Tracer kinetic modelling
Basic concepts

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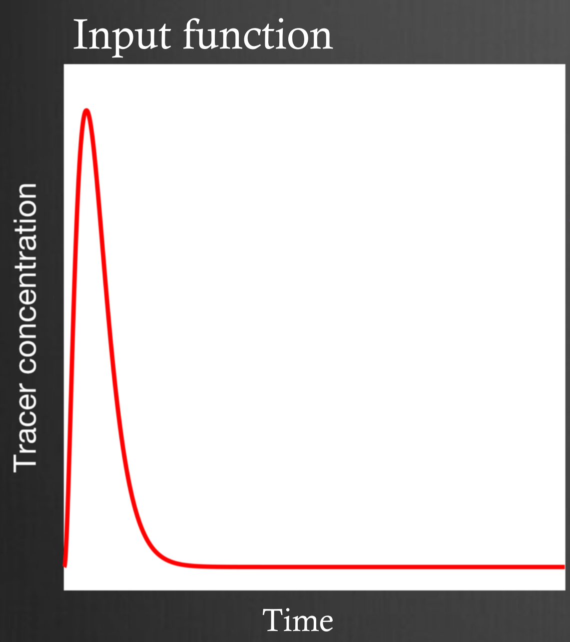
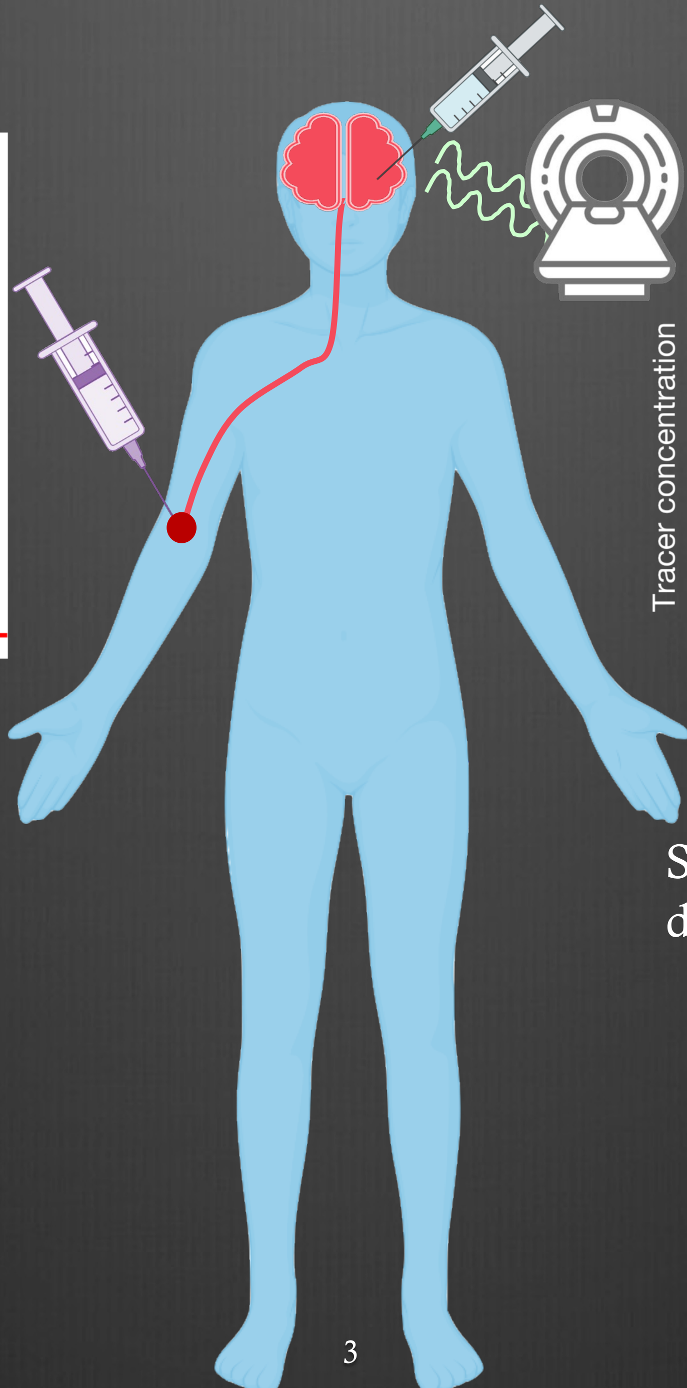
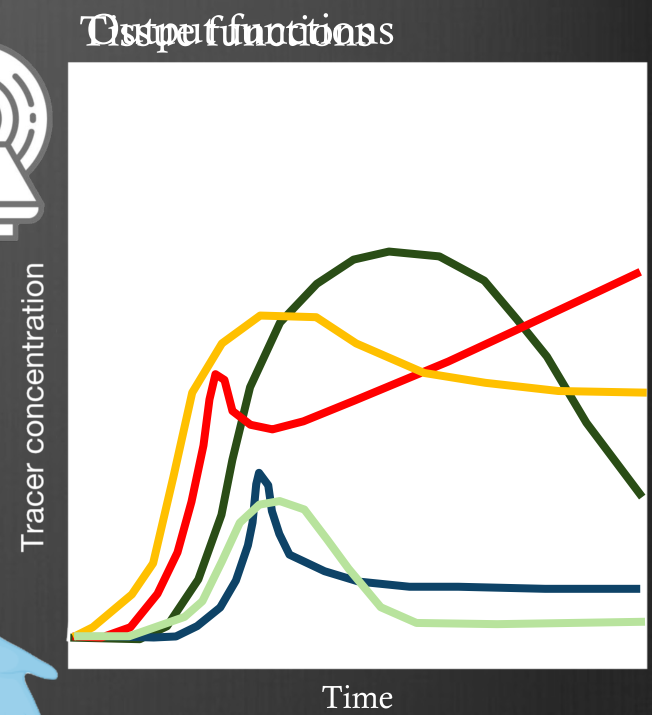
What is tracer kinetic modelling?

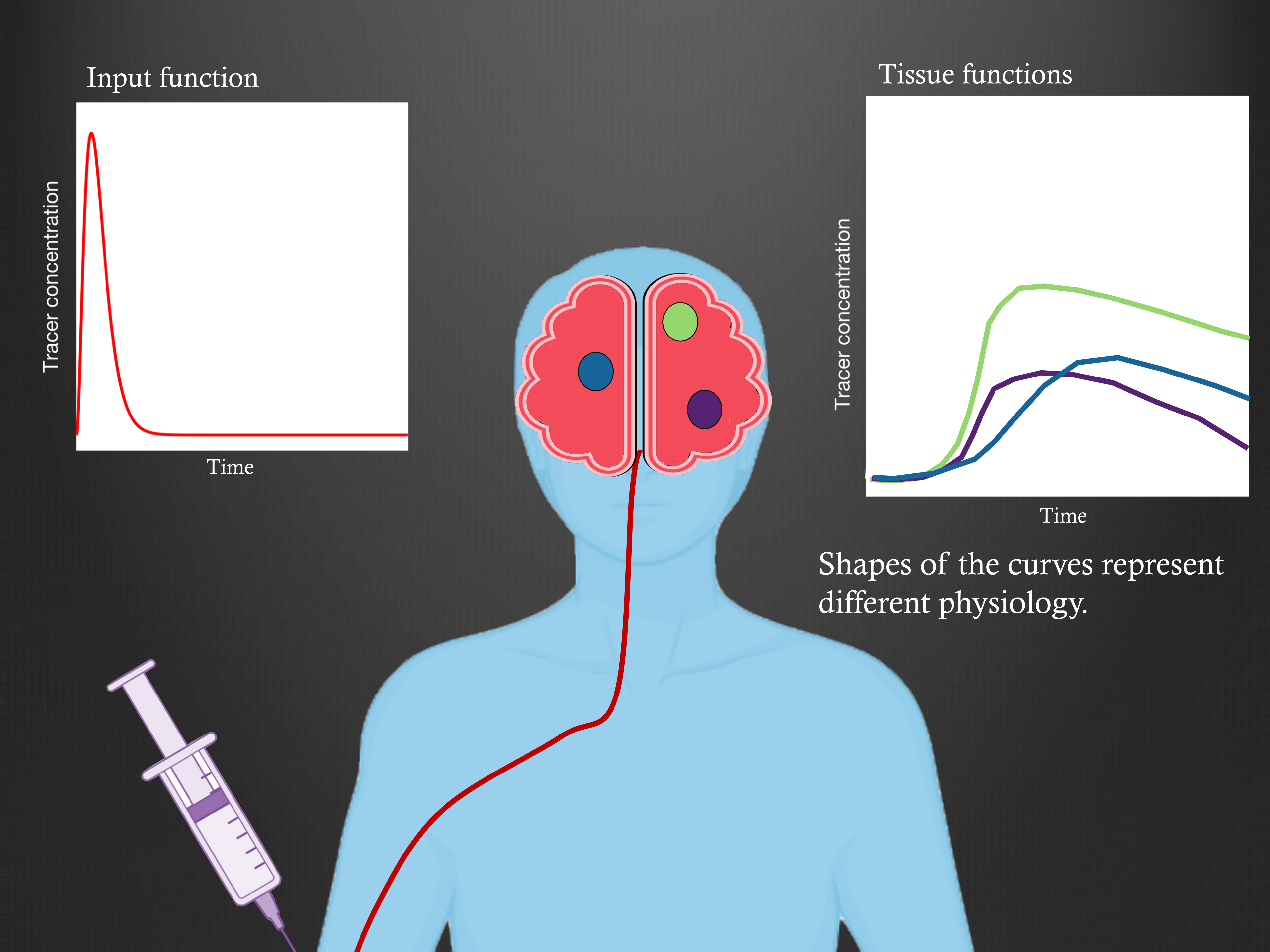
- Mathematical description of a tracer behavior in the body
- From the mathematical description the physiological system can be examined

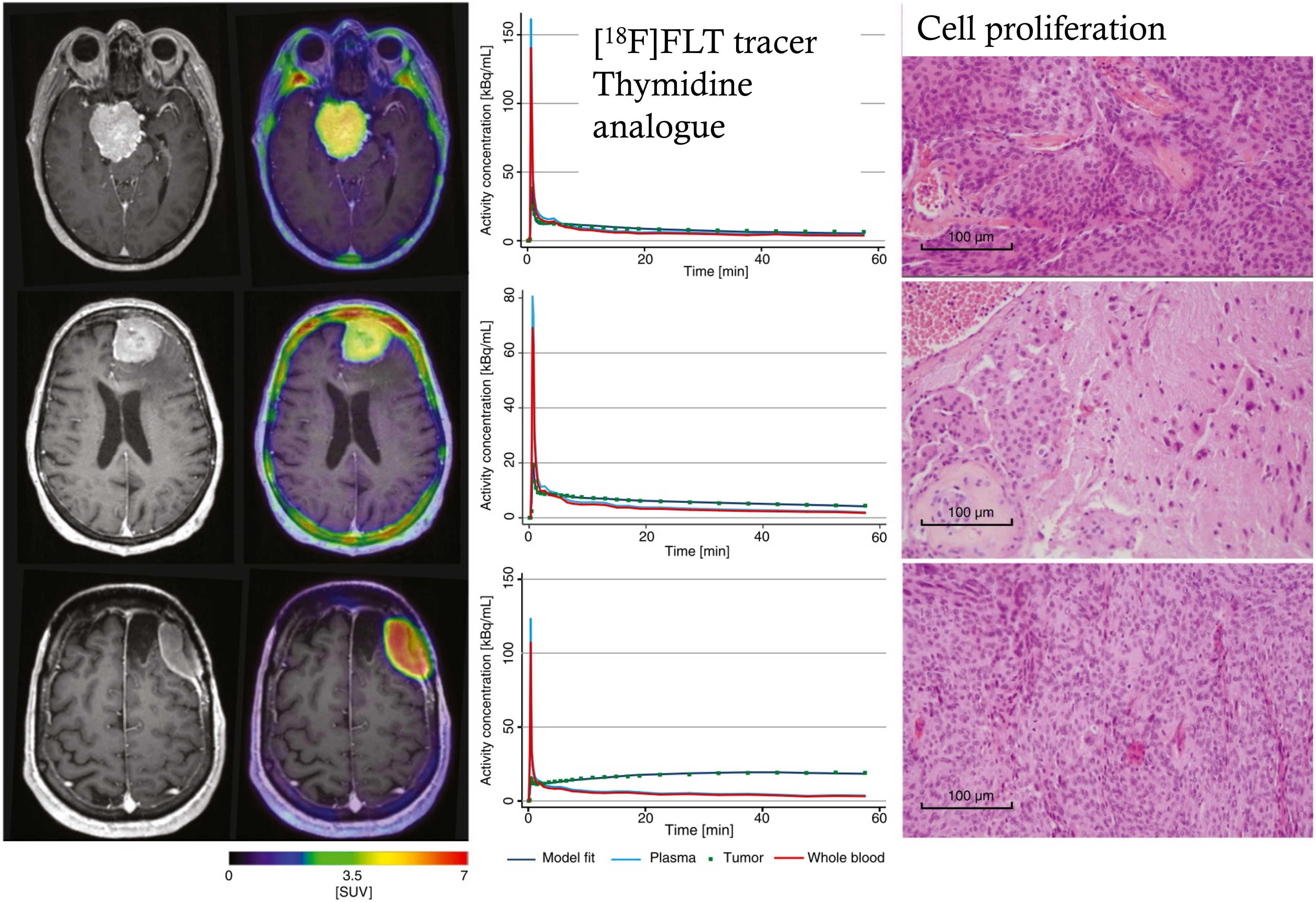




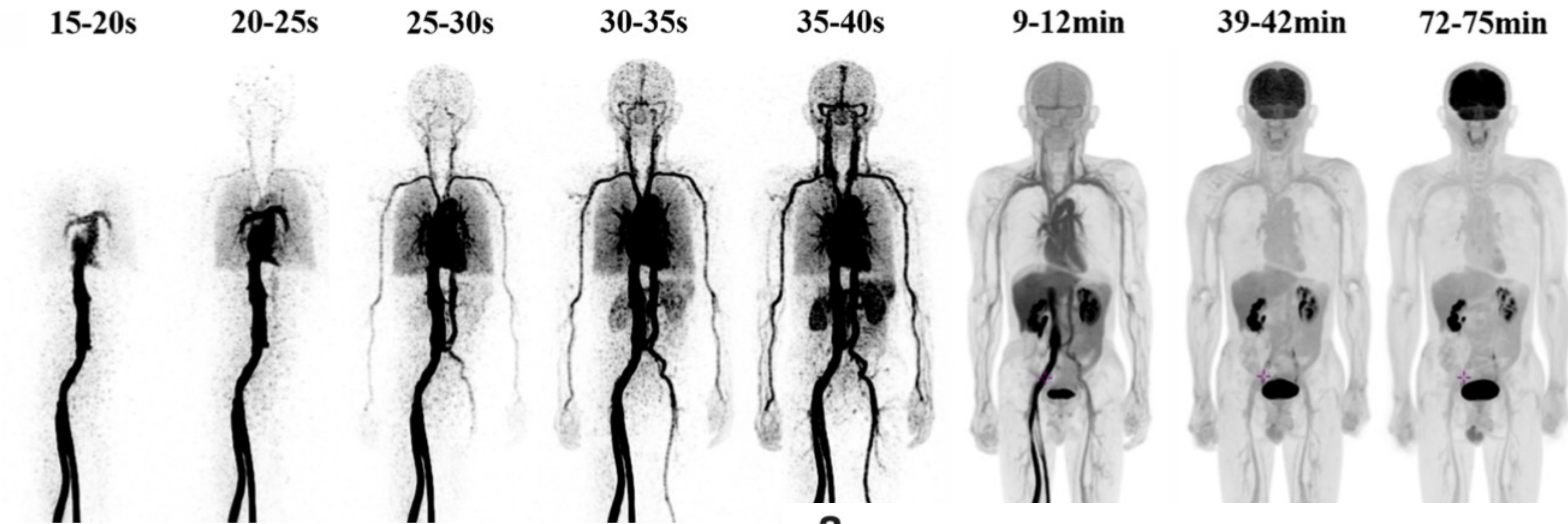


Shapes of the curves represent different physiology.


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



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



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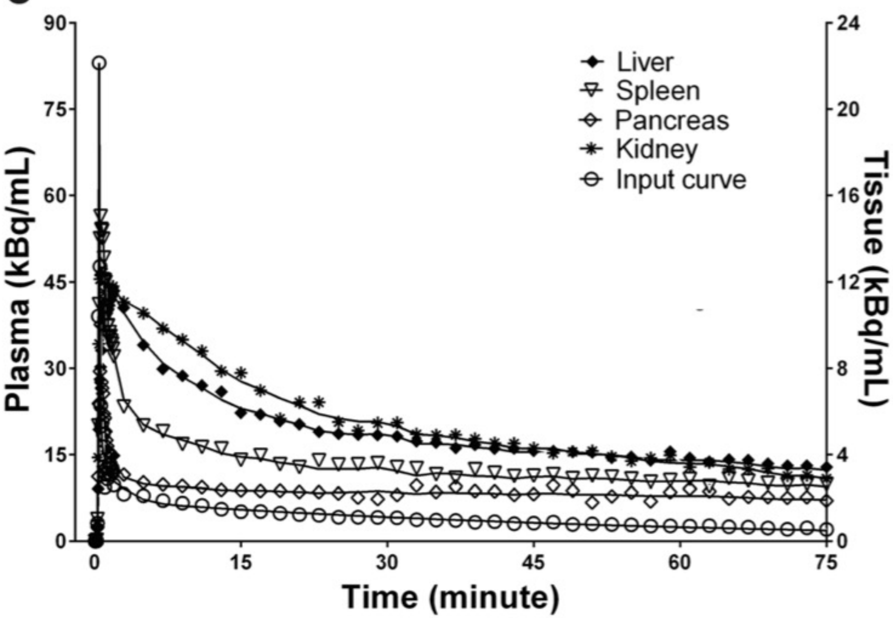

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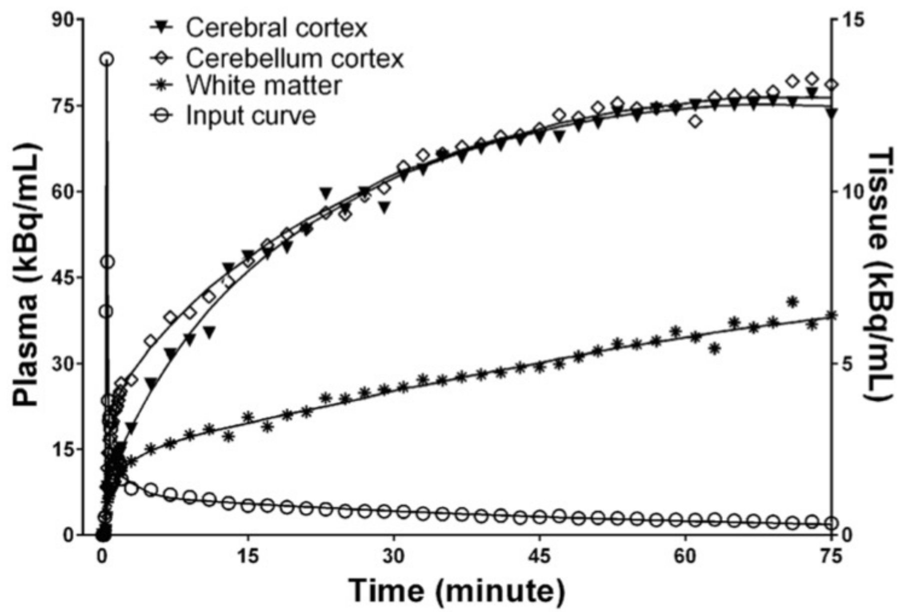


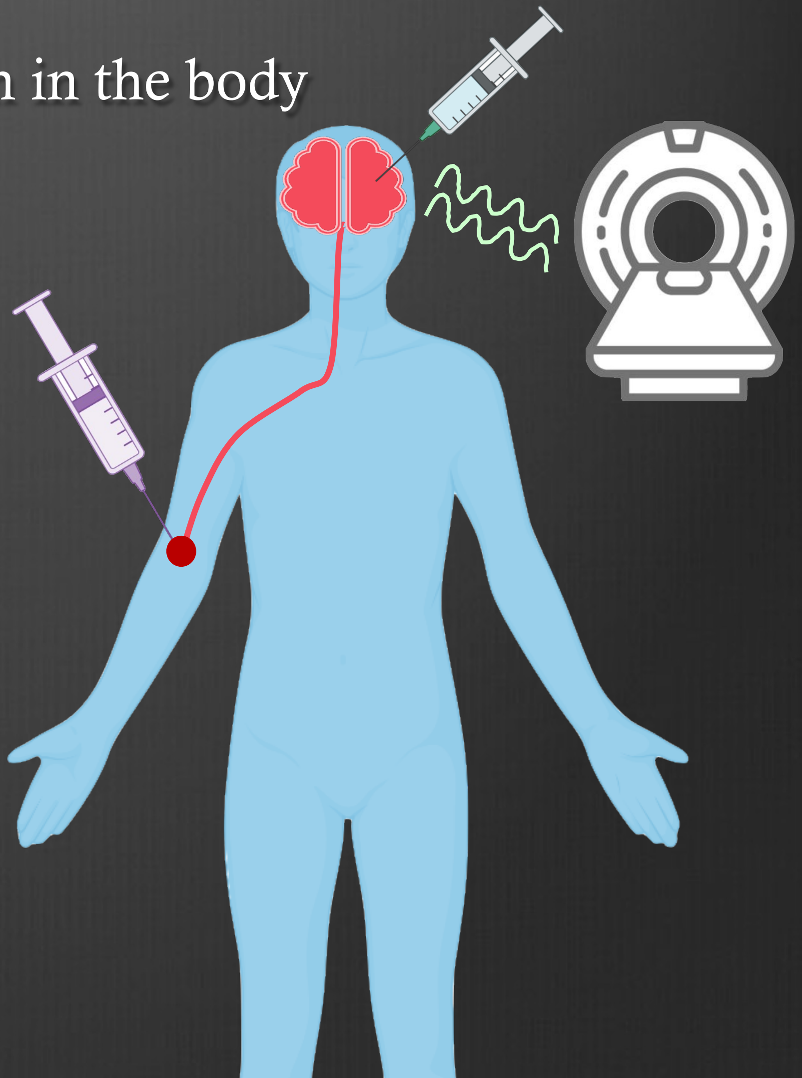
Liu et al. European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:2363–2372

What is tracer kinetic modelling?

- Mathematical description 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

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



Tracers

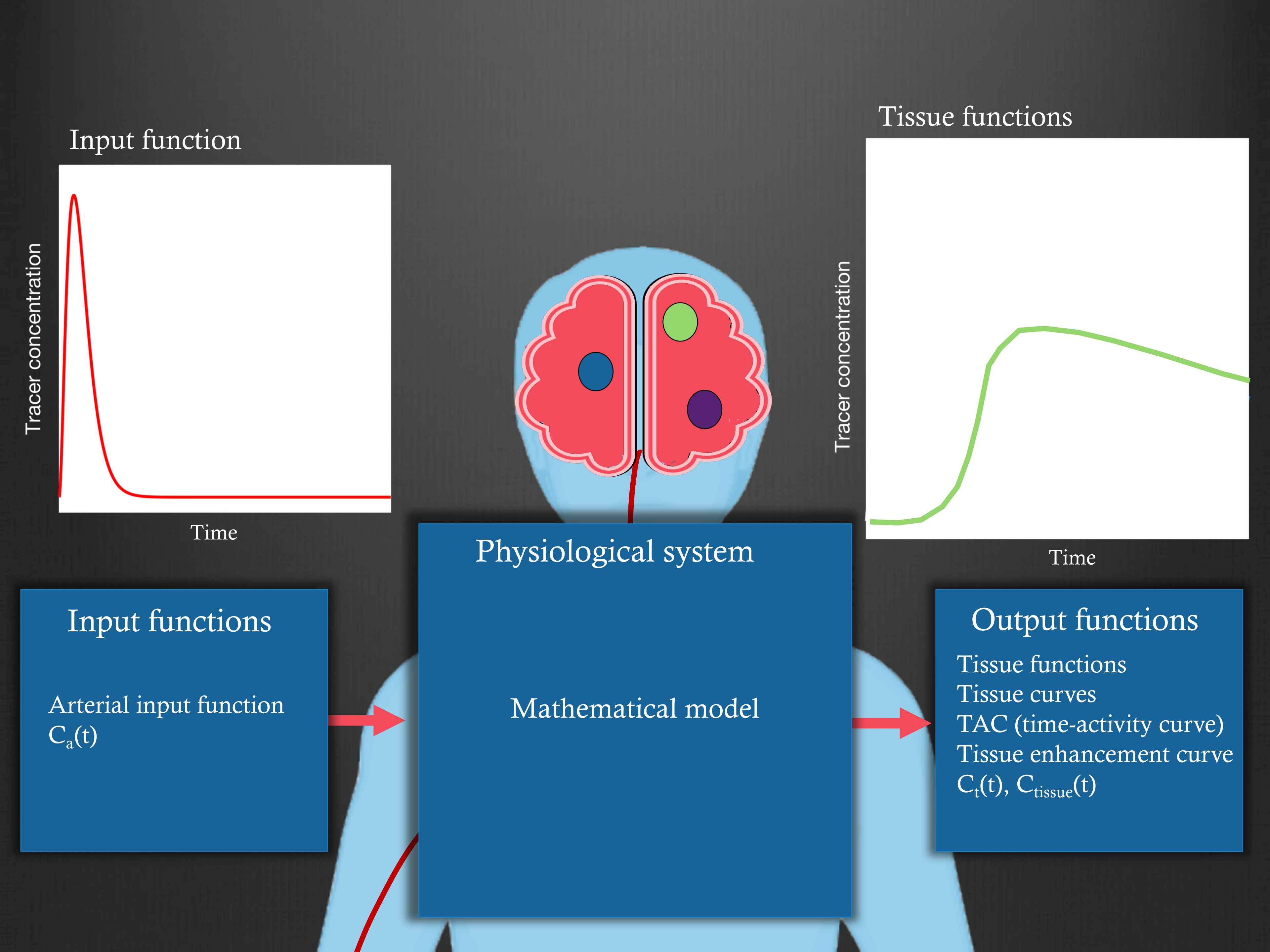
- Tracer should provide information of certain physiology
  - Labelled substances, (nearly) behaving physically and chemically like other substance
    - ^{15}O-H_2O, ^{18}F-FDG
  - Tracer binding to certain receptors
    - Somatostatin receptors, Serotonin receptors, Vascular endothelial growth factor receptors
  - Indicators not related to physiological substance
    - MRI gadolinium based agents, 99mTc-HMPAO

- Tracers can be intravascular, extracellular, free difussible, bound to a receptor or behave in a more specific way.

