Tracer kinetic modelling
Basic concepts

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What is tracer kinetic modelling?

- Mathematical discription of a tracer behavior in the body
- From the mathematical description the physiological system can be examined

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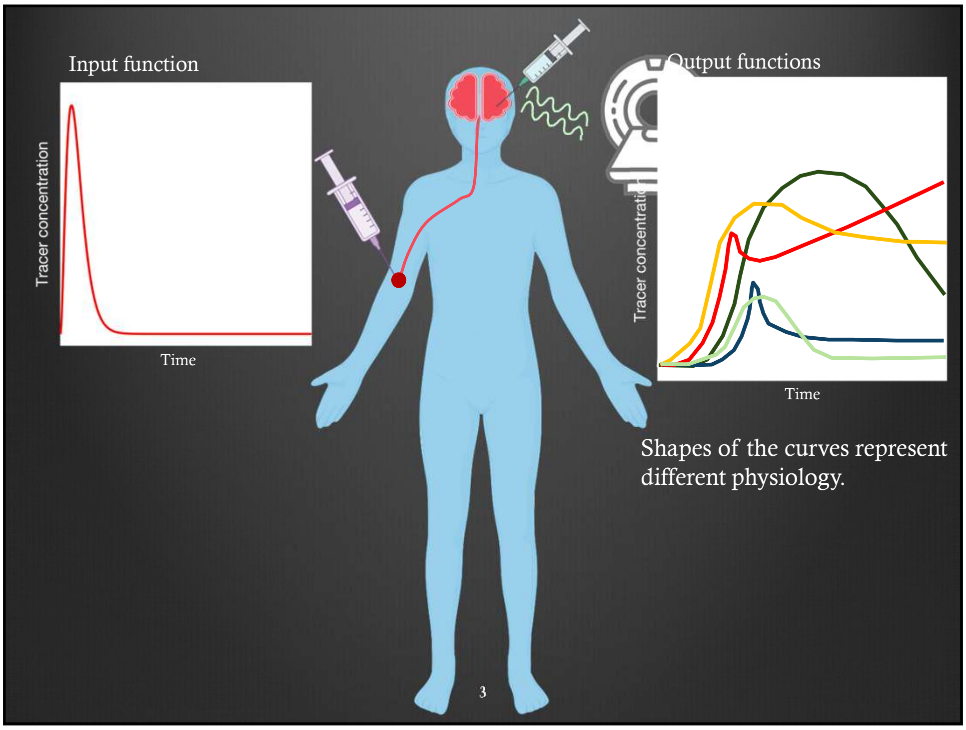
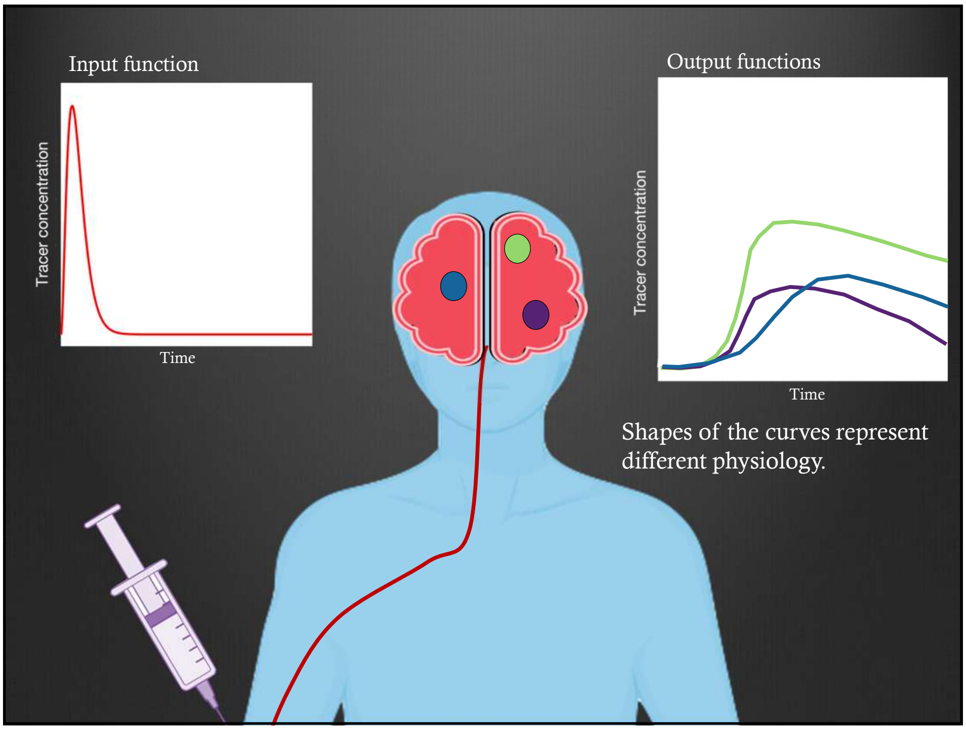

Input function
Tracer concentration
Time
Output functions
Tracer concentration
Time
Shapes of the curves represent different physiology.
3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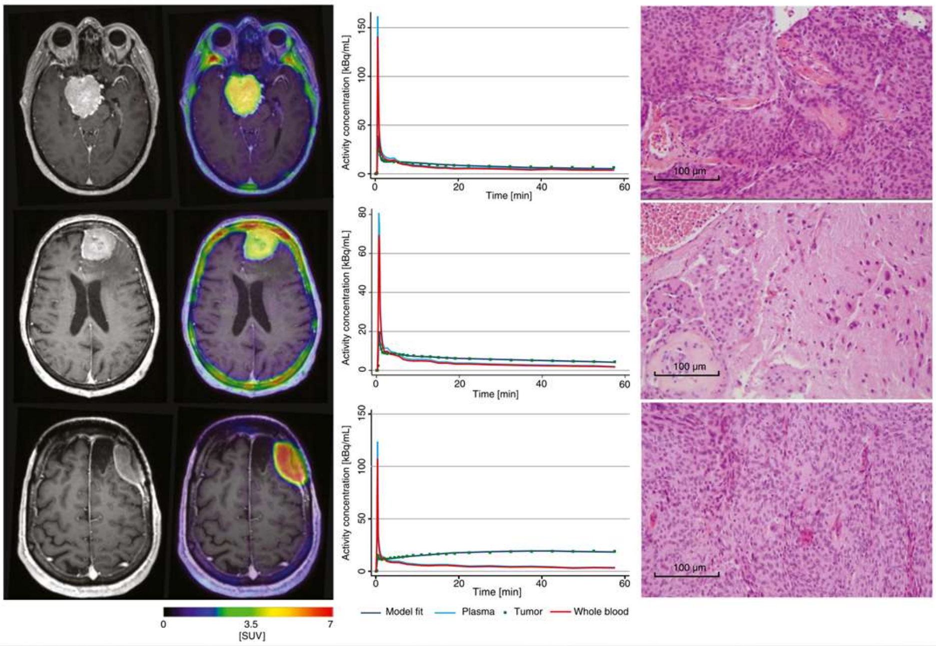


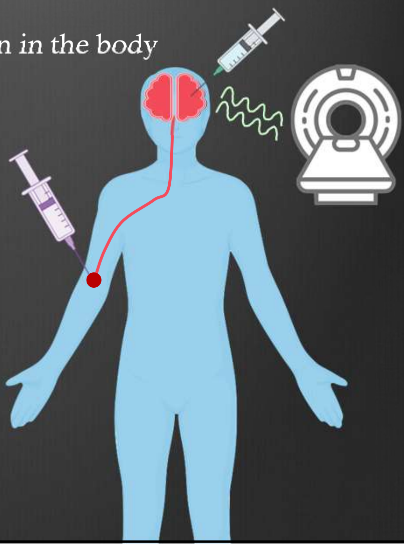
Asma Bashir et al. European Journal of Nuclear Medicine and Molecular Imaging (2020) 47:1496–1509

What is tracer kinetic modelling?

