Basic Tracer Kinetic Concepts

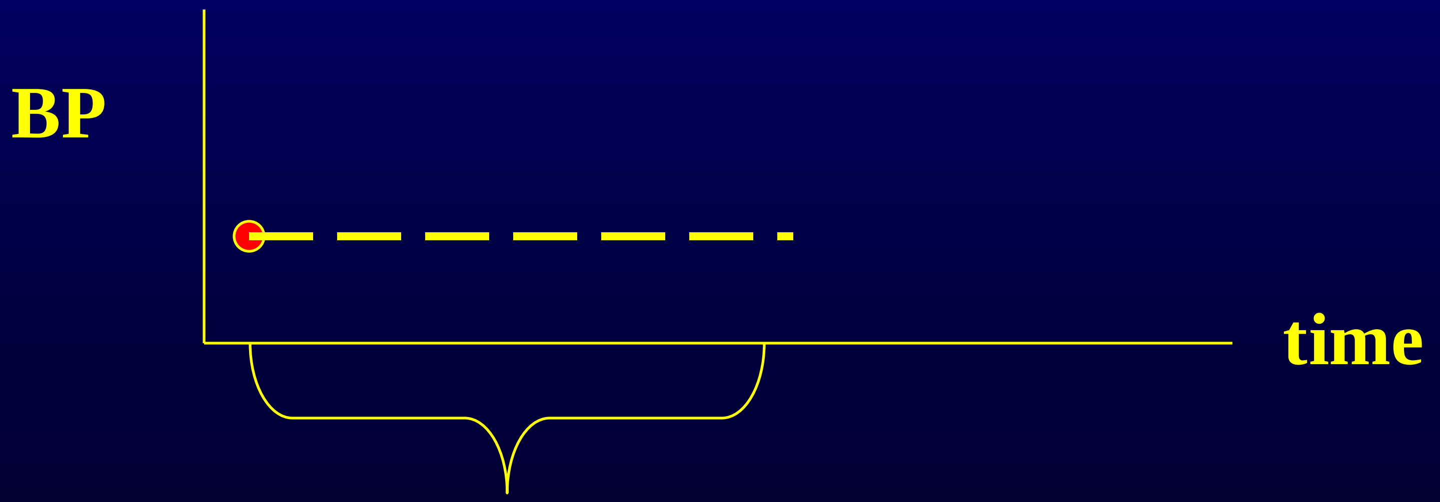
Henrik BW Larsson, Professor, DMSc.
Institute for Clinical Medicin,
University of Copenhagen
Dept. for clinical physiology, nuclearmedicine
Rigshospitalet
henrik.bo.wiberg.larsson@regionh.dk
2025

Steady state of the system

- i.e. the physiologic parameter is constant during the measurement
- Examples: flow (ml/s), perfusion (ml/g/s), CMRO2 (mmol/g/s), glucose uptake (mmol/g/s)
- Consider: duration of the measurement in relation to the a spontaneous change of the parameter or timing of a pertubation of the parameter

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

Tracers and indicators

- Tracers: labelled substances, behaves physically and chemically like the modersubstances;
- e.g. $H_2{}^{15}O$, $^{17}O_2$, ^{57}Co-vitB12, ^{131}I-thyroxin
- Or behaves nearly like the modersubstance
- e.g. ^{18}FDG , ^{125}I-albumin, ^{131}I-insulin

- Indicators: not necessary related to a modersubstance
- e.g. contrast agents – x-rays – SPECT (99mTc-HMPAO, 99mTc-sestamibi), - MRI (Gd-DTPA, Mn-DPDP)
- Law of conservation: mass balance
- Note: tracers can be intravascular,extracellular, free difussible, bound to a receptor or behave in a more specific way

Should not disturb the system we are studying

HBWL

- Note:

tracers can be intravascular, extracellular, free difussible, or behave in a more specific way

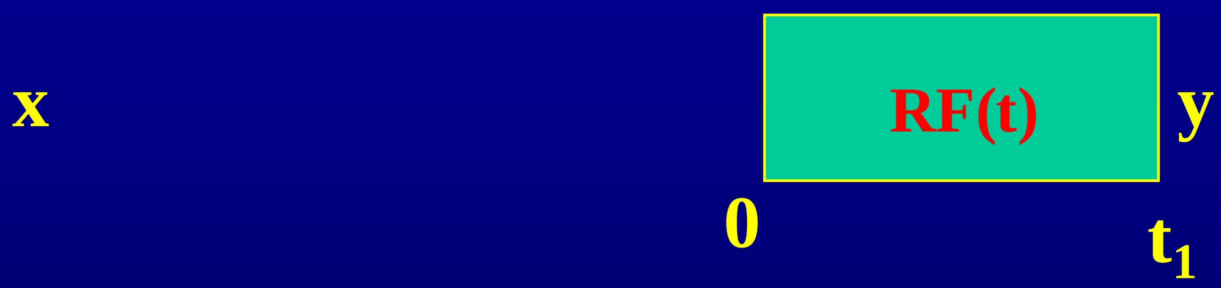
Intravascular
- Radioactive microsphere
- Radioactive erytrocytes
- Radioactiv albumin

Ekstravascular
- ^{51}Cr-EDTA
- sucrose
- inulin
- Gd-DTPA (MR)

Freely diffusible
- ^{133}Xe
- heat
- NO
- H_2
- $^{15}H_20$
- ^{17}O

Specials
- ^{99m}Tc-HMPAO (brain)
- ^{99m}Tc-sestamibi (heart)
- ^{18}Fluor-DeoxyGlucose

Linearity of a system



RF(t) : response function or more correctly

: The impulse response function

Linearity of a system

x —RF(t)→ y

scaling a x —RF(t)→ a y

Linearity of a system

x_1

RF(t)

y_1
y_2

x_2

0 t_1

RF(t)

$x_1 + x_2$ ⟶ $y_1 + y_2$

Principle of superposition

HBWL

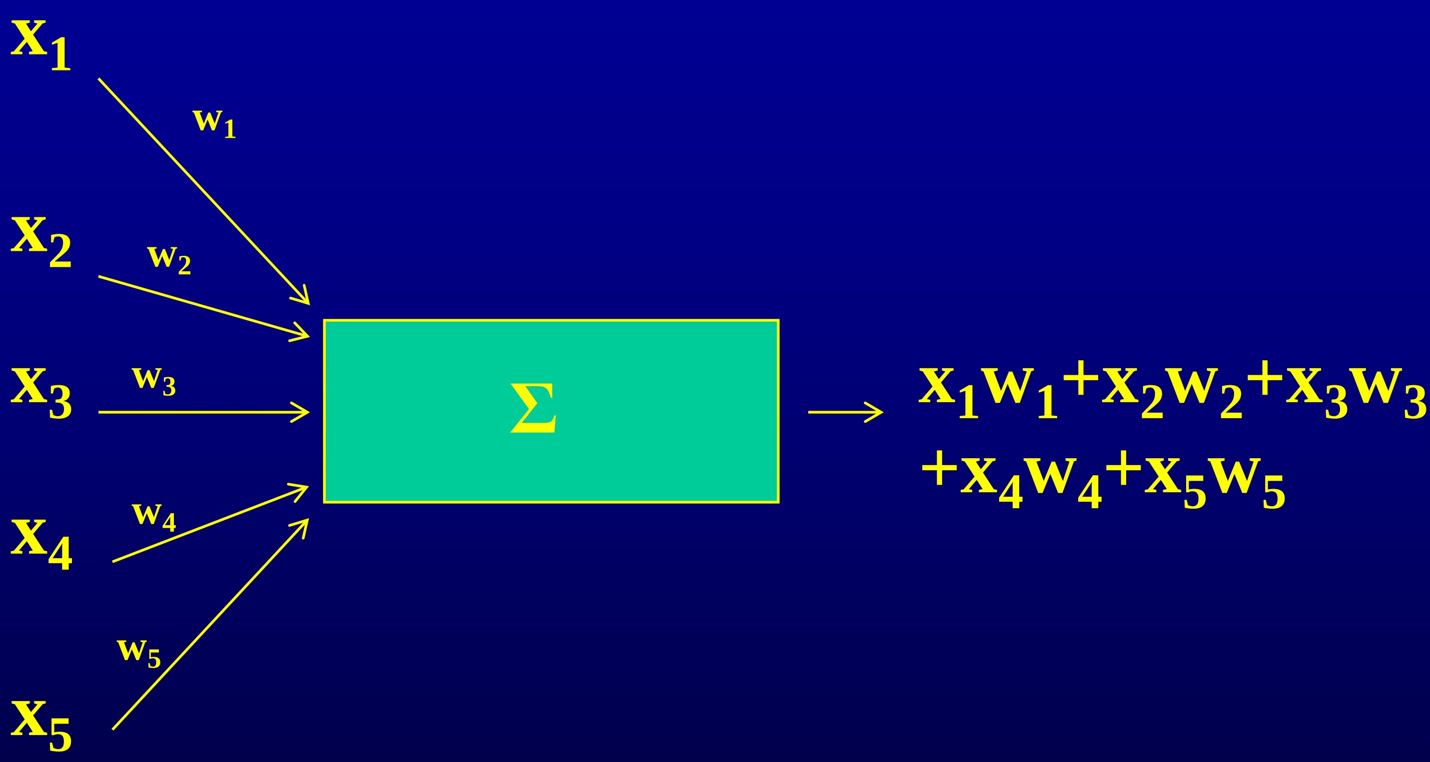
Examples

3
3 +4
4

x 2

6
14
8

Examples



Examples

3
3 +4
4

log

log3
log(3+4)
log4

log3 + log4 ≠ log(3+4)

HBWL

Linearity of a system

RF(t)

$$a\,x_1 + b\,x_2 \longrightarrow a\,y_1 + b\,y_2$$

Time invariance of a system

x

x

RF(t)

y

y

0

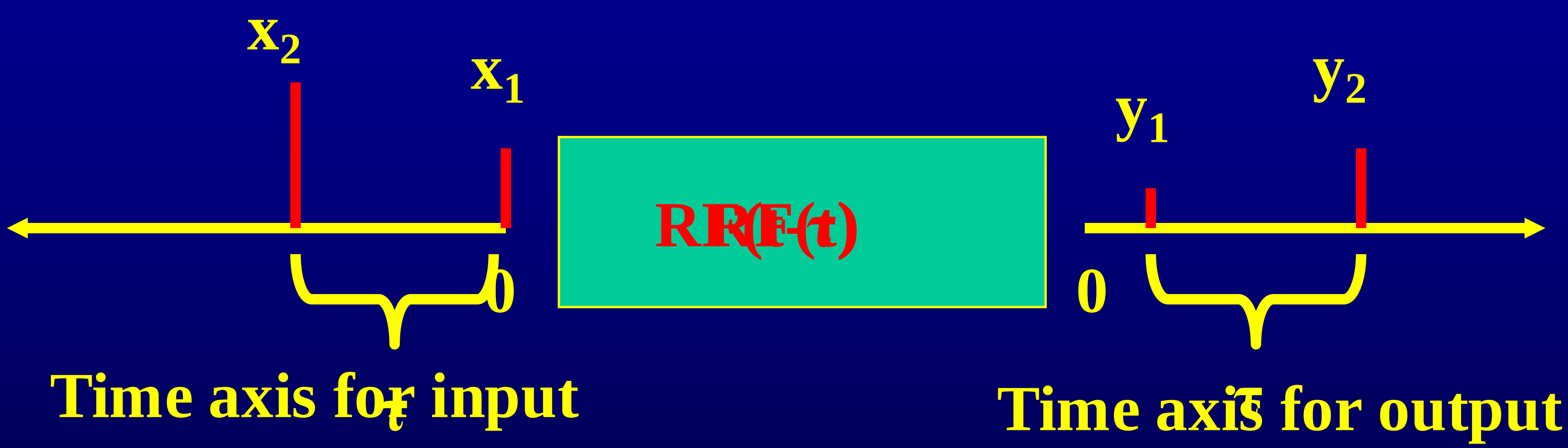
+ 10s

t_2 + 10s

t_2

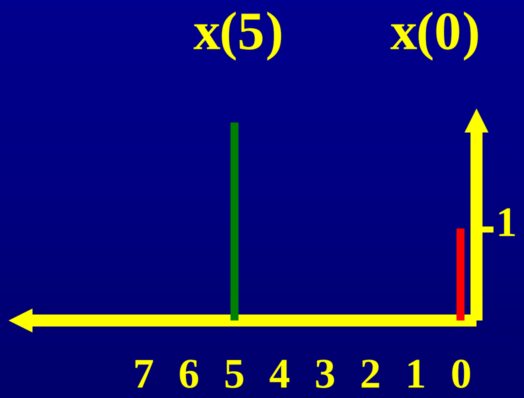
HBWL

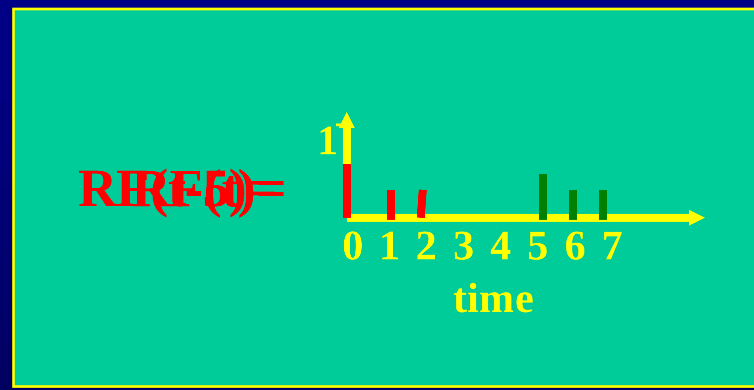
Specification of time

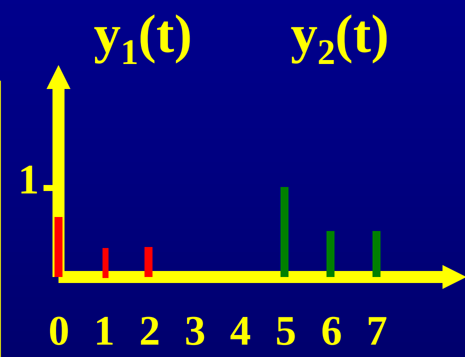


HBWL

Example







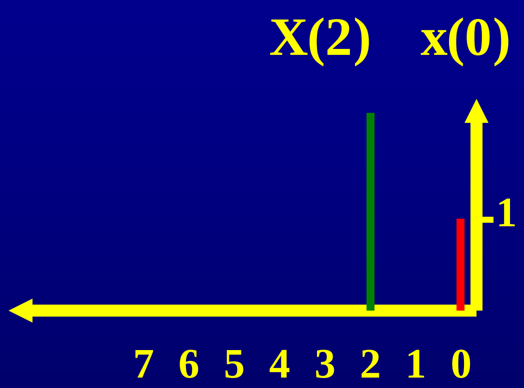
$y_1(t) = x(0) \cdot RF(t)$

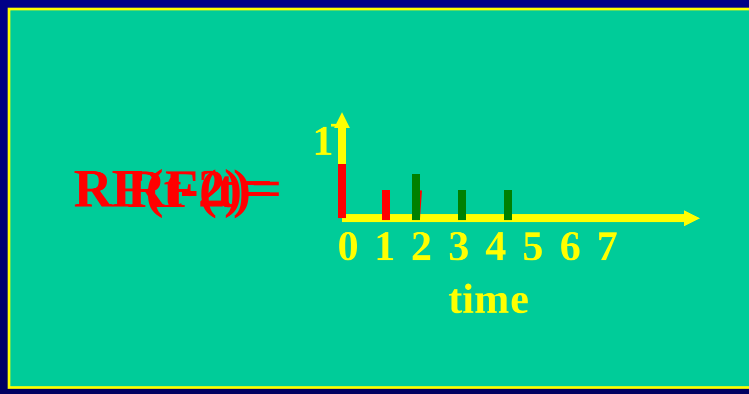
$y_2(t) = x(5) \cdot RF(t)$

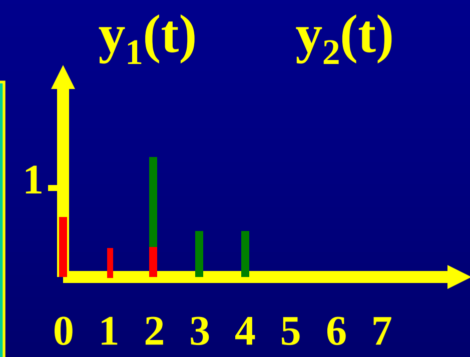
$y_2(t) = x(5) \cdot RF(t-5)$

Does not work !!!

Example







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

$y_2(t) = x(2) \cdot RF(t)$

Does not work !!!

$y_2(t) = x(2) \cdot RF(t-2)$

HBWL

Causality of a system

Output is only observed after an input has enter the system

Causality of a system

Output is only observed after an input has enter the system

Can a biological system behave like such a system? Describe in words how a biological system could interact with a instantaneous tracer input !

HBWL

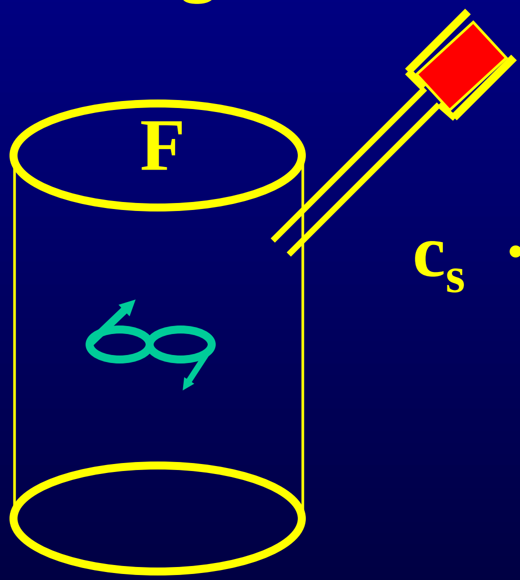
Linearity of a imaging system?
!

Break

Indicator-dilution methods

Constant Infusion (Stewart principle)

The aim : to measure the flow of an organ or a vessel or a pipeline



[F]= ml/s

$$c_s \cdot F_s = j_{in}$$ **flux !!!!**

$[c_s]$ = mmol/ml

$[F_s]$ = ml/s

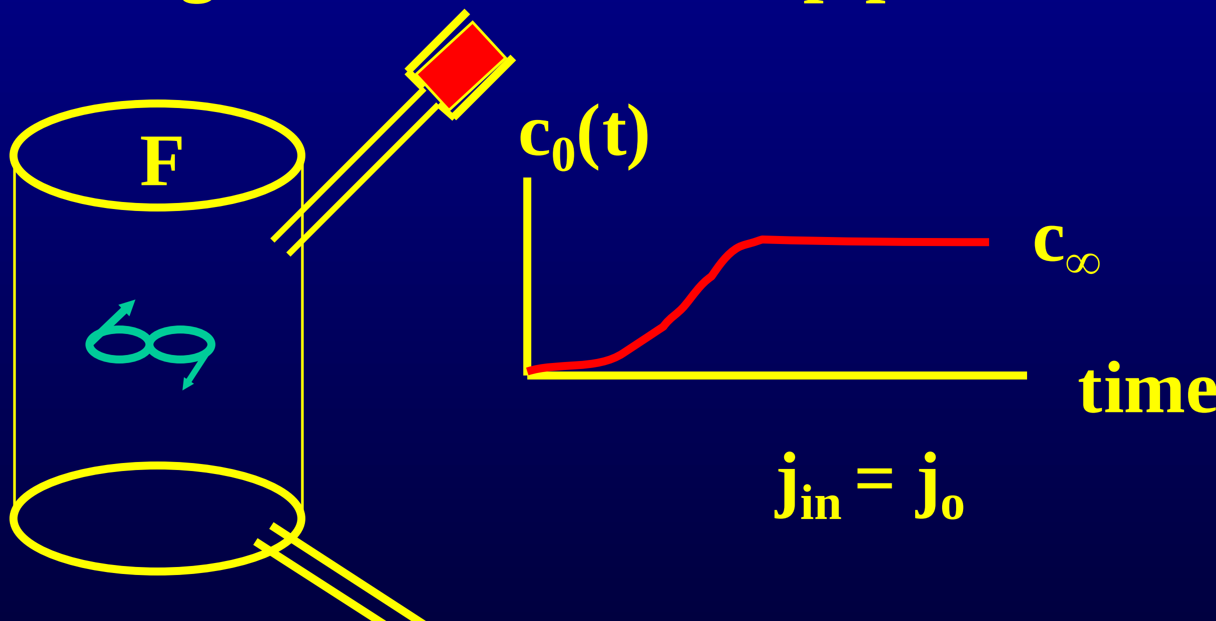
$[j_{in}]$ = mmol/s

HBWL

Indicator-dilution methods

Constant Infusion (Stewart principle)

The aim : to measure the flow of an organ or a vessel or a pipeline



$$j_{in} = j_o$$

$$c_s \cdot F_s = (F+F_s) \cdot c_\infty$$

HBWL

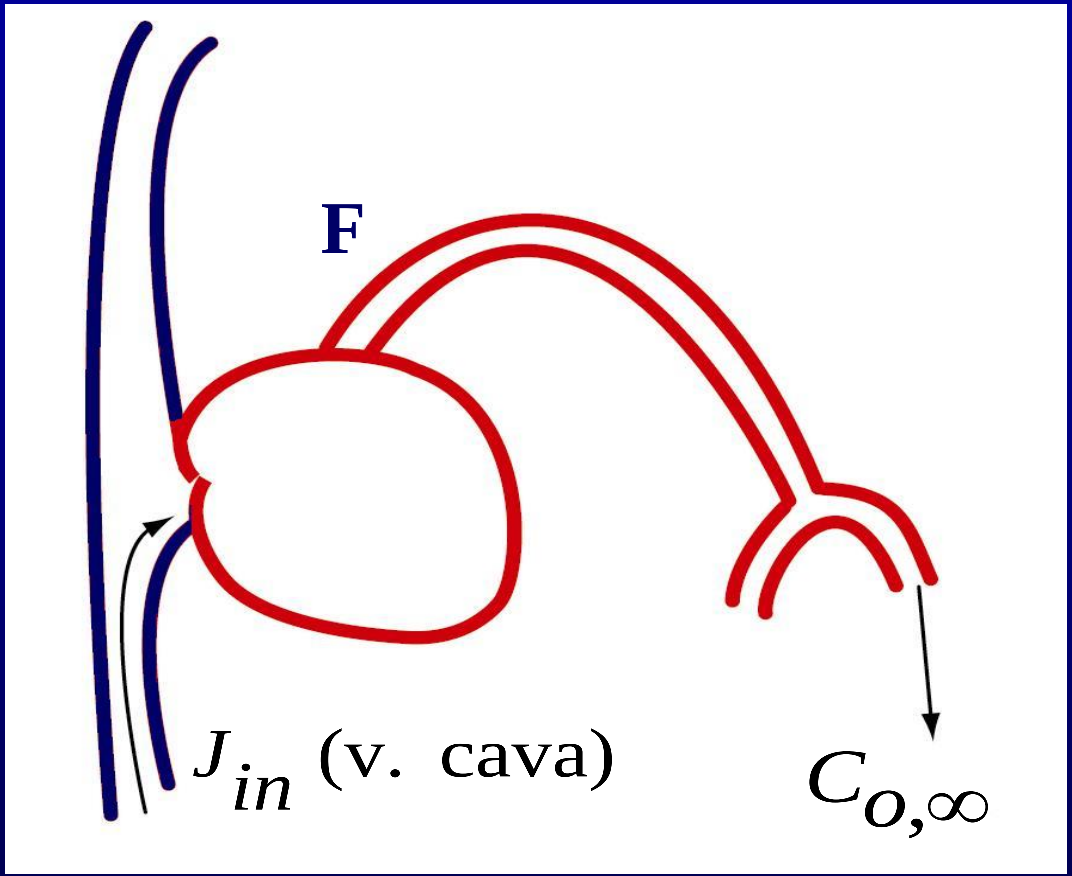
$$c_s \cdot F_s = (F+F_s) \cdot c_\infty$$

$$F_s << F \Rightarrow \qquad F = F_s \cdot c_s/c_\infty$$

$$F = j_{in}/c_\infty$$

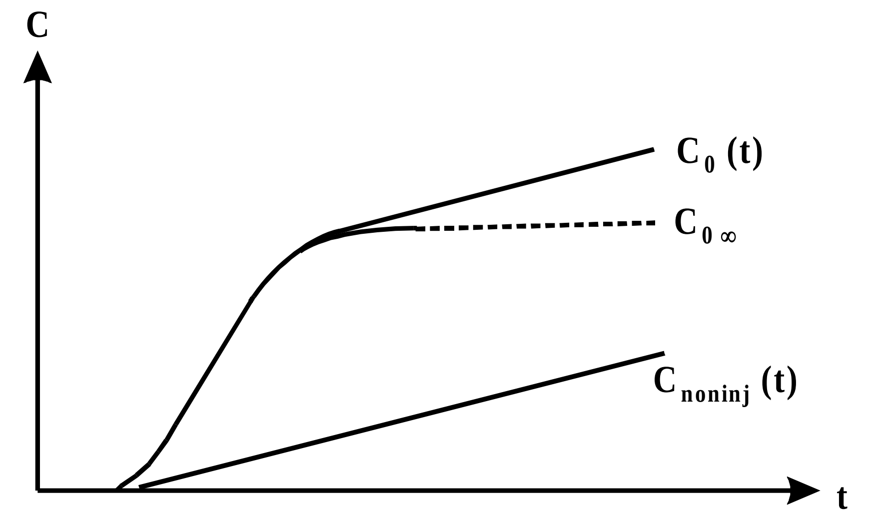
HBWL

Examples and recirculation



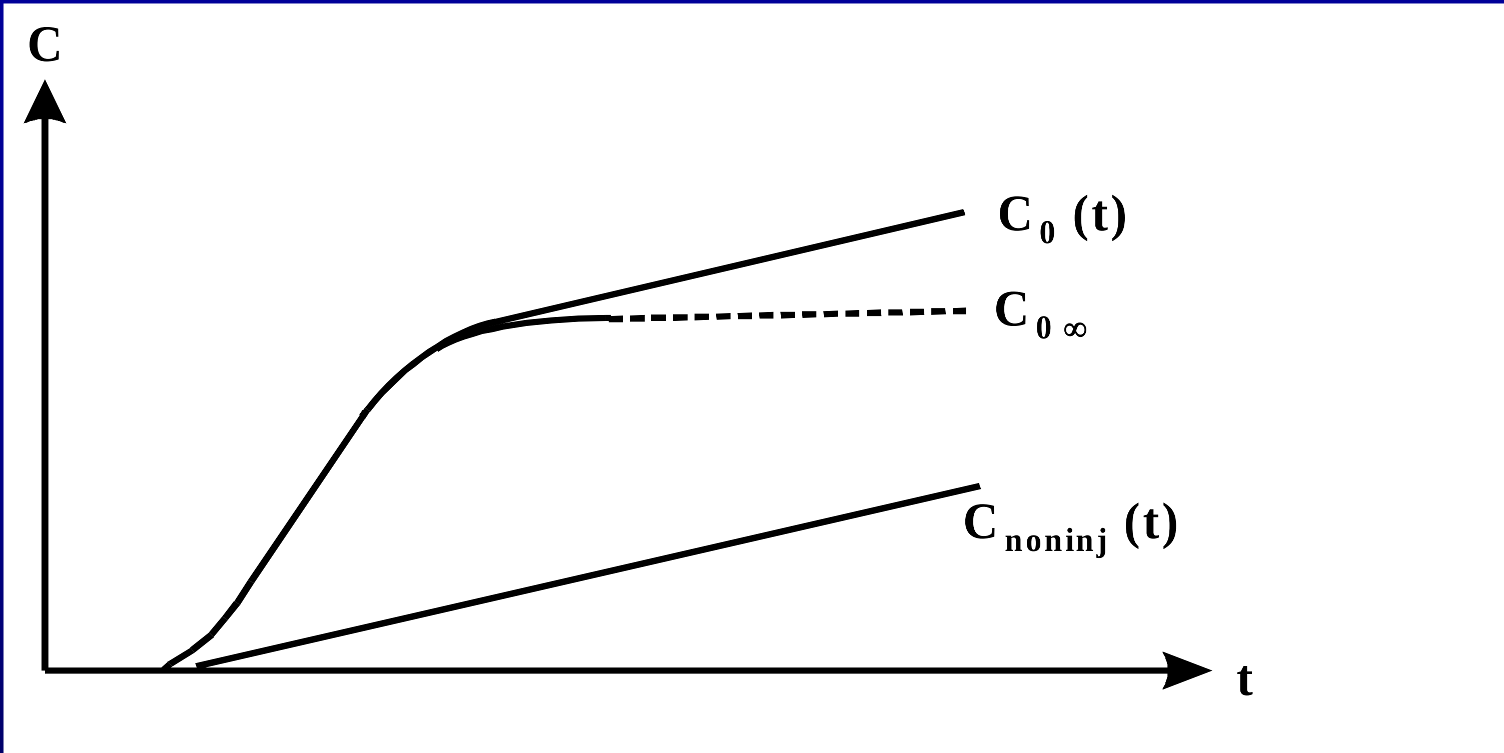
Stewarts principle: Continuously infusion in vena cava, and outlet concentration measurement from a peripheral artery.

HBWL



Measurement of concentration at the outlet and the "noninj" side.

HBWL



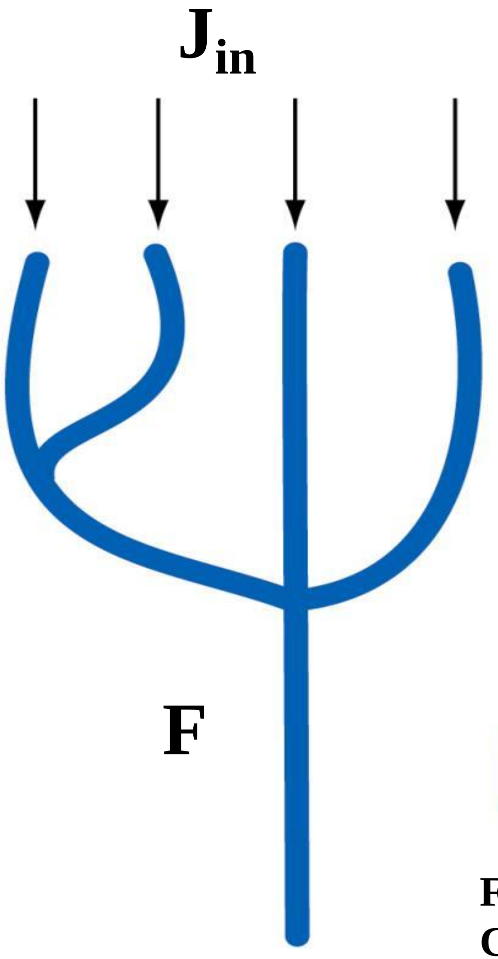
$$J_o = J_{in} + FC_{noninj}(t) \Rightarrow$$

$$FC_o(t) = J_{in} + FC_{noninj}(t) \Leftrightarrow$$

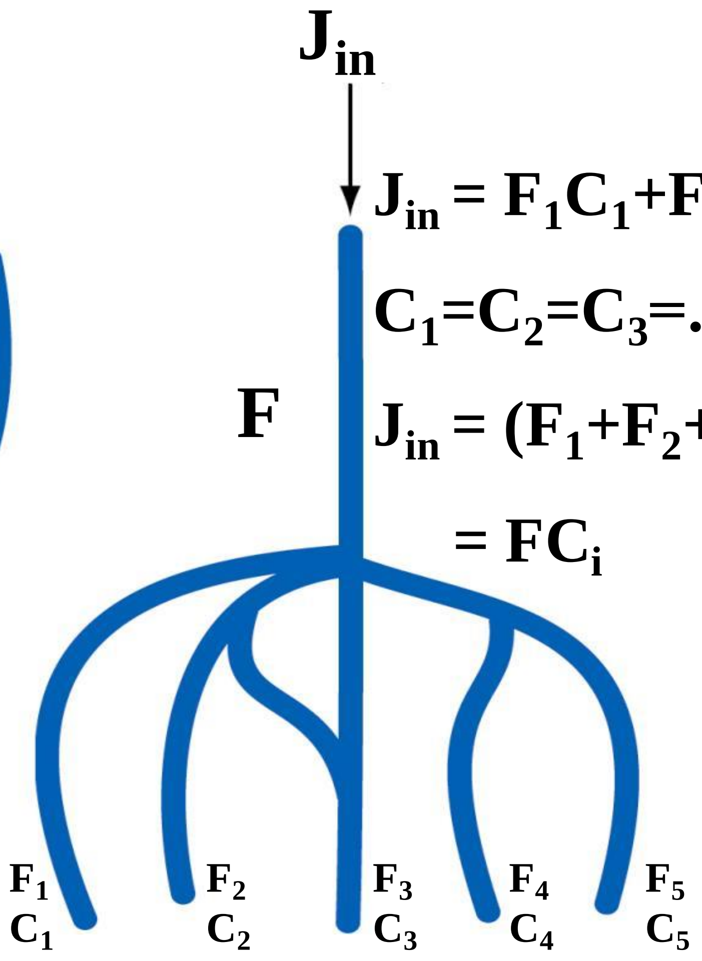
$$F = \frac{J_{in}}{C_o(t) - C_{noninj}(t)}$$

HBWL

Bolus Fraktion principle - Sapirsteins principle



$$J_{in} = F\,C_o$$



$$J_{in} = F_1C_1+F_2C_2+F_3C_3+\ldots$$

$$C_1=C_2=C_3=\ldots$$

$$J_{in} = (F_1+F_2+F_3+F_4+F_5)C_i$$

$$= FC_i$$

HBWL

Fick’s-principle

The conservation of matter

HBWL

The principle of Fick

Stady state; Concentration here is constant , fluxes are here constant

$$\frac{dc}{dt} = 0$$

$$j_{in} = F \cdot c_{in}$$

Convective input by blood entering the tissue

$$j_o = F \cdot c_o$$

Convective output

$$j_{in} = j_o + j$$

conservation of mass

$$j$$

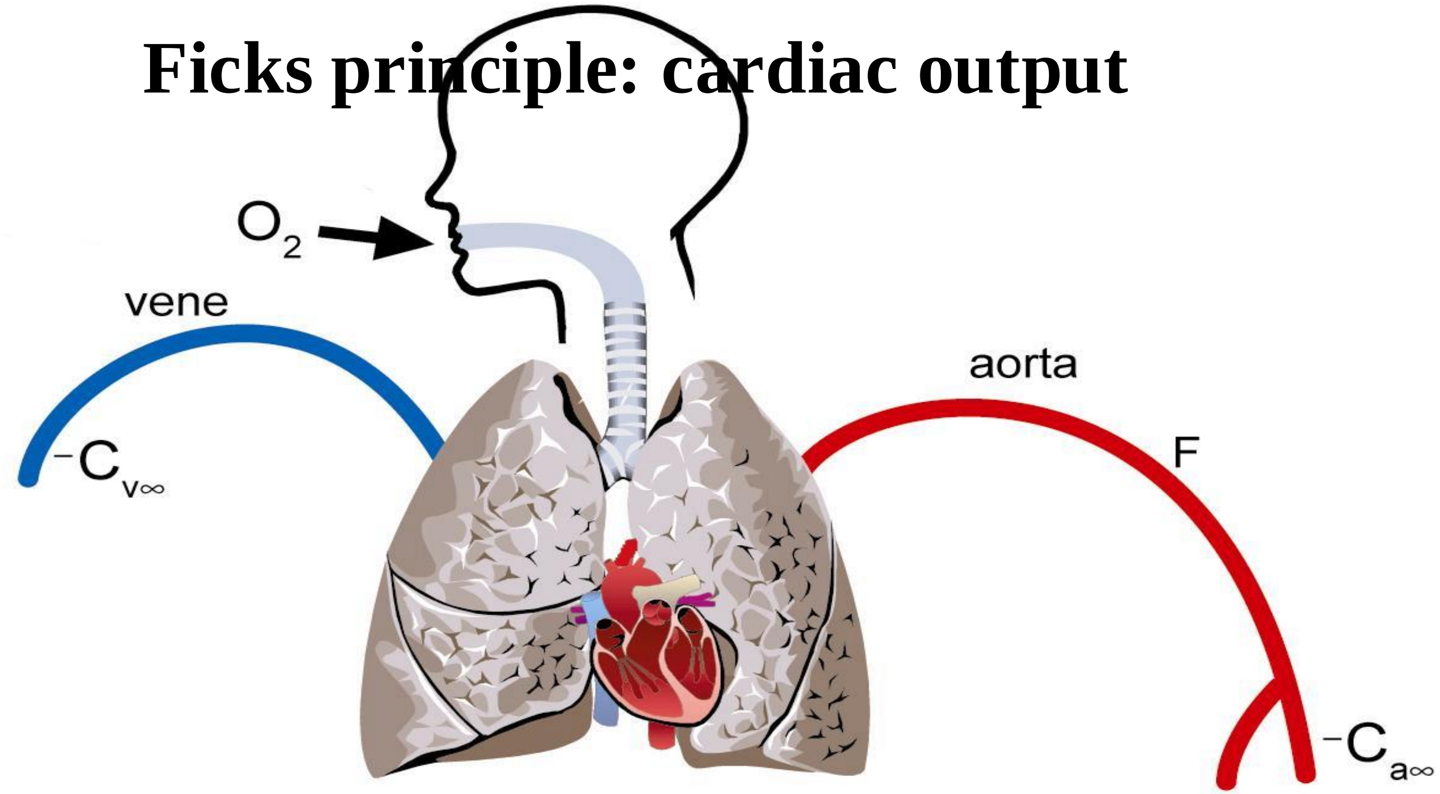
Non-convective uptake of a tissue

$$F \cdot c_{in} = F \cdot c_o + j$$

$$F = j / (c_{in} - c_o)$$

HBWL

Ficks principle: cardiac output



$$J_a = J_{O_2} + J_v$$

$$F \cdot C_{a\infty} = J_{O_2} + F \cdot C_{v\infty} \Rightarrow$$

$$F = \frac{J_{O_2}}{C_{a\infty} - C_{v\infty}}$$

HBWL

Cerebral metabolic rate of oxygen $CMRO_2$

- Ficks formel

Bloodsample

$$CMRO_2 = 4 \cdot [Hgb] \cdot CBF \cdot (S_aO_2 - S_vO_2)$$

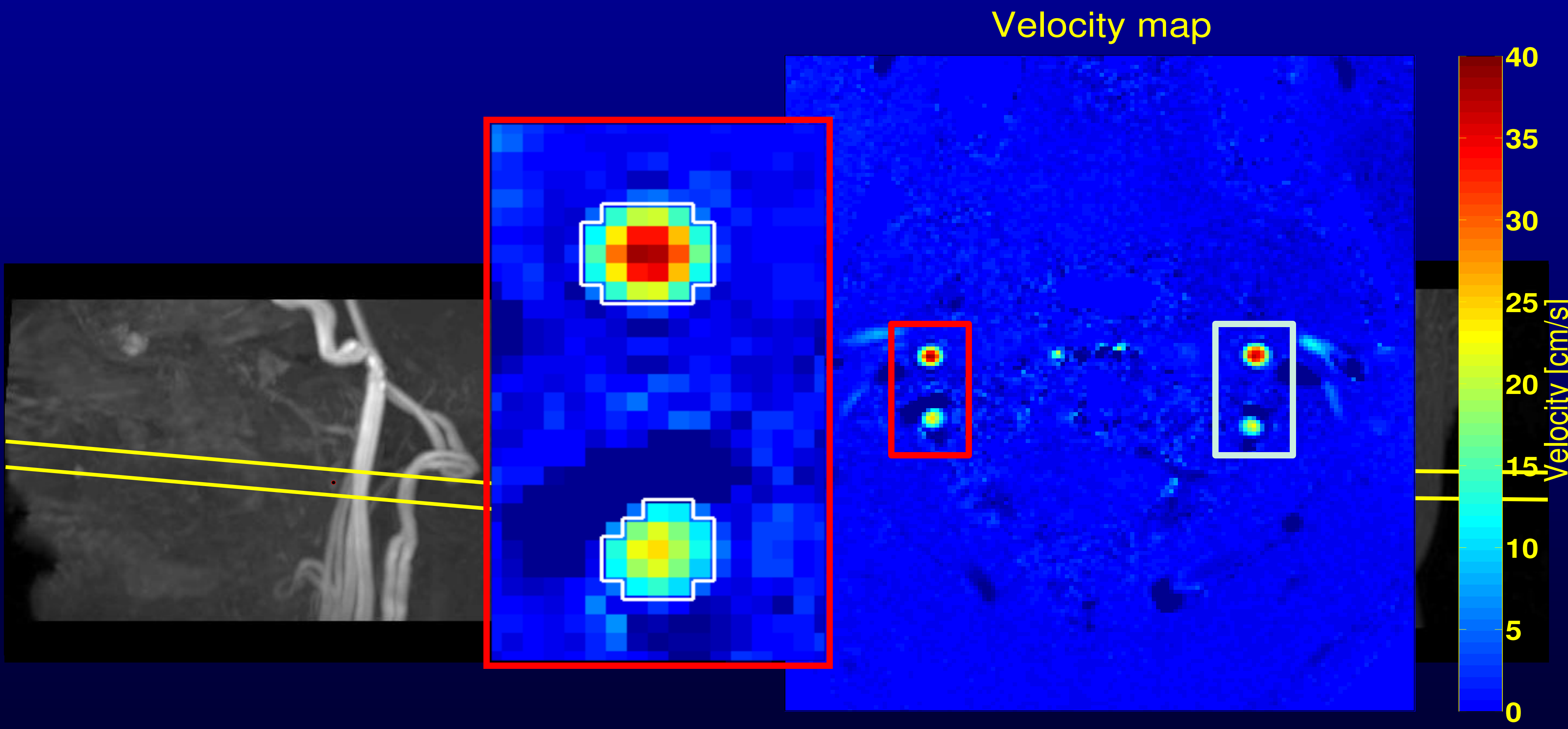
MRI phase contrast mapping

Puls-oximetri (A-cath)

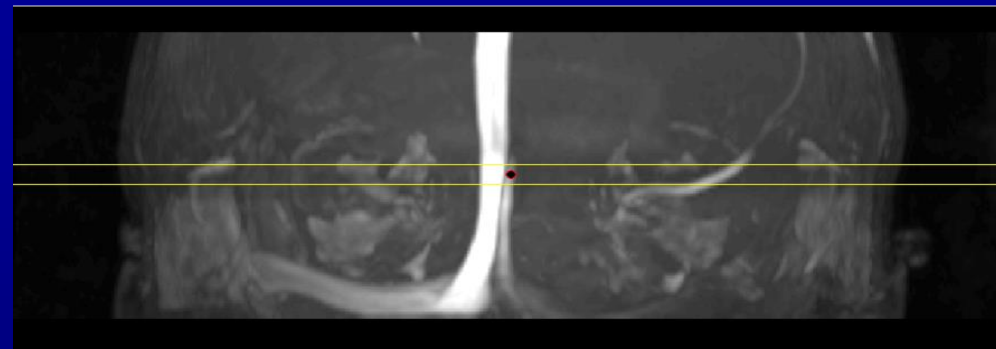
MRI susceptibility-based oximetry from Saggital sinus: venous blood from brain

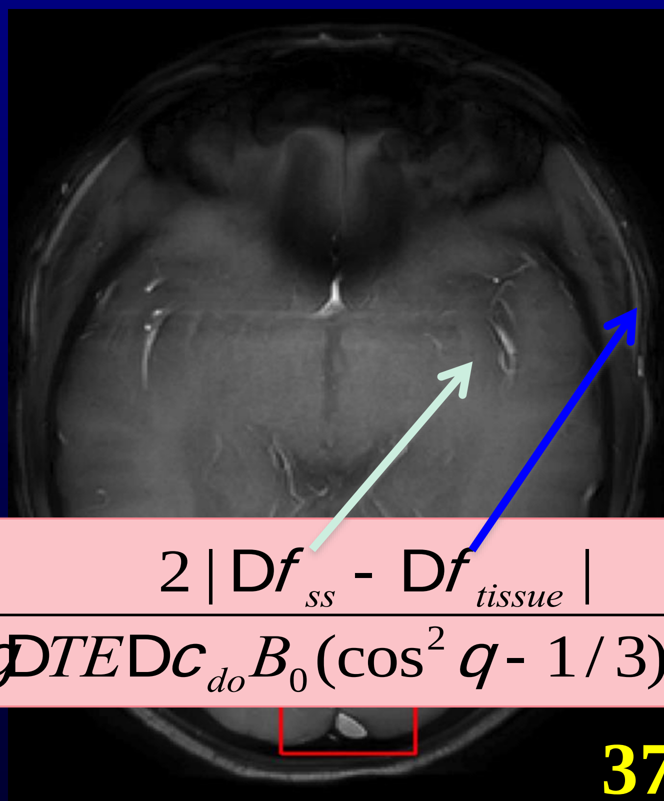
CBF – Fase kontrast MRI

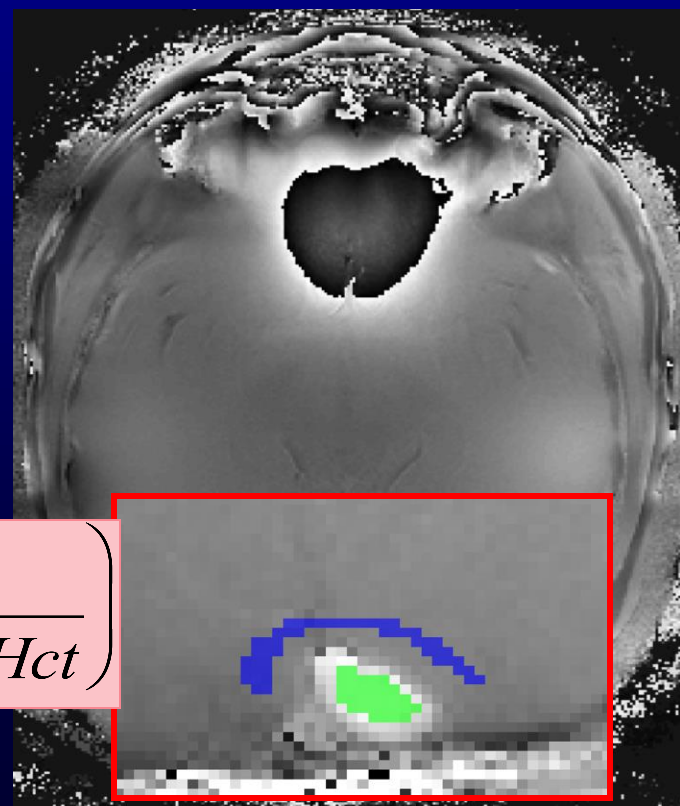
- Velocity through plane (orthogonal the arteries) and area



Susceptibility based oximetry





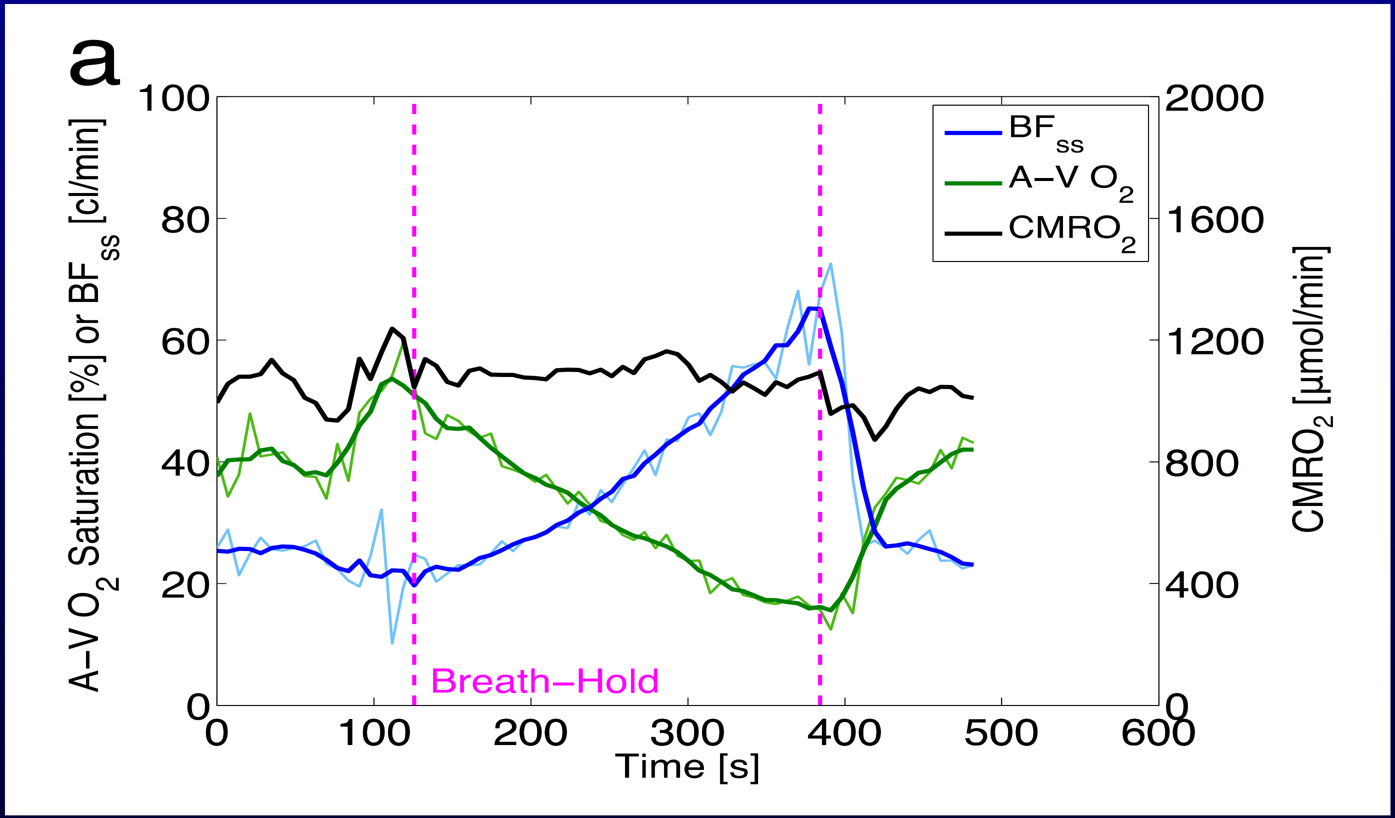


$$SvO_2 = \left(1 - \frac{2\,|\Delta\varphi_{ss} - \Delta\varphi_{tissue}|}{\gamma \Delta TE \Delta\chi_{do} B_0 (\cos^2\theta - 1/3) Hct} \right)$$

Breathold: $CMRO_2$

Vestergaard MB, Larsson HBW. Cerebral metabolism and vascular reactivity during breath-hold and hypoxic challenge in freedivers and healthy controls. J Cereb Blood Flow Metab 2017 .

- $CMRO_2 = 4 \cdot [Hgb] \cdot BFss \cdot (S_aO_2 - S_vO_2)$
- Blod-flow i sagittal sinus (BFss)
- Arteriovenous oxygen-difference (A-V O_2)



Extending the principle of Fick

The fluxes are not constant, but functions of time

The concentration here is not constant

$$j_{in}(t) = F \cdot c_{in}(t) \longrightarrow \frac{dc(t)}{dt} \longrightarrow j_o(t) = F \cdot c_o(t)$$

conservation of mass

$$v\frac{dc(t)}{dt} = F \cdot c_{in}(t) - F \cdot c_o(t) - j(t)$$

$$j_{in}(t) \neq j_o(t) + j(t)$$

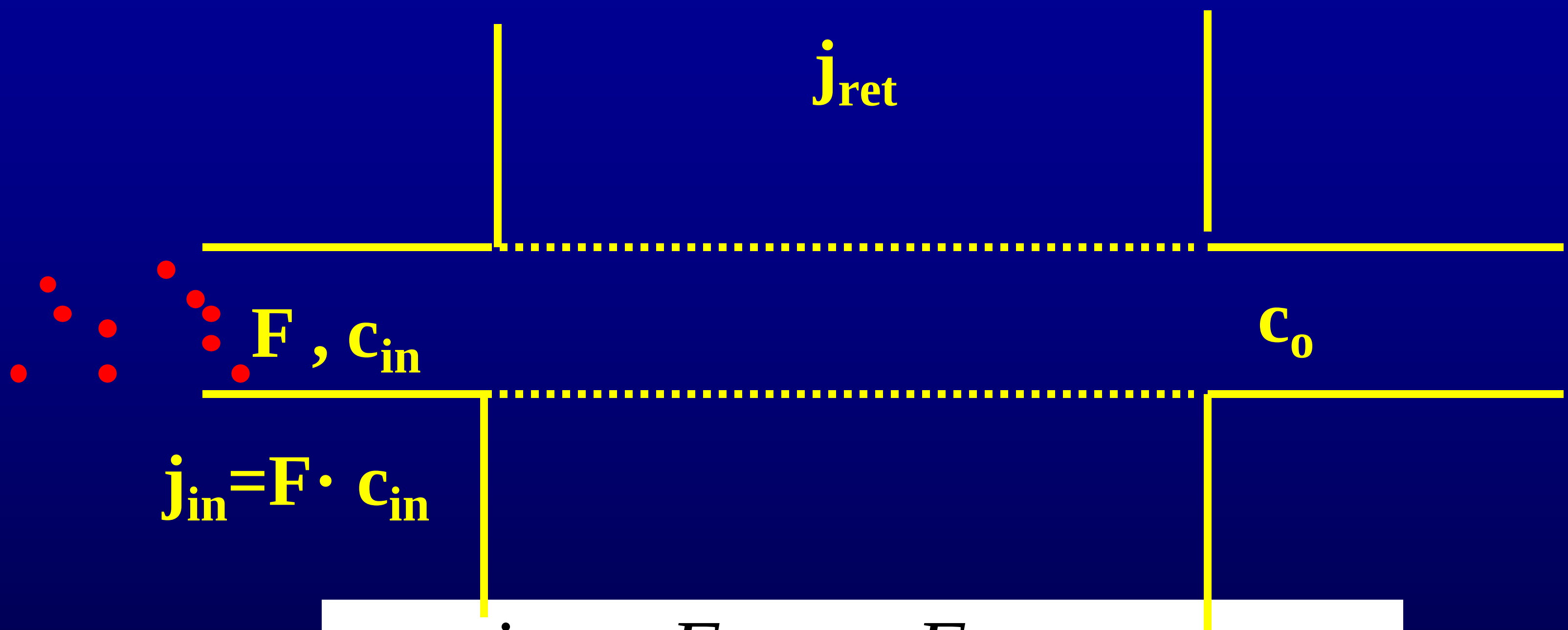
$$j(t) = K_i \cdot c(t)$$

$$v\frac{dc(t)}{dt} = F \cdot c_{in}(t) - F \cdot c_o(t) - K_i \cdot c(t)$$

HBWL

Break

Extraction fraction



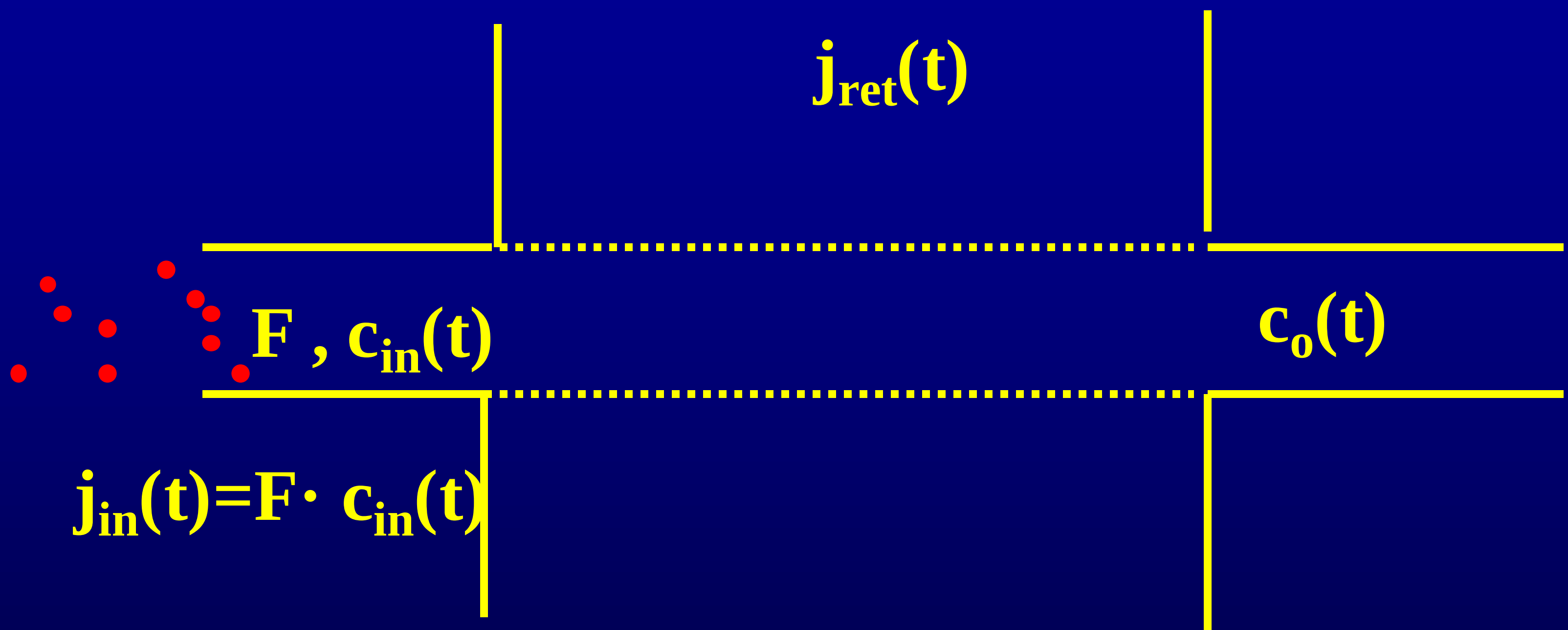
Extraction:

$$E = \frac{j_{ret}}{j_{in}} = \frac{F \cdot c_{in} - F \cdot c_o}{F \cdot c_{in}} = \frac{c_{in} - c_o}{c_{in}}$$

The transmitted fraction = 1-E

HBWL

Extraction fraction



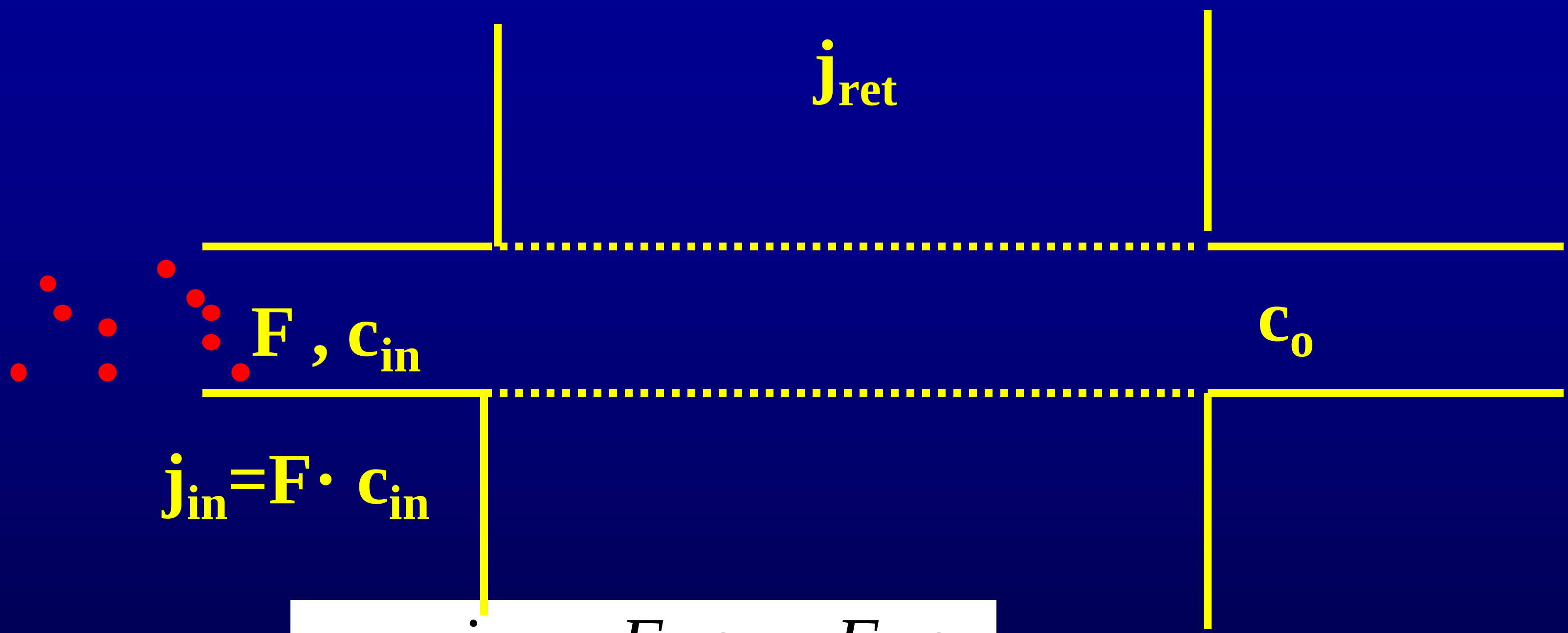
Extraction:

$$E=\frac{j_{ret}(t)}{j_{in}(t)}=\frac{F\cdot c_{in}(t)-F\cdot c_o(t)}{F\cdot c_{in}(t)}=\frac{c_{in}(t)-c_o(t)}{c_{in}(t)}$$

E constant ?