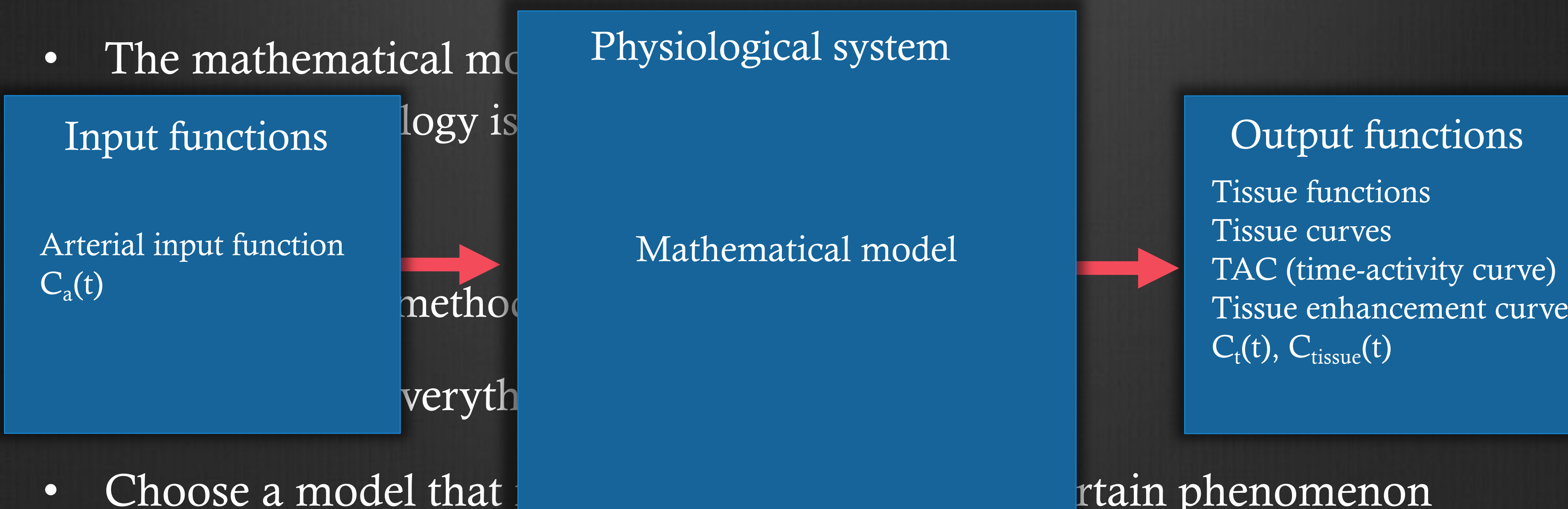
- New tracers are being developed

- Should not disturb the system we are studying

Mathematics to describe the tracer concentration

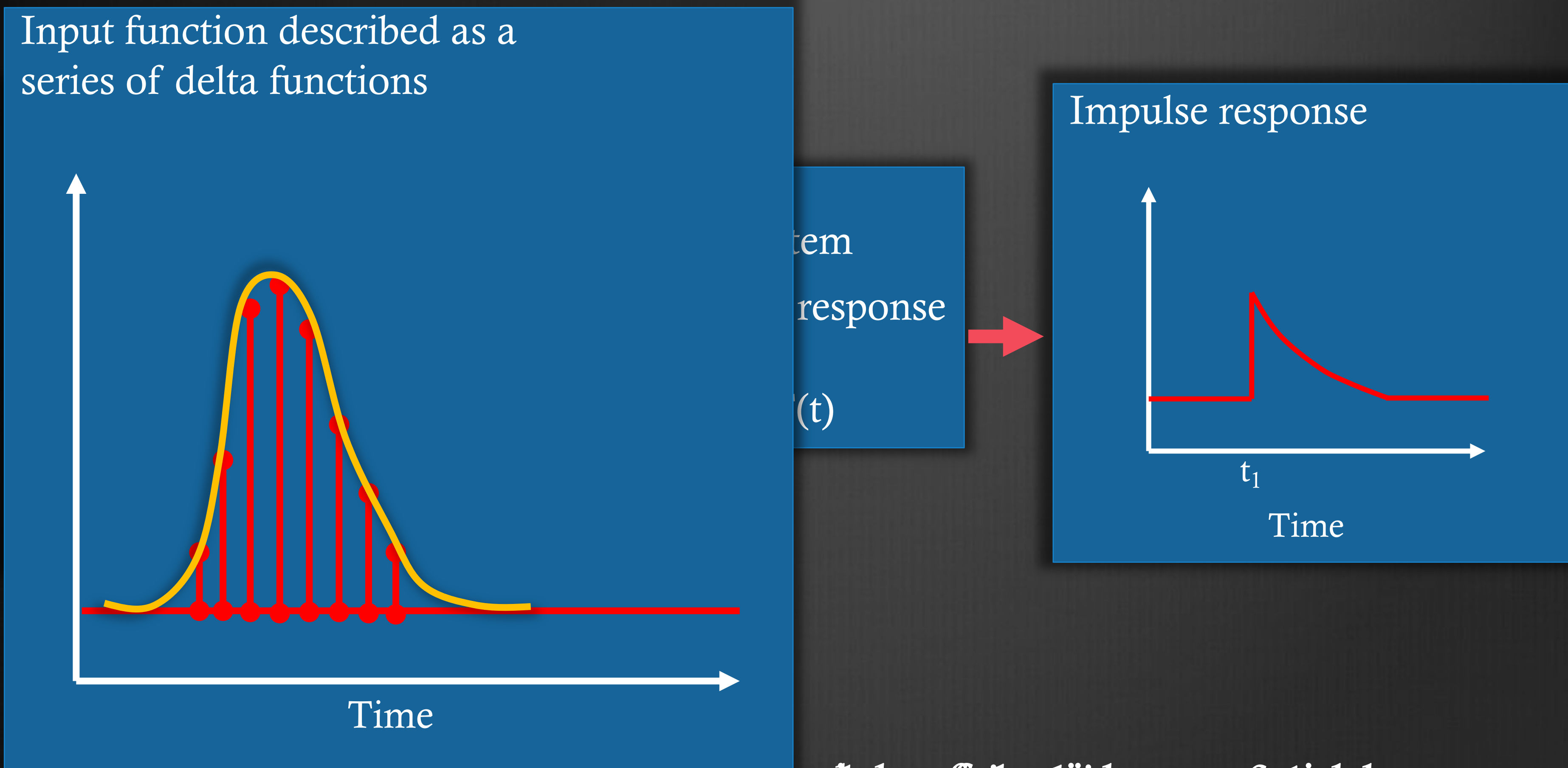

Input function
Tracer concentration
Time
Tissue functions
Tracer concentration
Time
Physiological system
Input functions
Arterial input function
$C_a(t)$
Mathematical model
Output functions
Tissue functions
Tissue curves
TAC (time-activity curve)
Tissue enhancement curve
$C_t(t)$, $C_{tissue}(t)$

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



Impulse response

Description of system by impulse response function



[illegible]

Linearity of a system

$$x \xrightarrow{RF(t)} y$$

scaling $$a\,x \xrightarrow{RF(t)} a\,y$$

Linearity of a system

x_1

RF(t)

y_1

y_2

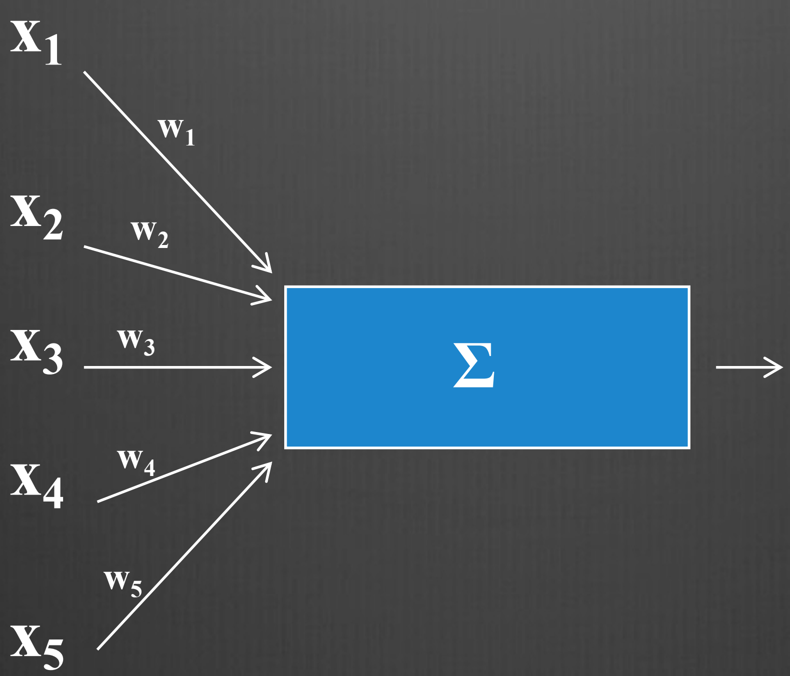
x_2

RF(t)

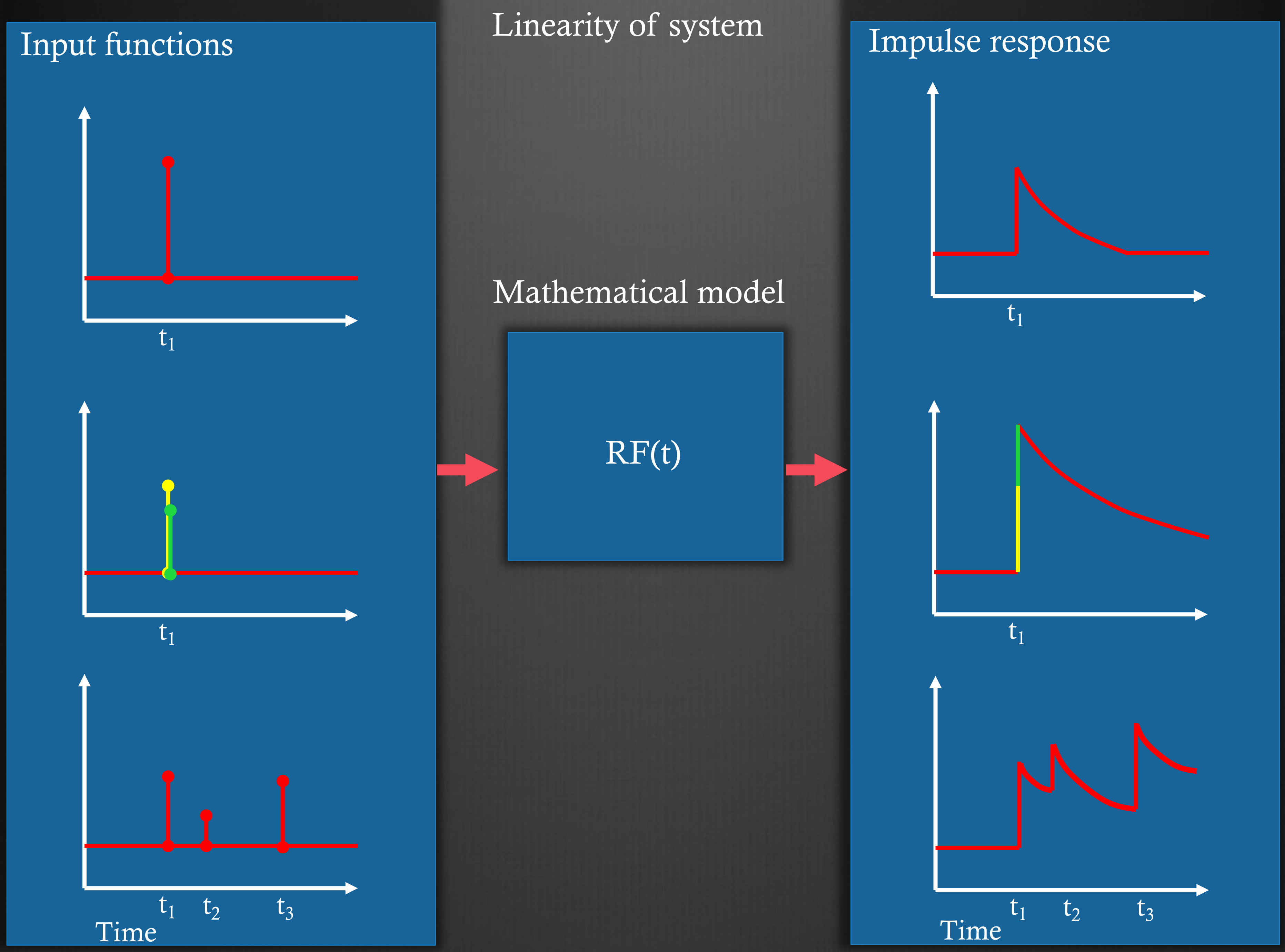
$x_1 + x_2 \longrightarrow y_1 + y_2$

Principle of superposition

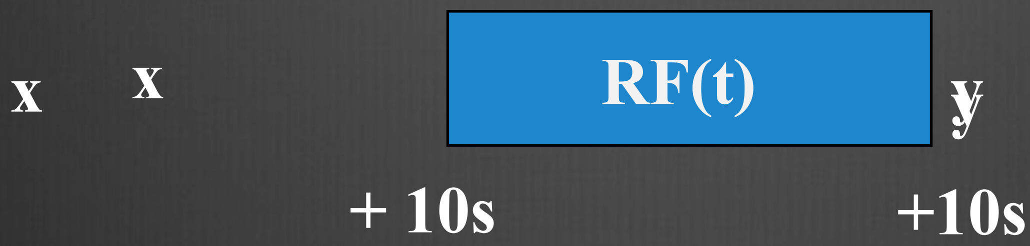
Examples



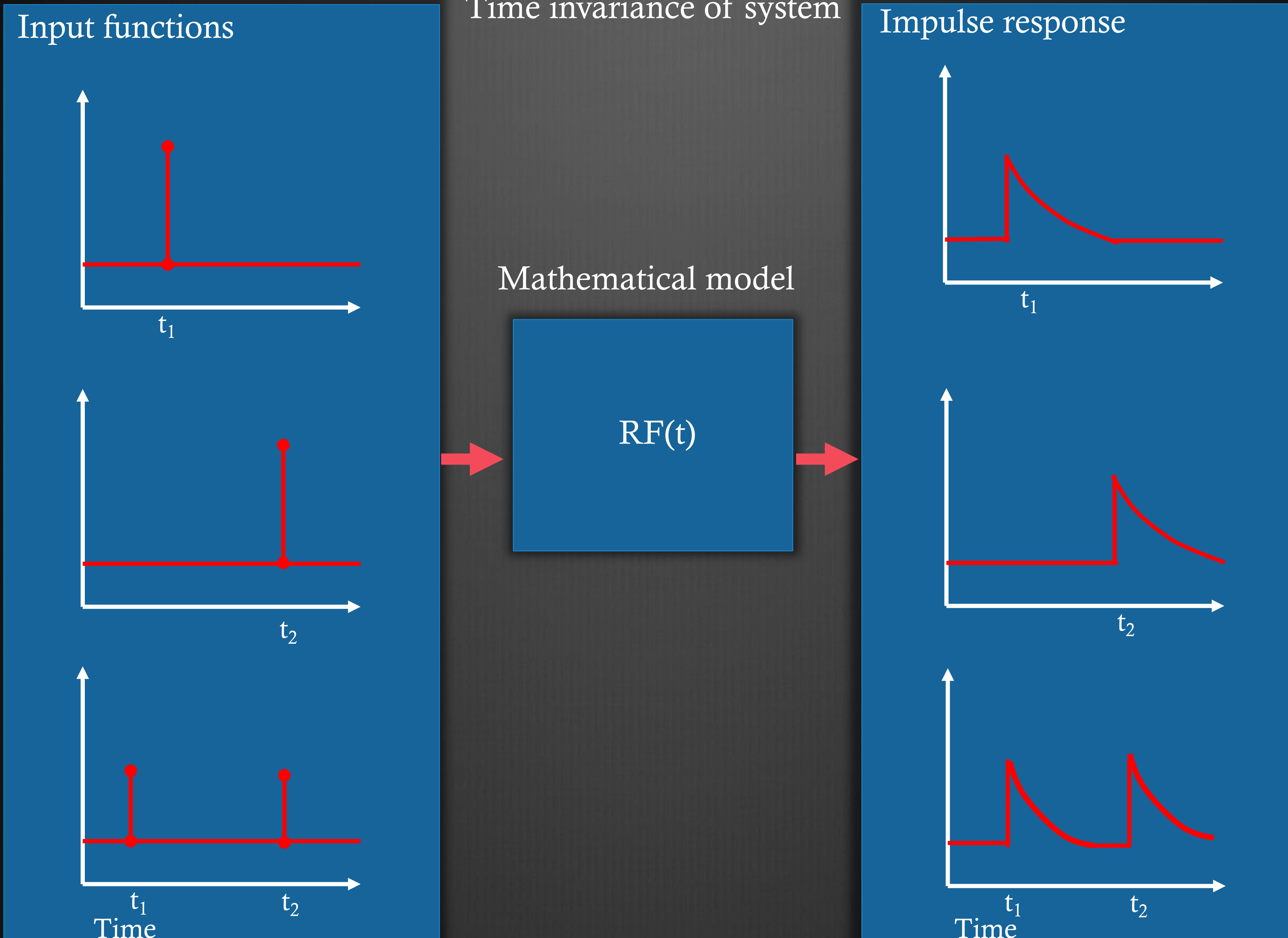
$$y_{total} = x_1 w_1 + x_2 w_2 + x_3 w_3 + x_4 w_4 + x_5 w_5$$


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

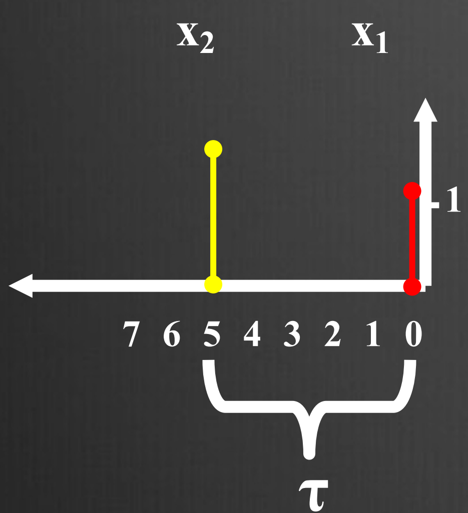
Time invariance of a system

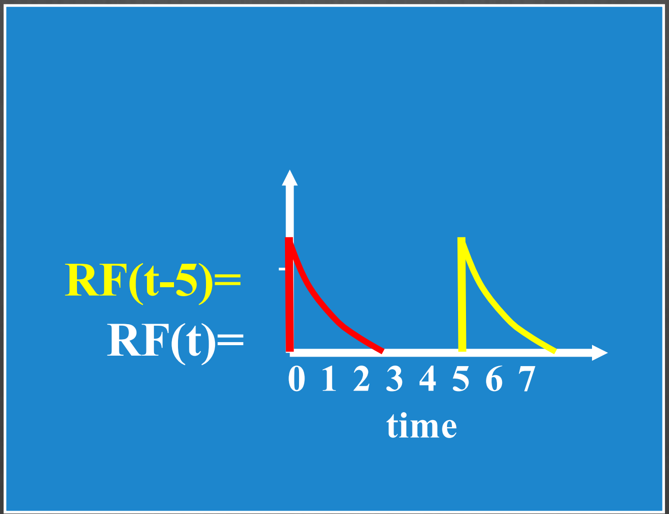


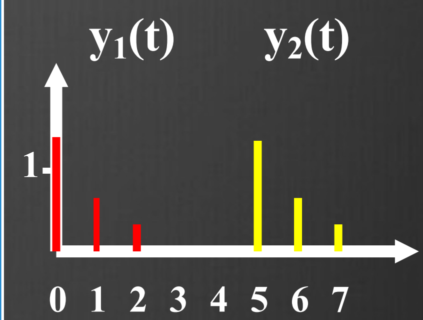
Time invariance of system



Time delay, τ







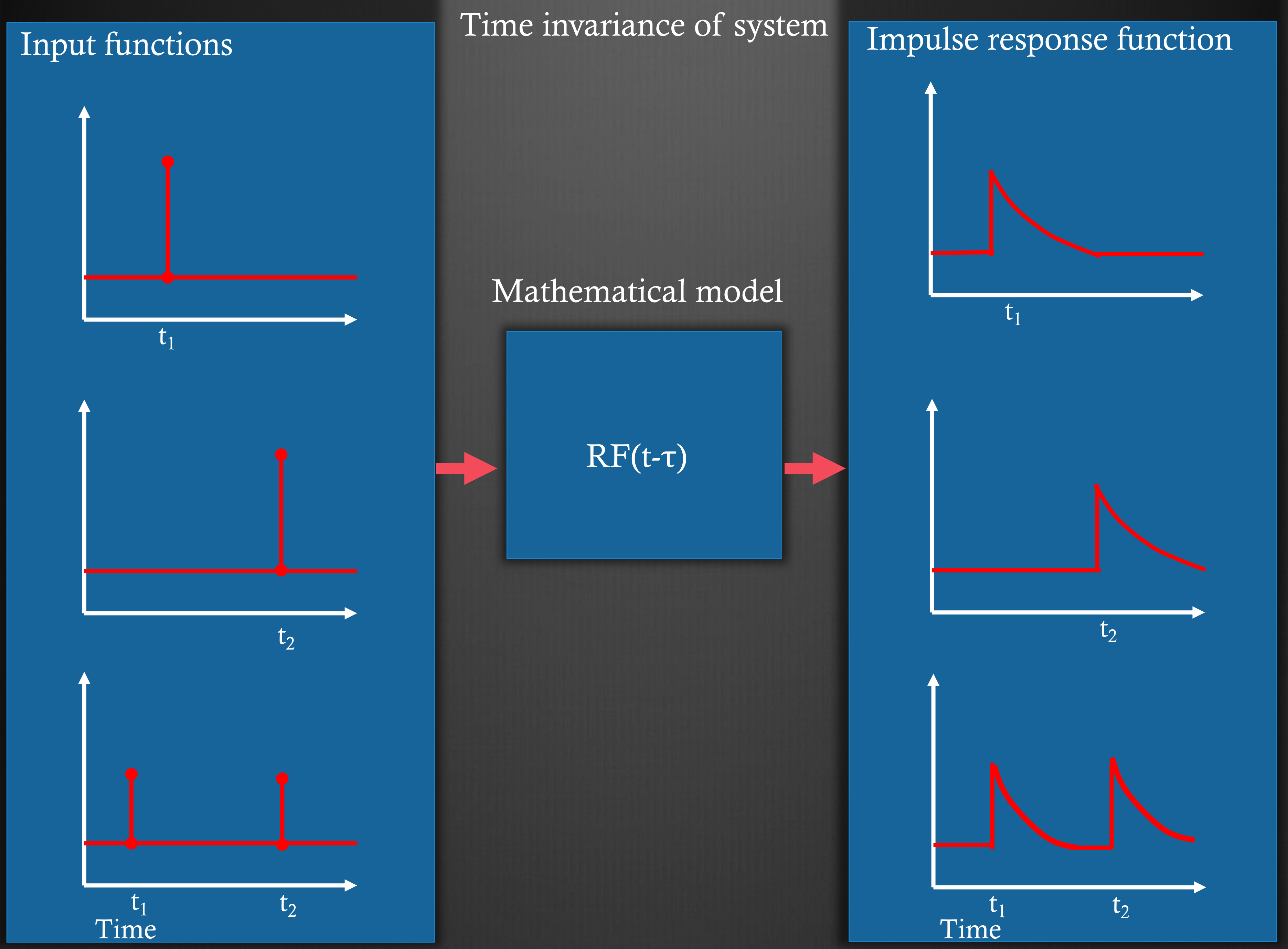
$y_1(t) = x(t) \cdot RF(t)$

We add τ describing the delay

$y_1(t) = x(t) \cdot RF(t-\tau)$

$y_1(t) = x(0) \cdot RF(t-0)$

$y_2(t) = x(5) \cdot RF(t-5)$

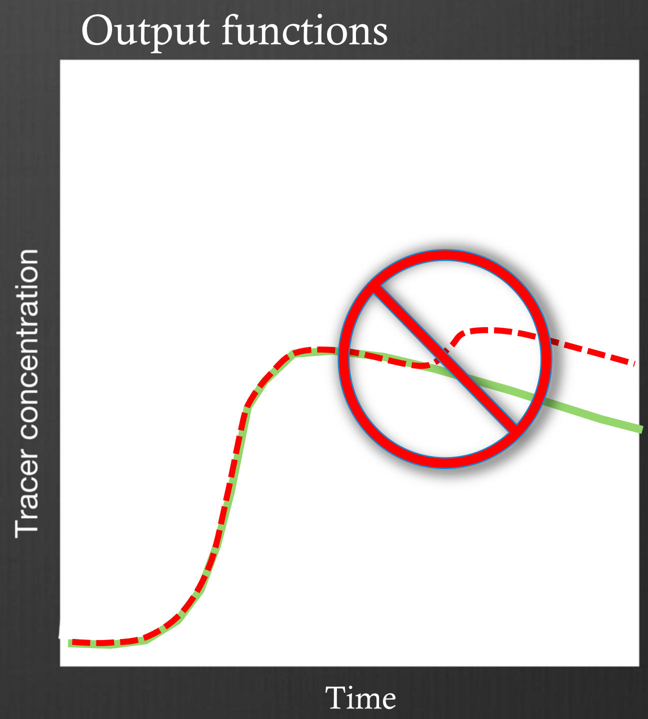

Time invariance of system
Input functions
t1
t2
t1
t2
Time
Mathematical model
RF(t-τ)
Impulse response function
t1
t2
t1
t2
Time

Causality of a system

Output is only observed after an input has enter the system

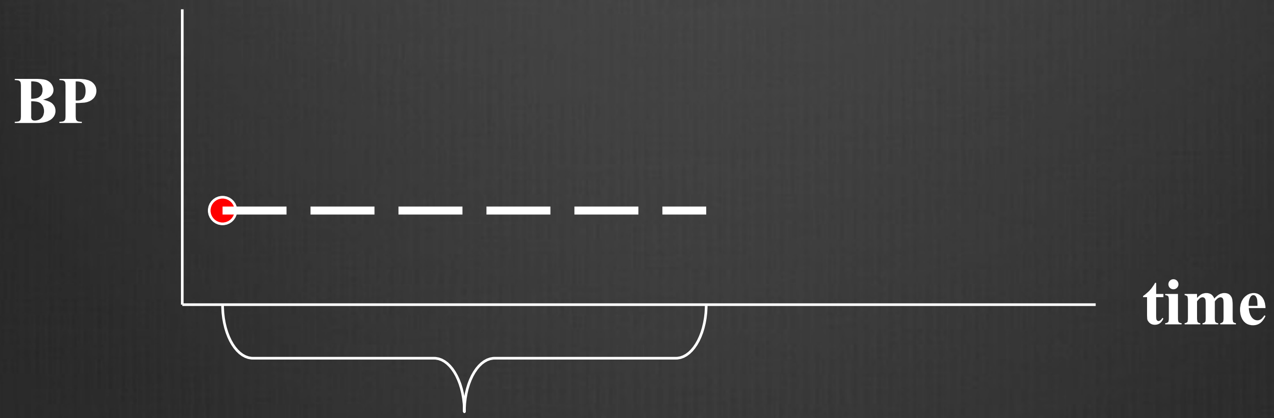
Steady state of the system

- The physiologic parameter is constant during the measurement
- Examples: Blood flow, glucose uptake
- Consider: Duration of the measurement in relation change of parameters

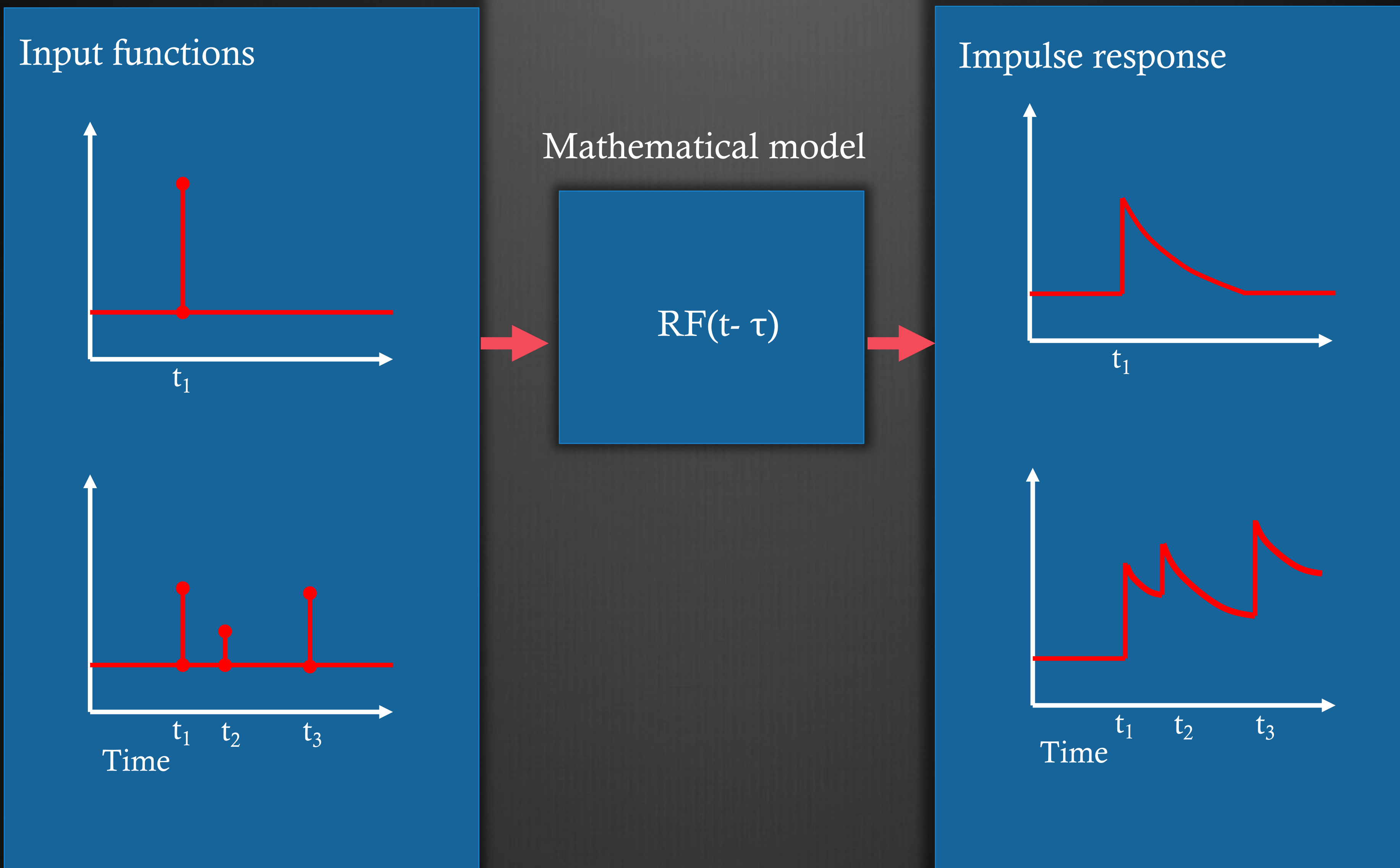


Steady state of the system

- Parameter oscillates fast compared to the duration of the measurement



Linear time-invariant causal steady-state system!