- Mathematical discription of a tracer behavior in the body
- From the mathematical description the physiological system can be examined
- A tracer is injected in a physiological system
- The dynamic changes of the tracer concentration in the tissue is measured
  - Tracer concentration as a function of time
- Create a mathematical model which relate tracer input to measured tracer concentration in tissue

Tracers

- Injected into the body
- Measure the tracer concentration *in the body*
  - Radioactive
  - Affect MRI-signal
  - Blood sampling
  - Other



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Tracers

- Tracer should provide information of certain physiology
  - Labelled substances, (nearly) behaving physically and chemically like the mother substance
    - ^{15}O-H$_2$0, ^{18}F-FDG
  - Indicators not related to a mother substance
    - MRI gadolinium based agents, 99mTc-HMPAO
  - Tracer binding to certain receptors
    - Somatostatin receptors, Serotonin receptors, Vascular endothelial growth factor receptors
- Tracers can be intravascular,extracellular, free difussible, bound to a receptor or behave in a more specific way.
- New tracers er being developed

Should not disturb the system we are studying!

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Mathematics to describe the tracer concentration

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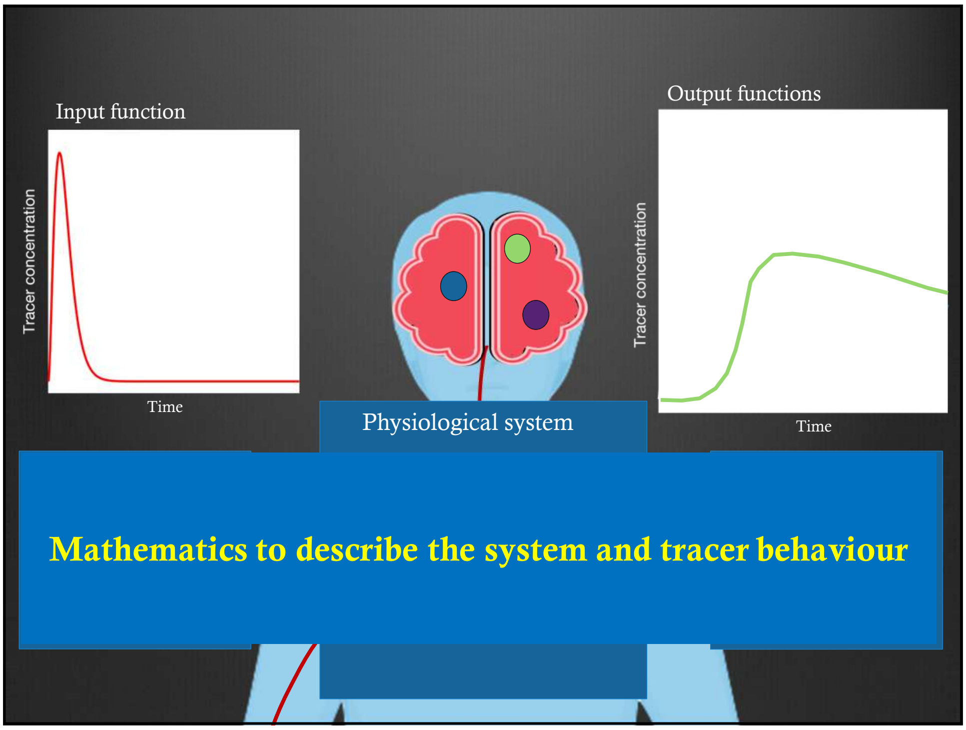


- Mathematical describe the tracer behavior in the physiological system
- The mathematical mo
- logy is
- metho
- veryth
- Choose a model that
- wanted phenomenon

Input functions

Arterial input function
$C_a(t)$

Physiological system

Mathematical model

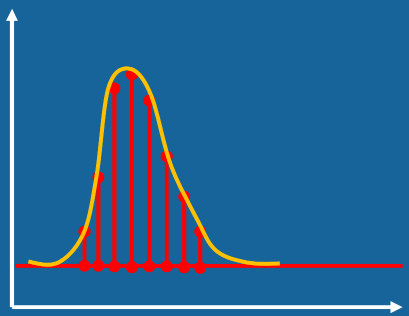
Output functions

Tissue functions
Tissue curves
TAC (time-activity curve)
Tissue enhancement curve
$C_t(t)$, $C_{tissue}(t)$

Impulse response

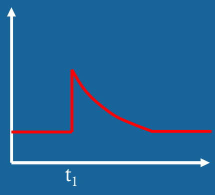
Description of system by impulse response function

Input function described as a series of delta functions



em
response
(t)

Impulse response function



theoretically with zero width
delta function

Linearity of a system

RF(t)

x → y

RF(t)