HBWL

Clearence



clearence:

$$Cl = \frac{j_{ret}}{c_{ref}} = \frac{F \cdot c_{in} - F \cdot c_o}{c_{ref}}$$

[Cl] = ml/s

HBWL

Clearence

It is a fictive flow: the volume of reference fluid containing the indicator amount taken up or cleared per unit time

Clearence

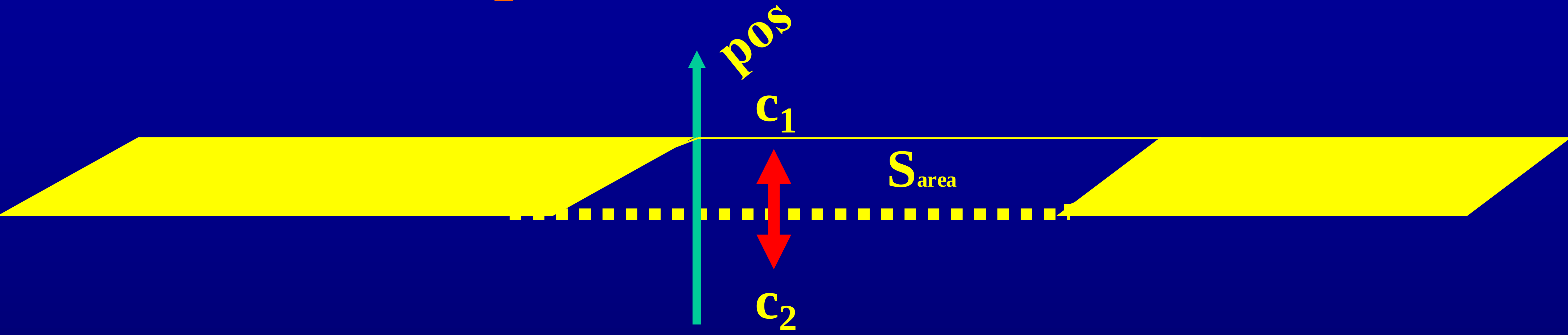
clearence:

$$Cl=\frac{j_{ret}}{c_{ref}}=\frac{j_{ret}}{c_{in}}=\frac{F\cdot c_{in}-F\cdot c_{o}}{c_{in}}=F\cdot E$$

$$j_{ret}=Cl\cdot c_{in}=K_{i}\cdot c_{in}=F\cdot E\cdot c_{in}$$

Break

Transport over a membrane



j ? c_2-c_1

$$j/S = P(c_2 - c_1)$$

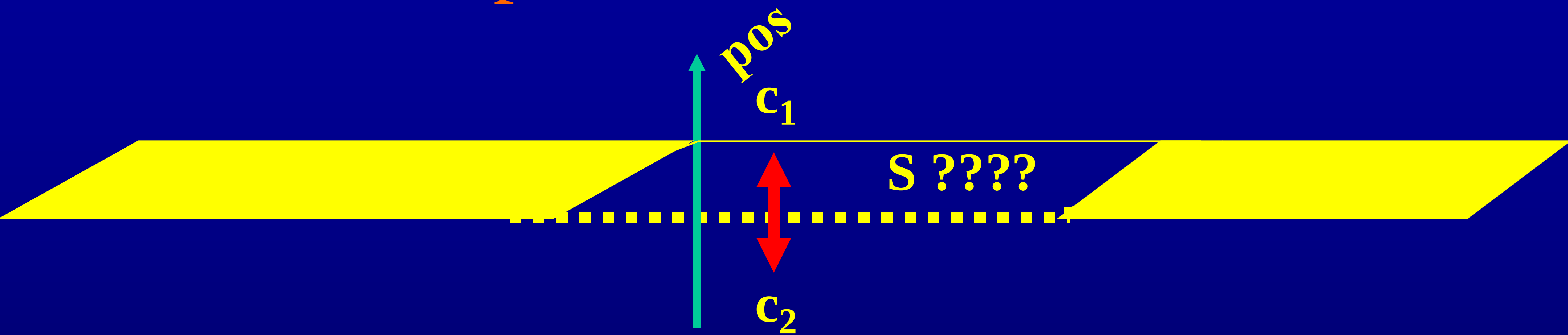
$$mol/cm^2/s = [P]\ mol/ml$$

$$j/S = -P(c_1 - c_2)$$

$$[P] = cm/s$$

HBWL

Transport over a membrane



$$j = -PS(c_1 - c_2)$$

S=surface area

mol/s =[PS] mol/ml

[PS] = cm^3/s = ml/s

[PS] = $cm^3/g/s$ = ml/g/s

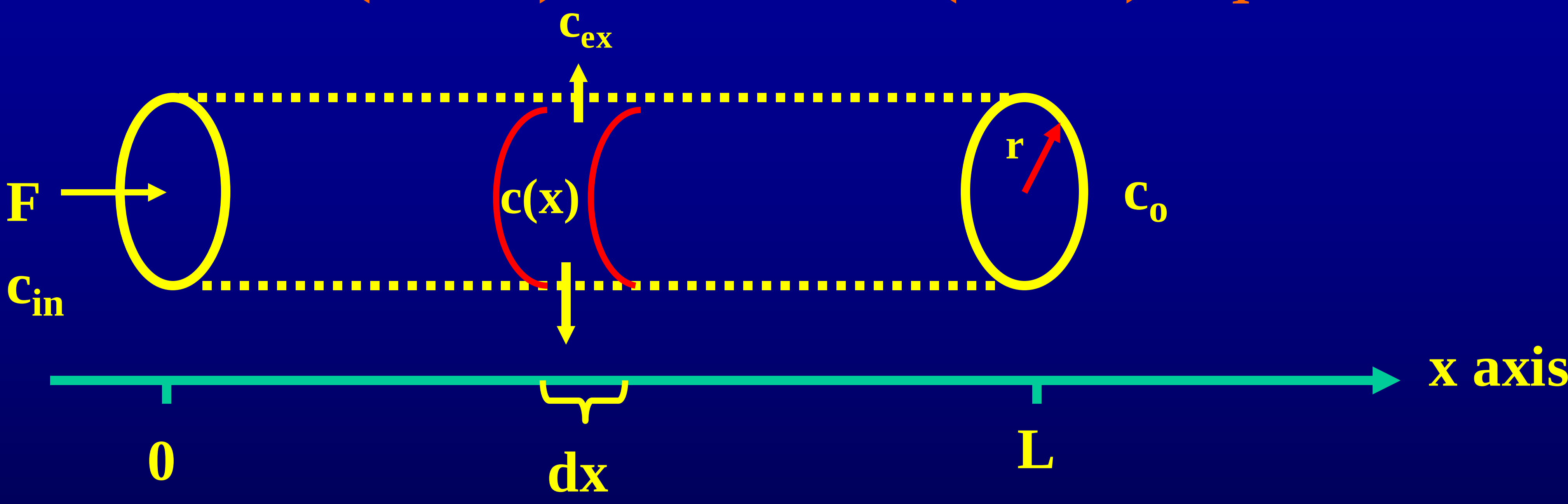
HBWL

Crone (1963) & Renkin (1959) equation

Transport over the capillary membrane

$$c_o = c_{in} \exp(-PS/F)$$

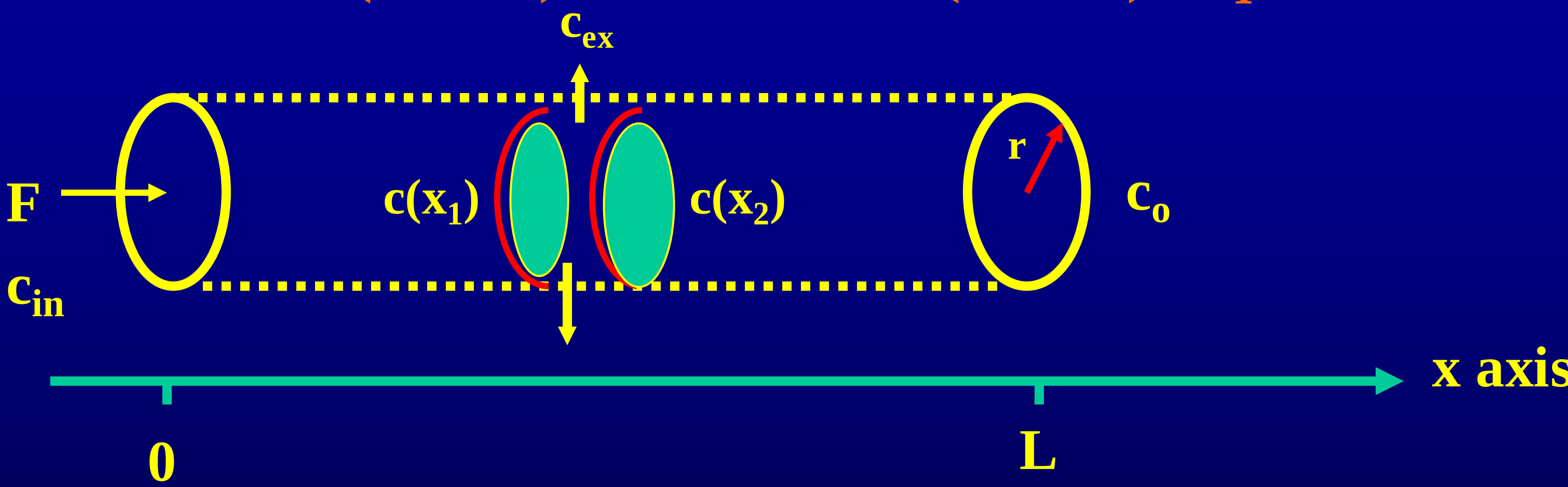
Crone (1963) & Renkin (1959) equation



The flux out of dx :

$$dj = -\frac{dS}{S} PS(c_{ex} - c(x)) = \frac{2\pi\, r dx}{2\pi\, r L} PS\, c(x)$$

Crone (1963) & Renkin (1959) equation



The loss inside the capillary:

$$dj = -F(c(x_2) - c(x_1))$$

Fick's principle

$$dj = -Fdc(x)$$

HBWL

Crone (1963) & Renkin (1959) equation

Transport over the capillary membrane

$$\left.\begin{aligned} dj &= \frac{2\pi\, r\, dx}{2\pi\, r\, L}\, PS\, c(x) \\ dj &= -F\, dc(x) \end{aligned}\right\} \Rightarrow \frac{dc(x)}{c(x)} = -\frac{PS}{LF}\, dx$$

$$\int_{c_{in}}^{c_o} \frac{dc(x)}{c(x)} = -\int_0^L \frac{PS}{LF}\, dx$$

$$\ln \frac{c_o}{c_{in}} = -\frac{PS\, L}{L\, F}$$

$$\mathbf{c_o = c_{in}\, exp(-PS/F)}$$

HBWL

Crone (1963) & Renkin (1959) equation

$$c_0 = c_i\, e^{-\frac{PS}{F}} \Rightarrow \frac{c_o}{c_i} = e^{-\frac{PS}{F}}$$

$$1 - \frac{c_o}{c_i} = 1 - e^{-\frac{PS}{F}} \Rightarrow \frac{c_i - c_o}{c_i} = 1 - e^{-\frac{PS}{F}}$$

$$E = 1 - e^{-\frac{PS}{F}} \wedge Cl = FE \Rightarrow Cl = K_i = F(1 - e^{-\frac{PS}{F}})$$

HBWL

Accumulation of tracer in tissue can be

Flow Limited or Diffusion Limited

Flow limited : **PS/F is large**

$$E = 1 - \exp(-PS/F) \qquad E \rightarrow 1 \text{ for } PS/F \rightarrow \infty$$

$$Cl = F\,E \rightarrow F$$

HBWL

Accumulation of tracer in tissue can be

Flow Limited or Diffusion Limited

Diffusion limited : **PS/F is small**

$$E = 1 - \exp(-PS/F) \qquad E \rightarrow 0 \text{ for } PS/F \rightarrow 0$$

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

$$Cl = F\,E \rightarrow PS$$

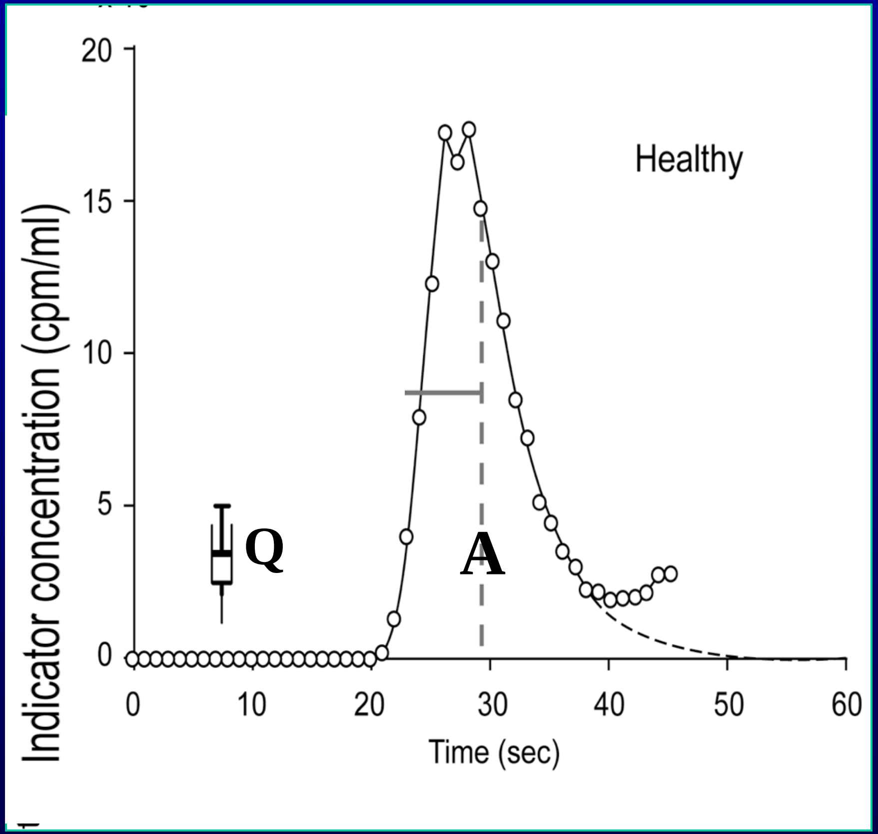
HBWL

Break

Indicator-technique

Stewart-Henriques-Hamilton

Bolus injection



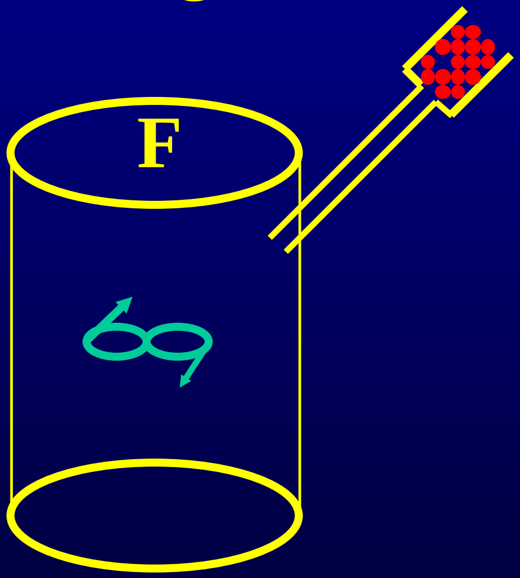
CO= Q/A

HBWL

Indicator-dilution methods continued

Bolus injection (Henriques-Hamilton-Bergner principle)

The aim : to measure the flow of an organ or a vessel or a pipeline



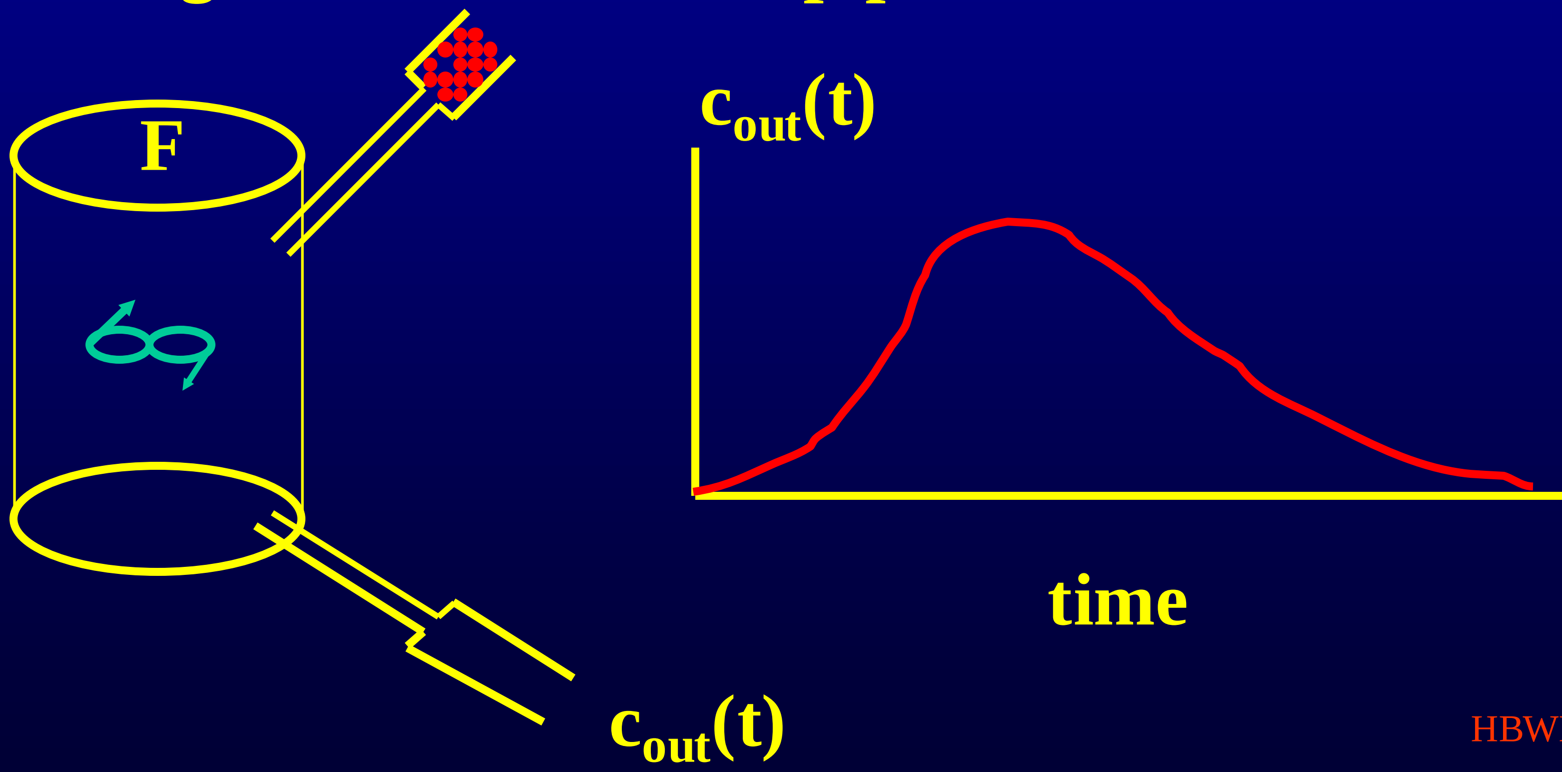
Injection of bolus Q_0 , a known amount of tracer

HBWL

Indicator-dilution methods continued

Bolus injection (Henriques-Hamilton-Bergner principle)

The aim : to measure the flow of an organ or a vessel or a pipeline



HBWL

Indicator-dilution methods continued

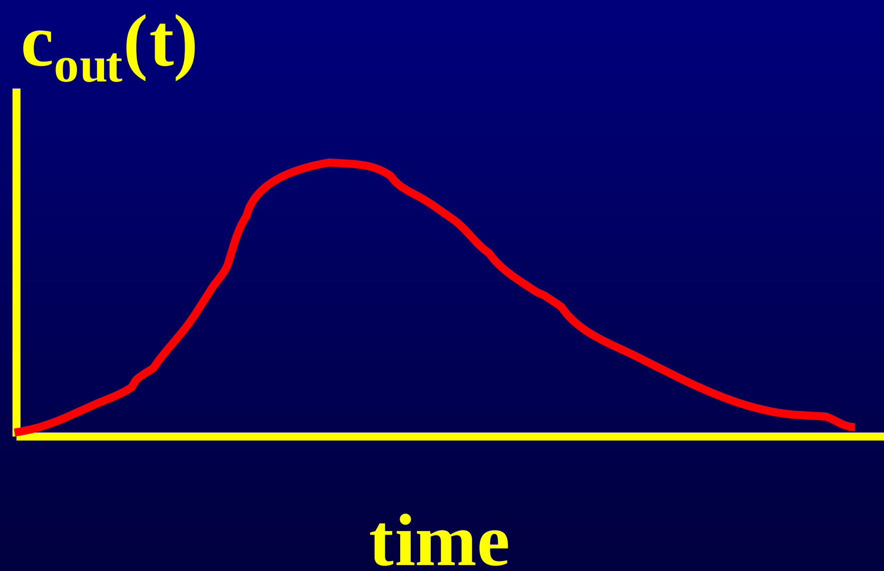
Bolus injection (Henriques-Hamilton-Bergner principle)

The aim : to measure the flow of an organ or a vessel or a pipeline

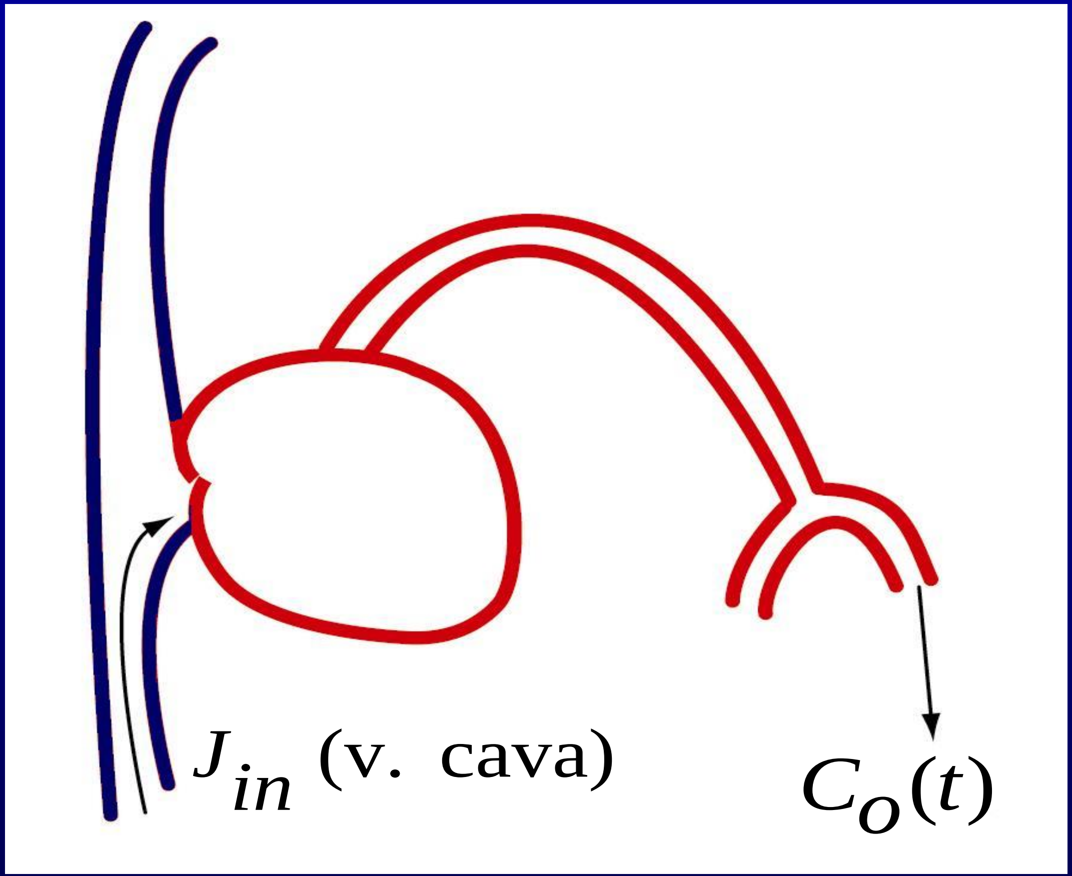
$$dQ(t) = F \cdot c_{out}(t) \cdot dt$$

$$\int_0^{\propto} Q_0 = \int_0^{\infty} F \cdot c_{out}(t) \cdot dt\, t) \cdot dt$$

$$F = \frac{Q_0}{\int_0^{\infty} c_{out}(t)dt}$$

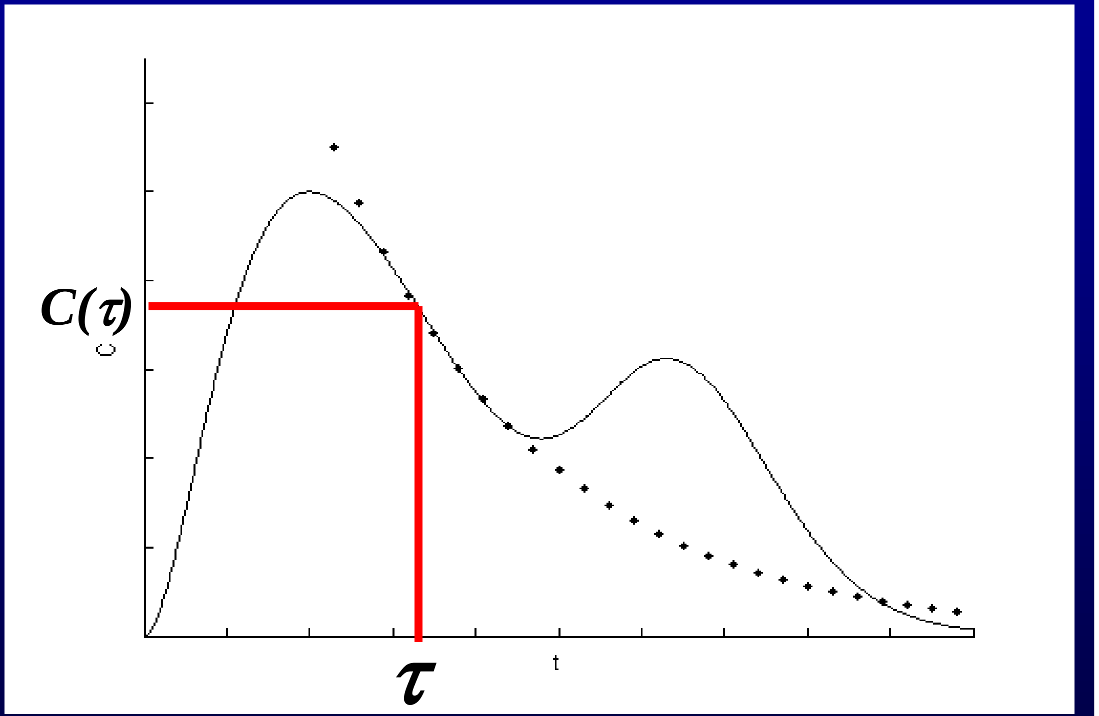


HBWL



Bolus injection in vena cava/periferal vein, and outlet concentration measurement from a peripheral artery.

HBWL



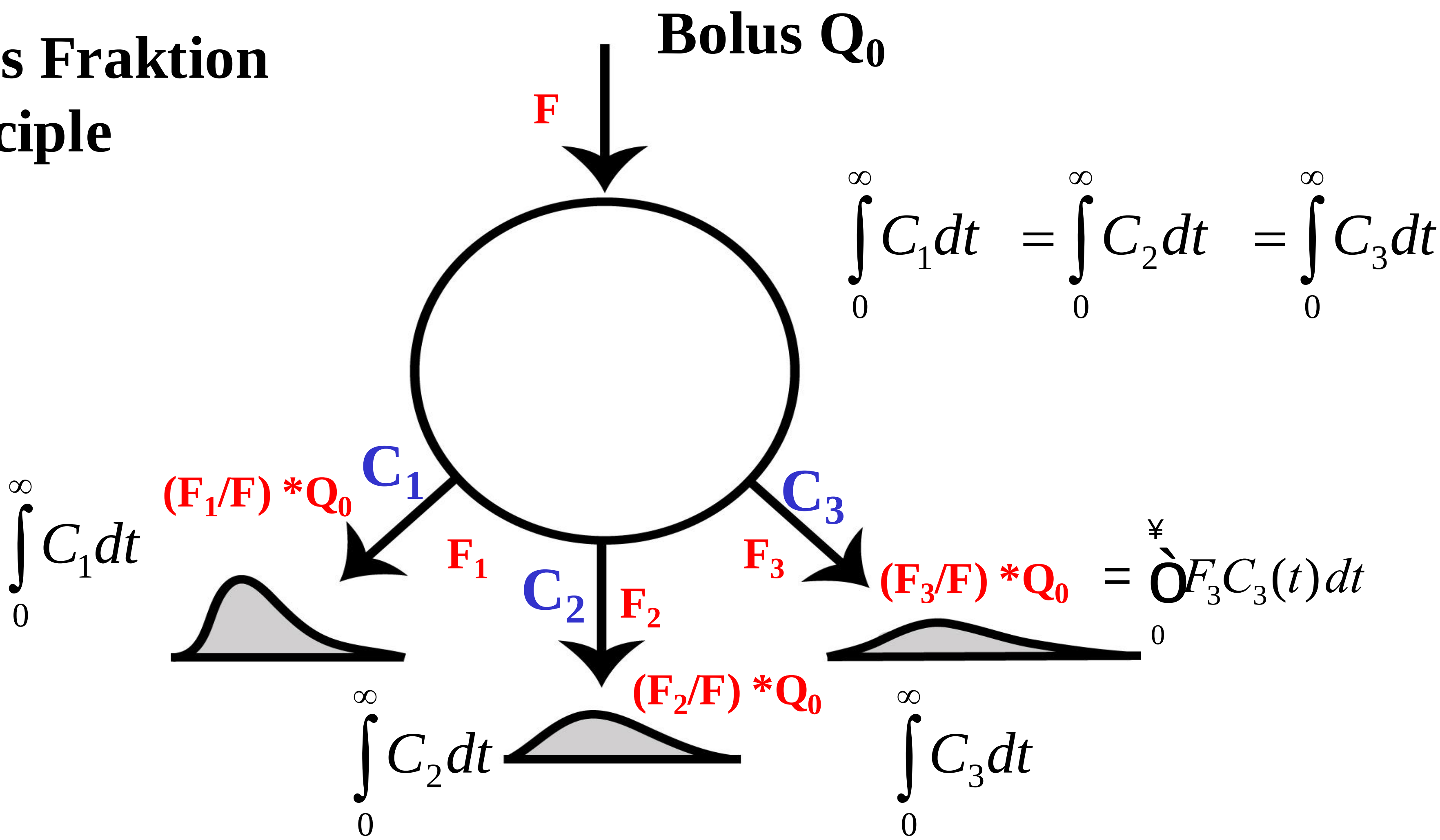
$$\int_o^{\infty} C_o(t)dt = \int_o^{\tau} C_o(t)dt + \int_{\tau}^{\infty} C(\tau)e^{-k(t-\tau)}dt =$$

$$\int_o^{\tau} C_o(t)dt + \frac{C(\tau)}{-k}\left[e^{-k(t-\tau)}\right]_{\tau}^{\infty} =$$

$$\int_o^{\tau} C_o(t)dt + \frac{C(\tau)}{k} \Rightarrow$$

$$F = \frac{Q_o}{\int_o^{\tau} C_o(t)dt + \frac{C(\tau)}{k}}$$

Bolus Fraktion principle

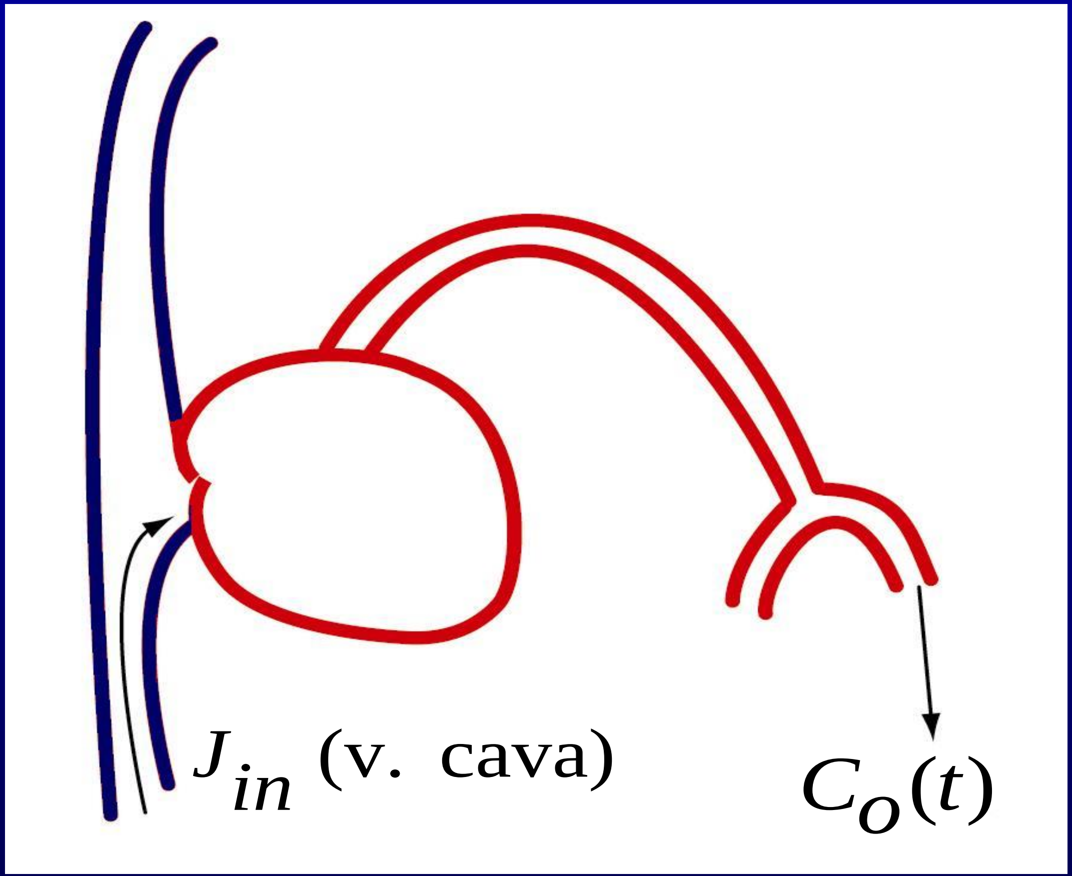


Equal area rule. The shape is different but the areas of the different outles are equal. This allows us to choose freely the most appropriate sampling point with regards the outlet concentration measurement.

HBWL

$$(F_i/F) * Q_0 = \int_0^{\infty} F_i C_i(t)\,dt$$

$$F = \frac{Q_0}{\int_0^{\infty} C_i(t)\,dt}$$

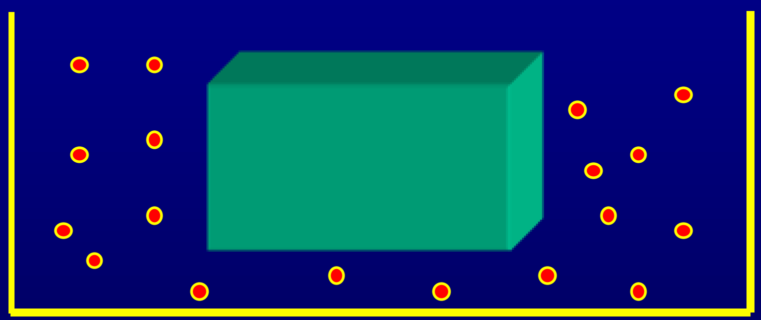


So the outlet concentration can be measured from a convenient artery

Bolus injection in vena cava/periferal vein, and outlet concentration measurement from a peripheral artery.

The volume of distribution: V_d

A tissue element



Incubation with a reference fluid

with a concentration c_{ref}

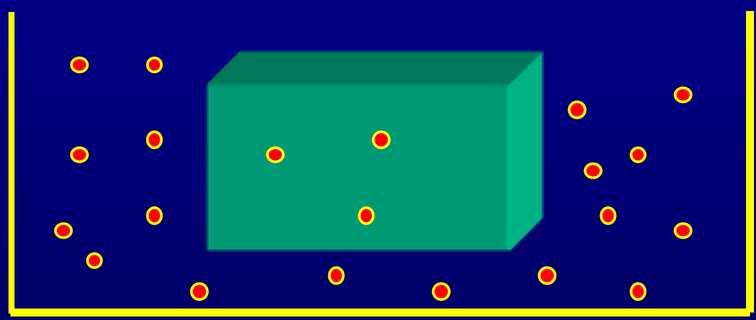
$$V_d \equiv Q/c_{ref}$$

$[V_d]$ = mmol/mmol/ml = ml

HBWL

The volume of distribution: V_d

A tissue element



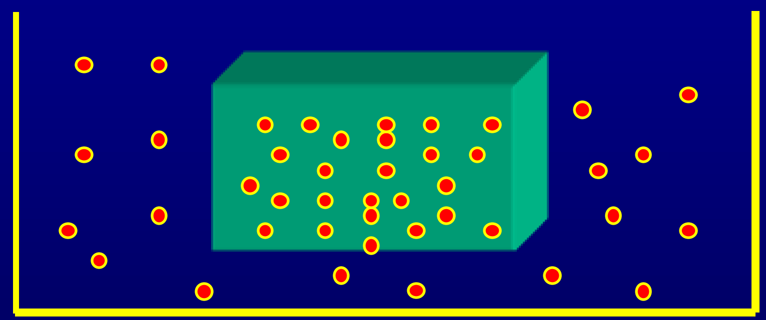
$V_d \equiv Q/c_{ref}$

V_d larger or smaller than the real volume of the tissue ?

HBWL

The volume of distribution: V_d

A tissue element



$V_d \equiv Q/c_{ref}$

V_d larger or smaller than the real volume of the tissue ?

HBWL

The volume of distribution: V_d

$$V_d \equiv Q/c_{ref}$$

It is the volume of the reference fluid which contains the amount Q

The partition coefficient $\lambda \equiv V_d/W$ or V_d/V

W is either the (real) mass of the tissue : [λ] = ml/g

or

V is the (real) volume of the tissue : [λ] = ml/ml

The partition coefficient λ

c_{tissue} = Q/W **c_{tissue} = Q/V**

Where W is either the real mass of tissue: [c_{tissue}]=mmol/g

Or

V is the (real) volume of the tissue: [c_{tissue}]=mmol/ml

$$\lambda \equiv \frac{V_d}{W} = \frac{Q}{c_{ref} \cdot W} = \frac{c_{tissue}}{c_{ref}}$$

HBWL

Examples

- Plasma concentration is 200 ng/ml
- Total amount of substance 10 mg
- Volume of distribution is 10mg/200 mg/ml = 50 L

Examples

- Regional tissue concentration: 100 kBq/cm^3
- Plasma concentration: 5 kBq/ml
- Volume of distribution:
  (100 kBq/cm^3) / (5 kBq/ml)= 20 ml/cm^3

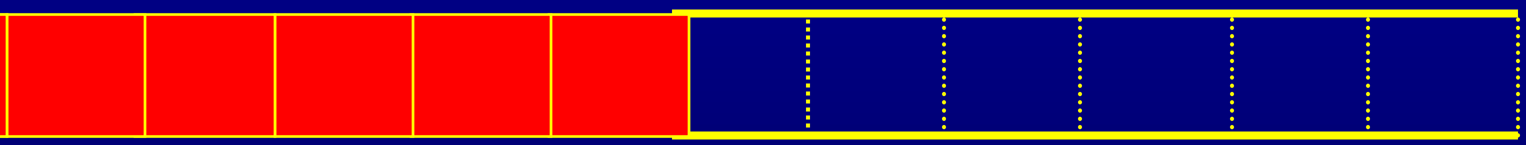
That 20 ml plasma would be required to account for the tracer in just 1 cm^3 of tissue

HBWL

Break

Mean transit time

The simplicity of this concept



$V_d = 6$ ml

A flow F = 1 ml/s

What is the (mean) transit time of the tracer in this compartment ?

$$\bar{t} = V_d/F = 6 \text{ ml} / 1 \text{ ml/s} = 6 \text{ s}$$

HBWL

Mean transit time

$$\bar{t} = V_d/F$$

$$\lambda = V_d/W$$

$$f = F/W$$

$$\bar{t} = \lambda / f$$

HBWL

Mean transit time

The definition

$$\bar{t} = \frac{1}{Q_0}(t_1 \cdot \Delta Q_1 + t_2 \cdot \Delta Q_2 + t_3 \cdot \Delta Q_3 + \ldots\ldots + t_i \cdot \Delta Q_i + \ldots) \wedge Q_0 = \sum_i \Delta Q_i$$

$$\bar{t} = \frac{1}{Q_0}\sum_i t_i \cdot \Delta Q_i = \sum_i t_i \cdot \frac{\Delta Q_i}{Q_0} = \sum_i t_i \cdot \frac{\Delta Q_i}{Q_0 \cdot \Delta t} \cdot \Delta t \xrightarrow{\lim} \int_0^\infty t \cdot \boxed{\frac{dQ(t)}{Q_0 \cdot dt}} \cdot dt$$

Define the frequency function of transit times:

$$h(t) \equiv \frac{dQ(t)}{Q_0 \cdot dt}$$

[h(t)] = 1/s

HBWL

The frequency function

$$h(t) \equiv \frac{dQ(t)}{Q_0 \cdot dt}$$

In words : It is the fraction of the dose given as an impuls (a delta function), which leaves the system per unit time !!!! , at time t, (and therefore a function of time)

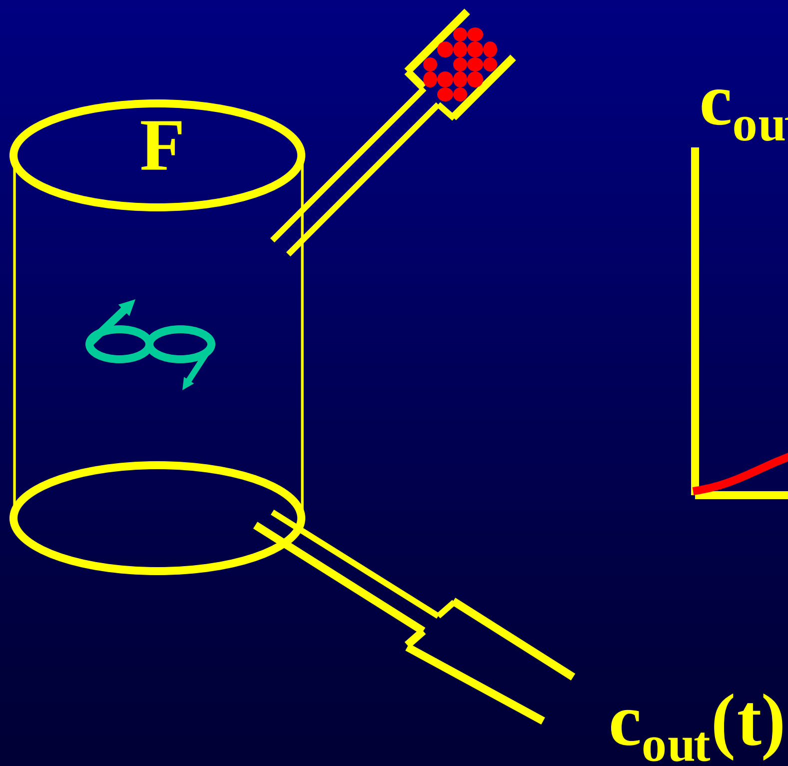
$$\bar{t} = \int_0^\infty t \cdot h(t) \cdot dt$$

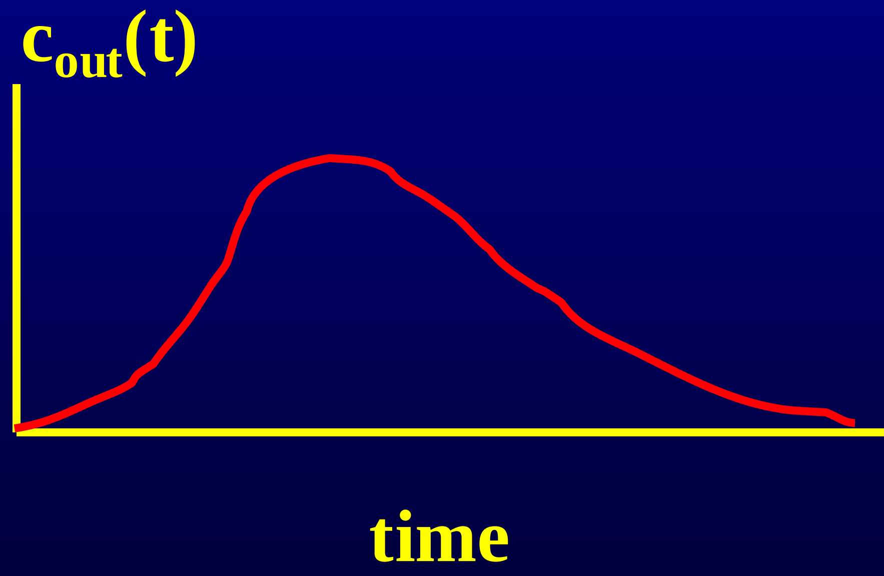
HBWL

Finding h(t)

$$h(t) = \frac{c_{out}(t)}{\int_0^\infty c_{out}(t)\cdot dt} = \frac{F\cdot c_{out}(t)}{\ldots}$$

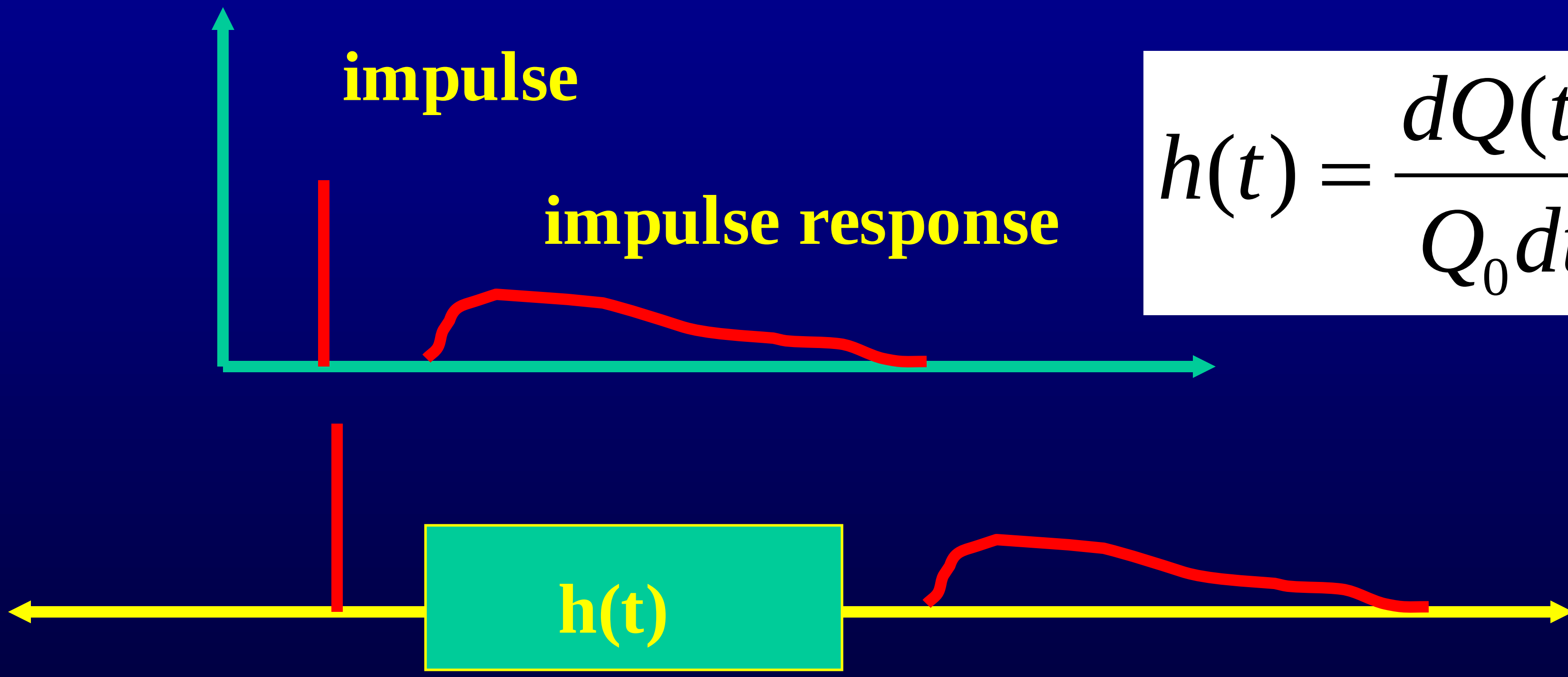
$$\bar{t} = \int_0^\infty t\cdot h(t)\cdot dt$$





Break

The impulse response of a inlet and outlet system (artery – vein system)

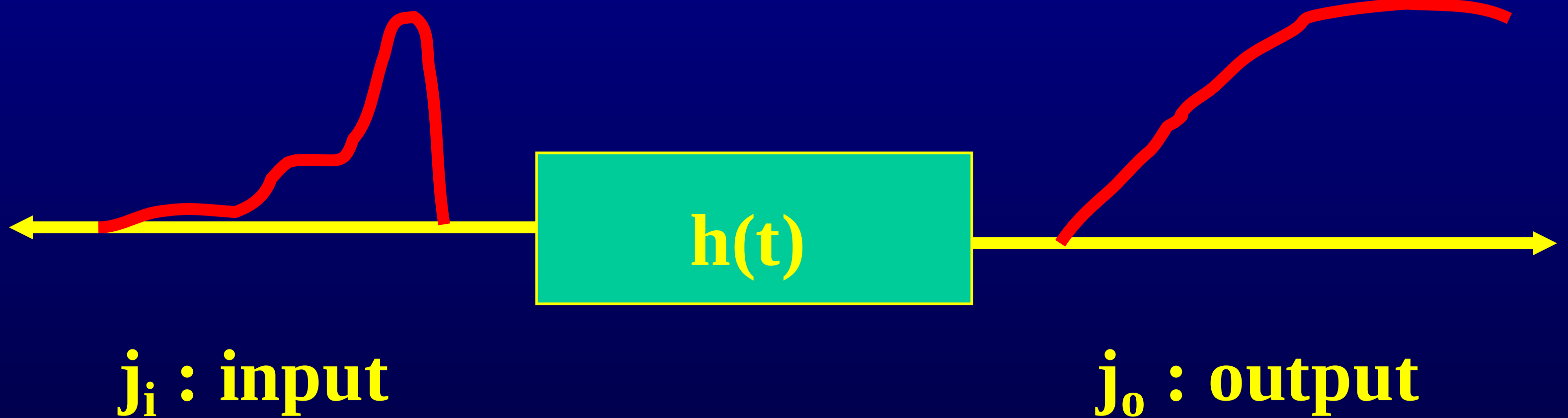


$$h(t) = \frac{dQ(t)}{Q_0 dt}$$

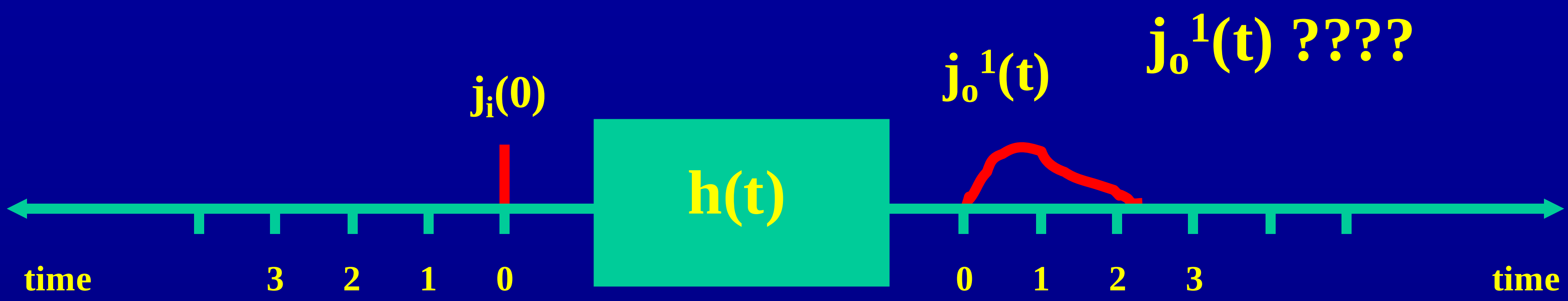
HBWL

Why is h(t) interesting ?

Because it relates input to an output in the case of the input not being a bolus (a deltafunction) !



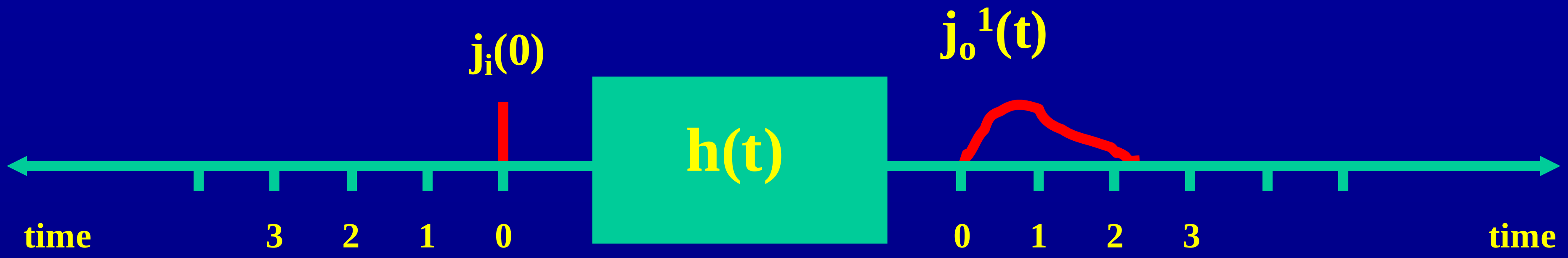
$$j_o(t) = j_i(t) \otimes h(t) = \int_0^t j_i(\tau)\, h(t-\tau)\, d\tau$$



e.g $j_i(0) = 1$ mmol / 0.01s

$$j_o^1(t) = j_i(0)\,\Delta\tau\, h(t)$$

Flux (number pr unit time - as a functon of time) leaving the system due to an input at time zero

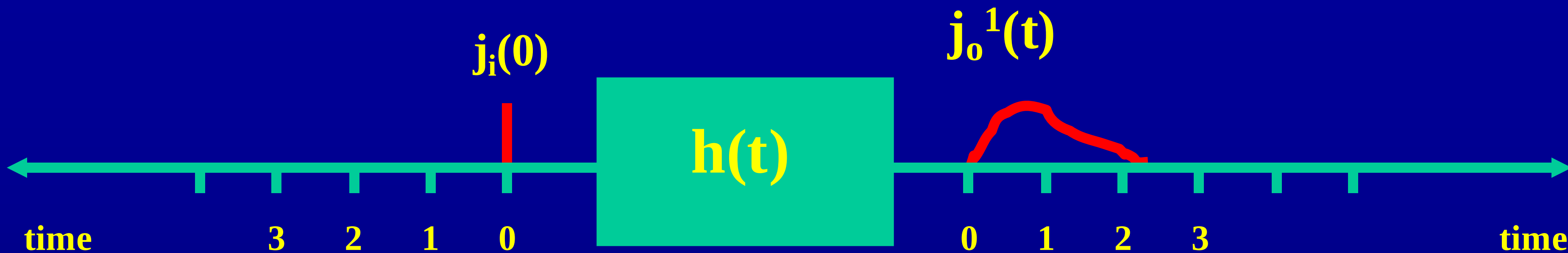


e.g $j_i(0)$ = 1 mmol / 0.01s

$$j_o^1(t) = j_i(0)\, \Delta\tau\, h(t)$$

Flux entering the system at time zero

HBWL

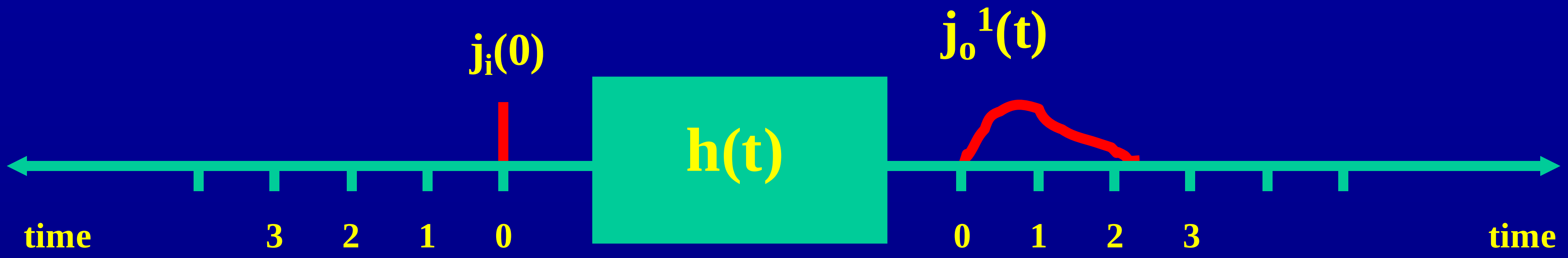


e.g $j_i(0) = 1$ **mmol / 0.01s**

$$j_o^1(t) = j_i(0)\,\Delta\tau\,h(t)$$

A small time interval

HBWL

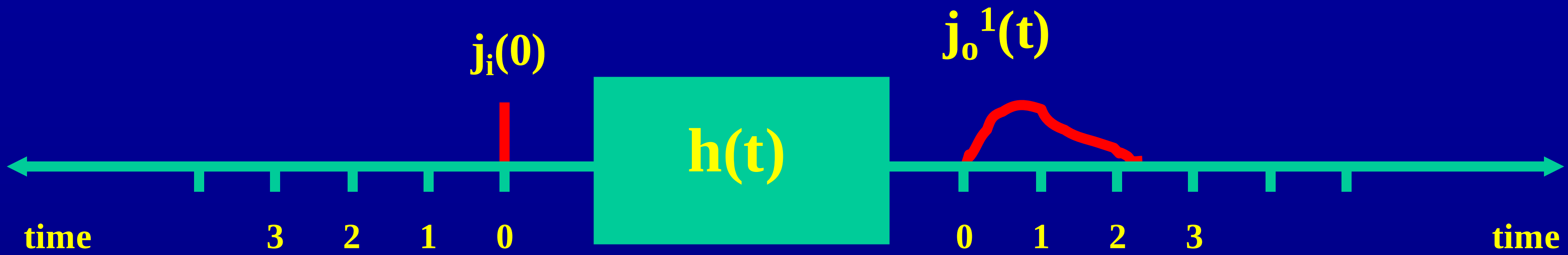


e.g $j_i(0) = 1$ mmol / 0.01s

$$j_o^1(t) = j_i(0)\,\Delta\tau\, h(t)$$

The amount (the number) of tracer entering the system at time zero

HBWL

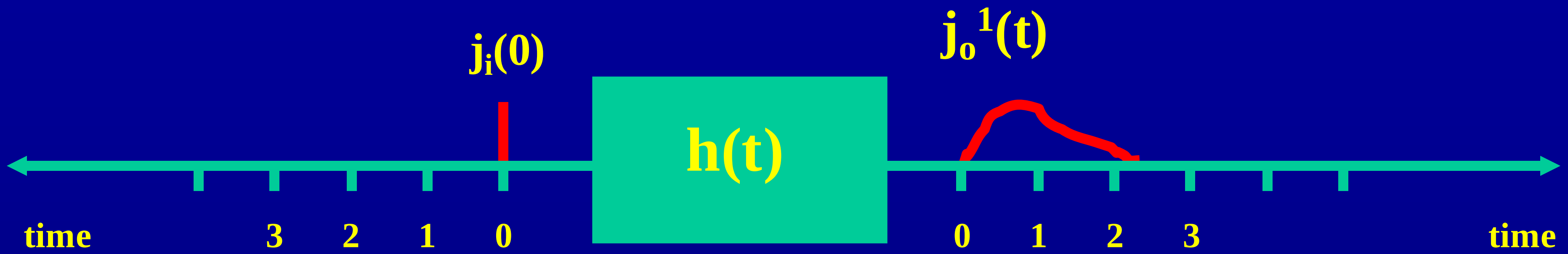


e.g $j_i(0) = 1$ mmol / 0.01s

$$j_o^1(t) = j_i(0)\,\Delta\tau\, h(t)$$

The impulse response function: the fractional amount (the number) pr. unit time - leaving the system as a function of time

HBWL

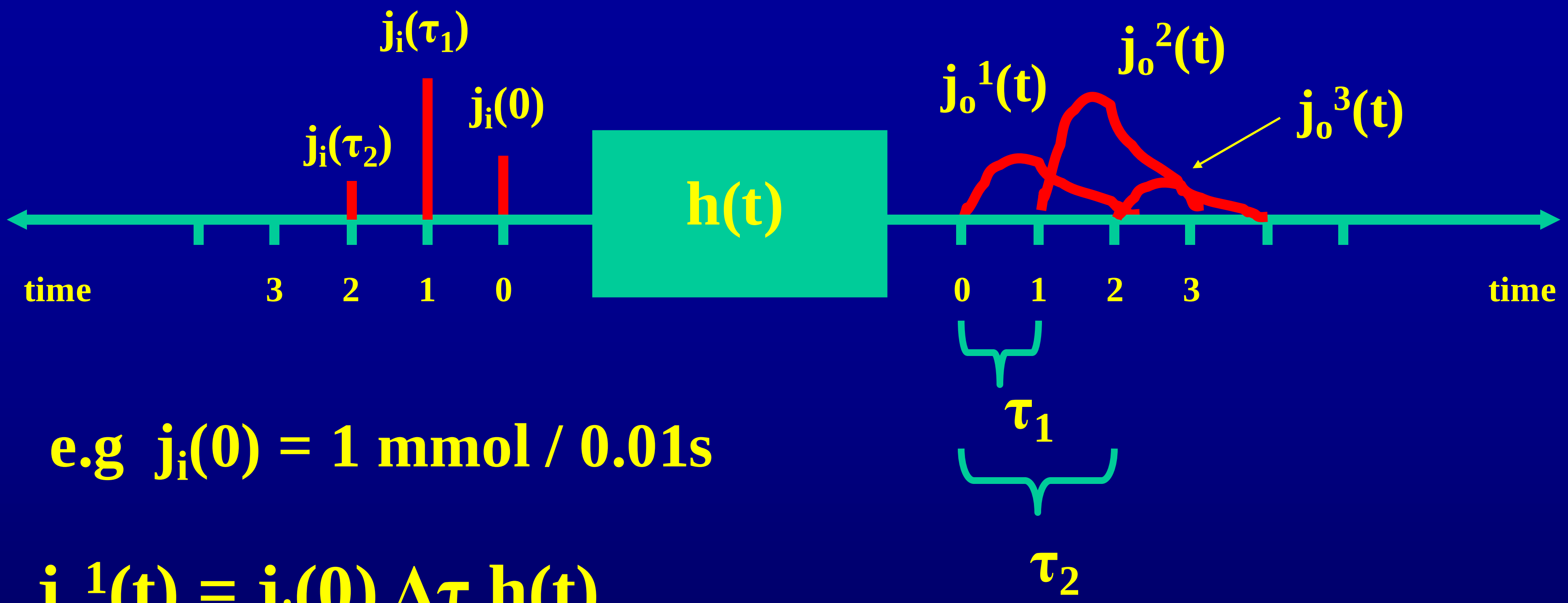


e.g $j_i(0)$ = 1 mmol / 0.01s

$$j_o^1(t) = j_i(0)\,\Delta\tau\, h(t)$$

Flux (number pr unit time - as a functon of time) leaving the system due to an input at time zero

HBWL



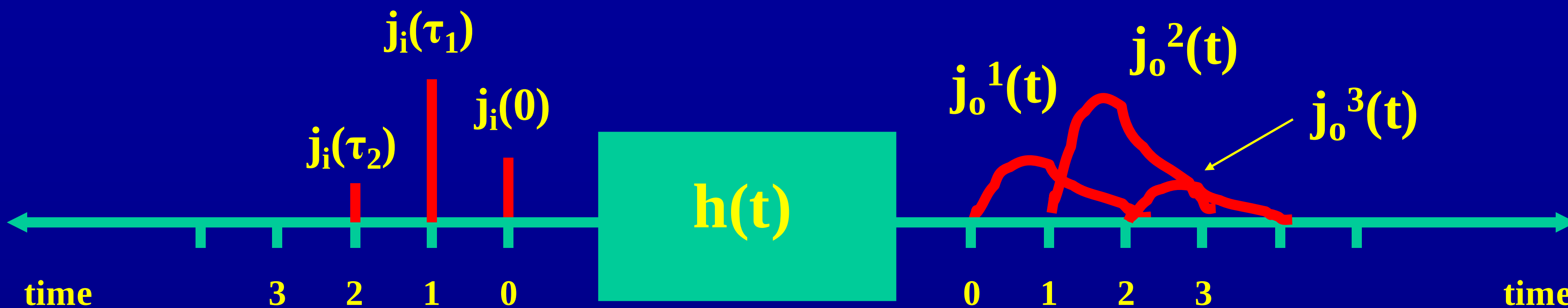
e.g $j_i(0) = 1$ mmol / 0.01s

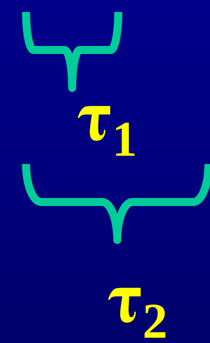
$$j_o^1(t) = j_i(0)\,\Delta\tau\, h(t)$$

$$j_o^2(t) = j_i(\tau_1)\,\Delta\tau\, h(t-\tau_1) = j_i(\tau_1)\, h(t-\tau_1)\,\Delta\tau$$

$$j_o^3(t) = j_i(\tau_2)\, h(t-\tau_2)\,\Delta\tau$$

HBWL





$$j_o^1(t) = j_i(0)\, \Delta\tau\, h(t)$$

$$j_o^2(t) = j_i(\tau_1)\, h(t- \tau_1)\, \Delta\tau$$

$$j_o^3(t) = j_i(\tau_2)\, h(t- \tau_2)\, \Delta\tau$$

Total flux $j_o(t) = j_o^1(t) + j_o^2(t) + j_o^3(t) =$

$$j_i(0)\, h(t-0)\, \Delta\tau + j_i(\tau_1)\, h(t- \tau_1)\, \Delta\tau + j_i(\tau_2)\, h(t- \tau_2)\, \Delta\tau$$

HBWL

$$j_0(t) = \sum_{0}^{N} j_i(\tau_n)\, h(t-\tau_n)\, \Delta\tau$$

$$\Delta\tau \to 0 \Rightarrow j_0(t) = \int_0^t j_i(\tau)\, h(t-\tau)\, d\tau$$

HBWL

$$j_o(t) = j_i(t) \otimes h(t)$$

$$j_o(t) = F\,c_o(t)$$

$$j_i(t) = F\,c_i(t)$$

$$c_o(t) = c_i(t) \otimes h(t)$$

HBWL

Break

h(t) & H(t) !!

$$\int_{0}^{+\infty} h(t)dt = \frac{1}{\int_{0}^{\infty} c_o(t)dt} \int_{0}^{\infty} c_o(t)dt = 1$$

h(t) is an analogous to a probability density function

The first moment of this function corresponds to the mean value or expectation value

$$\bar{x} = E(x) = \int_{0}^{\infty} x\, p(x)\, dx$$

$$\bar{t} = \int_{0}^{\infty} t\, h(t)\, dt$$

HBWL

Mean transit time

The definition

$$\bar{t} = \frac{1}{Q_0}(t_1 \cdot \Delta Q_1 + t_2 \cdot \Delta Q_2 + t_3 \cdot \Delta Q_3 + \ldots\ldots + t_i \cdot \Delta Q_i + \ldots) \wedge Q_0 = \sum_i \Delta Q_i$$

$$\bar{t} = \frac{1}{Q_0} \sum_i t_i \cdot \Delta Q_i = \sum_i t_i \cdot \frac{\Delta Q_i}{Q_0} = \sum_i t_i \cdot \frac{\Delta Q_i}{Q_0 \cdot \Delta t} \cdot \Delta t \xrightarrow{\lim} \int_0^\infty t \cdot \boxed{\frac{dQ(t)}{Q_0 \cdot dt}} \cdot dt$$

Define the frequency function of transit times:

$$h(t) \equiv \frac{dQ(t)}{Q_0 \cdot dt}$$

[h(t)] = 1/s

h(t) & H(t) !!

$$h(t) = \frac{dQ(t)}{Q_0 dt} = \frac{c_o(t)}{\int_0^\infty c_0(\tau)d\tau}$$

The fraction that leaves the system as a function of time pr unit time after a bolus inj

$$h(t)dt = \frac{dQ(t)}{Q_0}$$

The fraction that leaves the system as a function of time in a short time interval[HBWL]

h(t) & H(t) !!

$$\int_0^{t_1} h(t)\,dt = \frac{1}{Q_0}\int_0^{t_1} dQ(t) = \frac{1}{Q_0}(Q(t_1) - Q(0))$$

The fraction having left the system in the time interval 0:t_1 (after a bolus injection)

$$\int_{t_1}^{t_2} h(t)\,dt = \frac{1}{Q_0}\int_{t_1}^{t_2} dQ(t) = \frac{1}{Q_0}(Q(t_2) - Q(t_1))$$

The fraction having left the system in the time interval t_1:t_2

HBWL

h(t) & H(t) !!

$$H(t) \equiv \int_0^t h(\tau)\,d\tau = \frac{1}{Q_0}\int_0^t dQ(\tau) = \frac{Q(t)}{Q_0}$$

The fraction having left the system in the time interval 0:t (after a bolus injection)

The fraction remaining in the system at time t after a bolus inj

$$1 - H(t) = 1 - \int_0^t h(\tau)d\tau$$

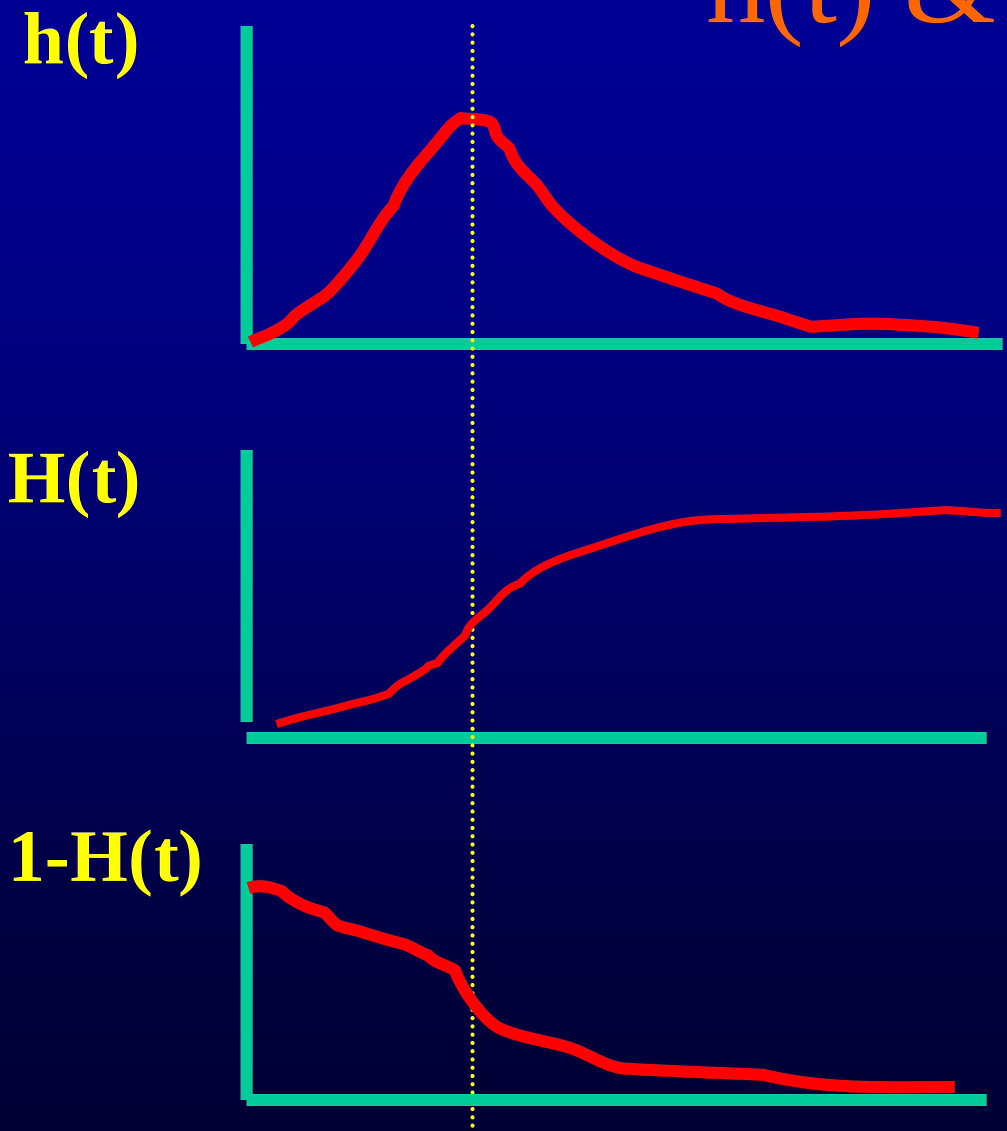
h(t) & H(t) !!

