Basic Tracer Kinetic Concepts

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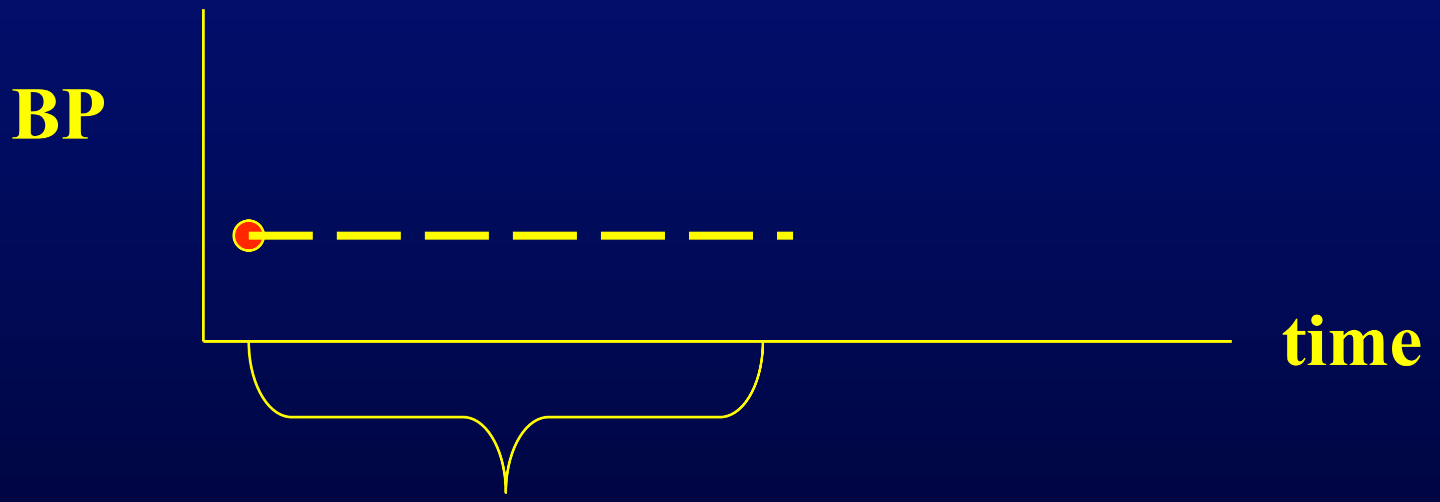
Steady state of the system

- 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



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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

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- 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

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Linearity of a system

RF(t) : response function or more correctly

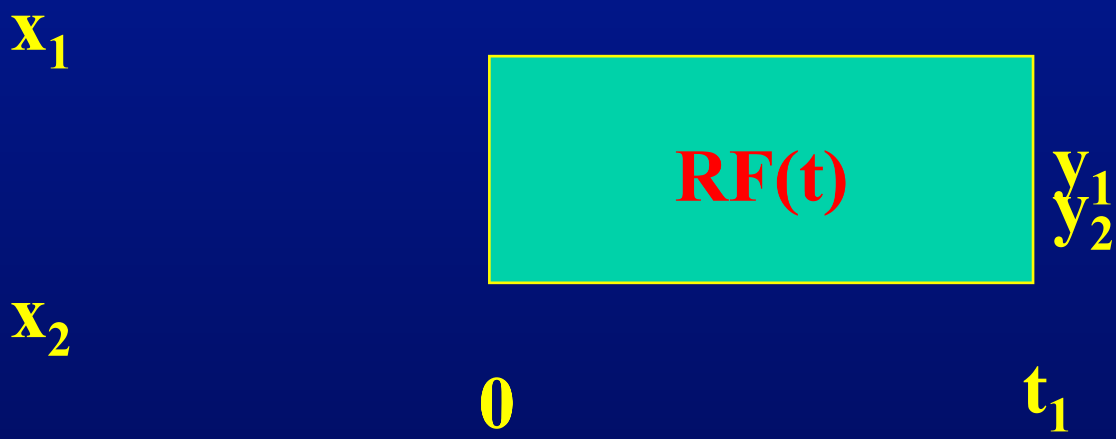
: The impulse response function

Linearity of a system

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

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

Linearity of a system



RF(t)