scaling a x → a y

HBWL

Linearity of a system

x_1

RF(t) y_1 y_2

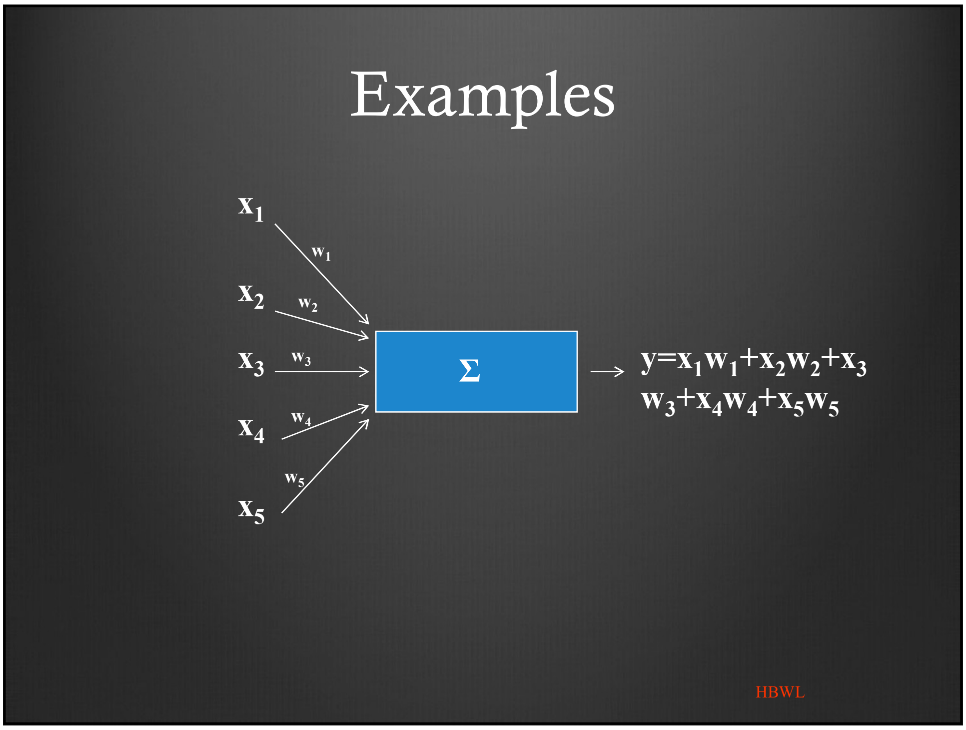
x_2

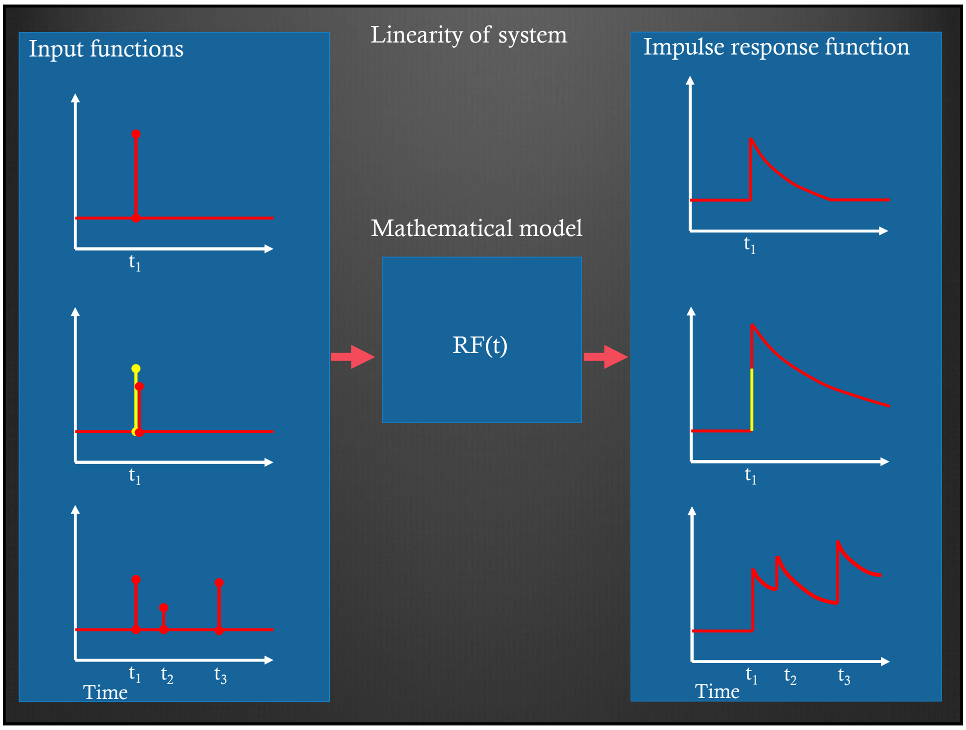
RF(t)

