Two Compartment Model (40 min)

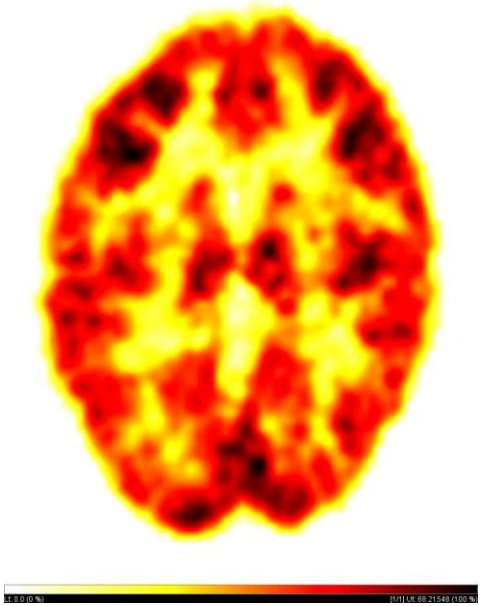
K_1



k_3

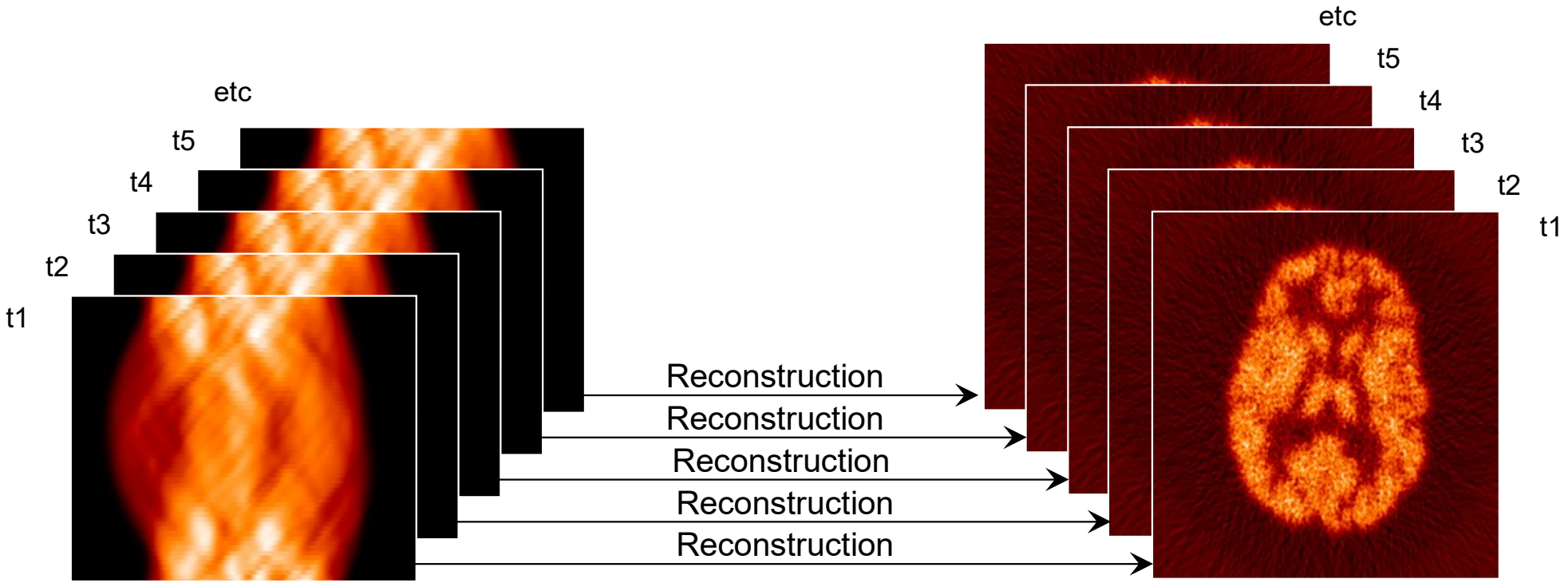


Patlak Plot (20 s)



Advanced Pharmacokinetic Modeling Computing: Direct Parametric Image Reconstruction