The residue impulse response function

$$1 - H(t)$$

HBWL

h(t) & H(t) !!

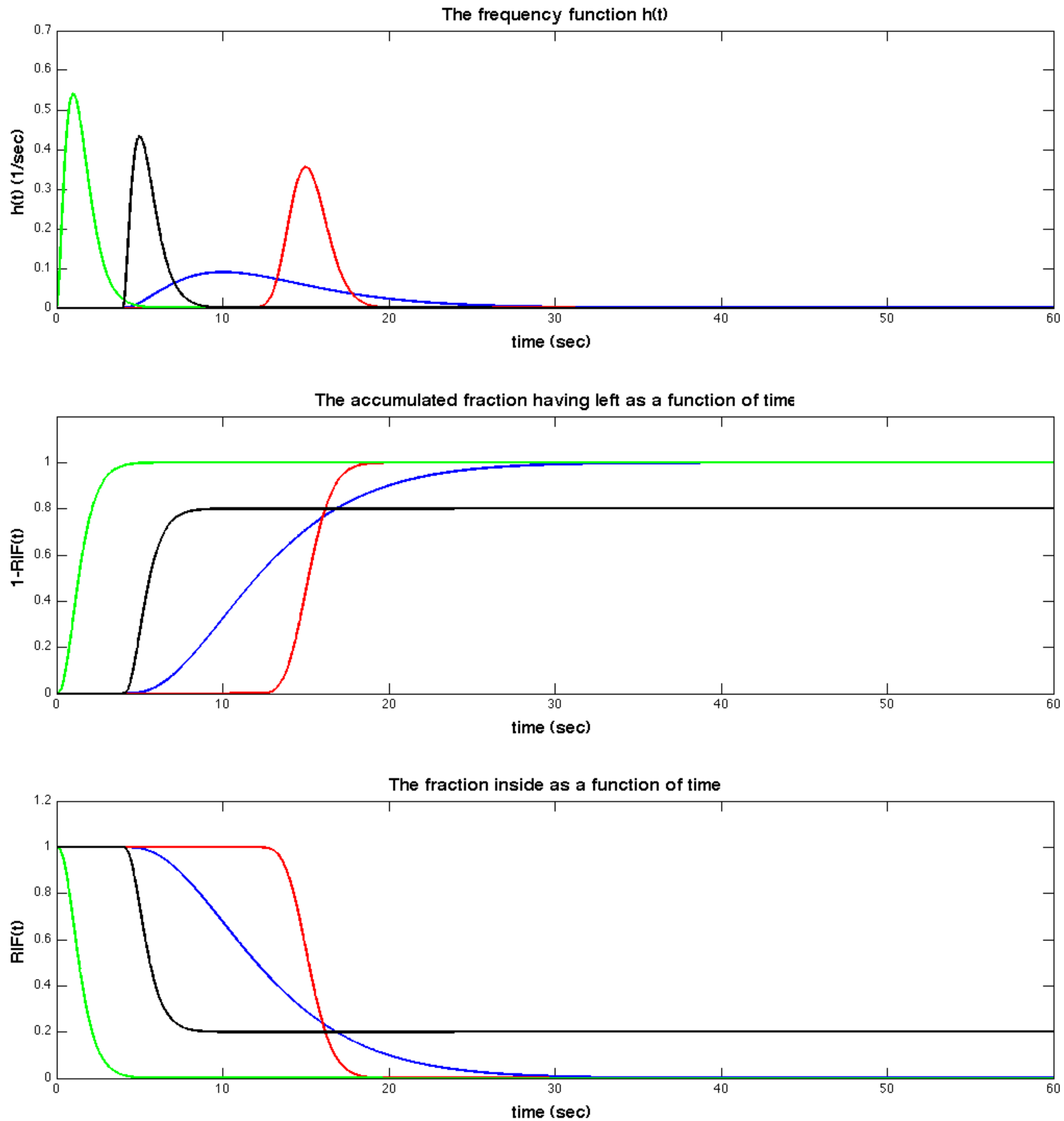


$$h(t) = \frac{dH(t)}{dt}$$

$$H(t) = \int_0^t h(\tau)d\tau$$

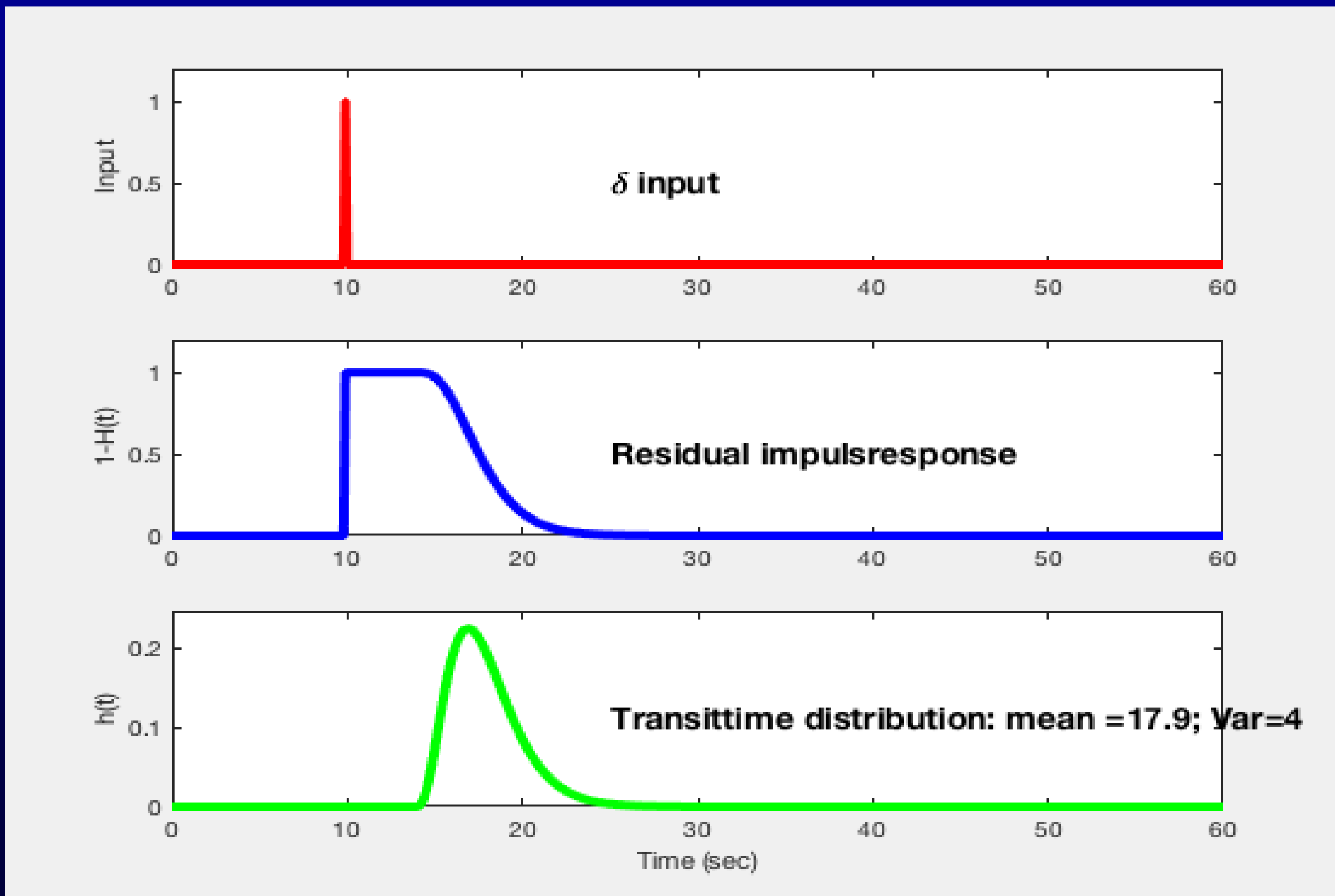
$$1 = H(t) + (1 - H(t))$$

HBWL


The frequency function h(t)
h(t) (1/sec)
time (sec)
The accumulated fraction having left as a function of time
1-RIF(t)
time (sec)
The fraction inside as a function of time
RIF(t)
time (sec)

HBWL

CTH modeling



input

tissue

output

h(t) & H(t) !!

$$\bar{t} = \int_0^\infty [1 - H(t)]\,dt$$

HBWL

$$\bar{t} = \frac{1}{Q_0}(t_1 \cdot \Delta Q_1 + t_2 \cdot \Delta Q_2 + t_3 \cdot \Delta Q_3 + \ldots\ldots + t_i \cdot \Delta Q_i + \ldots)$$

$$\bar{t} = \int_0^{\infty} (1 - H(t))\,dt$$

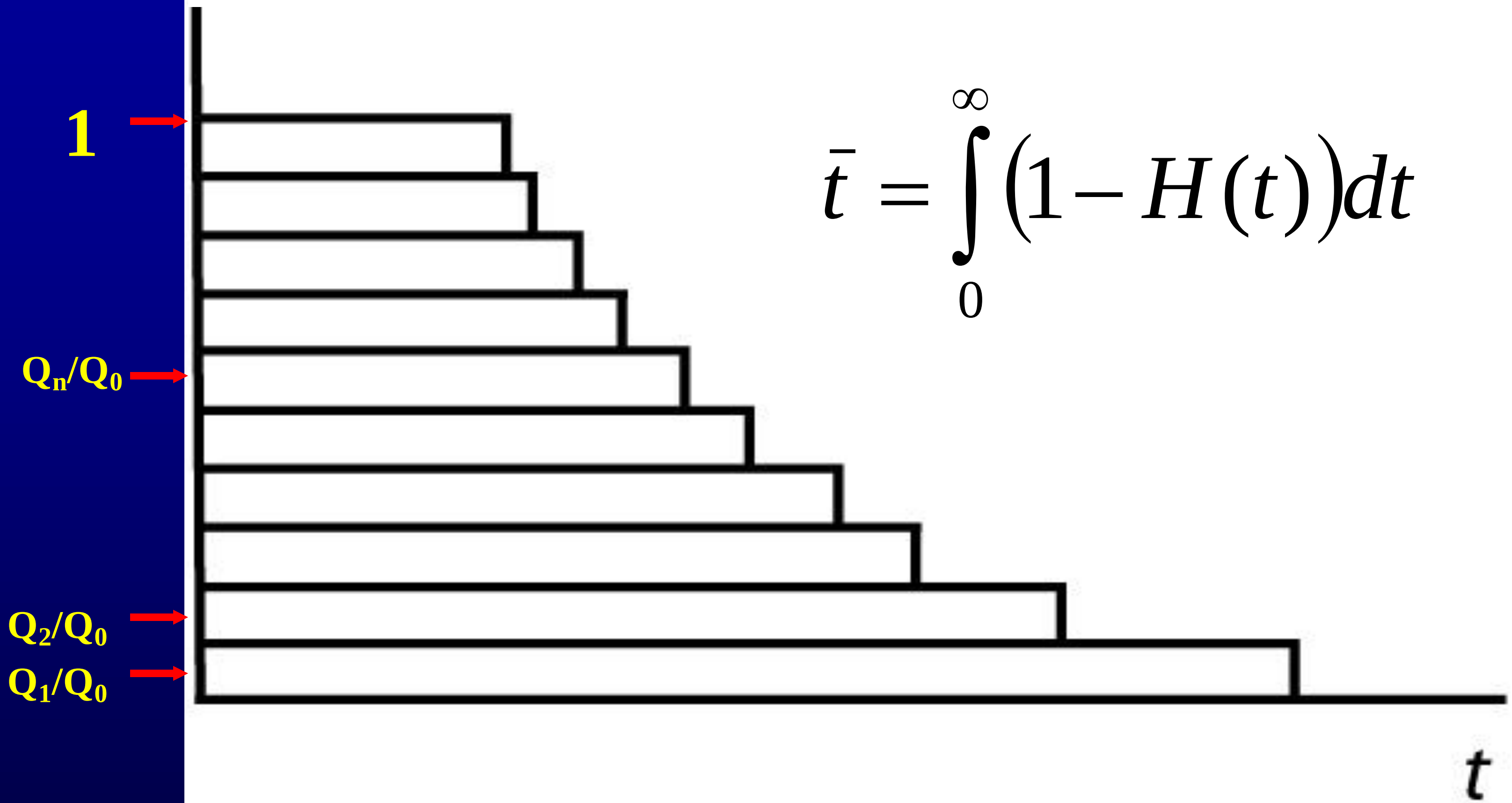


Illustration of transittimes and mean transittime estimated by residual measurement.

Mean transit time

The definition

$$\bar{t} = \frac{1}{Q_0}(t_1 \cdot \Delta Q_1 + t_2 \cdot \Delta Q_2 + t_3 \cdot \Delta Q_3 + \ldots\ldots + t_i \cdot \Delta Q_i + \ldots) \wedge Q_0 = \sum_i \Delta Q_i$$

$$\bar{t} = \frac{1}{Q_0}\sum_i t_i \cdot \Delta Q_i = \sum_i t_i \cdot \frac{\Delta Q_i}{Q_0} = \sum_i t_i \cdot \frac{\Delta Q_i}{Q_0 \cdot \Delta t} \cdot \Delta t \xrightarrow{\lim} \int_0^\infty t \cdot \boxed{\frac{dQ(t)}{Q_0 \cdot dt}} \cdot dt$$

Define the frequency function of transit times:

$$h(t) \equiv \frac{dQ(t)}{Q_0 \cdot dt}$$

[h(t)] = 1/s

HBWL

Break

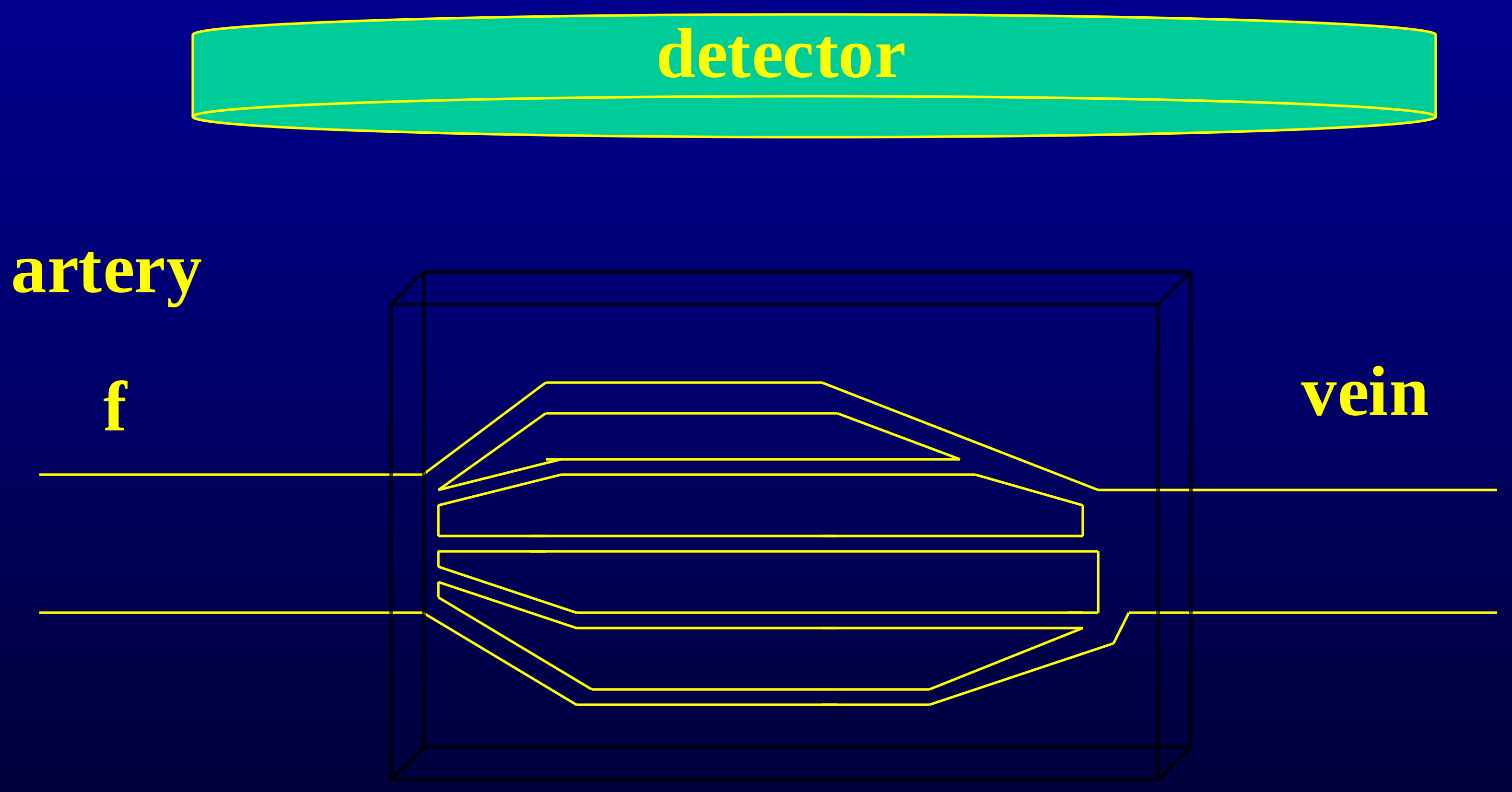
Residue detection in CT-PET- SPECT-MRI

The residue impulse response function: The fraction remaining in the tissue at time t after a brief (delta) input

$$1 - H(t)$$

HBWL

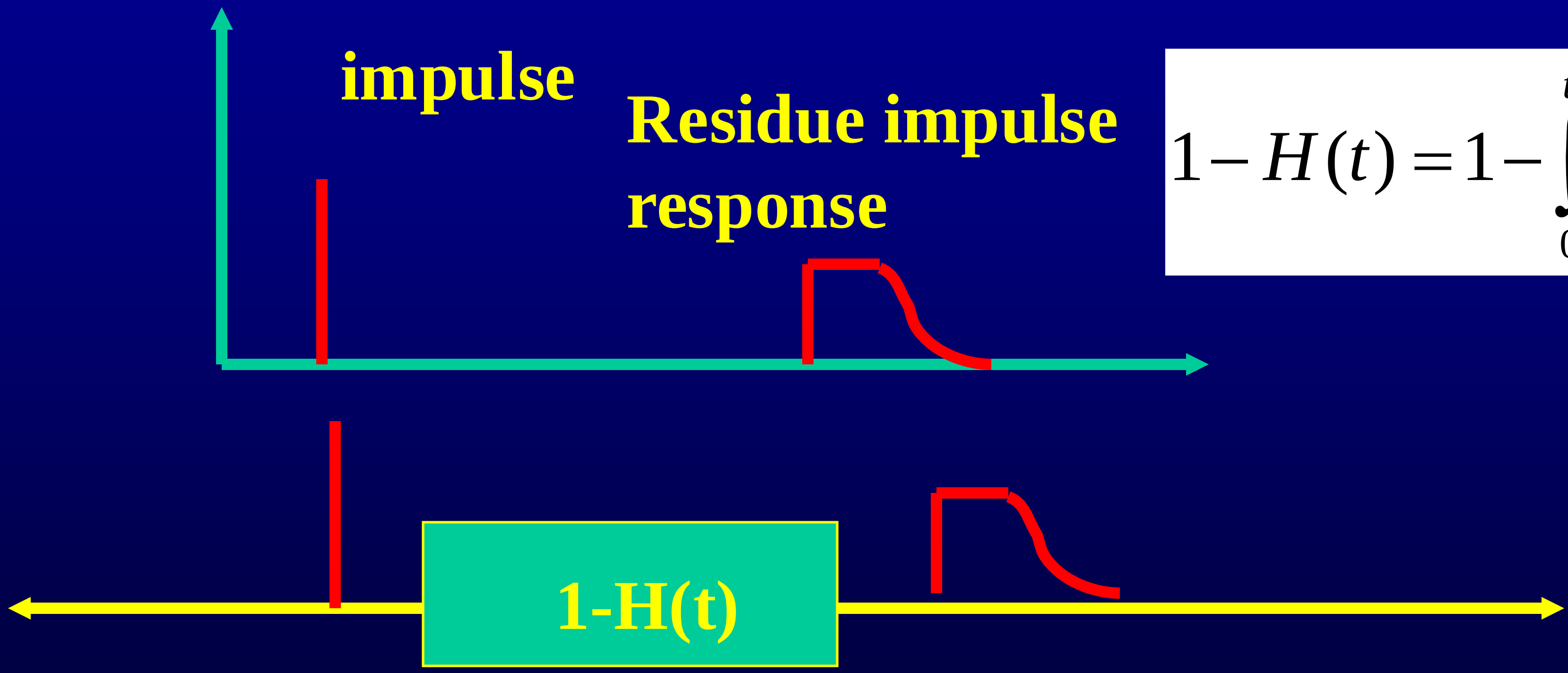
Measuring perfusion by an external registration: CT,SPECT,PET,MRI



f: flow or perfusion [ml/min /100g]

HBWL

The impulse response as measured by an external measuring system



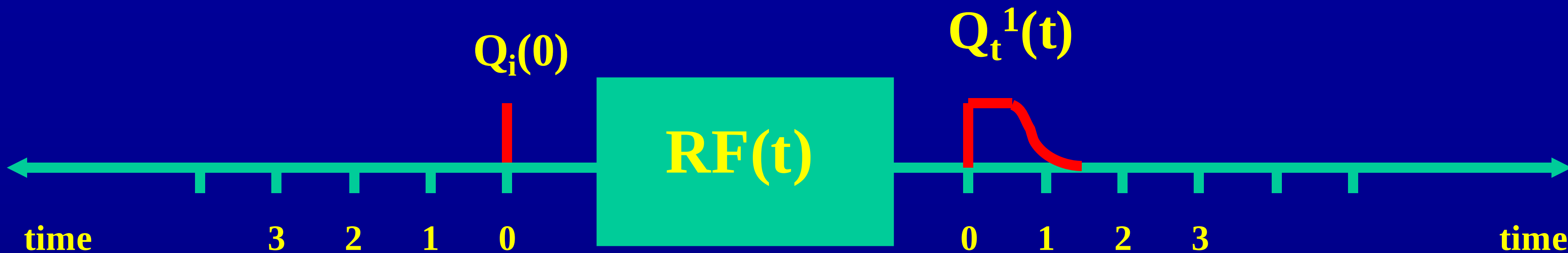
$$1 - H(t) = 1 - \int_0^t h(t)\,dt$$

Why is 1-H(t) interesting ?

Because it relates the input to the tracer amount in tissue in the case of the input not being a bolus (a deltafunction) !

Q_i : input **Q_t : output**

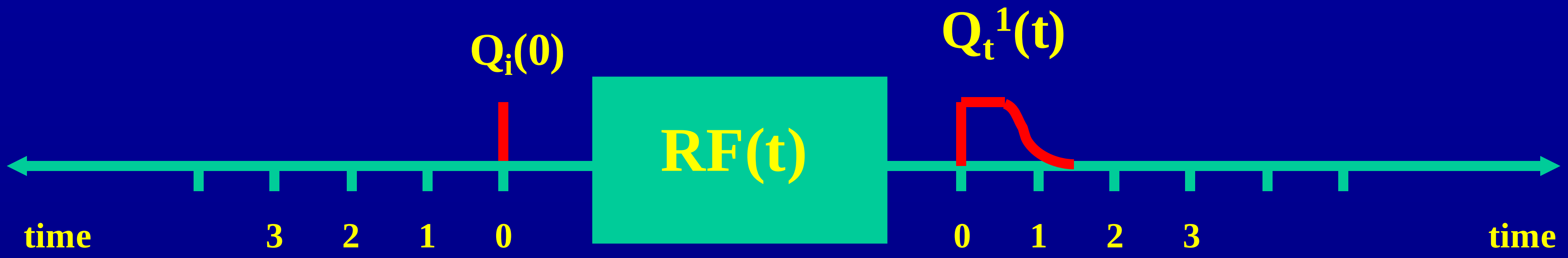
$$C_t(t) = f\ C_a(t) \otimes RF(t) = f \int_0^t C_i(\tau) RF(t-\tau) d\tau$$



$$Q_i(0) = F\,C_i(0)\,\Delta\tau$$

The number which enters the system at time zero

HBWL



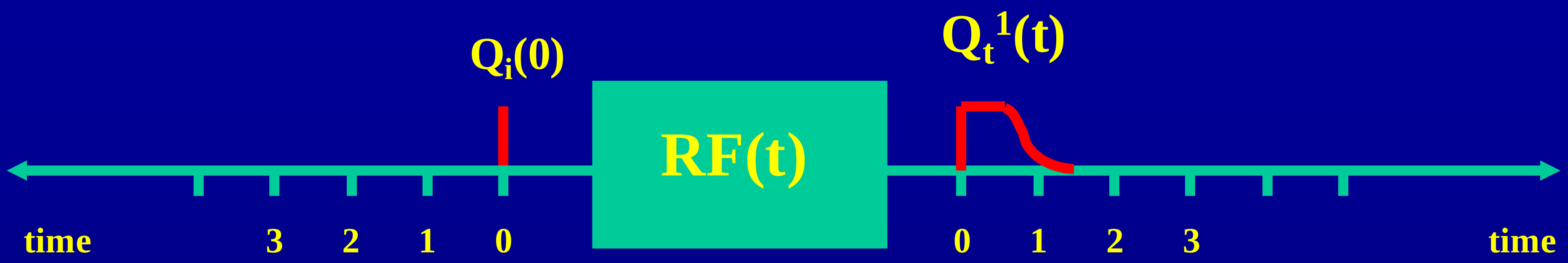
$$Q_i(0) = F\ C_i(0)\ \Delta\tau$$

The total perfusion (Flow)

HBWL

$$Q_i(0) = F\,C_i(0)\,\Delta\tau$$

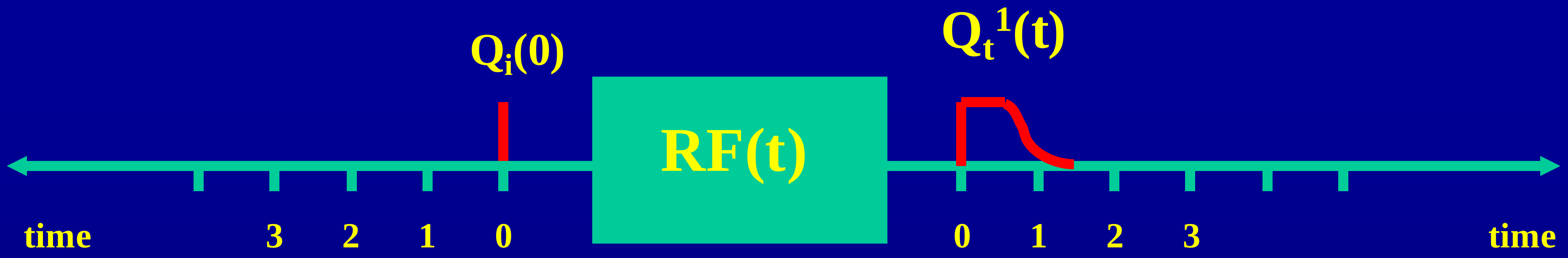
The concentration of the tracer at the inlet at time zero



$$Q_i(0) = F\, C_i(0)\, \Delta\tau$$

Infinitively small time interval

HBWL



$$Q_i(0) = F\,C_i(0)\,\Delta\tau$$

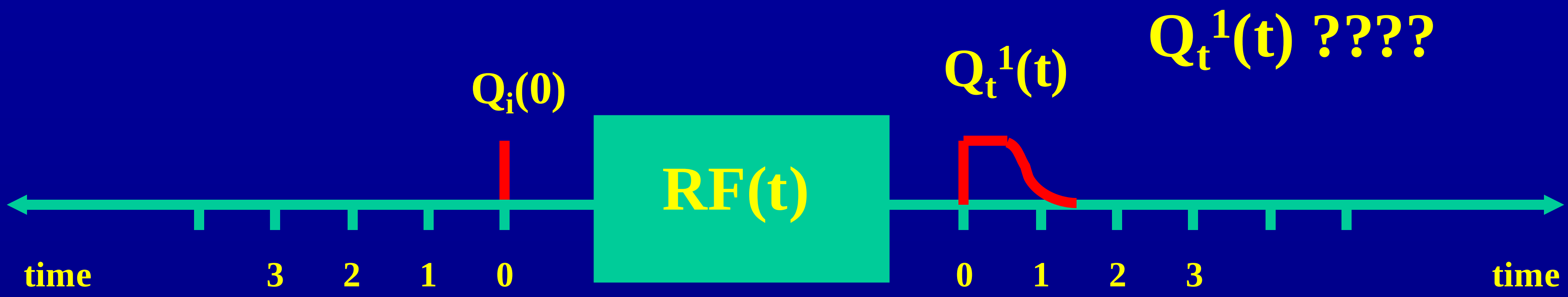
The flux which enters the system at time zero

HBWL

$$Q_i(0) = F\, C_i(0)\, \Delta\tau$$

The number which enters the system at time zero

HBWL

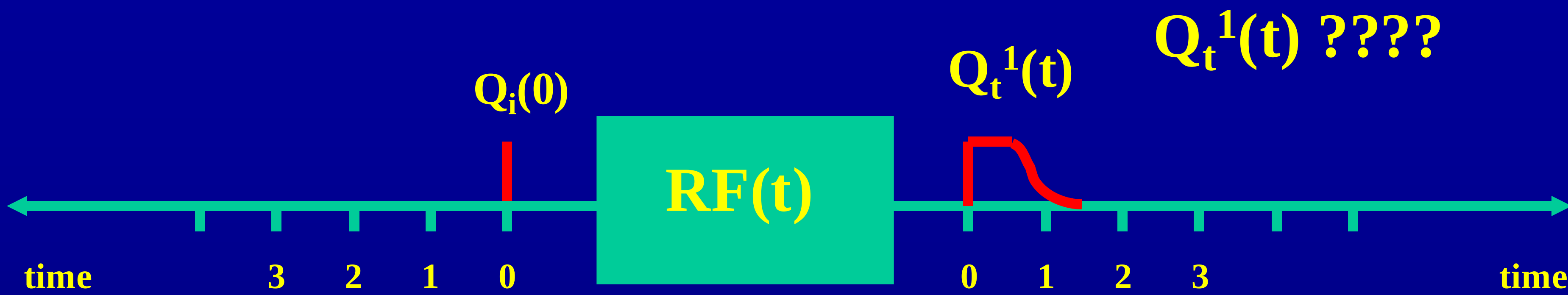


$$Q_i(0) = F\, C_i(0)\, \Delta\tau$$

$$Q_t^1(t) = Q_i(0)\, RF(t)$$

The number (amount) of tracer in tissue as a function of time due to an input at time zero

HBWL



$$Q_i(0) = F\,C_i(0)\,\Delta\tau$$

$$Q_t^1(t) = Q_i(0)\,RF(t)$$

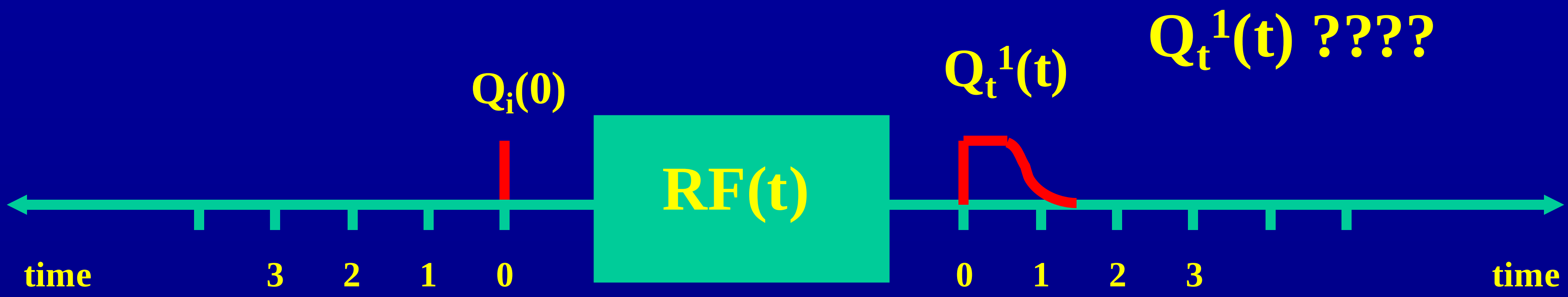
The relative number (amount) of tracer in tissue as a function of time due to an input at time zero

$$Q_i(0) = F\,C_i(0)\,\Delta\tau$$

$$Q_t^1(t) = Q_i(0)\,RF(t)$$

The number (amount) of tracer which enters the tissue at time zero

HBWL



$$Q_i(0) = F\, C_i(0)\, \Delta\tau$$

$$Q_t^1(t) = \underbrace{Q_i(0)\, RF(t)}$$

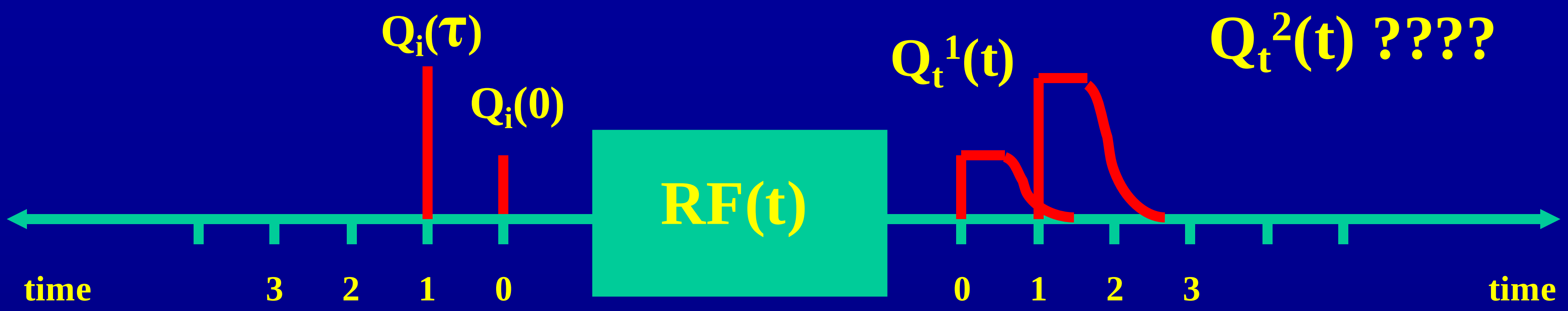
The number (amount) of tracer in tissue as a function of time due to an input at time zero

HBWL

$Q_t^1(t)$????

$$Q_i(0) = F\ C_i(0)\ \Delta\tau$$

$$Q_t^1(t) = Q_i(0)\ RF(t) = F\ C_i(0)\ \Delta\tau\ RF(t)$$



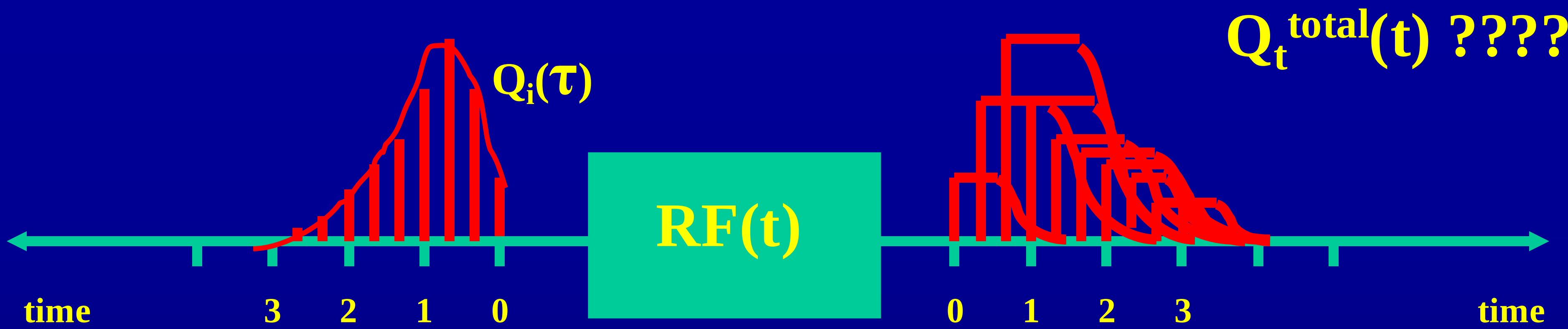
$$Q_i(0) = F\,C_i(0)\,\Delta\tau$$

$$Q_t^{1}(t) = Q_i(0)\,RF(t) = F\,C_i(0)\,\Delta\tau\,RF(t)$$

$$Q_t^{2}(t) = Q_i(\tau)\,RF(t-\tau) = F\,C_i(\tau)\,\Delta\tau\,RF(t-\tau)$$

Total amount in tissue at time t: $Q_t^{total}(t) = Q_t^{1}(t) + Q_t^{2}(t)$

HBWL



Total amount in tissue at time t:

$$Q_t^{total}(t) = Q_t^{1}(t) + Q_t^{2}(t) + Q_t^{3}(t) + Q_t^{4}(t) + \ldots\ldots\ldots \Rightarrow$$

$$Q_t^{total}(t) = \sum F\, C_i(\tau)\, RF(t-\tau)\, \Delta\tau$$

$$Q_t^{total}(t) = \int_0^t F\, C_i(\tau)\, RF(t-\tau)\, d\tau$$

$$Q_t^{total}(t) = \int_0^t F\ C_i(\tau)\ RF(t-\tau)\,d\tau$$

$$Q_t^{total}(t) = C_t(t)\,Weight$$

$$C_t(t) = \frac{F}{W}\int_0^t C_i(\tau)\ RF(t-\tau)\,d\tau$$

$$C_t(t) = f\int_0^t C_i(\tau)\ RF(t-\tau)\,d\tau$$

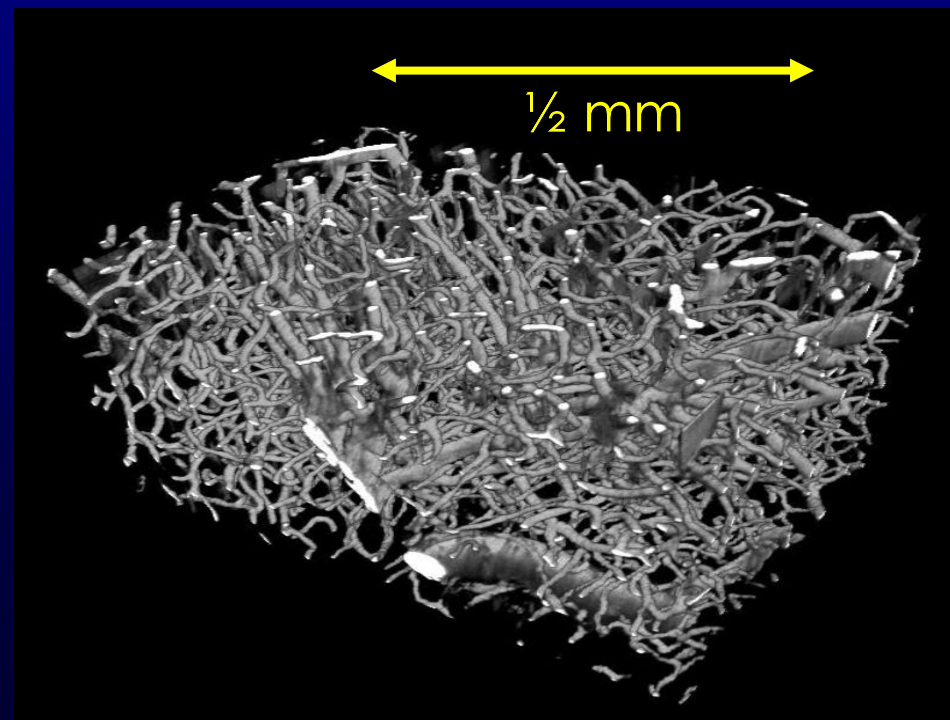
Convolution from the MAT point

- MATLAB

Break

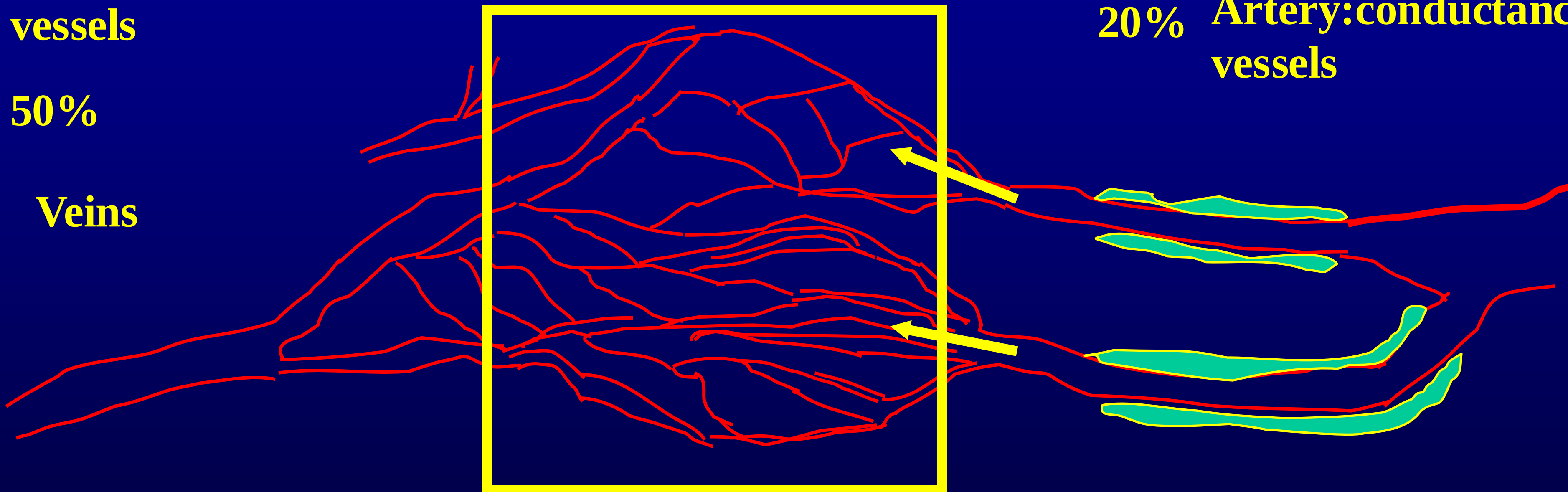
What is perfusion?

Large vessels : flow

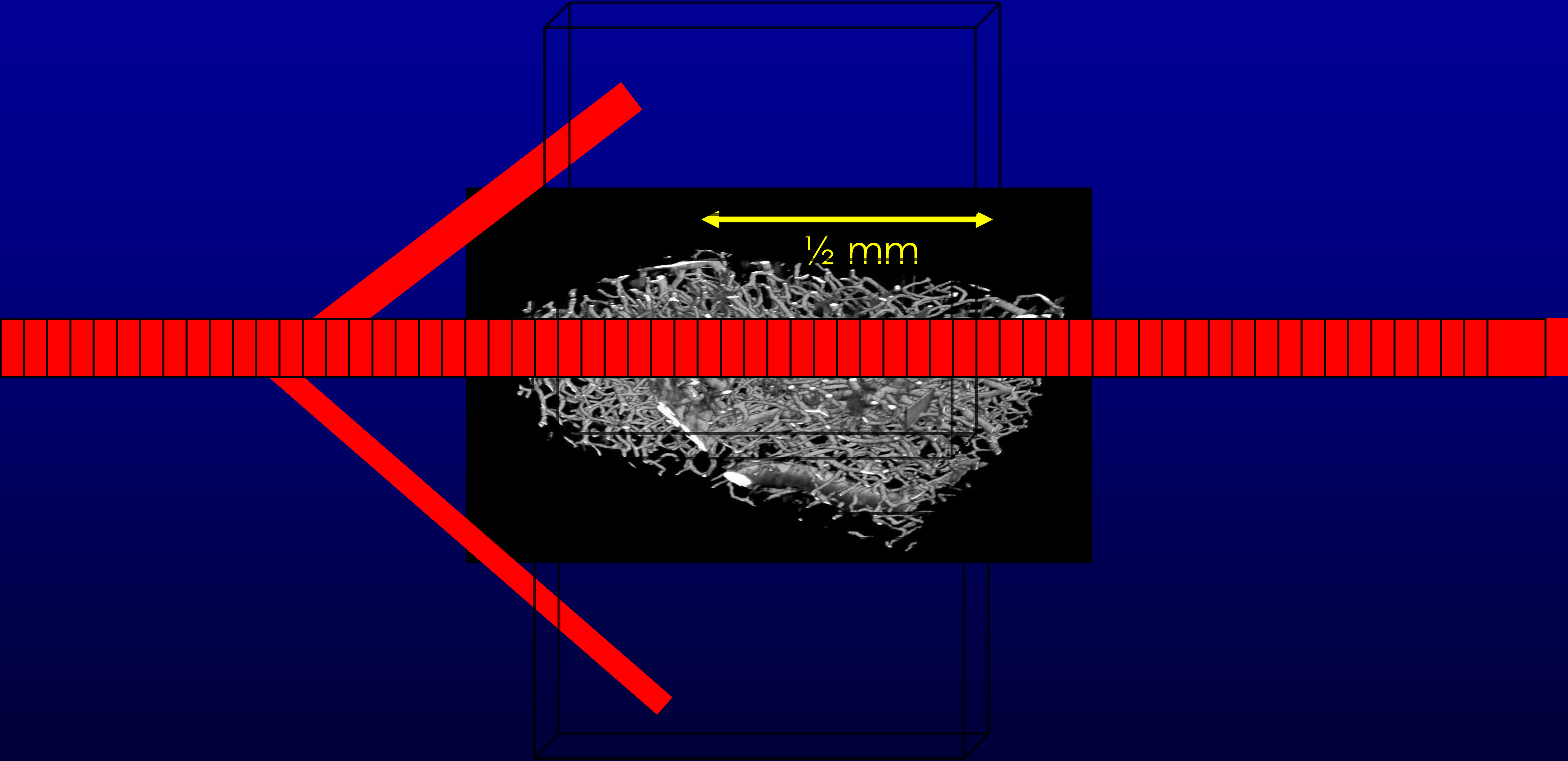


Perfusion: related to the microvascular system ~ the capillaries

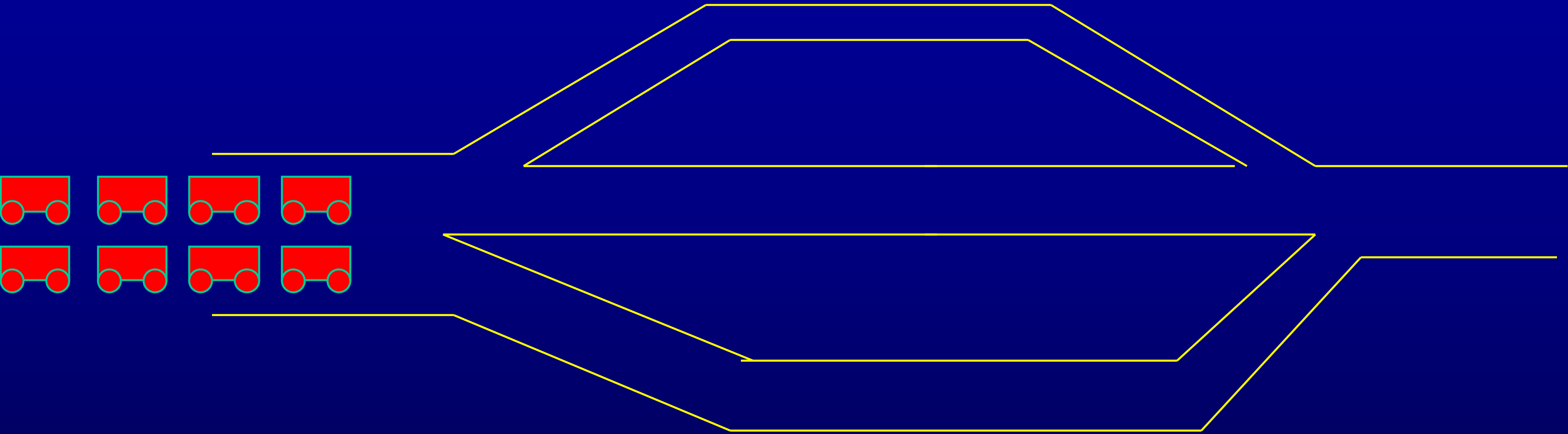
The vascular system of the brain and perfusion



Perfusion metrics in imaging: ml/min/100g or ml/min/100ml



HBWL

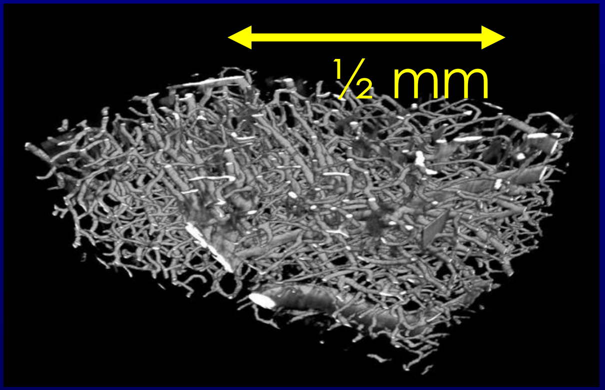


Number of transport (ml) vehicles entering 100 ml tissue pr. time unit::
20 - 80 ml/min/100 ml tissue volume

HBWL

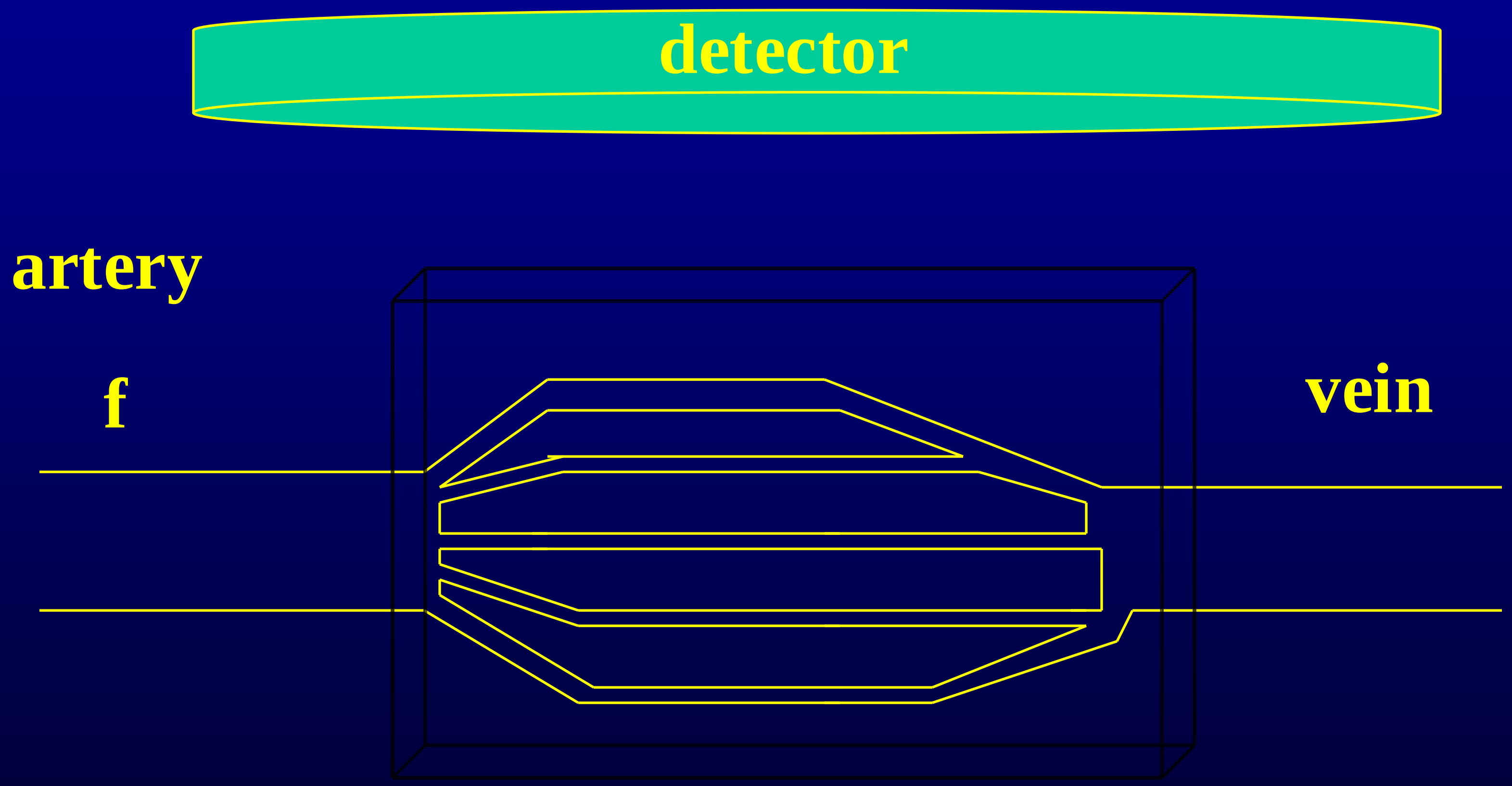
Important metrics

- **Perfusion: – f [ml/min/100g] or [ml/min/100ml]**
- **Brain Perfusion ('flow') : Cerebral blood flow CBF [ml/100g/min]**
- **Cerebral blood volume: CBV [ml/100g]**



- **Mean transit time: MTT [s]**
- **Blood brain permeability: PS product [ml/100g/min]**

Measuring perfusion by an external registration: CT,SPECT,PET,MRI



f: perfusion in [ml/min /100g]

HBWL

How can it be measured ?

Add a contrast agent carried by the blood to the tissue

How can it be measured ?