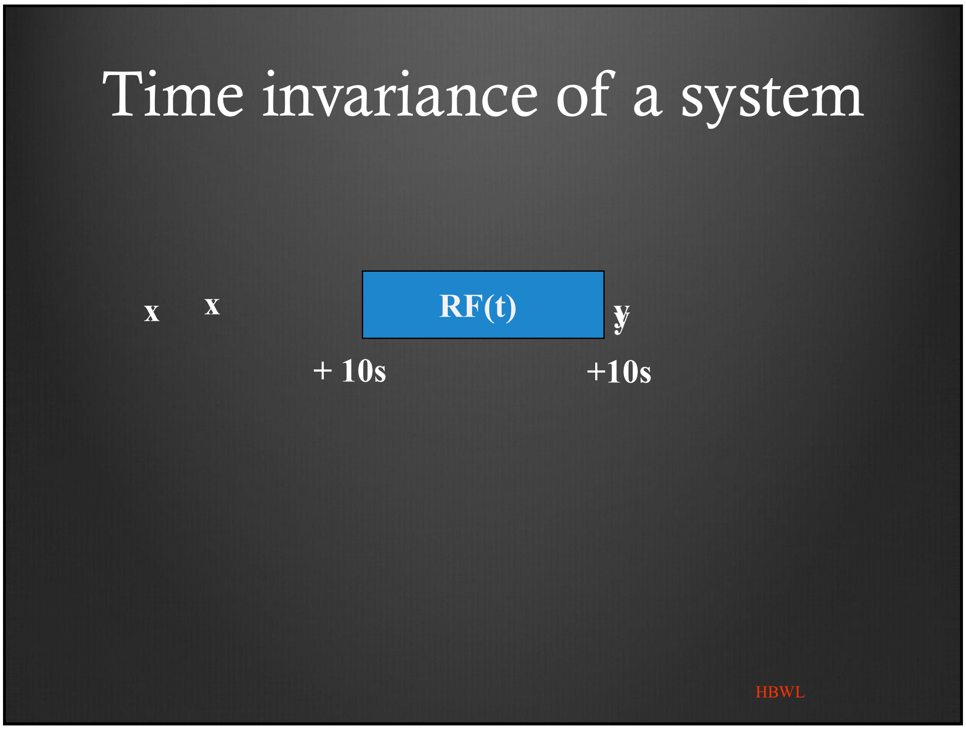
$x_1 + x_2$ → $y_1 + y_2$

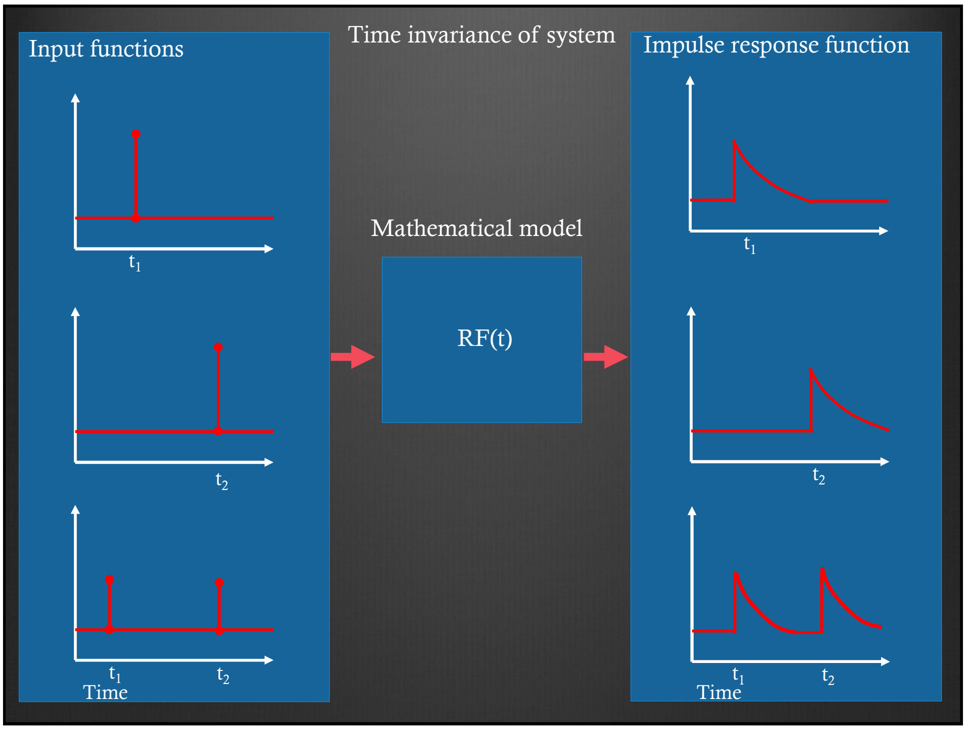
Principle of superposition

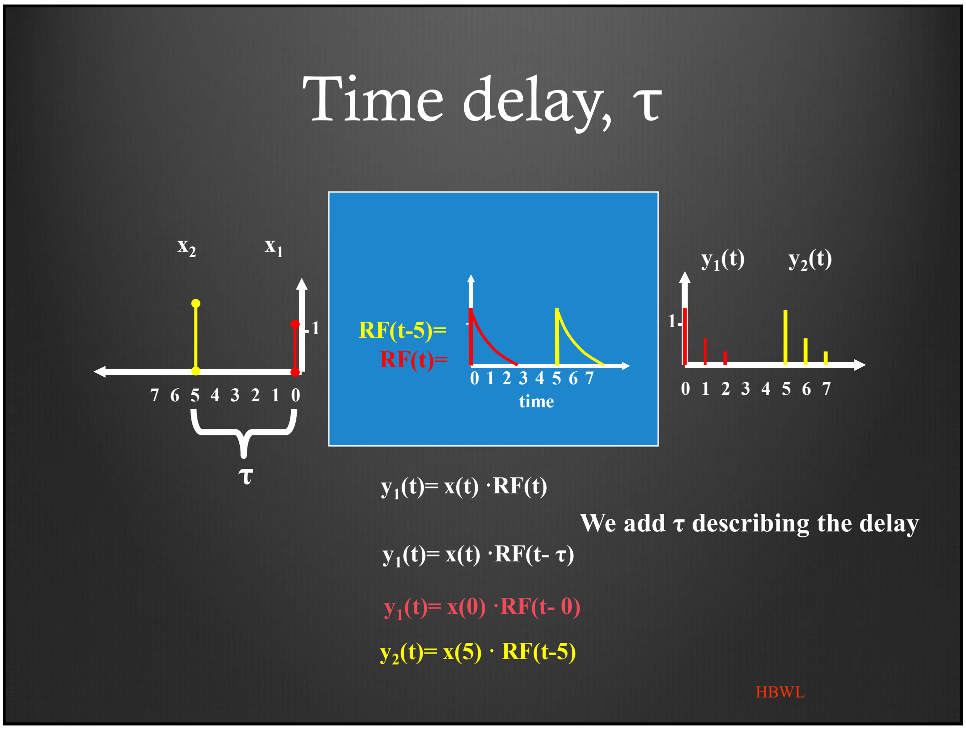
HBWL

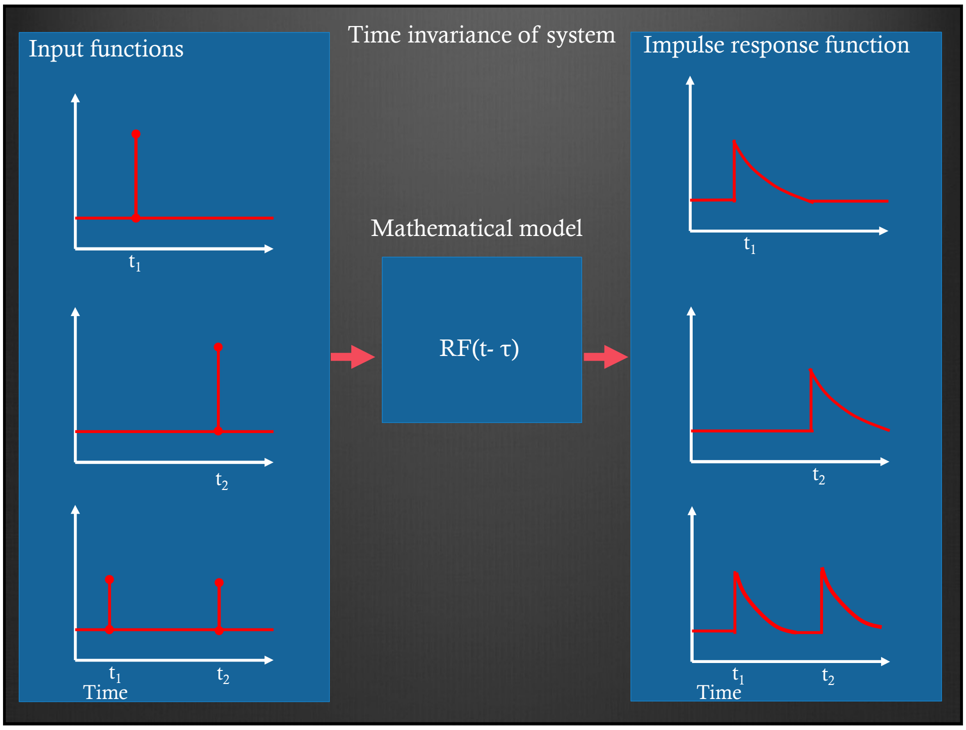

Examples
x1
x2
x3
x4
x5
w1
w2
w3
w4
w5
Σ
y=x1w1+x2w2+x3w3+x4w4+x5w5
HBWL


Input functions
Linearity of system
Impulse response function
Mathematical model
RF(t)
t1
t1
t1 t2 t3
Time
t1
t1
t1 t2 t3
Time


Time invariance of a system
x
x
RF(t)
y
+ 10s
+10s
HBWL


Input functions
Time invariance of system
Impulse response function
Mathematical model
RF(t)
t1
t2
t1
t2
Time
t1
t2
t1
t2
Time


Time delay, τ
x2
x1
1
7 6 5 4 3 2 1 0
τ
RF(t-5)=
RF(t)=
0 1 2 3 4 5 6 7
time
y1(t)
y2(t)
1
0 1 2 3 4 5 6 7
y1(t)= x(t) ·RF(t)
We add τ describing the delay
y1(t)= x(t) ·RF(t- τ)
y1(t)= x(0) ·RF(t- 0)
y2(t)= x(5) · RF(t-5)
HBWL


Input functions
Time invariance of system
Impulse response function
t1
t2
t1
t2
Time
Mathematical model
RF(t- τ)
t1
t2
t1
t2
Time