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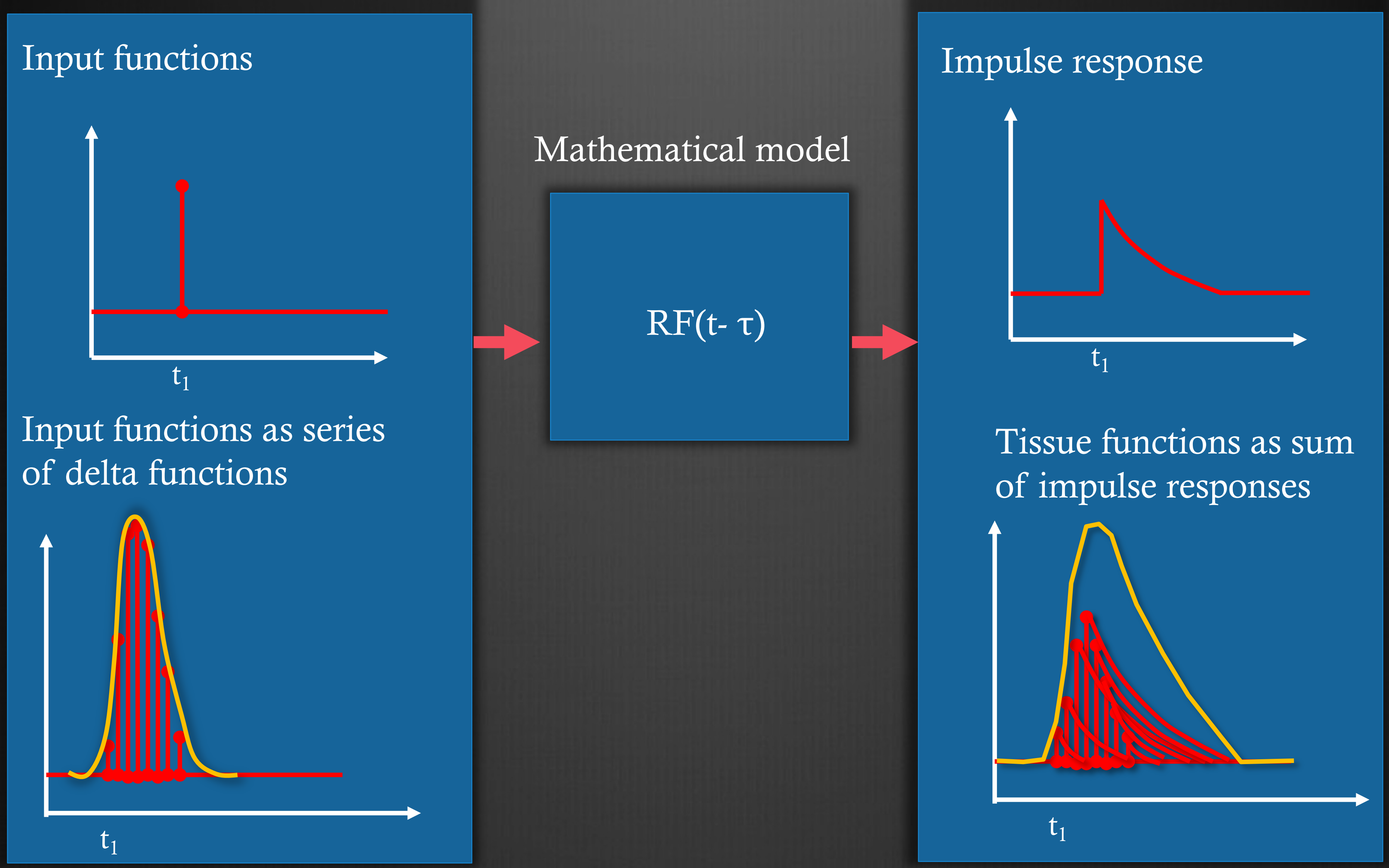
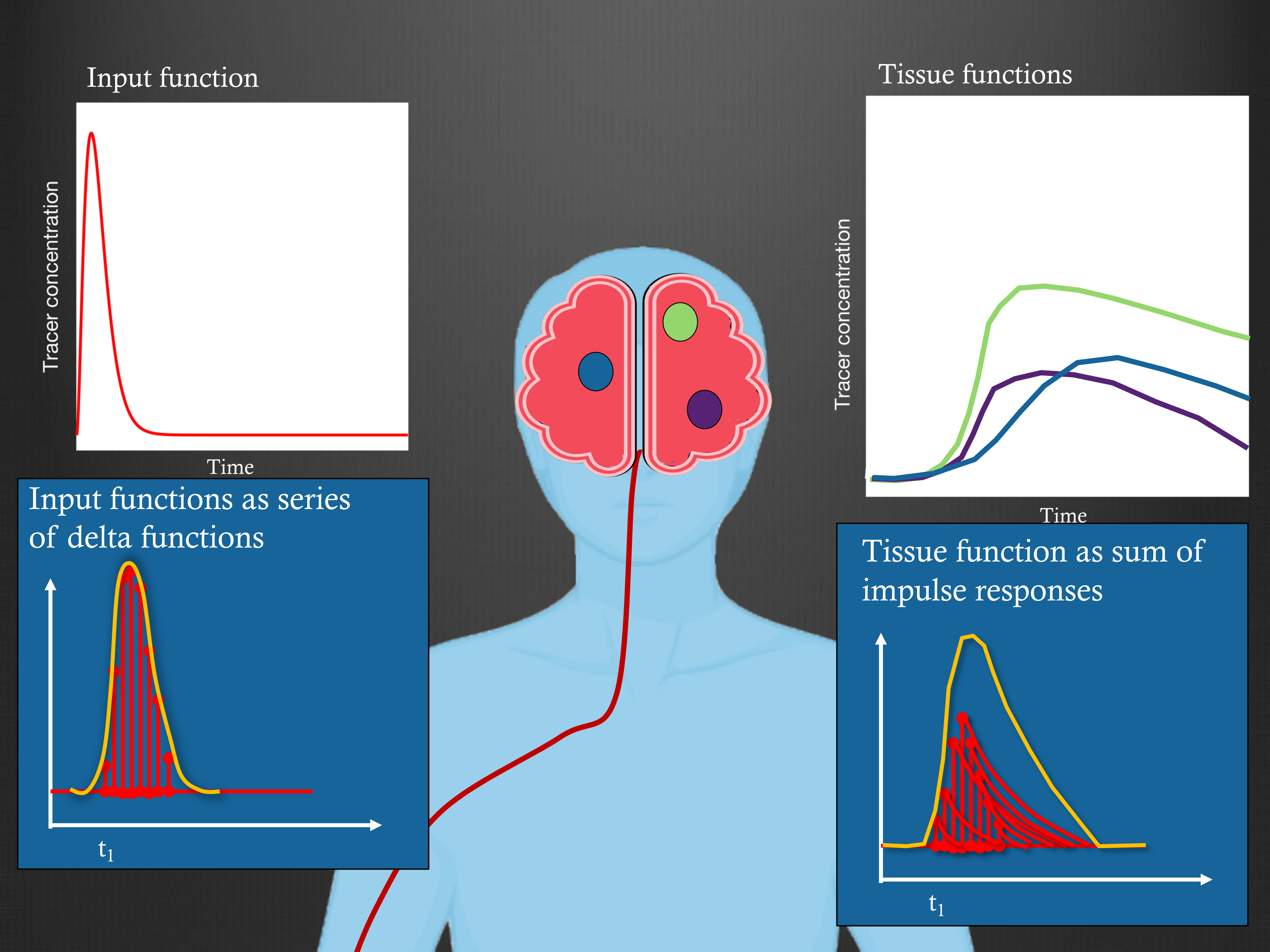
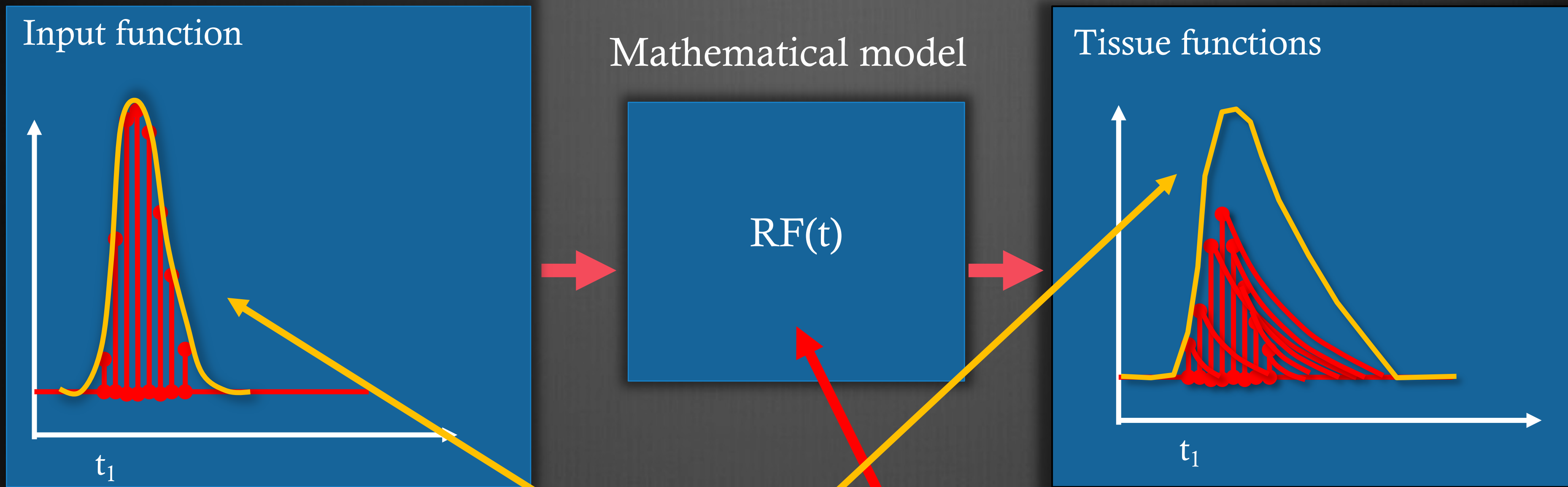




Input function
Tracer concentration
Time
Tissue functions
Tracer concentration
Time
Input functions as series of delta functions
t1
Tissue function as sum of impulse responses
t1



The system can be described by:

$$C_{\text{tissue}}(t) = C_{\text{a}}(t) \otimes \text{RF(t)}$$

We measure these two

Convolution

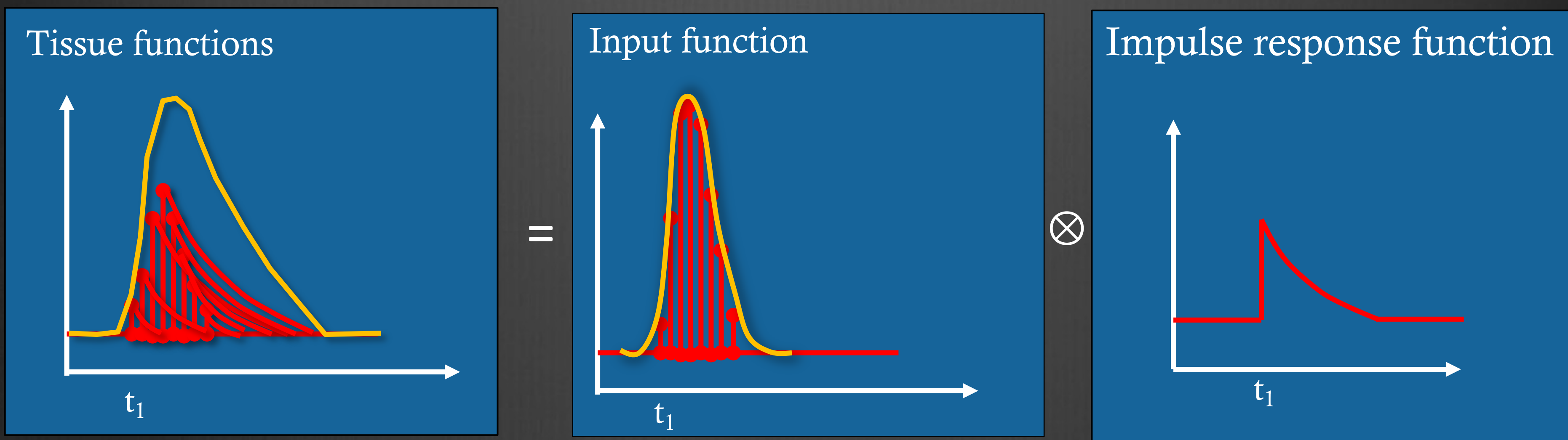
We make an educated guess

Tracer kinetic modelling is to relate C_a to $C_{tissue}(t)$ by estimating RF(t)

Fundamental tracer kinetic equation

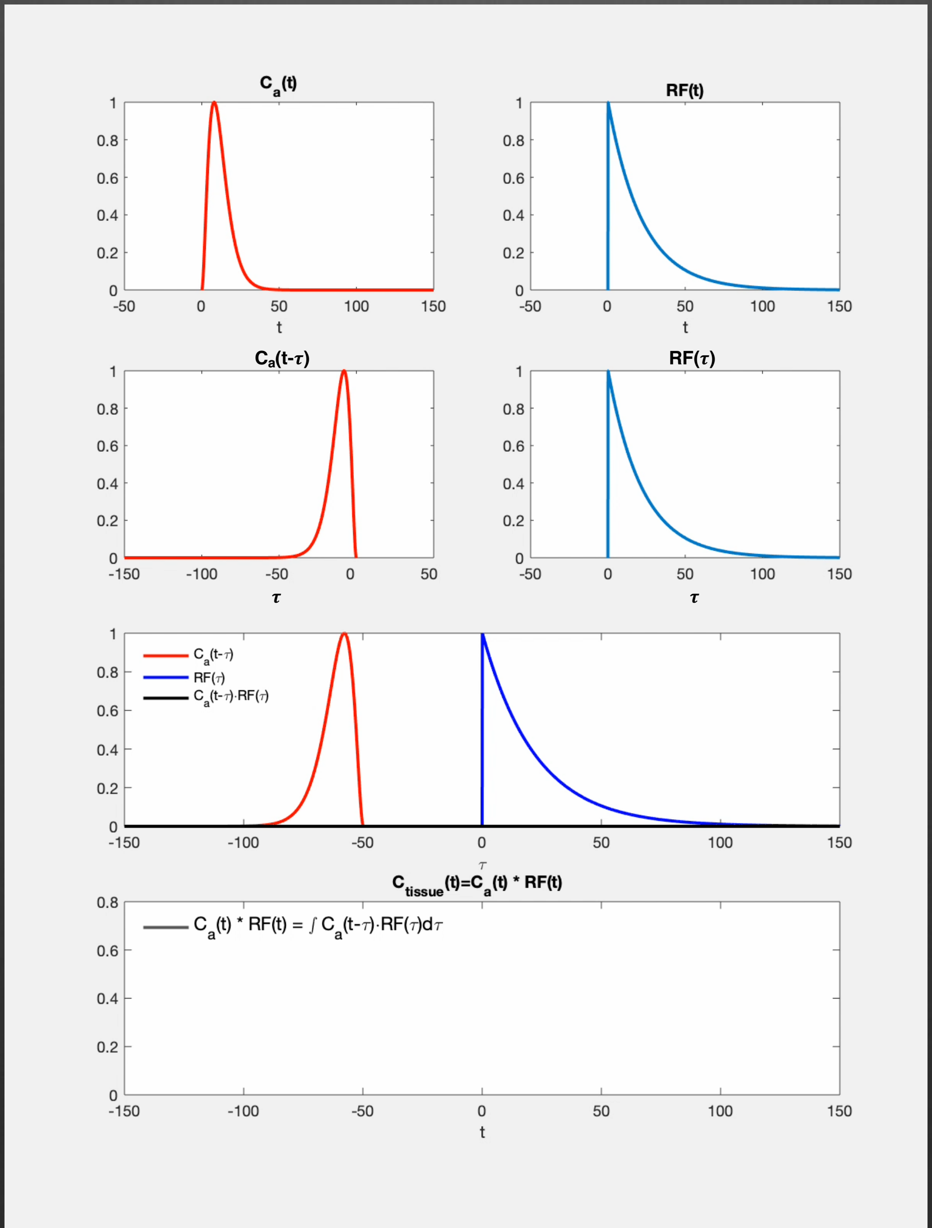
Convolution

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



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

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



How shall we model RF(t)?

- Simple model, one tissue compartment model

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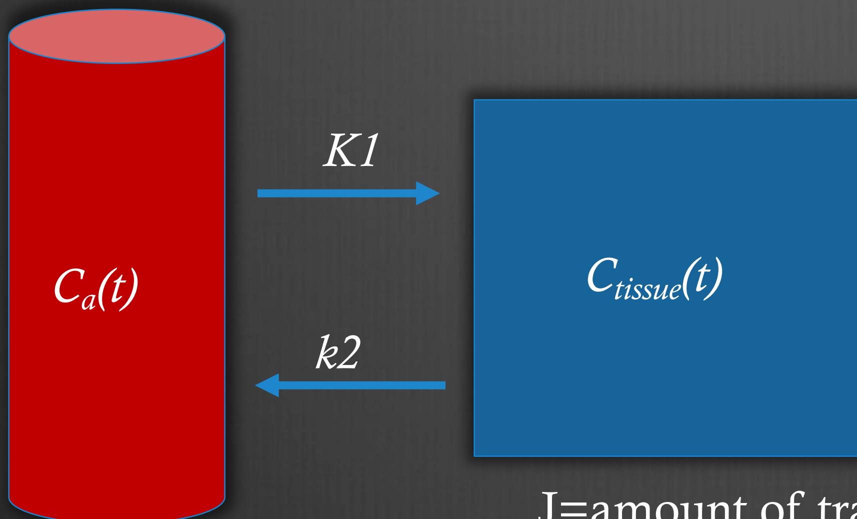
- Simple model, one tissue compartment model

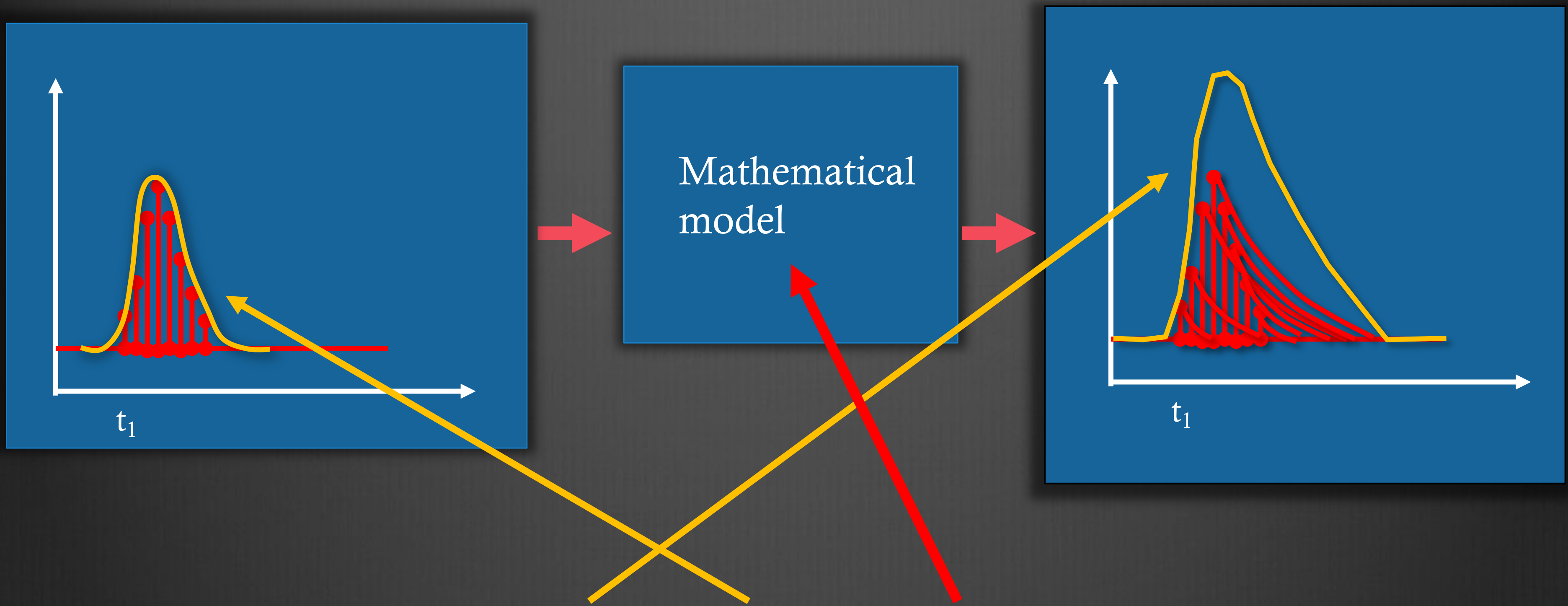


J=amount of tracer going into compartment

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

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

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

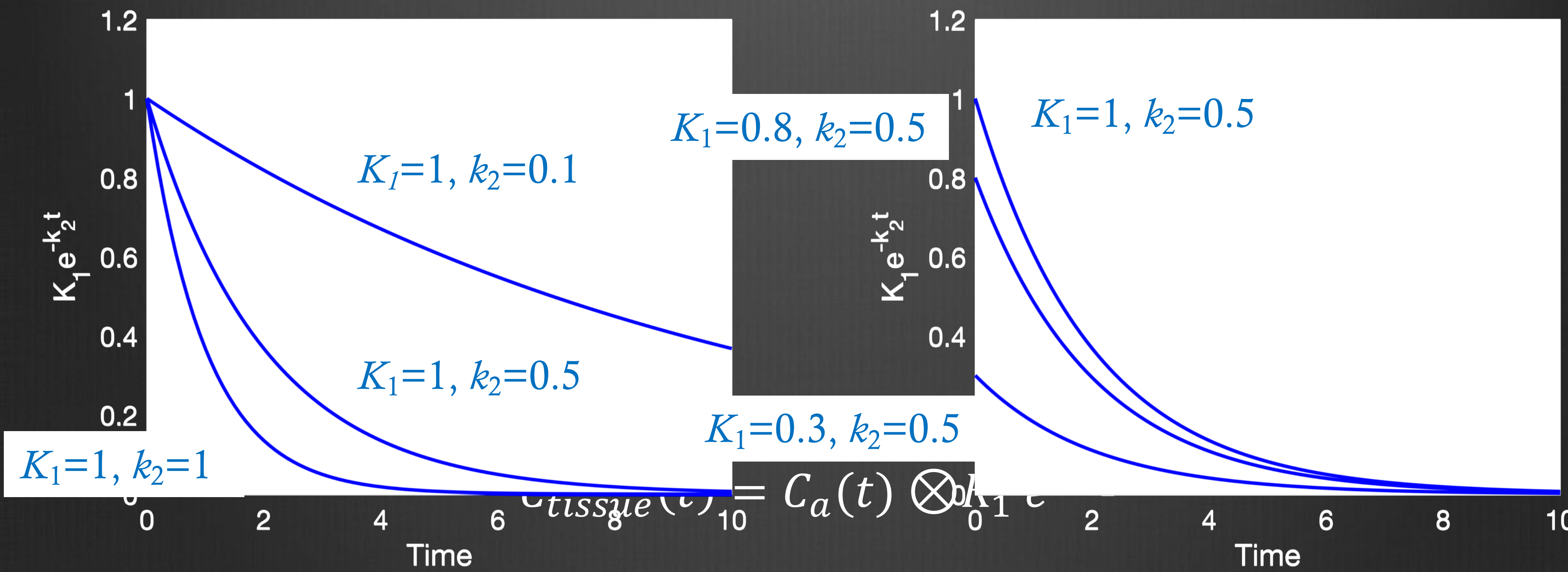


$$C_{\text{tissue}}(t) = C_{\text{a}}(t) \otimes \text{RF(t)}$$

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

We can “guess” K_1 and k_2 from $C_a(t)$ and $C_{tissue}(t)$ curves

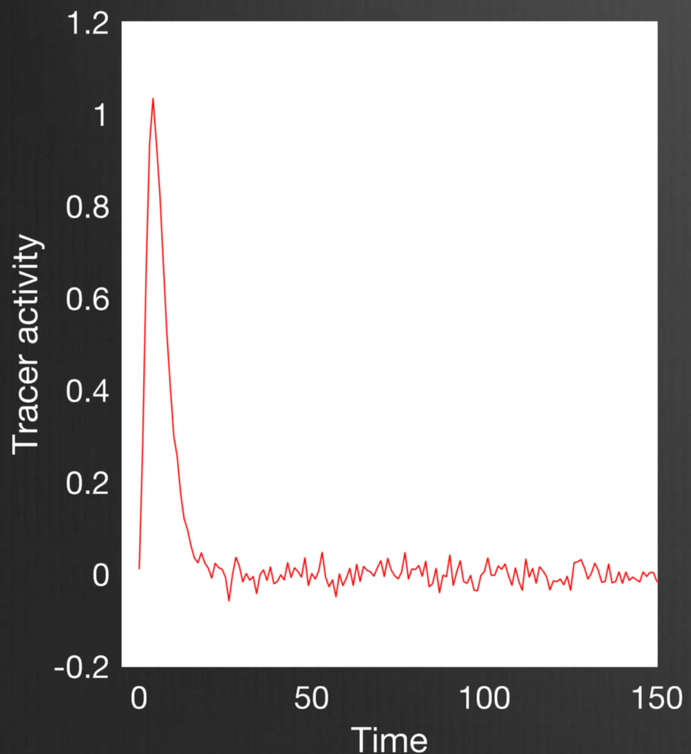
We use a computer for optimal guess



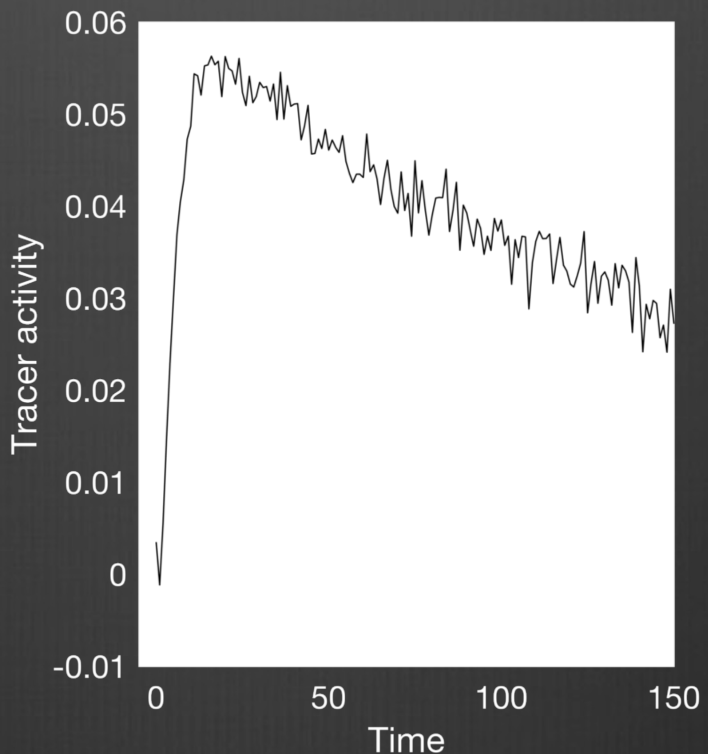
K1=1, k2=0.1
K1=1, k2=0.5
K1=1, k2=1
K1=0.8, k2=0.5
K1=0.3, k2=0.5
K1=1, k2=0.5
K1e-k2t
Time
= Ca(t) ⊗

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

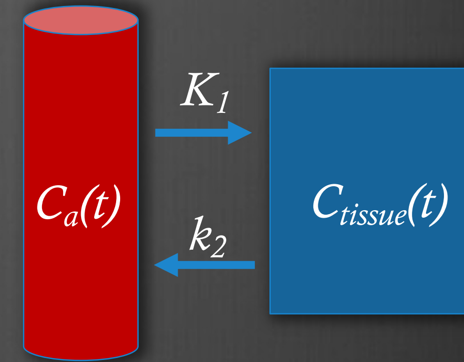
Input function, $C_a(t)$



Tissue function, $C_{tissue}(t)$



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



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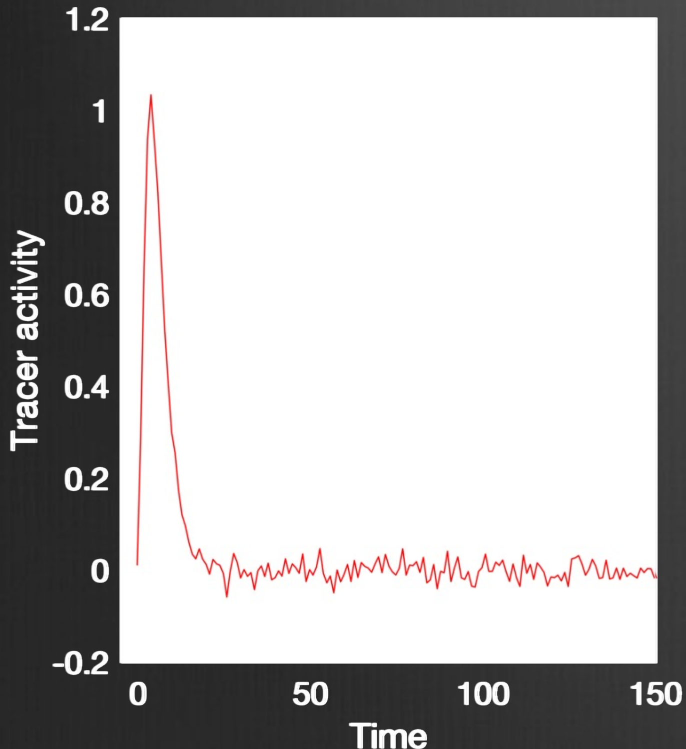
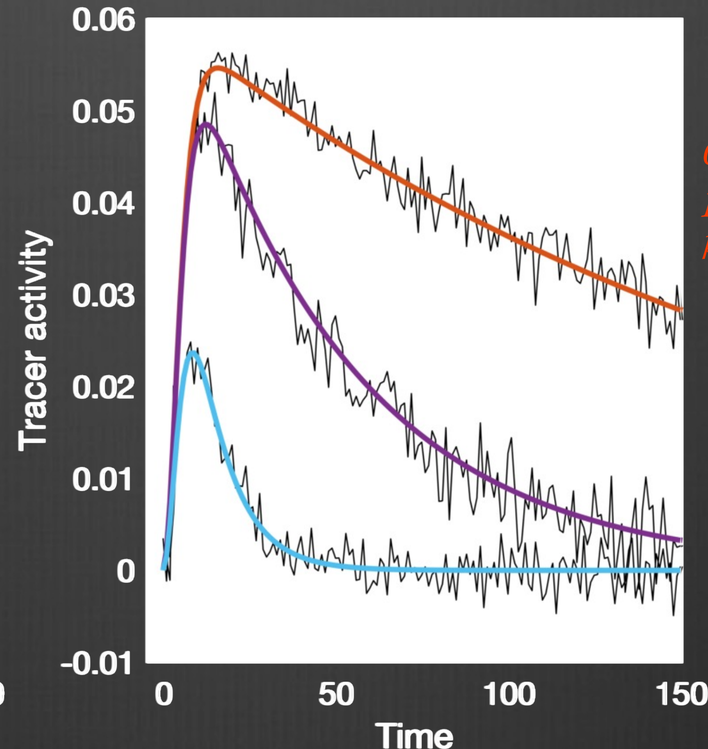