$x_1 + x_2 \longrightarrow y_1 + y_2$

Principle of superposition

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Examples

3

3 +4

4

x 2

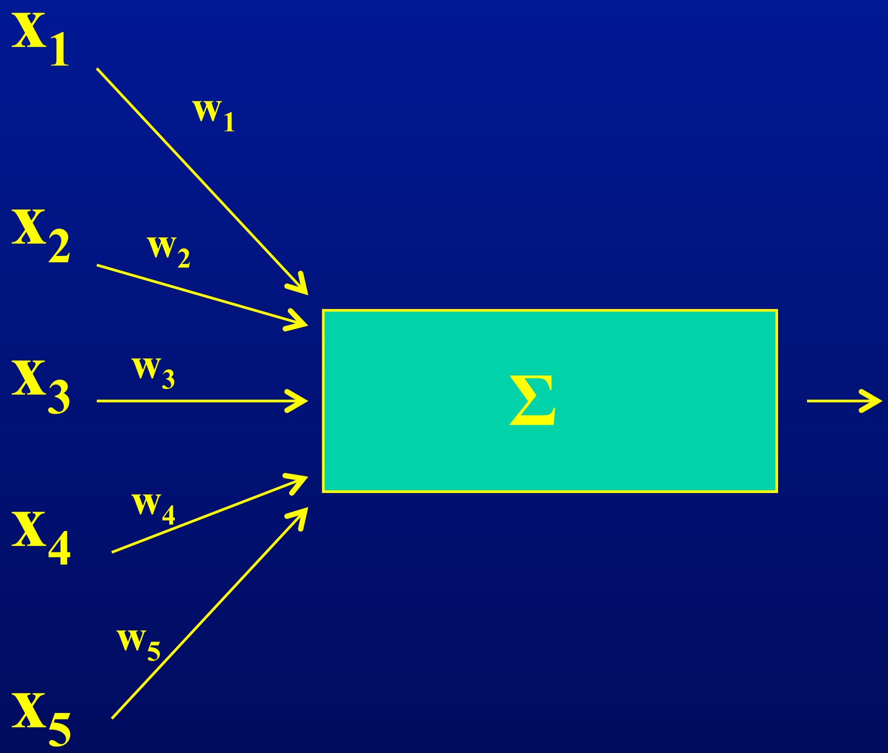
6

14

8

HBWL

Examples



$$x_1w_1+x_2w_2+x_3w_3+x_4w_4+x_5w_5$$

Examples

3

3 +4

4

$\boxed{\text{log}}$

log3

log(3+4)

log4

$$\log 3 + \log 4 \neq \log(3+4)$$

Linearity of a system

$$a\,x_1 + b\,x_2 \xrightarrow{RF(t)} a\,y_1 + b\,y_2$$

Time invariance of a system

x x

RF(t)