Causality of a system

Output is only observed after an input has enter the system

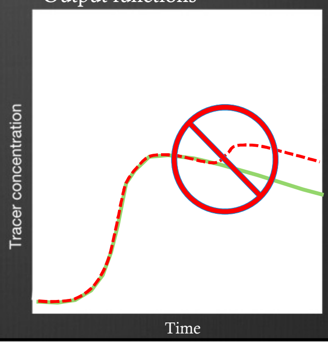
x **RF(t)** **y**

HBWL

Steady state of the system

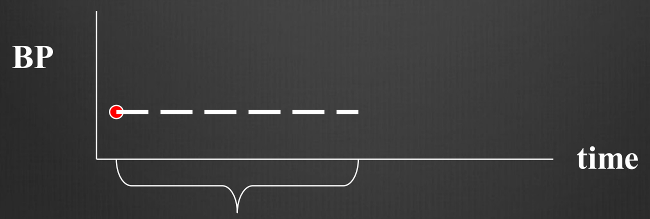
- The physiologic parameter is constant during the measurement
- Examples: Blood flow, glucose uptake
- Consider: duration of the measurement in relation to the a spontaneous change of the parameter or timing of a pertubation of the parameter

Output functions



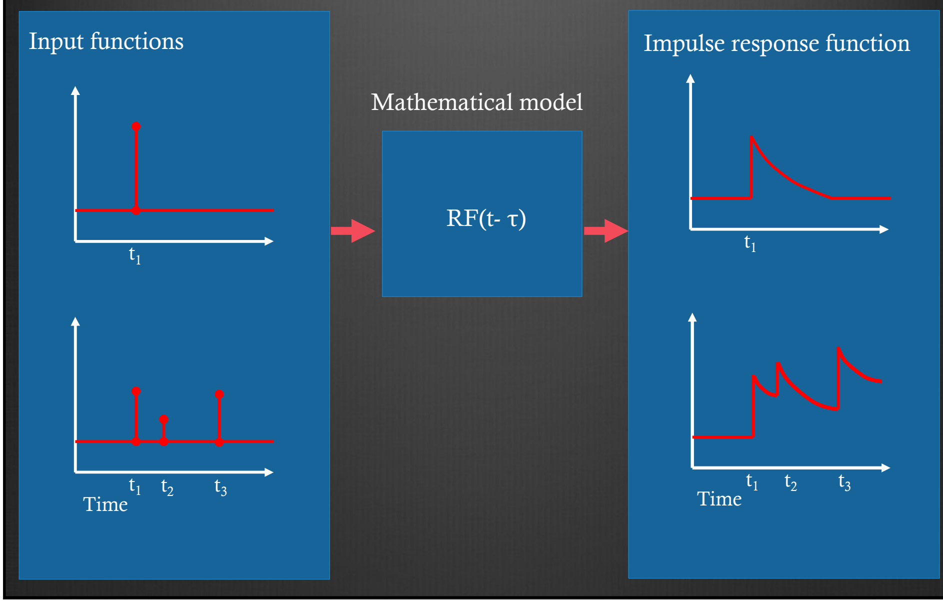
Steady state of the system

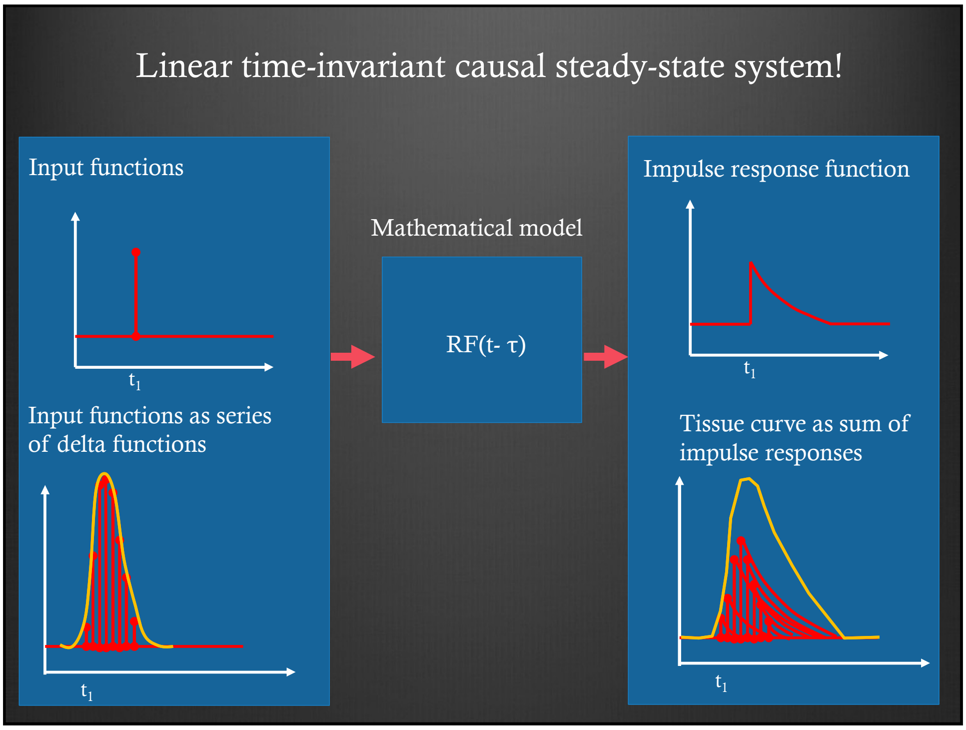
- Exceptions: the physiologic parameter oscillates relative fast compared to the duration of the measurement
- Note: steady state not necessary implies that fluxes or concentration is constant in time