Tissue function, $C_{tissue}(t)$



$C_{tissue}(t) = C_a(t) \otimes 0.95e^{-0.005t}$

K_1=0.95

k_2=0.005

$C_{tissue}(t) = C_a(t) \otimes 0.95e^{-0.02t}$

K_1=0.95

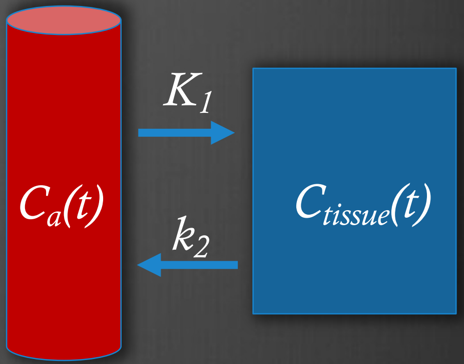
k_2=0.02

$C_{tissue}(t) = C_a(t) \otimes 0.6e^{-0.1t}$

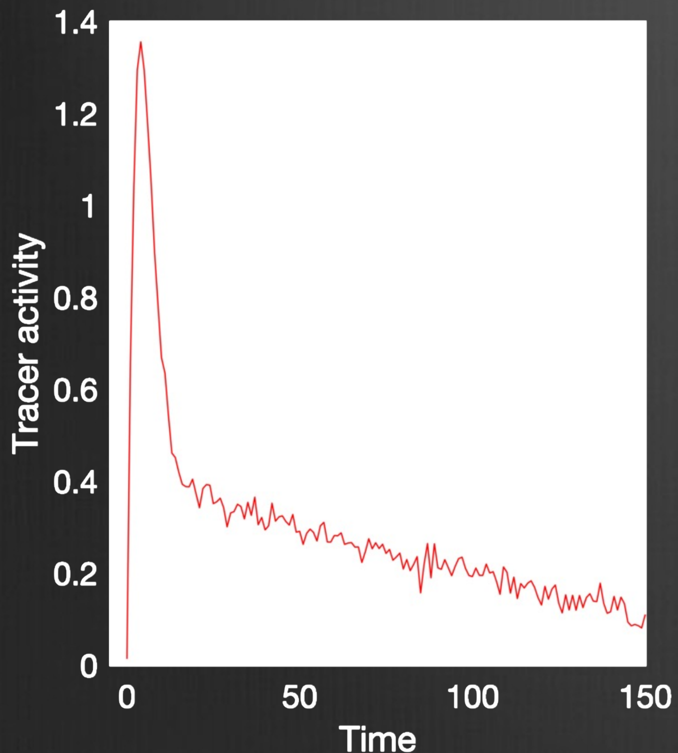
K_1=0.6

k_2=0.1

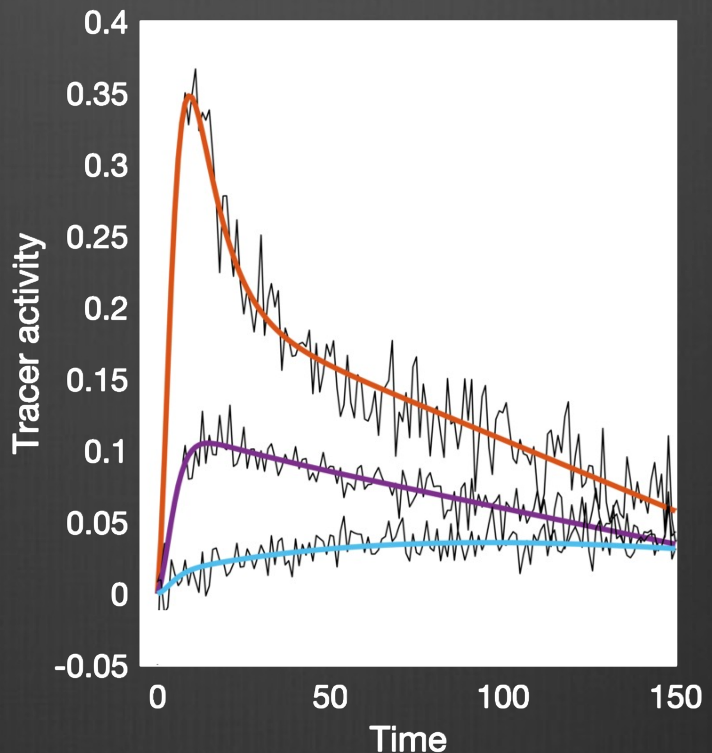
$$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$$



Input function, $C_a(t)$



Tissue function, $C_{tissue}(t)$



$C_{tissue}(t) = C_a(t) \otimes 0.5e^{-0.12t}$

K_1=0.5
k_2=0.12

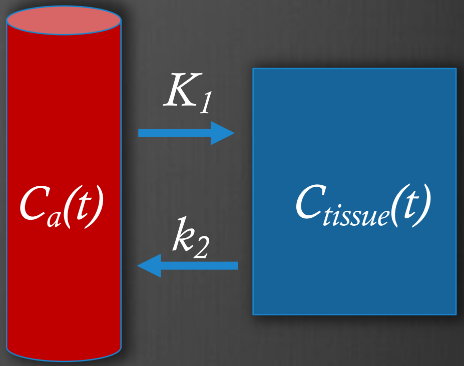
$C_{tissue}(t) = C_a(t) \otimes 0.25e^{-0.05t}$

K_1=0.25
k_2=0.05

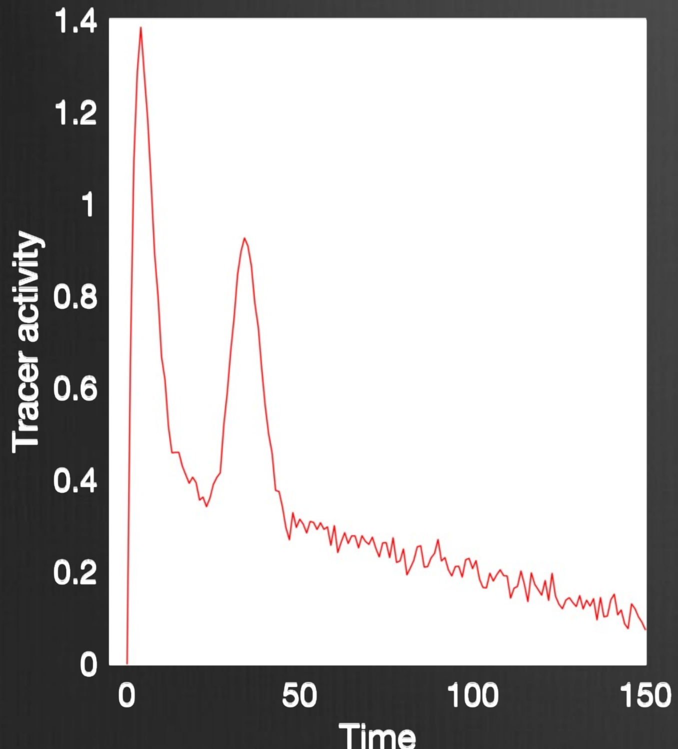
$C_{tissue}(t) = C_a(t) \otimes 0.15e^{-0.1t}$

K_1=0.15
k_2=0.01

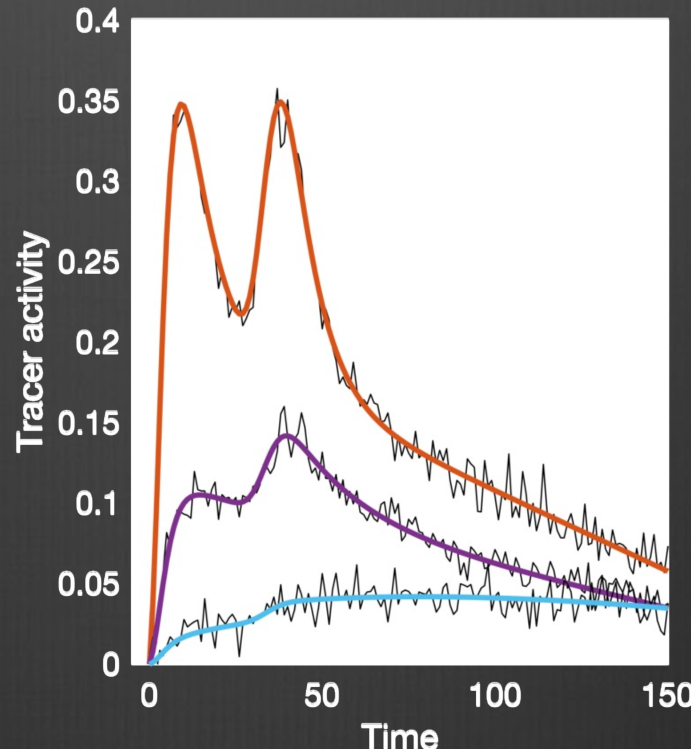
$$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$$



Input function, $C_a(t)$



Tissue function, $C_{tissue}(t)$



$C_{tissue}(t) = C_a(t) \otimes 0.5e^{-0.12t}$

K_1=0.5

k_2=0.12

$C_{tissue}(t) = C_a(t) \otimes 0.25e^{-0.05t}$

K_1=0.25

k_2=0.05

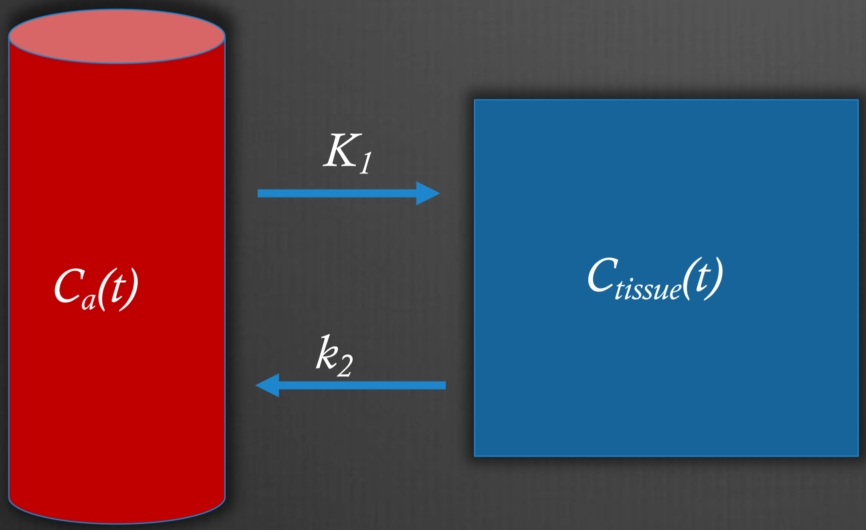
$C_{tissue}(t) = C_a(t) \otimes 0.15e^{-0.1t}$

K_1=0.15

k_2=0.01

How shall we model RF(t)?

- Simple model, one tissue compartment model

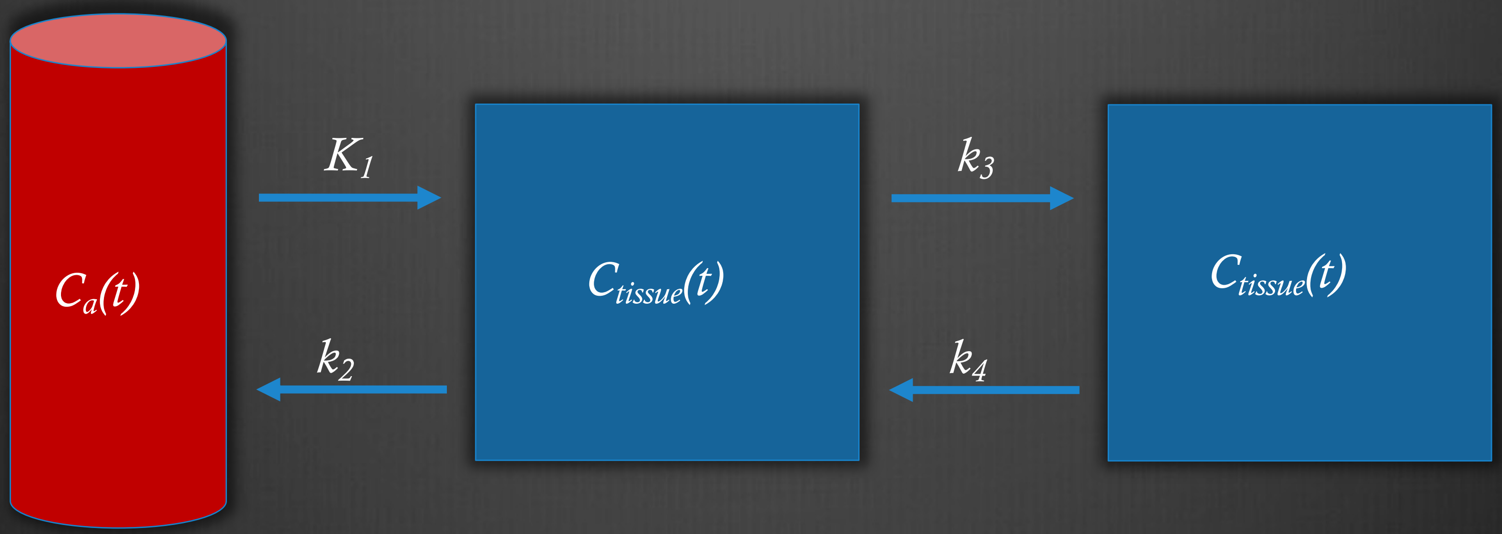


$$\frac{d}{dt}C_{tissue}(t) = K_1 C_a(t) - k_2 C_{tissue}(t)$$

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

How shall we model RF(t)?

- Complex model, two tissue compartment model



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

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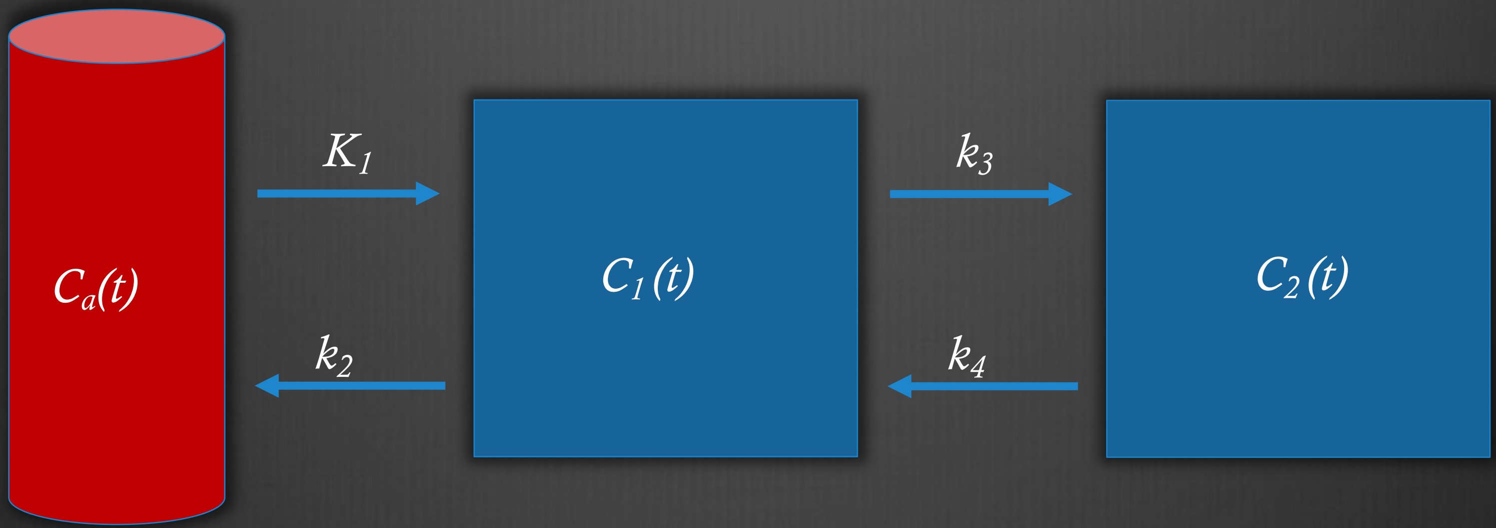
How shall we model RF(t)?

- Complex model, two tissue compartment model

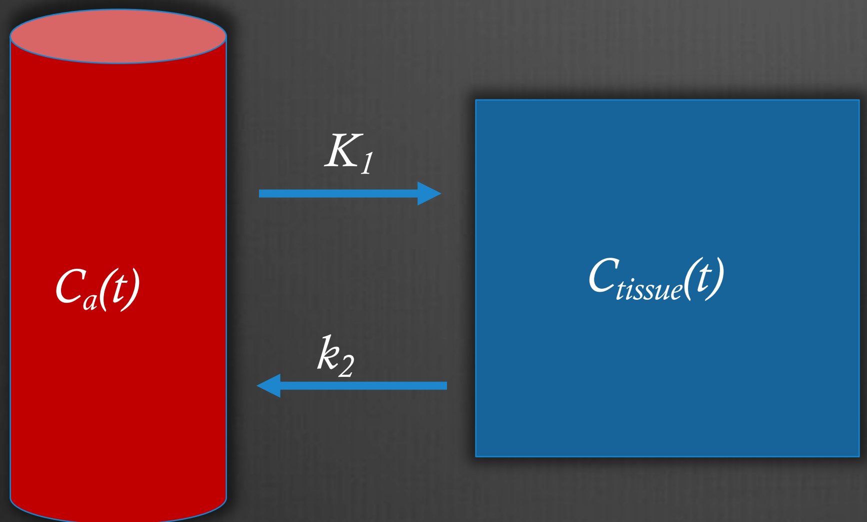


$$\frac{d}{dt}C_1(t) = K_1 C_a(t) - (k_2 + k_3)C_1(t) + k_4 C_2(t)$$

$$\frac{d}{dt}C_2(t) = K_3 C_1(t) - k_4 C_2(t)$$

How shall we model RF(t)?

- Simple model, one tissue compartment model

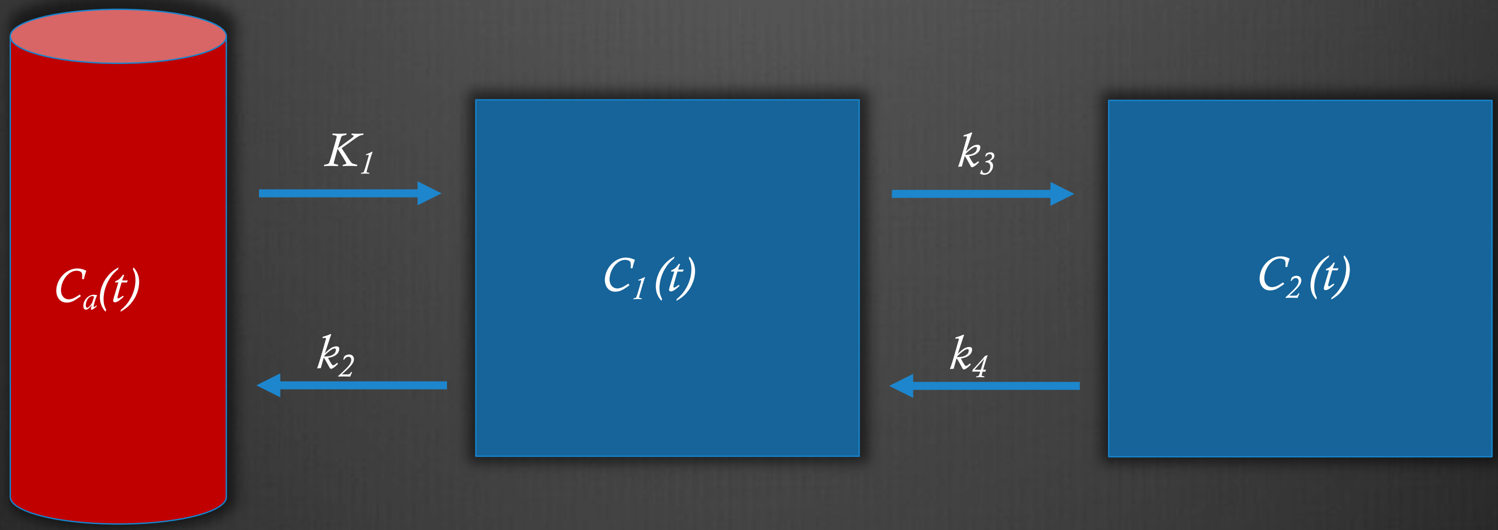


$$\frac{d}{dt}C_{tissue}(t) = K_1 C_a(t) - k_2 C_{tissue}(t)$$

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

How shall we model RF(t)?

- Complex model, two tissue compartment model

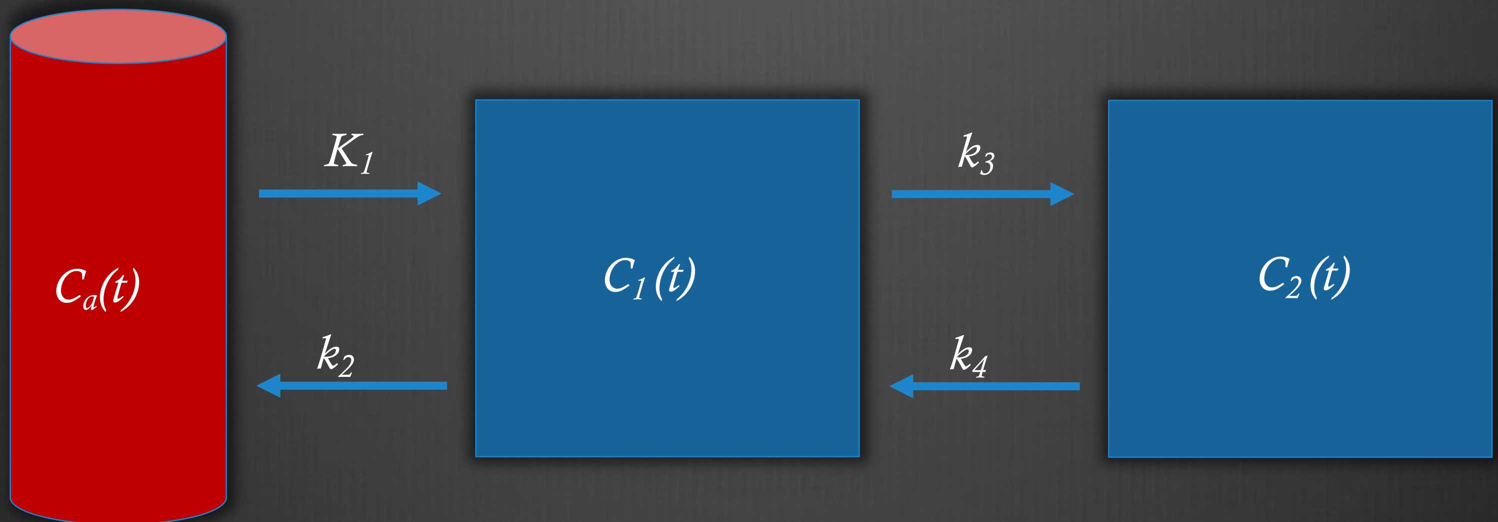


$$\frac{d}{dt}C_1(t) = K_1 C_a(t) - (k_2 + k_2)C_1(t) + k_4 C_2(t)$$

$$\frac{d}{dt}C_2(t) = K_3 C_1(t) - k_4 C_2(t)$$

How shall we model RF(t)?

- Complex model, two tissue compartment model

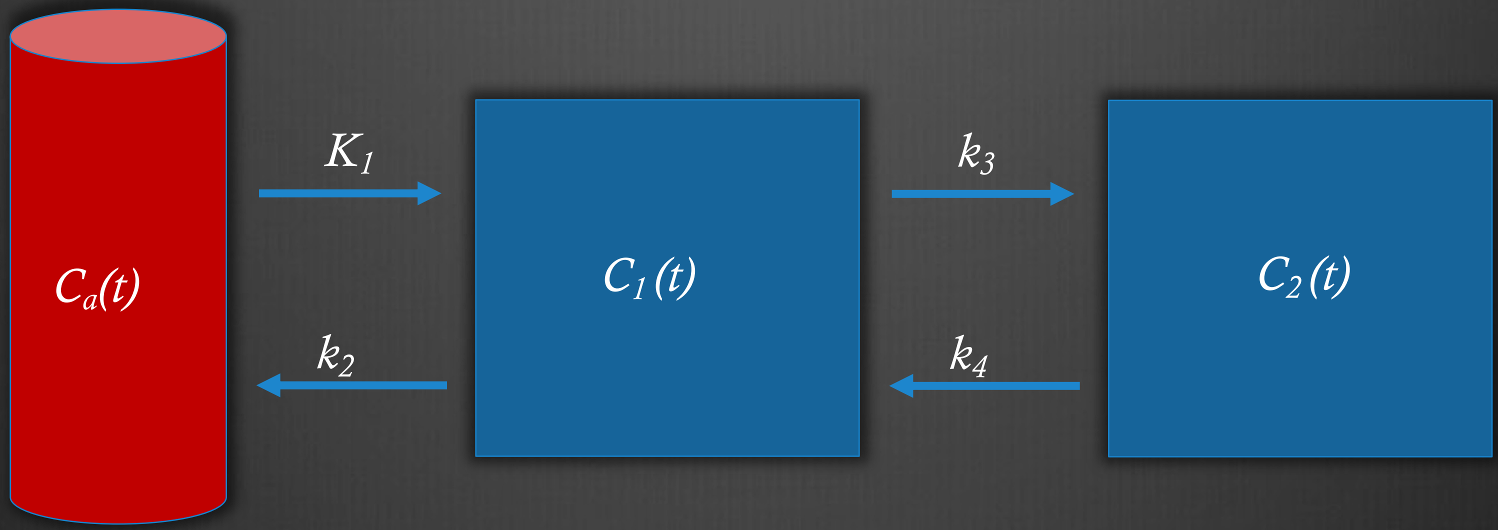


$$C_1 = C_a(t) \otimes \frac{K_1}{\frac{k_2+k_3+k_4+\sqrt{(k_2+k_3+k_4)^2-4k_2k_4}}{2} - \frac{k_2+k_3+k_4-\sqrt{(k_2+k_3+k_4)^2-4k_2k_4}}{2}} *$$

$$\left[\left(K_4 - \frac{k_2+k_3+k_4-\sqrt{(k_2+k_3+k_4)^2-4k_2k_4}}{2} \right) e^{-t*\frac{k_2+k_3+k_4-\sqrt{(k_2+k_3+k_4)^2-4k_2k_4}}{2}} + \left(\frac{k_2+k_3+k_4-\sqrt{(k_2+k_3+k_4)^2-4k_2k_4}}{2} - K_4 \right) e^{-t*\frac{k_2+k_3+k_4+\sqrt{(k_2+k_3+k_4)^2-4k_2k_4}}{2}} \right]$$

How shall we model RF(t)?

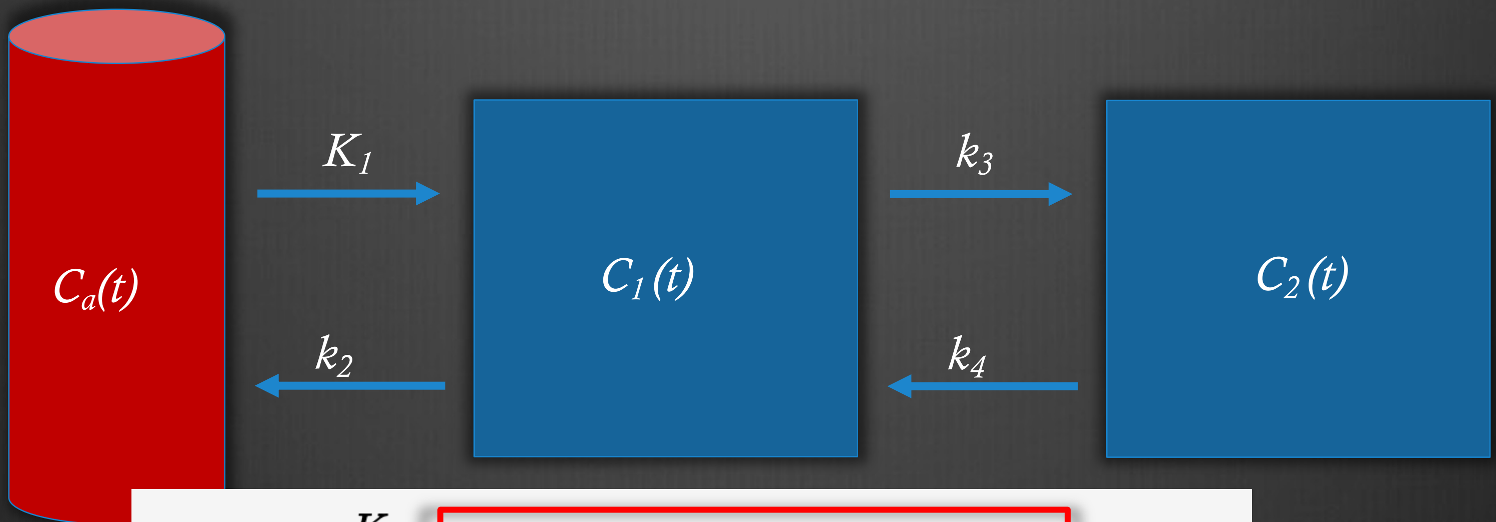
- Complex model, two tissue compartment model



$$C_2 = C_a(t) \otimes \frac{K_1 K_3}{\frac{k_2+k_3+k_4+\sqrt{(k_2+k_3+k_4)^2-4k_2k_4}}{2} - \frac{k_2+k_3+k_4-\sqrt{(k_2+k_3+k_4)^2-4k_2k_4}}{2}} * \left[e^{-t*\frac{k_2+k_3+k_4-\sqrt{(k_2+k_3+k_4)^2-4k_2k_4}}{2}} - e^{-t*\frac{k_2+k_3+k_4+\sqrt{(k_2+k_3+k_4)^2-4k_2k_4}}{2}}\right]$$

How shall we model RF(t)?