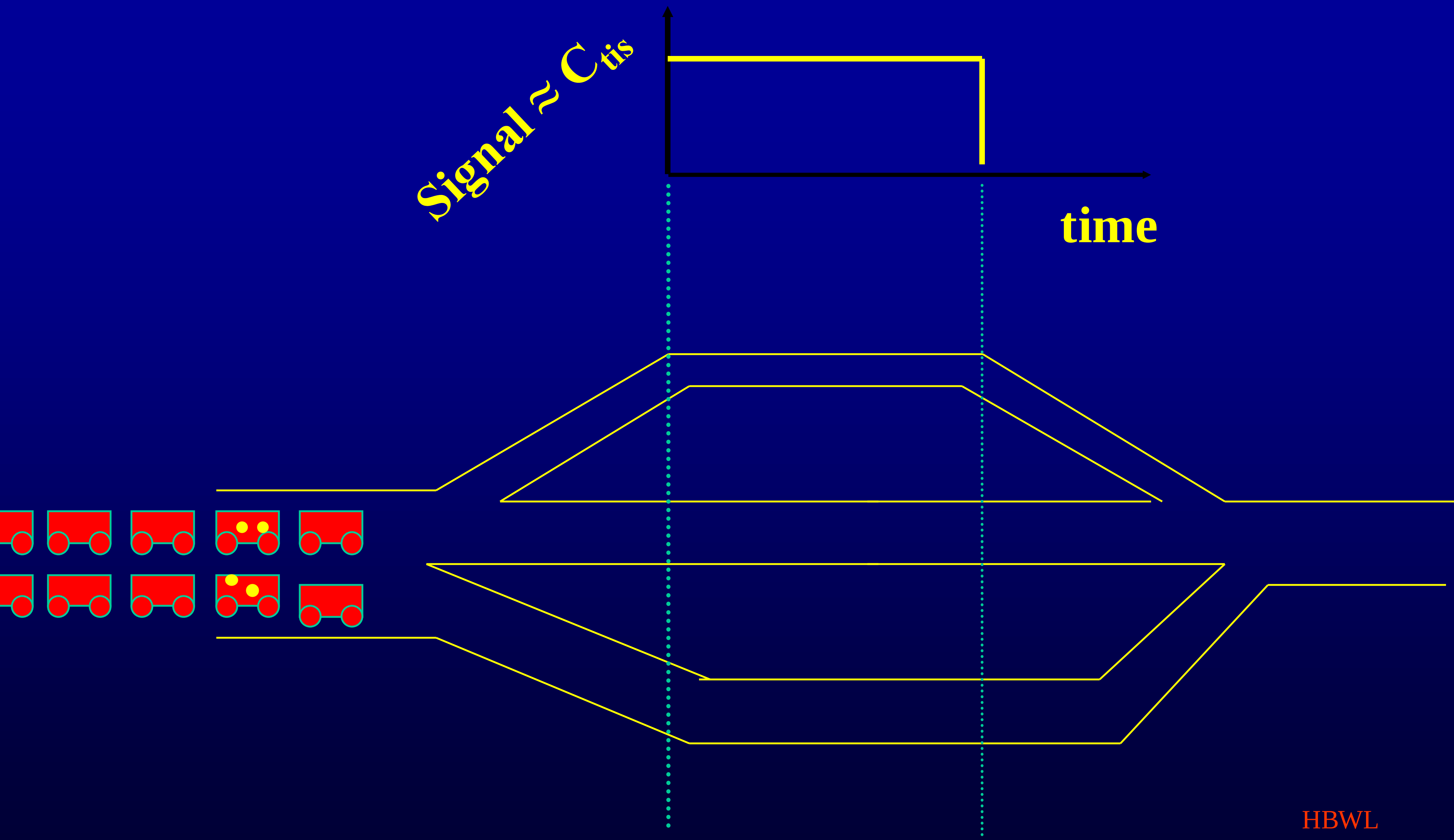
Add a contrast agent carried by the blood to the tissue

Contrast agent → **exogent**

Contrast agent → **endogent**

The complicated part: Single bolus injection and external registration

HBWL



HBWL

Signal ≈ $C_{tis}(0)$: f $C_a(0)$

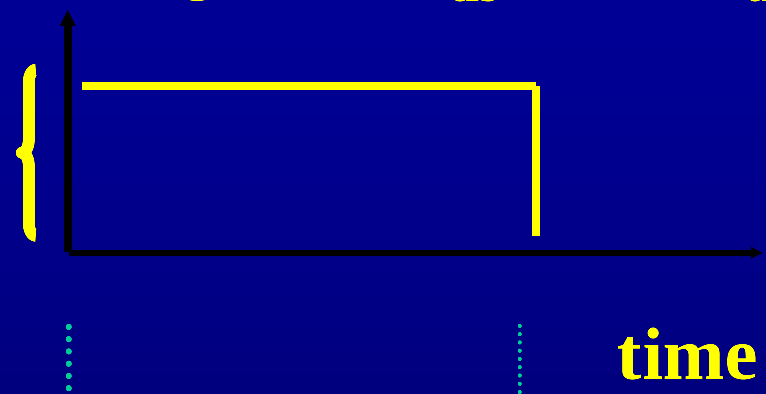
Perfusion (f) = vehicles/min

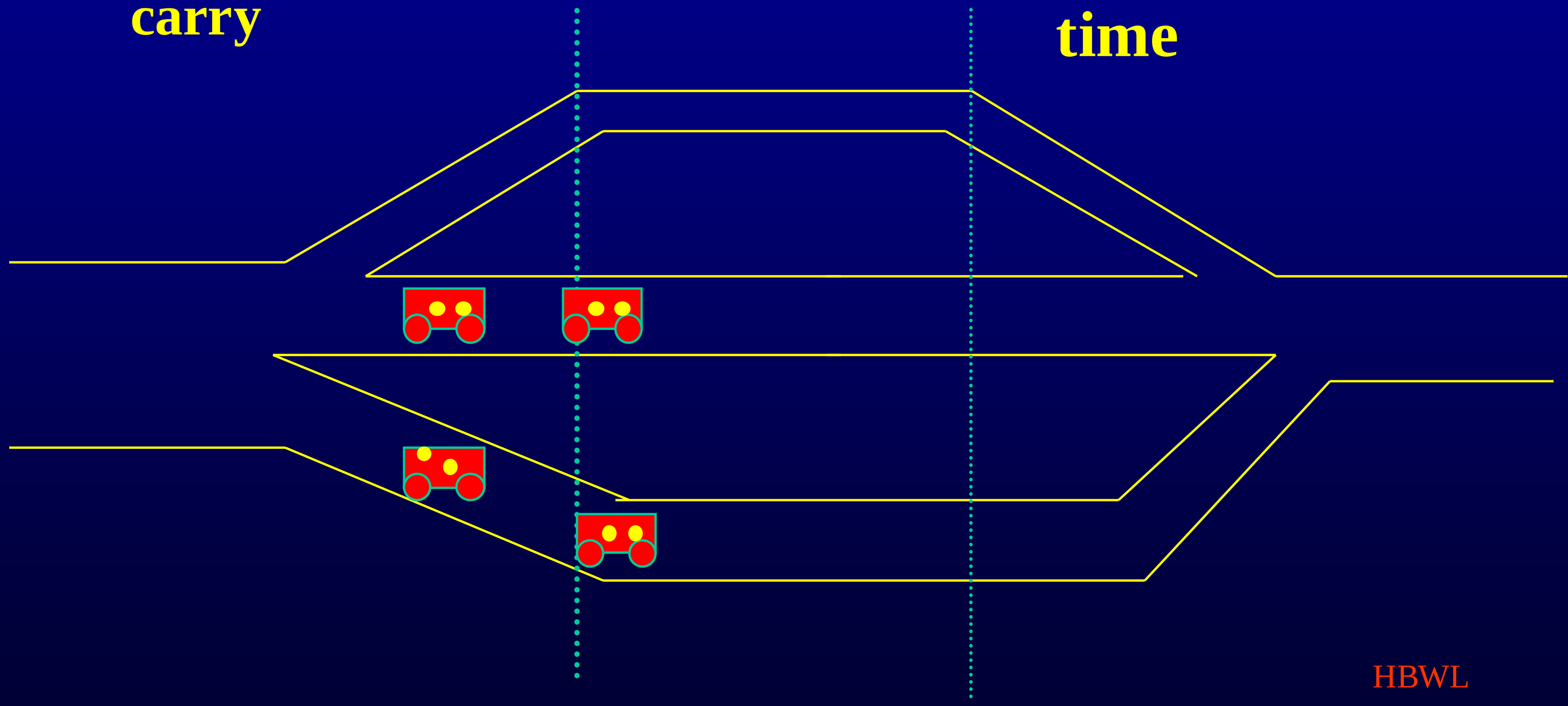
ml/min

x

Conc (C_a) = the cargo they carry

mmol/ml





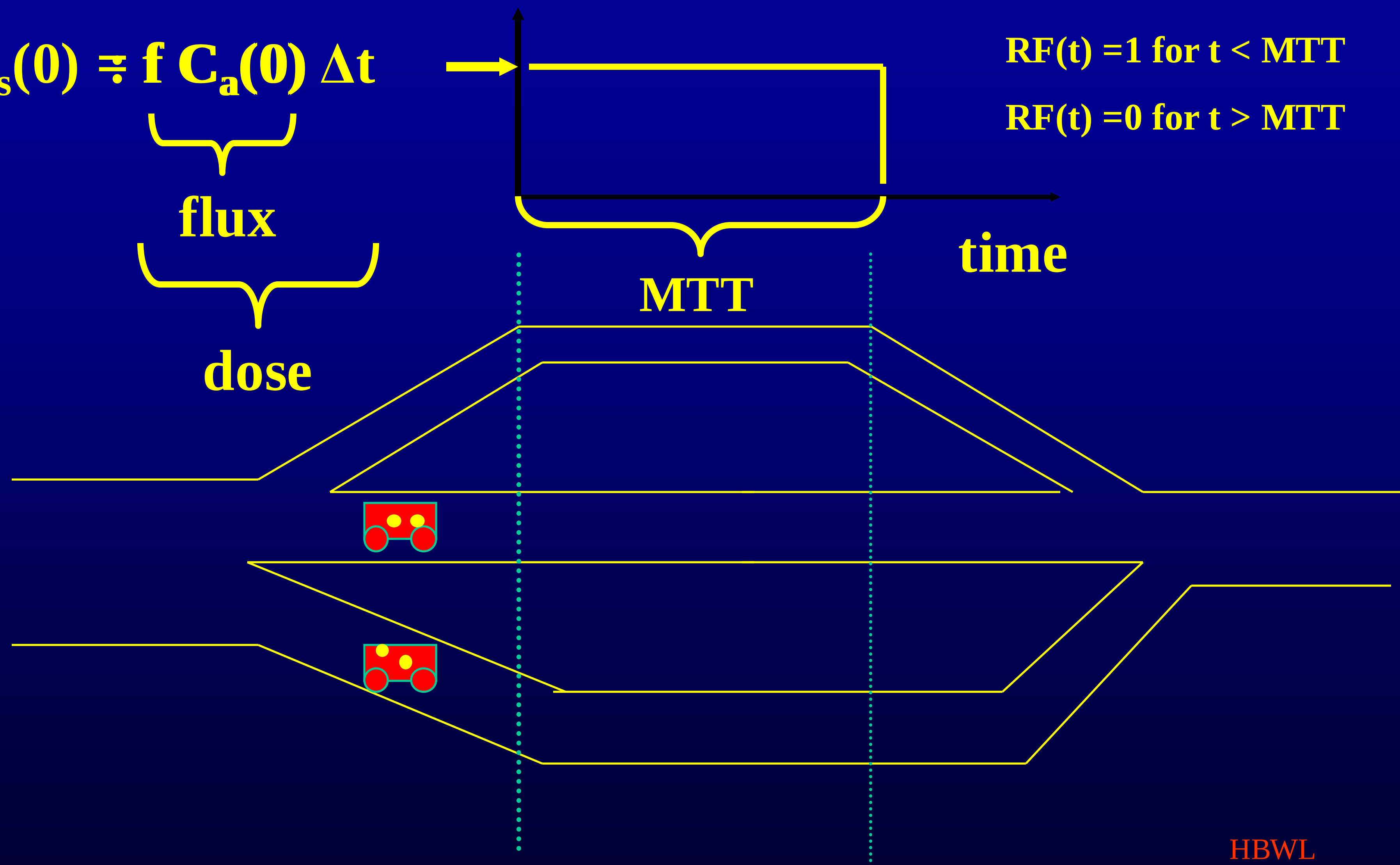
HBWL

$$C_{tis}(t) = f\, C_a(0)\, \Delta t\, RF(t)$$

$$C_{tis}(0) \doteq f\, C_a(0)\, \Delta t$$

RF(t) =1 for t < MTT

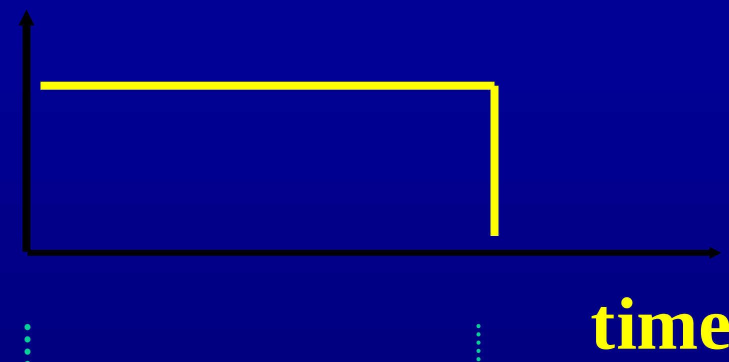
RF(t) =0 for t > MTT



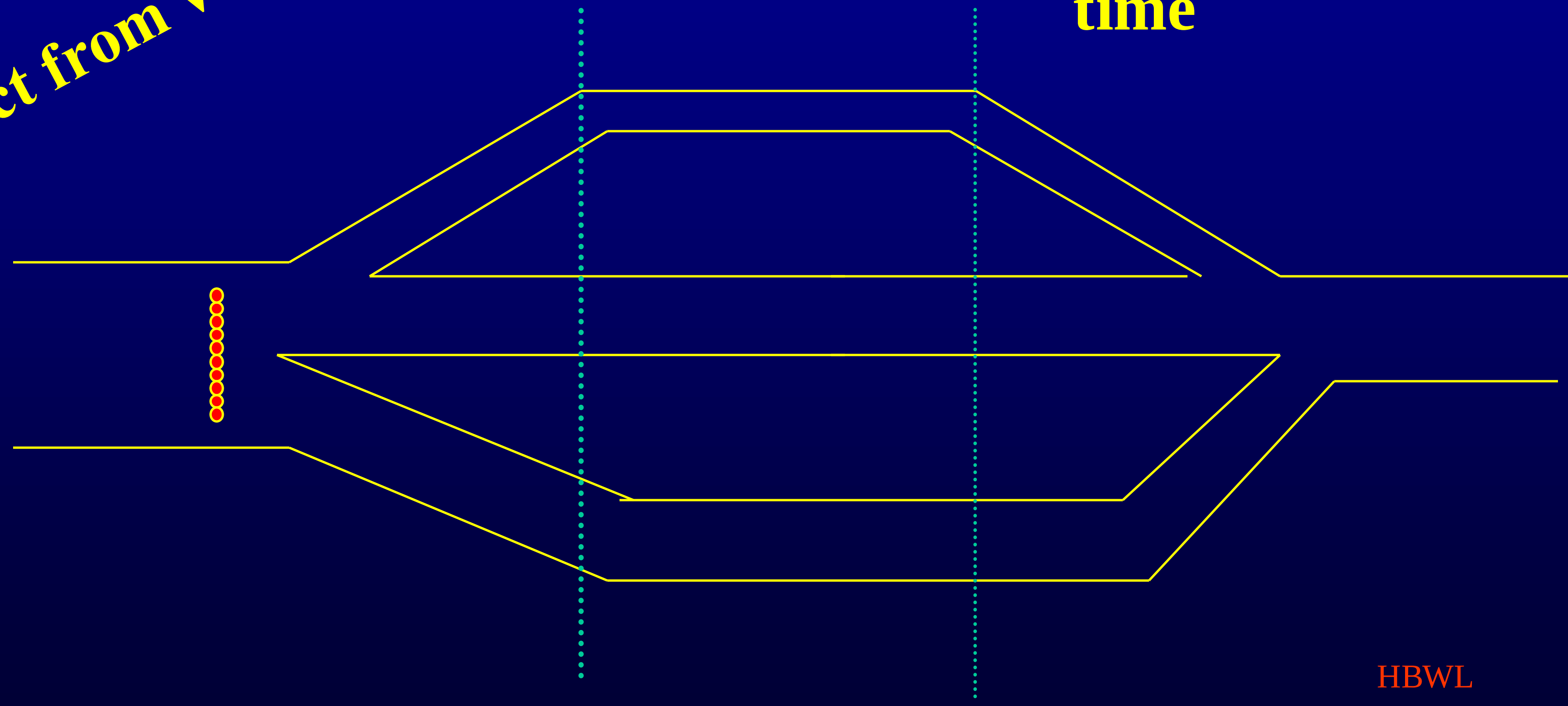
HBWL

$$C_{tis}(t) = f\ C_a(0)\ \Delta t\ RF(t)$$

$$C_{tis}(0) = f\ C_a(0)\ \Delta t$$



Abstract from vehicles



HBWL

Summing up: direct short bolus

Measure the tissue conc

Measure the input conc i.e. input function

Scanner signal : $C_{tis}(t) = f\ C_a(0)\ \Delta t\ RF(t)$

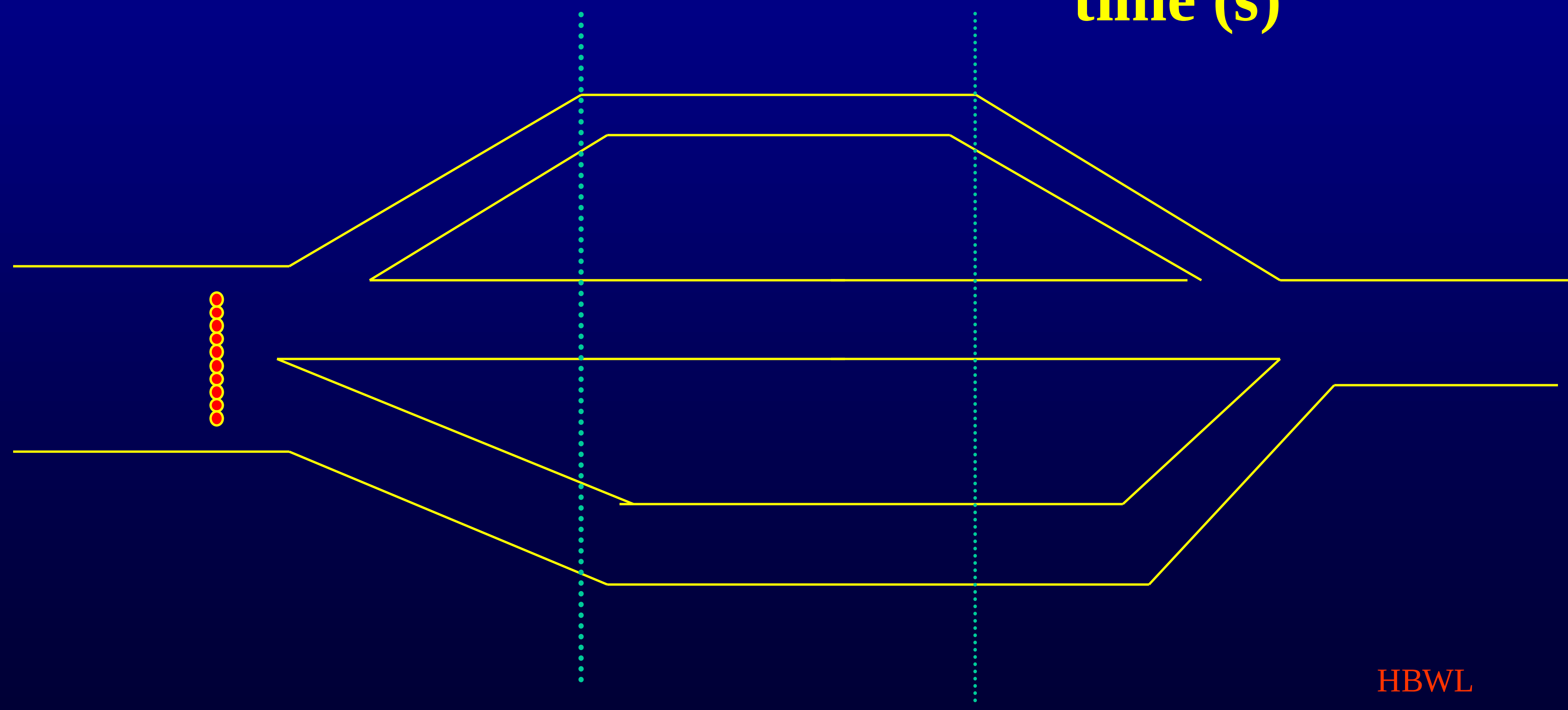
Estimate f and RF(t)

Different perfusion tracers behaves differently

HBWL

$$C_{tis}(t) = f\ C_a(0)\ RF(t)$$

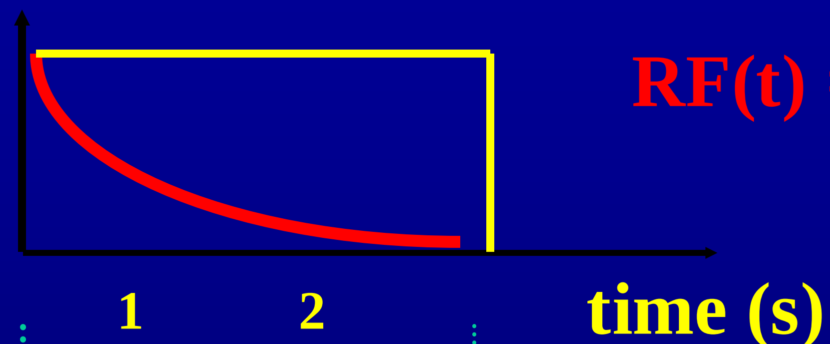
$$C_{tis}(0) = f\ C_a(0)\ \Delta t \rightarrow$$



HBWL

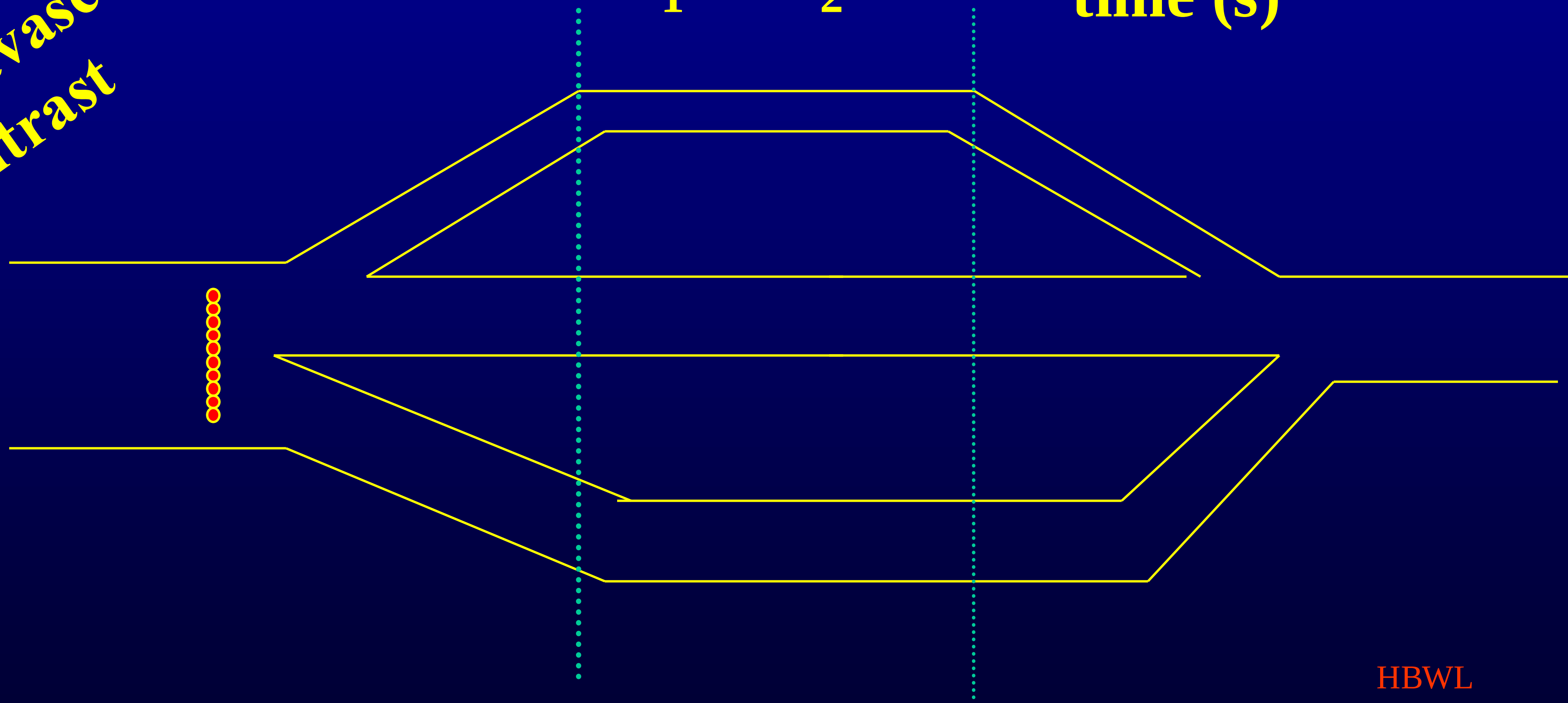
$$C_{tis}(t) = f\ C_a(0)\ \Delta t\ RF(t)$$

$$C_{tis}(0) = f\ C_a(0)\ \Delta t$$



$$RF(t) = e^{-k2t}$$

Intravascular contrast

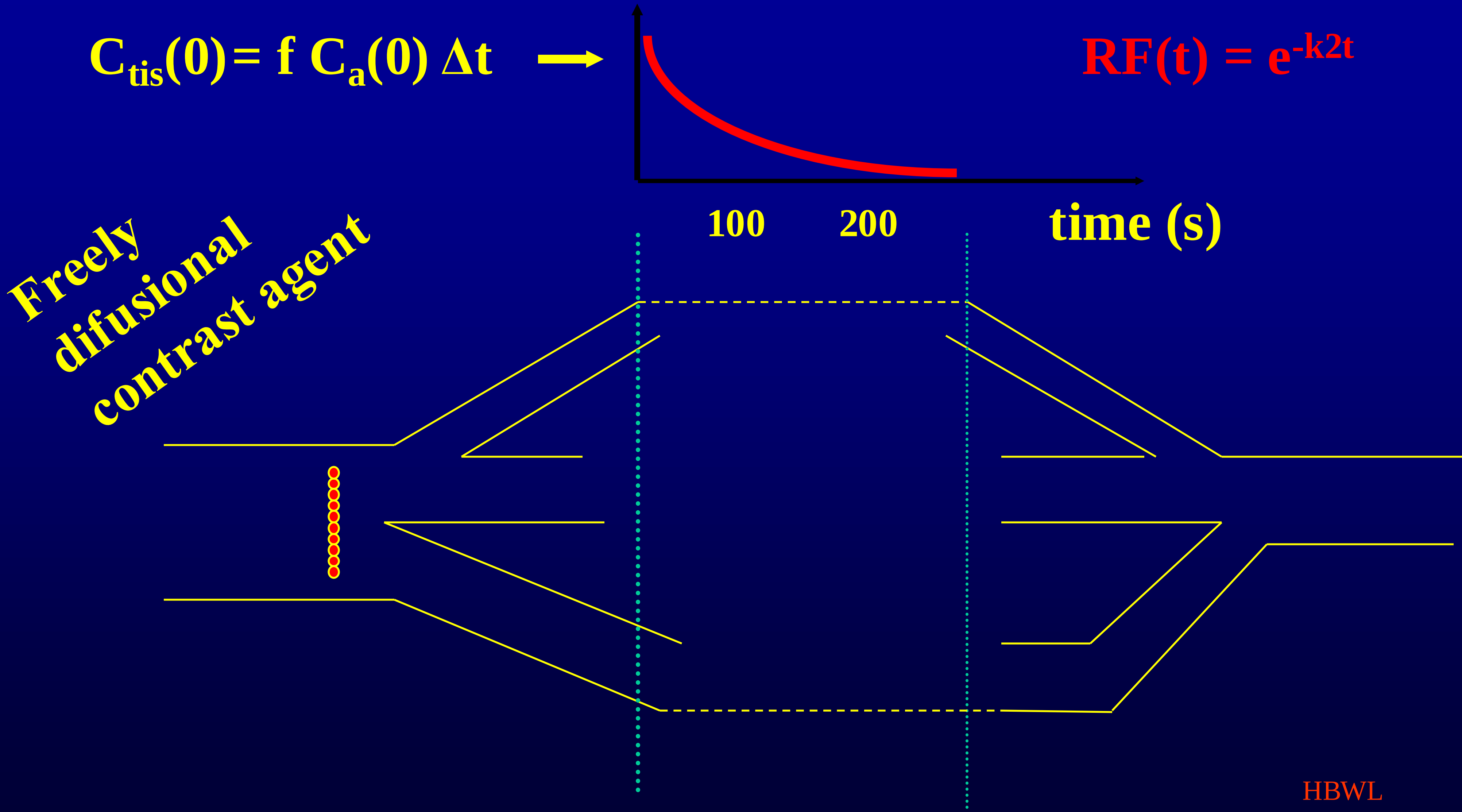


HBWL

$$C_{tis}(t) = f\ C_a(0)\ \Delta t\ RF(t)$$

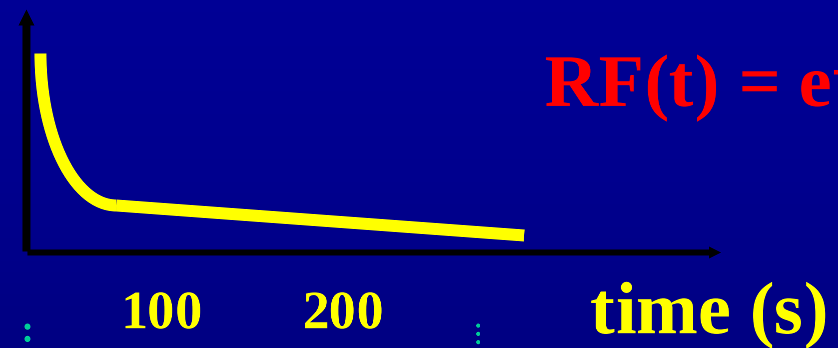
$$C_{tis}(0) = f\ C_a(0)\ \Delta t$$

$$RF(t) = e^{-k2t}$$

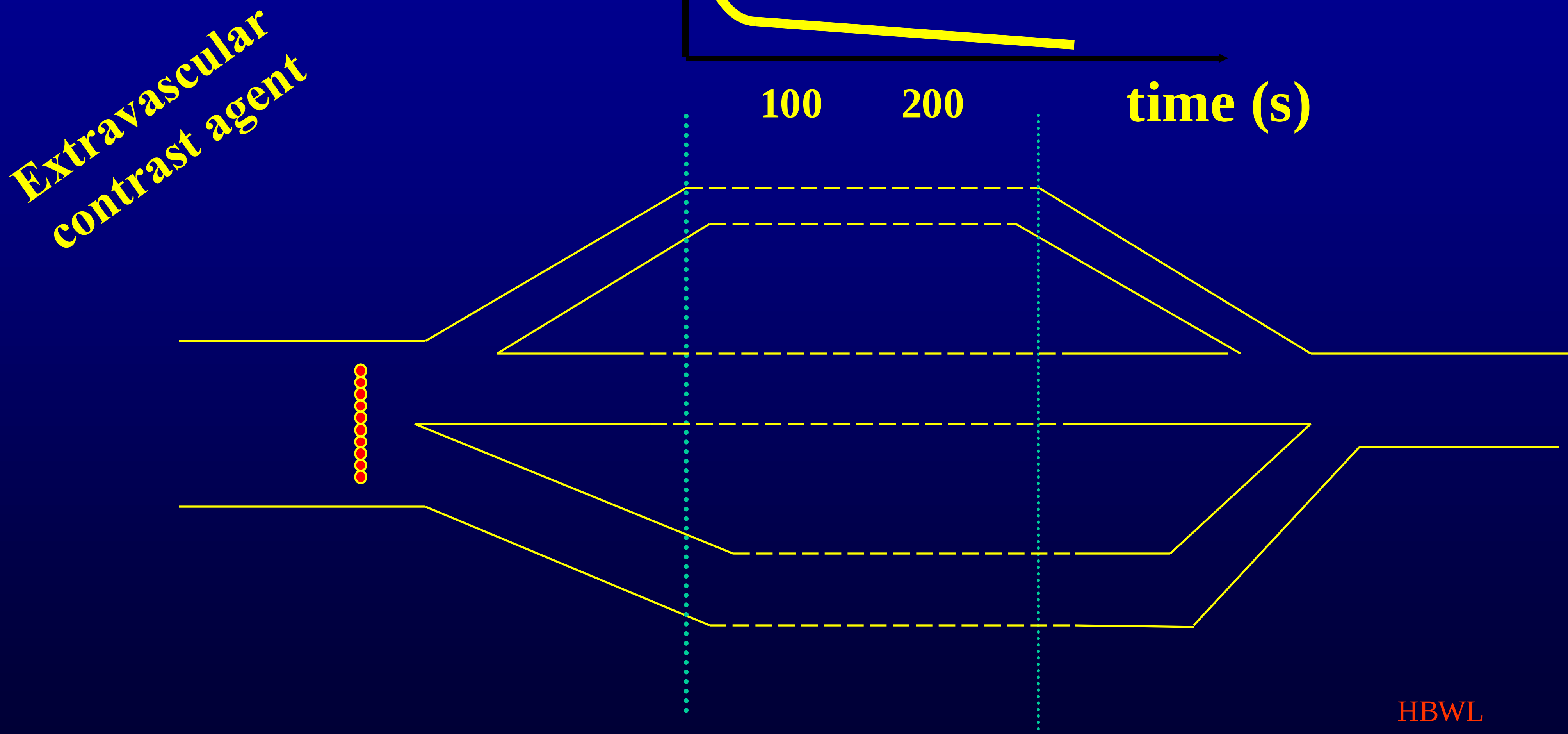


$$C_{tis}(t) = f\, C_a(0)\, \Delta t\, RF(t)$$

$$C_{tis}(0) = f\, C_a(0)\, \Delta t \rightarrow$$



$$RF(t) = e^{-k2t} + e^{-k3t}$$



HBWL

The residue impulse response function RF(t)

RF(t) : the fraction of the injected dose remaining in the tissue (voxel) as a function of time

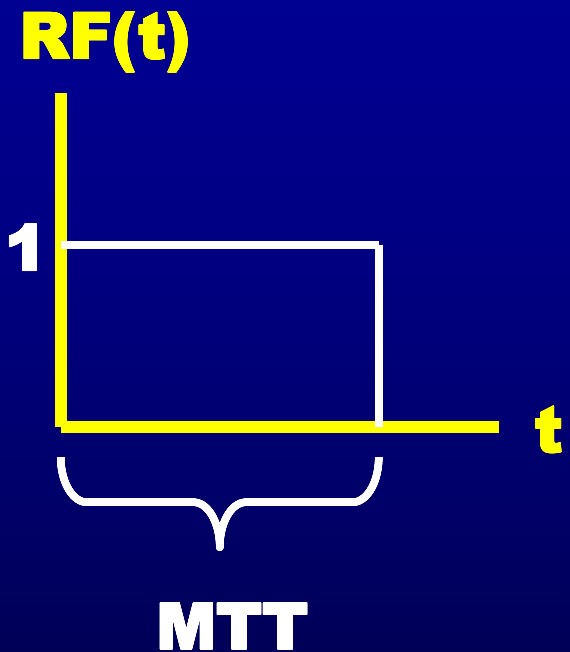
Mean transit time : MTT

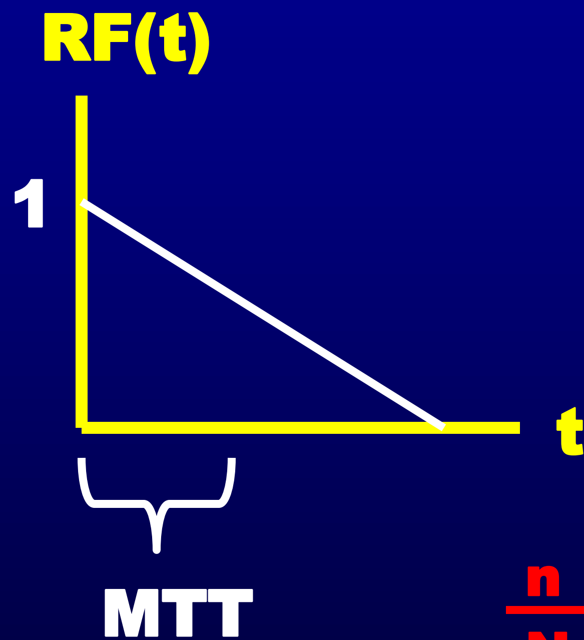
$$\mathbf{MTT} = \int_{0}^{\infty} \mathbf{RF(t)}$$

HBWL

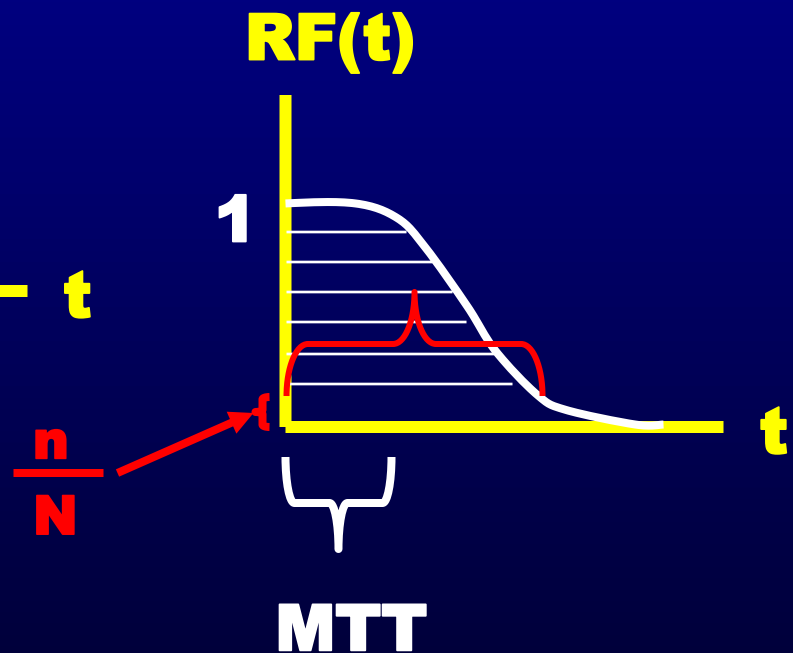
Mean transit time : MTT

$$MTT = \int_0^\infty RF(t)\,dt$$





$$MTT = \sum \frac{n}{N} t$$



Generally

Perfusion: f

Distribution vol: V_d

Mean transit time: MTT

$$f = \frac{V_d}{MTT}$$

For an intravascular contrast agent, e.g. in brain MRI we have:

Brain perfusion: CBF

Brain blood volume: CBV

Mean transit time: MTT

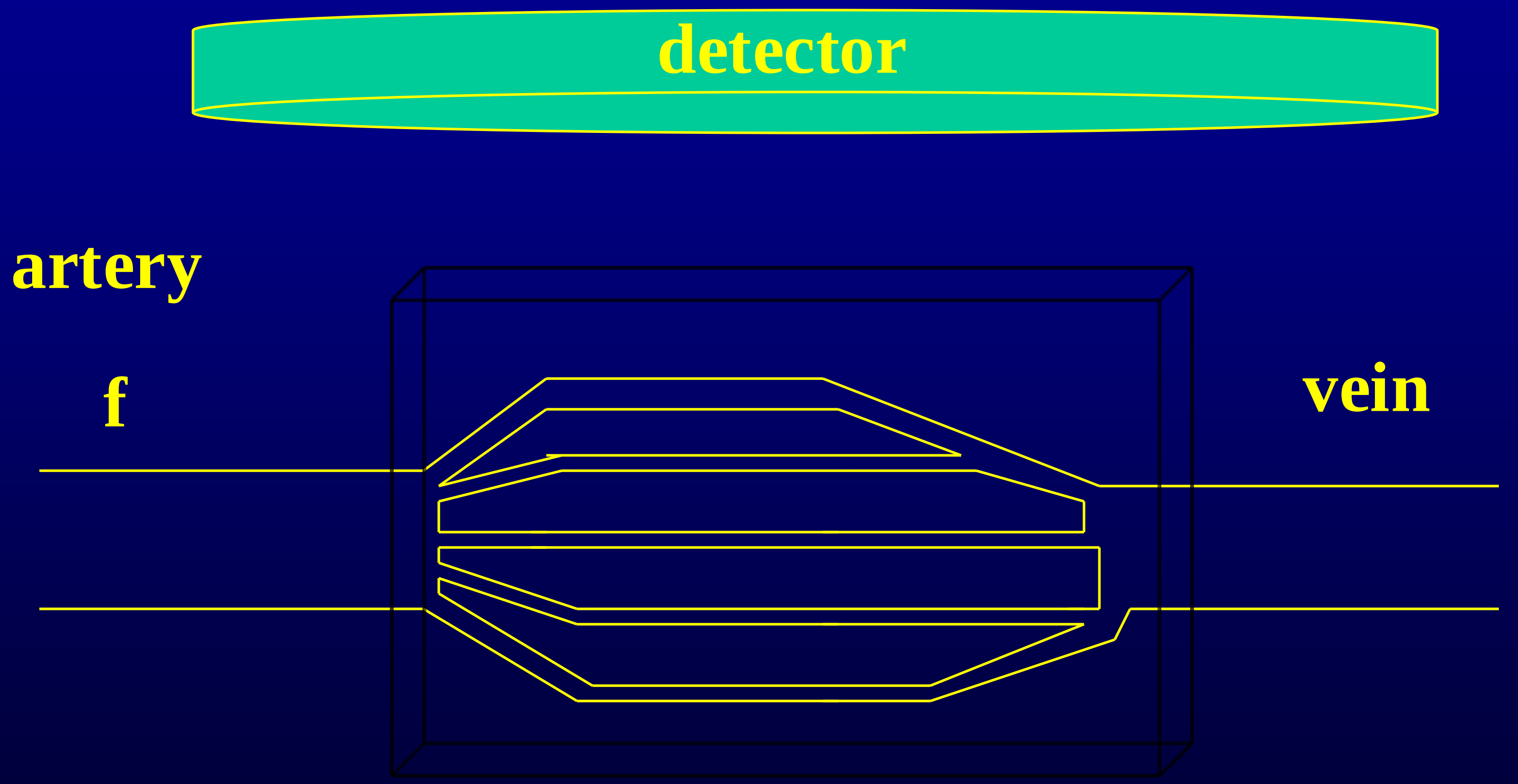
$$CBF = \frac{CBV}{MTT}$$

The really complicated part: Deconvolution

We cannot apply a bolus directly in the tissue !

HBWL

Measuring perfusion by an external registration: CT,SPECT,PET,MRI



f: flow or perfusion [ml/min /100g]

HBWL

The final step

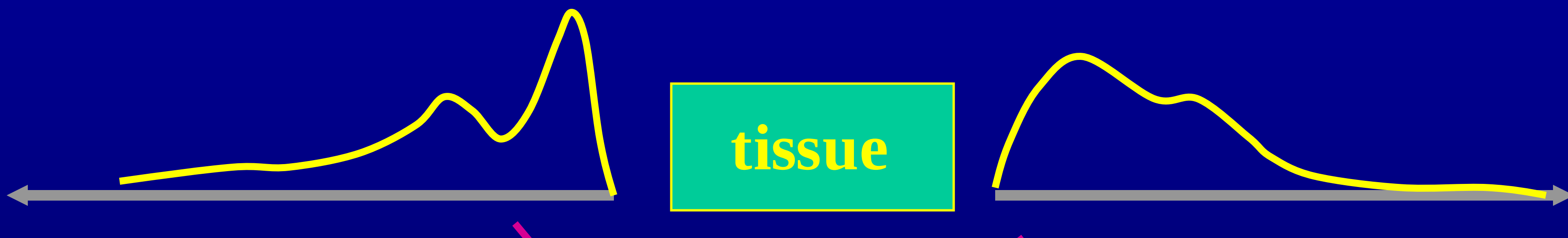
We cannot apply a bolus directly in the tissue !

Input :

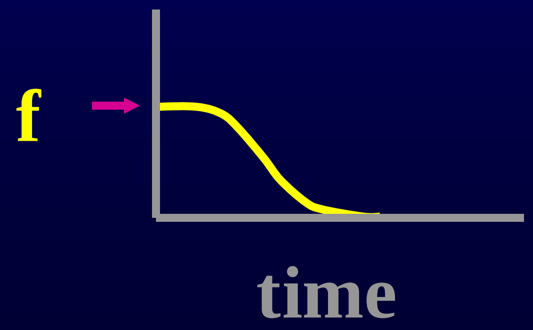
$C_a(t)$

Tissue enhancement :

$$C_{tis}(t) = \int_0^\infty f\, C_a(\tau)\, RF(t-\tau)\, d\tau$$



Deconvolution :
find f RF(t)

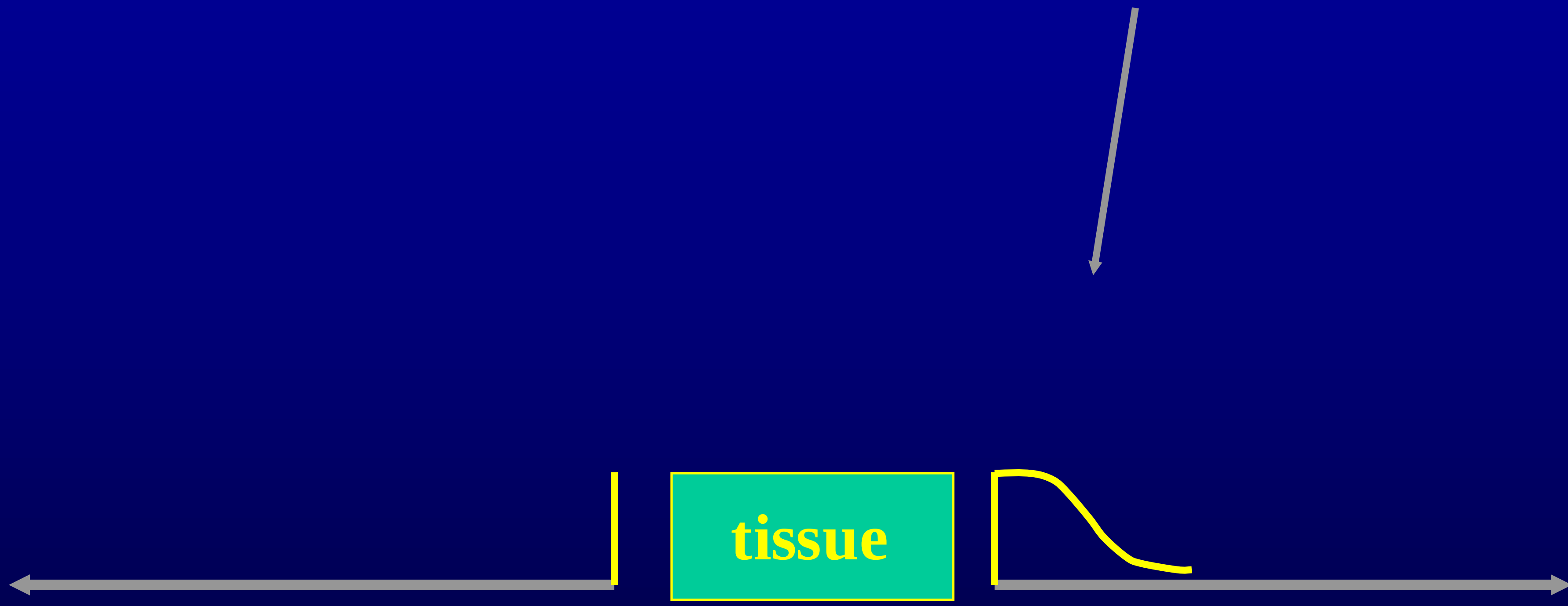


HBWL

Input : $C_a(t)$

Tissue enhancement :

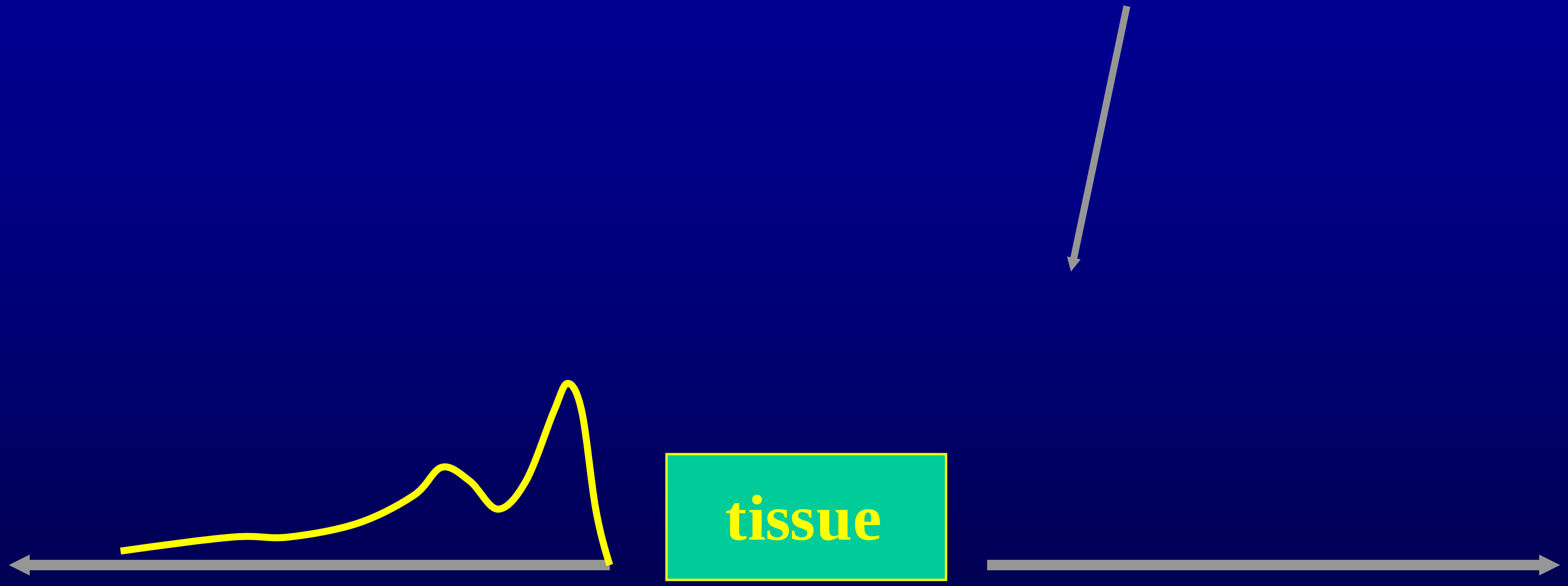
$$C_{tis}(t) = f\, C_a(0)\, RF(t)\, \Delta t$$



Input : $C_a(t)$

Tissue enhancement :

$C_{tis}(t)$ = ?

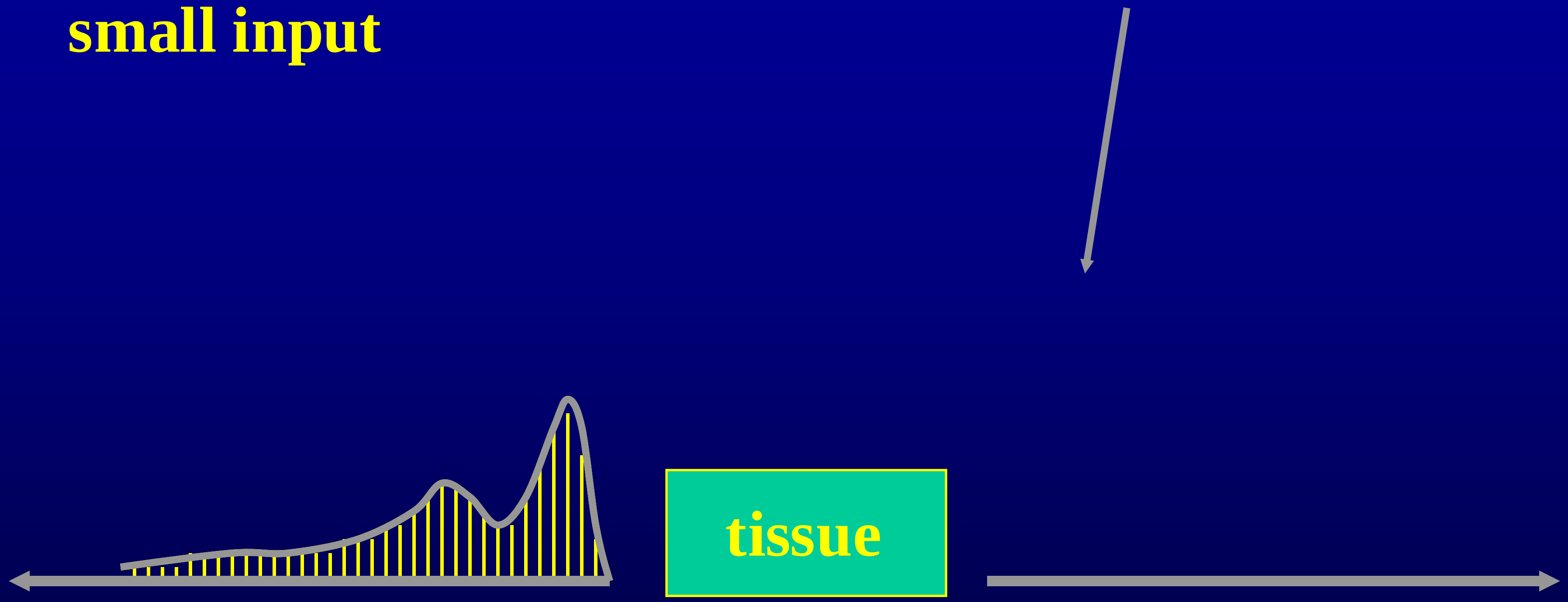


Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t)$ = ?



If the linearity of the system exist →

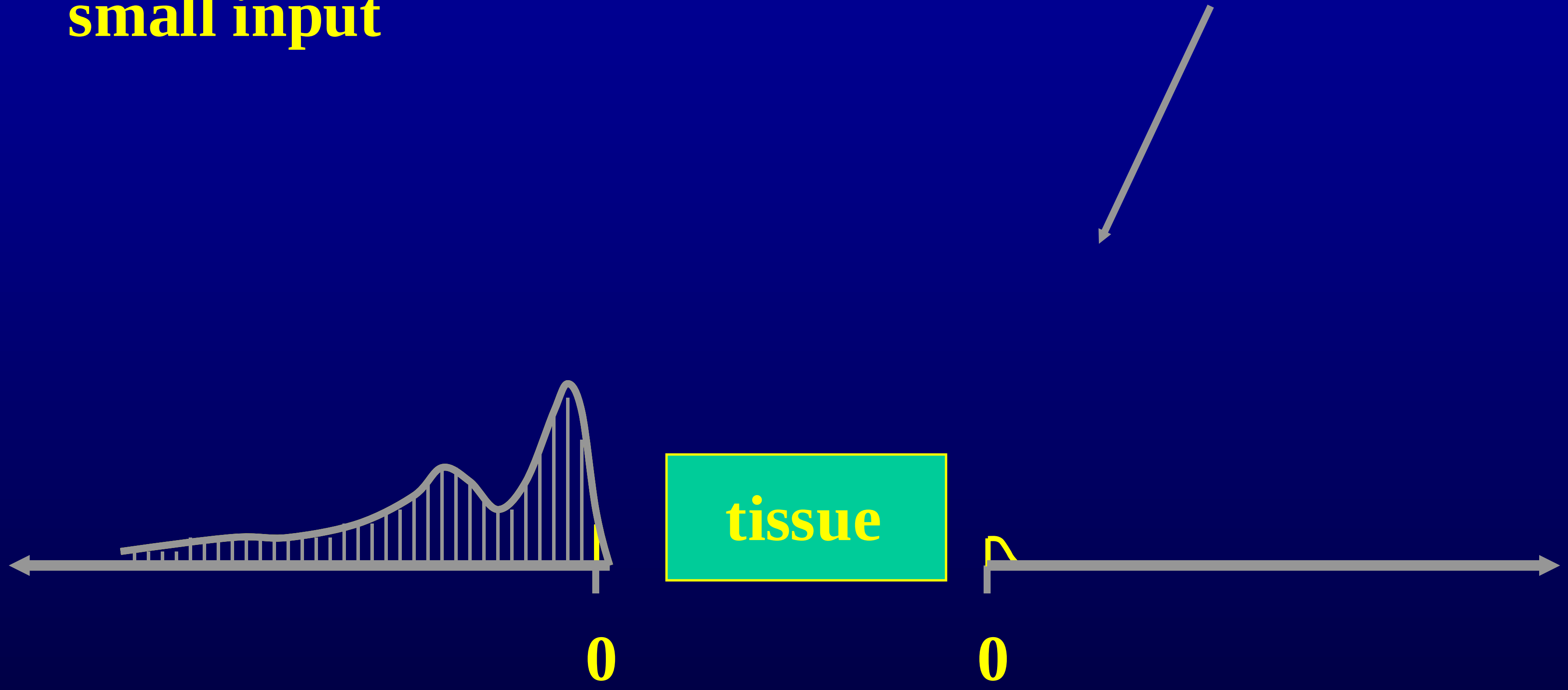
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(0)\ RF(t - 0)\ \Delta\tau$



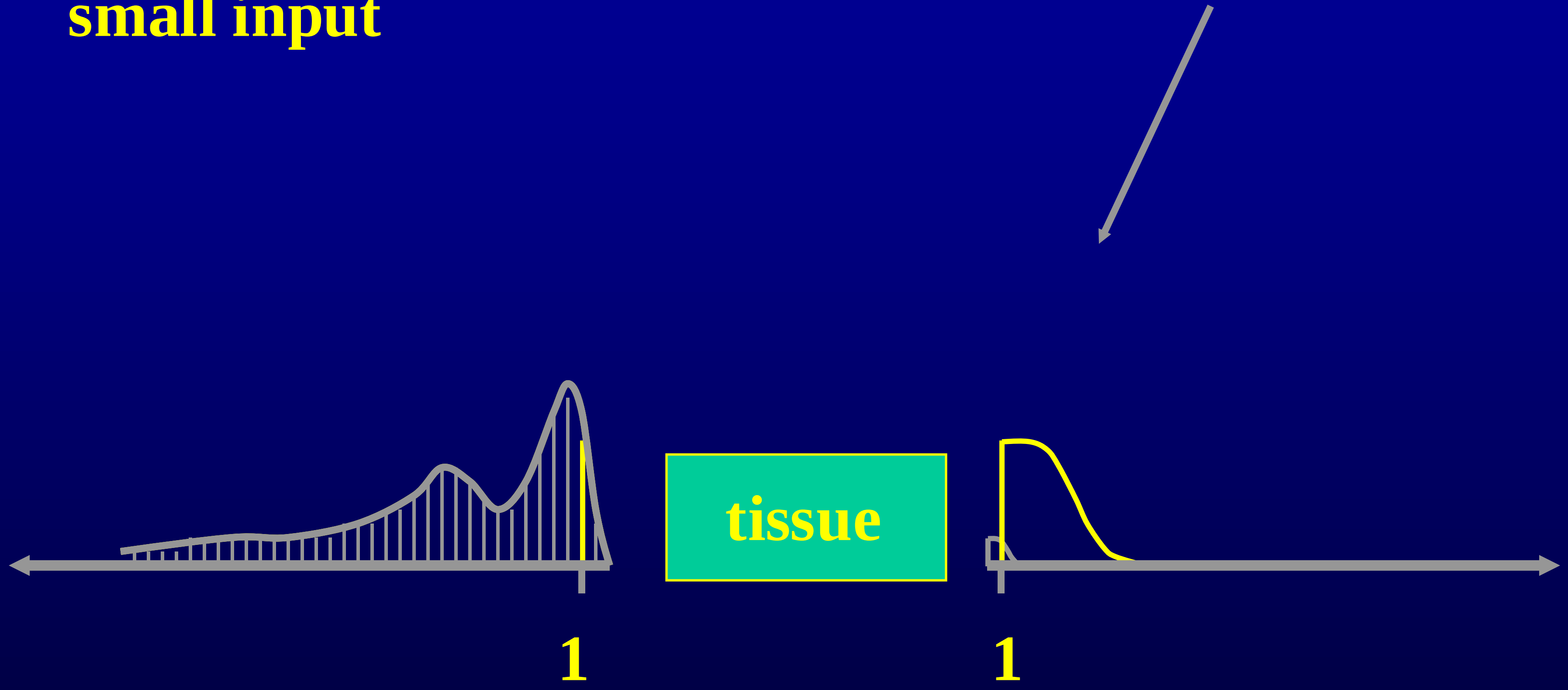
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(1)\ RF(t - 1)\ \Delta\tau$



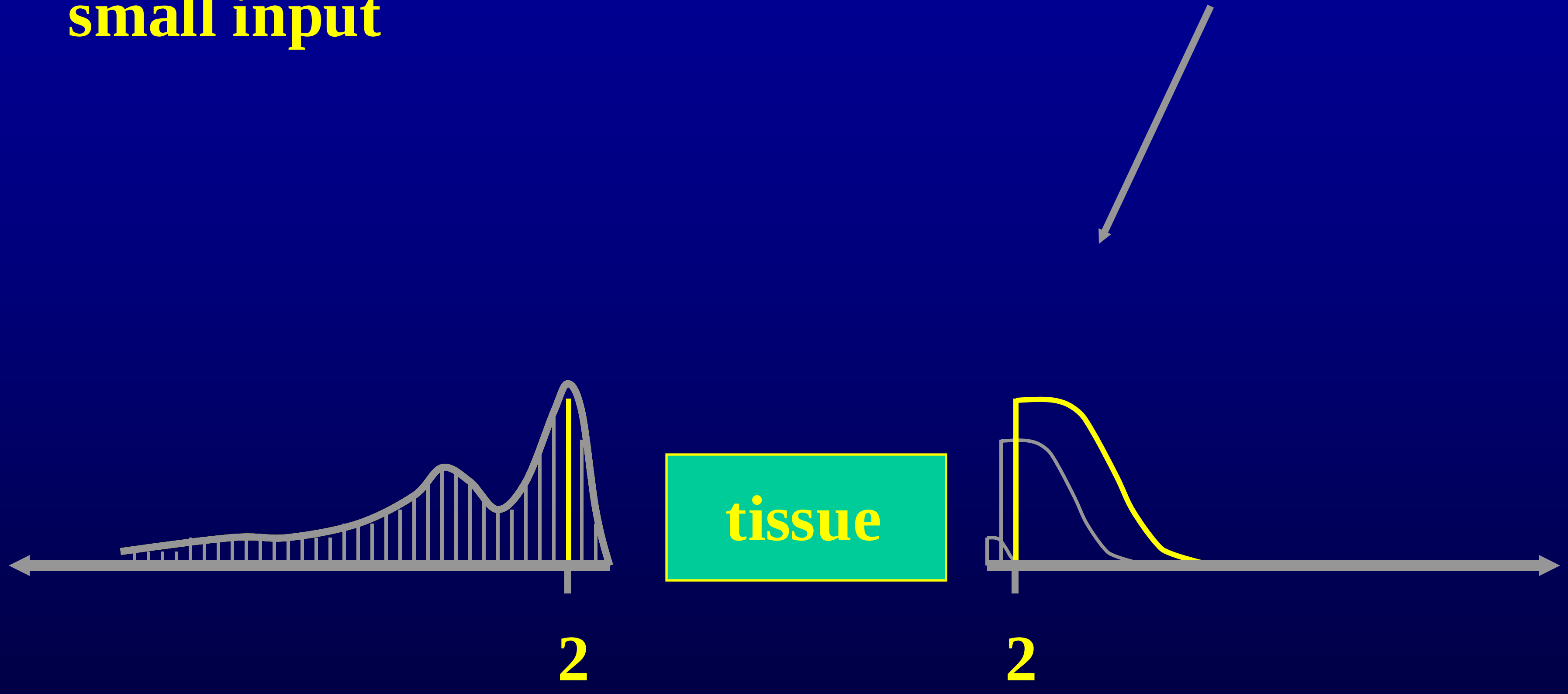
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$$C_{tis}(t) = f\ C_a(2)\ RF(t - 2)\ \Delta\tau$$



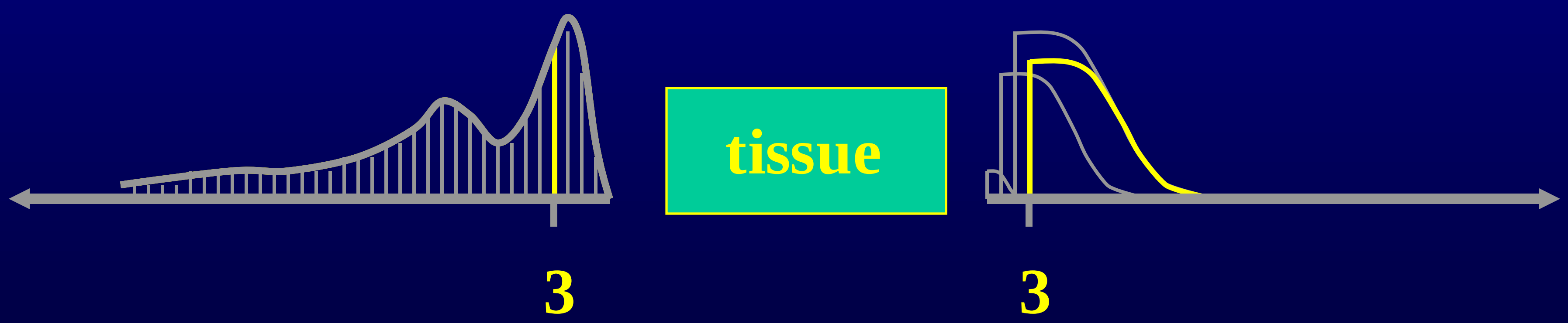
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(3)\ RF(t - 3)\ \Delta\tau$



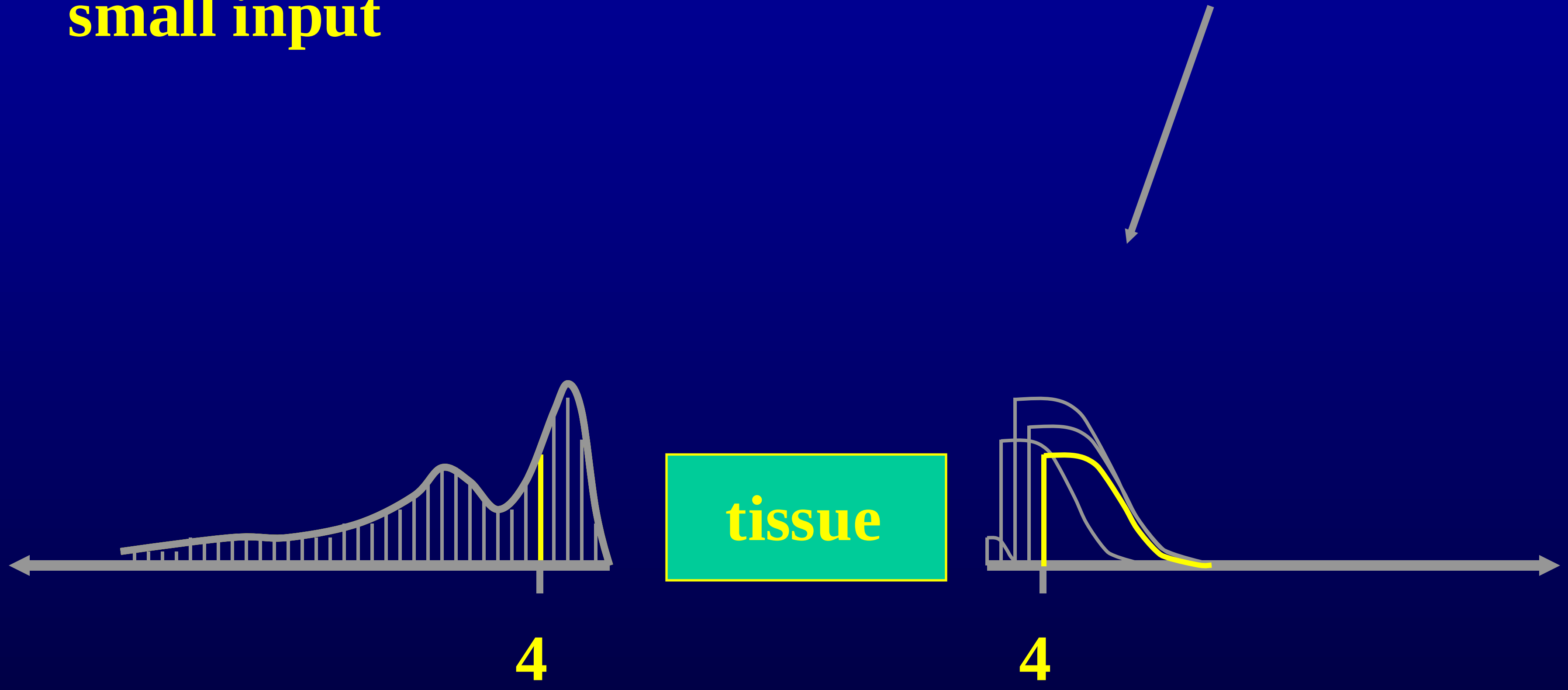
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(4)\ RF(t - 4)\ \Delta\tau$



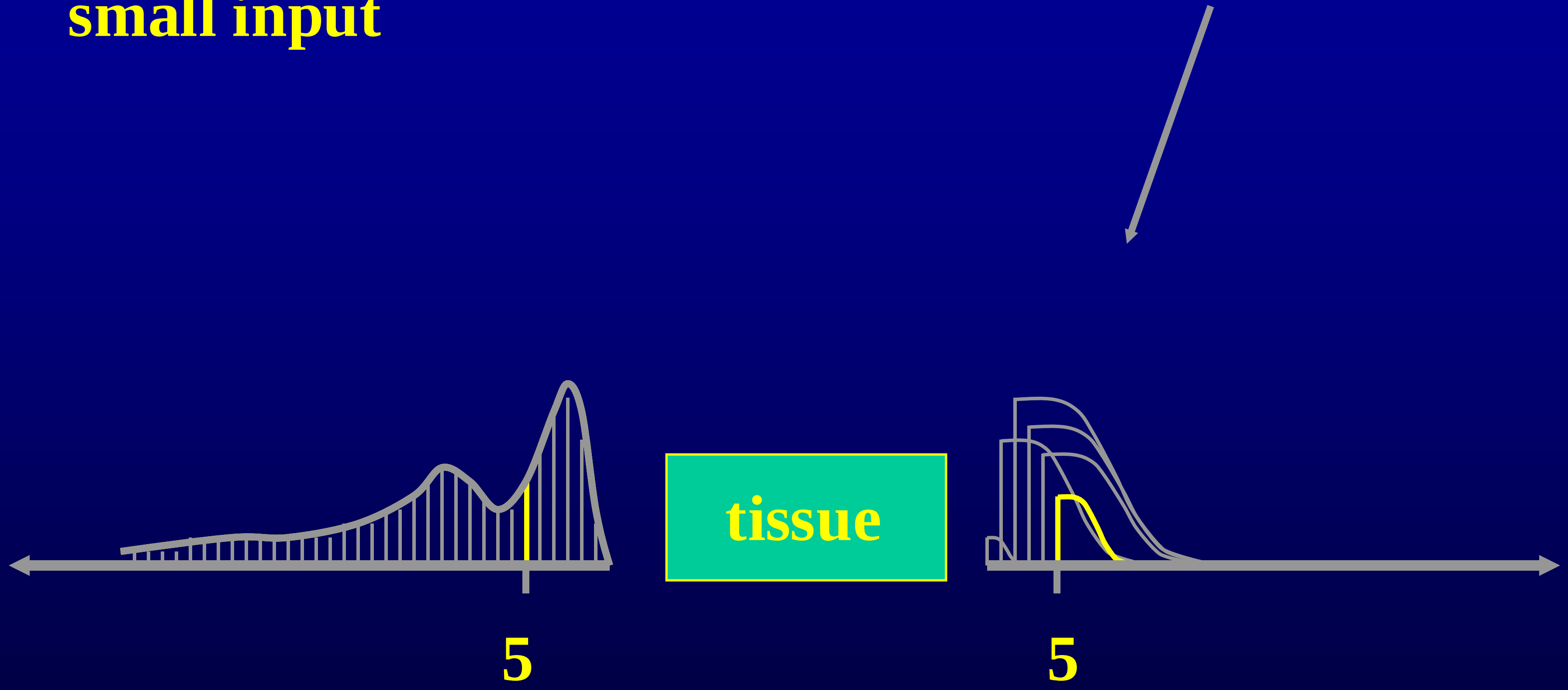
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(5)\ RF(t - 5)\ \Delta\tau$



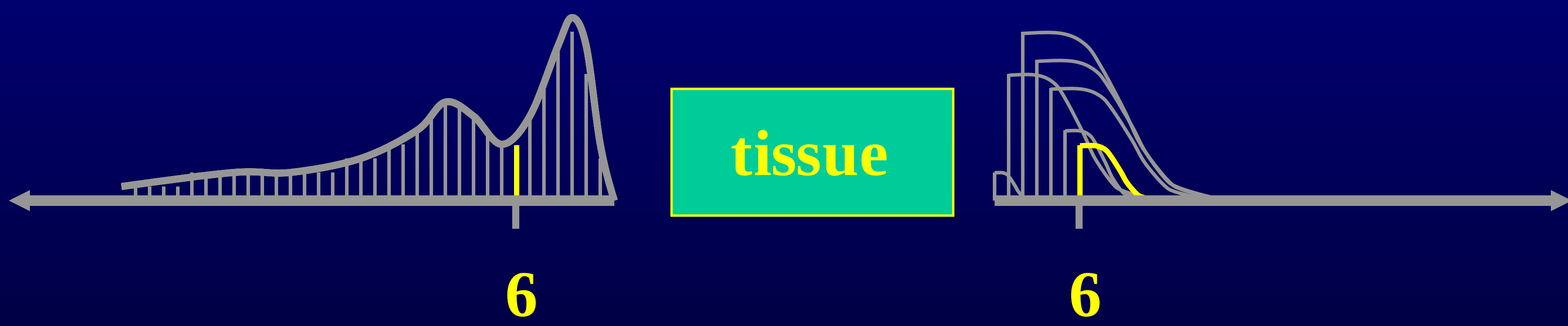
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(6)\ RF(t - 6)\ \Delta\tau$