❑ PET Reconstruction



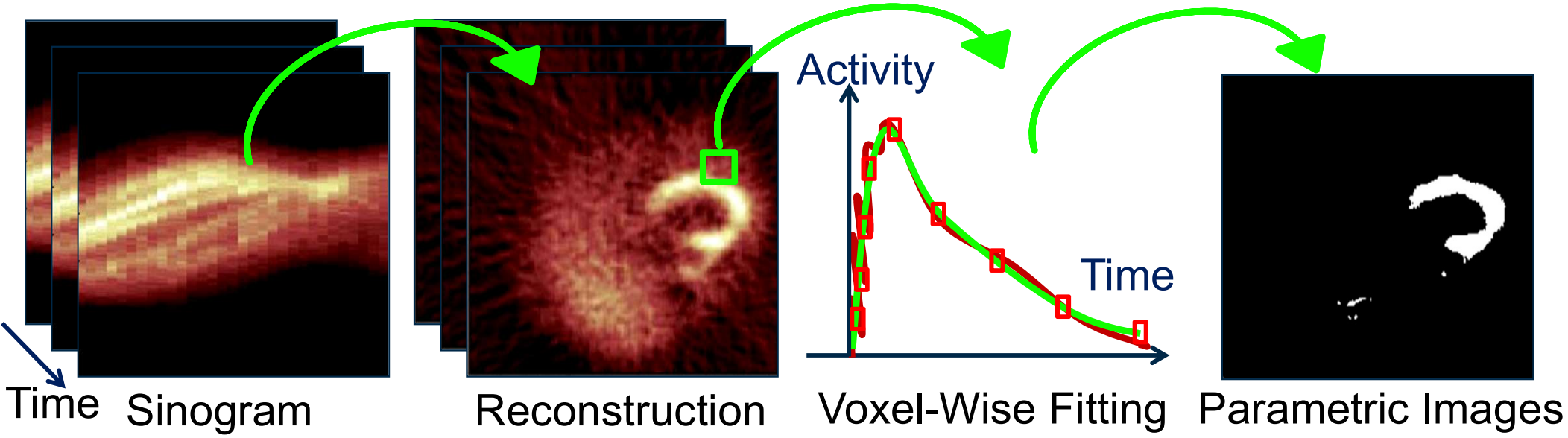
Detections

4D Tomographic images

Advanced Pharmacokinetic Modeling Computing: Direct Parametric Image Reconstruction

[Cheng et al. SNM 2012]

- Low SNR:
  - → Indirect parametric image generation:

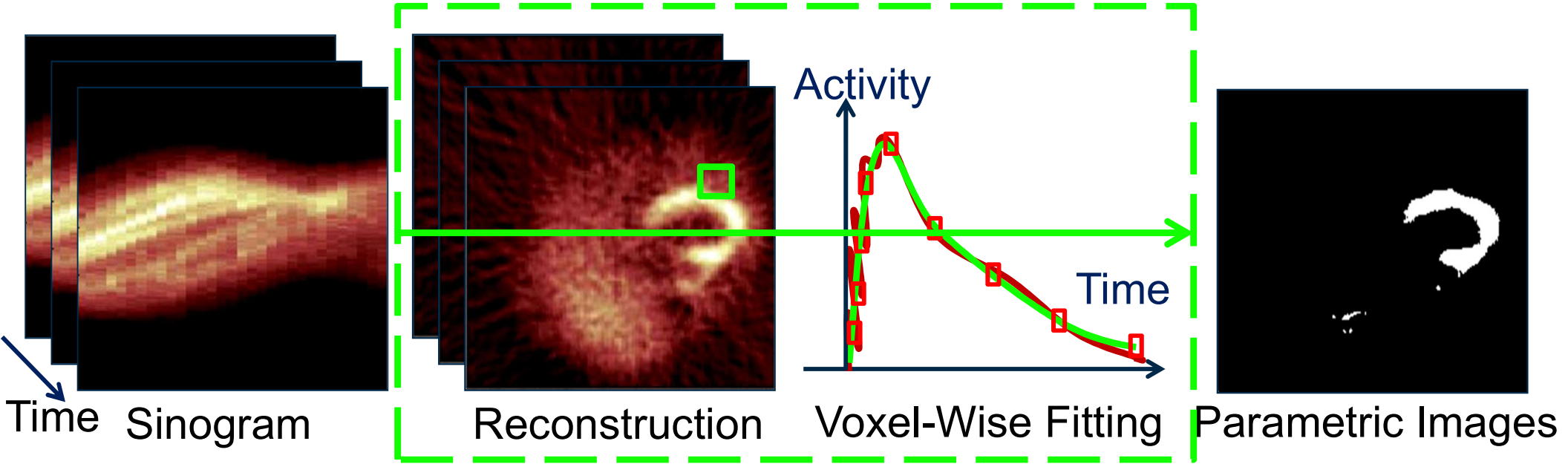


Spatial Information Temporal Information

Advanced Pharmacokinetic Modeling Computing: Direct Parametric Image Reconstruction

[Mattews et al. Phys. Med. Biol. 1997]
[Tsoumpas et al. Med. Phys. 2008]
[Wang et al. Phys. Med. Biol. 2008]