- Complex model, two tissue compartment model



$$C_1(t) = \frac{K_1}{\alpha_2 - \alpha_1}\left[(k_4 - \alpha_1)e^{-\alpha_1 t} + (\alpha_2 - k_4)e^{-\alpha_2 t}\right] \otimes C_0(t)$$

$$C_2(t) = \frac{K_1 k_3}{\alpha_2 - \alpha_1}\left[e^{-\alpha_1 t} - e^{-\alpha_2 t}\right] \otimes C_0(t)$$

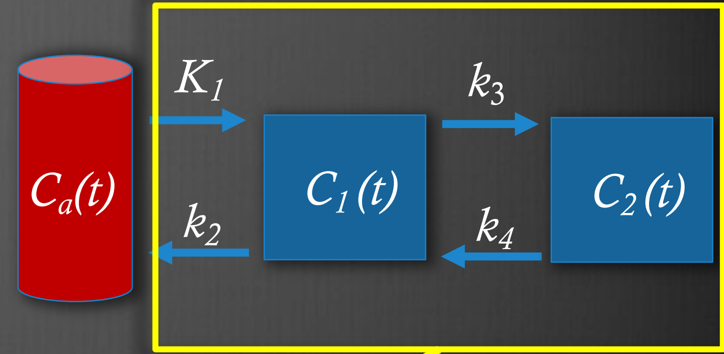
, where

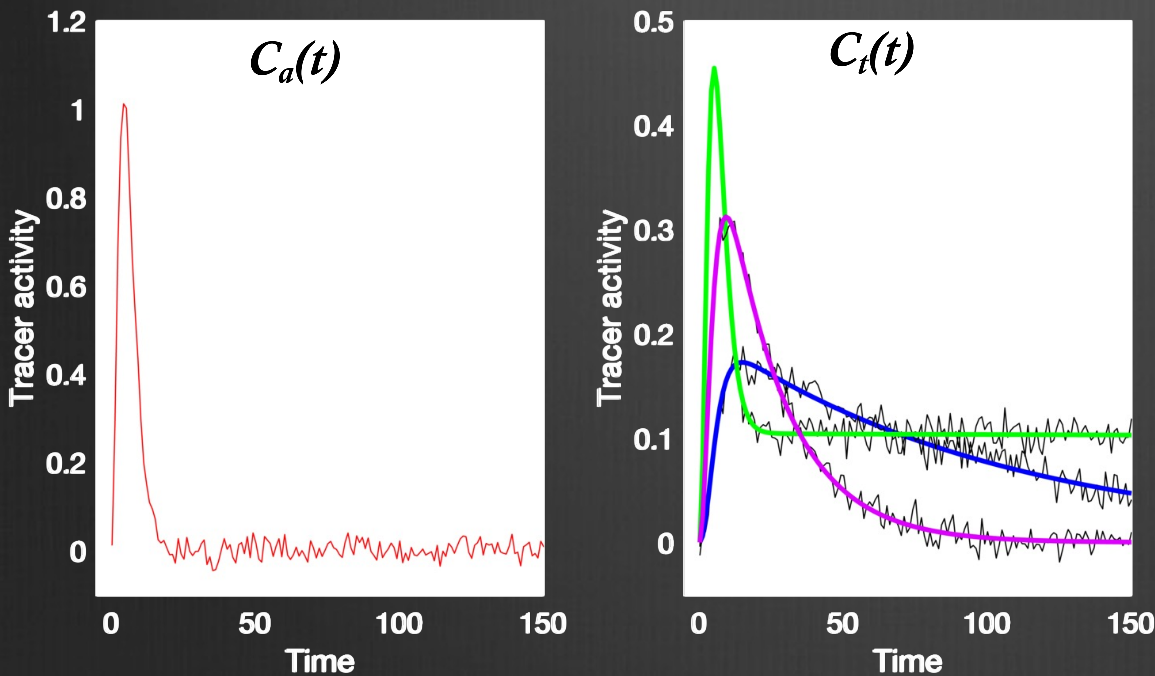
$$\alpha_1 = \frac{k_2 + k_3 + k_4 - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}}{2}$$

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

$$\frac{d}{dt}C_1(t) = K_1 C_a(t) - (k_2 + k_2)C_1(t) + k_4 C_2(t)$$

$$\frac{d}{dt}C_2(t) = K_3 C_1(t) - k_4 C_2(t)$$

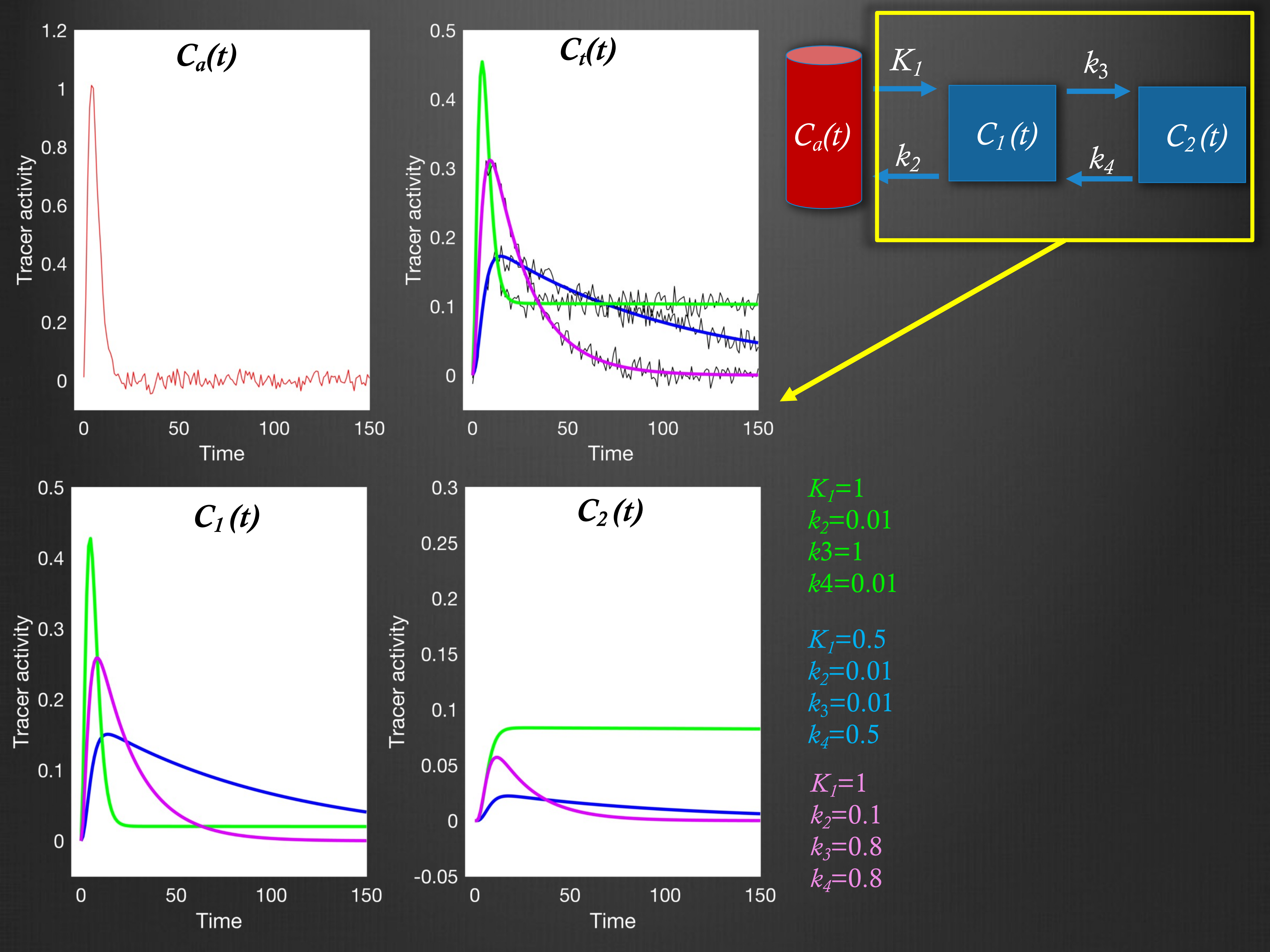




K_1=1
k_2=0.01
$k3$=1
$k4$=0.01

K_1=0.5
k_2=0.01
k_3=0.01
k_4=0.5

K_1=1
k_2=0.1
k_3=0.8
k_4=0.8



Ca(t)
Ct(t)
C1(t)
C2(t)
K1
k2
k3
k4
Tracer activity
Time
K1=1
k2=0.01
k3=1
k4=0.01
K1=0.5
k2=0.01
k3=0.01
k4=0.5
K1=1
k2=0.1
k3=0.8
k4=0.8

Summary

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

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

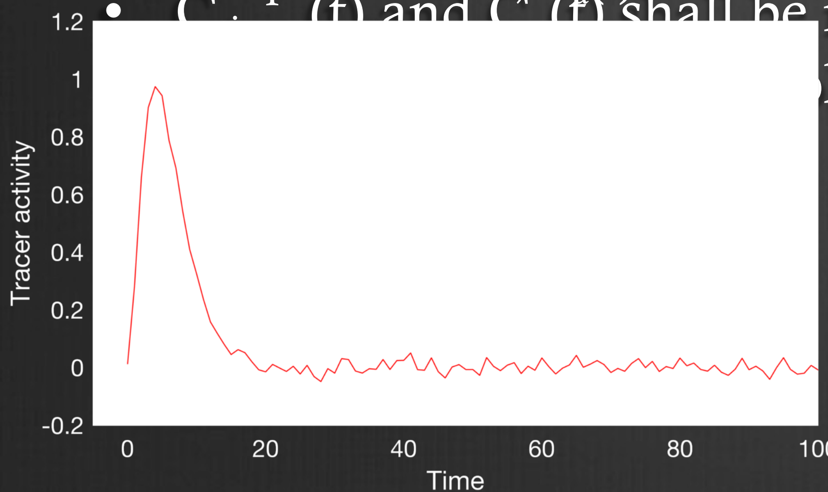
- The input function is related to tissue function by modelling
- The input function and tissue functions is related by the impulse reponse function of the system

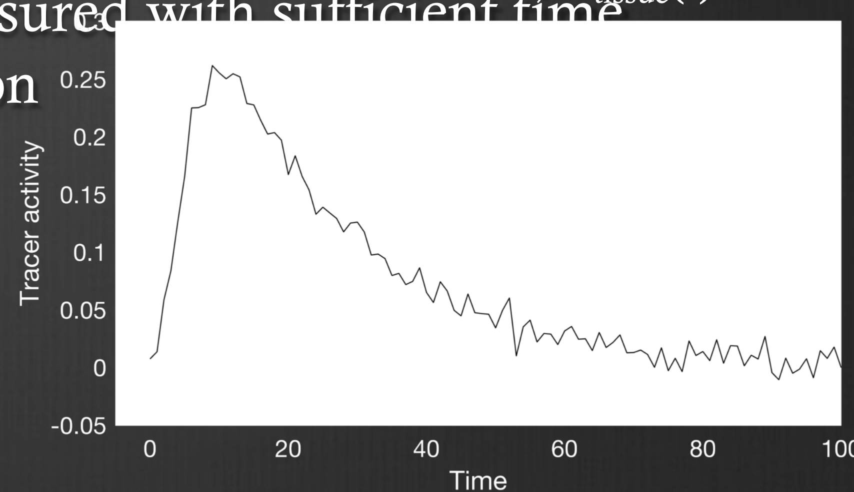
$$C_{tissue}(t) = C_a(t) \otimes RF(t)$$

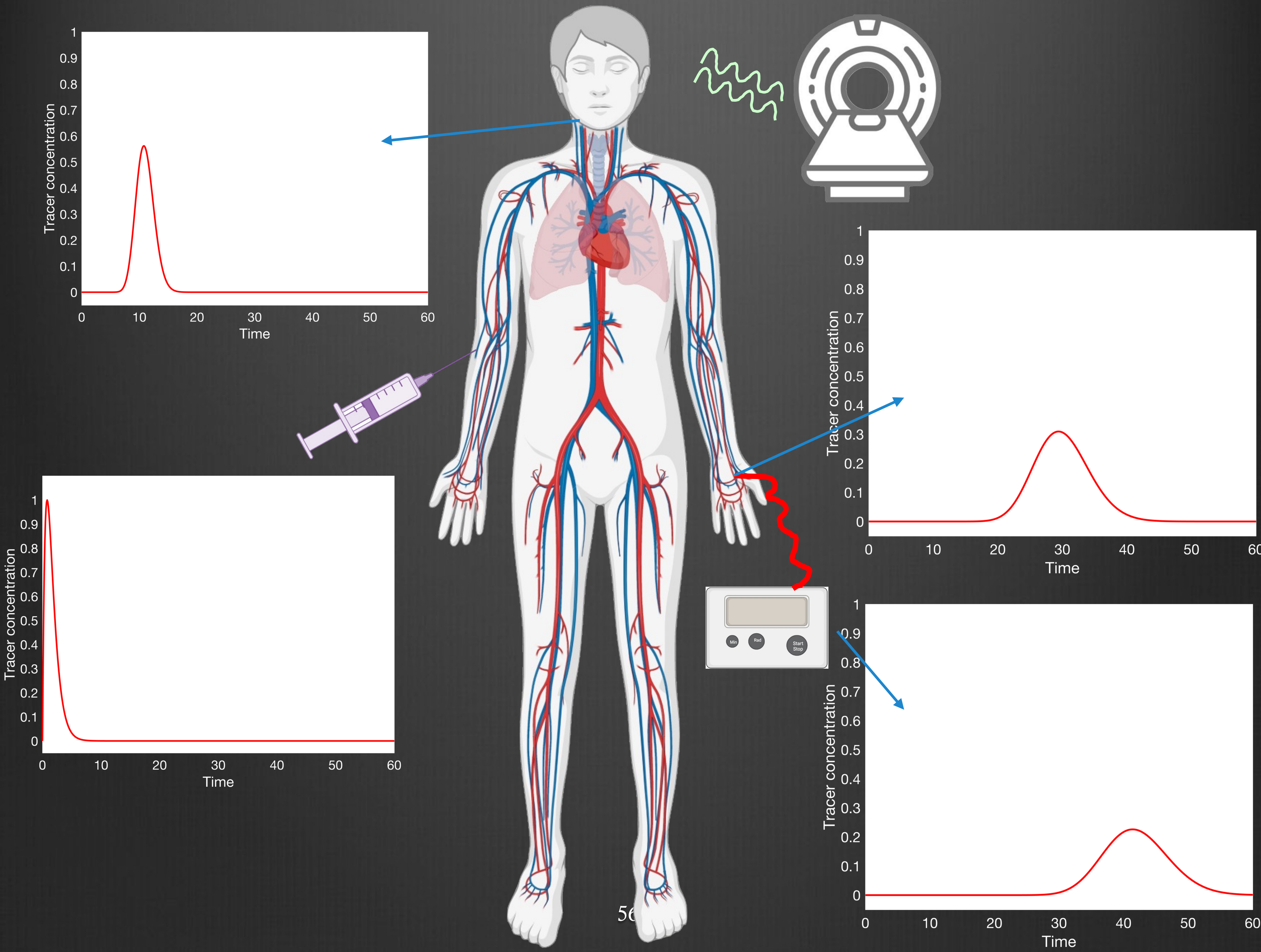
- We model the impulse response function of the system
  - Compartment model
    - Choose most simple but correct model
  - The parameters used to fit the model can be related to physiology

Tracer functions

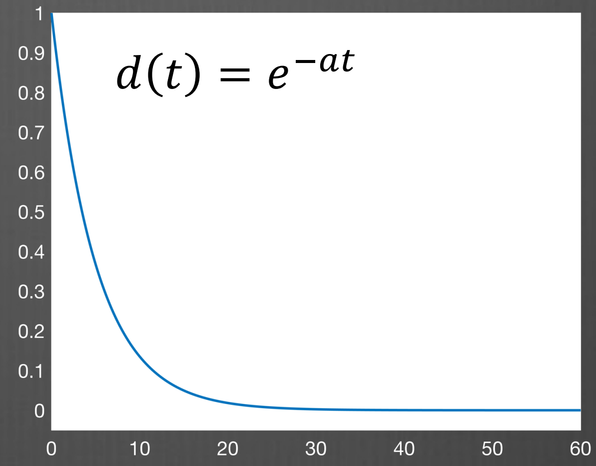
- $C_{tissue}(t)$
  - Scanners
- $C_a(t)$
  - Scanners, image-derived input function
  - Blood sampling
- $C_{tissue}(t)$ and $C_a(t)$ must be in same units or same reference
- C (t) and C (t) shall be measured with sufficient time ... lution

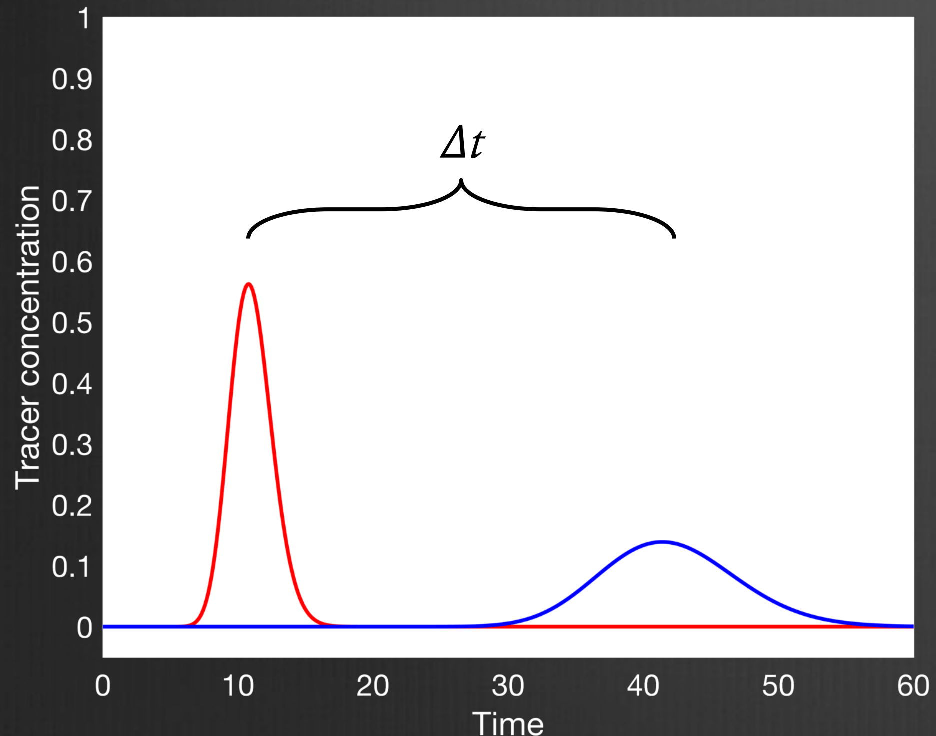


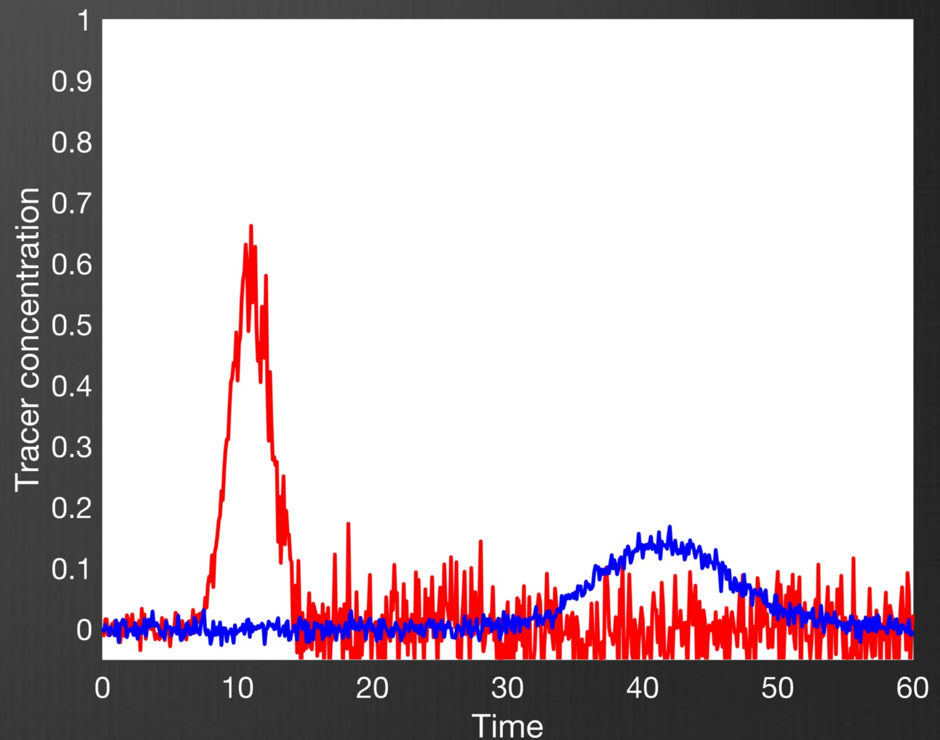


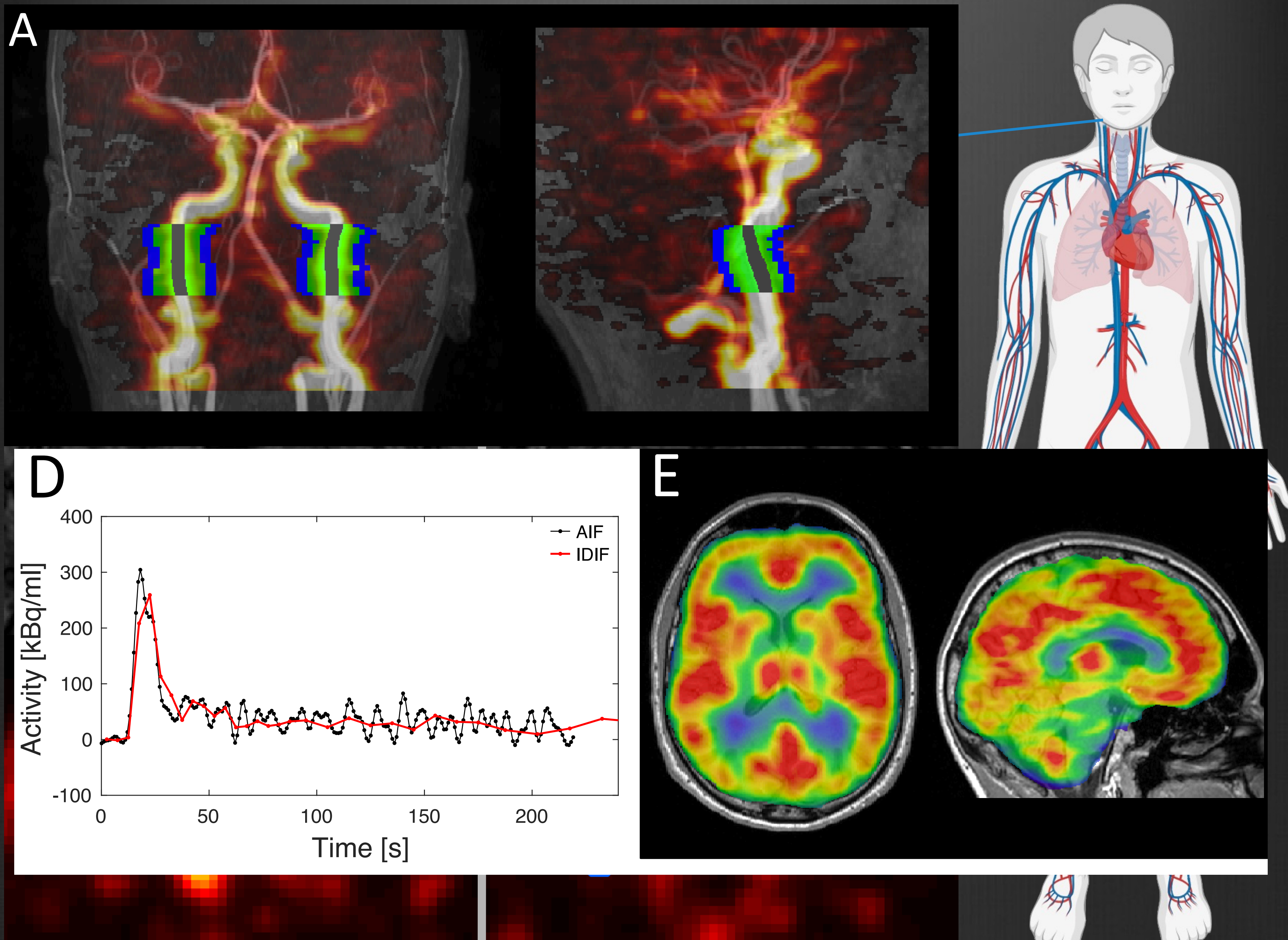

Tracer concentration
Time
0 10 20 30 40 50 60
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
Tracer concentration
Time
0 10 20 30 40 50 60
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
Tracer concentration
Time
0 10 20 30 40 50 60
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
Tracer concentration
Time
0 10 20 30 40 50 60
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
Min
Rad
Start Stop

$$C_{\mathrm{meas}}(t) = C_{\mathrm{true}}(t) \otimes d(t)$$

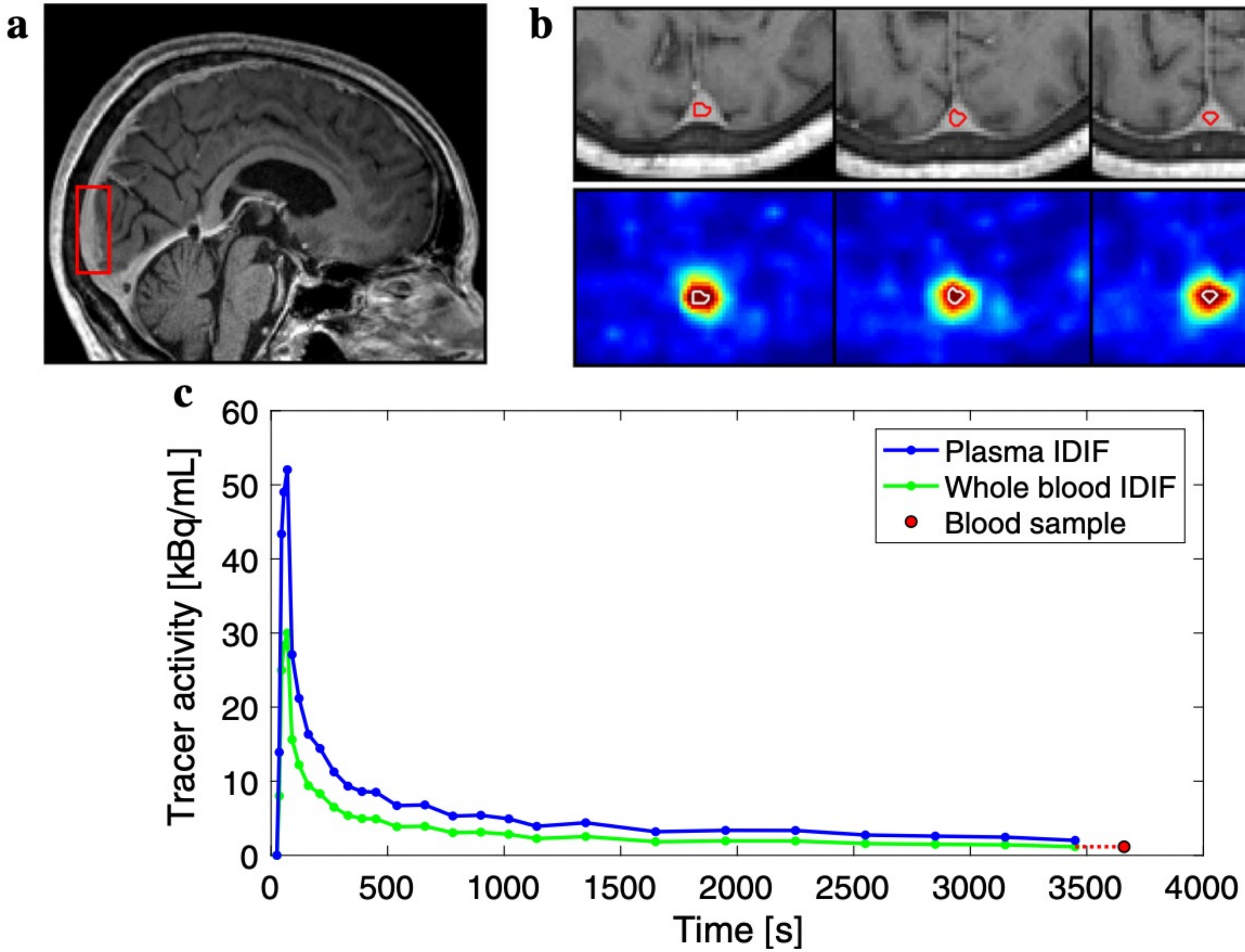




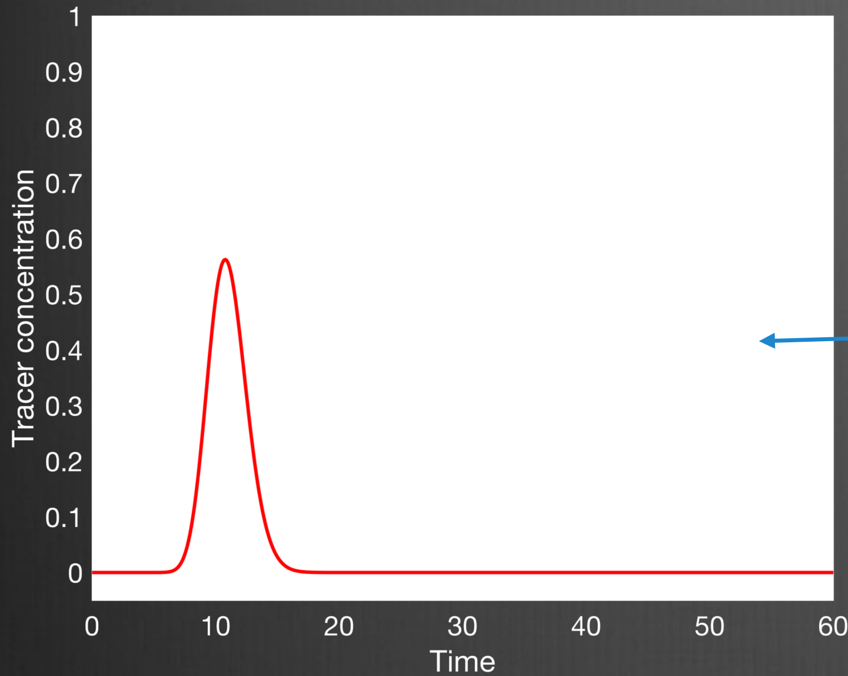


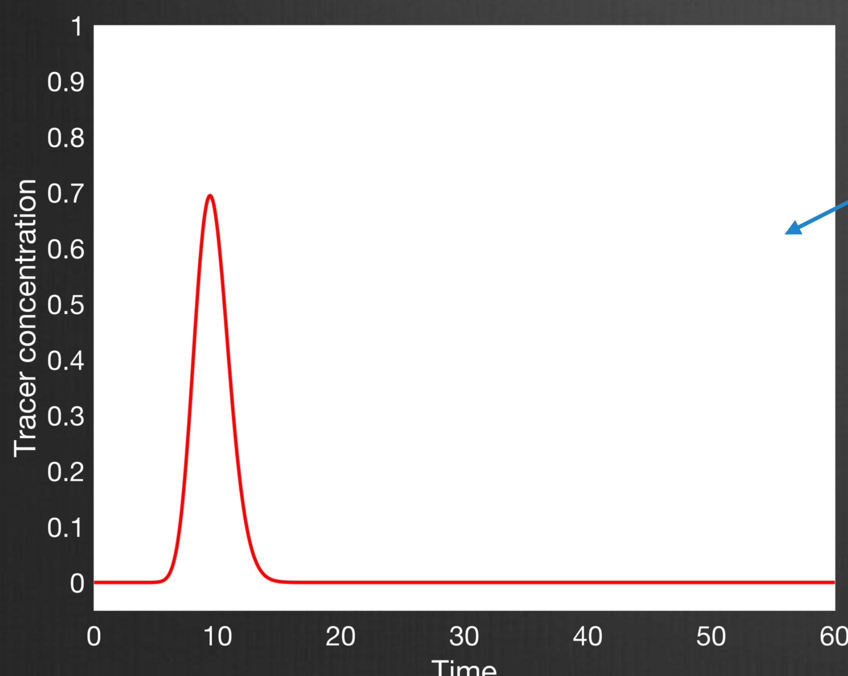


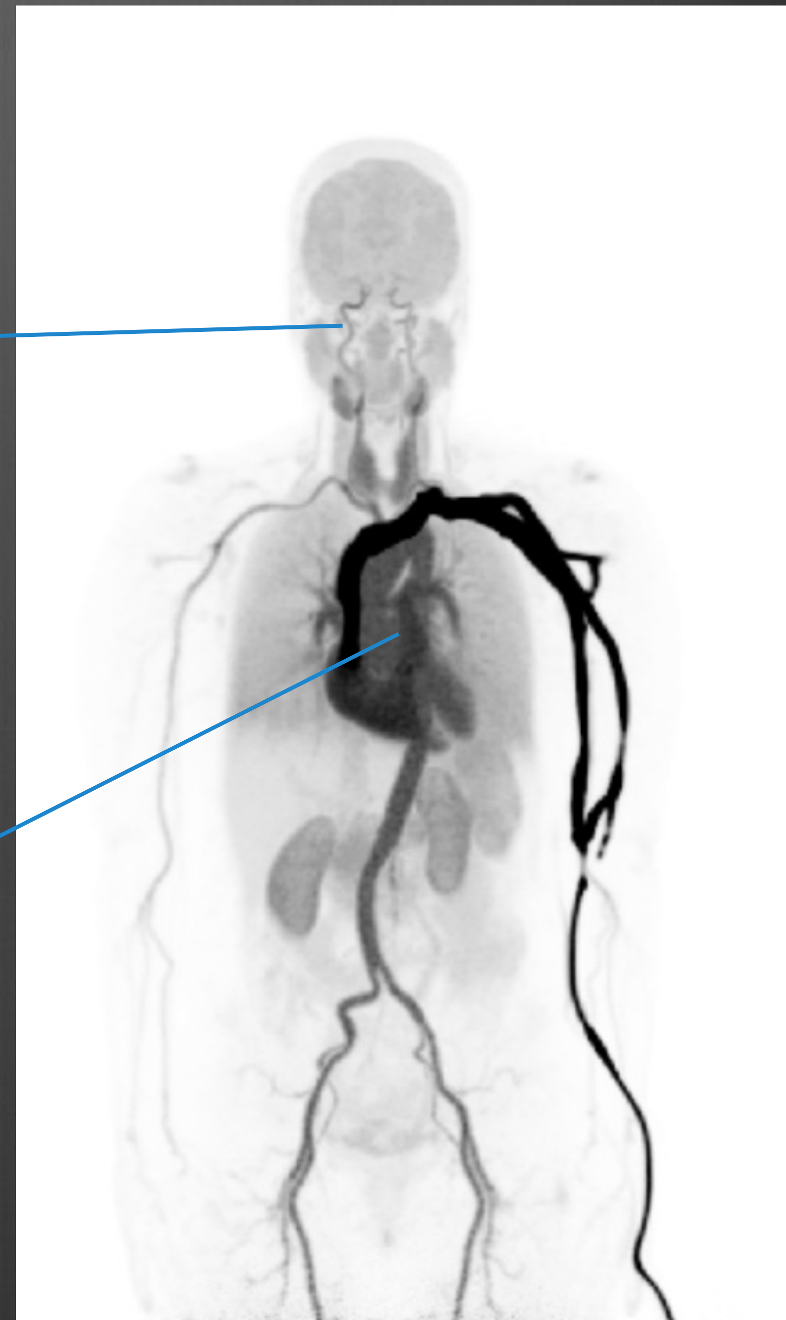
Vestergaard et al. NeuroImage 233 (2021) 117950