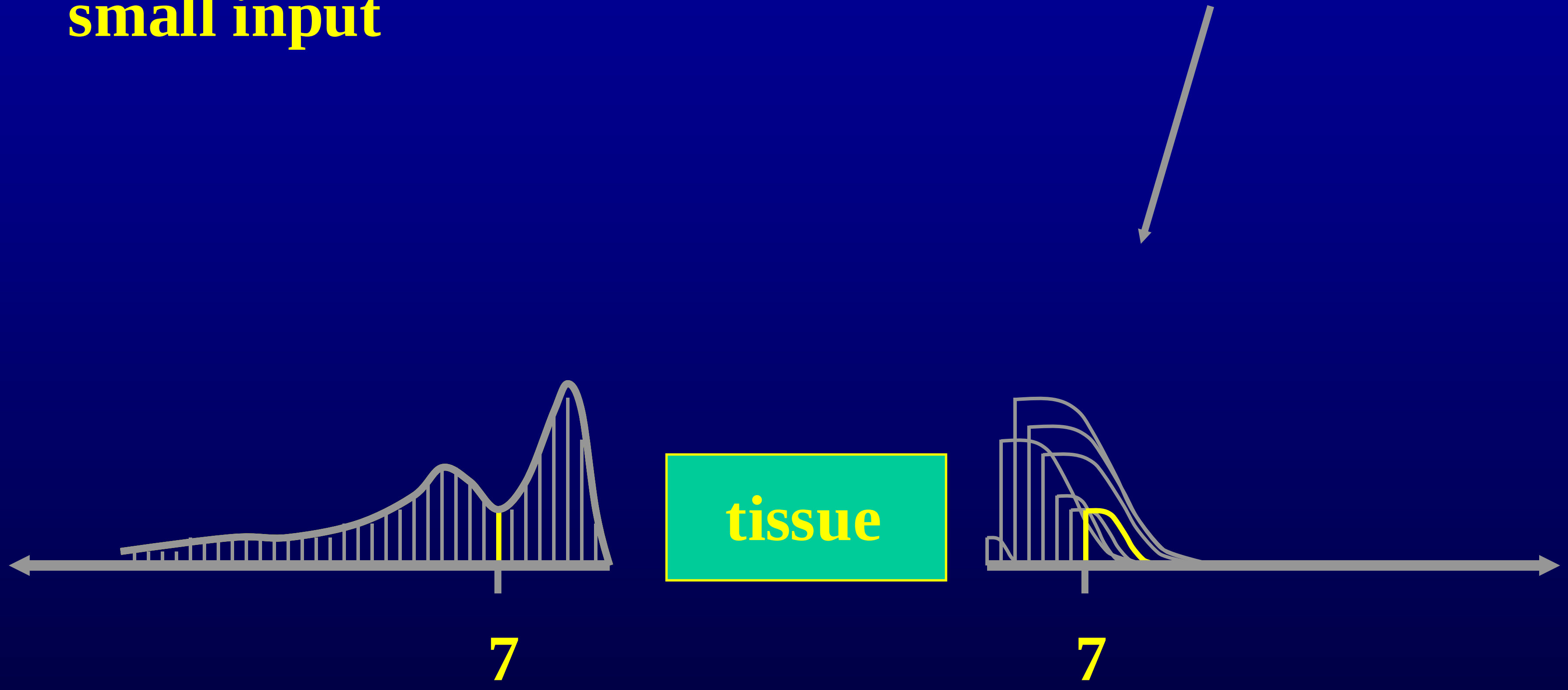


Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(7)\ RF(t - 7)\ \Delta\tau$



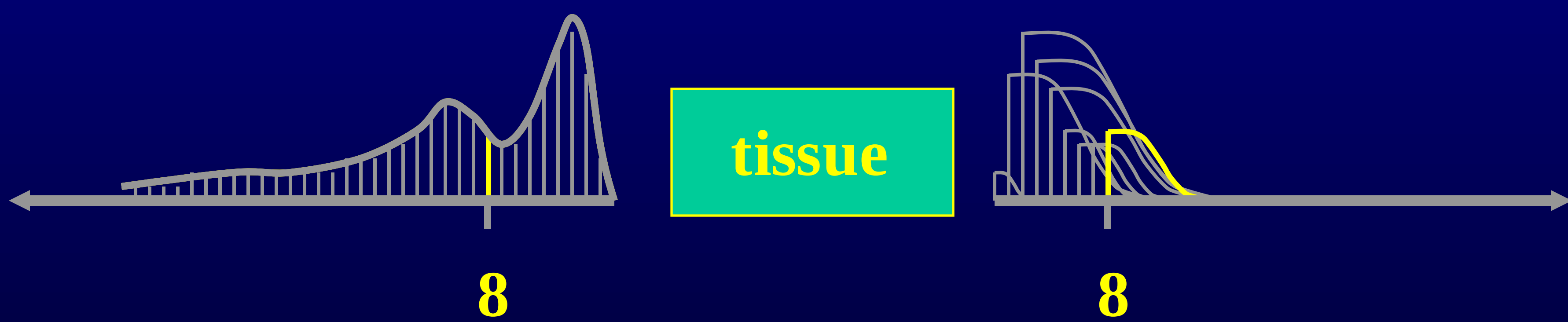
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$$C_{tis}(t) = f\ C_a(8)\ RF(t - 8)\ \Delta\tau$$



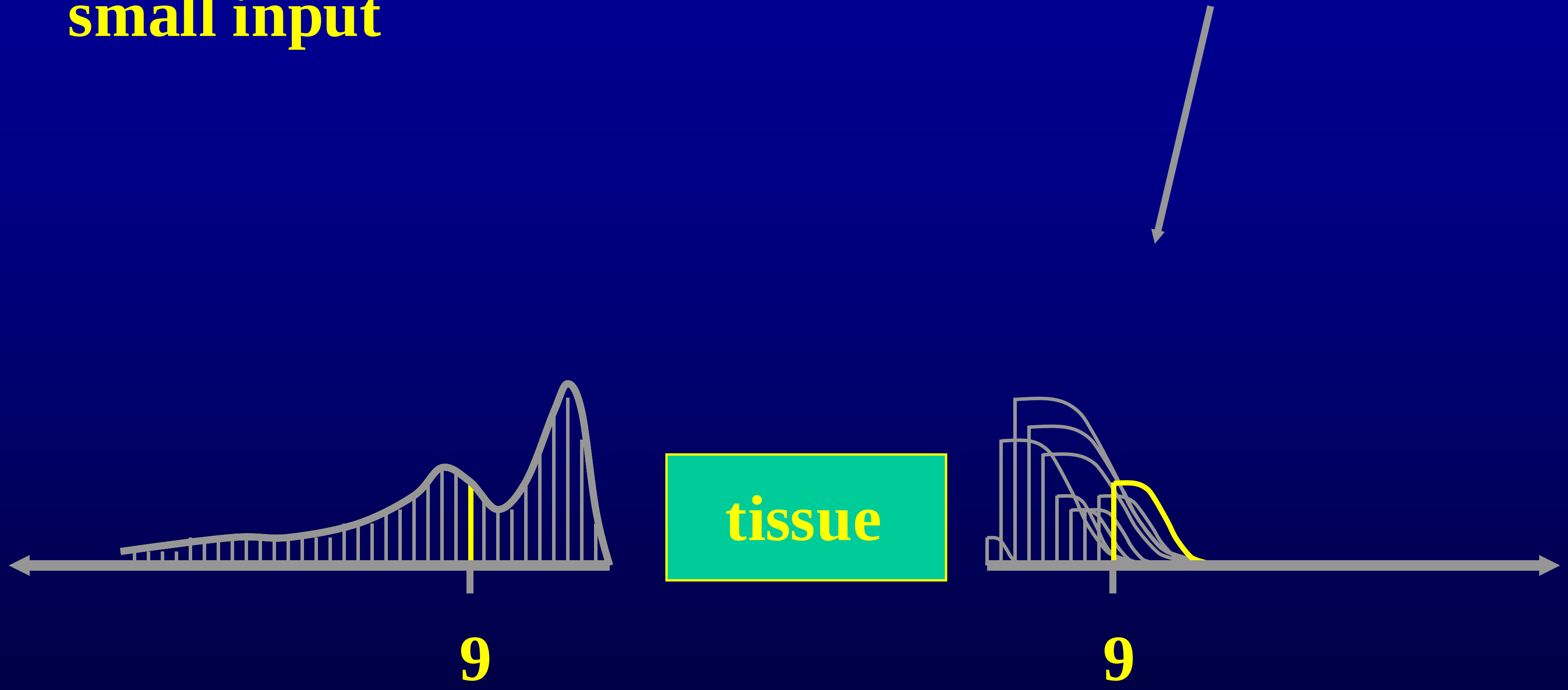
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(9)\ RF(t - 9)\ \Delta\tau$



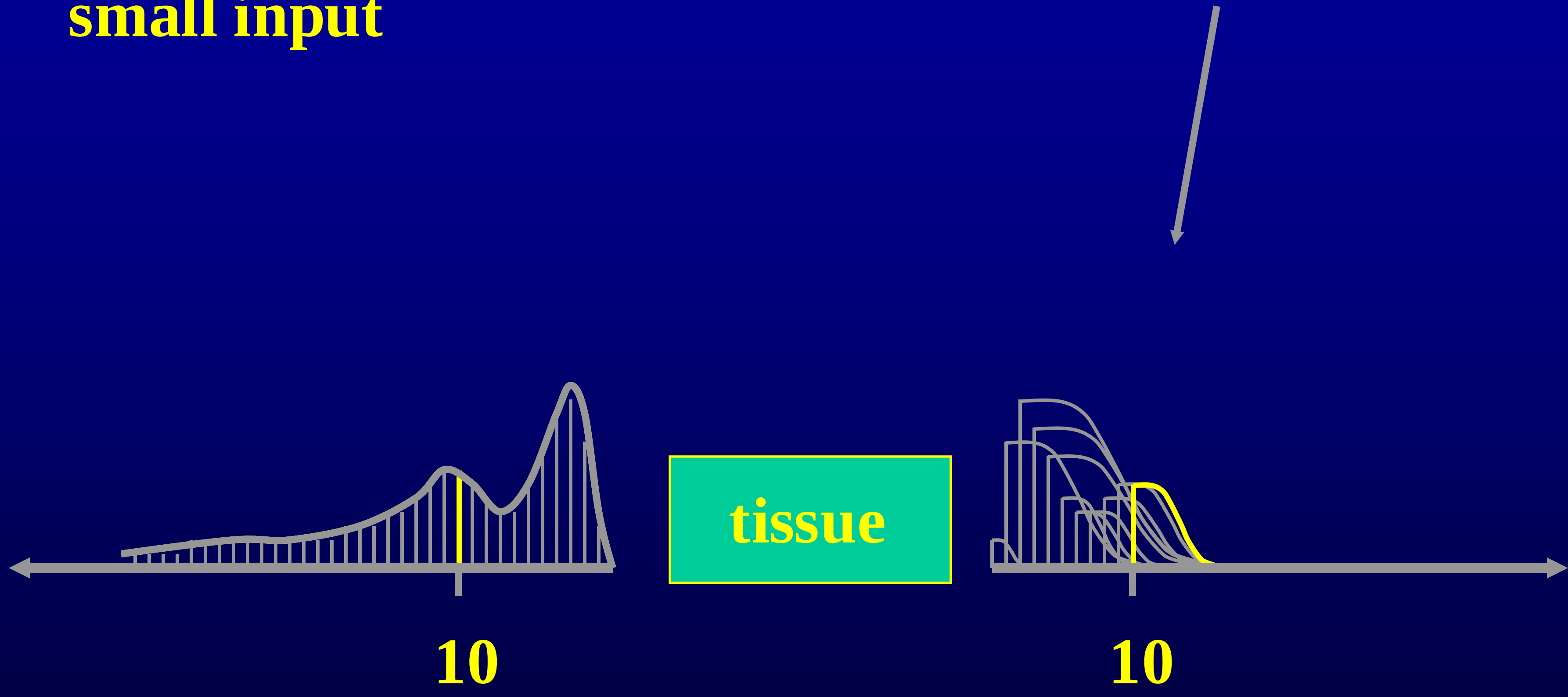
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(10)\ RF(t - 10)\ \Delta\tau$



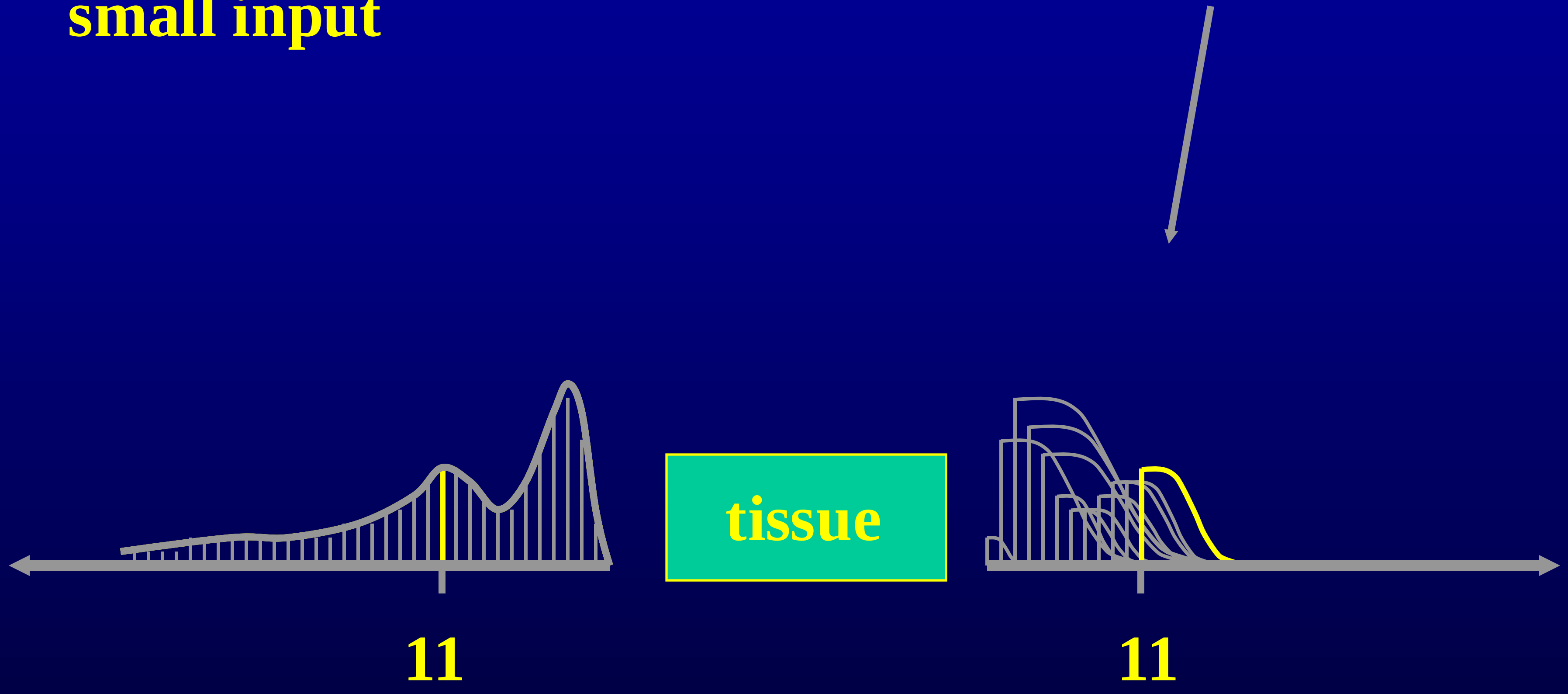
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(11)\ RF(t - 11)\ \Delta\tau$

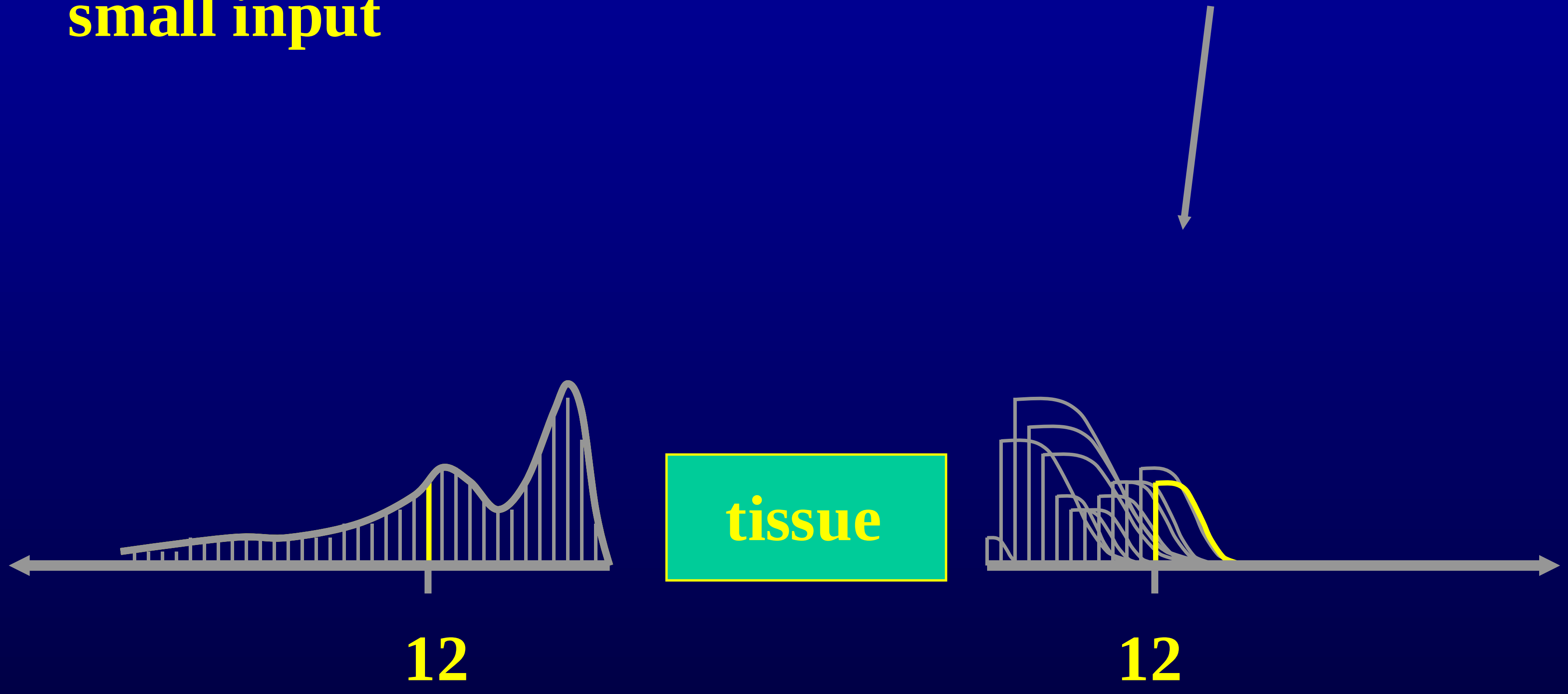


Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$$C_{tis}(t) = f\ C_a(12)\ RF(t - 12)\ \Delta\tau$$



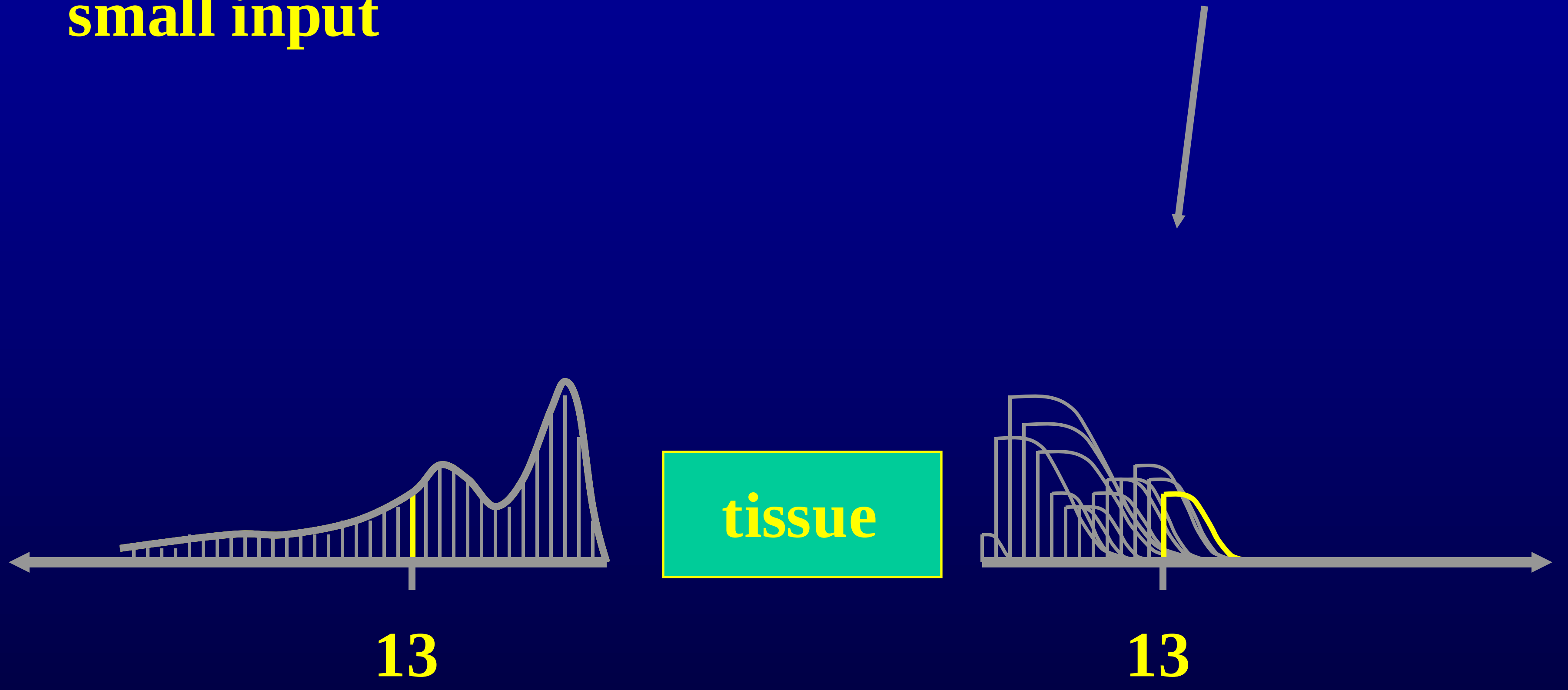
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$$C_{tis}(t) = f\ C_a(13)\ RF(t - 13)\ \Delta\tau$$



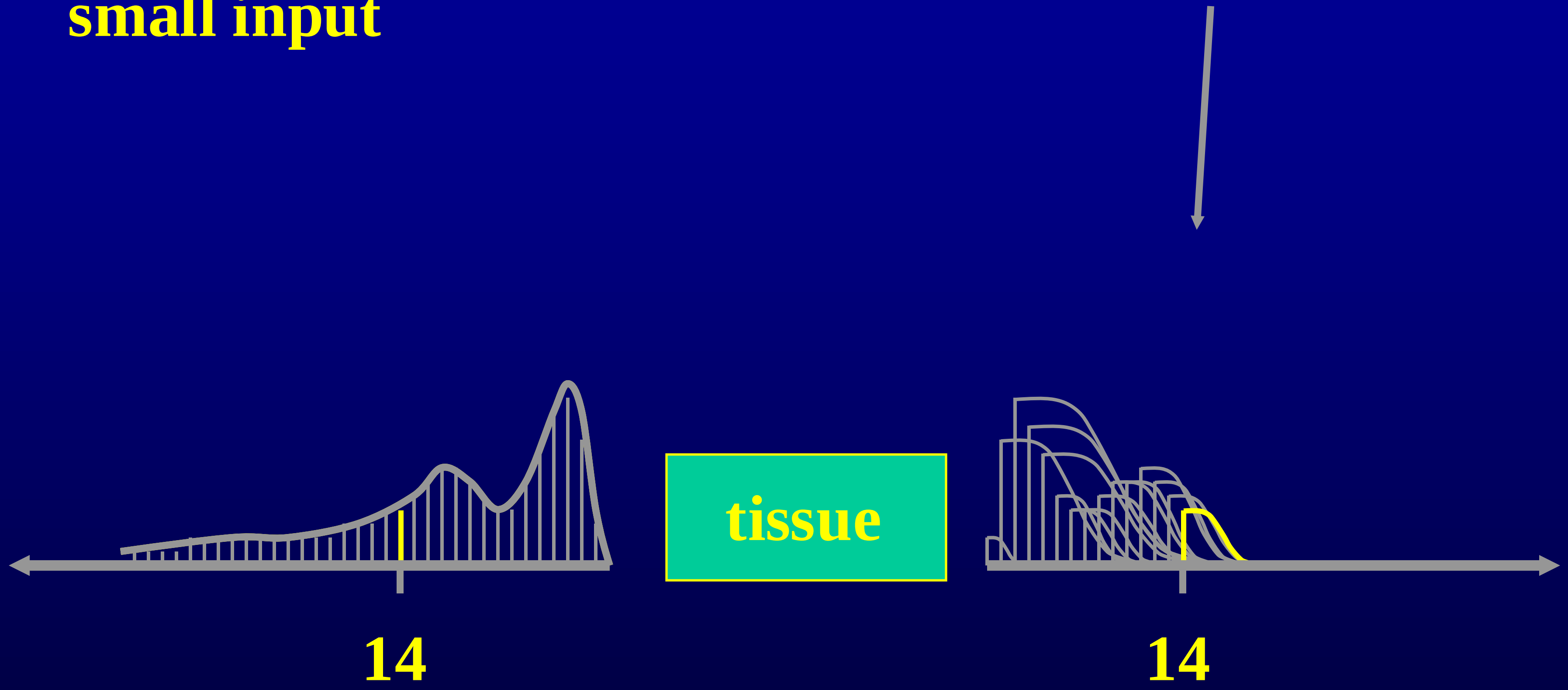
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(14)\ RF(t - 14)\ \Delta\tau$



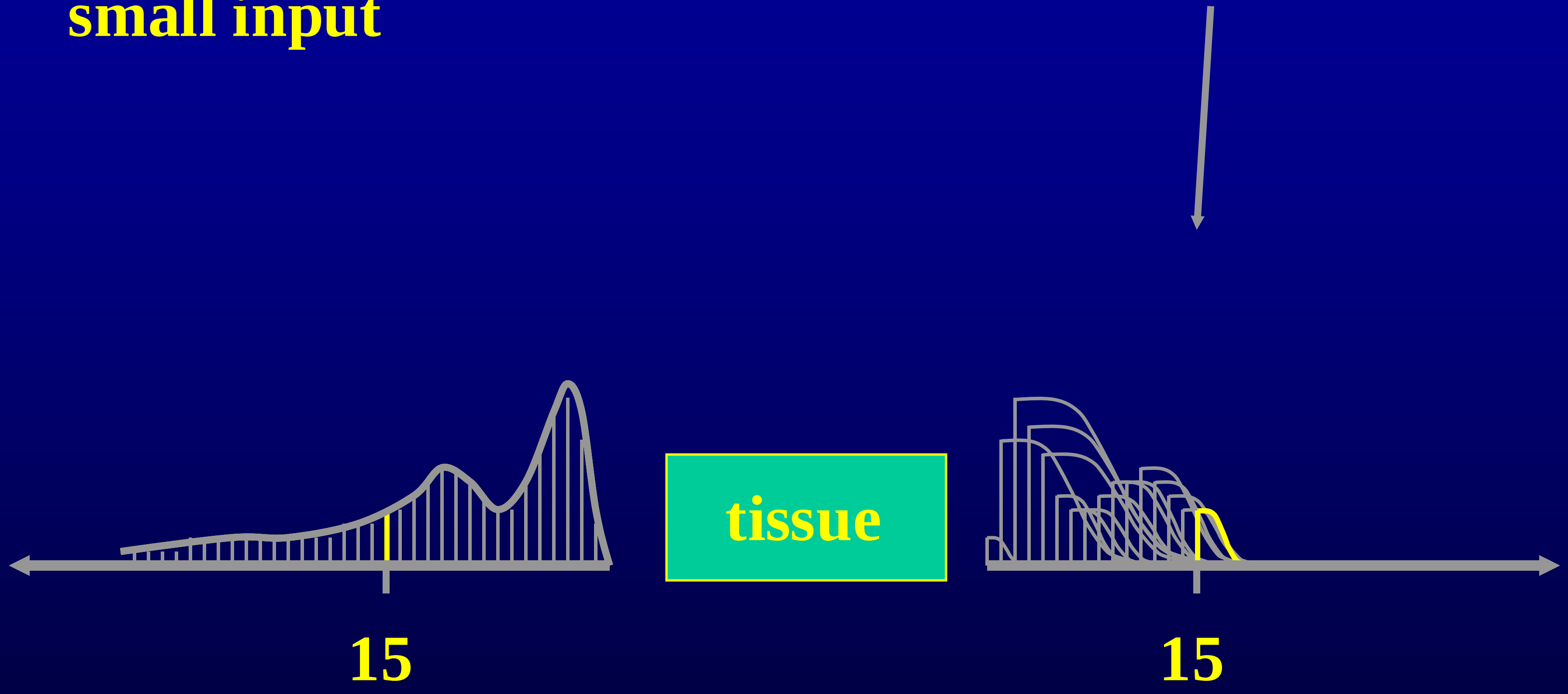
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(15)\ RF(t - 15)\ \Delta\tau$



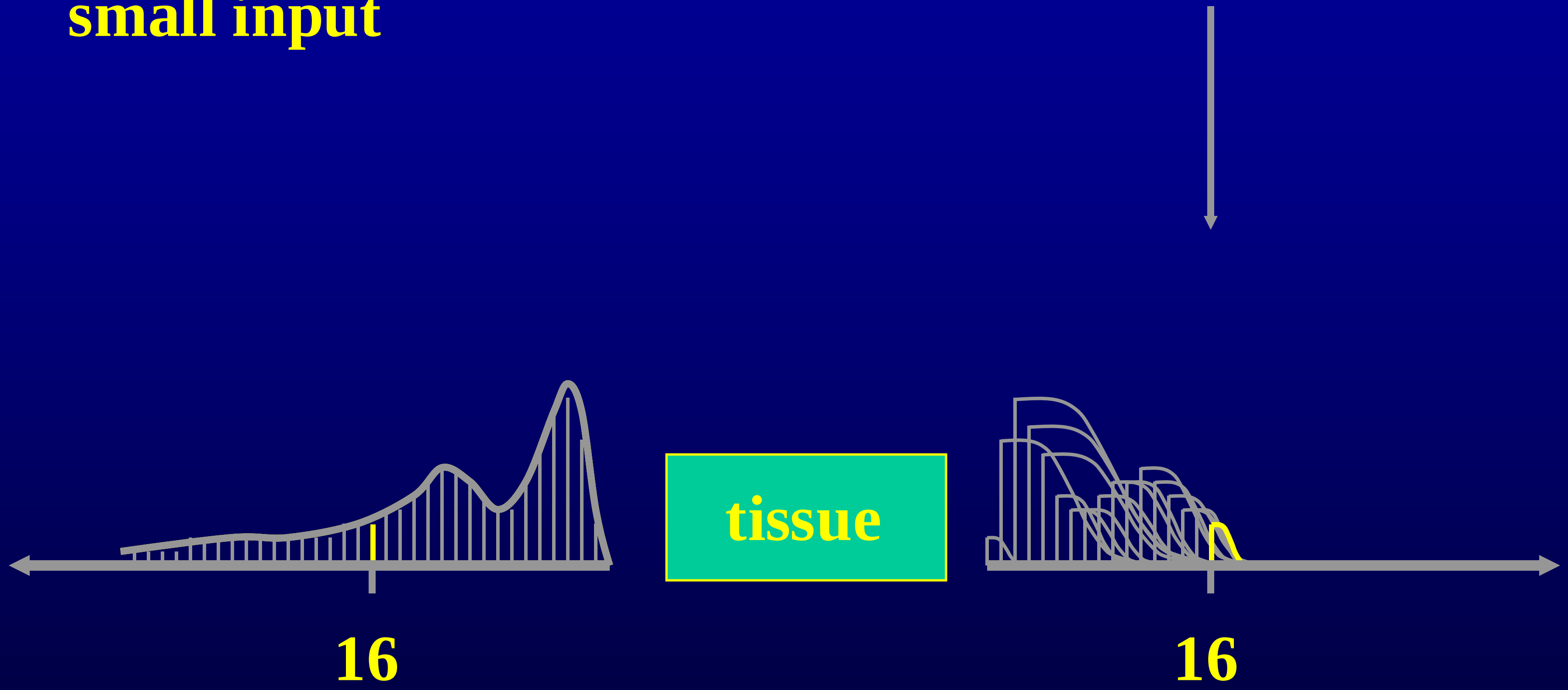
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\, C_a(16)\, RF(t - 16)\, \Delta\tau$



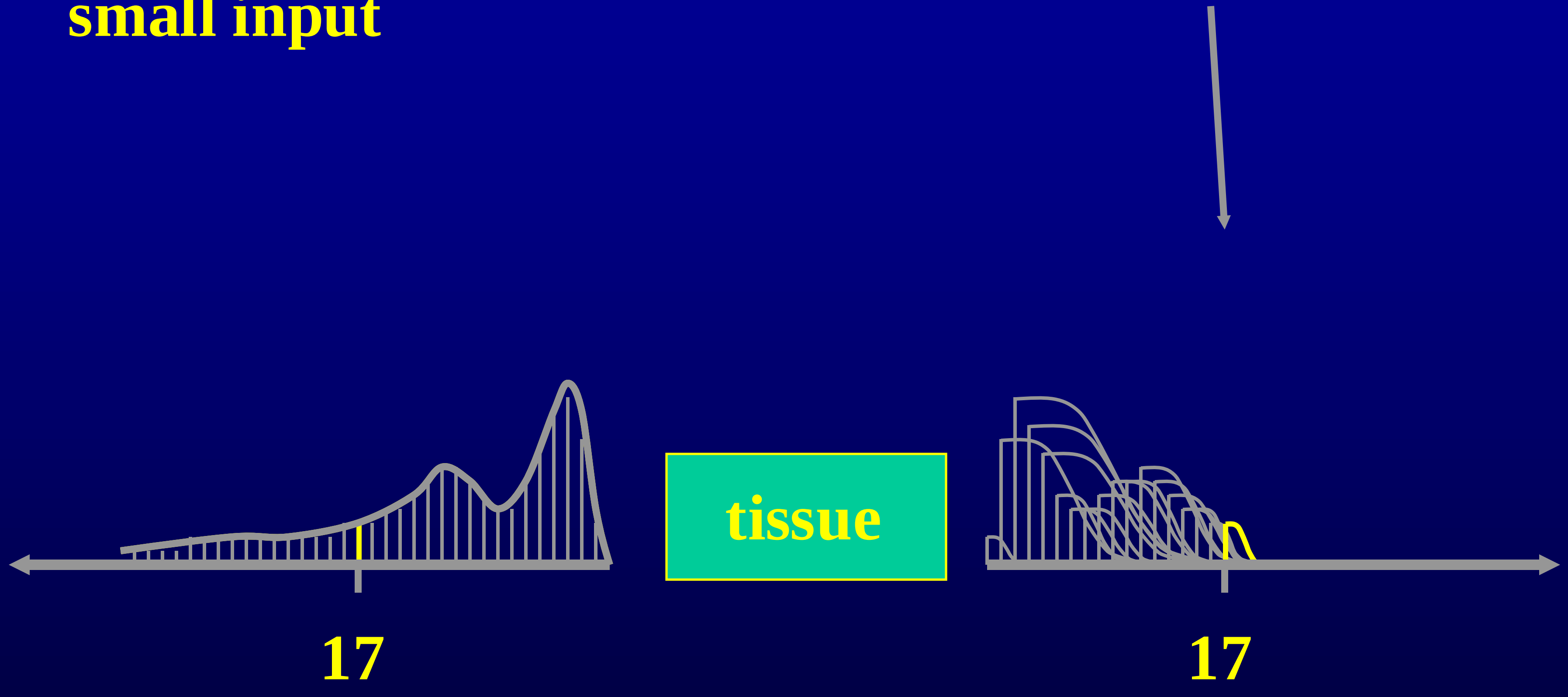
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(17)\ RF(t - 17)\ \Delta\tau$



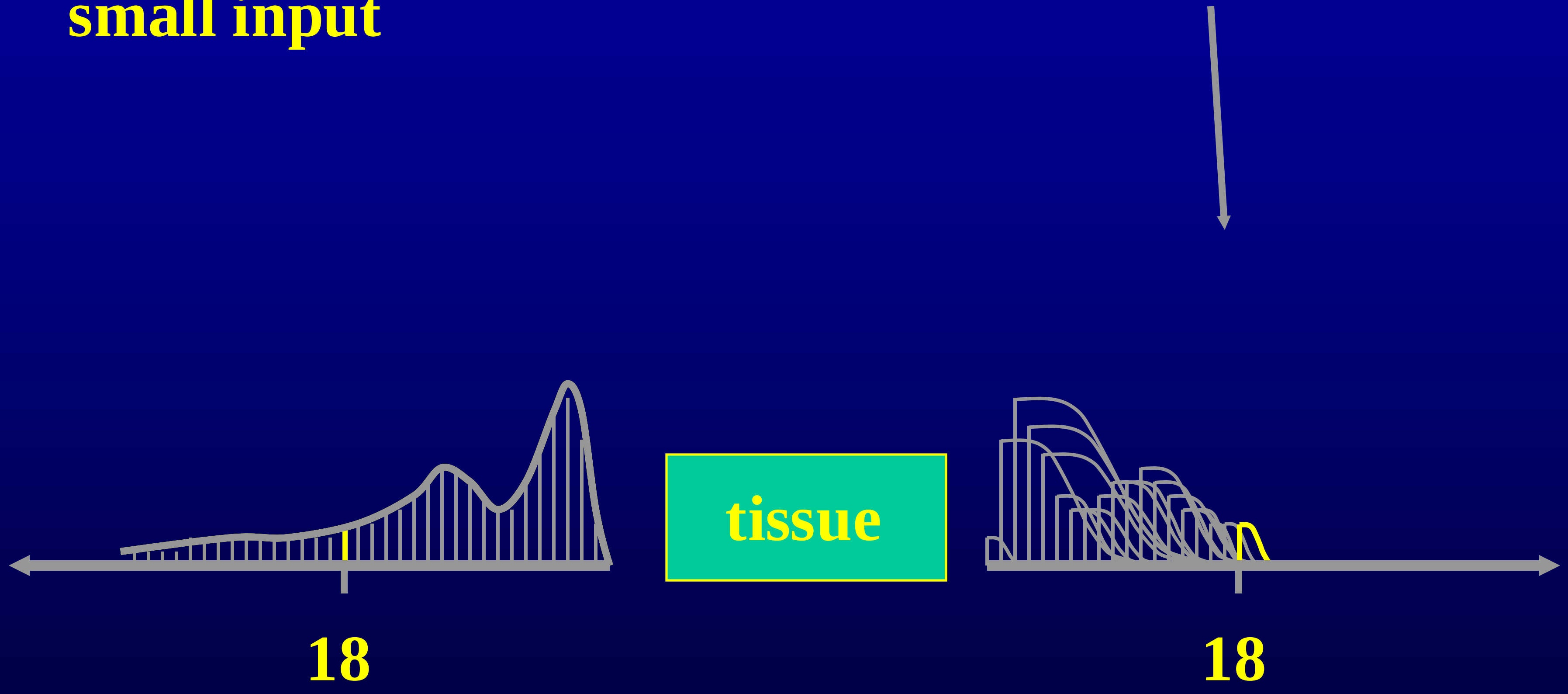
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\, C_a(18)\, RF(t - 18)\, \Delta\tau$



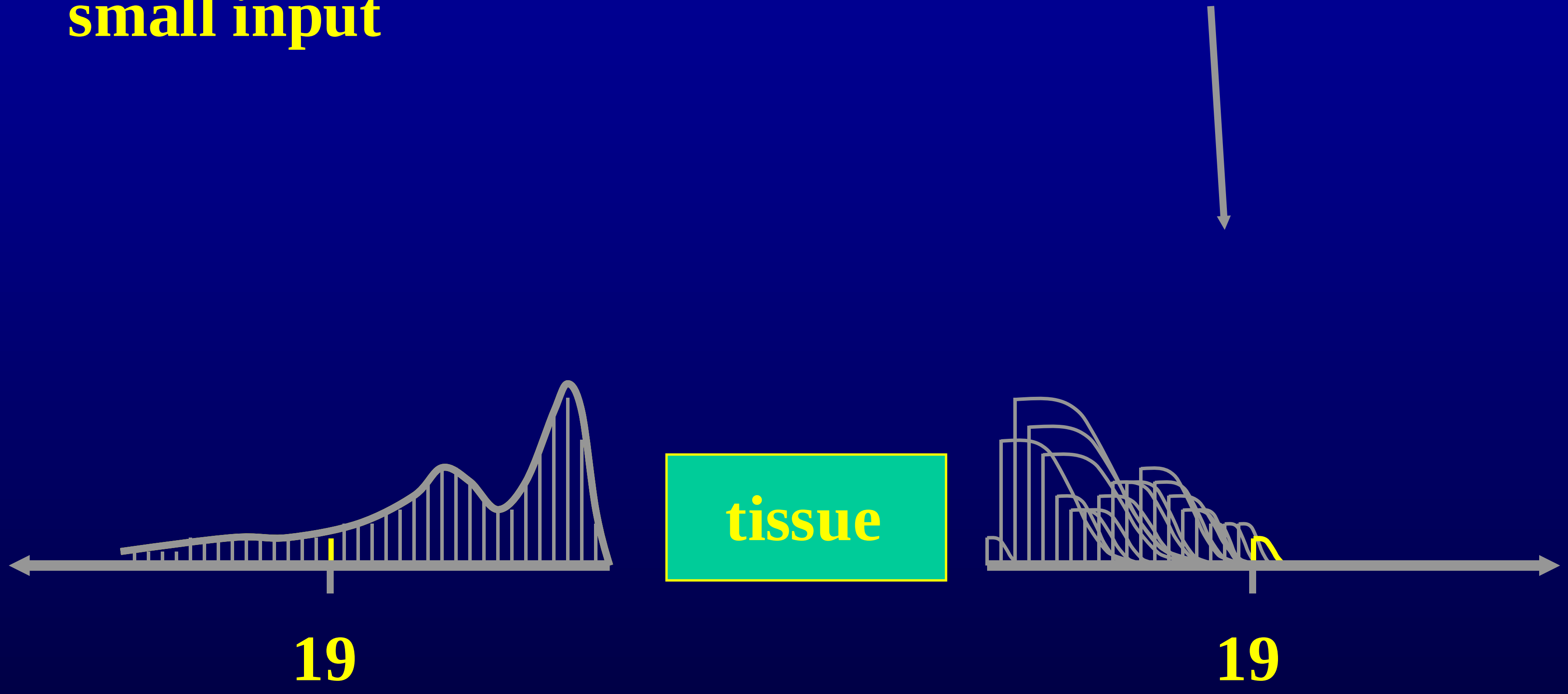
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(19)\ RF(t - 19)\ \Delta\tau$



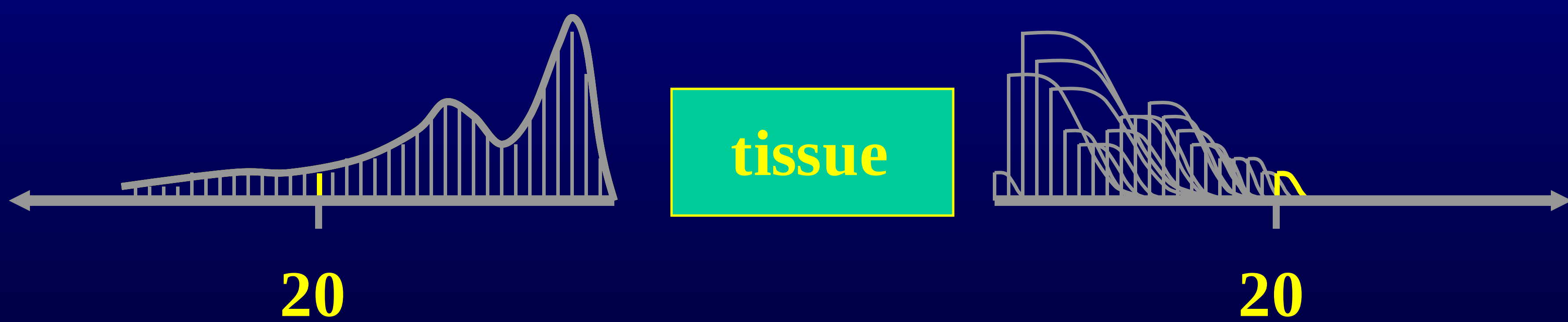
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(20)\ RF(t - 20)\ \Delta\tau$



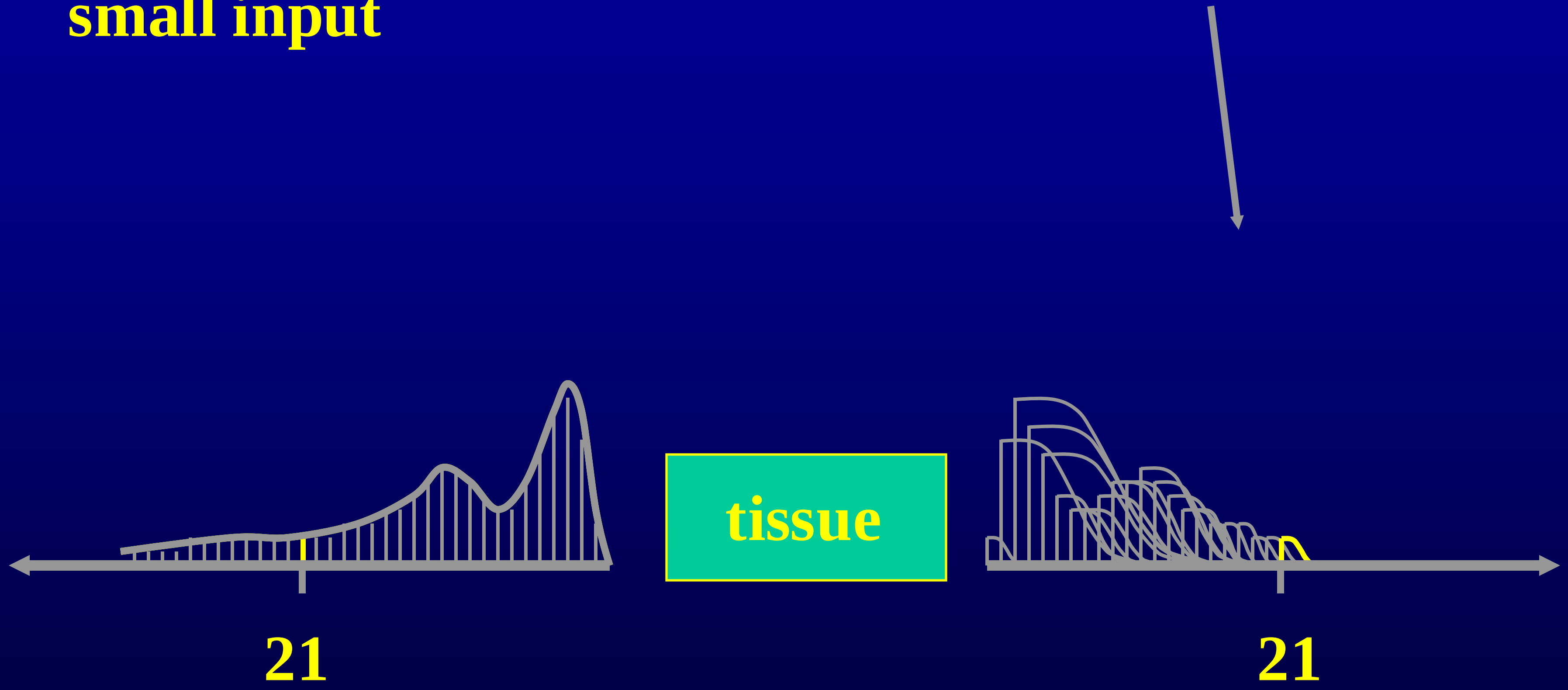
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(21)\ RF(t - 21)\ \Delta\tau$



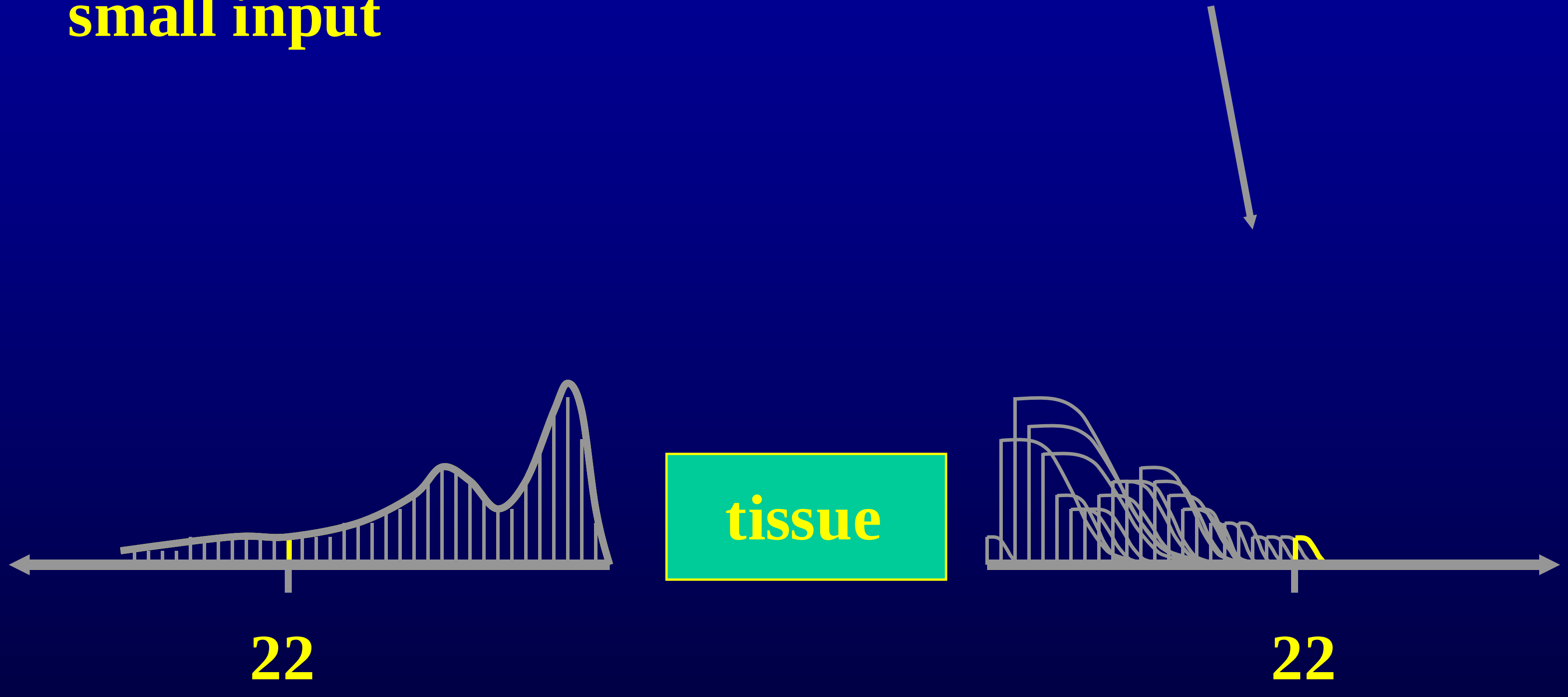
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(22)\ RF(t - 22)\ \Delta\tau$



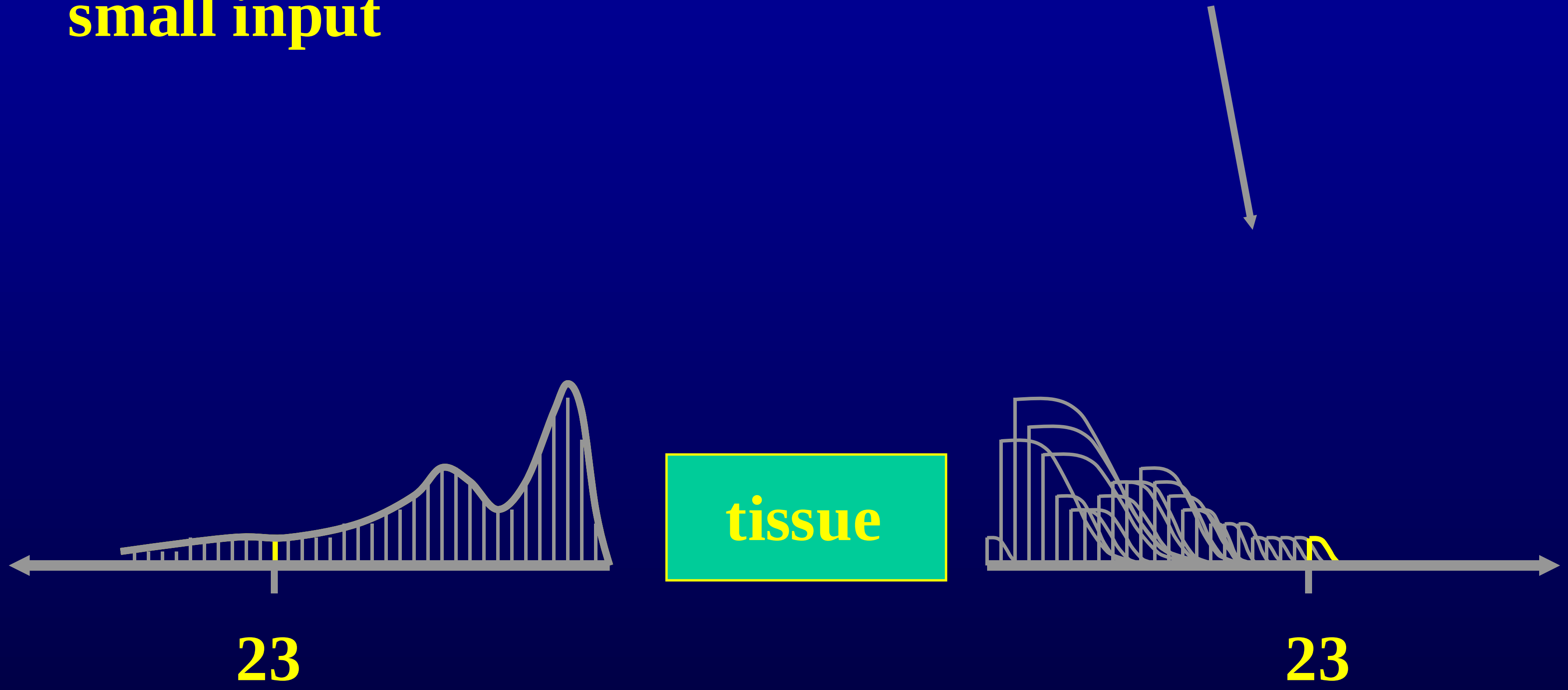
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(23)\ RF(t - 23)\ \Delta\tau$



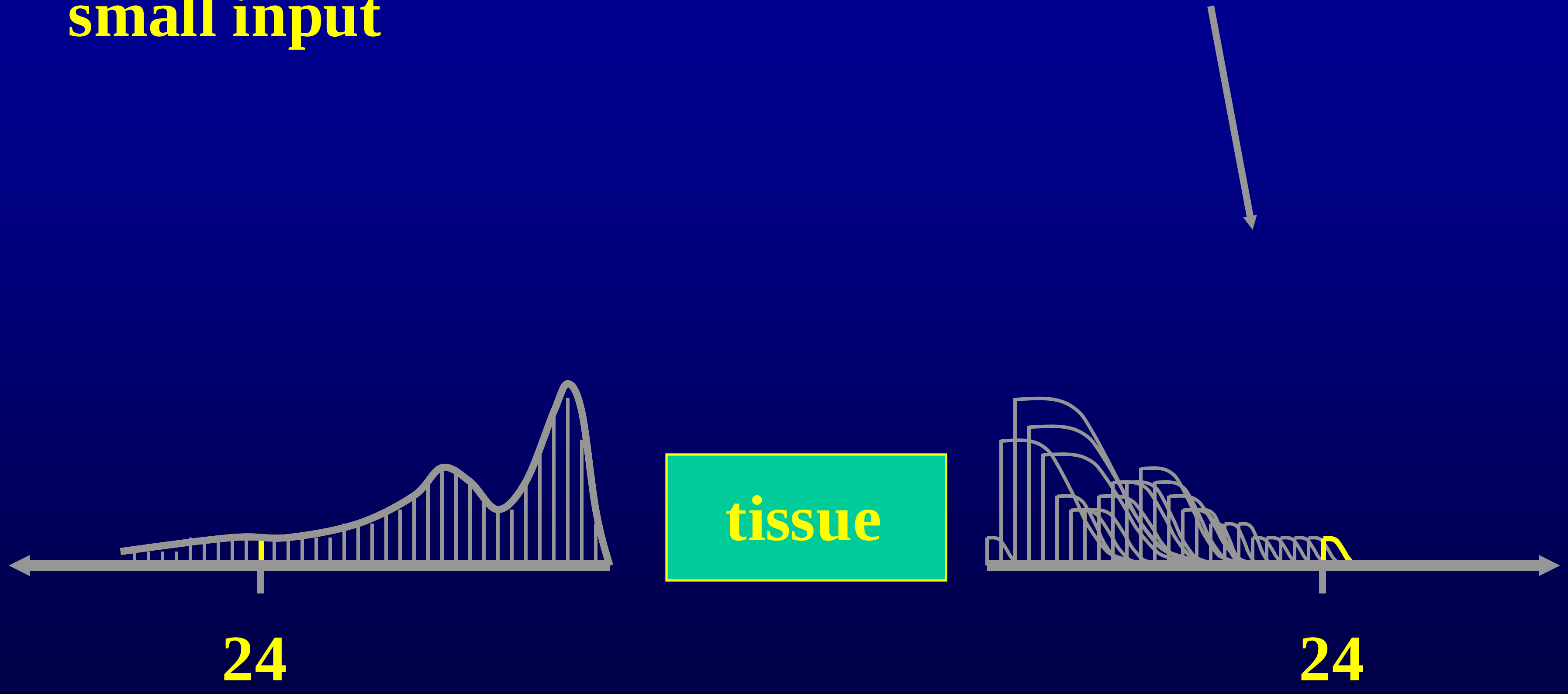
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(24)\ RF(t - 24)\ \Delta\tau$



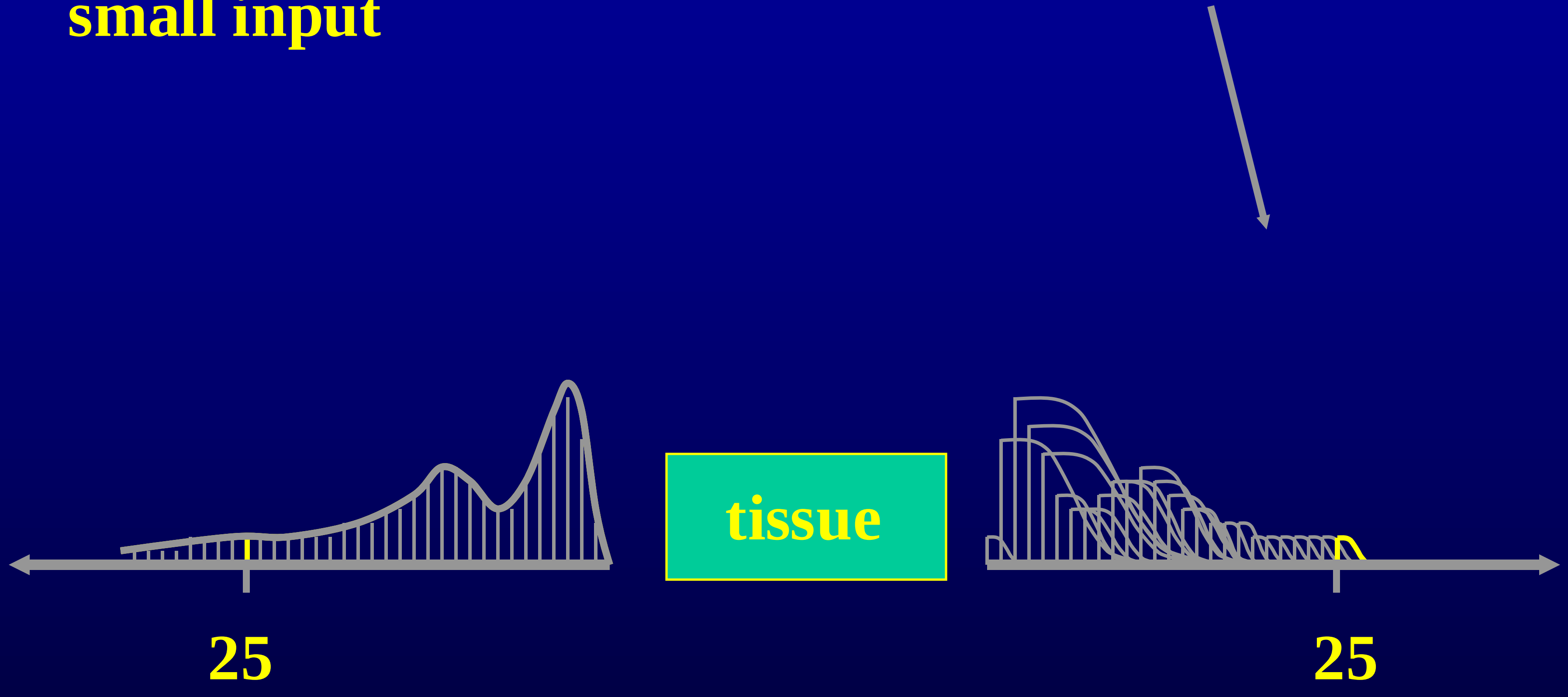
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(25)\ RF(t - 25)\ \Delta\tau$



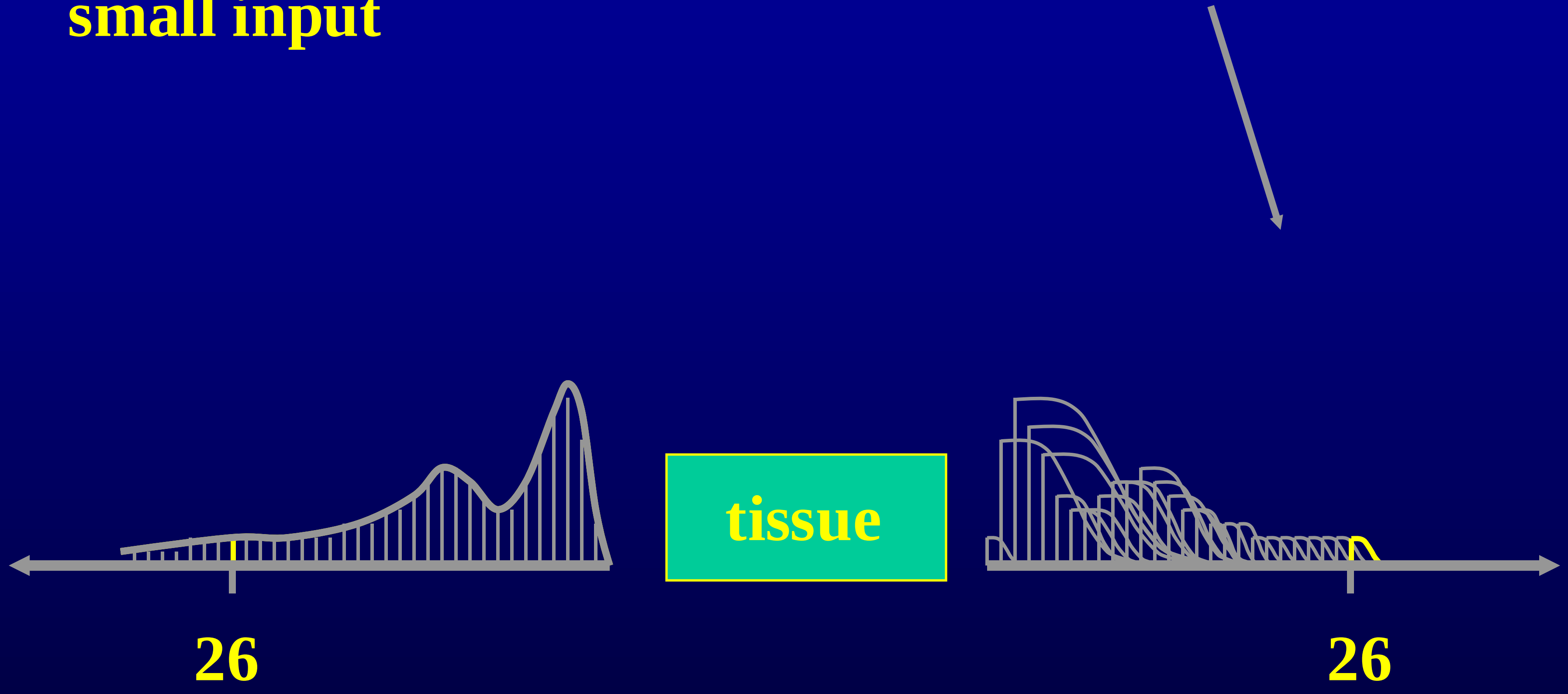
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\, C_a(26)\, RF(t - 26)\, \Delta\tau$