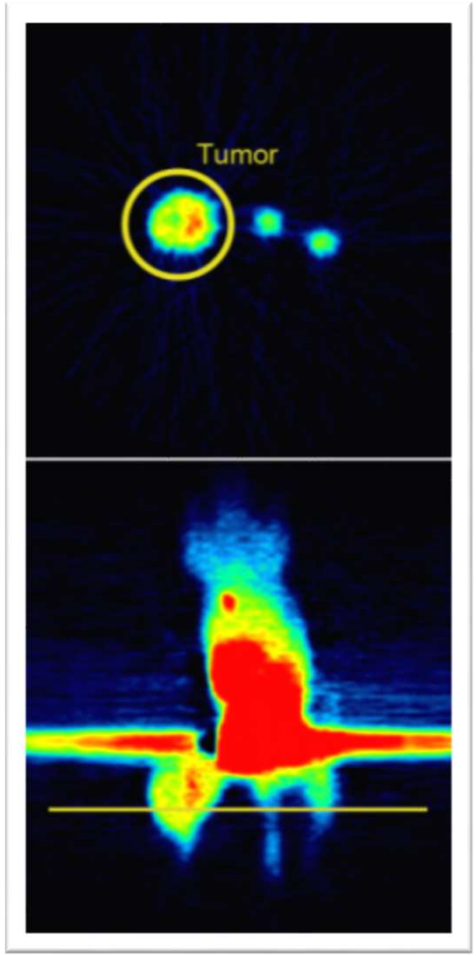
- Improve SNR:
  - → Direct parametric image reconstruction:



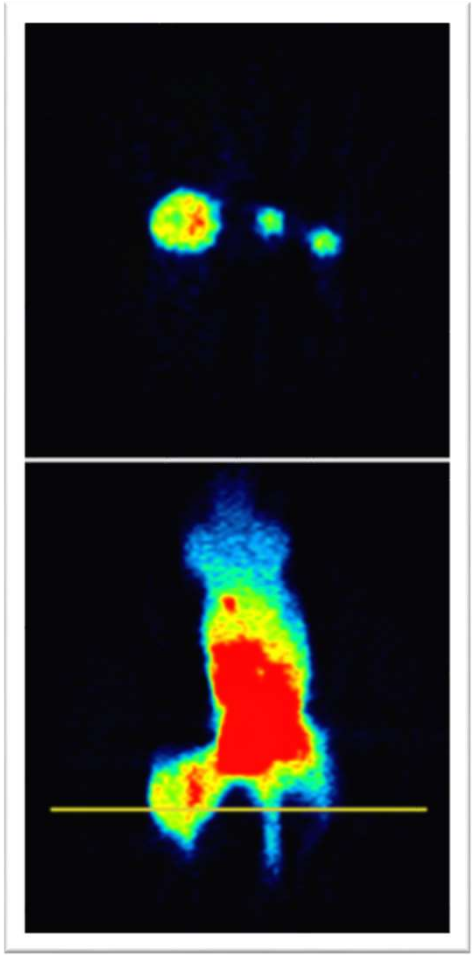
Spatial Information + Temporal Information

Advanced Pharmacokinetic Modeling Computing: Direct Parametric Image Reconstruction

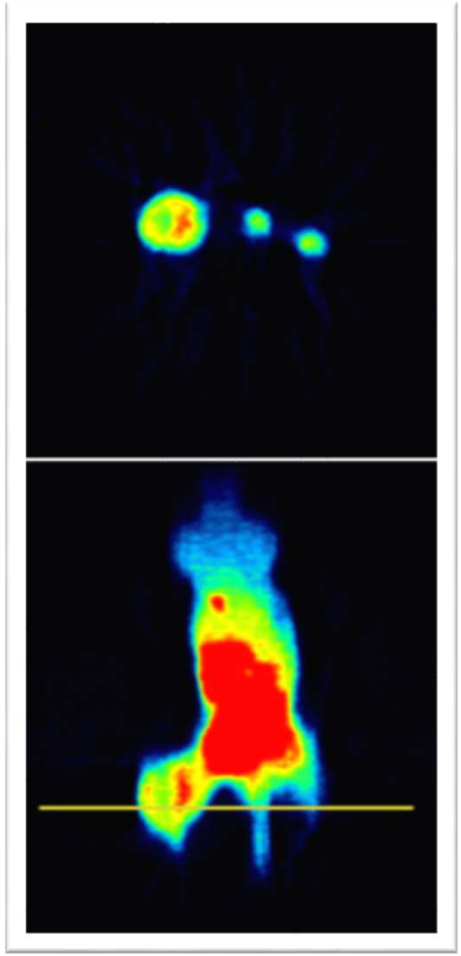
[Cheng et al. Phys. Med. Biol. 2014]