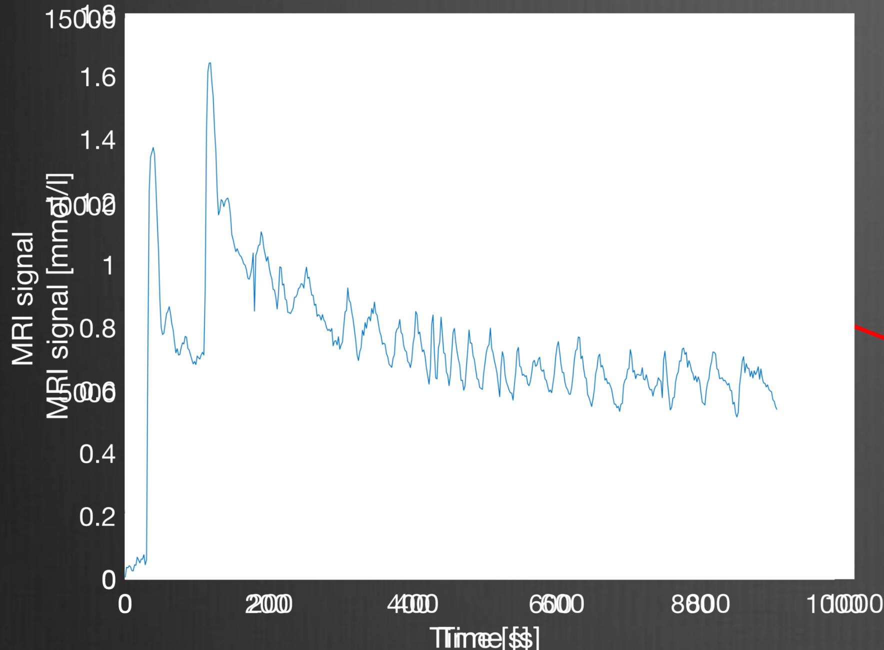


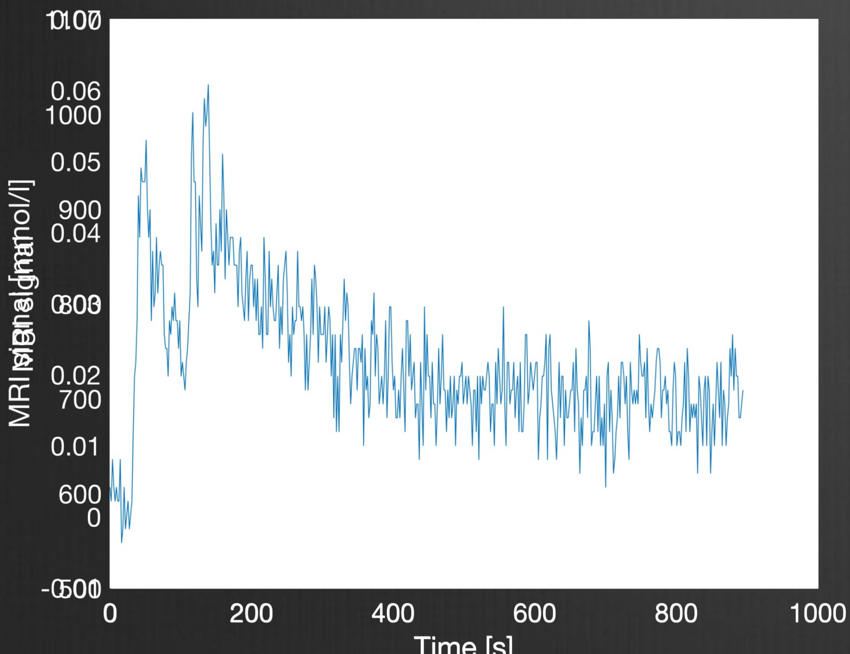
Asma Bashir et al. European Journal of Nuclear Medicine and Molecular Imaging (2020) 47:2577–2588

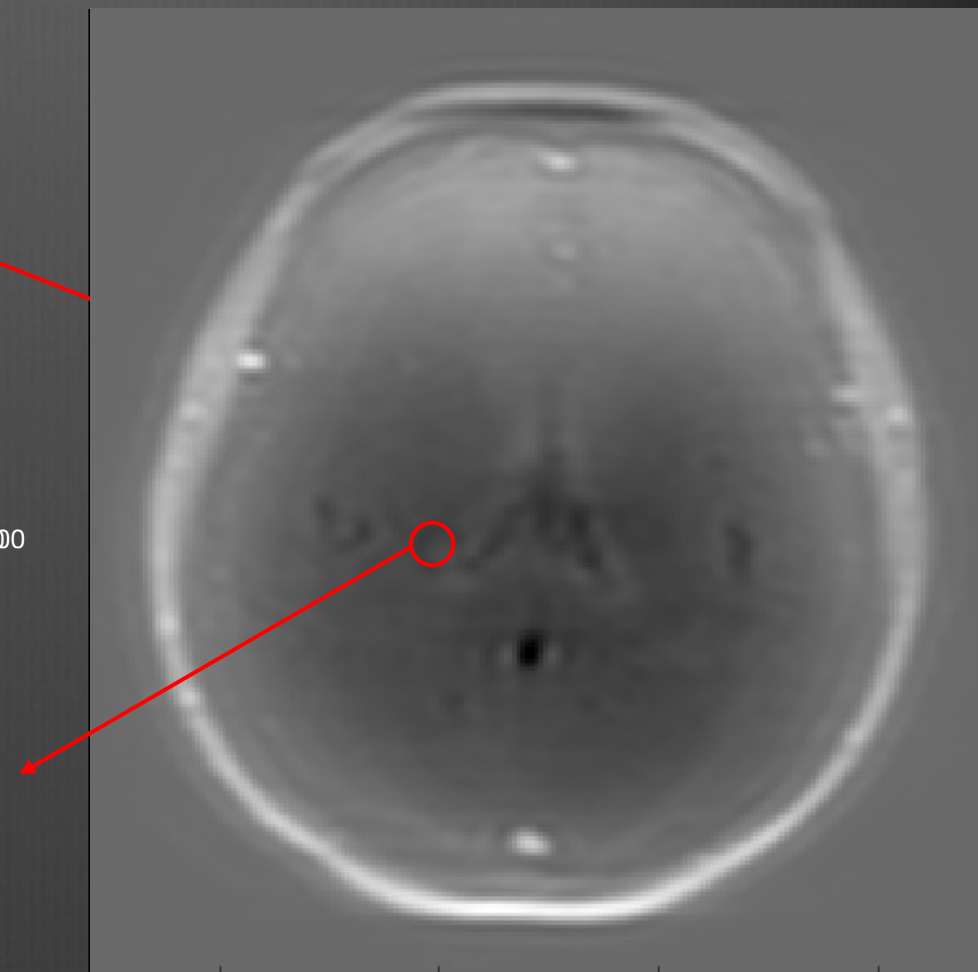

Tracer concentration
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
Time

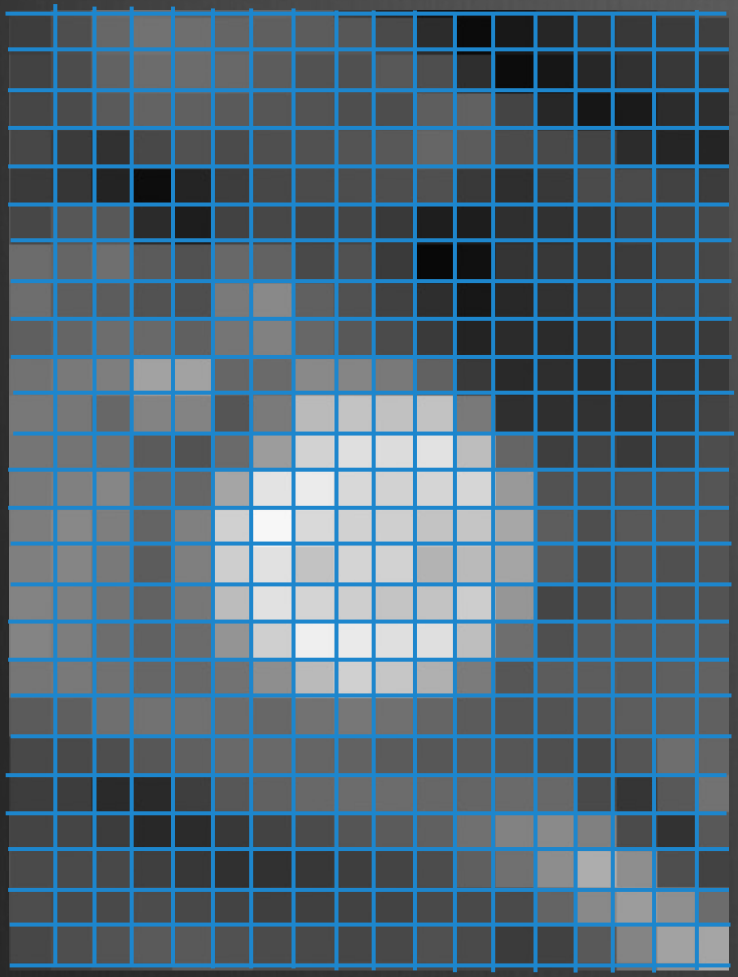

Tracer concentration
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
Time

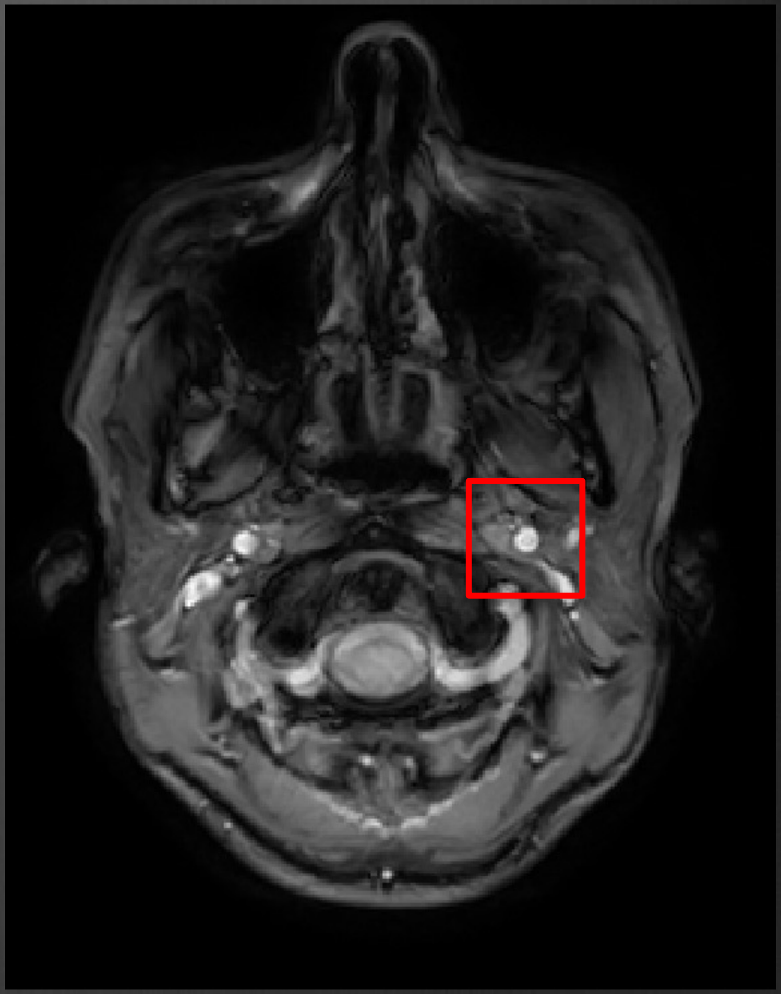


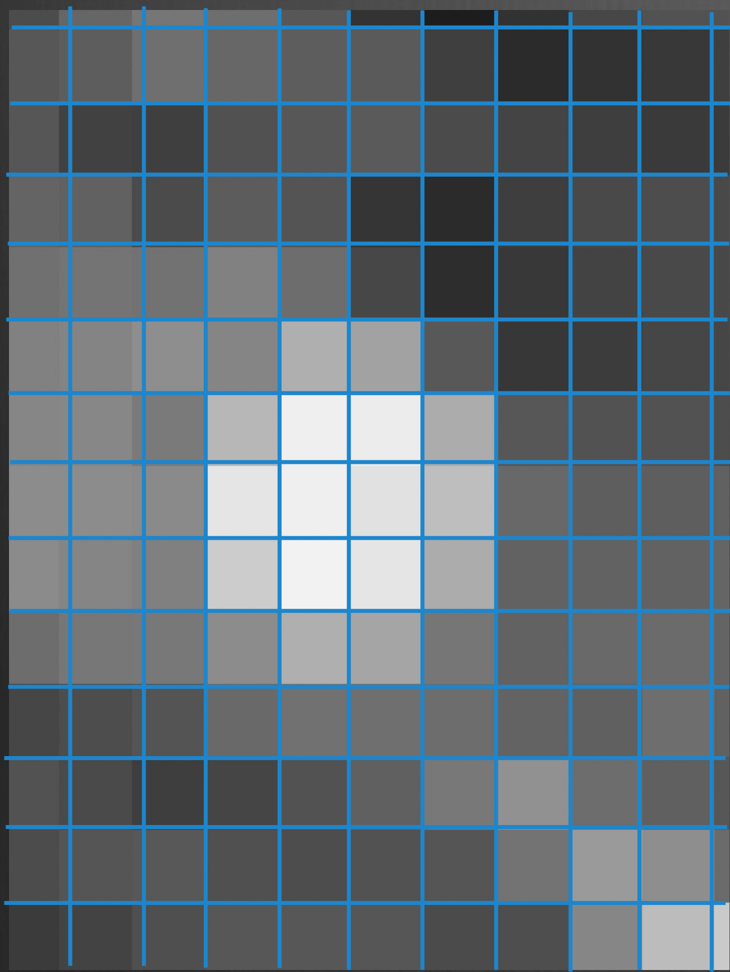

1.6
1.4
1
0.8
0.4
0.2
0
MRI signal

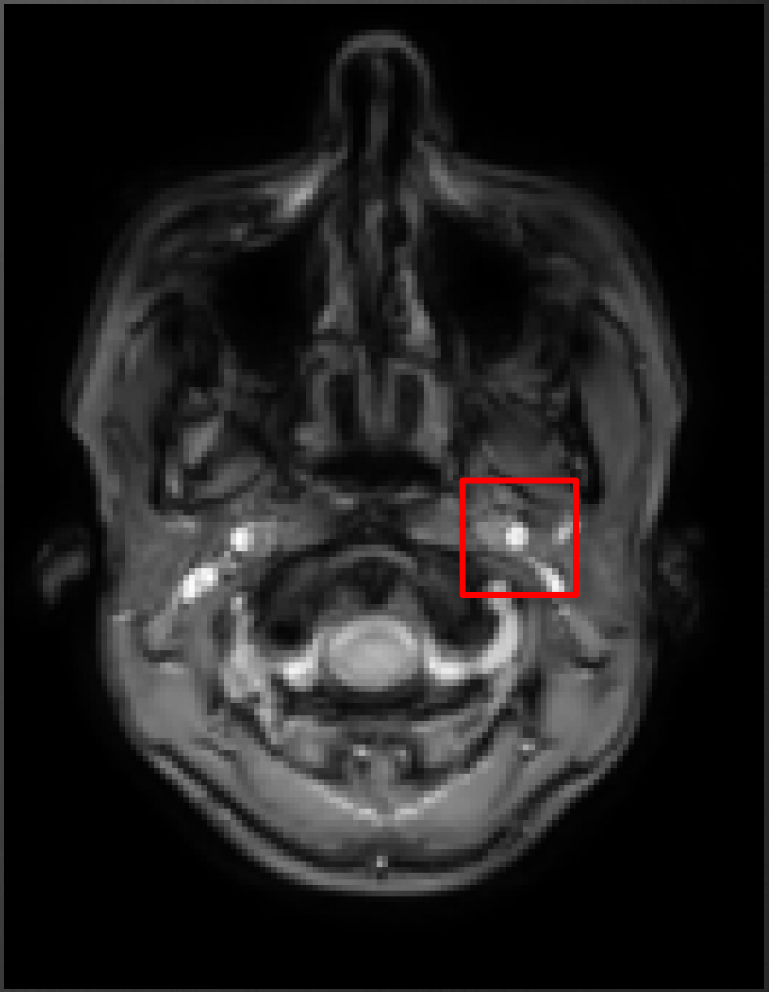

0.06
1000
0.05
900
0.04
0.02
700
0.01
600
0
0
200
400
600
800
1000
Time [s]



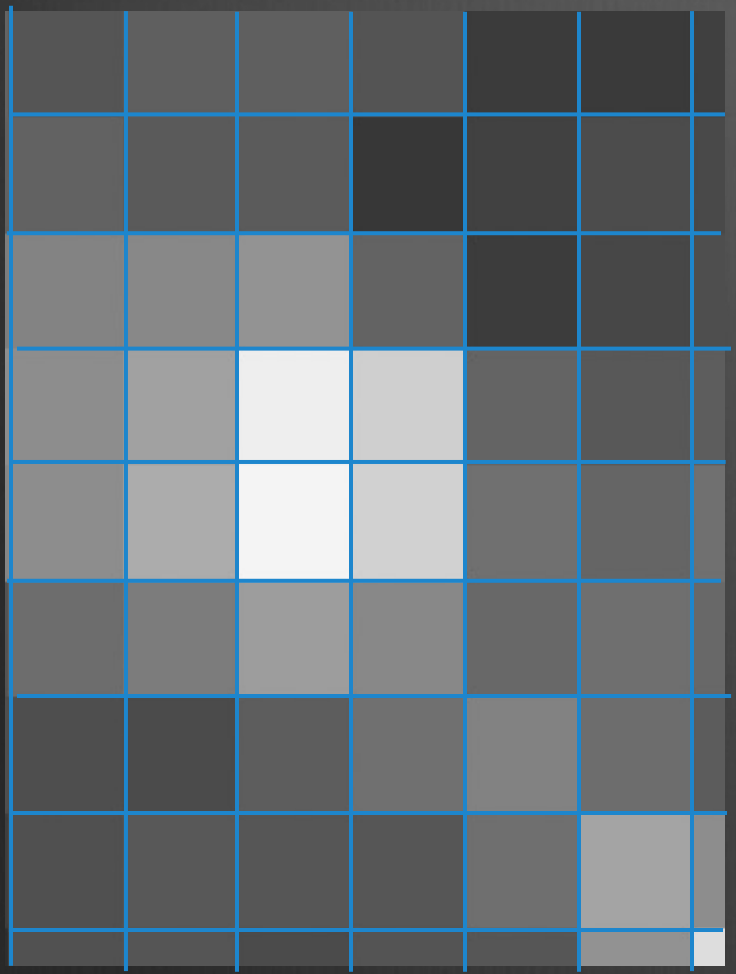




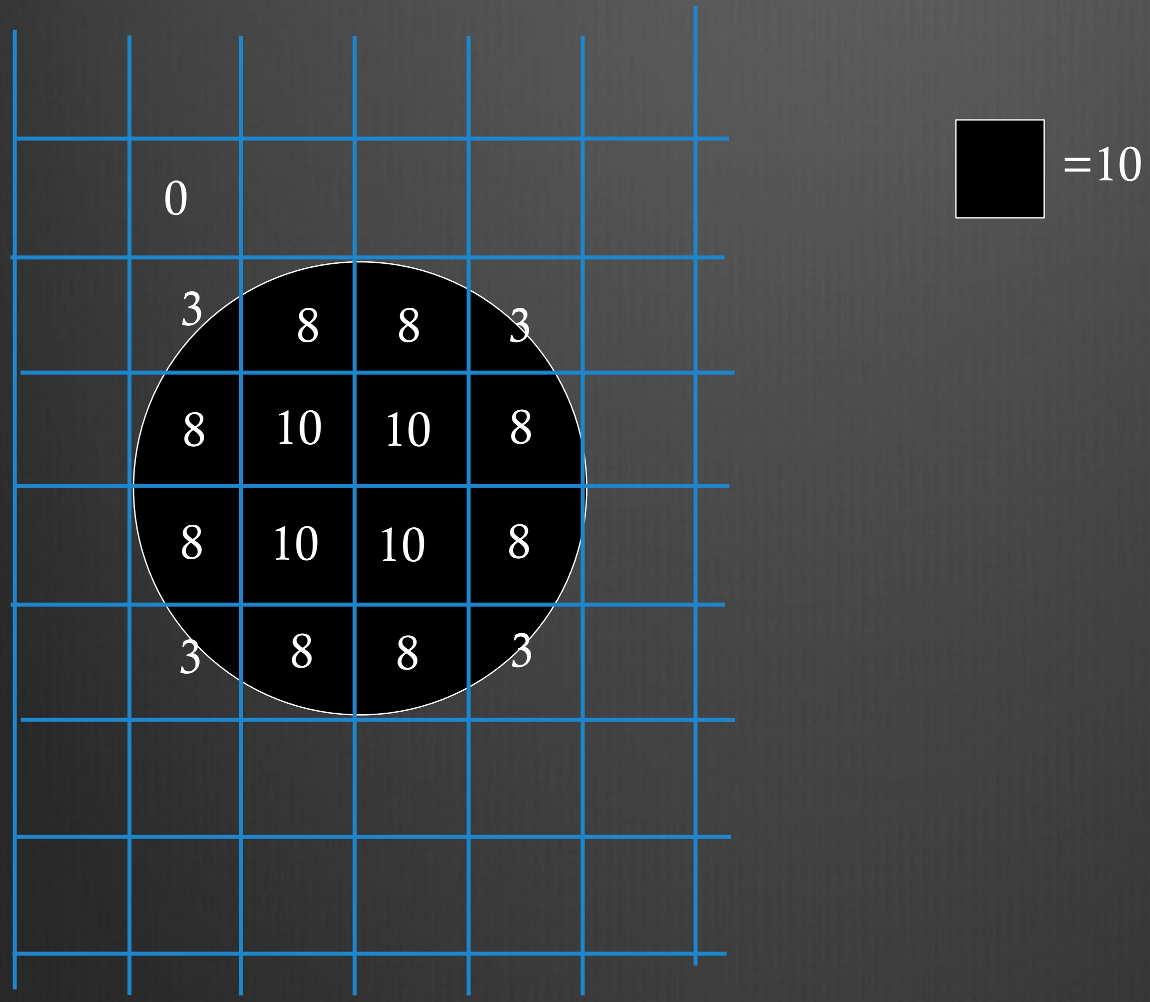




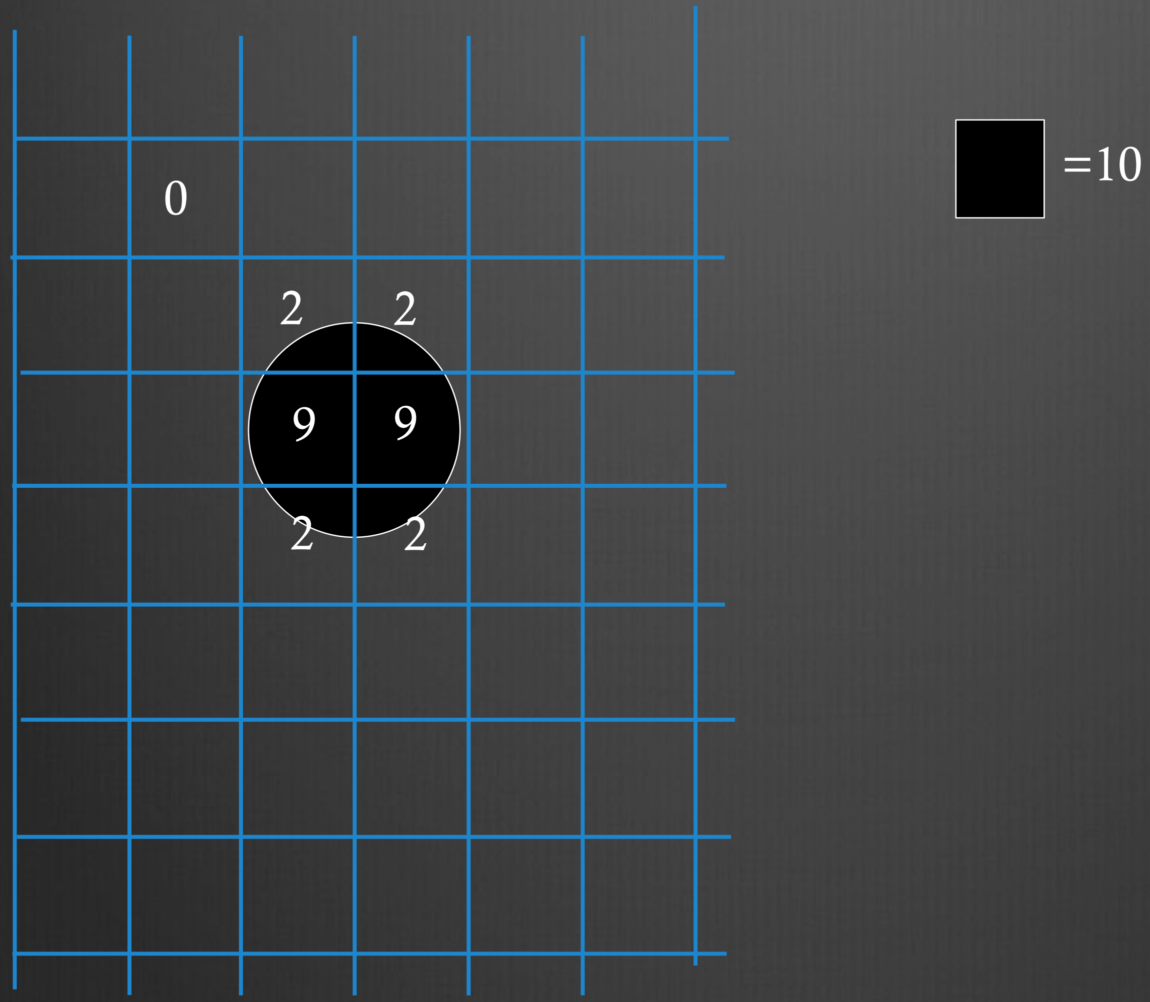
Partial volume errors



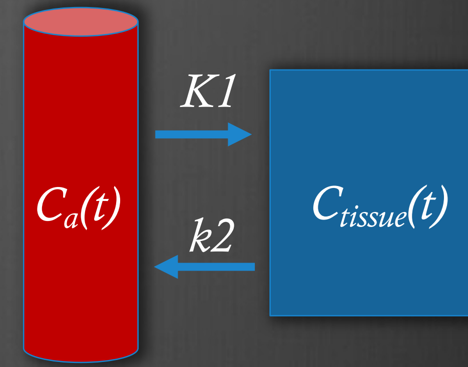
Partial volume errors



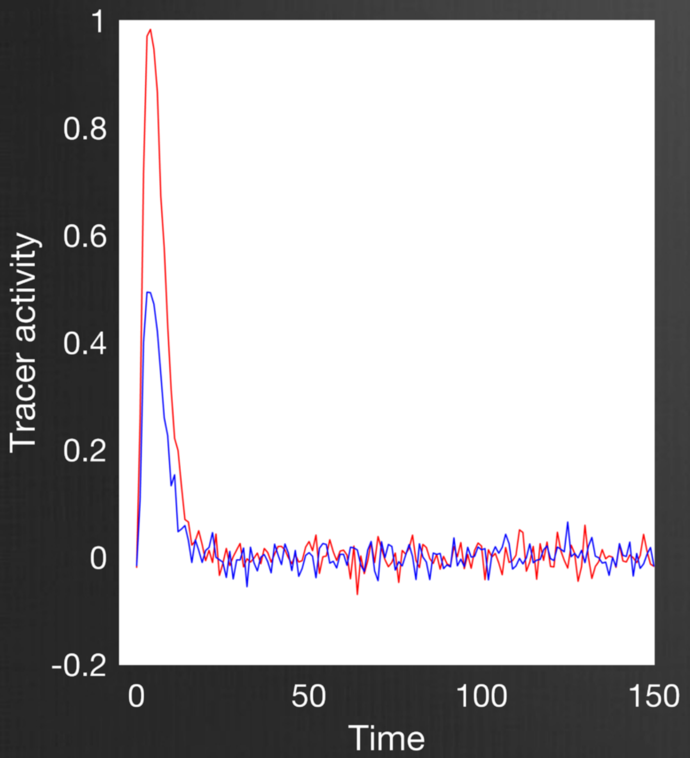
Partial volume errors



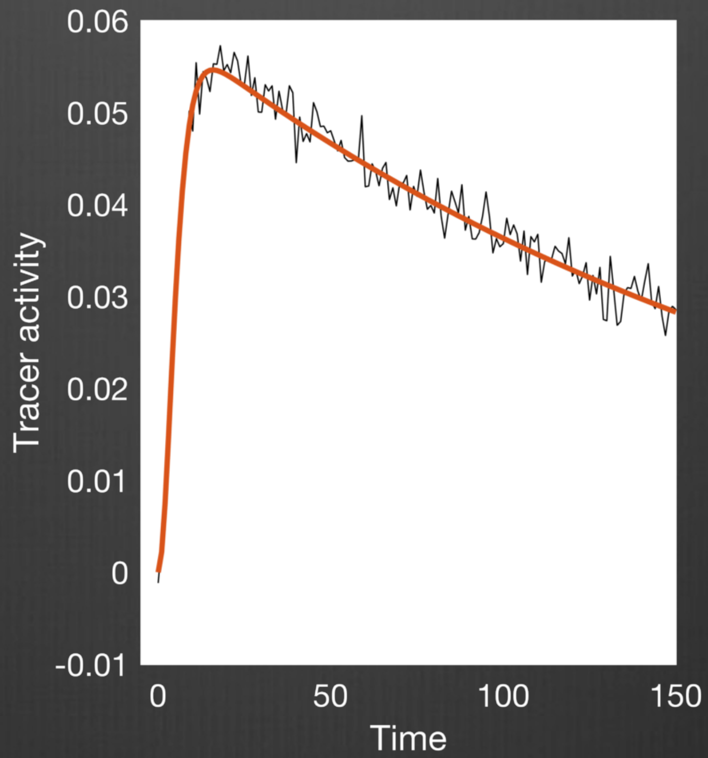
$$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$$