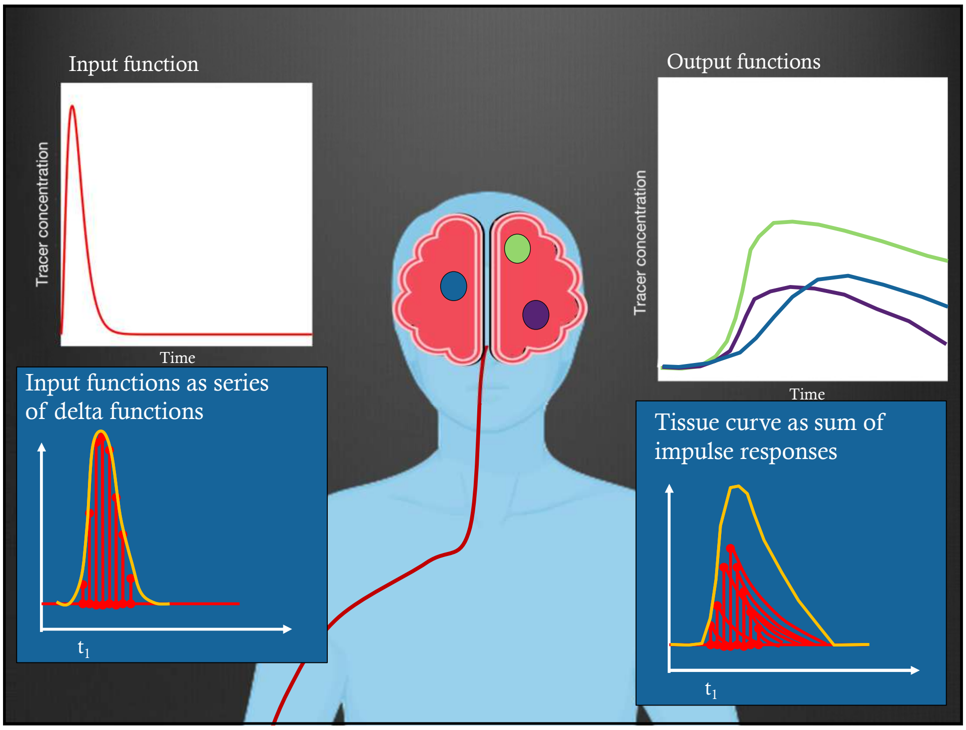


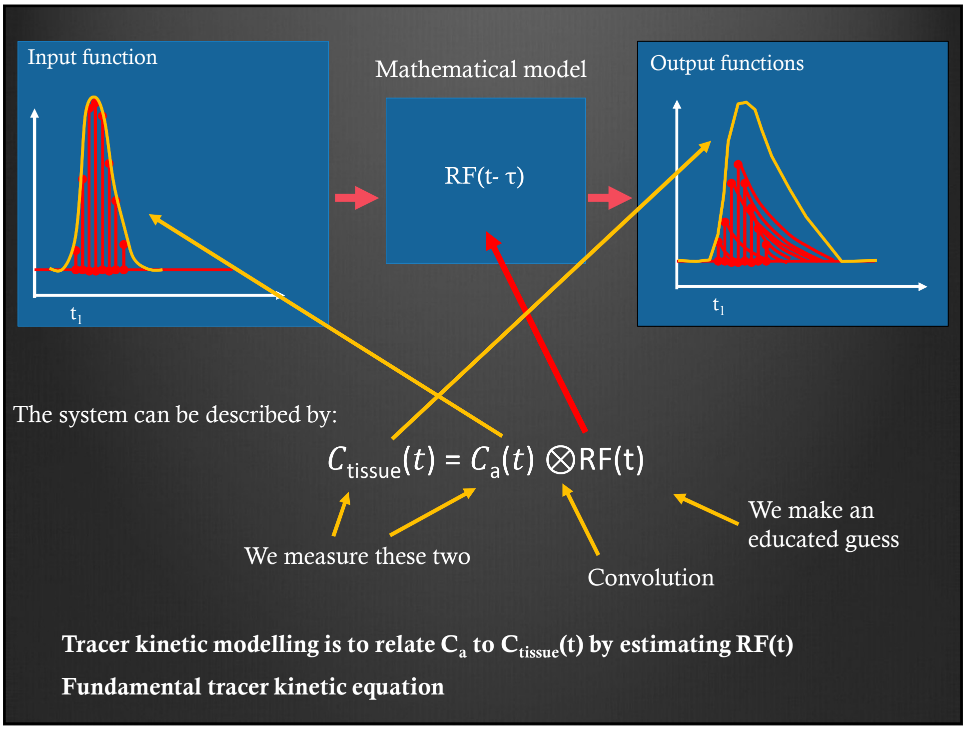
HBWL

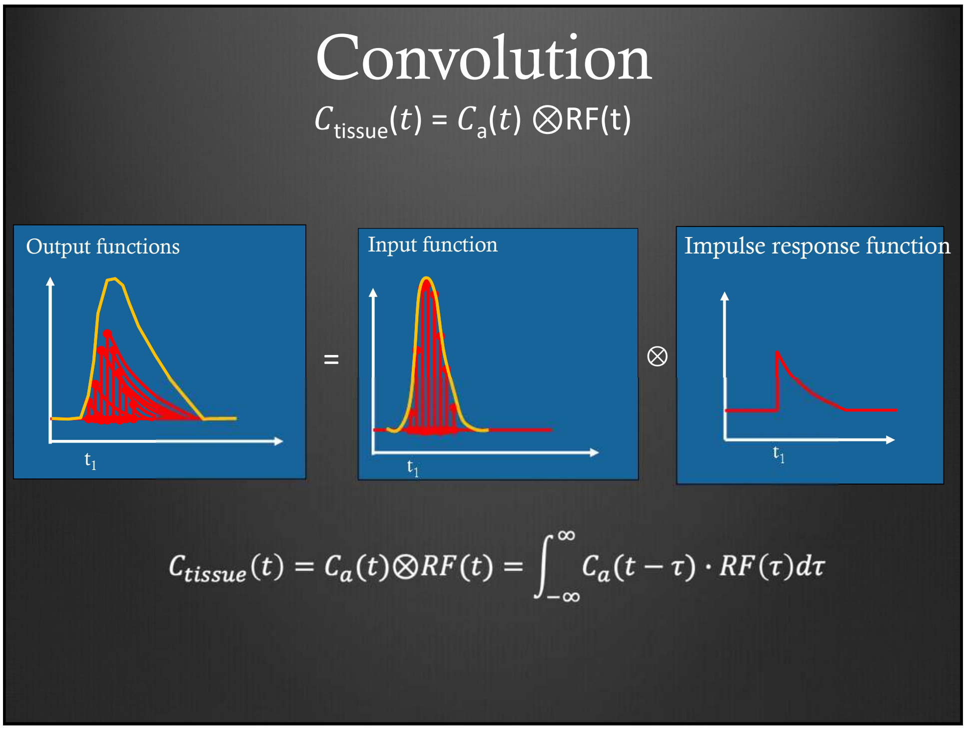
Linear time-invariant causal steady-state system!




Linear time-invariant causal steady-state system!
Input functions
t1
Input functions as series of delta functions
t1
Mathematical model
RF(t- τ)
Impulse response function
t1
Tissue curve as sum of impulse responses
t1


Input function
Tracer concentration
Time
Input functions as series of delta functions
t1
Output functions
Tracer concentration
Time
Tissue curve as sum of impulse responses
t1


Input function
Mathematical model
Output functions
RF(t- τ)
t_1
t_1
The system can be described by:
$C_{tissue}(t) = C_a(t) \otimes RF(t)$
We measure these two
Convolution
We make an educated guess
Tracer kinetic modelling is to relate C_a to $C_{tissue}(t)$ by estimating RF(t)
Fundamental tracer kinetic equation


Convolution
$C_{tissue}(t) = C_a(t) \otimes RF(t)$
Output functions
=
Input function
⊗
Impulse response function
t_1
t_1
t_1
$C_{tissue}(t) = C_a(t) \otimes RF(t) = \int_{-\infty}^{\infty} C_a(t-\tau) \cdot RF(\tau) d\tau$

$$C_{tissue}(t) = C_a(t) \otimes RF(t) = \int_{-\infty}^{\infty} C_a(t-\tau) \cdot RF(t) d\tau$$

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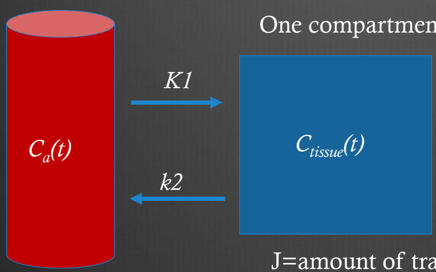
Simple model