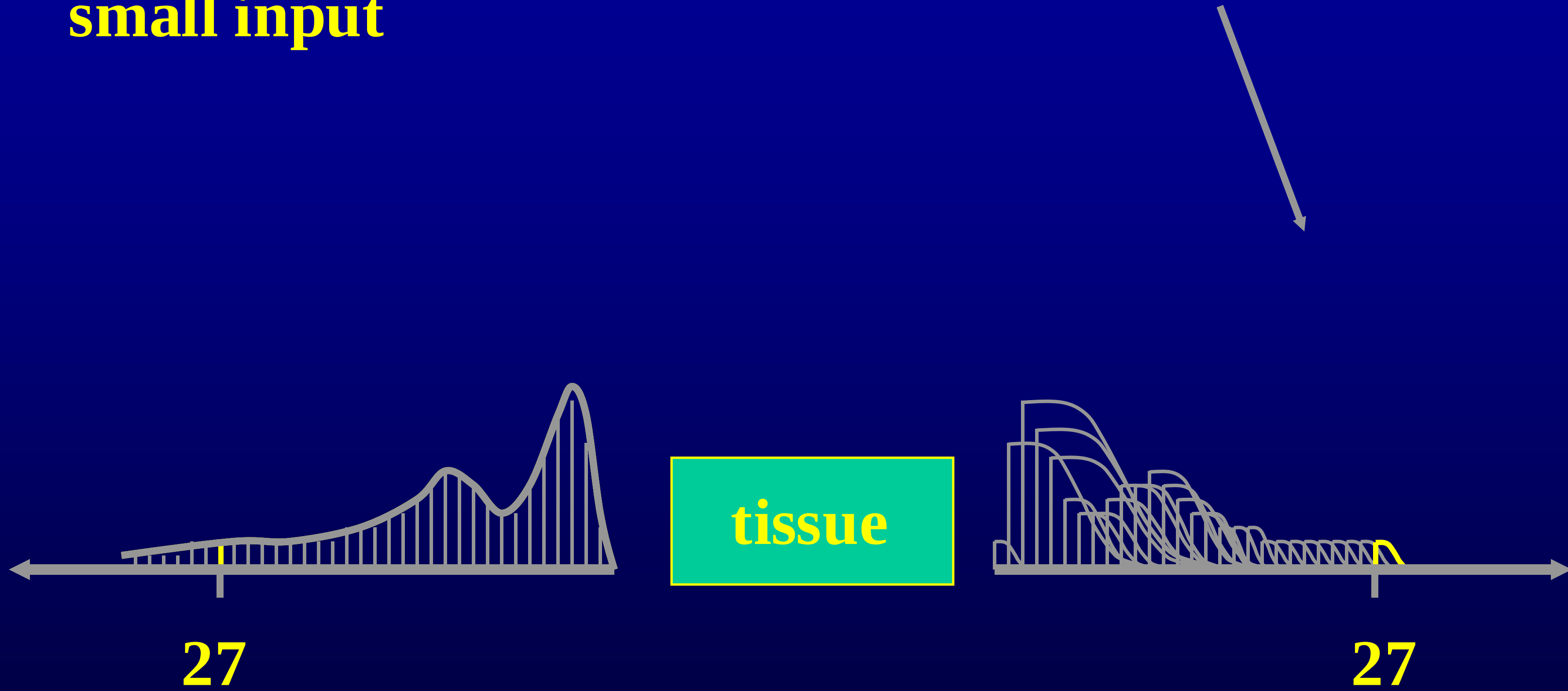
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$$C_{tis}(t) = f\ C_a(27)\ RF(t - 27)\ \Delta\tau$$



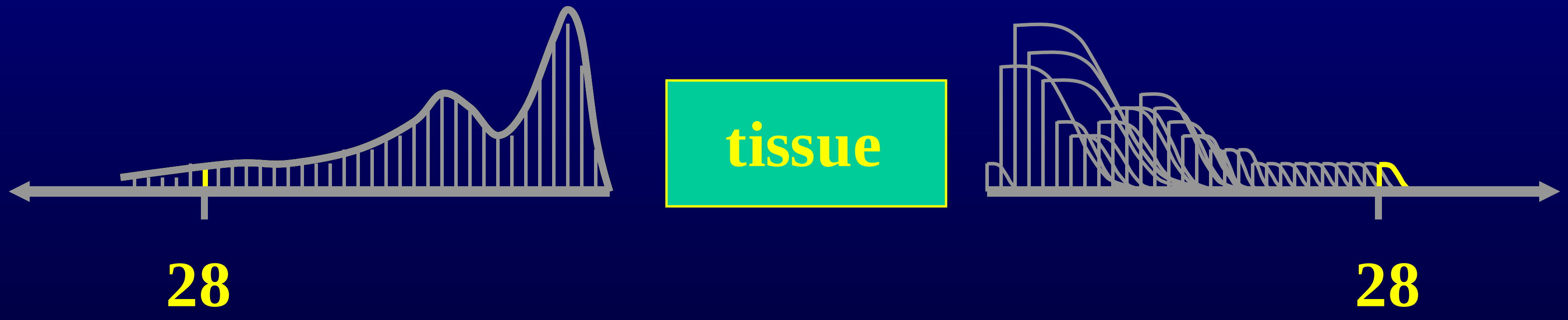
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(28)\ RF(t - 28)\ \Delta\tau$



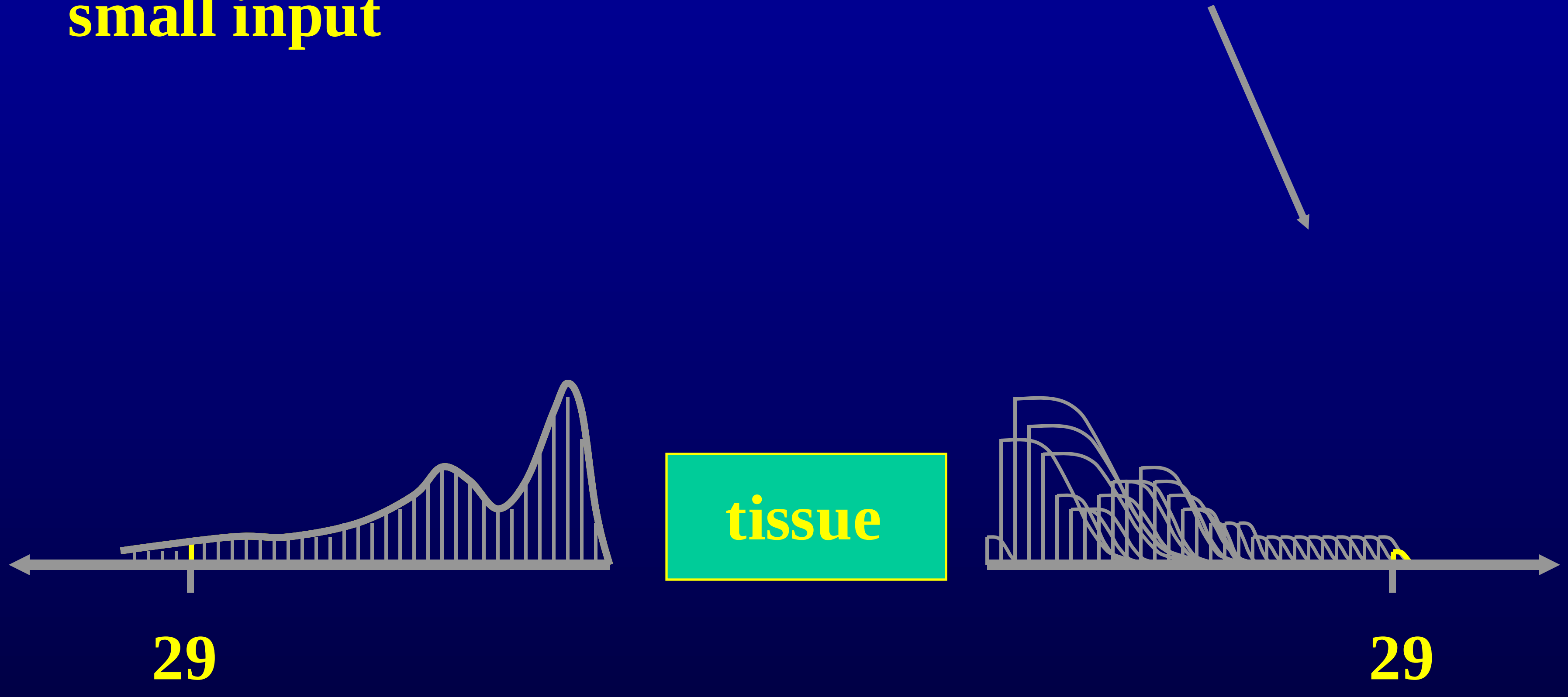
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(29)\ RF(t - 29)\ \Delta\tau$



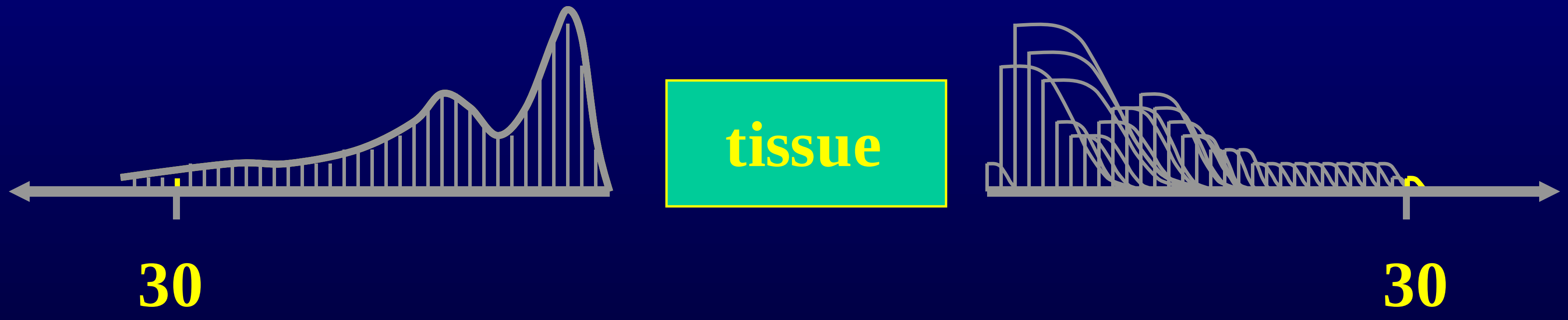
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(30)\ RF(t - 30)\ \Delta\tau$



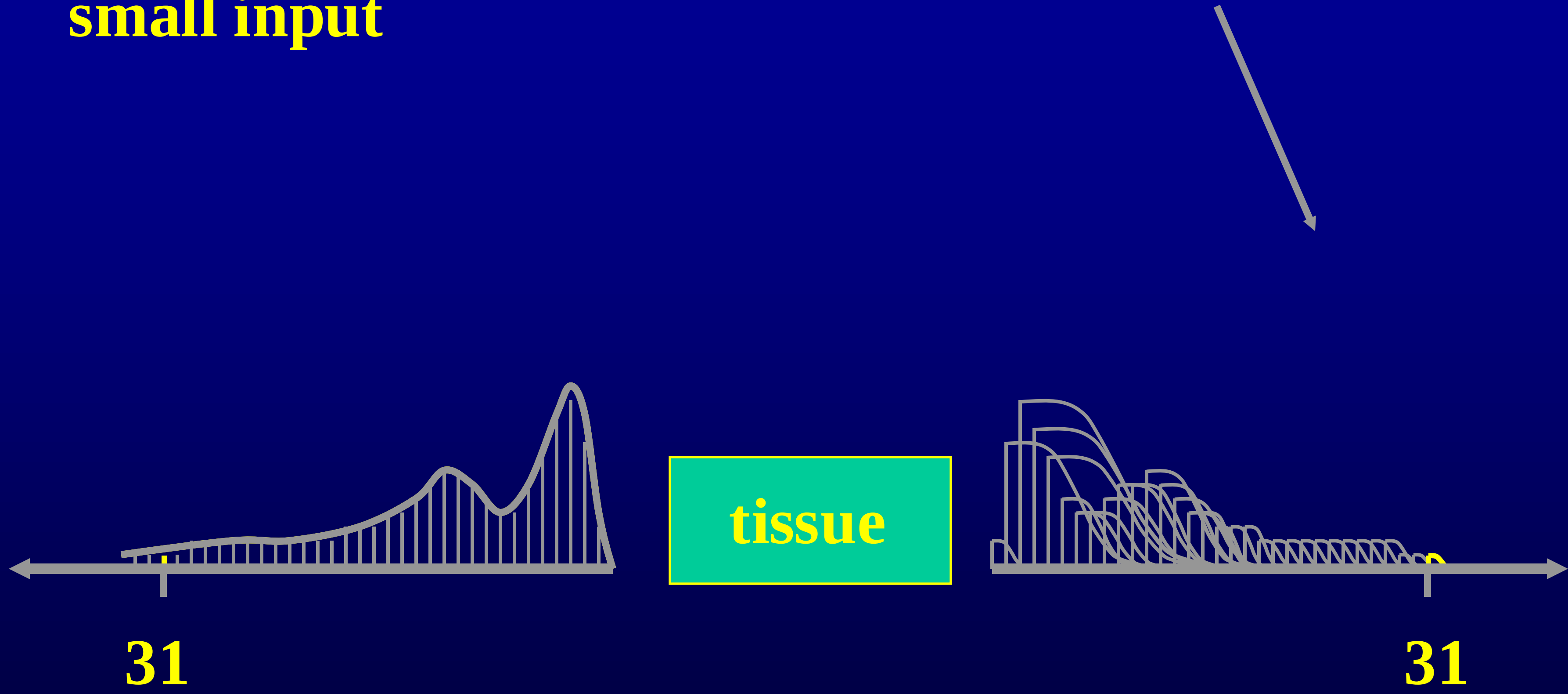
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$$C_{tis}(t) = f\, C_a(31)\, RF(t - 31)\, \Delta\tau$$



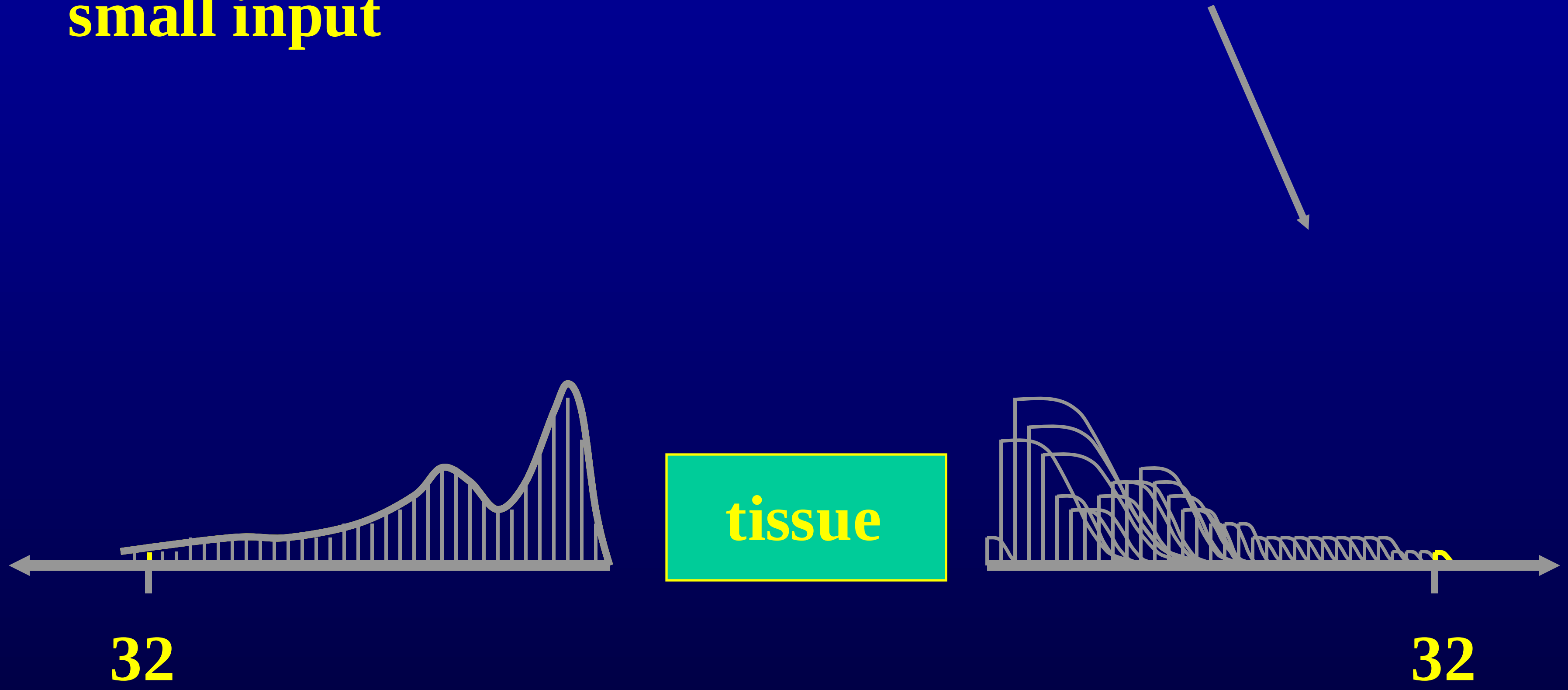
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$$C_{tis}(t) = f\ C_a(32)\ RF(t - 32)\ \Delta\tau$$



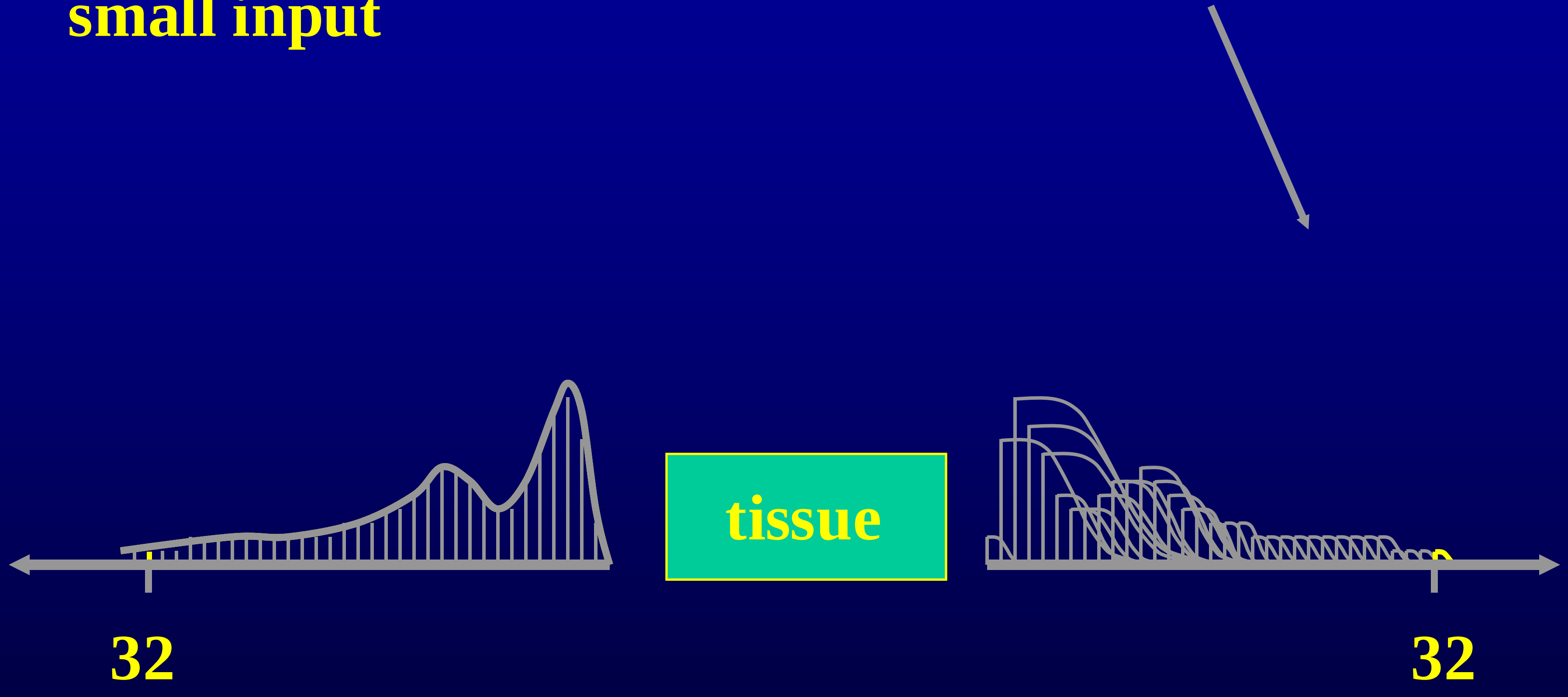
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

$C_{tis}(t) = f\ C_a(32)\ RF(t - 32)\ \Delta\tau$



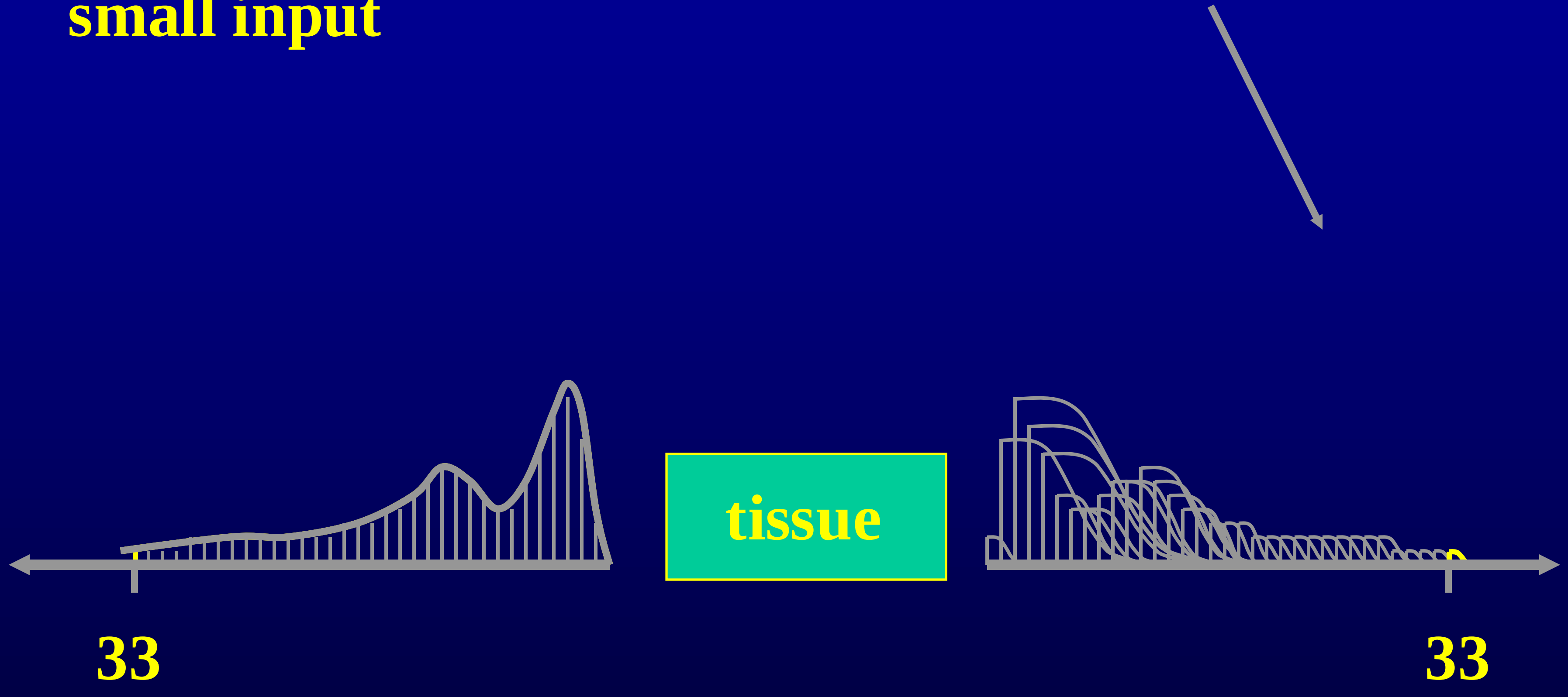
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

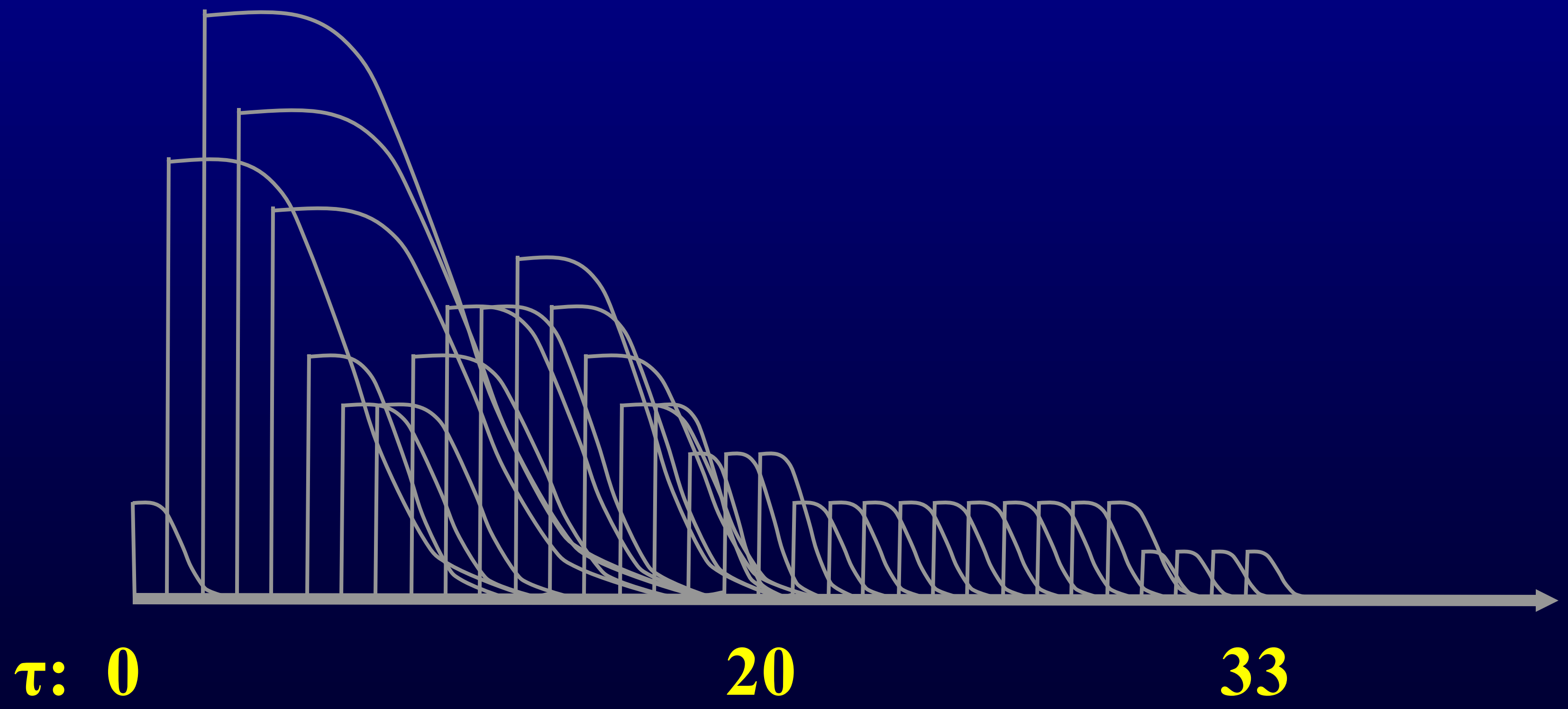
$C_{tis}(t) = f\ C_a(33)\ RF(t - 33)\ \Delta\tau$



HBWL

Tissue enhancement :

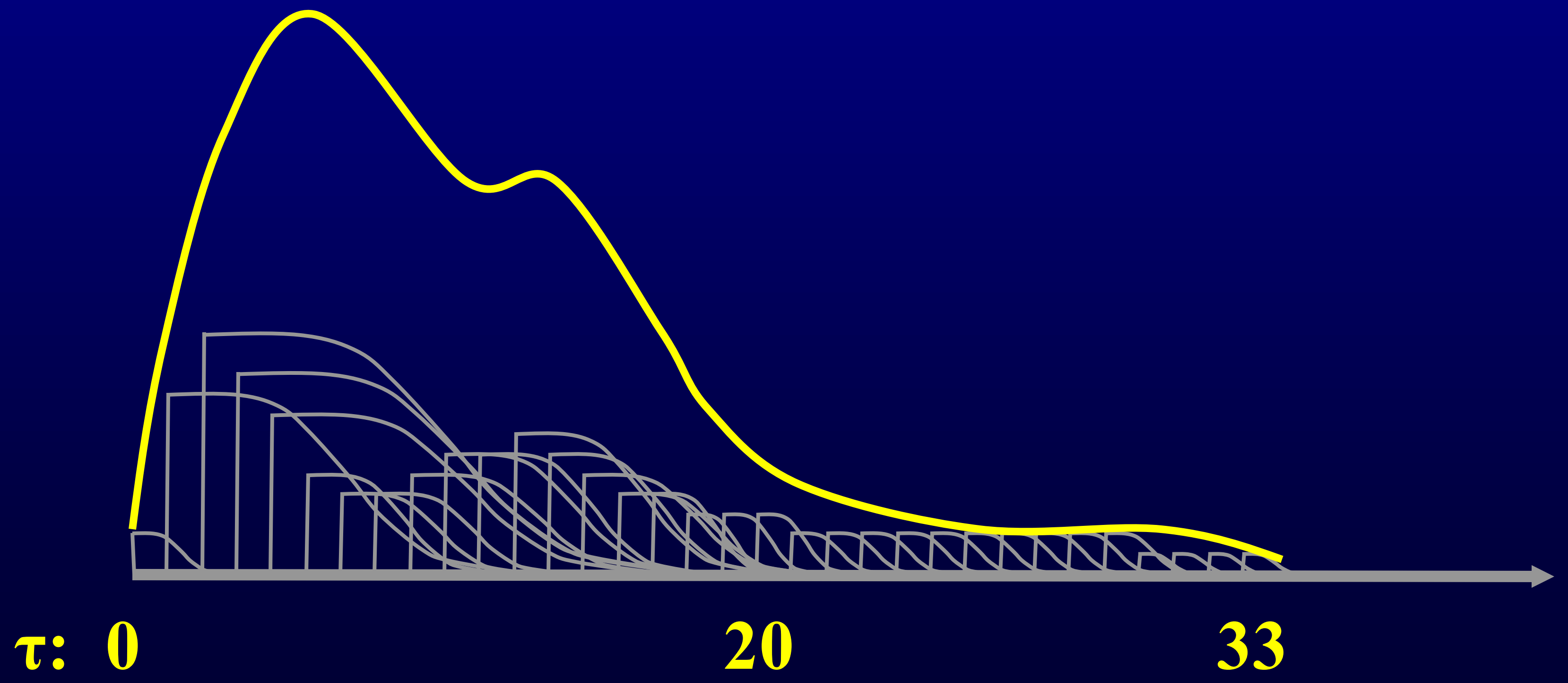
$$\int C_a(\tau)\ RF(t - \tau)\ \Delta\tau\ ;\ \tau = 0{:}33$$



HBWL

Total tissue enhancement :

$$C_{tis}(t) = \sum f\ C_a(\tau)\ RF(t - \tau)\ \Delta\tau\ ;\ \tau = 0{:}33$$

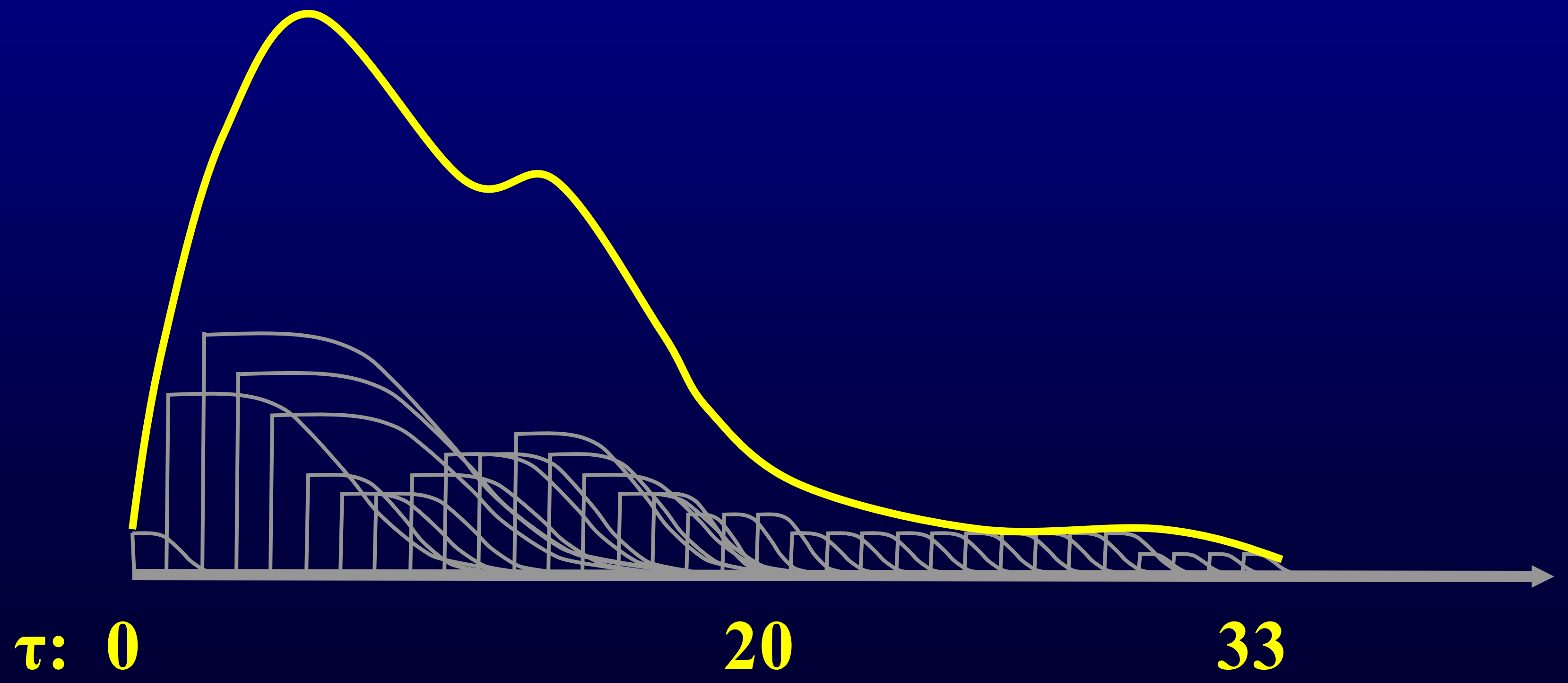


HBWL

Total tissue enhancement :

$$C_{tis}(t) = \int f\, C_a(\tau)\, RF(t - \tau)\, d\tau \; ; \; \tau = 0{:}t$$

The convolution integral



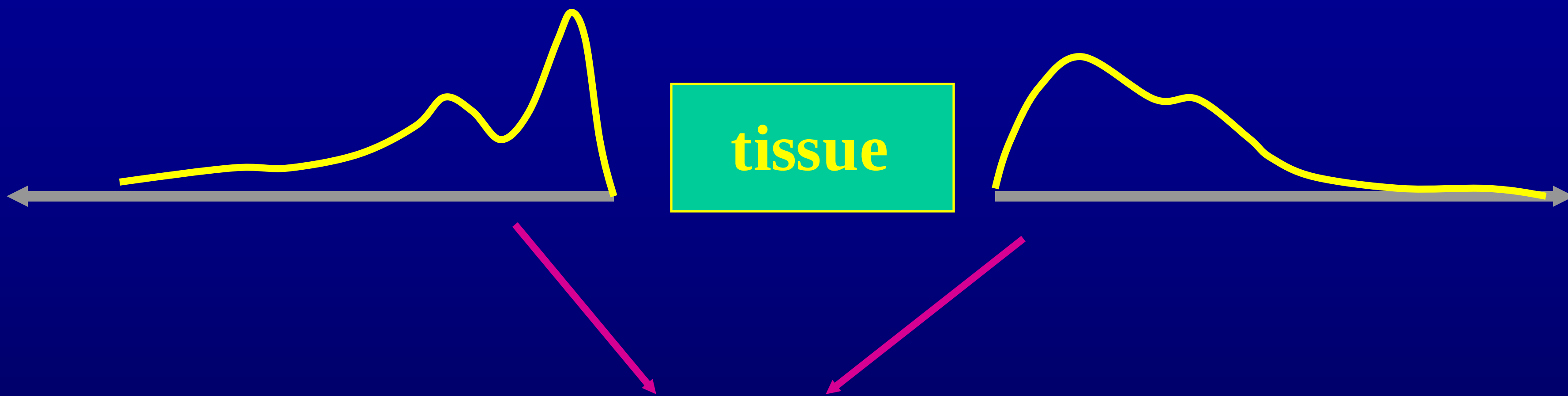
HBWL

Input :

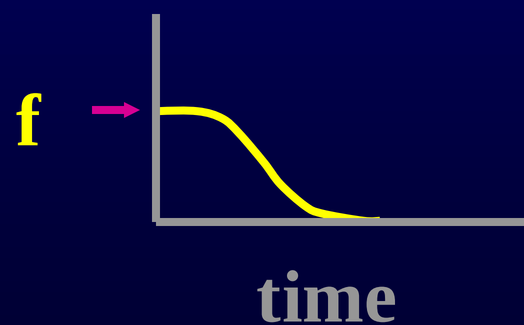
$C_a(t)$

Tissue enhancement :

$C_{tis}(t) = \int f\, C_a(\tau)\, RF(t- \tau)\, d\tau$



Deconvolution :
find f and RF(t)



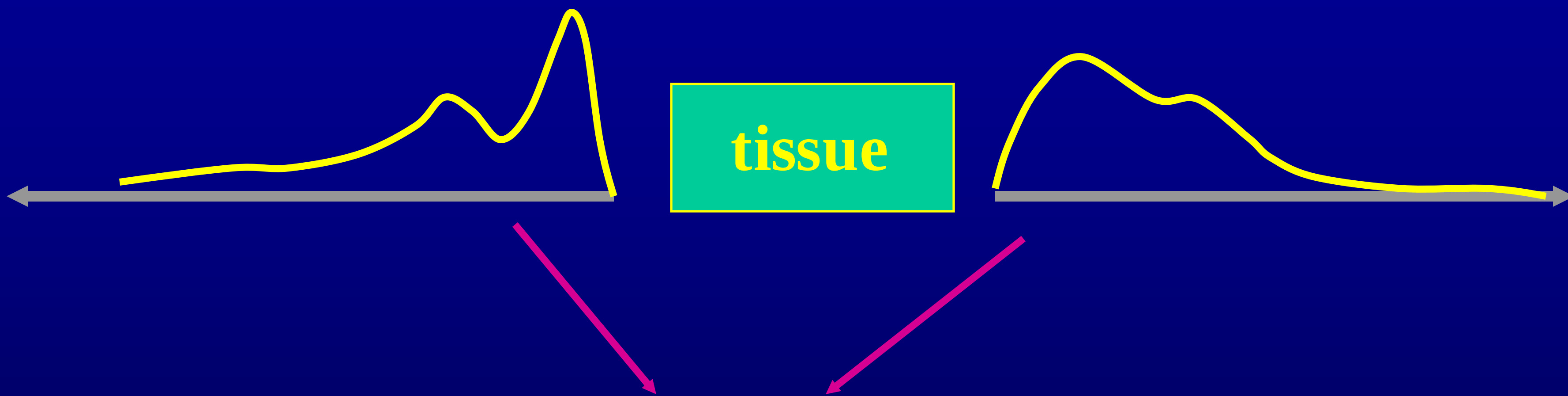
HBWL

Input :

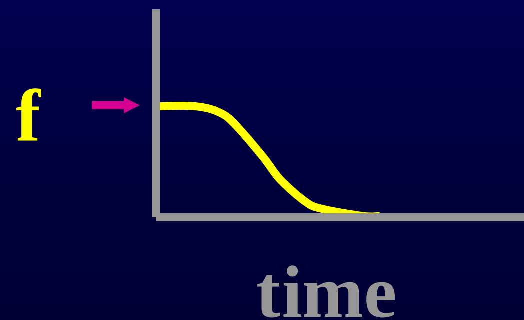
$C_a(t)$

Tissue enhancement :

$C_{tis}(t) = f \int C_a(\tau)\, RF(t-\tau)\, d\tau$



Deconvolution :
find f and RF(t)



HBWL

Conclusion

Measure the tissue conc → **Measure the input conc i.e. input function**

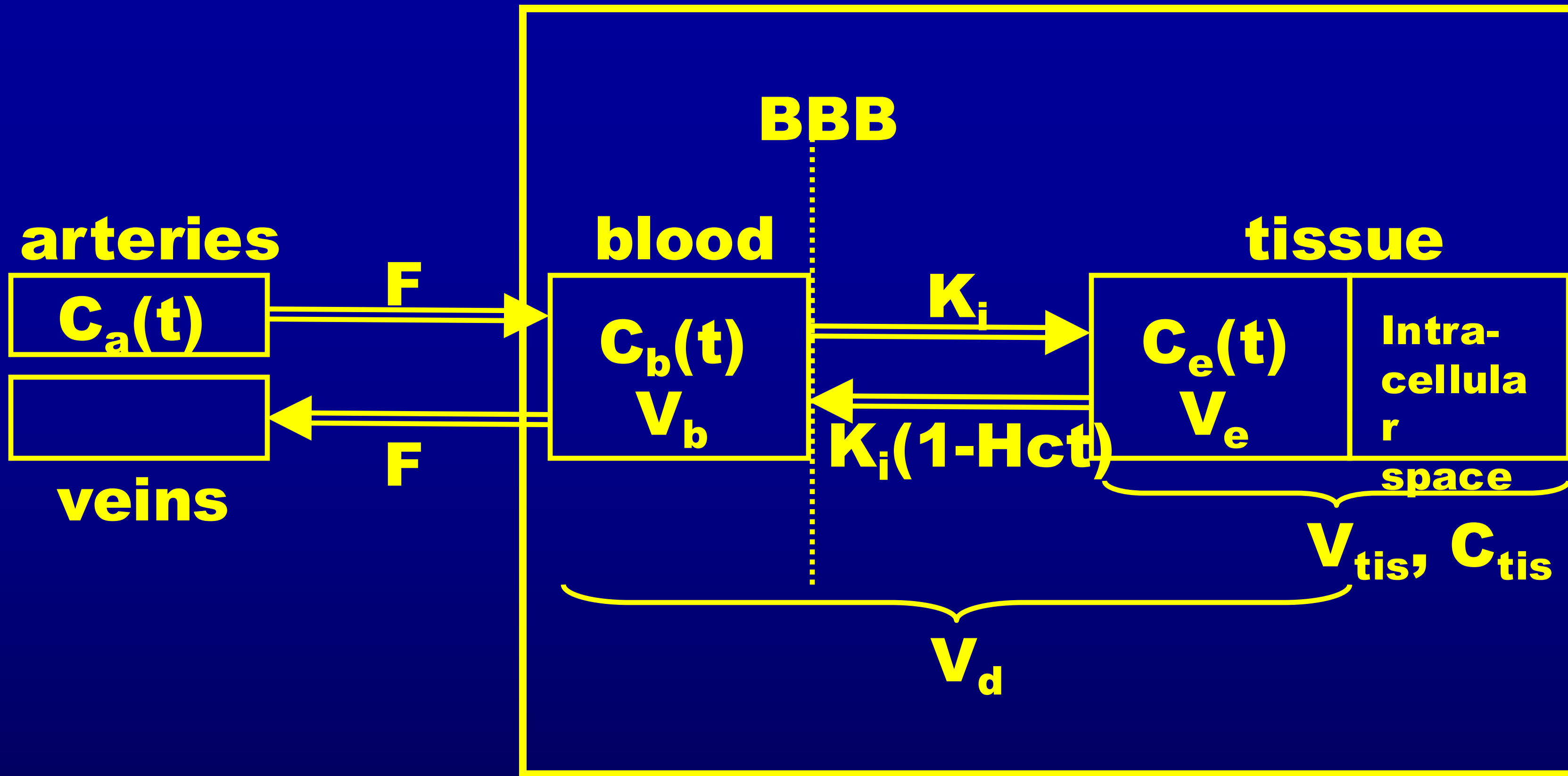
Bolus input : $C_{tis}(t) = f\, C_a(0)\, \Delta t\, RF(t)$

Estimate f and RF(t)

Vein injection : $C_{tis}(t) = f \int C_a(\tau)\, RF(t-\tau)\, d\tau$

Deconvolution ~ Modelbased

- Use a model e.g.: Monoexponentiel, biexponentiel,
- Optimise the free parameters by least square fit to tissue enhancement curve
- It is robust
- Relative insensitive to noise
- Incorrect if the model is inappropriately chosen



$$V_b \frac{dC_b(t)}{dt} = F\, C_a(t) - (F + K_i)\, C_b(t) + K_i (1 - \text{Hct})\, C_e(t)$$

$$V_e \frac{dC_e(t)}{dt} = K_i\, C_b(t) - K_i (1 - \text{Hct})\, C_e(t)$$

$$V_e C_e = V_{\text{tis}} C_{\text{tis}}$$

$$\alpha = \frac{F + K_i}{V_b}$$

$$\beta = \frac{V_{\text{tis}}(1 - \text{Hct}) K_i}{V_b V_e}$$

$$\gamma = \frac{K_i}{V_{\text{tis}}}$$

$$\theta = \frac{K_i (1 - \text{Hct})}{V_e}$$

$$(a,b) = (\frac{1}{2}[\theta + \alpha + \sqrt{\theta^2 + \alpha^2 - 2\theta\alpha + 4\gamma\beta}], \frac{1}{2}[\theta + \alpha - \sqrt{\theta^2 + \alpha^2 - 2\theta\alpha + 4\gamma\beta}])$$

$$C_b(t) = C_a(t) \otimes \frac{F}{V_b} \frac{(a-\theta)e^{-at} - (b-\theta)e^{-bt}}{a-b}$$

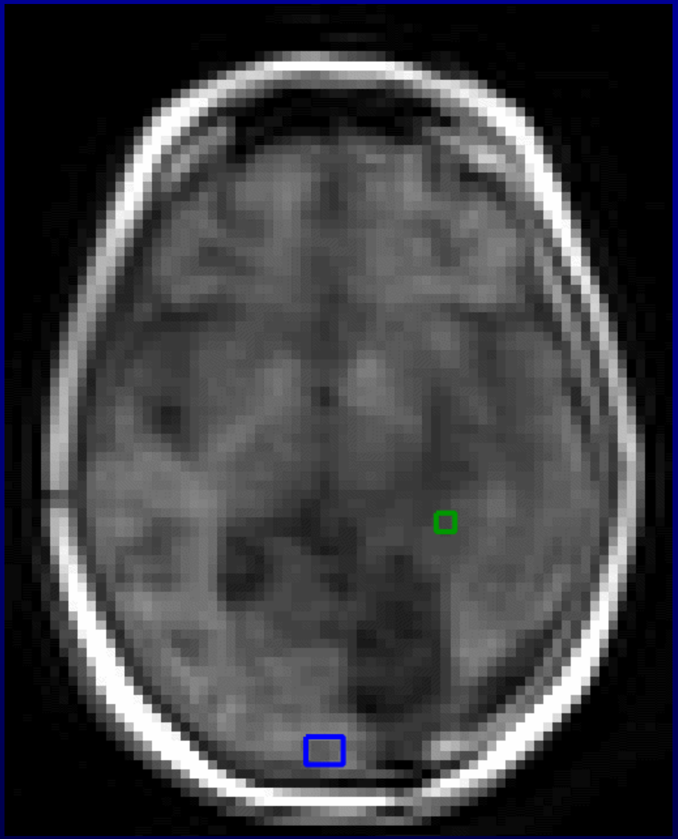
$$C_{\text{tis}}(t) = C_a(t) \otimes \frac{F}{V_b} \frac{K_i}{V_{tis}} \frac{e^{-bt} - e^{-at}}{a-b}$$

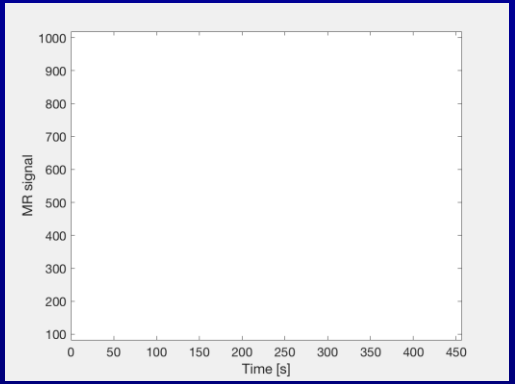
$$C_t(t) = V_b C_b(t) + (1 - V_b) C_{\text{tis}}(t) \Leftrightarrow$$

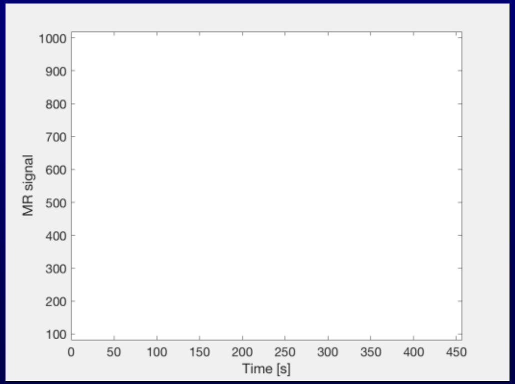
$$C_t(t) = F\ C_a(t) \otimes \left[\frac{(a - \theta - K_i / V_b) e^{-at} + (-b + \theta + K_i / V_b) e^{-bt}}{a-b} \right]$$

HBWL

Dynamic Contrast Enhanced



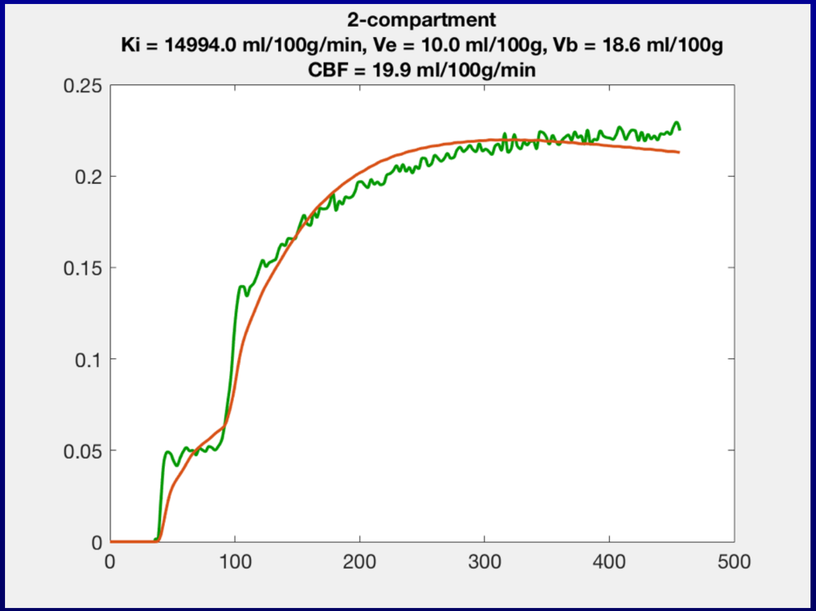




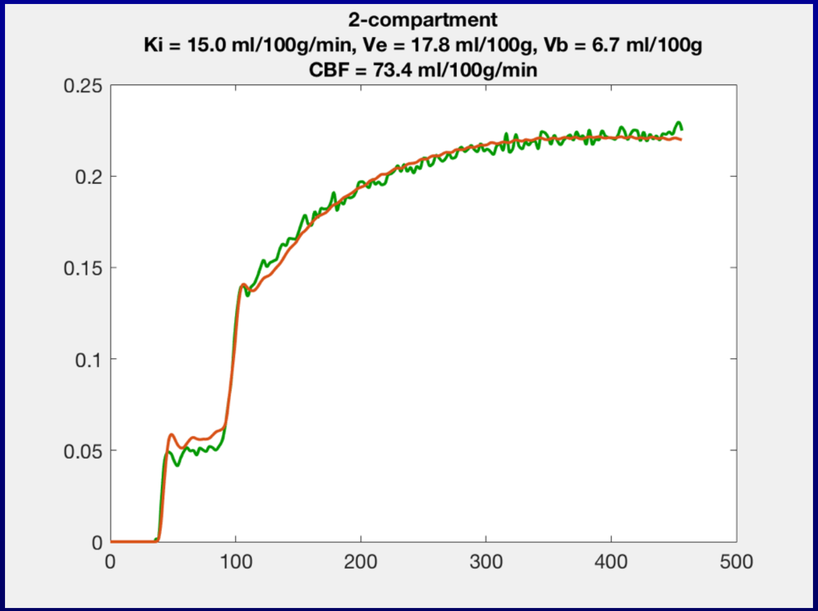
Voxel size: 2.4 x 2.4 x 5 mm
Time resolution: 2.55 sec

Power injector:
3 mL/s or 1 mL/s

No constrain, naïve start guess



Model constrain, model start guess



F: Fixed from Tikhonov (model-free deconvolution)

Ki:

- LB = 10% of initial guess,
- UB
  - 2000% of initial guess (if from Patlak)
  - 120% of initial guess (if from CTH)

Volume: Ve + Vb = Vd +/- 30% (from Tikhonov)

Deconvolution ~ Modelfree

- No model a priory
- Very flexible: many of free parameters
- A projection
- Very sensitive to noise
- Incorrect if not regularized rigoriously
- Fourier transform, SVD, GSVD, Tikhonov, GPD

Convolution written in matrix notation

$$C_t(t) = C_a(t) \otimes f\, RIF(t) = f \int_0^t C_a(\tau) RIF(t-\tau)\, d\tau$$

C_a(t-1) C_a(t-2) ….. C_a(t-(N-1))

$$\begin{bmatrix} C_t(1) \\ C_t(2) \\ C_t(3) \\ \vdots \\ C_t(N) \end{bmatrix} = f\Delta t \begin{bmatrix} C_a(1) & 0 & 0 & \cdots & 0 \\ C_a(2) & C_a(1) & 0 & \cdots & 0 \\ C_a(3) & C_a(2) & C_a(1) & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ C_a(N) & C_a(N-1) & C_a(N-2) & \cdots & C_a(1) \end{bmatrix} \begin{bmatrix} RIF(1) \\ RIF(2) \\ RIF(3) \\ \vdots \\ RIF(N) \end{bmatrix}$$

Convolution written in matrix notation

Solution **Successive solving the matrix eq.**

Minimization

$$\min\{\|C_a RIF - C_t\|_2^2\}$$

Minimization and regularization

$$\min\{\|C_a RIF - C_t\|_2^2 + \lambda^2 \|RIF\|_2^2\}$$

$$\min\{\|C_a RIF - C_t\|_2^2 + \lambda^2 \|L\ RIF\|_2^2\}$$

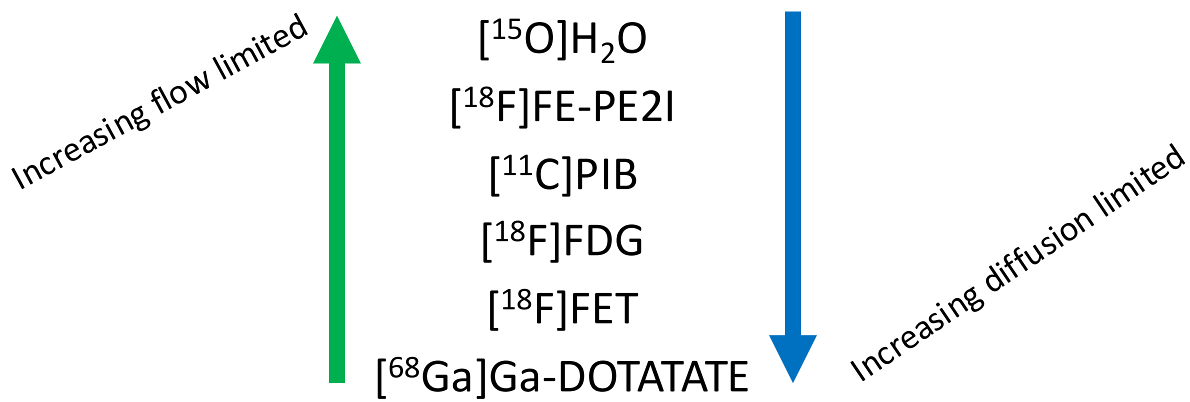
$$L = \begin{pmatrix} -1 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & -1 & 1 \end{pmatrix}$$

HBWL

Question

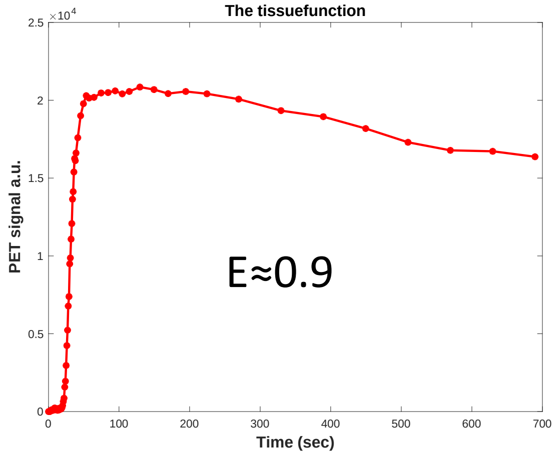
Can we estimate perfusion from any type of PET tracers

This should work irrespectively tracer type flow or diffusion limited

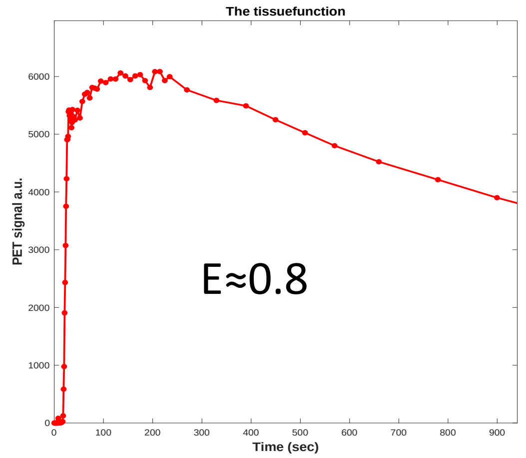


Time resolution : 1 sec

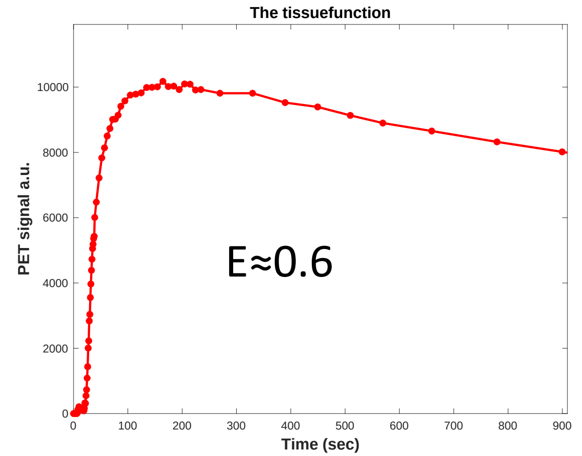
$[^{15}O]H_2O$



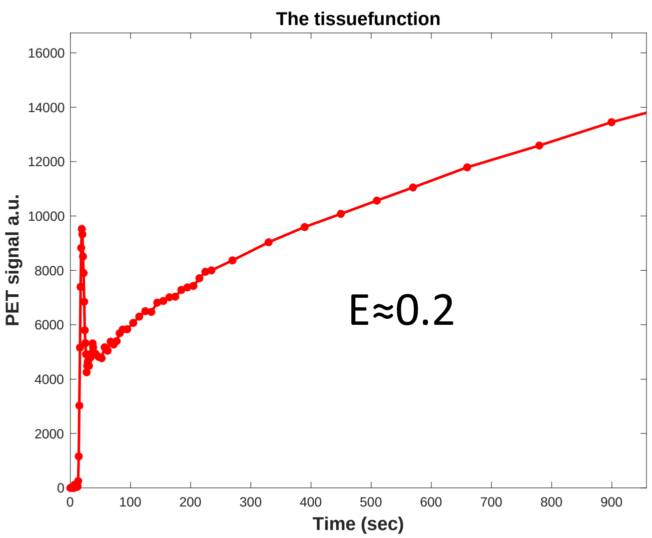
$[^{18}F]$FE-PE2I



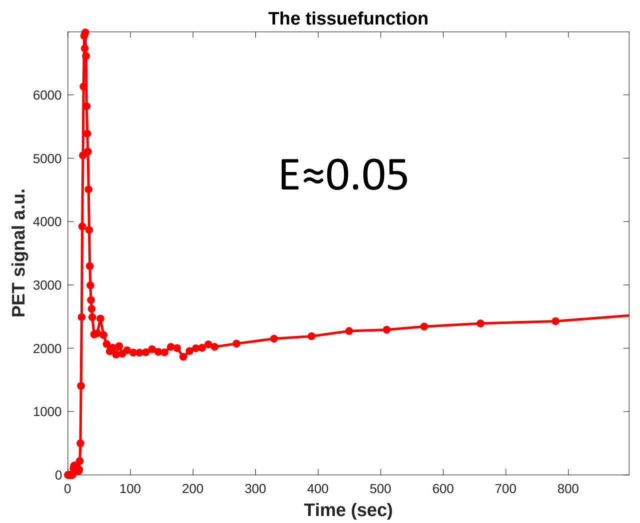
$[^{11}C]$PIB



$[^{18}F]$FDG



$[^{18}F]$FET



What about time resolution ??