Input function, $C_a(t)$



Tissue function, $C_{tissue}(t)$



$C_{tissue}(t) = C_a(t) \otimes 0.95e^{-0.005t}$

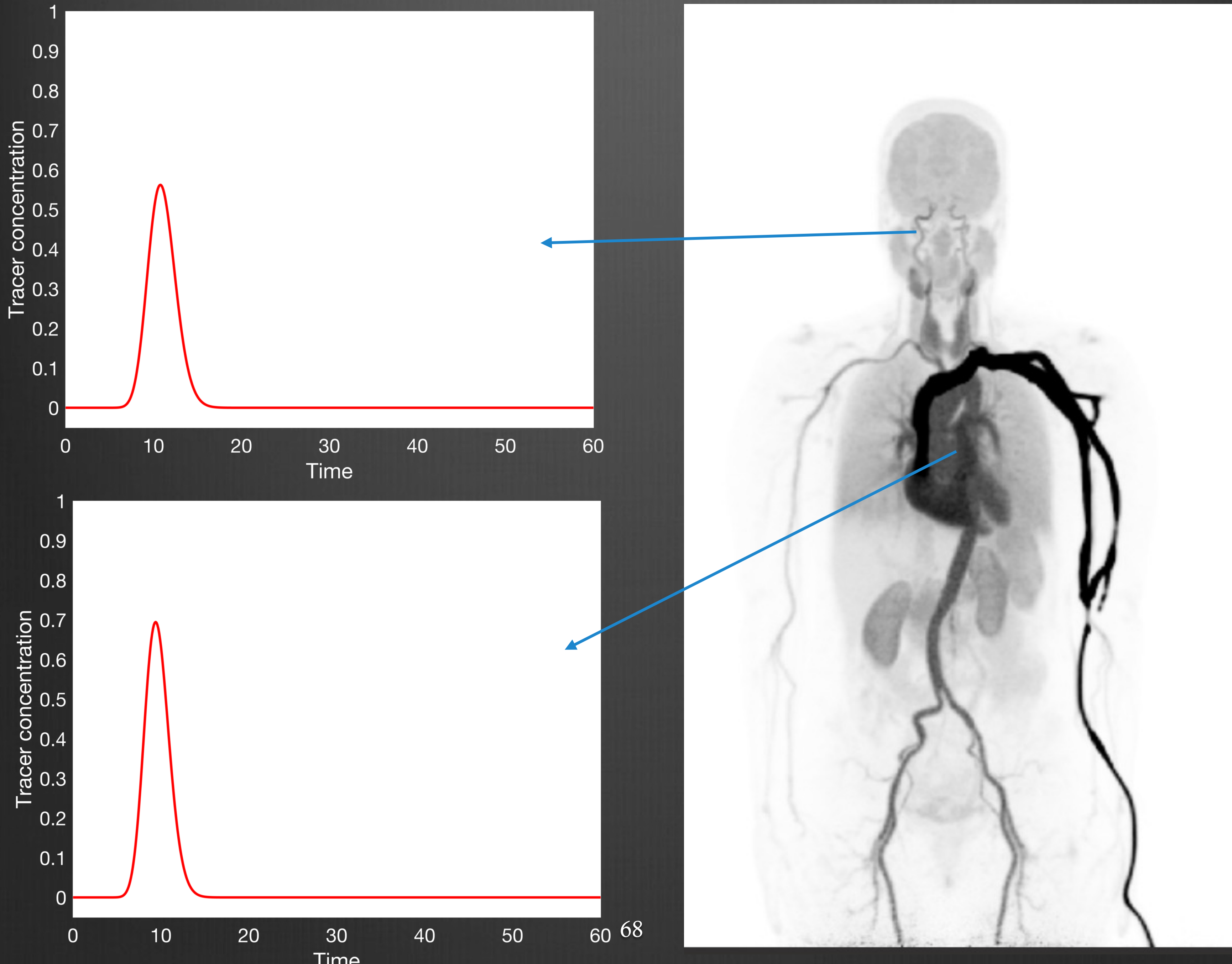
K1=0.9

k2=0.005

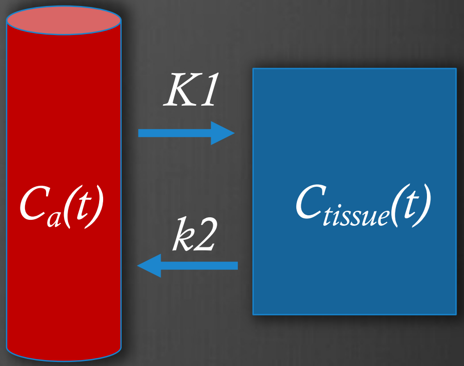
$C_{tissue}(t) = C_a(t) \otimes 0.95e^{-0.005t}$

***K1*=1.8**

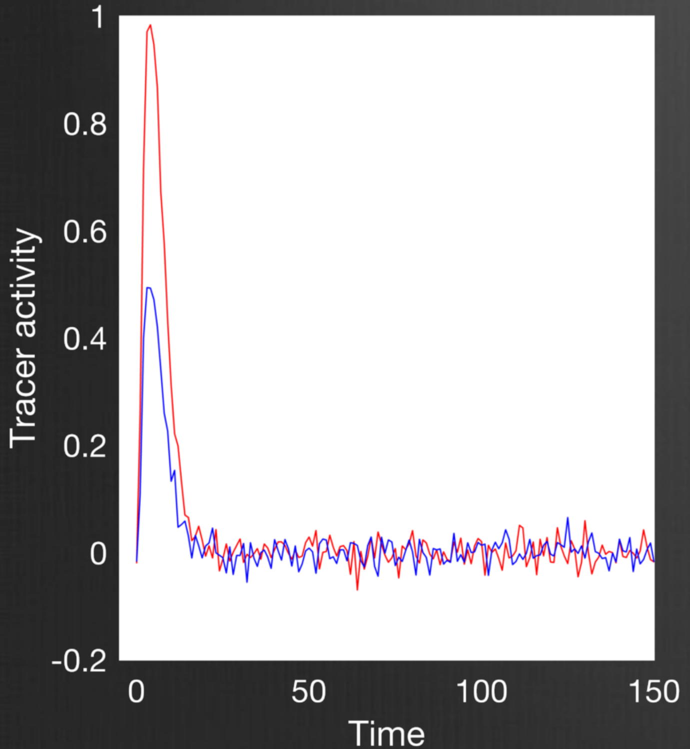
k2=0.005


Tracer concentration
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 10 20 30 40 50 60
Time
Tracer concentration
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 10 20 30 40 50 60
Time

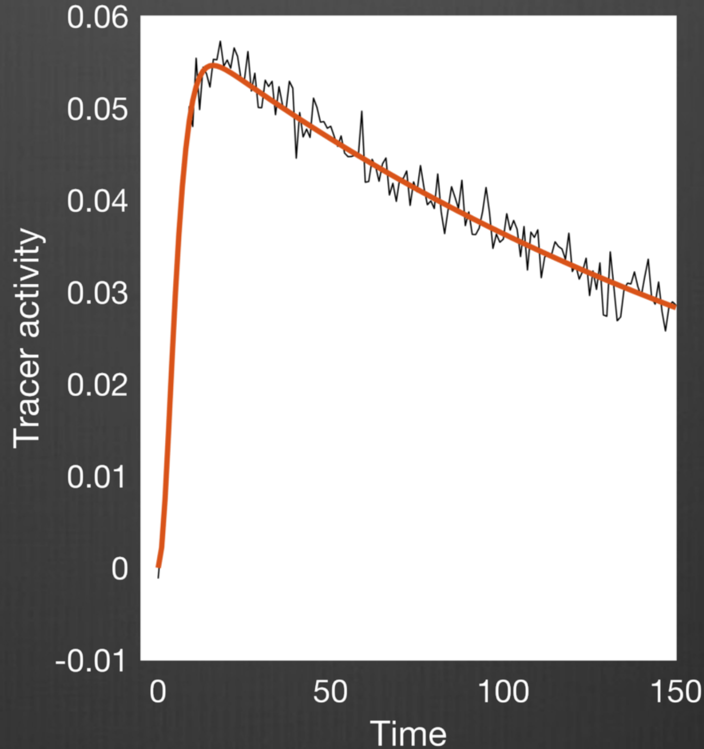
$$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$$



Input function, $C_a(t)$



Tissue function, $C_{tissue}(t)$



$C_{tissue}(t) = C_a(t) \otimes 0.95e^{-0.005t}$

K1=0.9

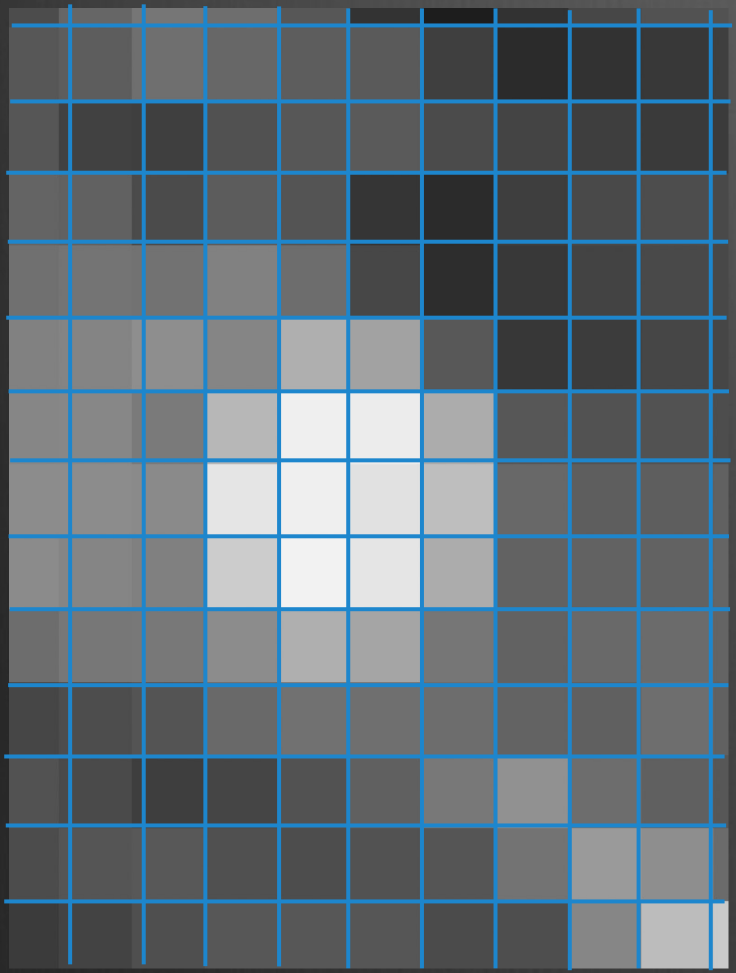
k2=0.005

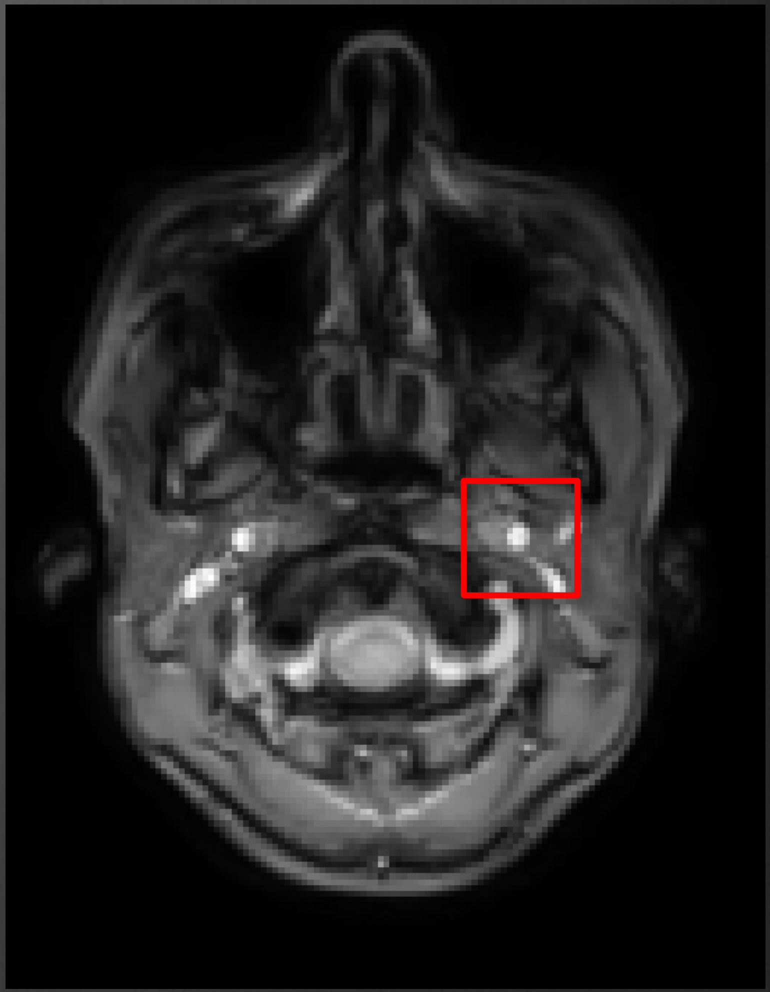
$C_{tissue}(t) = C_a(t) \otimes 0.95e^{-0.005t}$

***K1*=1.8**

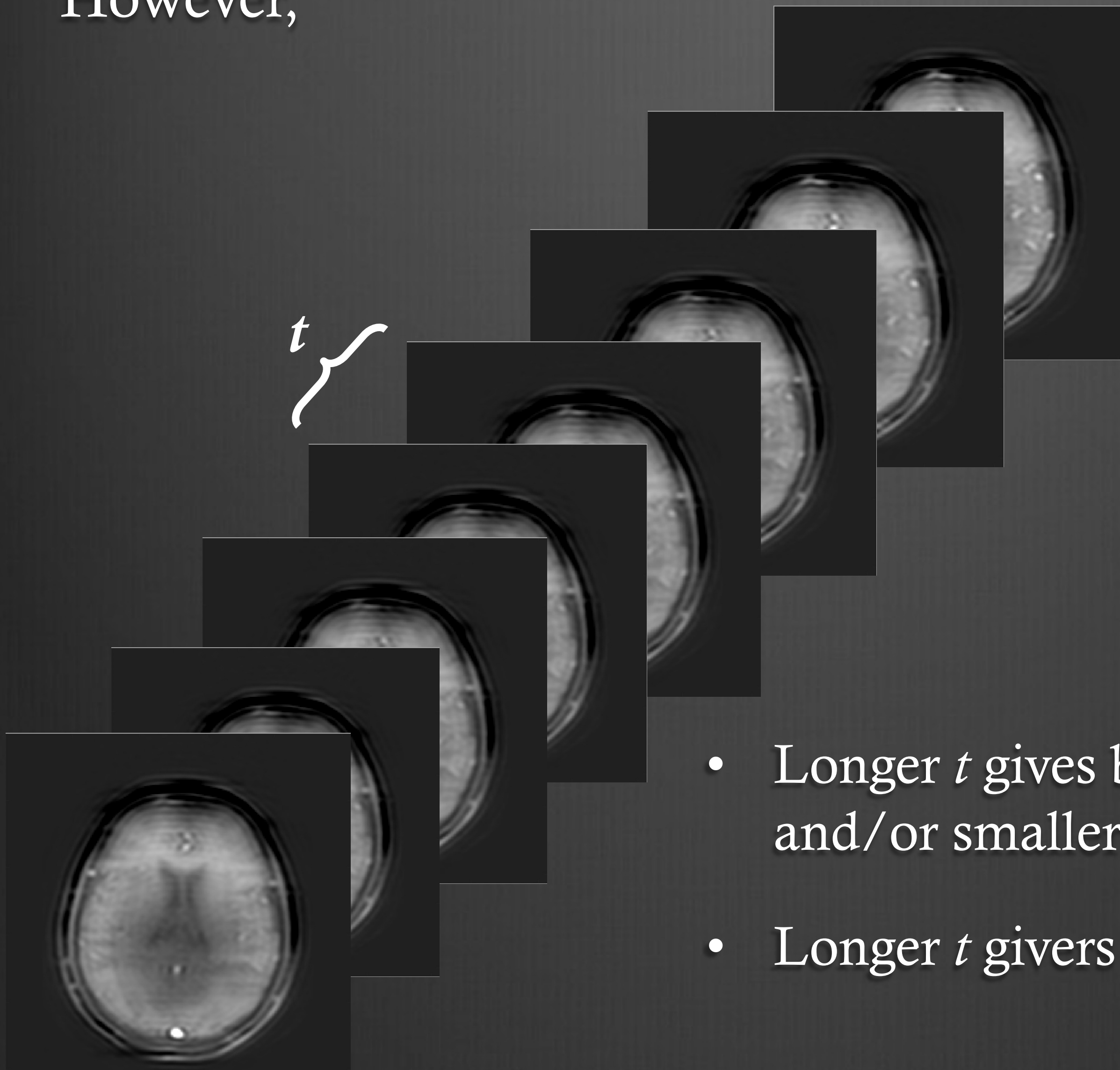
k2=0.005

Important to measure small voxels

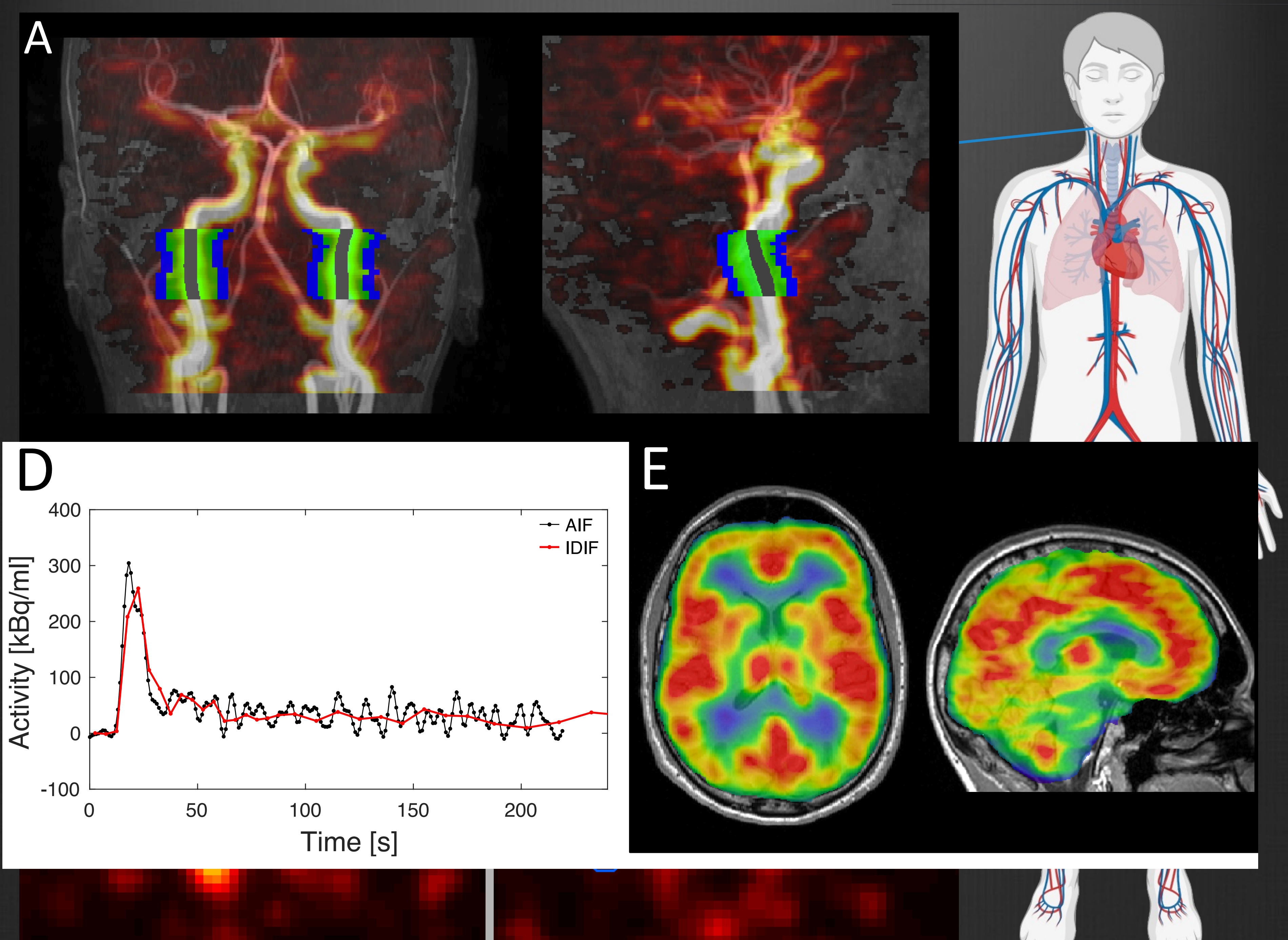




However,



- Longer *t* gives better image quality and/or smaller voxel sizes
- Longer *t* givers poorer time resolution



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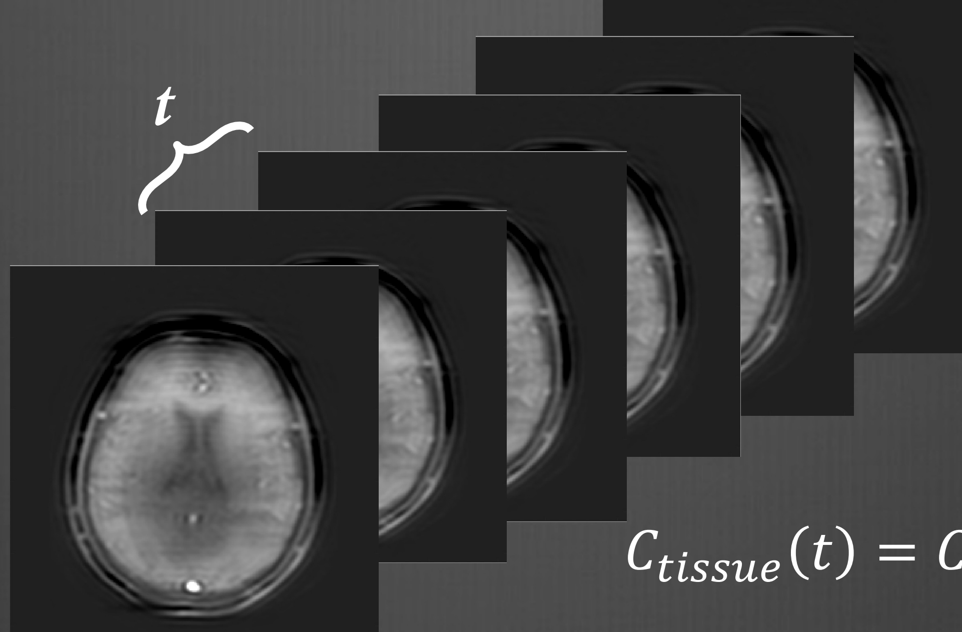
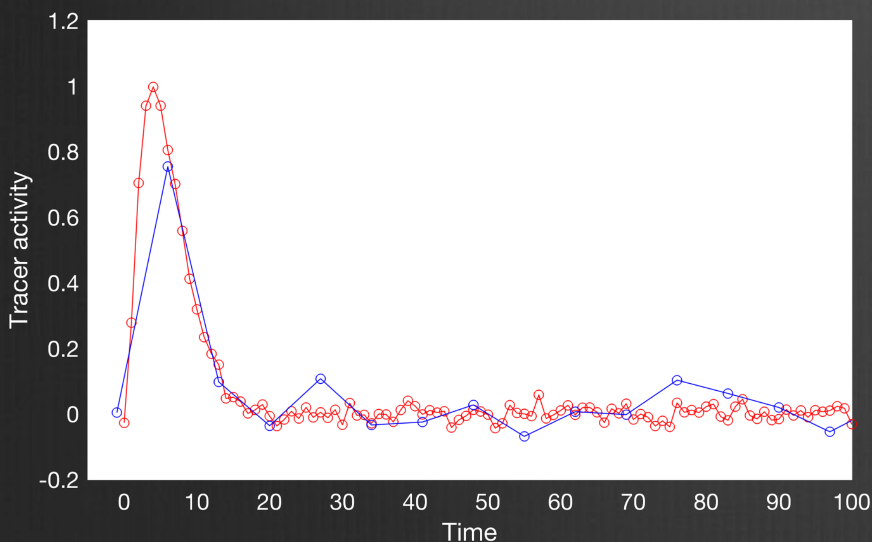
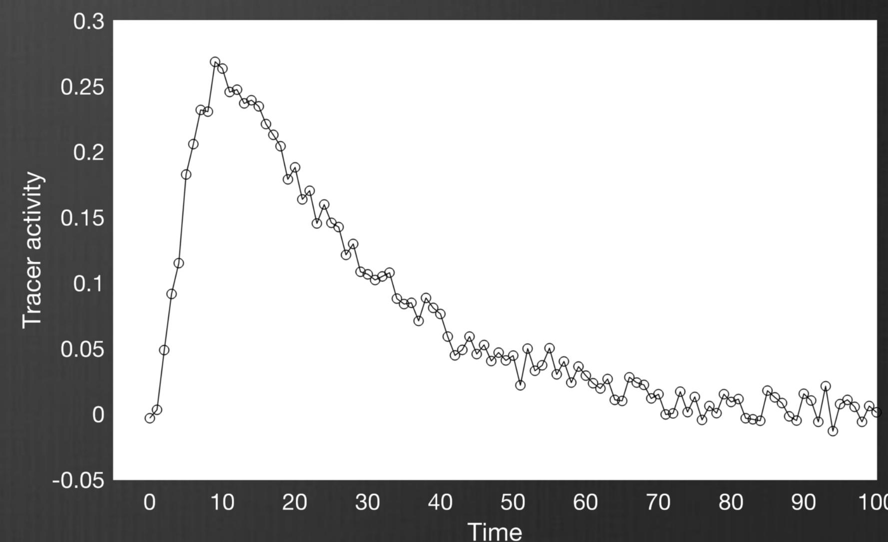


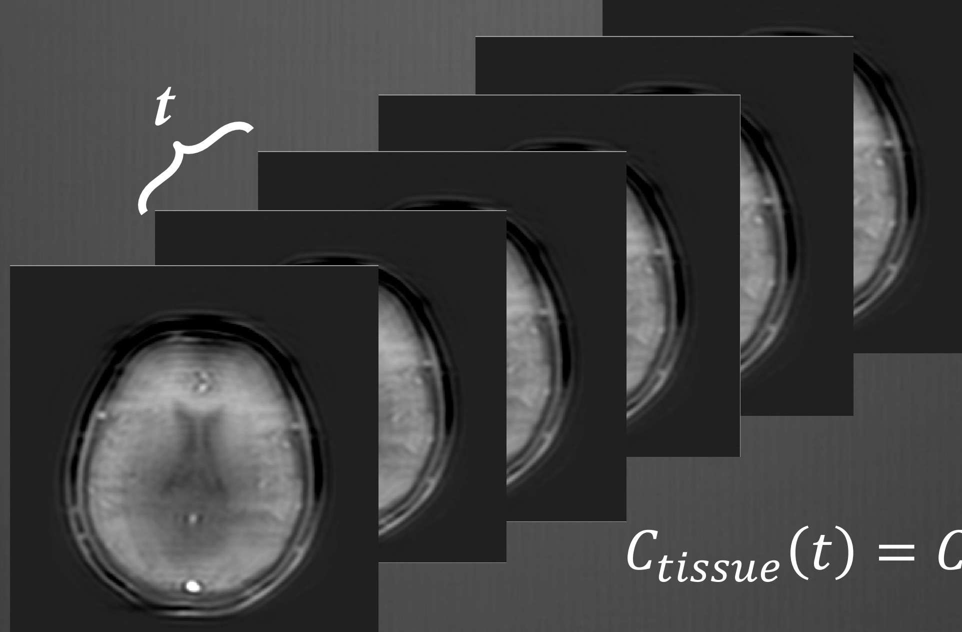
$$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$$

