Deutsche
Gesellschaft
für Nuklearmedizin
e.V.

SUMMER SCHOOL 2015

Translational Research
in Molecular Imaging and Radionuclid Therapy

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Tracer Kinetic Modelling for Quantification
in Nuclear Medicine Imaging

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Quantification by tracer kinetic modelling…

- …what is it all about?
- …is it interesting in research? (example: brain FDG PET)
- …how does it work?
- …is it useful in routine patient care?
- …very short summary

two technical issues (statistical noise, nonlinearity)

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Quantification in nuclear medicine

Level 1 („dosimetry"): tracer concentration (kBq/ml)

Level 2 („diagnostics"): physiological parameters

- metabolic rates (µmol substrate / g tissue / min)
- perfusion (ml blood / g tissue / min)
- receptor density (fmol / mg)
- affinity of tracer for target (nM)
- density of pathological targets (Aß-paques, τ-tangles…)
- …

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[F-18]-fluorodeoxyglucose (FDG): function / target depends on the region of interest

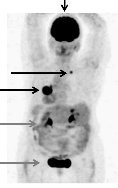
?

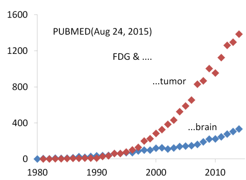
- 20% energy consumption
- 2% body weight

information processing
via neurotransmitter systems

tumor: glycolysis (Warburg effect)

kidneys / bladder: renal clearance





FDG-PET of the brain: surrogate for signaling-related synaptic activity

Kadekaro, Crane, Sokoloff
Proc. Natl. Acad. Sci USA 1985; 82: 6010-13

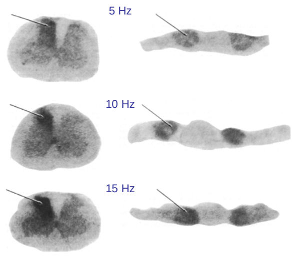
electrical stimulation of sciatic nerve (rat)

C-14-glucose i.v.

45 min uptake period

post mortem autoradiography

*: europil
- axonterminals
- dendritic processes
- astrozytic processes



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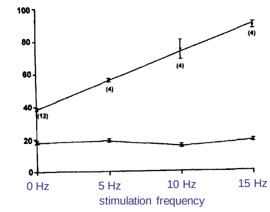
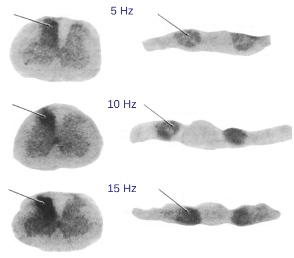
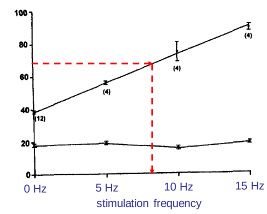
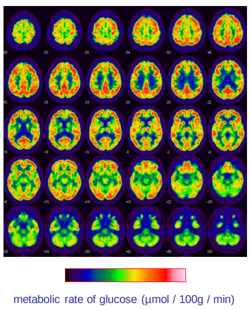




FDG-PET: mapping of spike frequency of the brain („rest“ / stimulation)

Sokoloff, Neurochem Res 1999; 24: 321-329





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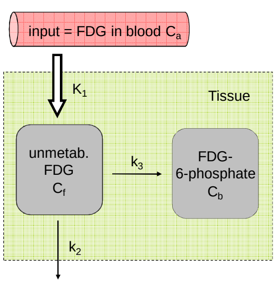
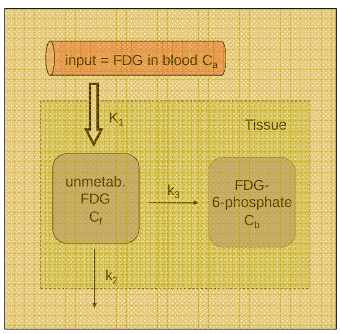
Quantification of physiologic parameters in PET: problem



compartments defined
by function
not localization

Quantification of physiologic parameters in PET: problem



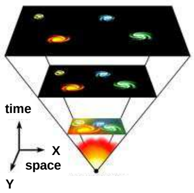
PET image volume element (voxel)

sum of signals from all compartments

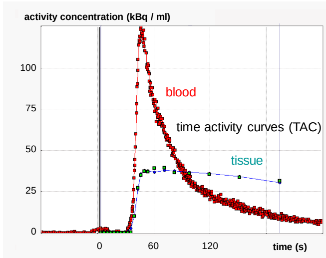
compartments defined by function, not localization