FBP + Patlak Model



OSEM + Patlak Model



POSEM + Patlak Model

Indirect Methods

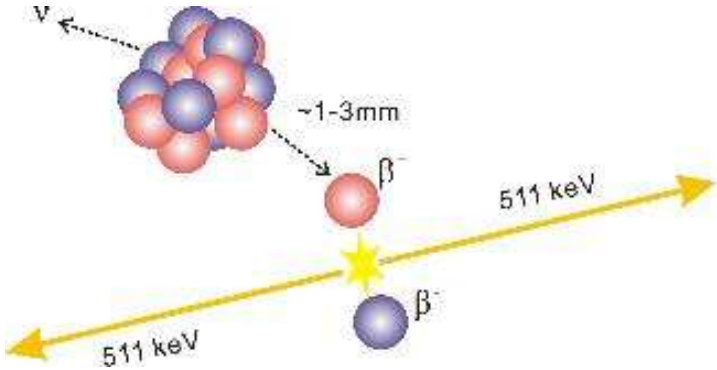
Direct Methods

Advanced Pharmacokinetic Modeling Computing: Multiple Tracer Imaging

- Different tracer: different tumor phenotype
  - [^{18}F]FDG: Glucose metabolism
  - [^{18}F]FMISO: Tumor hypoxia
  - [^{18}F]FLT: Proliferation
  - [^{11}C]Acetate: Oxidative metabolism
- Pulmonary lesion (16 malignant tumor, 16 tuberculosis, 23 benign lesions)
  - [^{18}F]FDG: sensitivity 87.5% specificity 59.0%
  - [^{18}F]FLT: sensitivity 68.8% specificity 76.9% *[Tian et al. J Nucl Med 2008]*
  - [^{18}F]FDG+[^{18}F]FLT: sensitivity 100% specificity 89.7%
- Hepatocellular carcinoma (99 HCC, 13 cholangiocellular carcinoma)
  - [^{18}F]FDG: sensitivity 60.9% *[Park et al J Nucl Med 2008]*
  - [^{11}C]Acetate: sensitivity 75.4%
  - [^{18}F]FDG+[^{11}C]Acetate: sensitivity 82.7%

Advanced Pharmacokinetic Modeling Computing: Multiple Tracer Imaging

- Multi-Tracers and Multi-Scans
  - Additional dose from multiple CT scans
  - Registration problem
  - Staff-consuming, time-consuming



- Multiple Tracer in one Scan, technical challenging:
  - Different isotopes emitting positrons of different energy
  - The gamma photons generated by positron annihilation: save energy level (511KeV)
  - Can not be physically differentiated

- Identify the individual tracer based on intrinsic pharmacokinetic differences

Advanced Pharmacokinetic Modeling Computing: Multiple Tracer Imaging

[Cheng et al IEEE Trans Med Imaging 2015]

Challenges:

- Multi-tracer Model → **High fitting dimension**
- Voxel-wise fitting → **Low SNR of individual TAC**

→ Difficult for tracer separation

Objective:

- Reduced parameter space formulation **(RPS formulation)** [Kadrmas 2012,2013] → **Dimension reduction**
- Direct parametric image reconstruction **(DPIR)** → **Spatio-temporal consistency**

→ **Improve tracer separation**

Advanced Pharmacokinetic Modeling Computing: Multiple Tracer Imaging

Parameter Space Reduction

1. Formulate the original multi-tracer model (parameters $\boldsymbol{k}$) with parameters $\boldsymbol{\theta}$ and $\boldsymbol{\nu}$
2. Regularize the model with the measured TAC C_t as prior knowledge

$$\frac{\partial \boldsymbol{WSSE}}{\partial \boldsymbol{\theta}} = \frac{\partial}{\partial \boldsymbol{\theta}} \left\{ \sum_{t=1}^{N_T} \omega_t \, (C_t - \hat{C}_t)^2 \right\} = 0$$

3. Results in the representation of $\hat{C}_t$ with $\boldsymbol{\nu}$ instead of original parameter $\boldsymbol{k}$;

Direct image reconstruction

[Cheng, …, Shi. MICCAI 2013]
[Cheng, …, Shi. PMB 2014]