y y

0 + 10s

t t2 + 10s

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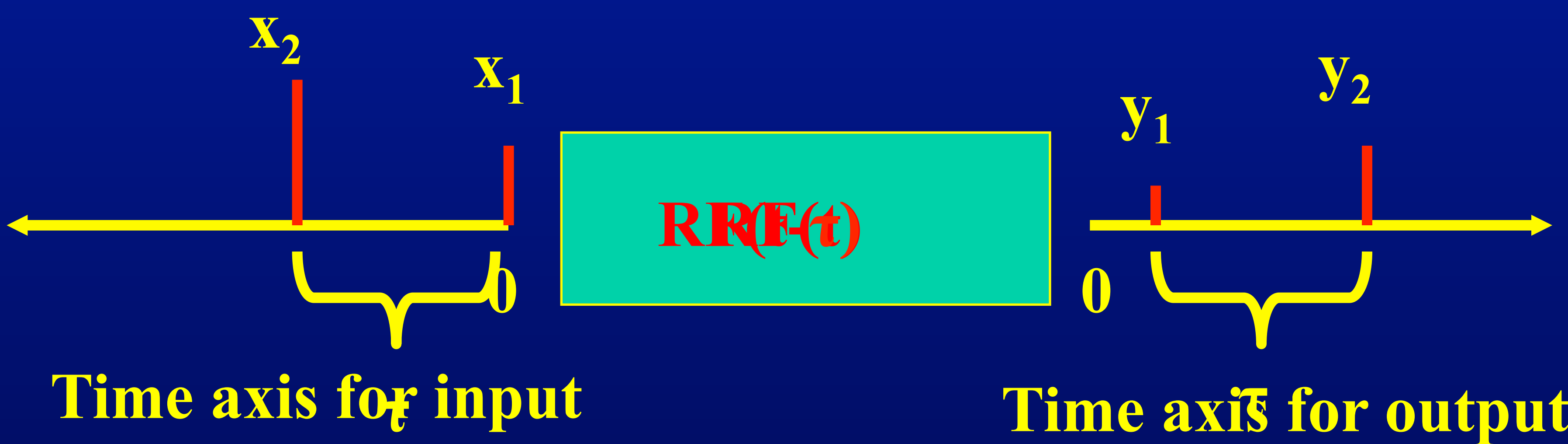
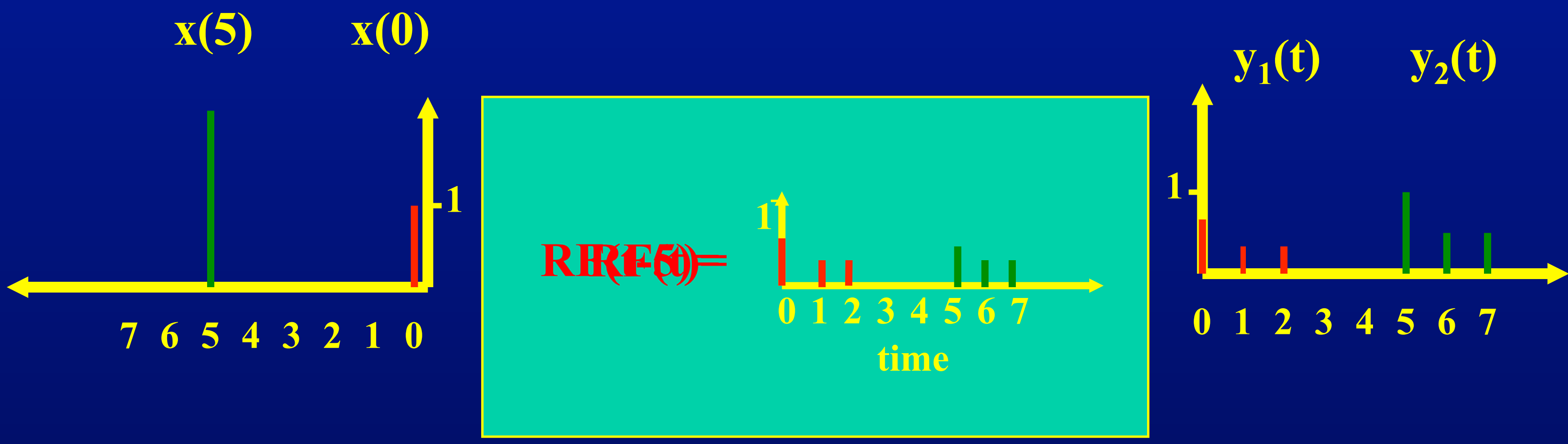
Specification of time



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 !!!

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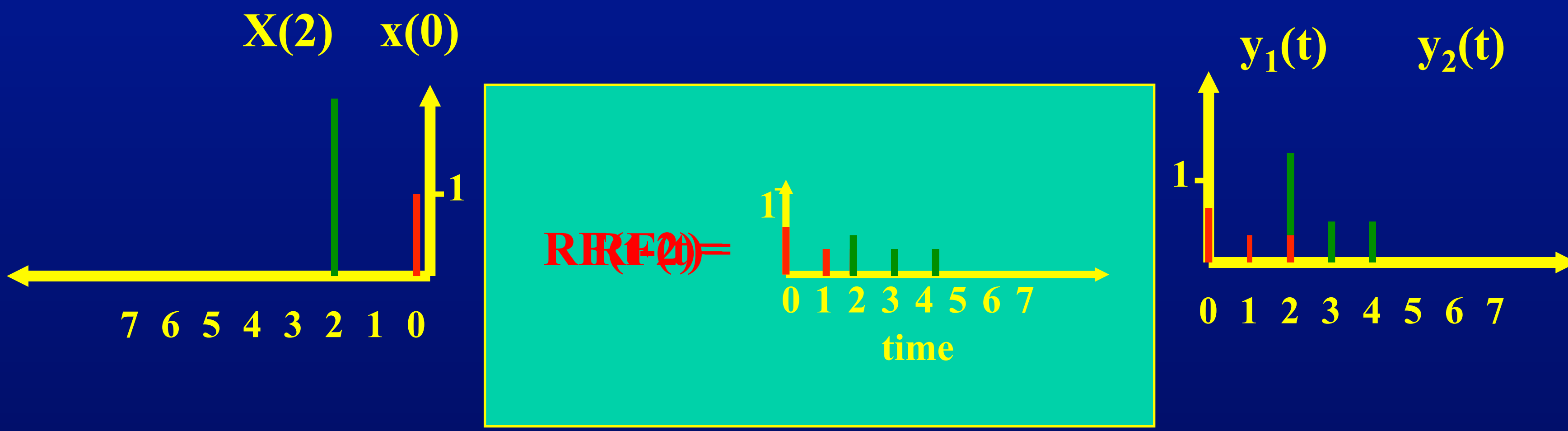
Example



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

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

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

Does not work !!!