Quantification of physiologic parameters in PET: solution

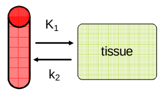
functional compartments might be separated in **time** (rather than space)



Quantification of physiologic parameters: tracer **kinetic** modelling



Compartment model



Workflow

1a) dynamic PET (SPECT) imaging

1b) sampling (arterial) blood (input function)

2. fit model to measured data

(→ „modelling")

3. maps of physiological parameters

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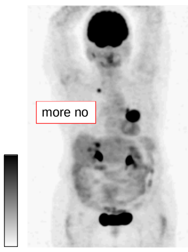
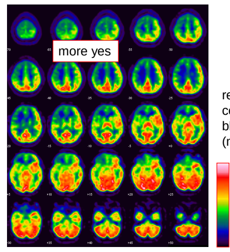
Kinetic modelling: To model or not to model?

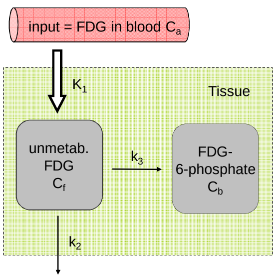
F-18-FDG (glucose metabolism)



O-15-water (perfusion)



FDG PET: quantification versus semi-quantification



$K_i = K_1 * k_3 / (k_2 + k_3)$

semi-quantification

Standardized Uptake Value

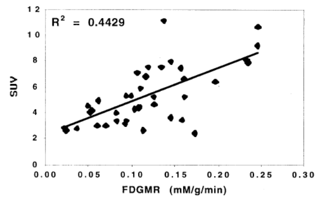
$$\text{SUV} = \frac{\text{tracer concentration in ROI}}{\text{injected tracer dose per kg bw}}$$

FDG-PET: tracer kinetic modelling versus retention image

Graham M et al., Nucl Med & Biol 2000; 27: 647-55

40 patients with colon cancer

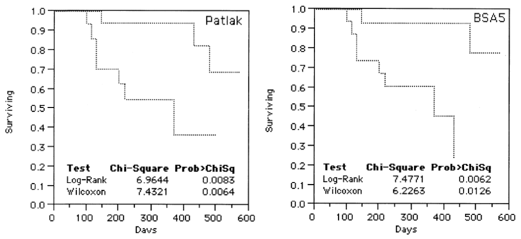
FDG retention
(standardized uptake value, SUV)



metabolic rate of glucose Ki
(kinetic modelling)

FDG-PET: tracer kinetic modelling versus retention image

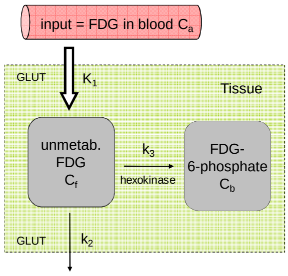
Graham M et al., Nucl Med & Biol 2000; 27: 647-55



metabolic rate of glucose (kinetic modelling, K_i)

FDG retention (standardized uptake value, SUV)

FDG: pharmacokinetics



healthy subjects (brain, euglycemia)
K_1 = 0.07 ml/g/min
k_2 = 0.12 min^{-1}
k_3 = 0.04 min^{-1}

- phosphorylation is irreversible
- single pass extraction fraction is small

$K_1 = E * F$

F = perfusion (ml / 100g / min)

E = extraction = $1 - \exp(-PS/F)$ (Renkin-Crone)