1. EM reconstruction of dynamic PET images

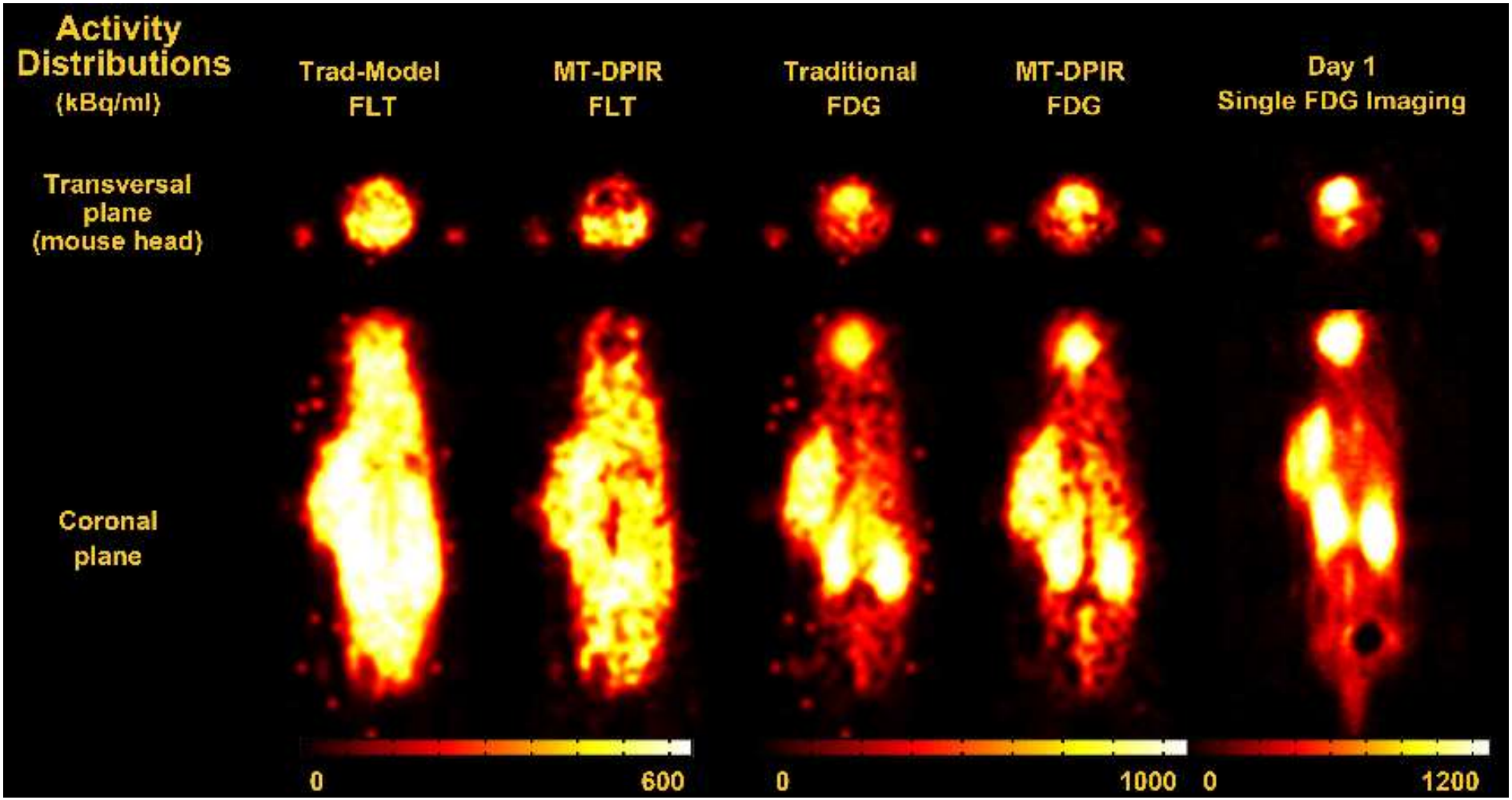
$$\hat{x}_{jt}^{(n+1)} = \frac{x_t(\boldsymbol{\nu}_j^{(n)})}{\sum_i a_{ij}} \sum_i a_{ij} \frac{y_{it}}{\sum_{j'} a_{ij'} x_t\left(\boldsymbol{\nu}_{j'}^{(n)}\right) + \boldsymbol{r}_t + \boldsymbol{s}_t}$$