This should work irrespectively tracer type flow or diffusion limited if time resolution is high enough

Increasing flow limited

[^{15}O]H_2O
[^{18}F]FE-PE2I
[^{11}C]PIB
[^{18}F]FDG
[^{18}F]FET
[^{68}Ga]Ga-DOTATATE

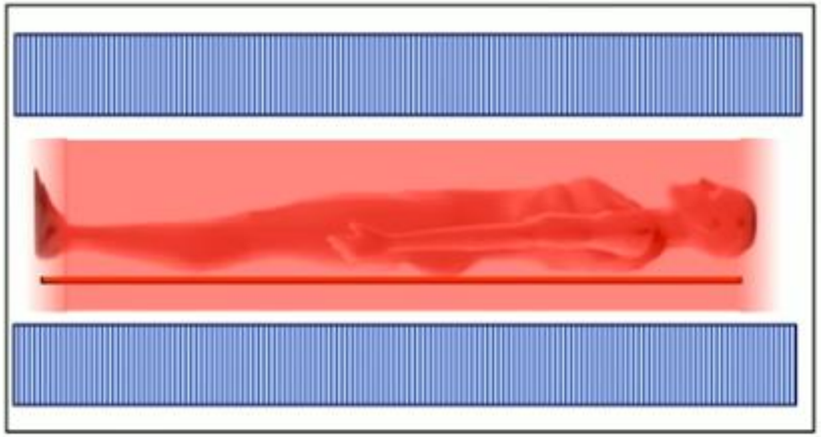
Increasing diffusion limited

Method

- Siemens Quadra PET/CT scanner
- Reconstruction TrueX PSF 2-3mm Gauss – 1.65x1.65mm^2
  - 1.6-3 mm slice thickness
- Framing: 40 x 1 s – 10 x 2 s – 10 x 5 s … up to 60 min
- Correction for metabolite
- Image derived input function – acquired in descending aorta.
- Standard Injected Activity
- Correction for regional arterial transit time delay between aorta and brain

Long Axial Field of View PET/CT Scanner

- 40x gain in effective sensitivity for total-body imaging!
- 4-5x gain in sensitivity for single organ imaging
- Total-body kinetics
  - All tissues/organs simultaneously
  - Better temporal resolution



CBF

Residue impuls response

V_d or late images

Extraction fraction

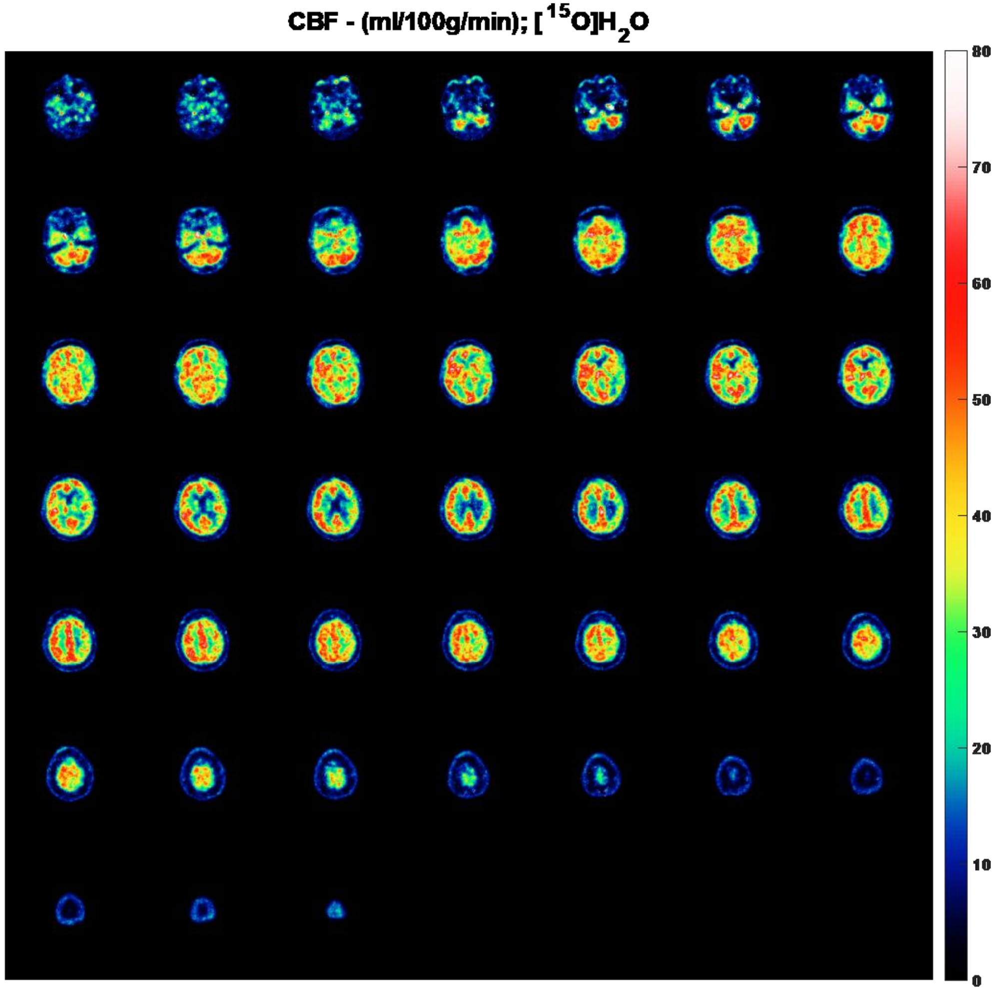
Mean transit time

Arterial transit time delay

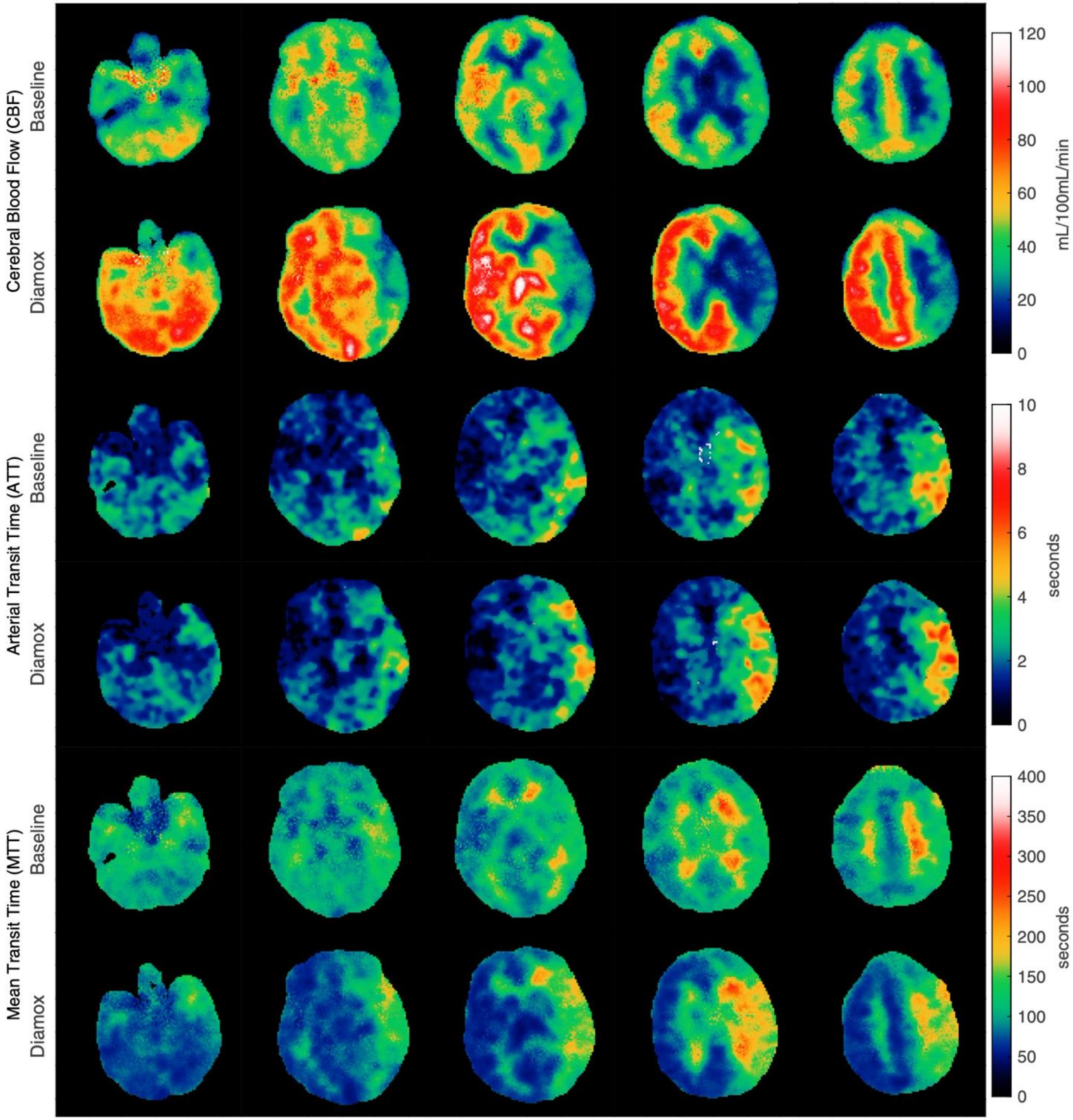
SUV - 0-40 seconds $[^{15}O]H_2O$

- [^{15}O]H_2O
- [^{18}F]FE-PE2I
- [^{11}C]PIB
- [^{18}F]FDG
- [^{18}F]FET
- [^{68}Ga]Ga-DOTATATE

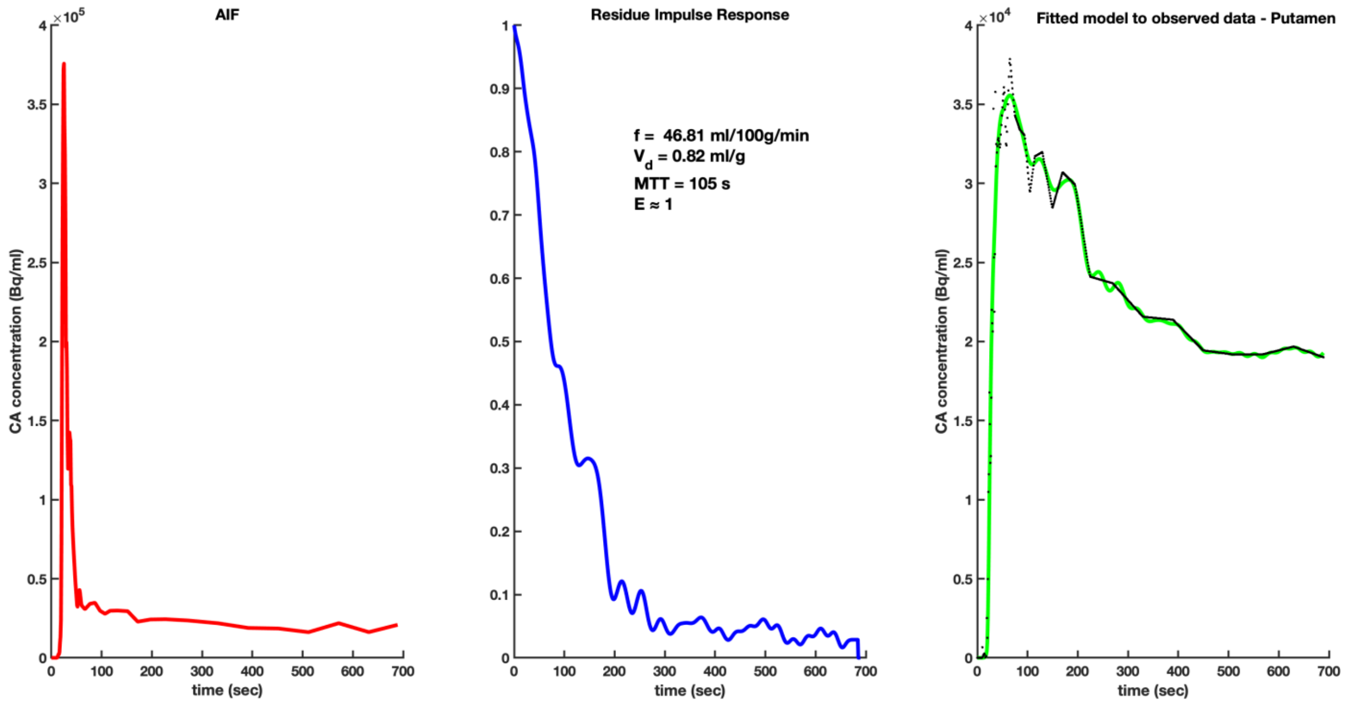
Increasing diffusion limited

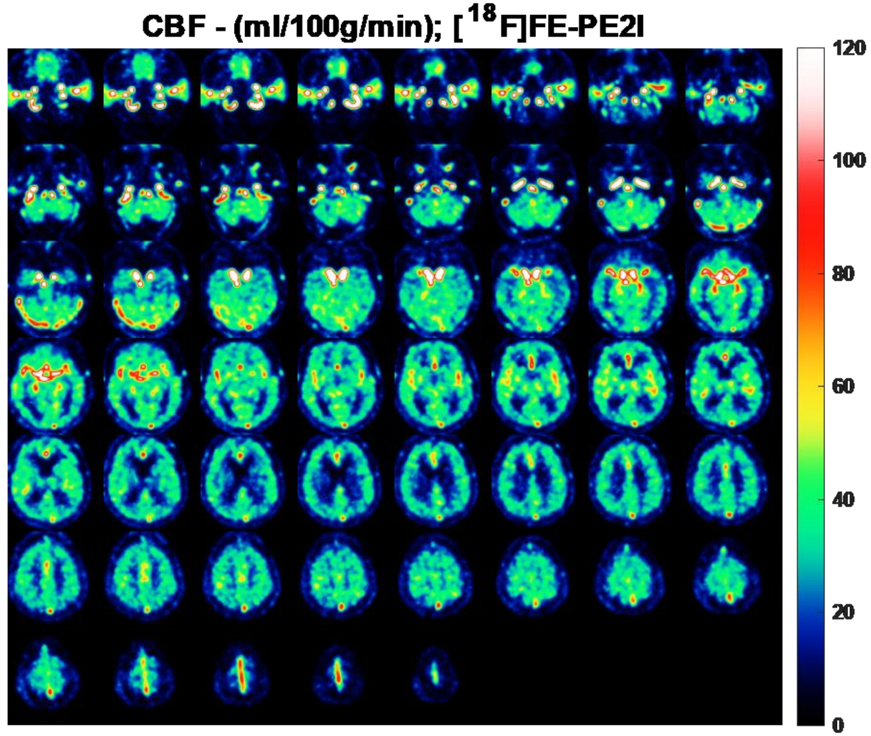


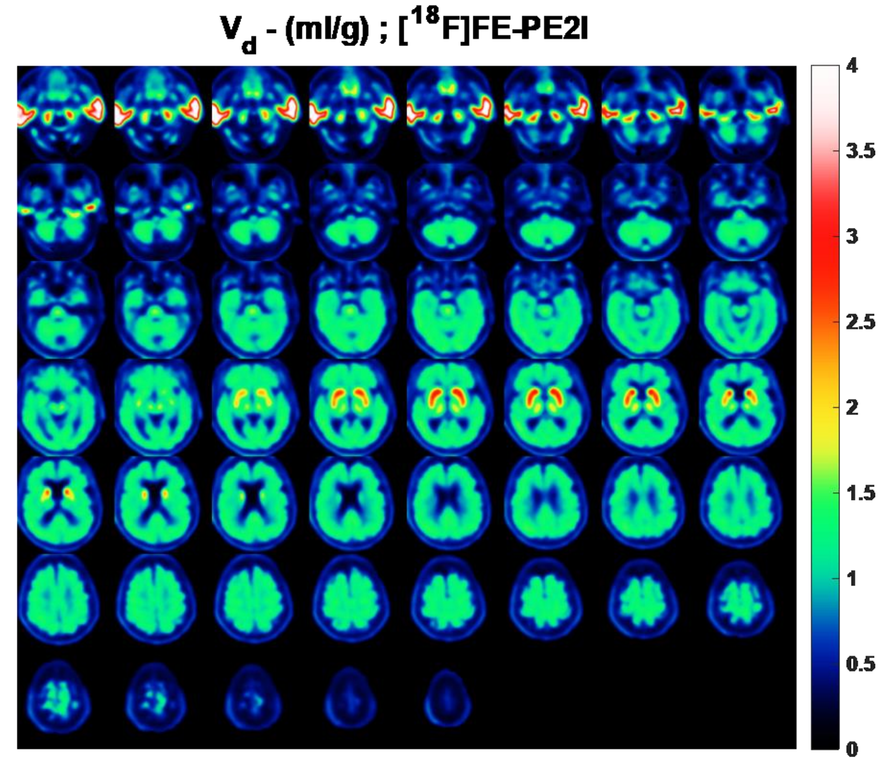
Patient:
Left ICA stenosis


Cerebral Blood Flow (CBF)
Baseline
Diamox
Arterial Transit Time (ATT)
Baseline
Diamox
Mean Transit Time (MTT)
Baseline
Diamox
120
100
80
60
40
20
0
mL/100mL/min
10
8
6
4
2
0
seconds
400
350
300
250
200
150
100
50
0
seconds

Dynamic [^{15}O]H_2O Quadra-PET scan



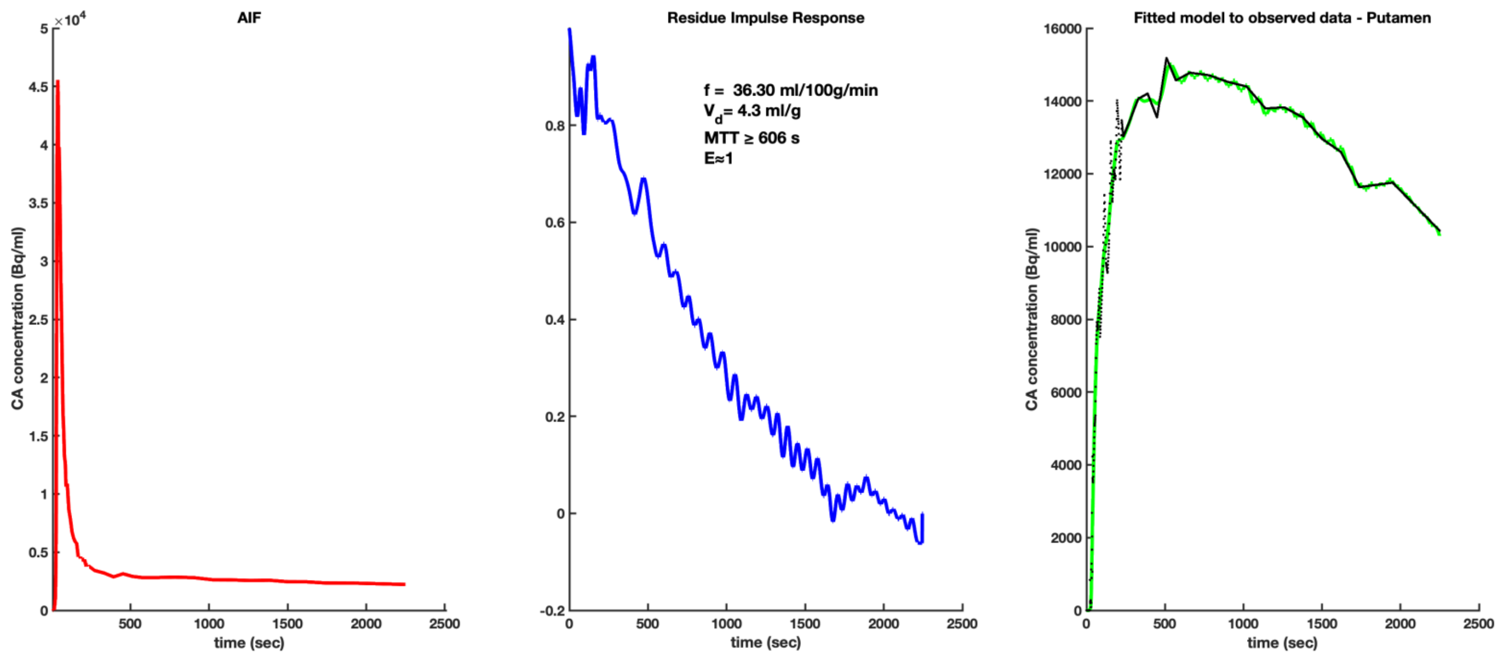


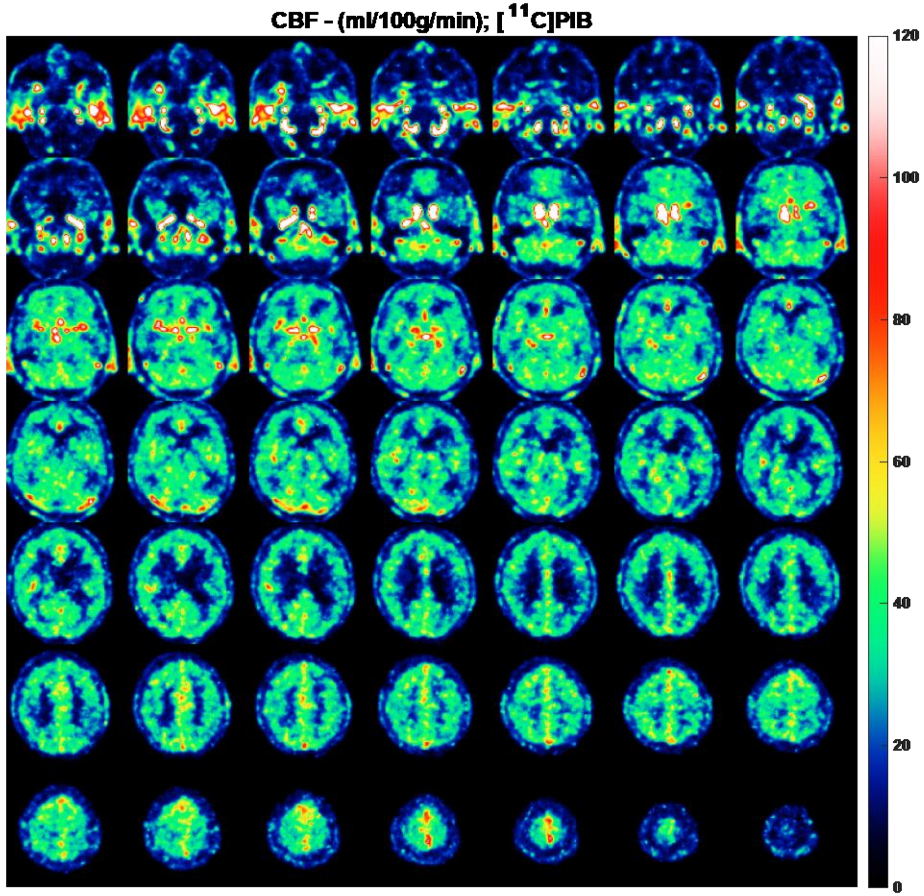


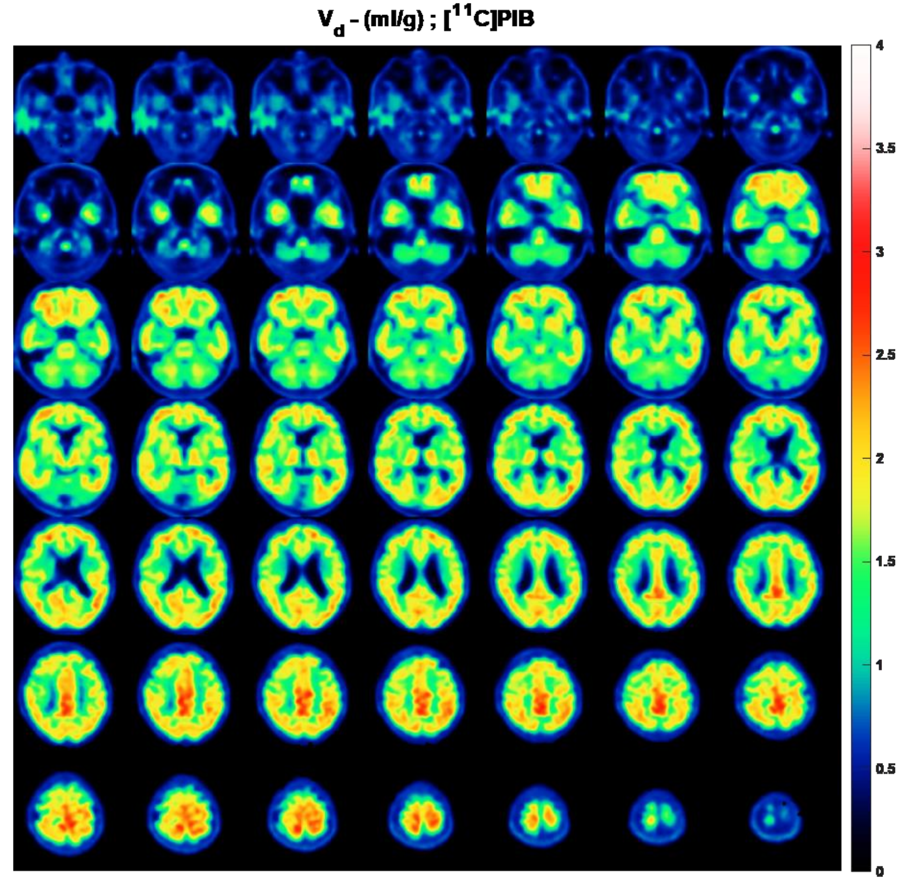
- [^{15}O]H_2O
- [^{18}F]FE-PE2I
- [^{11}C]PIB
- [^{18}F]FDG
- [^{18}F]FET
- [^{68}Ga]Ga-DOTATATE

Increasing diffusion limited

Dynamic [^{18}F]FE-PE2I Quadra-PET scan



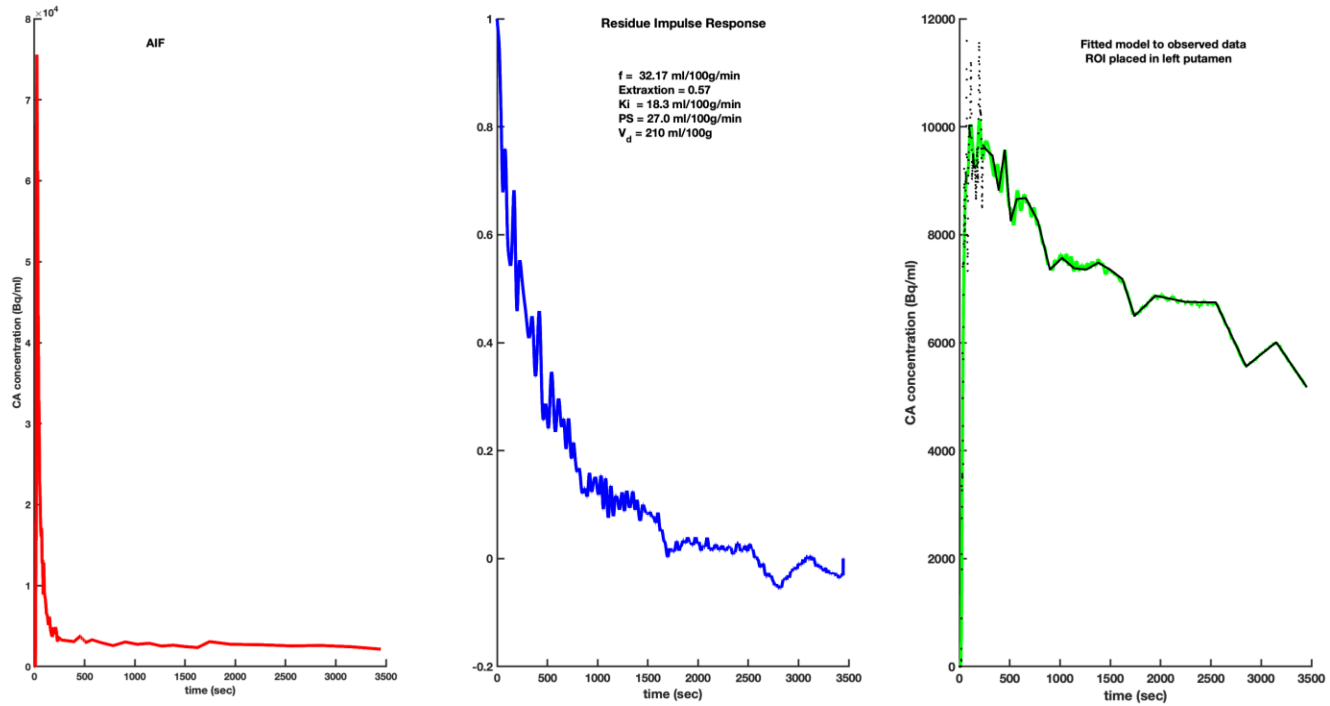


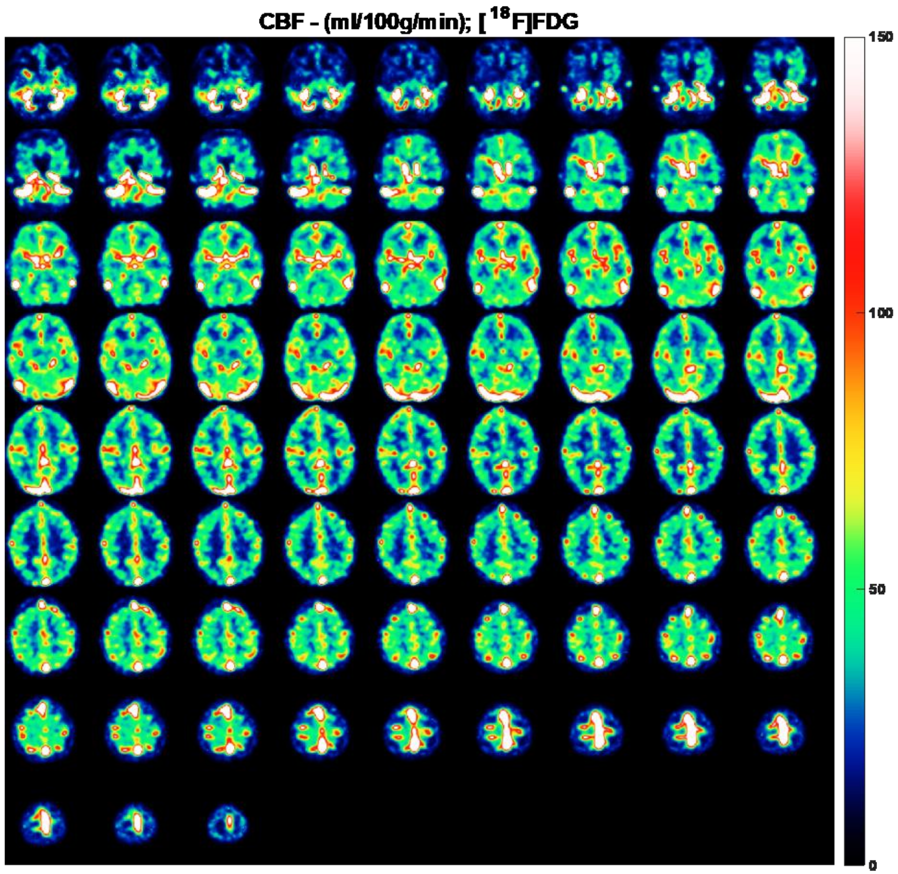


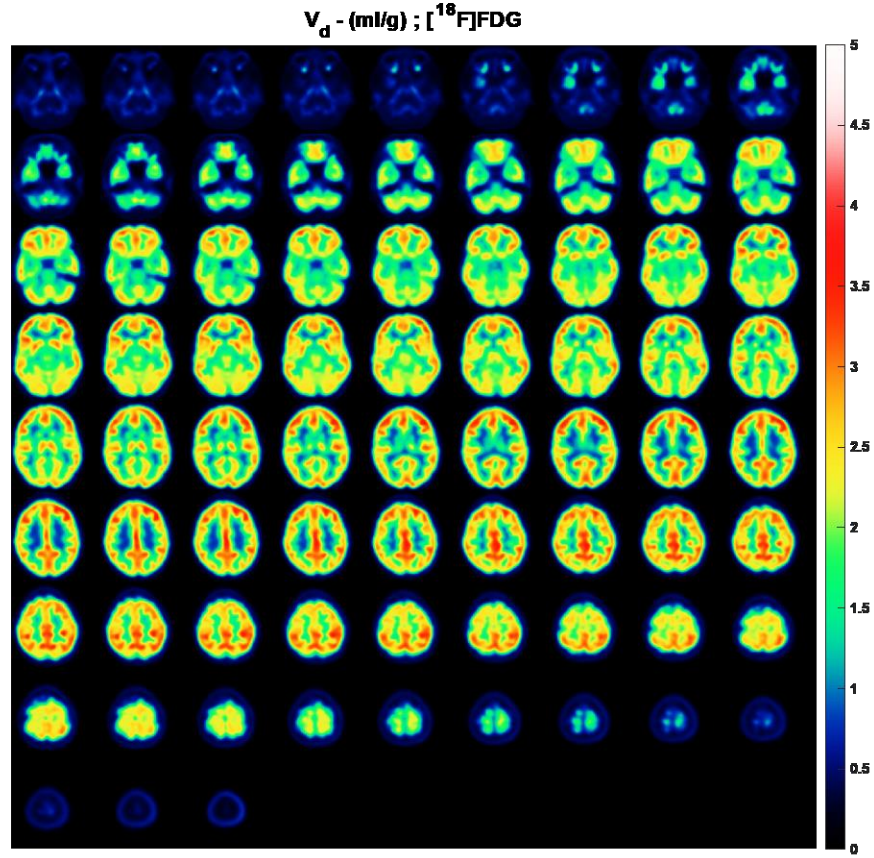
Increasing diffusion limited

- [^{15}O]H_2O
- [^{18}F]FE-PE2I
- [^{11}C]PIB
- [^{18}F]FDG
- [^{18}F]FET
- [^{68}Ga]Ga-DOTATATE

Dynamic [^{11}C]PIB Quadra-PET scan



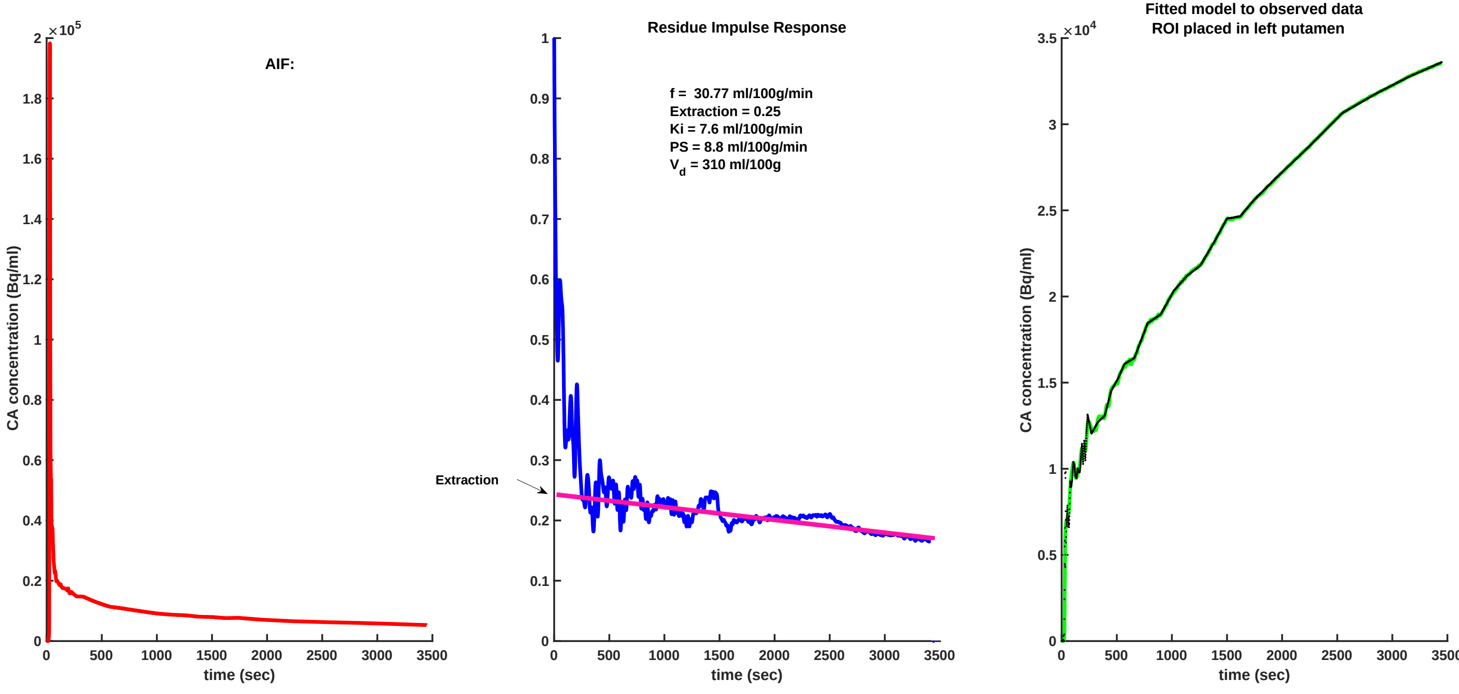




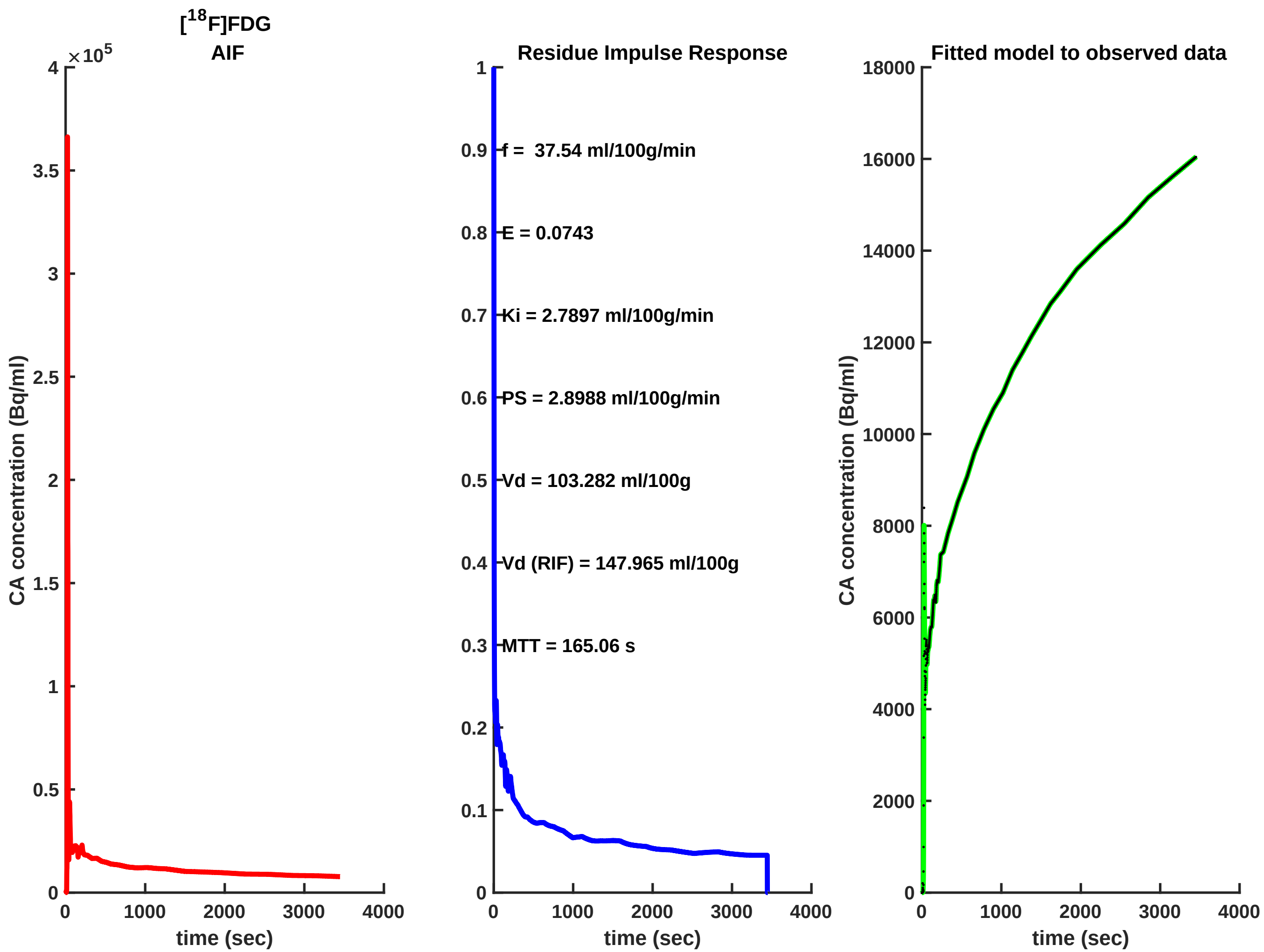
Increasing diffusion limited

- [^{15}O]H_2O
- [^{18}F]FE-PE2I
- [^{11}C]PIB
- [^{18}F]FDG
- [^{18}F]FET
- [^{68}Ga]Ga-DOTATATE

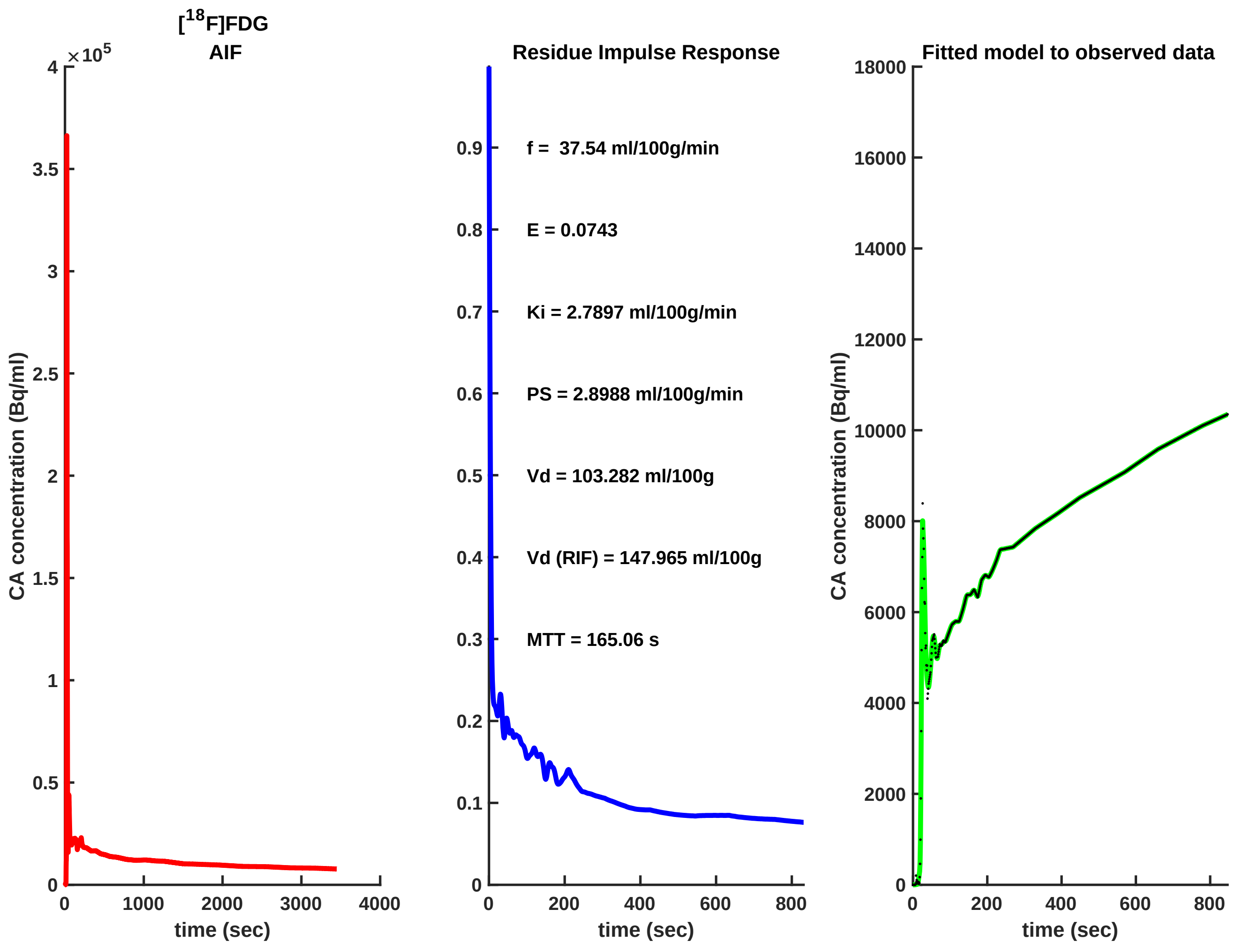
Dynamic [^{18}F]FDG Quadra-PET scan

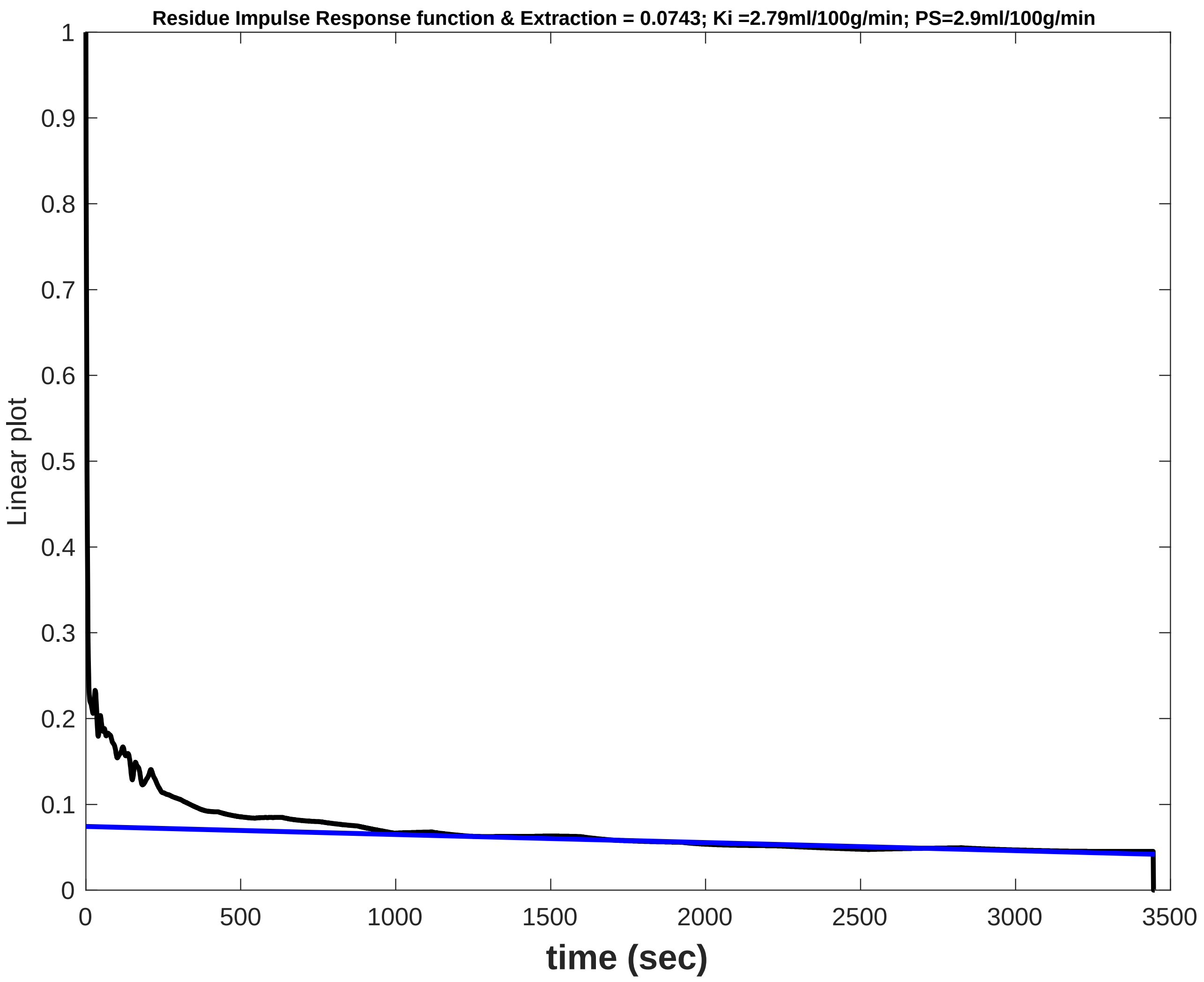


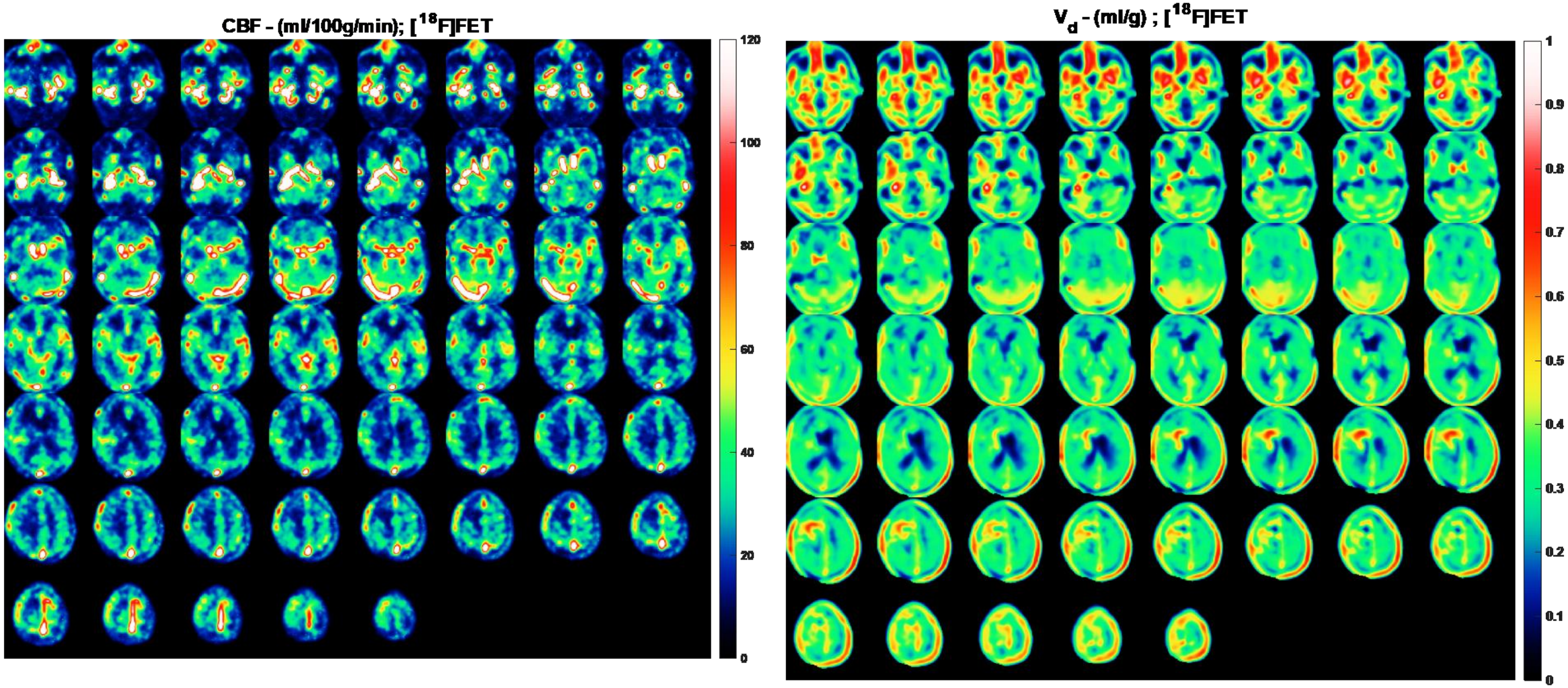
Large ROI – one slice

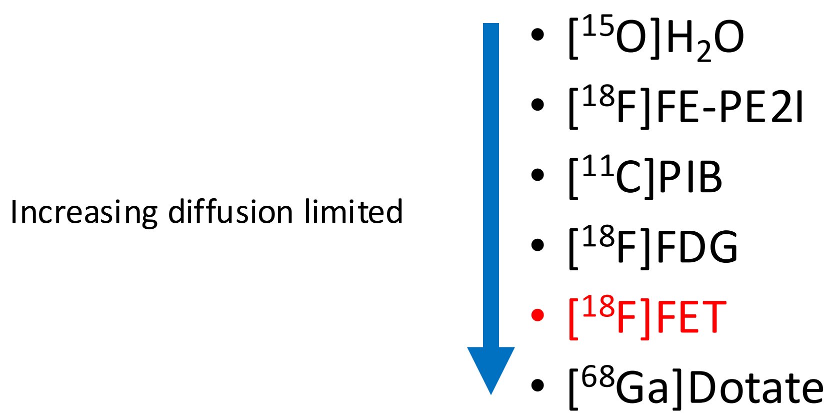


Large ROI – one slice

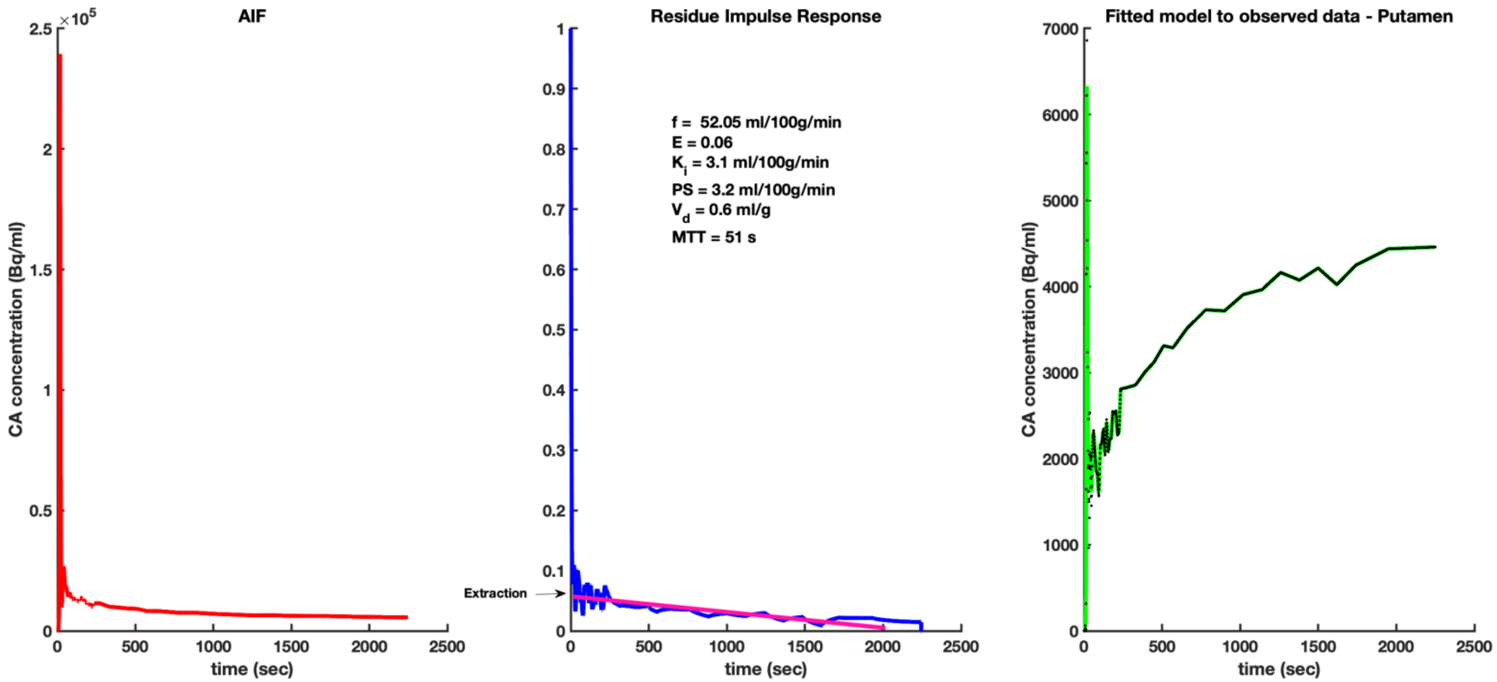



Residue Impulse Response function & Extraction = 0.0743; Ki =2.79ml/100g/min; PS=2.9ml/100g/min
Linear plot
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
500
1000
1500
2000
2500
3000
3500
time (sec)

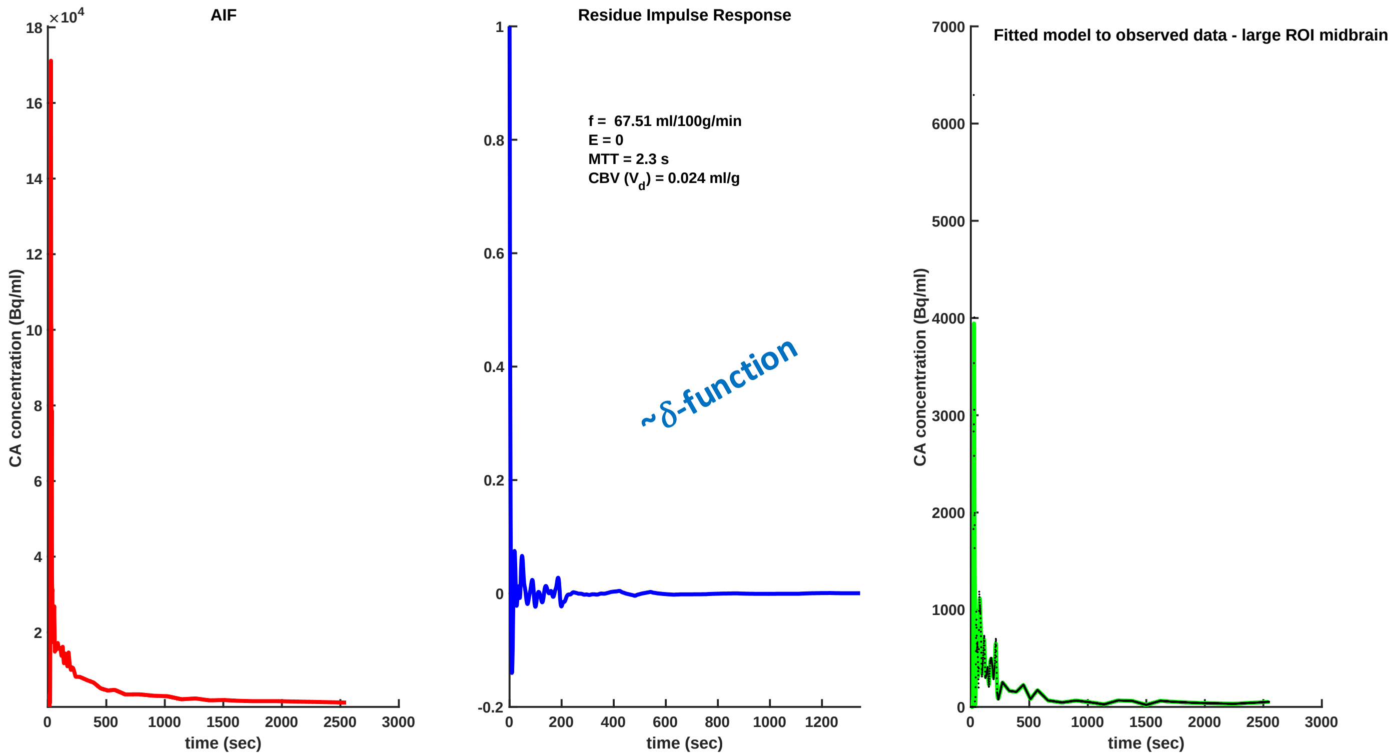

CBF - (ml/100g/min); [18F]FET
V_d - (ml/g) ; [18F]FET


Increasing diffusion limited
[15O]H_2O
[18F]FE-PE2I
[11C]PIB
[18F]FDG
[18F]FET
[68Ga]Dotate

Dynamic [^{18}F]FET Quadra-PET scan



Dynamic [^{68}Ga]Ga-DOTATATE Quadra-PET scan



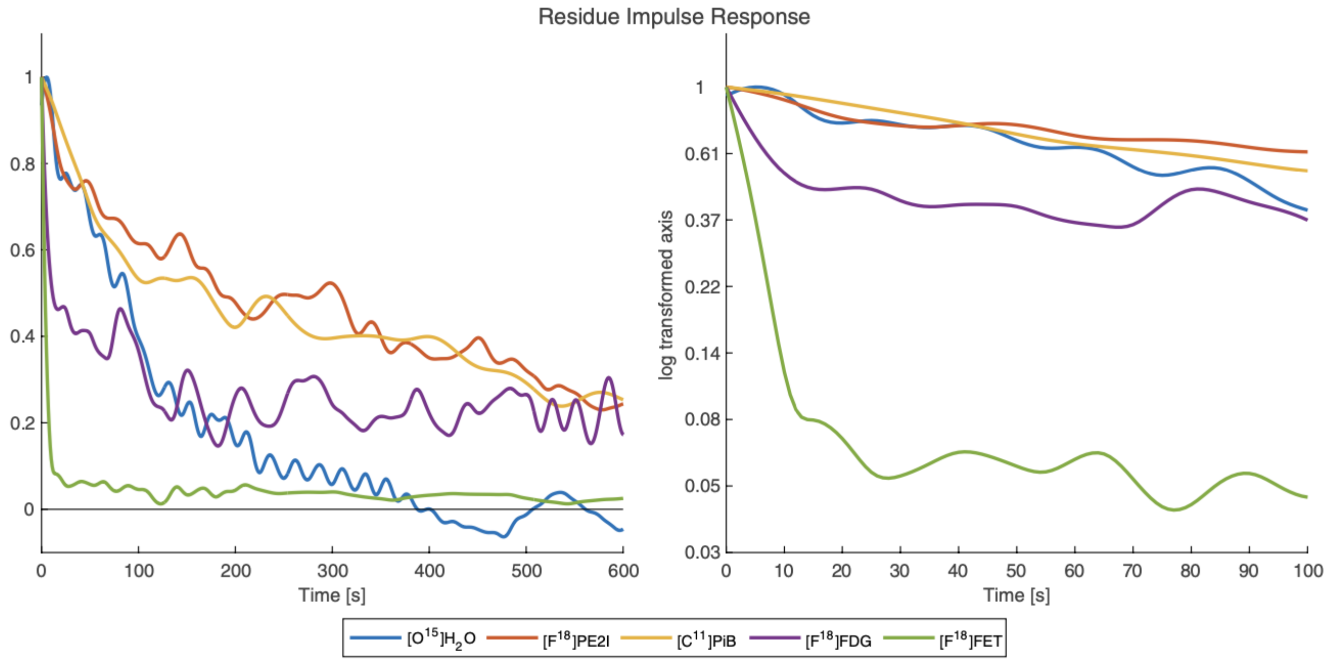


Fig. 2 The residue impulse response functions from Fig. 1 depicted on a smaller time scale for better comparison. Both linear and semilogarithmic plots are shown. The configurations of each tracer correspond to the expected behaviour of the tracers

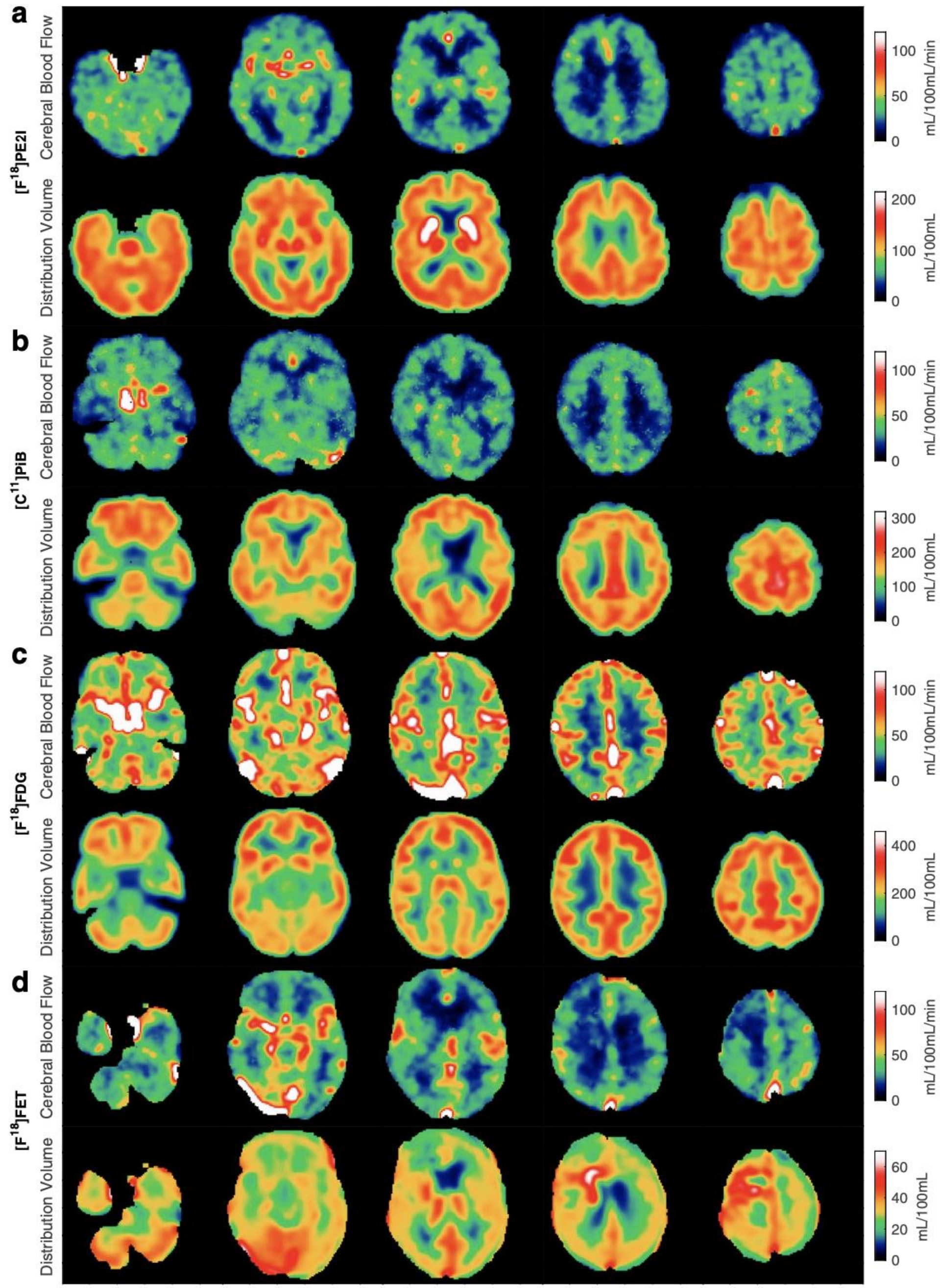


Fig. 4 Each row shows the perfusion maps and volume of distribution maps for **a** [^{11}C]PIB, **b** [^{18}F]FE-PE2I, **c** 2-[^{18}F]FDG and **d** [^{18}F]FET for four different patients. Patient (a) had Alzheimer's disease and pronounced beta-amyloid accumulation, and the CBF maps show typical parieto-temporal perfusion reduction (left-sided). Patient (b) was eventually diagnosed with major depression, and the CBF and volume of distribution maps were normal. Patient (c) had lung cancer with metastasis, but PET/CT of the brain did not disclose CNS involvement. Patient (d) had previously undergone surgery for brain cancer (glioblastoma), and the CBF maps show CBF reduction/no perfusion corresponding to the resection cavity, and the volume of distribution map shows abnormal frontal subcortical FET uptake, suggesting tumour recurrence. All images are shown in native orientation to avoid interpolation artefacts

Table 3 Tikhonov method

Radiopharmaceutical	Number of subjects/ROIs	Mean CBF ± SD (mL/min/100 mL)	Mean E ± SD	Mean K_1 ± SD (mL/min/100 mL)	Mean v_d ± SD (mL/100 mL)
[^{15}O]H_2O rest	5/5	69 ± 19	0.94 ± 0.06	-	90 ± 5.6
[^{15}O]H_2O acetazolamide	5/5	115 ± 31	0.96 ± 0.04	-	92 ± 6.9
[^{18}F]FE-PE2I	5/5	58 ± 15	0.78 ± 0.08	45 ± 16	383 ± 98
[^{11}C]PiB	5/5	50 ± 7	0.62 ± 0.08	31 ± 8	288 ± 90
[^{18}F]FDG	5/5	37 ± 13	0.19 ± 0.05	5.5 ± 1.2	-
[^{18}F]FET	5/5	53 ± 16	0.032 ± 0.008	1.7 ± 0.2	48 ± 9

CBF cerebral blood flow, *E* extraction fraction, K_1 unidirectional influx constant, v_d volume of distribution

Table 4 Conventional compartment model

Radiopharmaceutical	Number of subjects/ROIs	Mean K_1 ± SD (mL/min/100 mL)	Mean k_2 ± SD (1/min)	Mean k_3 ± SD (1/min)	Mean V_a ± SD (mL/100 mL)
[^{15}O]H_2O rest	5/5	72.6 ± 18.3	0.76 ± 0.17	-	0.88 ± 0.62
[^{15}O]H_2O acetazolamide	5/5	115.7 ± 30.2	1.21 ± 0.27	-	2.07 ± 1.16
[^{18}F]FE-PE2I	5/5	47.6 ± 12.3	0.12 ± 0.03	< 0.0004	3.26 ± 2.02
[^{11}C]PiB	5/5	41.1 ± 4.6	0.16 ± 0.05	0.003 ± 0.004	4.3 ± 0.82
[^{18}F]FDG	5/5	12.8 ± 1.2	0.13 ± 0.03	0.051 ± 0.008	1.93 ± 1.79
[^{18}F]FET	5/5	2.9 ± 0.7	0.082 ± 0.02	0.027 ± 0.010	2.94 ± 0.55

K_1 is the unidirectional influx rate constant over the blood–brain barrier, k_2 is a rate constant related to back diffusion of tracer from the reversible compartment to blood, k_3 is a rate constant related to the irreversible binding of tracer in tissue, V_a is the blood volume in tissue

Conclusion

Perfusion can be estimated for (nearly) all types of tracers - high time resolution

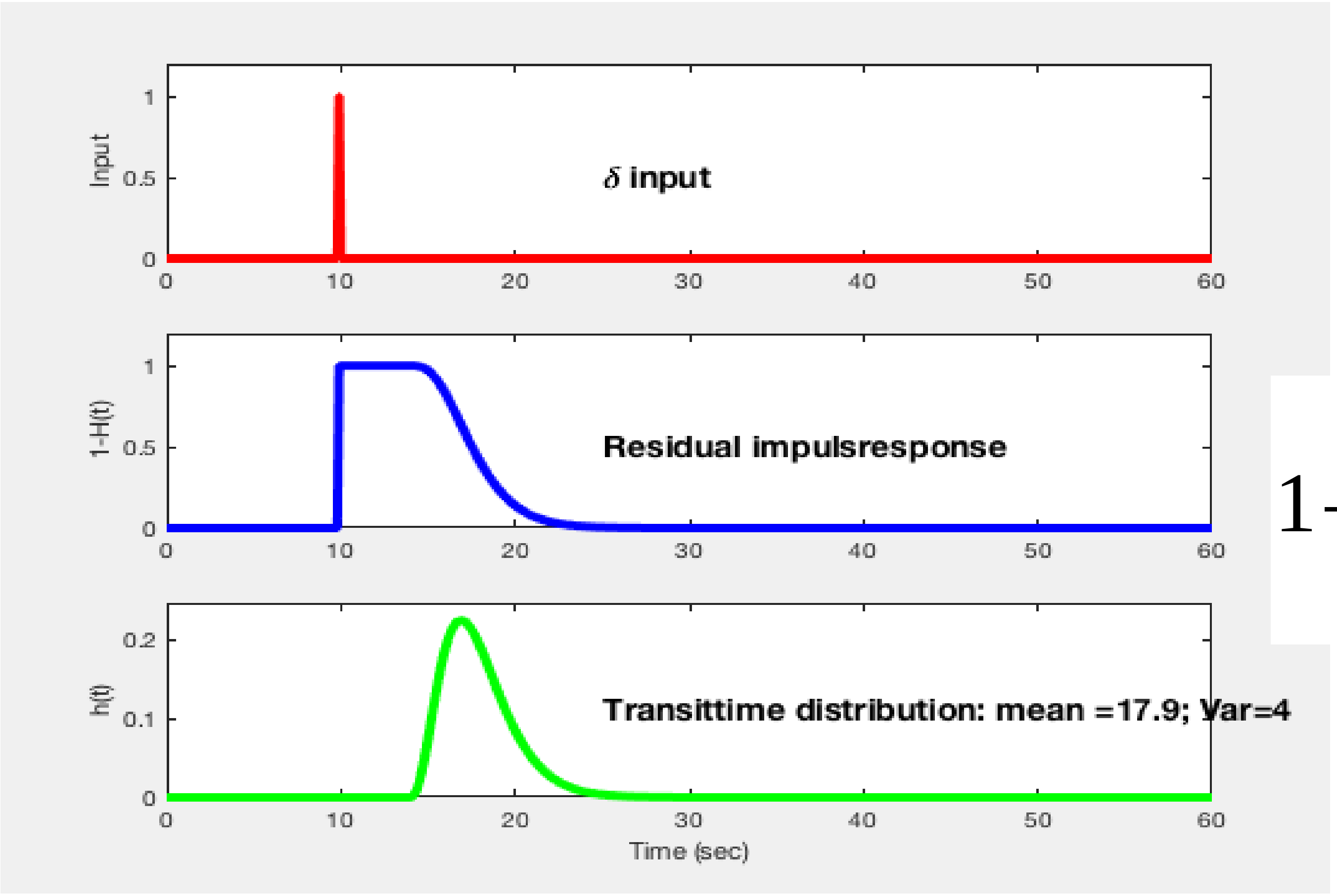
Residue impulse response function can be estimated-

giving K_i and E

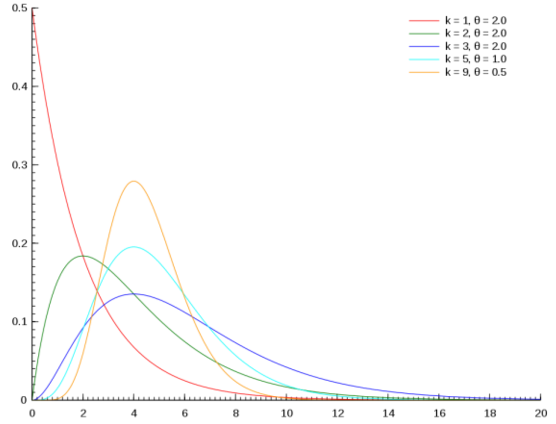
Yes we can !!!!