PS = permeability surface area product

$E \approx 1 - (1 - PS/F) = PS/F$

$K_1 = E * F \approx PS/F * F = PS$

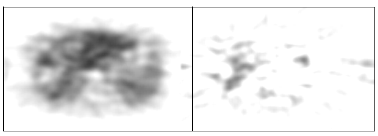
i.e., K_1 independent of perfusion

FDG retention ~ metabolic rate

FDG: cave in extreme conditions

Recurrence of hepatocellular carcinoma after chemoembolisation

FDG retention | metabolic rate of glucose

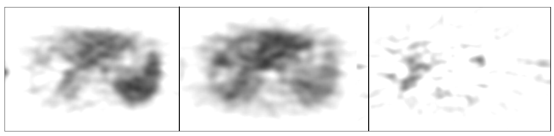


adapted from Wolfgang Burchert, Bad Oeynhausen

FDG: cave in extreme conditions

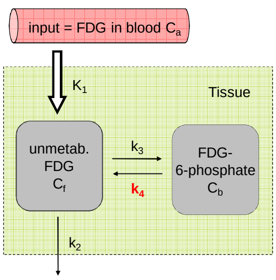
Recurrence of hepatocellular carcinoma after chemoembolisation

perfusion ($H_2{}^{15}O$) | FDG retention | metabolic rate of glucose

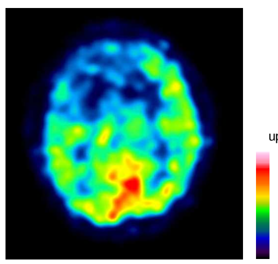


adapted from Wolfgang Burchert, Bad Oeynhausen

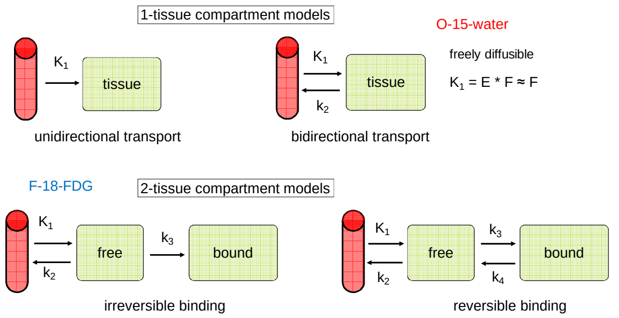
FDG: cave liver



O-15-water



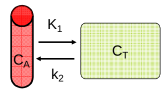
Compartment models



Bidirectional transport

graphical representation

formula representation



one-to-one

$$\frac{dC_T}{dt} = K_1 C_A - k_2 C_T$$

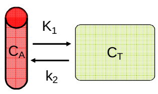
(analytical) solution

$$C_T = K_1 \int_0^t e^{-k_2(s-t)} C_A(s)ds$$

operational equation

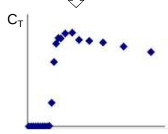
PET signal (time activity curve)

Fitting



$$C_T = K_1 \int_0^t e^{-k_2(s-t)} C_A(s)ds$$

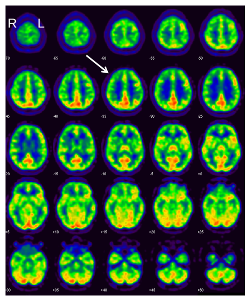
fit

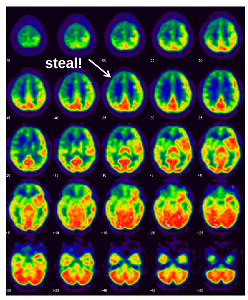


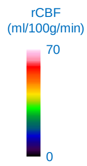
Perfusion reserve capacity

rest

maximum dilatation of blood vessels (Diamox)