2. Voxel-wise weighted nonlinear least square fitting (WNLS)

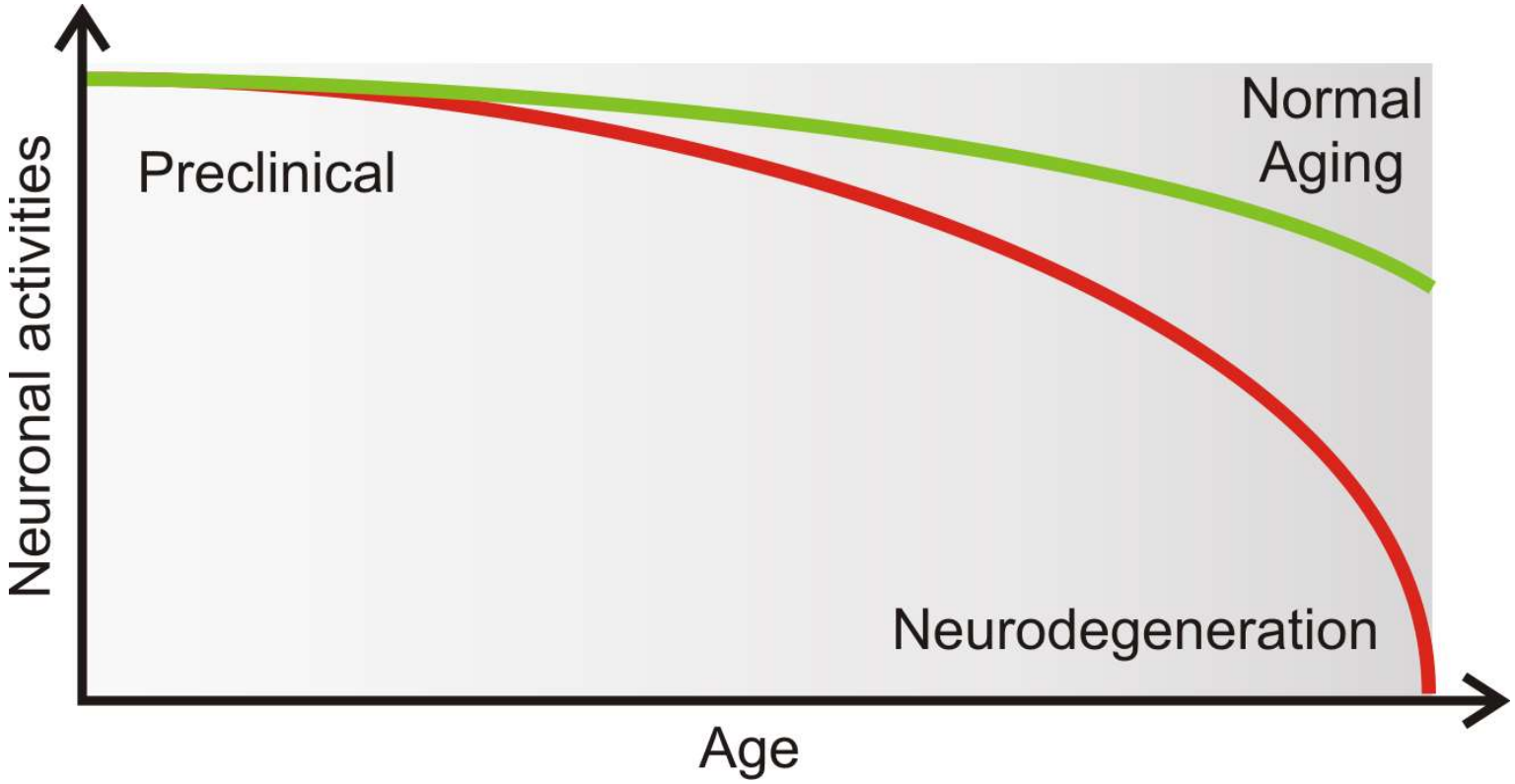
$$\boldsymbol{\nu}_j^{(n+1)} = \min_{\boldsymbol{\nu}} \sum_{jt} \omega_{jt} (\hat{x}_{jt}^{(n+1)} - \underbrace{x_t(\boldsymbol{\nu}_j^{(n)})}_{\text{Nonlinear RPS-Model}})^2$$