One compartment model



J=amount of tracer in compartment

$$J = K_1 C_a(t) - k_2 C_{tissue}(t)$$

$$\frac{dC_{tissue}(t)}{dt} = K_1 C_a(t) - k_2 C_{tissue}(t)$$

$$C_{tissue}(t) = C_a(t) \otimes K_1 e^{-k_2 t} \rightarrow C_{tissue}(t) = C_a(t) \otimes \mathrm{RF}(t)$$

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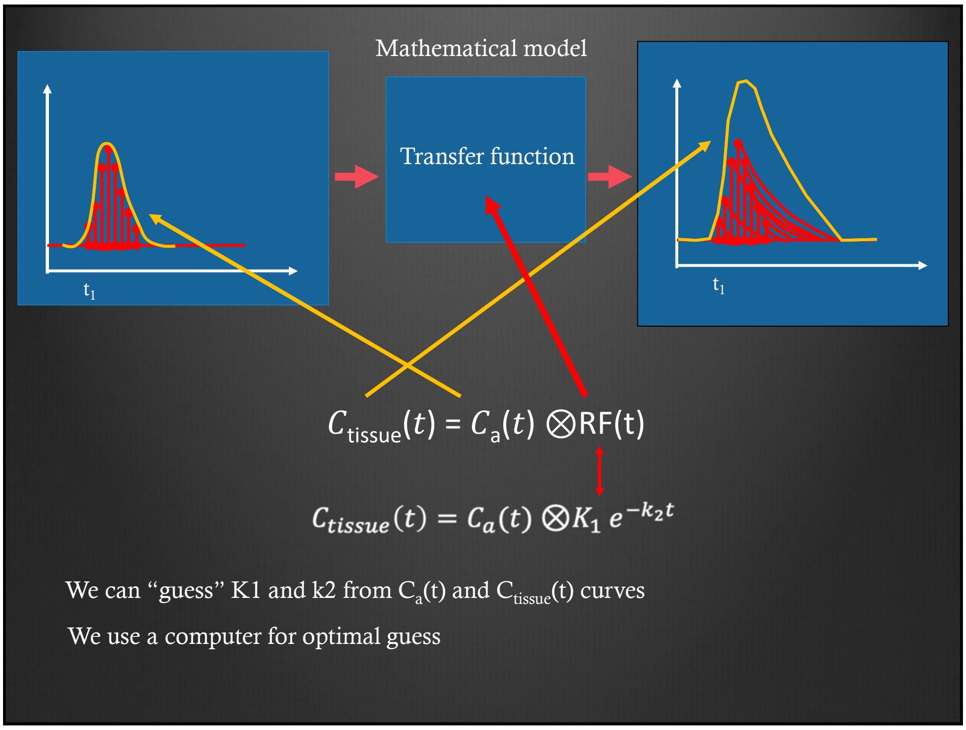
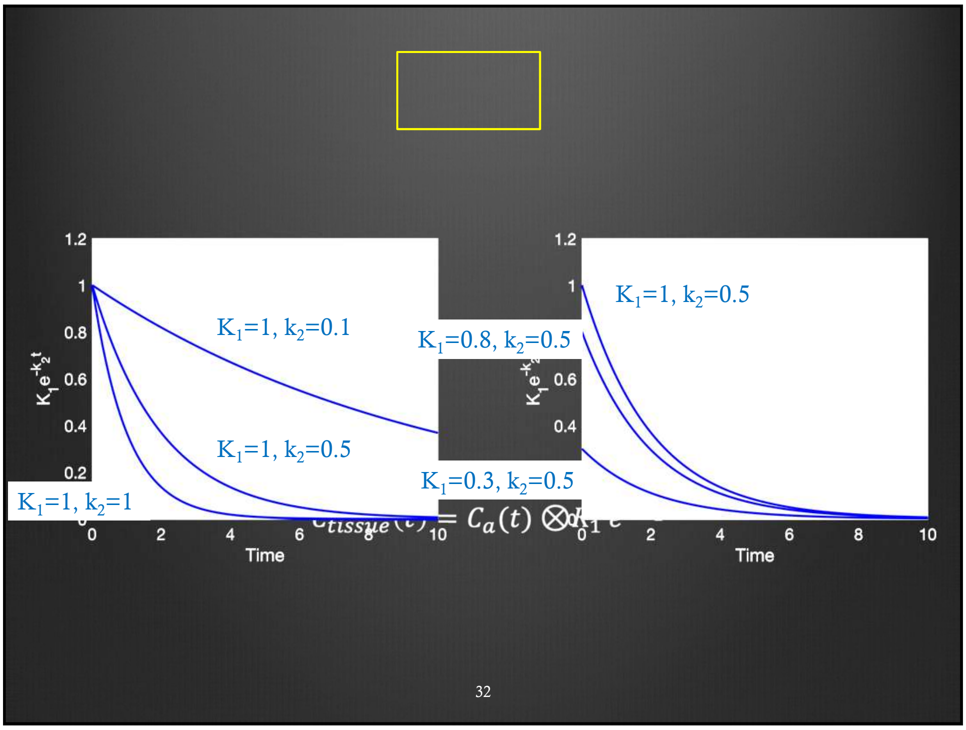
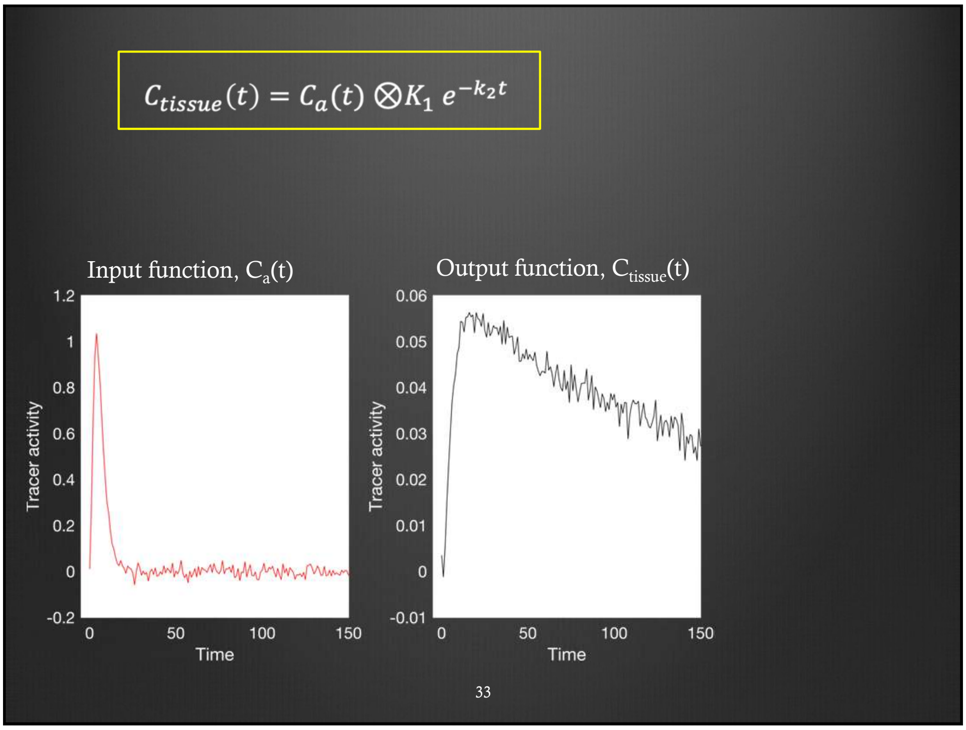
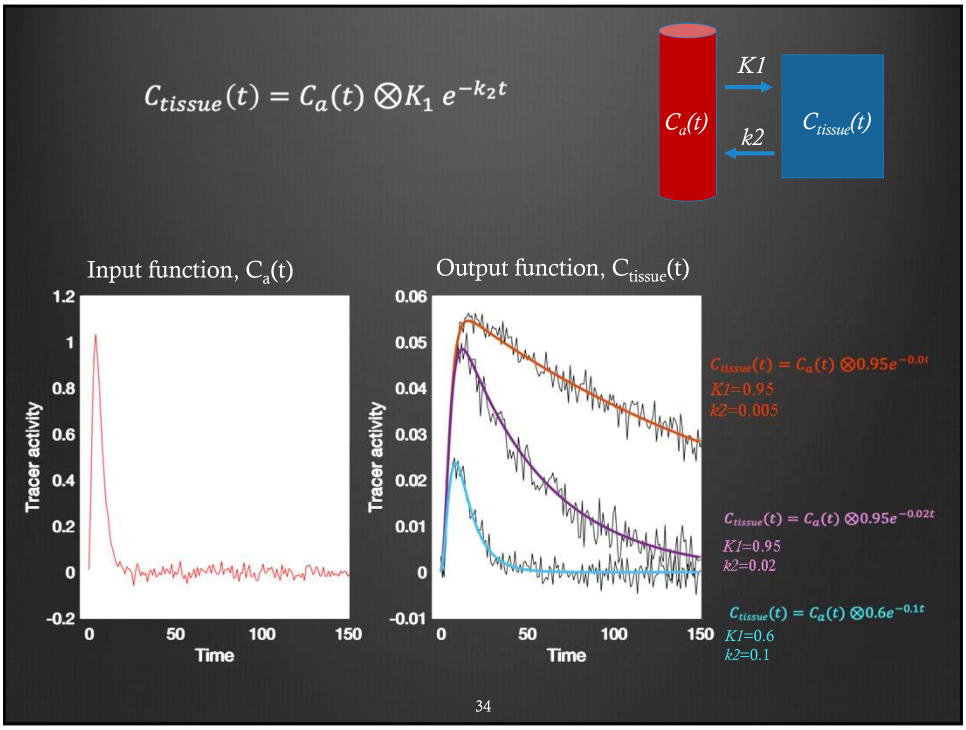