Input function, $C_a(t)$



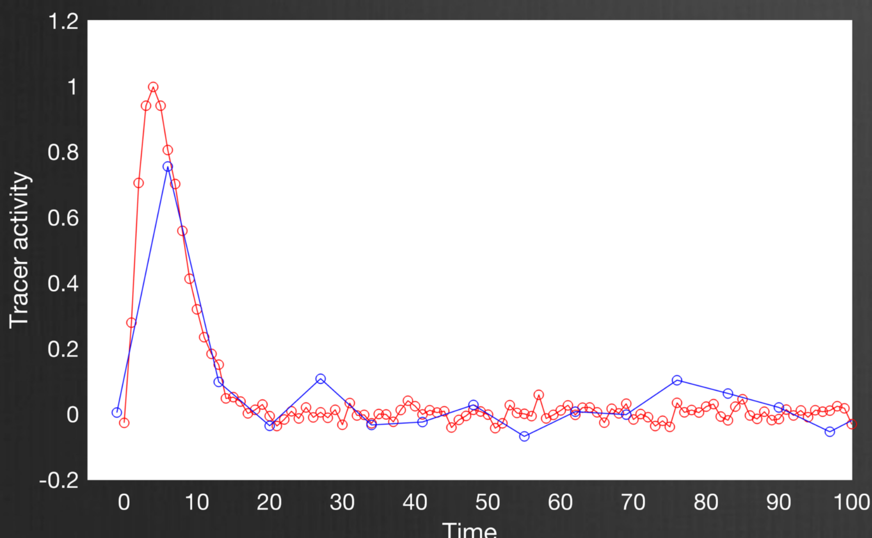
Tissue function, $C_{tissue}(t)$



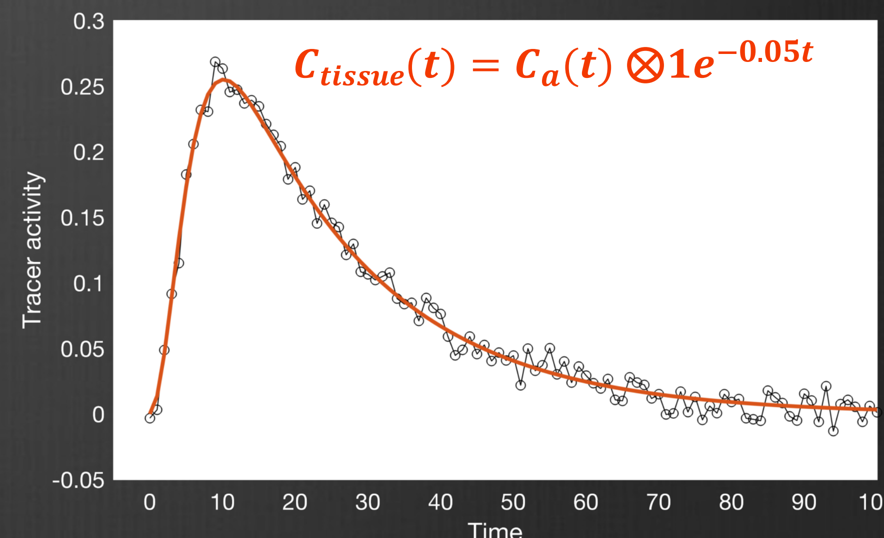


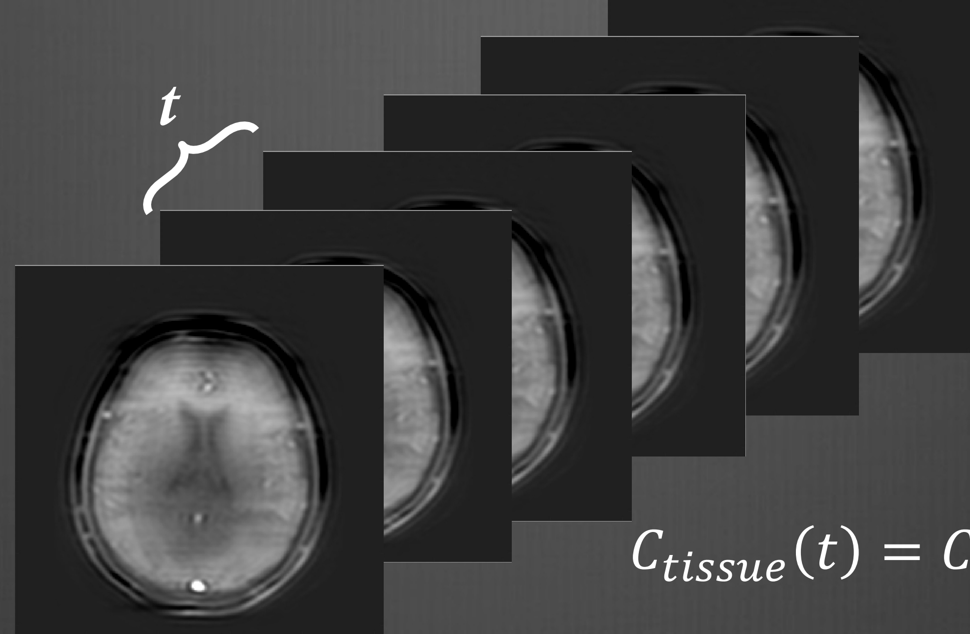
$$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$$

Input function, $C_a(t)$



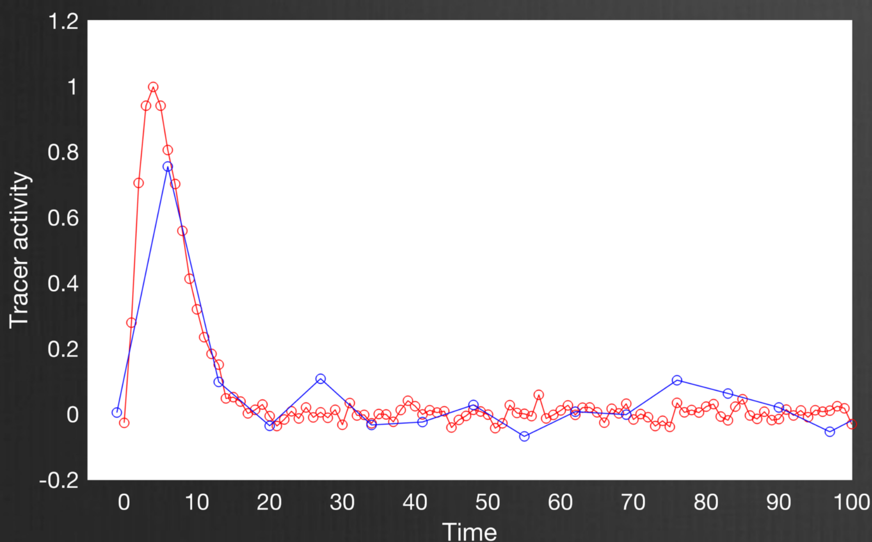
Tissue function, $C_{tissue}(t)$



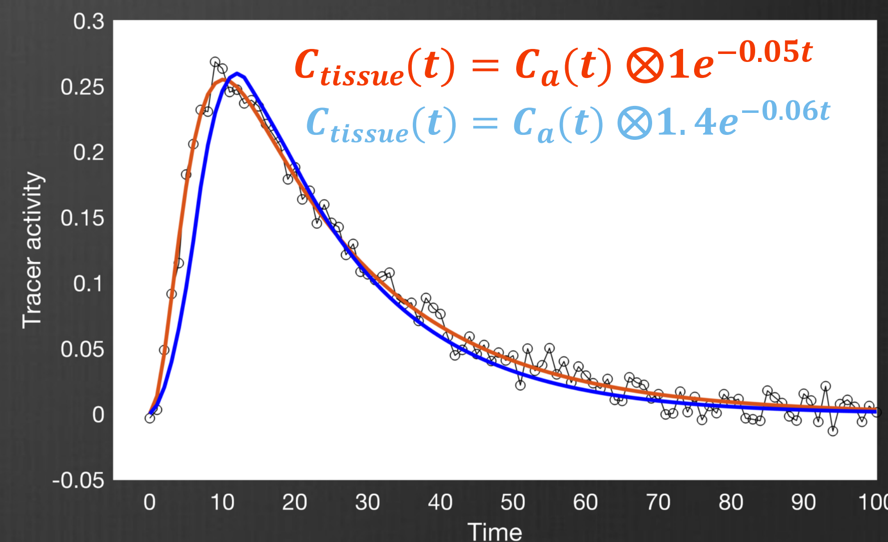


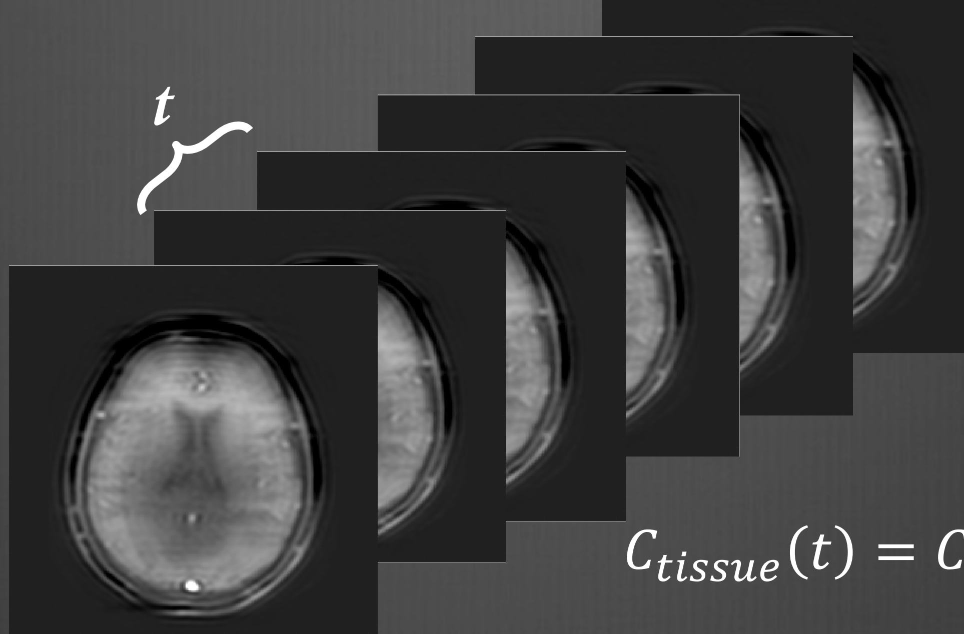
$$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$$

Input function, $C_a(t)$



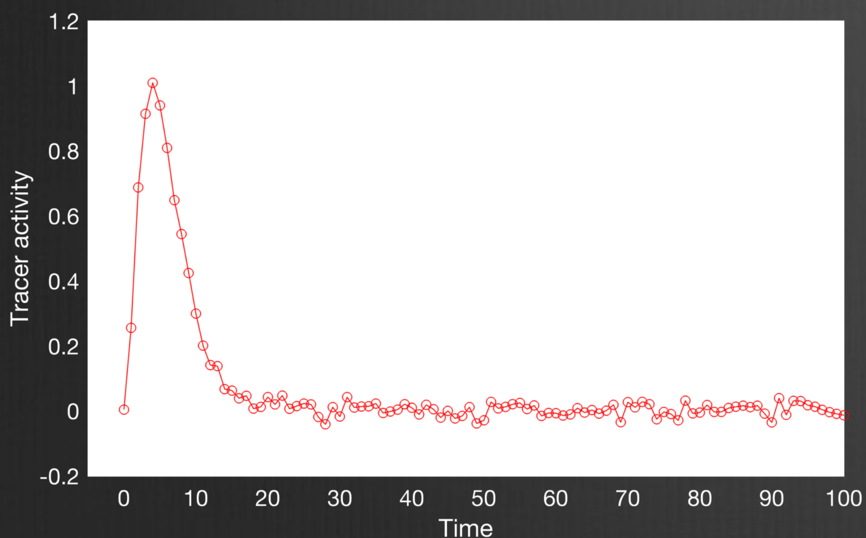
Tissue function, $C_{tissue}(t)$



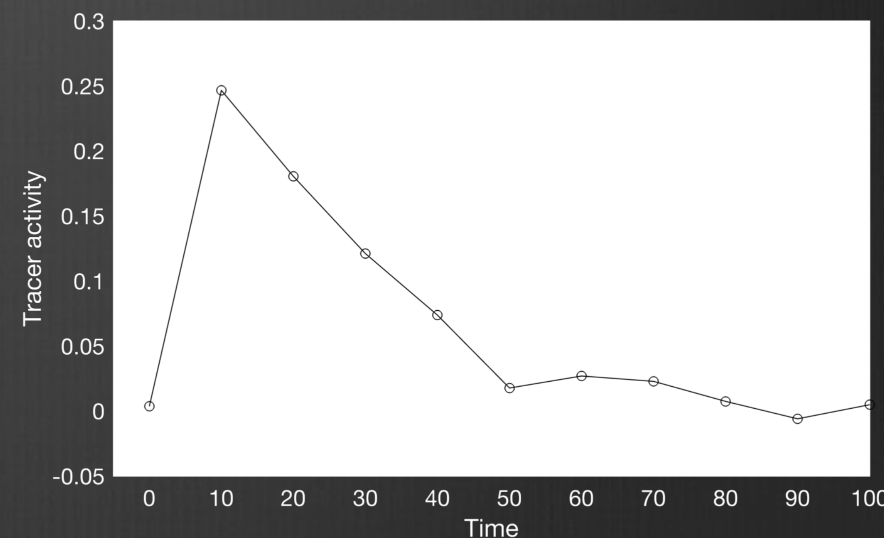


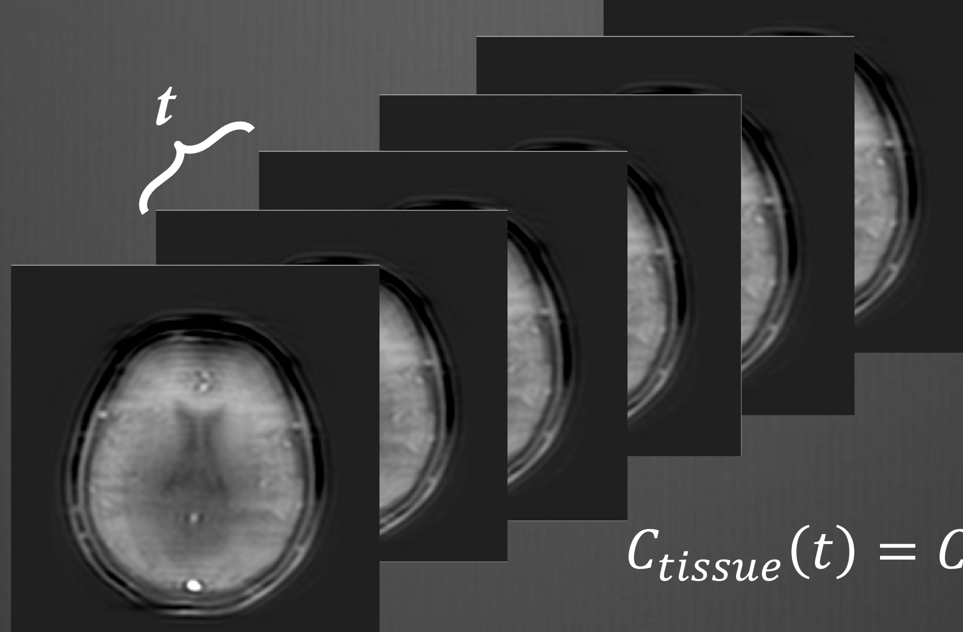
$$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$$

Input function, $C_a(t)$



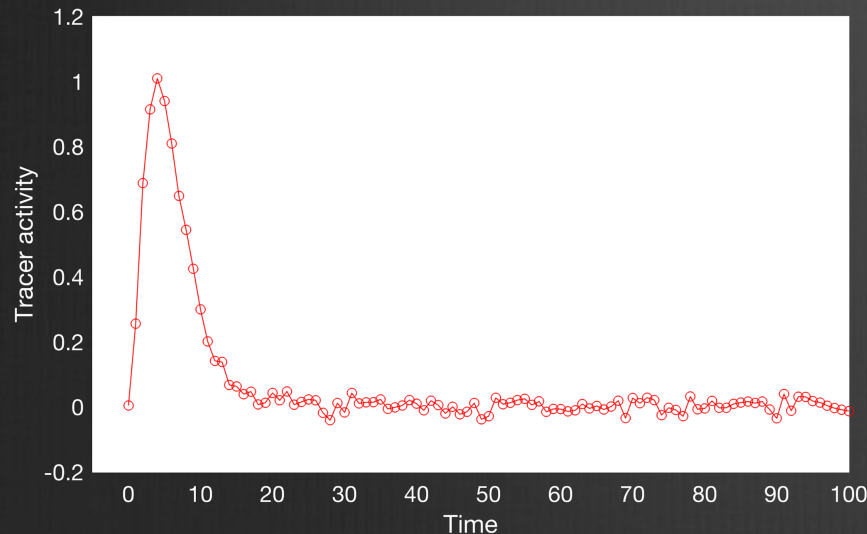
Tissue function, $C_{tissue}(t)$



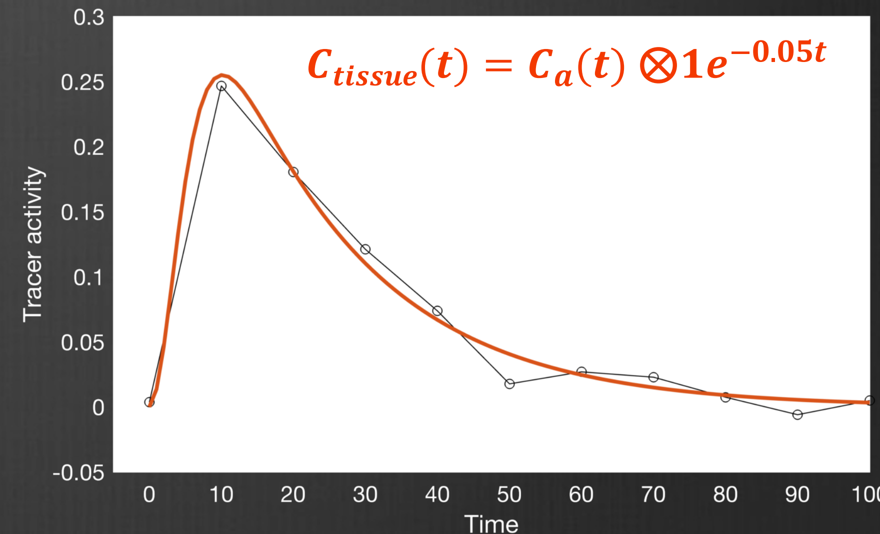


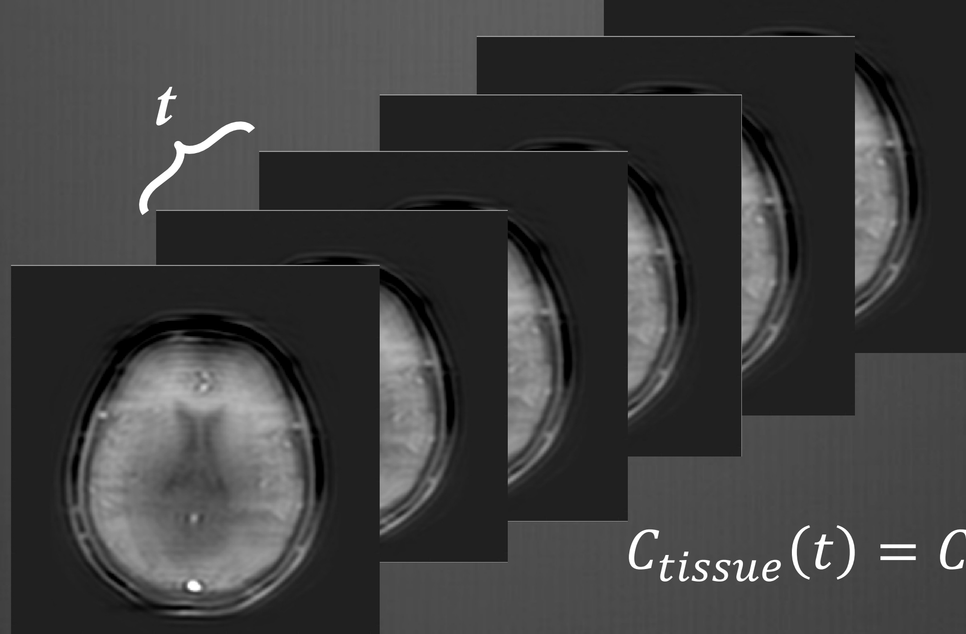
$$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$$

Input function, $C_a(t)$



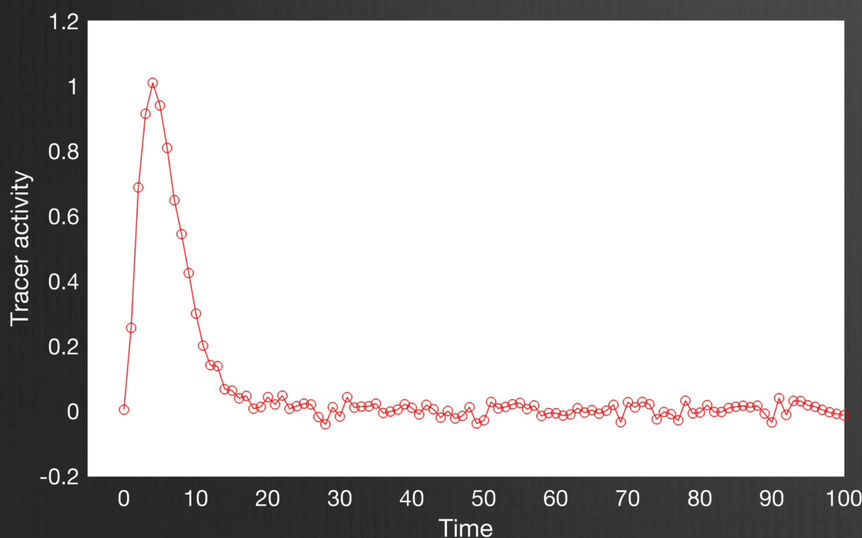
Tissue function, $C_{tissue}(t)$



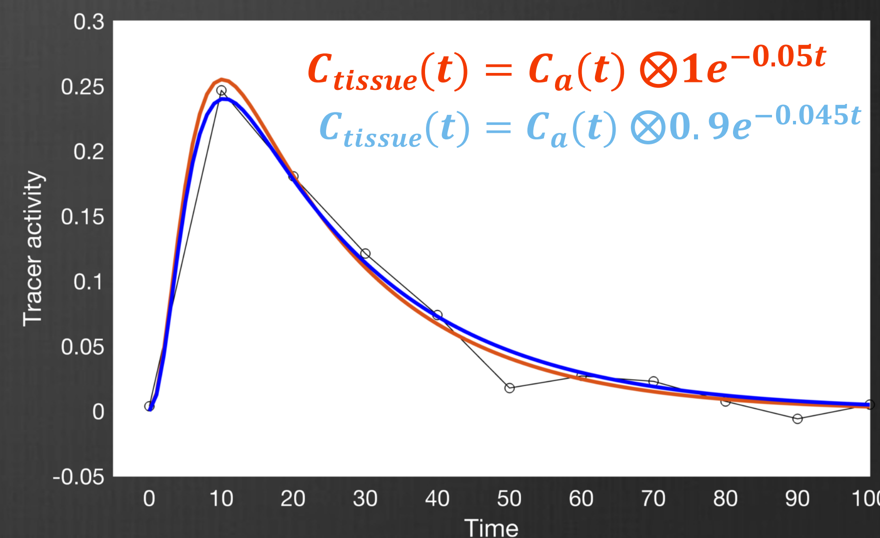


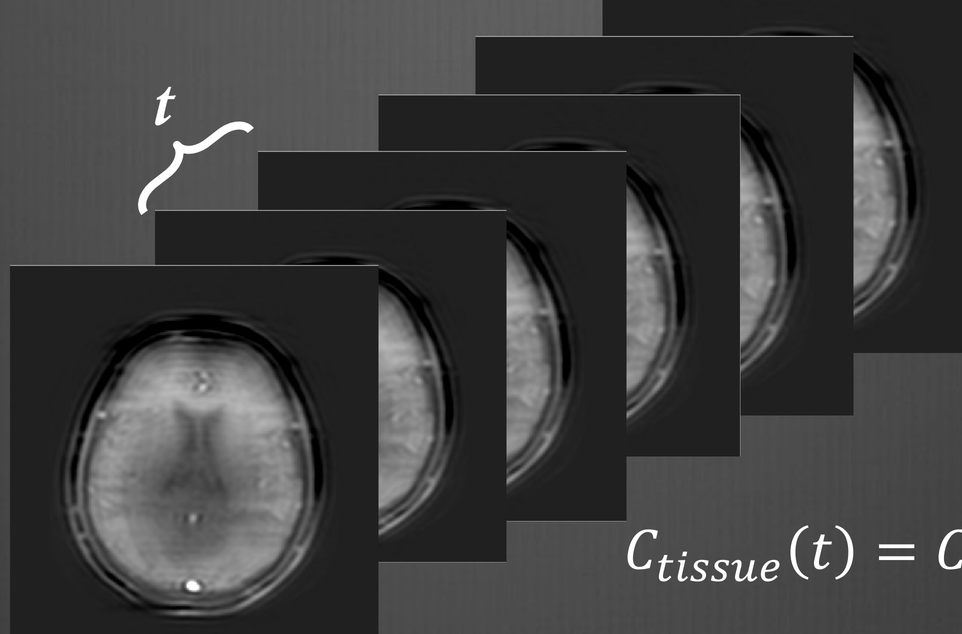
$$C_{tissue}(t) = C_a(t) \otimes K_1\, e^{-k_2 t}$$

Input function, $C_a(t)$



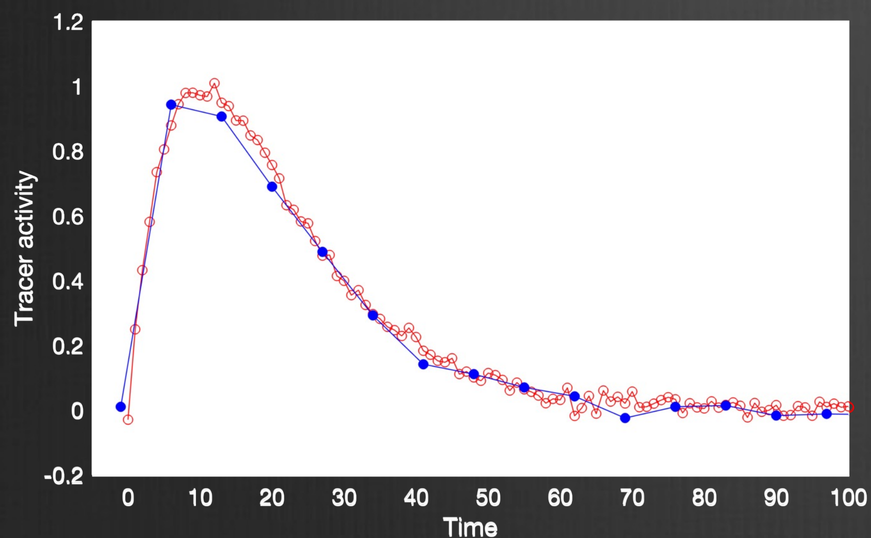
Tissue function, $C_{tissue}(t)$



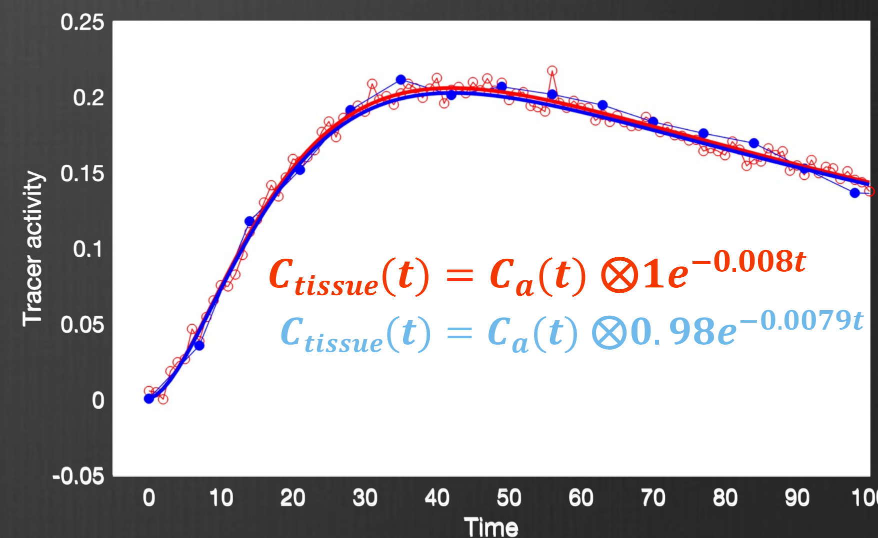


$$C_{tissue}(t) = C_a(t) \otimes K_1 \, e^{-k_2 t}$$

Input function, $C_a(t)$



Tissue function, $C_{tissue}(t)$



Summary

- Measurement of input function
  - Same unit or reference
  - Avoid partial volume errors from image-derived input function
  - Optimal measurement of input function depends on your equipment and experiment setup
- Spatial resolution (voxel size) vs. time resolution should be considered when acquiring data
- Poorer time resolution gives better spatial resolution and better image quality
- With poor time resolution the physiological dynamic might not be captured