Advanced Pharmacokinetic Modeling Computing: Multiple Tracer Imaging

Selected Results



Semi-Quantitative Analysis: Intensity Normalization for Age Adjustment



- Confounding factor on metabolic signal: age-associated metabolic change
- Early diagnosis may be more susceptible to this confounding factor

Semi-Quantitative Analysis: Intensity Normalization for Age Adjustment

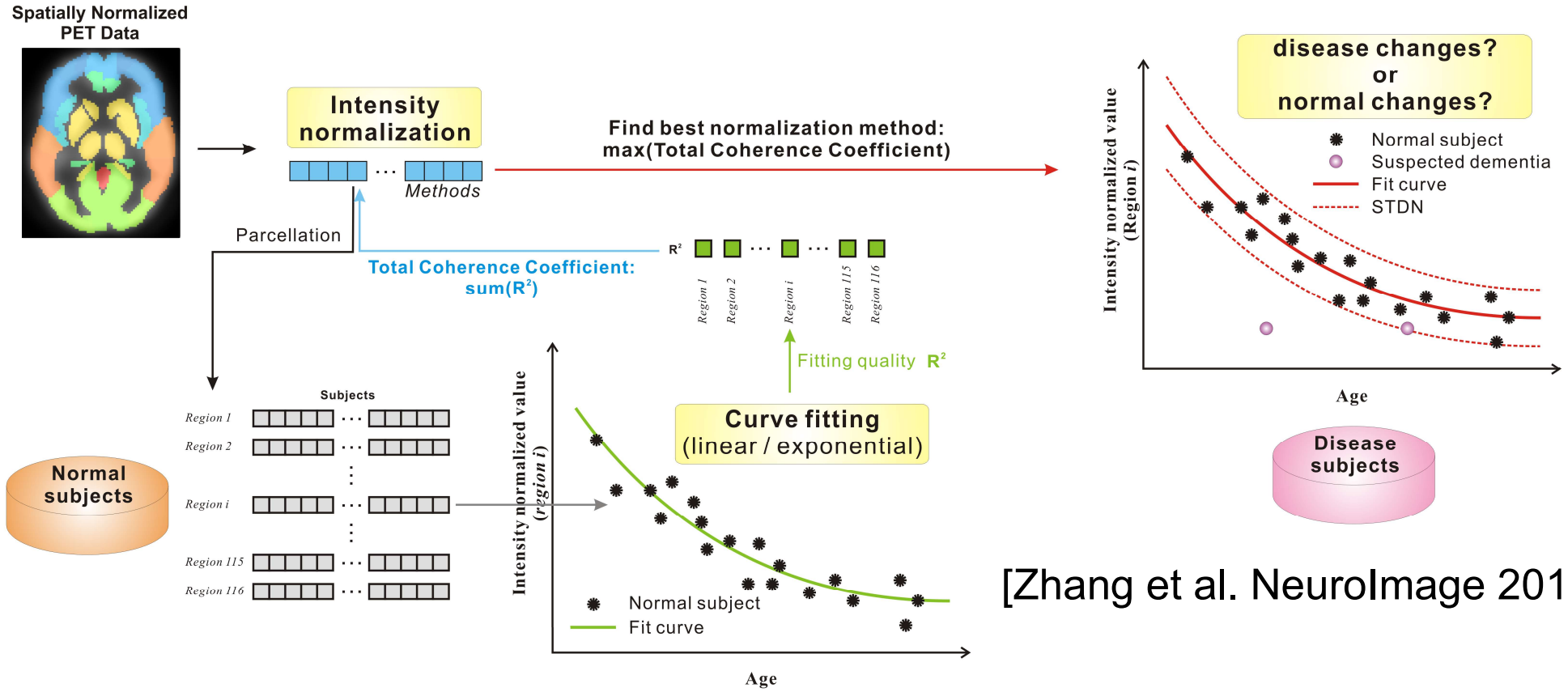
Parkinsonism

- Atypical parkinsonian syndromes [Goldman & Tanner 1998]
  - Multiple System Atrophy (MSA)
  - Progressive Supranuclear Palsy (PSP)
  - Look like Parkinson's Disease (PD) but much more severe
- About 20% of PD patients were misdiagnosed
- Diagnostic error → wrong treatment

How to differentiate the parkinsonism during the early stages of disease?

Semi-Quantitative Analysis: Intensity Normalization for Age Adjustment

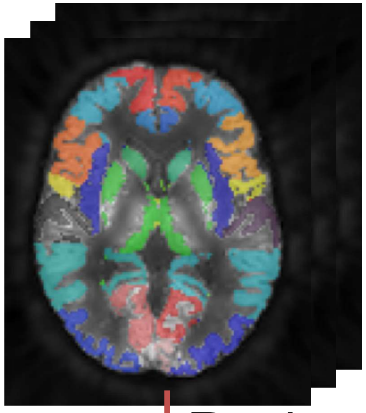
- Identify best normalization to describe age-related changes
- Define a quantity for age adjustment



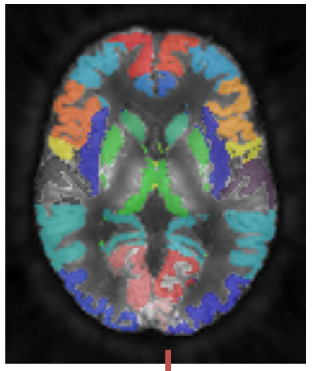
[Zhang et al. NeuroImage 2017]

Semi-Quantitative Analysis: Intensity Normalization for Age Adjustment

[Shi et al., SNMMI 2017]