Mathematical model
Transfer function
t1
t1
$C_{tissue}(t) = C_a(t) \otimes RF(t)$
$C_{tissue}(t) = C_a(t) \otimes K_1 e^{-k_2 t}$
We can "guess" K1 and k2 from $C_a(t)$ and $C_{tissue}(t)$ curves
We use a computer for optimal guess


$K_1=1, k_2=0.1$
$K_1=1, k_2=0.5$
$K_1=1, k_2=1$
$K_1=1, k_2=0.5$
$K_1=0.8, k_2=0.5$
$K_1=0.3, k_2=0.5$
$K_1e^{-k_2t}$
Time
Time
32



$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$
Input function, $C_a(t)$
Tracer activity
Time
Output function, $C_{tissue}(t)$
Tracer activity
Time
33



$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$
$C_a(t)$
K1
k2
$C_{tissue}(t)$
Input function, $C_a(t)$
Tracer activity
Time
Output function, $C_{tissue}(t)$
Tracer activity
Time
$C_{tissue}(t) = C_a(t) \otimes 0.95e^{-0.0}$
K1=0.95
k2=0.005
$C_{tissue}(t) = C_a(t) \otimes 0.95e^{-0.02t}$
K1=0.95
k2=0.02
$C_{tissue}(t) = C_a(t) \otimes 0.6e^{-0.1t}$
K1=0.6
k2=0.1
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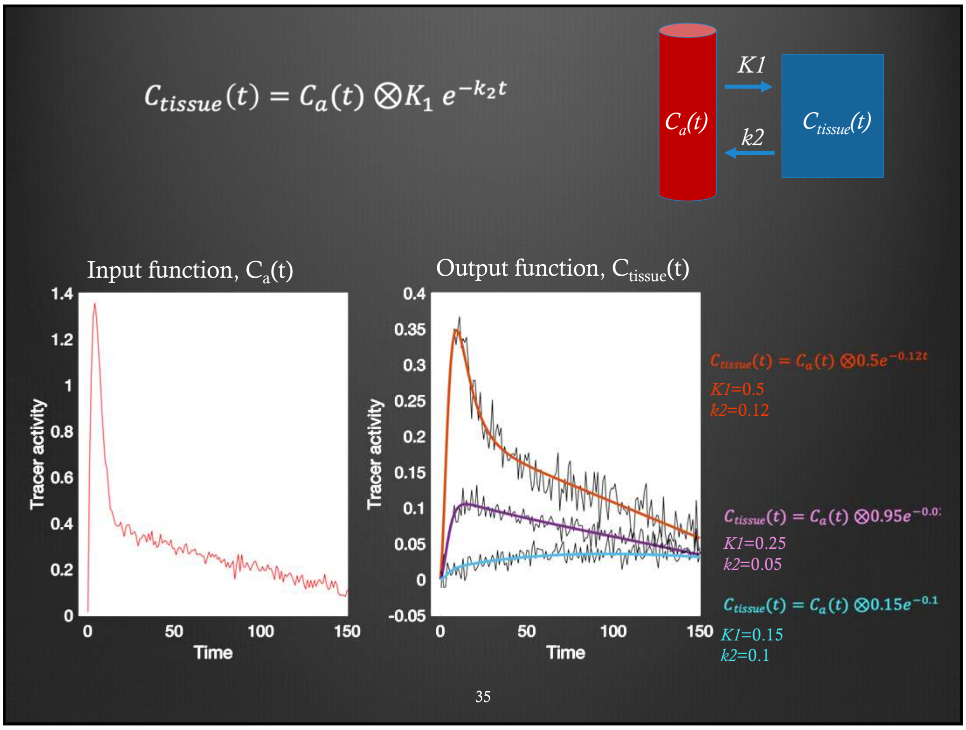

Summary

- Input function, $C_a(t)$
- Tissue function, $C_{tissue}(t)$

We measure $C_a(t)$ and $C_{tissue}(t)$

- The input function is related to tissue function by modelling
- The input function and tissue functions is related by the impulse reponse function of the system

$$C_{tissue}(t) = C_a(t) \otimes \mathrm{RF}(t)$$

- We model the impulse response function of the system
  - Compartment model
  - The parameters used to fit the model can be related to physiology

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