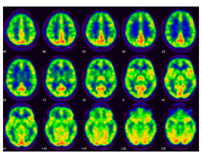
Female, 16 y, Moyamoya disease

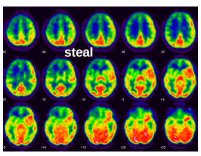
Perfusion reserve capacity

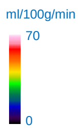
rest

Diamox

rCBF

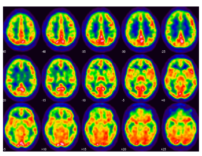


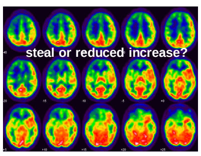


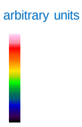


uptake

integral of 60 s after arrival in brain

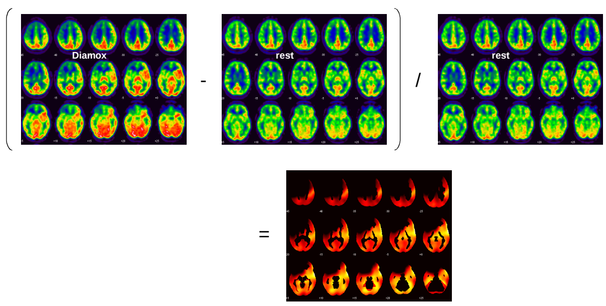






Female, 16 y, Moyamoya disease

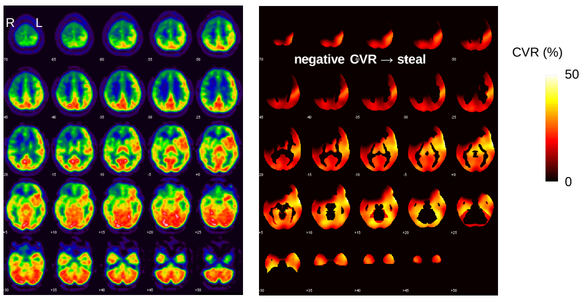
Image algebra



Perfusion reserve capacity

Diamox

cerebrovascular reserve (%)
= 100*(Diamox-rest)/rest



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- …what is it all about?
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- …very short summary

two technical issues (statistical noise, nonlinearity)

Quantification by tracer kinetic modelling…

- …what is it all about?
  - quantitative estimates of physiological parameters
- …is it interesting in research? (example: brain FDG PET)
  - yes!
- …how does it work?
  - expensive
- …is it useful in routine patient care?
  - yes, but for a few indications only

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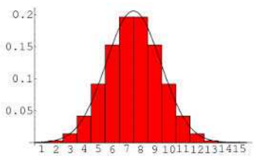
„technical“ issue: statistical noise

probability

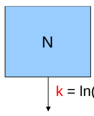


number of radioactive decays

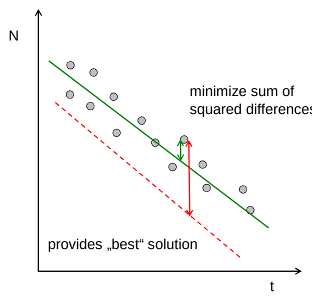
How to handle statistical noise

aim: determine half-life time of a radioactive source

model:



$k = \ln(2)/T_{1/2}$

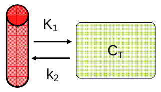


solution (operational equation):

$N = N_0 * \exp(-kt)$

$\ln(N) = \ln(N_0) - kt$

„technical“ issue: nonlinearity



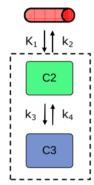
⟺

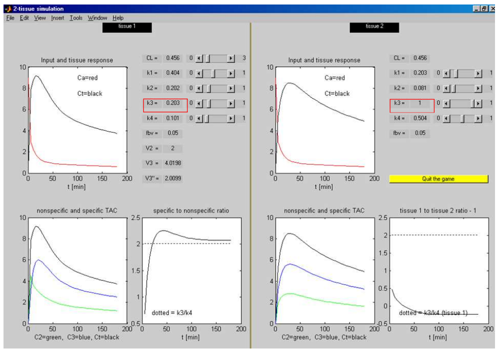
$$C_T = K_1 \int_0^t e^{-k_2 (s-t)} C_A(s) ds$$

nonlinear operational equation

(with respect to the rate constants)

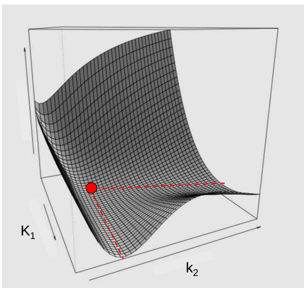
Nonlinearity → „ill-conditioned“





How to handle nonlinearity

sum of squared differences



No method that guarantees identification of the global minimum

particularly in presence of noise

Thank you!