HBWL

CTH modeling using gamma distribution

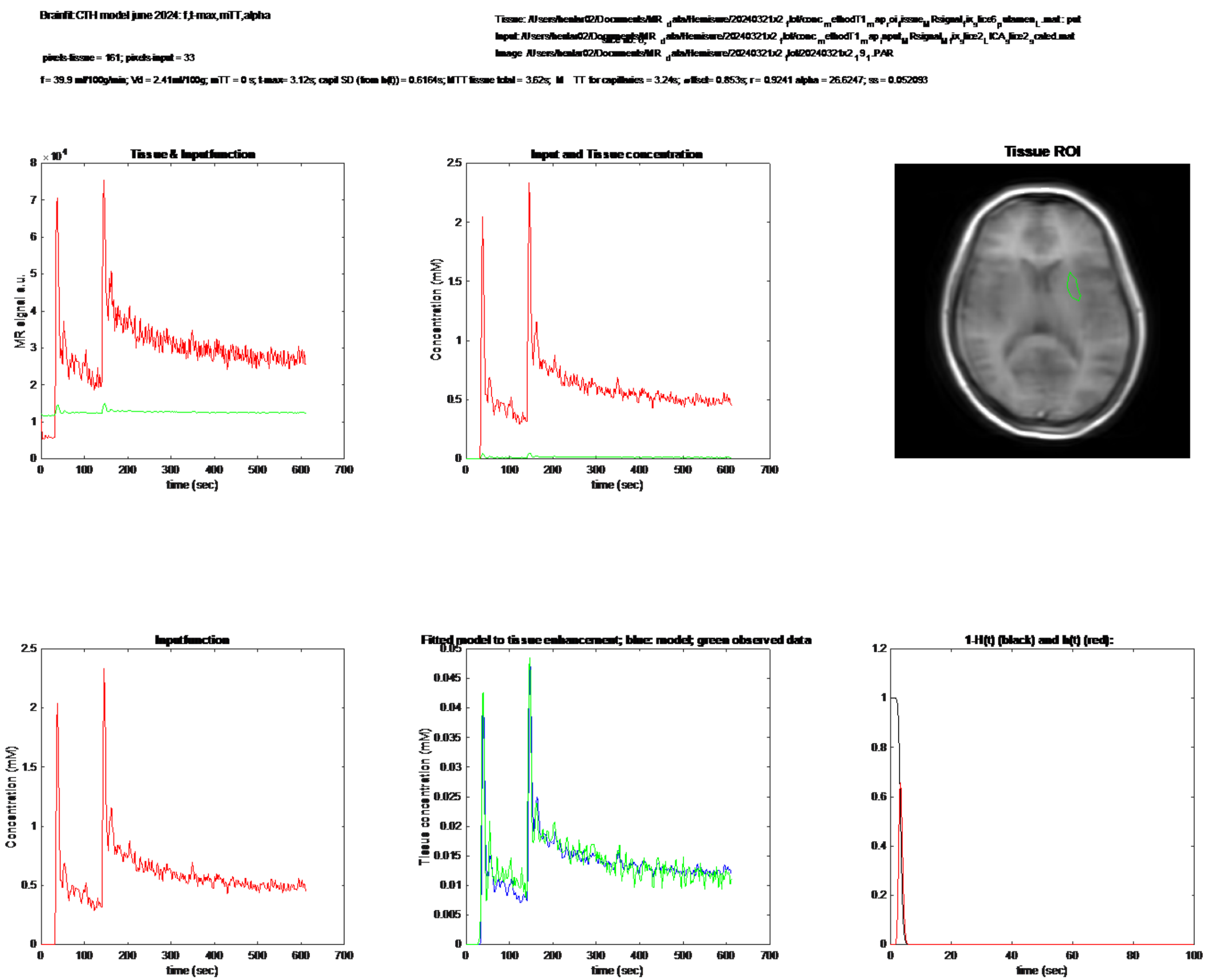


$$1-H(t)=1-\int_0^t h(\tau)d\tau$$

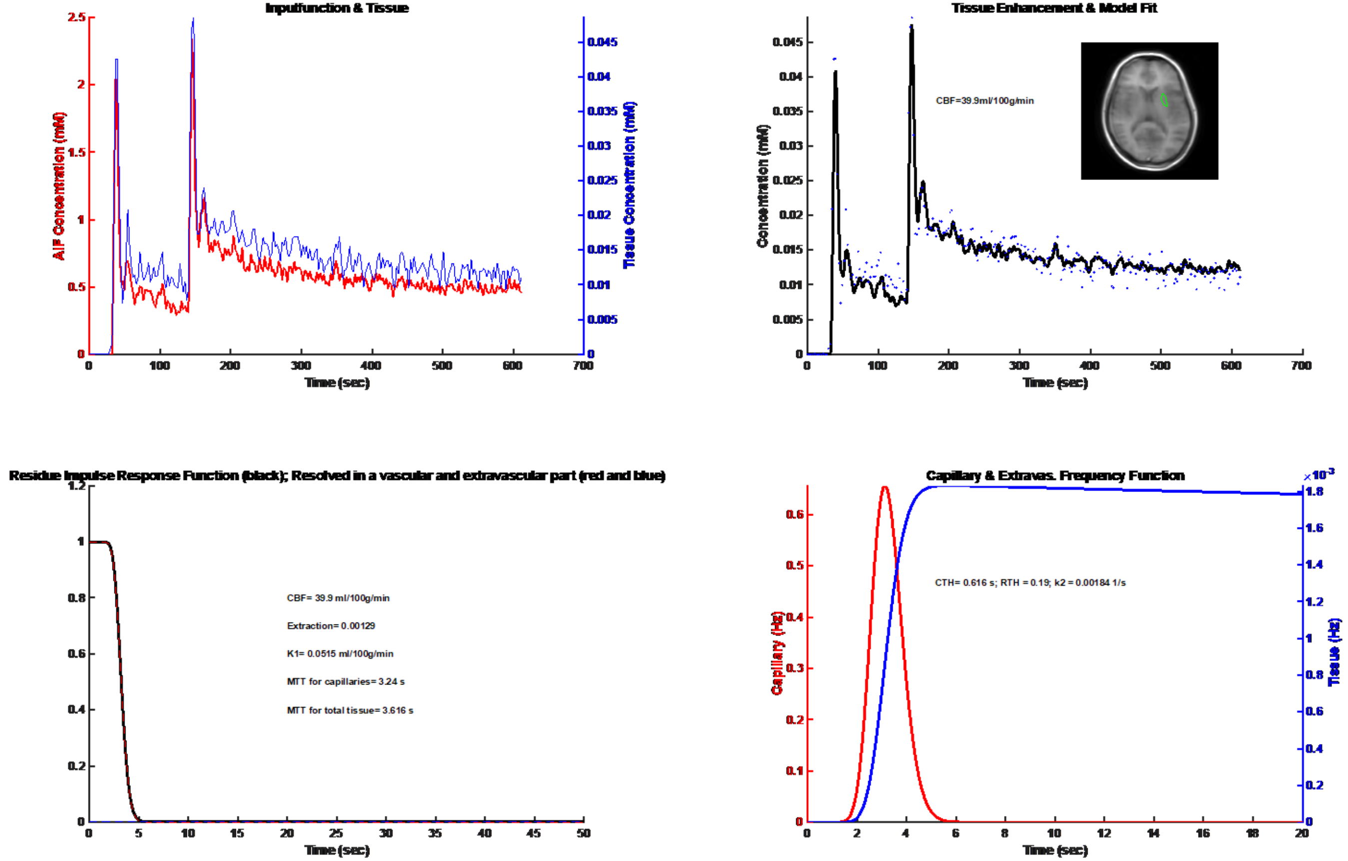


$$f(x;\alpha,\beta)=\frac{x^{\alpha-1}e^{-\beta x}\beta^{\alpha}}{\Gamma(\alpha)} \quad \text{for } x>0 \quad \alpha,\beta>0.$$

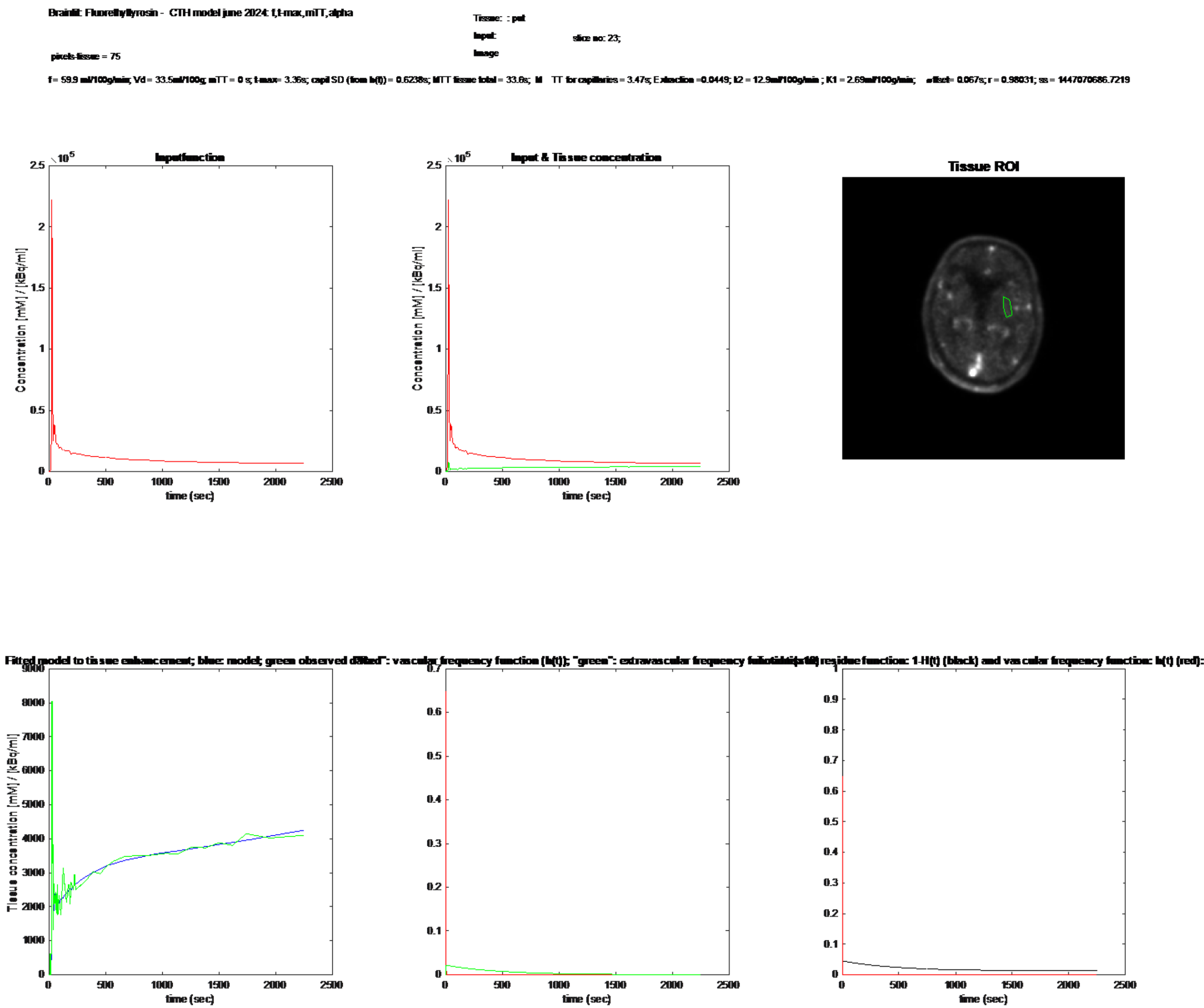
MRI using MR contrast agent



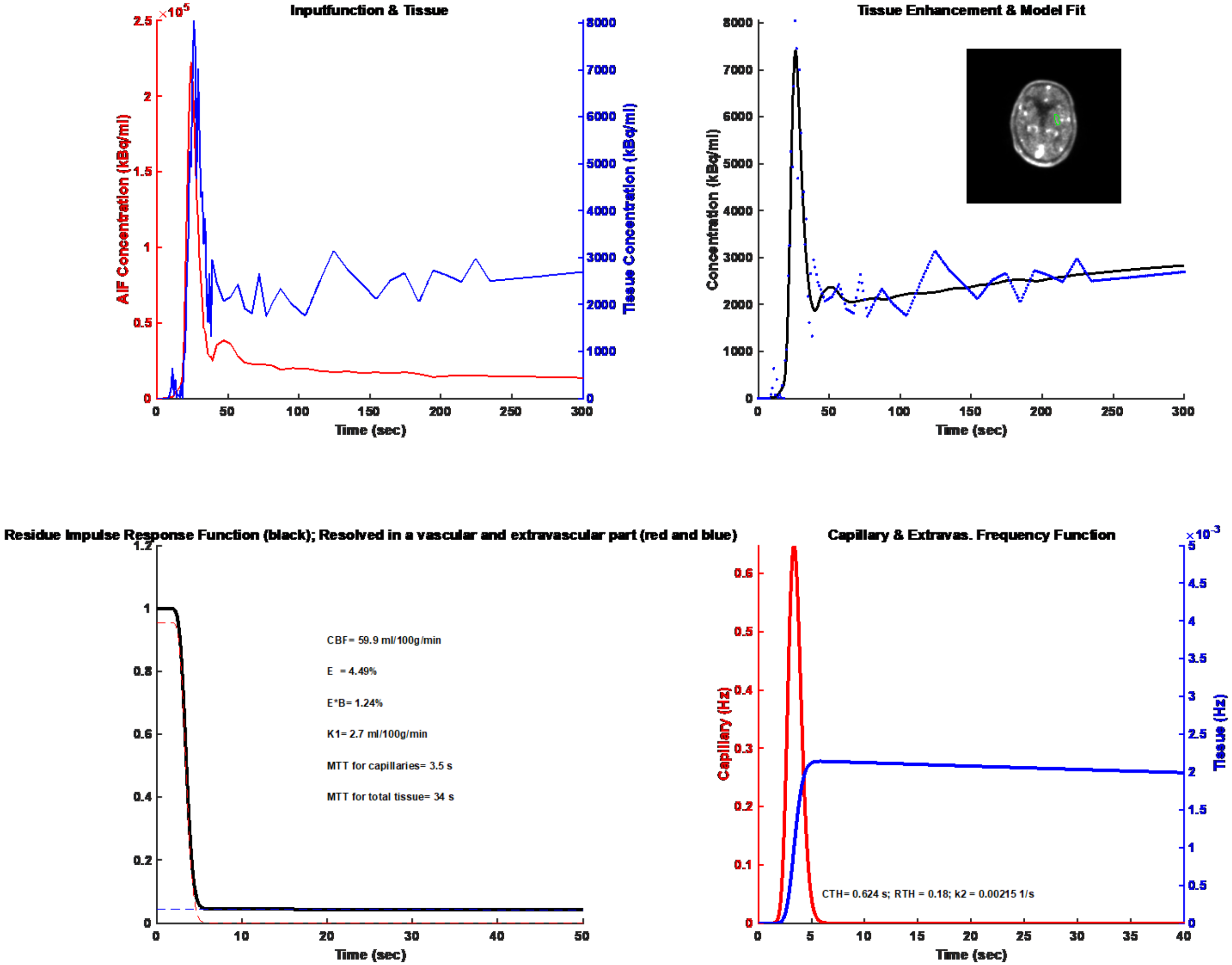
MRI using MR contrast agent



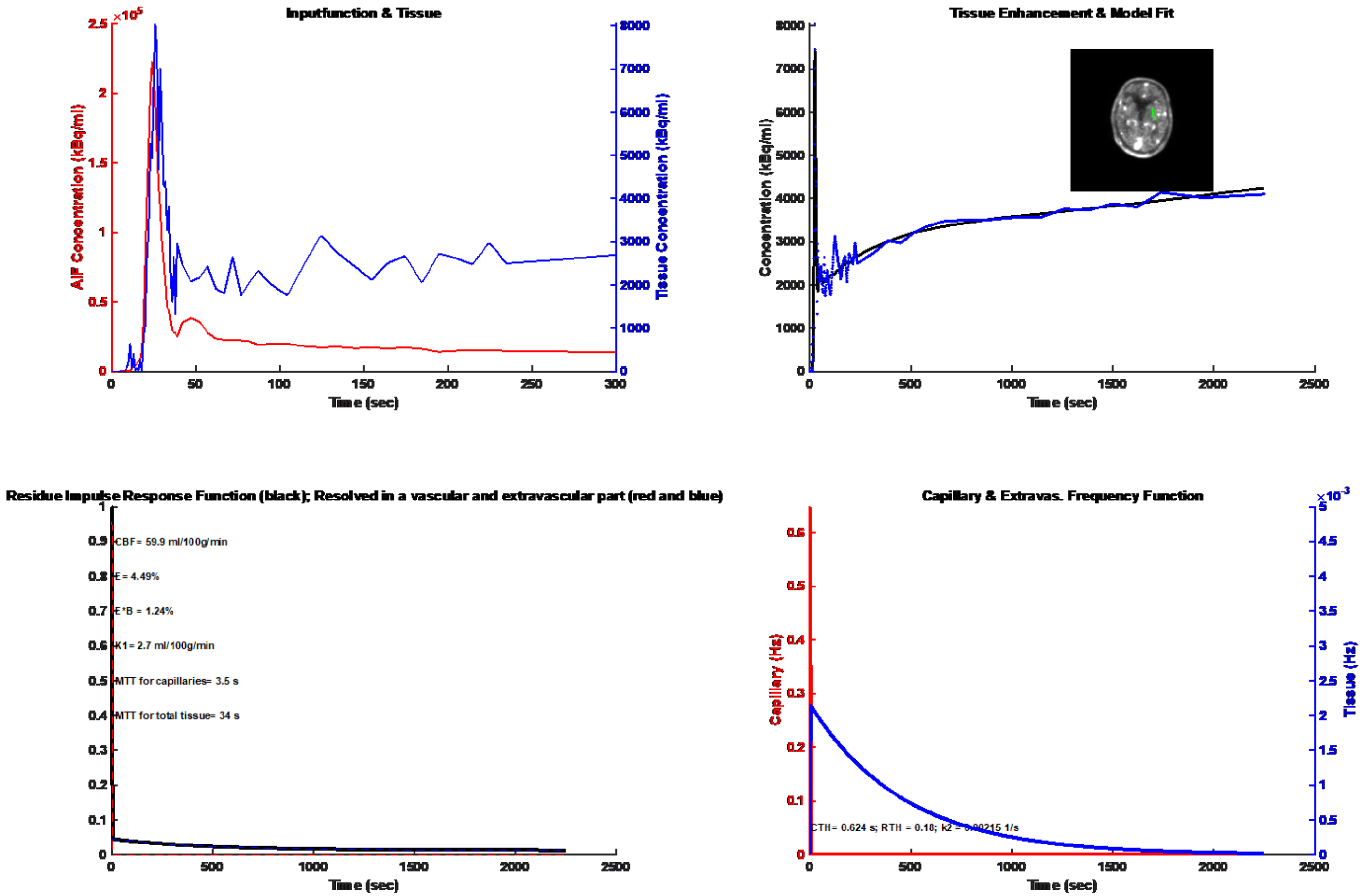
PET using [^{18}F]-FET



PET using [^{18}F]-FET



PET using [^{18}F]-FET



Yes we can !!!!

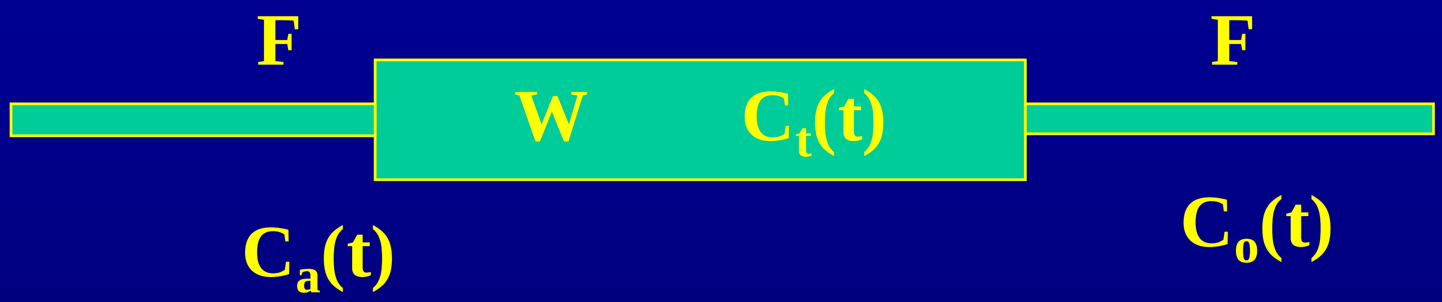
HBWL

Kety’s methods
The inventor of classic tracer kinetic theory

Measurement of local blood flow by the exchange of an innert, diffusible substance

CF_3I^{131} and I^{131}-antipyrine

Kety's methods (Residue detection)



$$C_t(t) \equiv \frac{n(t)}{W_{eight}}$$

or

$$C_t(t) \equiv \frac{n(t)}{V_{olume}}$$

$$\lambda \equiv \frac{C_t^{\infty}}{C_{blood}^{\infty}} \approx \frac{C_t(t)}{C_o(t)}$$

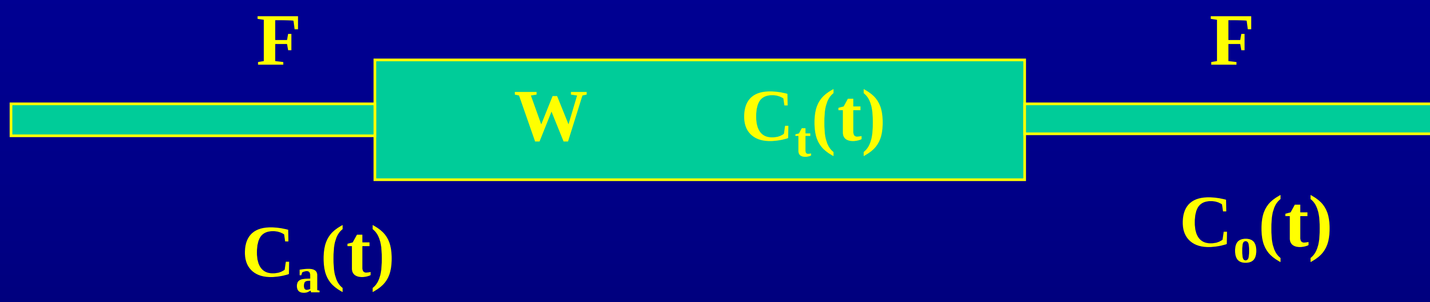
Kety's methods (Residue detection)

$$\frac{dn(t)}{dt} = j_i(t) - j_o(t)$$

$$W\,\frac{dC_t(t)}{dt} = F\,C_a(t) - F\,C_o(t)$$

$$W\,\frac{dC_t(t)}{dt} = F\,C_a(t) - \frac{F}{\lambda}\,C_t(t) \Leftrightarrow \frac{dC_t(t)}{dt} = \frac{F}{W}\,C_a(t) - \frac{F}{W\lambda}\,C_t(t)$$

Kety's methods (Residue detection)



$$\frac{dC_t(t)}{dt} = \frac{F}{W} C_a(t) - \frac{F}{W\lambda} C_t(t)$$

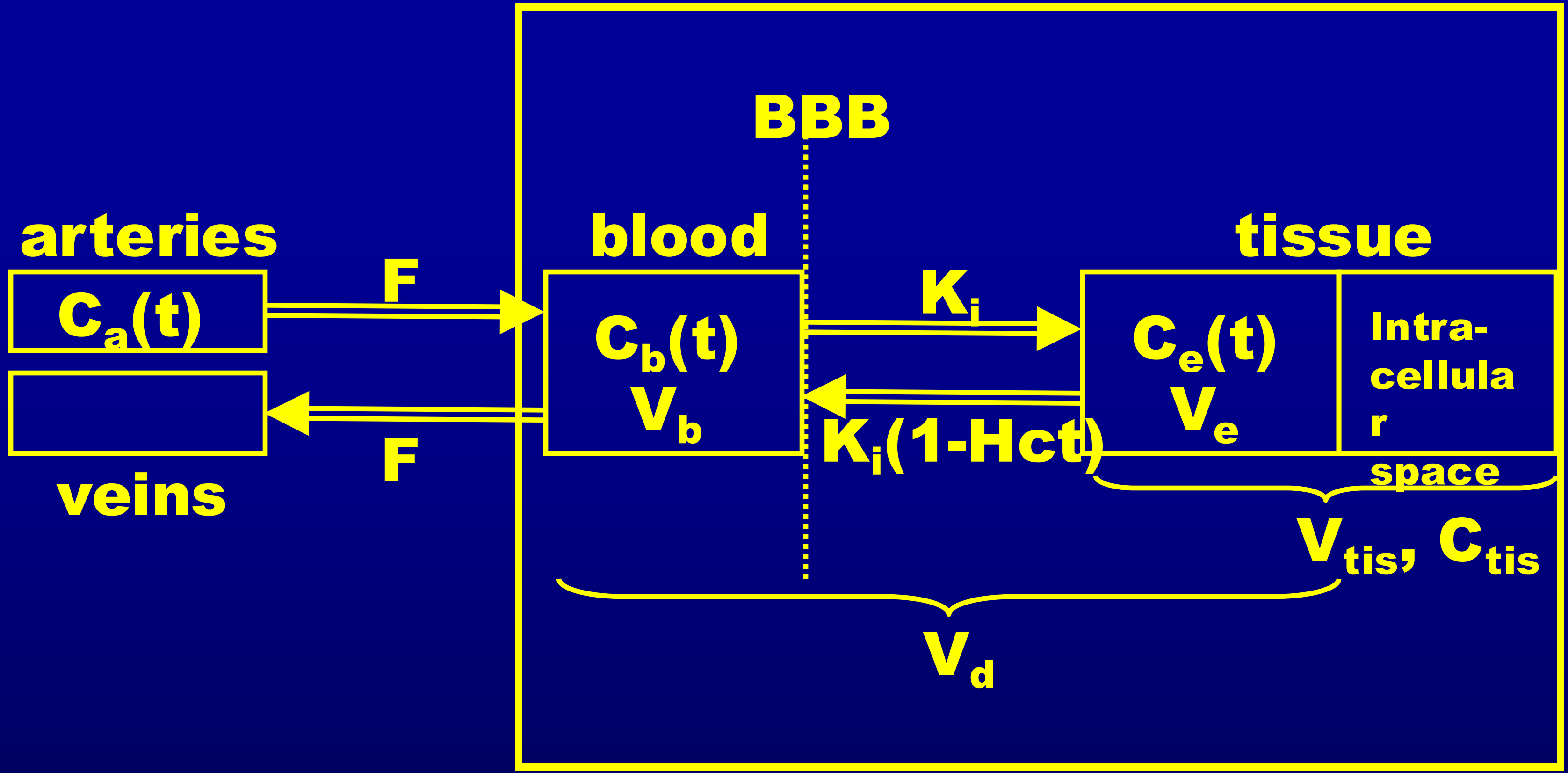
$$\frac{dC_t(t)}{dt} = f\, C_a(t) - \frac{f}{\lambda} C_t(t)$$

Solution:

$$C_t(t) = f \int_0^t C_a(\tau)\, e^{-\frac{f}{\lambda}(t-\tau)}\, d\tau$$

$$\Leftrightarrow \quad C_t(t) = f e^{-\frac{f}{\lambda}t} \int_0^t C_a(\tau)\, e^{\frac{f}{\lambda}\tau}\, d\tau$$

HBWL



$$V_b \frac{dC_b(t)}{dt} = F\ C_a(t) - (F + K_i)\ C_b(t) + K_i\,(1 - \mathrm{Hct})\ C_e(t)$$

$$V_e \frac{dC_e(t)}{dt} = K_i\ C_b(t) - K_i\,(1 - \mathrm{Hct})\ C_e(t)$$

HBWL

$$V_e C_e = V_{\text{tis}} C_{\text{tis}}$$

$$\alpha = \frac{F + K_i}{V_b}$$

$$\beta = \frac{V_{\text{tis}}(1 - \text{Hct})K_i}{V_b V_e}$$

$$\gamma = \frac{K_i}{V_{\text{tis}}}$$

$$\theta = \frac{K_i(1 - \text{Hct})}{V_e}$$

$$(a,b) = \left(\frac{1}{2}[\theta + \alpha + \sqrt{\theta^2 + \alpha^2 - 2\theta\alpha + 4\gamma\beta}], \frac{1}{2}[\theta + \alpha - \sqrt{\theta^2 + \alpha^2 - 2\theta\alpha + 4\gamma\beta}]\right)$$

$$C_b(t) = C_a(t) \otimes \frac{F}{V_b} \frac{(a-\theta)e^{-at} - (b-\theta)e^{-bt}}{a-b}$$

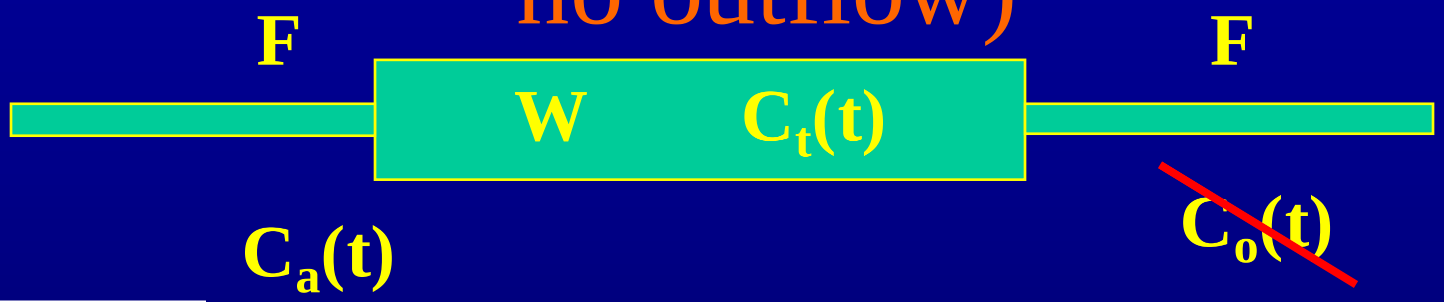
$$C_{\text{tis}}(t) = C_a(t) \otimes \frac{F}{V_b} \frac{K_i}{V_{tis}} \frac{e^{-bt} - e^{-at}}{a-b}$$

$$C_t(t) = V_b C_b(t) + (1 - V_b) C_{\text{tis}}(t) \Leftrightarrow$$

$$C_t(t) = F\ C_a(t) \otimes \left[\frac{(a - \theta - K_i / V_b) e^{-at} + (-b + \theta + K_i / V_b) e^{-bt}}{a-b} \right]$$

HBWL

Kety's methods (Residue detection and no outflow)



$$\frac{dn(t)}{dt} = j_i(t)$$

$$\Leftrightarrow W\frac{dC_t(t)}{dt} = F\,C_a(t)$$

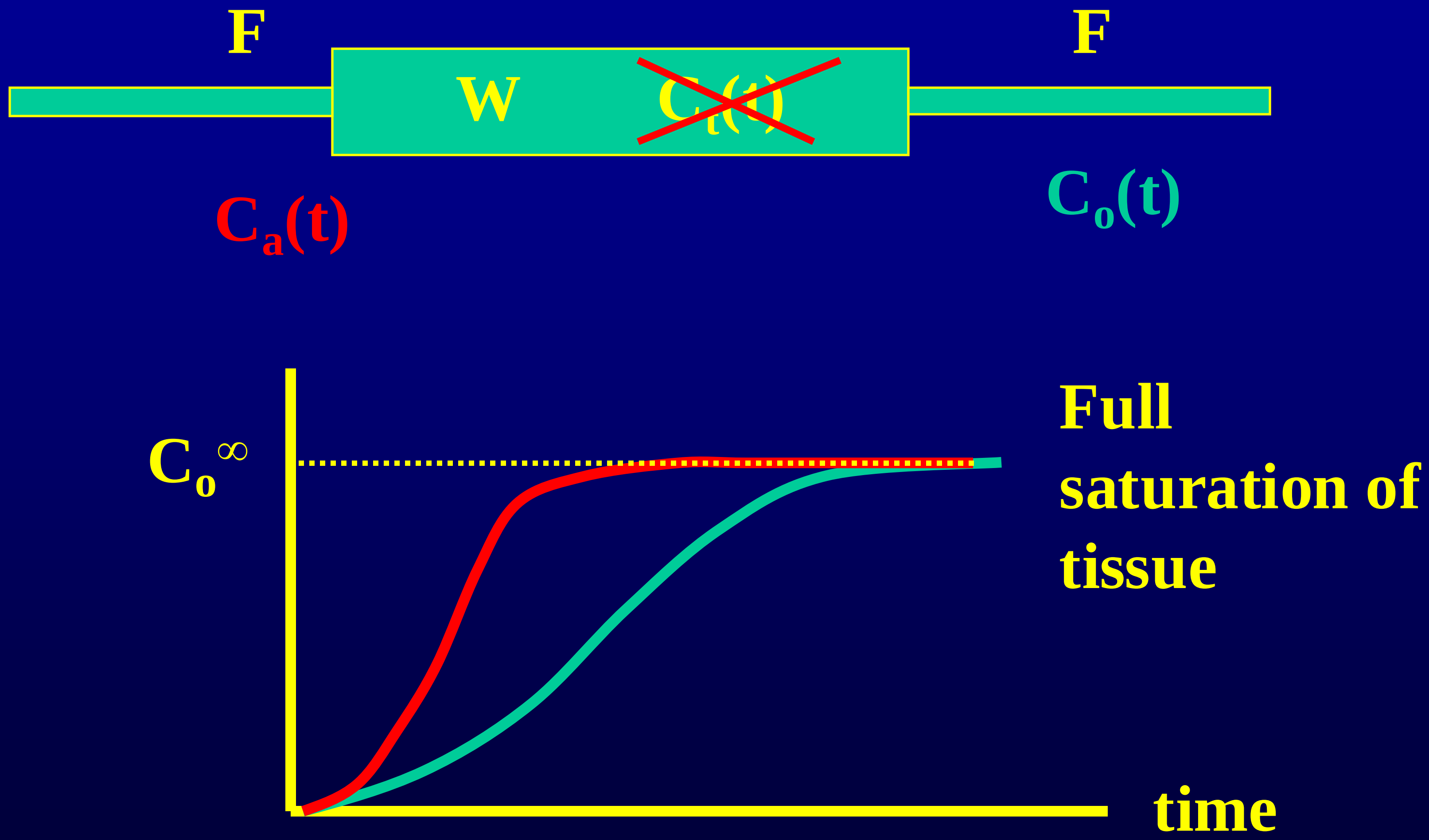
$$\Leftrightarrow dC_t(t) = \frac{F}{W}C_a(t)\,dt$$

$$\Rightarrow \int_0^T dC_t(t) = \int_0^T \frac{F}{W}C_a(t)\,dt$$

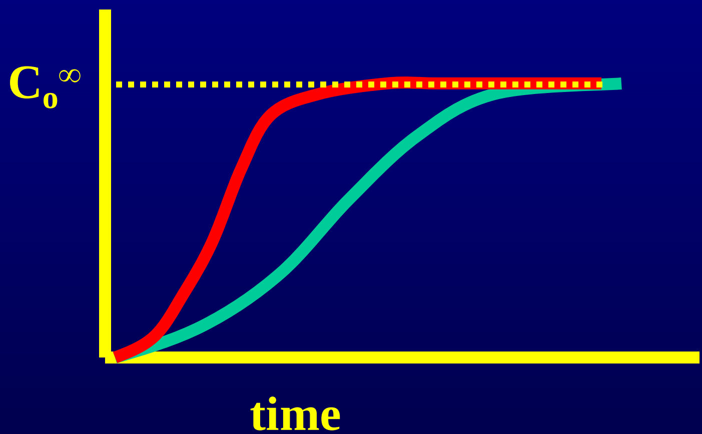
$$\Leftrightarrow C_t(T) = \frac{F}{W}\int_0^T C_a(t)\,dt \Leftrightarrow \frac{F}{W} = \frac{C_t(T)}{\int_0^t C_a(t)\,dt}$$

HBWL

Kety's methods (Inflow & outflow detection)



Kety's methods (Inflow & outflow detection)

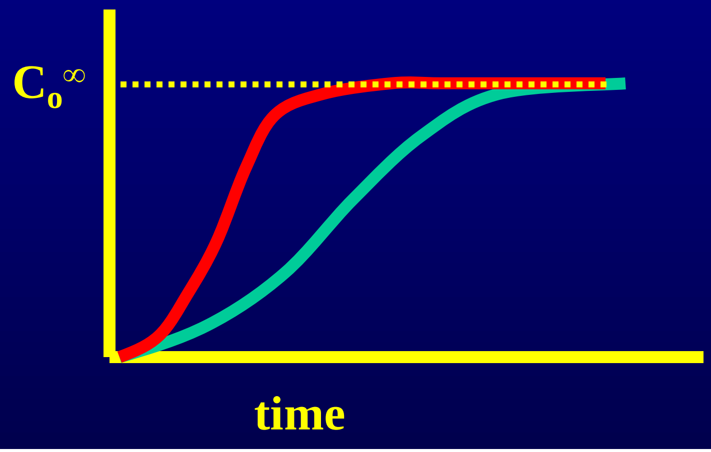


$$\frac{dn(t)}{dt} = j_i(t) - j_o(t)$$

$$\Leftrightarrow W \frac{dC_t(t)}{dt} = F\, C_a(t) - F\, C_o(t)$$

$$\Leftrightarrow dC_t(t) = \frac{F}{W} C_a(t)\, dt - \frac{F}{W} C_o(t)\, dt$$

Kety's methods (Inflow & outflow detection)



$$\Leftrightarrow dC_t(t) = \frac{F}{W} C_a(t)\, dt - \frac{F}{W} C_o(t)\, dt$$

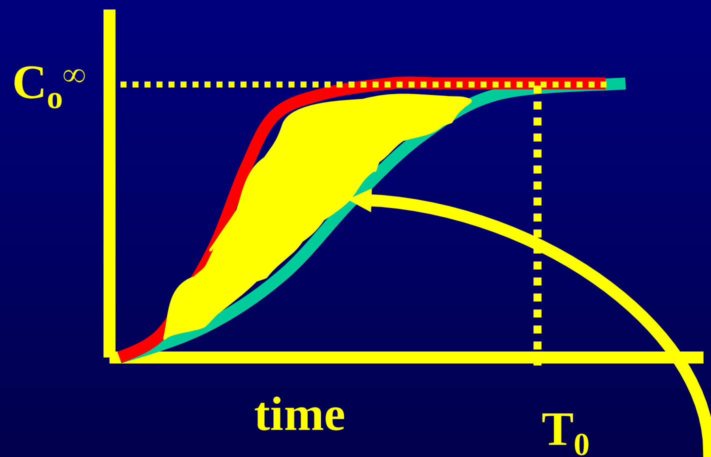
$$\Leftrightarrow dC_t(t) = \frac{F}{W} \left(C_a(t) - C_o(t) \right) dt$$

$$\Leftrightarrow \int_0^T dC_t(t) = \frac{F}{W} \int_0^T \left(C_a(t) - C_o(t) \right) dt$$

$$\Leftrightarrow C_t(T) = \frac{F}{W} \int_0^T \left(C_a(t) - C_o(t) \right) dt$$

HBWL

Kety's methods (Inflow & outflow detection)



$$C_t(T) = \lambda\, C_o(T) = \lambda\, C_o^\infty \quad for \;\; T > T_0$$

$$C_t(T) = \frac{F}{W}\int_0^T \left(C_a(t) - C_o(t) \right) dt$$

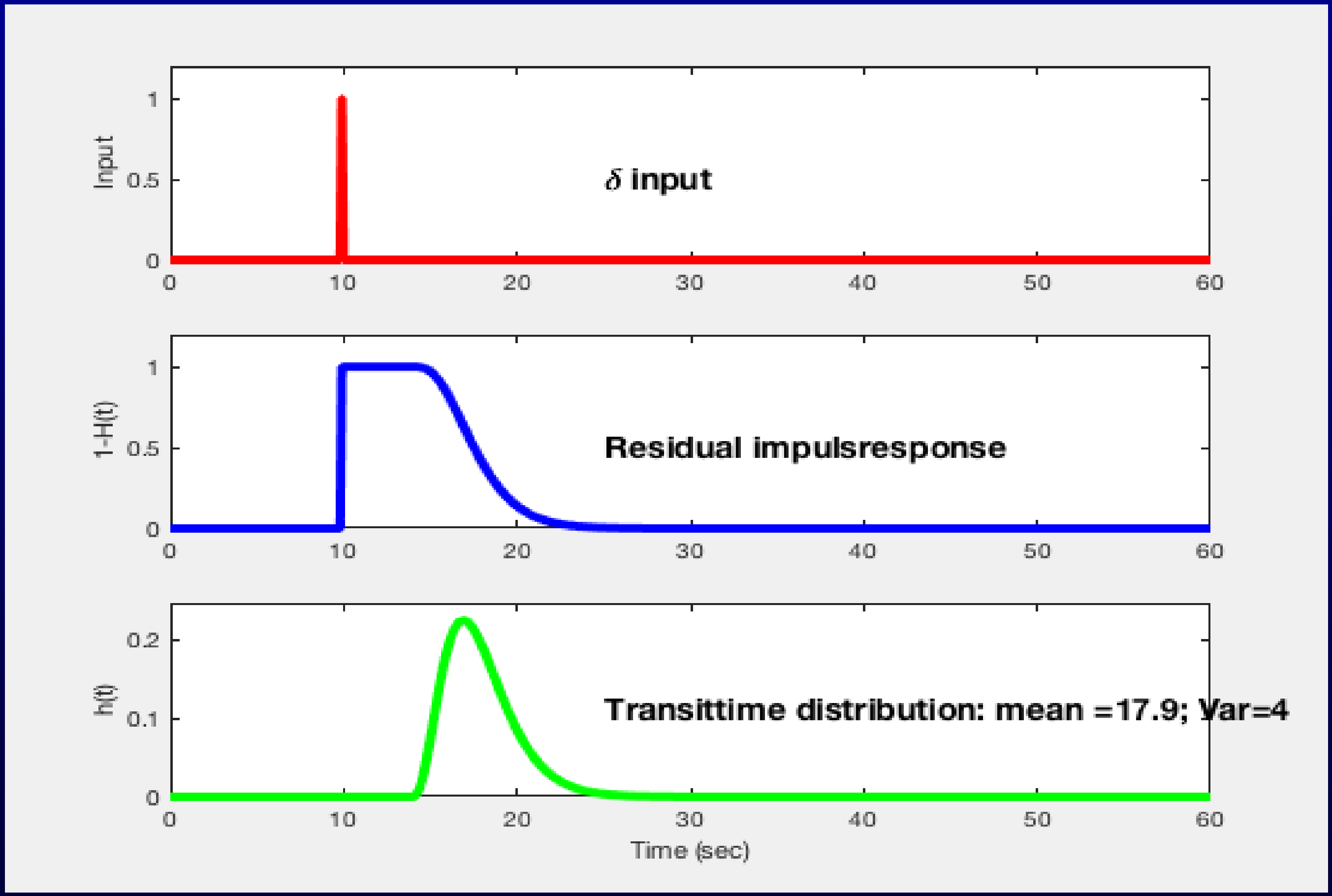
$$\Rightarrow \frac{F}{W} = \frac{\lambda\, C_o^\infty}{\int_0^\infty \left(C_a(t) - C_o(t) \right) dt}$$

HBWL

J Magn Reson Imaging. 2017 Jun;45(6):1809-1820. doi: 10.1002/jmri.25488. Epub 2016 Oct 12.

Brain capillary transit time heterogeneity in healthy volunteers measured by dynamic contrast-enhanced T_1 -weighted perfusion MRI.

Larsson HBW[1,2], Vestergaard MB[1], Lindberg U[1], Iversen HK[2,3], Cramer SP[1].



input

tissue

output

$$C_t(t) = C_a(t) \otimes f\, RIF(t) = f \int_0^t C_a(\tau) RIF(t-\tau)\, d\tau \quad [1]$$

$$RIF(t) = 1 - \int_0^t h(\tau)\, d\tau \quad [2]$$

The mean transit time (MTT) is given as:

$$MTT = \int_0^\infty t\, h(t)\, dt = \int_0^\infty RIF(t)\, dt \quad [3]$$

CTH can be defined as the standard deviation (SD) of the frequency function, h(t):

$$CTH = \sqrt{Var[h(t)]} = \sqrt{\int (t - MTT)^2 h(t)\, dt} \quad [4]$$

The frequency function, h(t), can be modelled as a simple gamma-variate function with the parametric form as (15):

$$h(t) = \left[\left(\frac{t - t_0}{t_{\max} - t_0} \right)^\alpha \exp\left(\alpha (1 - \frac{t - t_0}{t_{\max} - t_0}) \right) \right] / A \quad [5]$$

HBWL

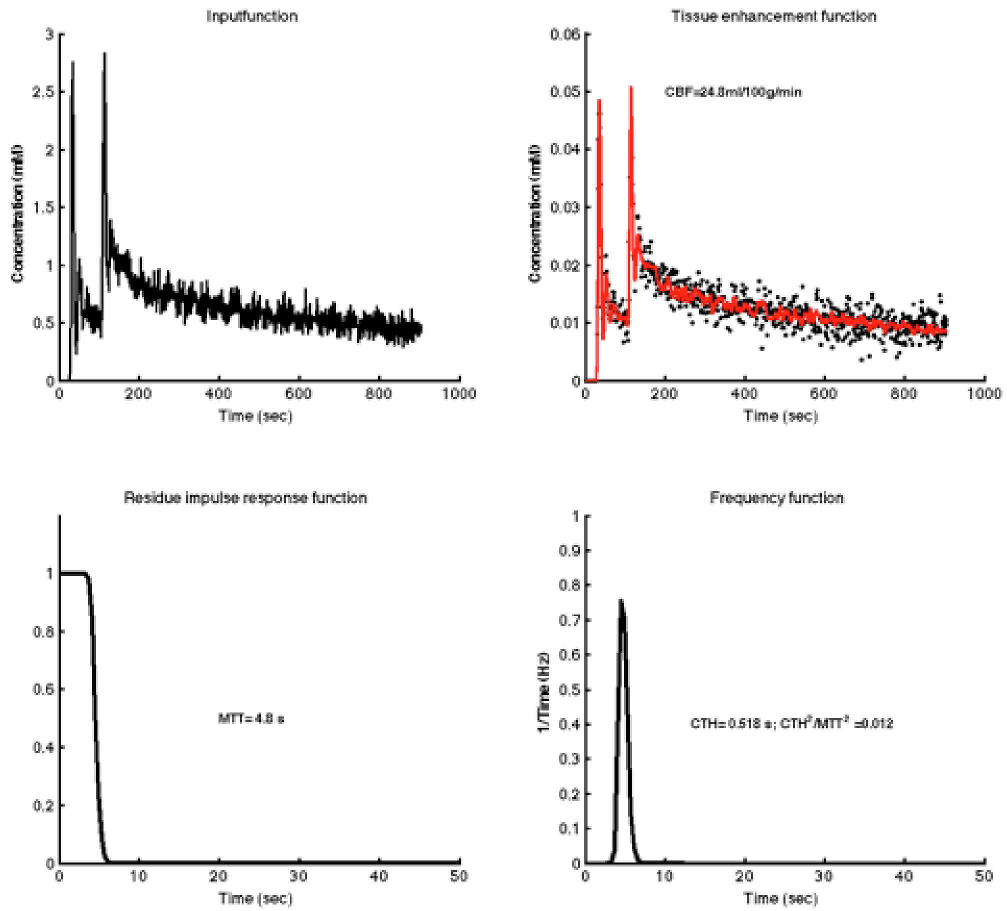


Figure 1. An example of calculation from a ROI placed in thalamus in a young healthy subject. Note the symmetrical shape of the h(t) function. Mean Transit time (MTT), the Capillary Transit time Heterogeneity (CTH) and CTH^2/MTT^2 values are inserted.

HBWL

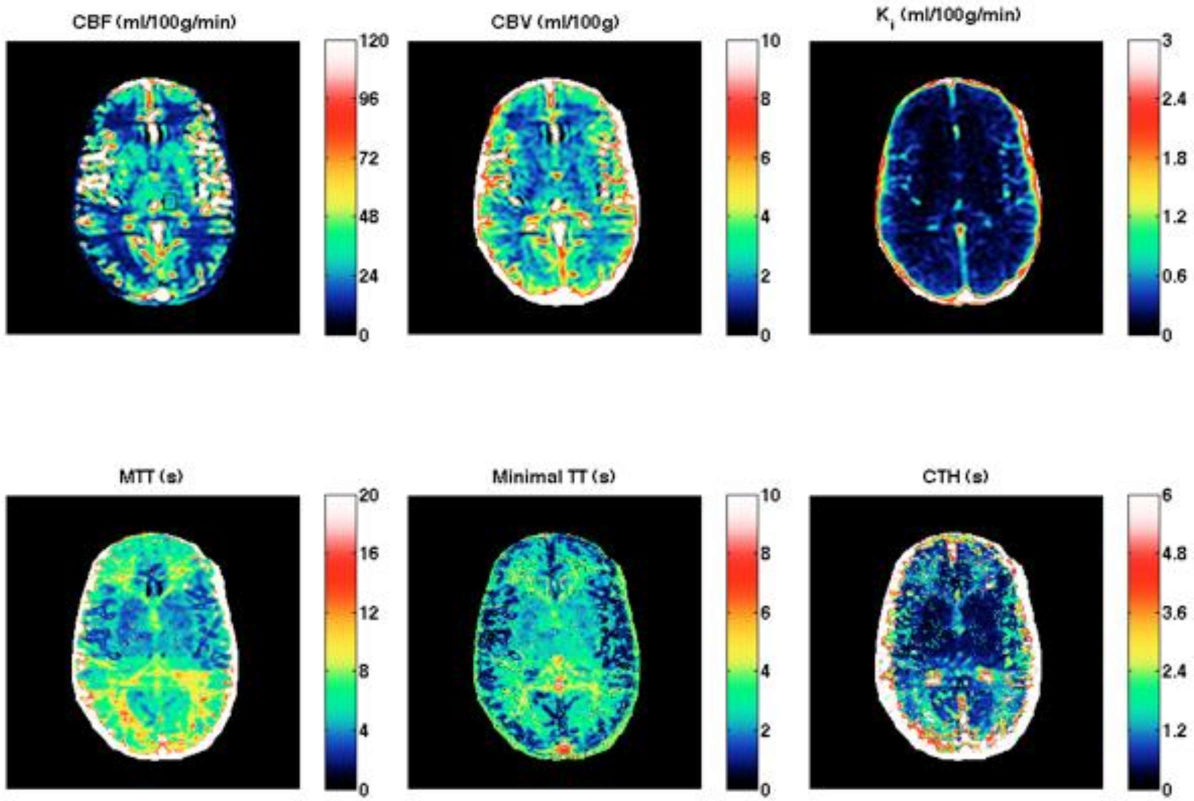


Figure 5. Pixel wise calculated maps of CBF, CBV, permeability K_i, mean transit time (MTT), minimal transit time (Minimal TT), and capillary transit time heterogeneity (CTH), of one healthy subject. The results from the ROI on the CBF map are shown in figure 1.

HBWL

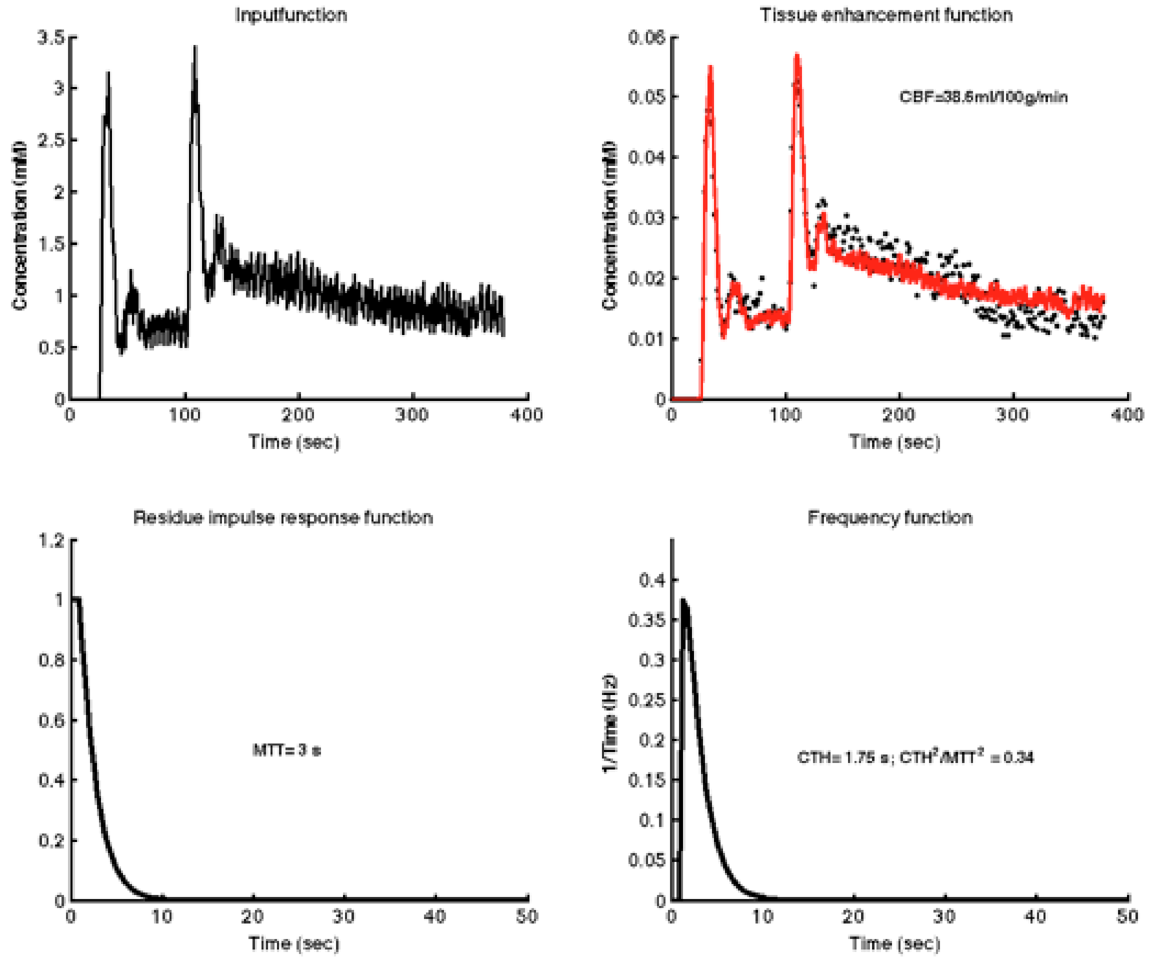


Figure 2. An example of calculation from a ROI placed in frontal WM of a 75-year-old man having internal carotid stenosis contralateral to the ROI placement.

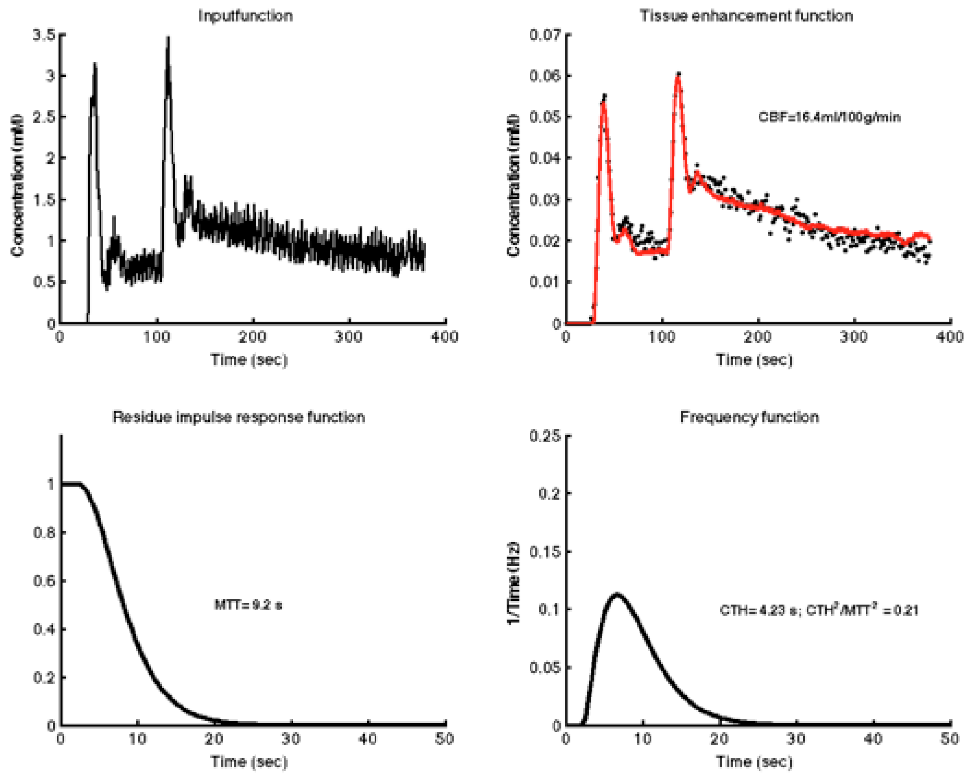


Figure 3. An example of calculation from a ROI placed in parietal WM ipsilateral to an internal carotid stenosis in a 75-year-old man. Mean Transit time (MTT), Capillary Transit time Heterogeneity (CTH) and CTH^2/MTT^2 values are inserted. Note the asymmetry of h(t) signifying a large heterogeneity in capillary transit times.

HBWL

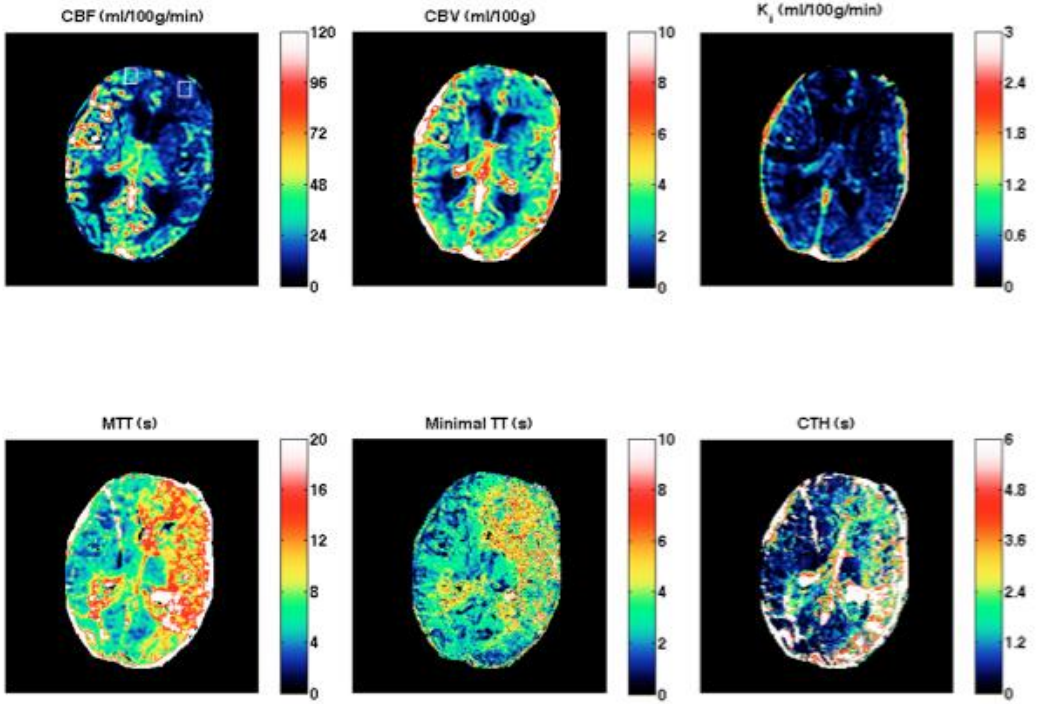


Figure 6. The figure shows results from a patient with left sided internal carotid stenosis, with multiple thrombo-embolic episodes. Perfusion (CBF) is decreased while the cerebral blood volume (CBV) is increased in the fronto-parietal region, but the permeability (K_i) seems relatively normal. The mean transit time (MTT), the minimal transit time (minimal TT) and capillary transit tine heterogeneity (CTH) is prolonged in the entire region showing altered perfusion.

HBWL