Database of ^{18}F-FDG PET of Normal Subjects



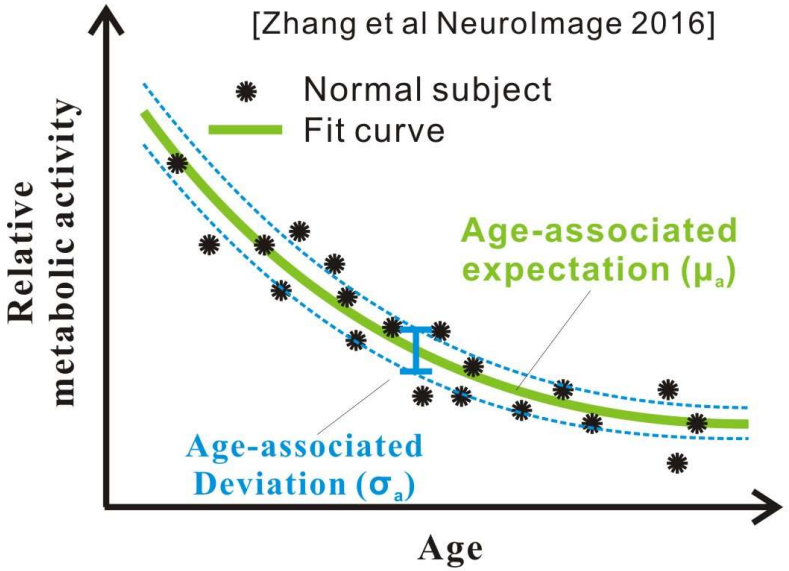
New Subject

Regional average

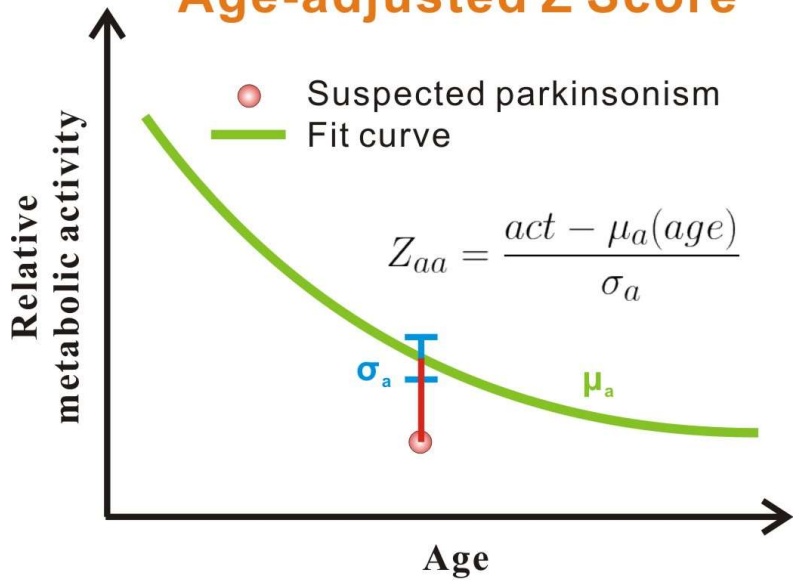
Regional average

Model of Age-related Changes

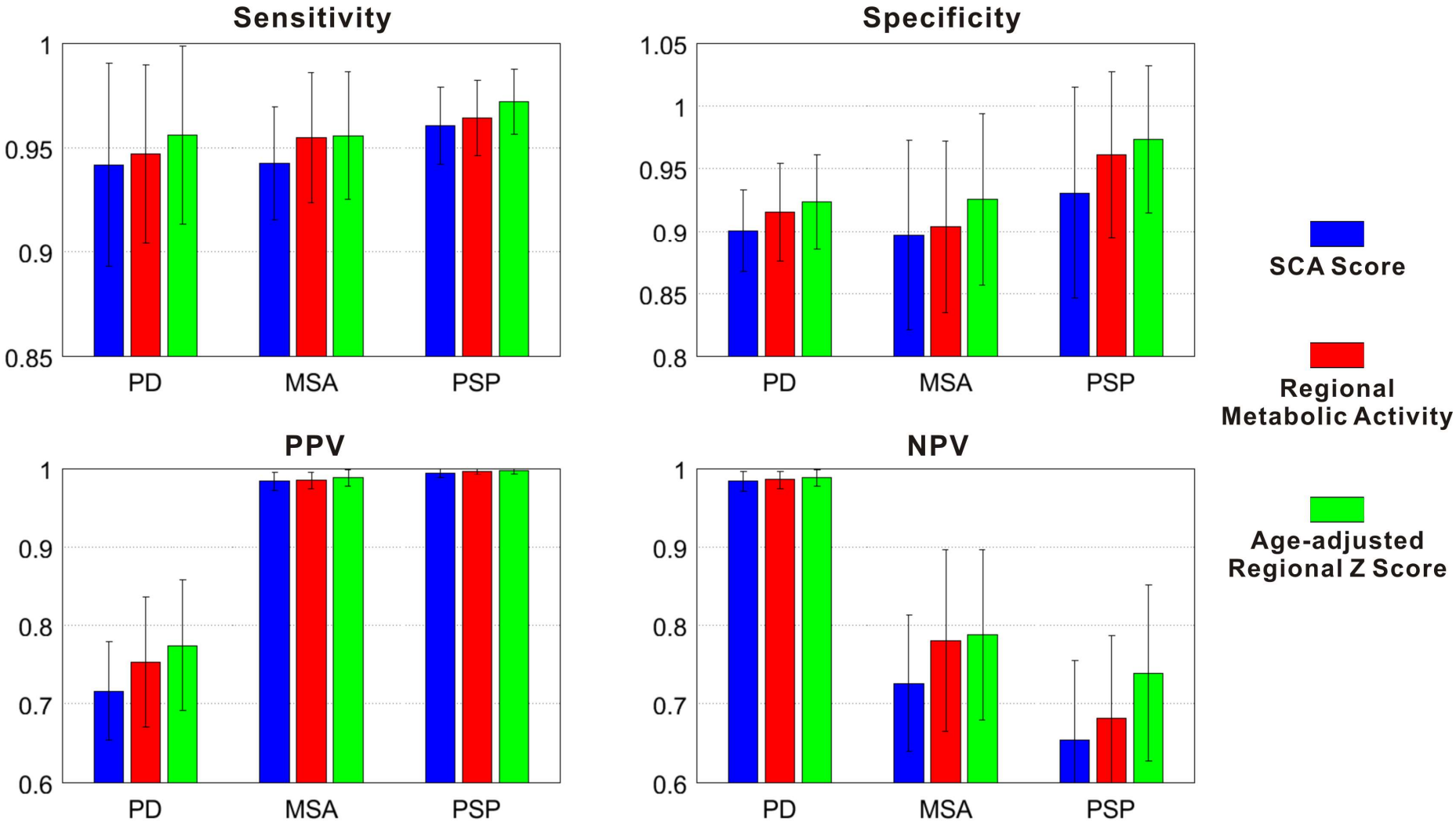
[Zhang et al NeuroImage 2016]



Age-adjusted Z Score



Semi-Quantitative Analysis: Intensity Normalization for Age Adjustment



Take Home Message

- Pharmacokinetic modeling
  - Quantitative analysis
  - Less susceptible to confounding factor but more sensitive to noise
  - Improve the robustness:
    - Linearization
    - Utilization of spatial-temporal consistency: direct parametric image reconstruction, hierarchical modeling
- Intensity normalization
  - Semi-quantitative analysis
  - Easily applicable

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