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Causality of a system

Output is only observed after an input has enter the system

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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
!

Linearity of a imaging system?

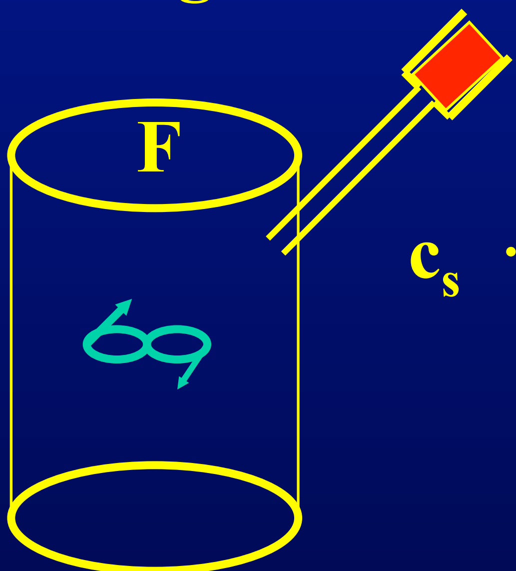
!

Break

Indicator-dilution methods

Constant Infusion (Stewart principle)

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



$$[F] = ml/s$$

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

$$[c_s] = mmol/ml$$

$$[F_s] = ml/s$$

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

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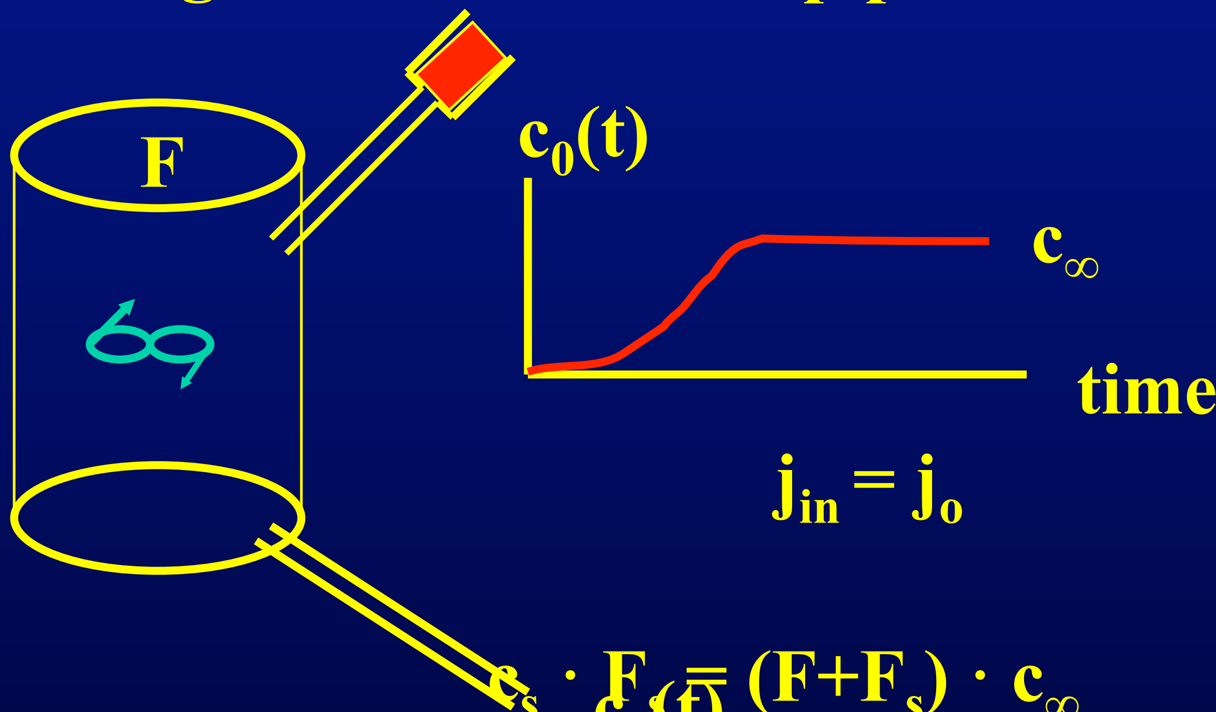
Indicator-dilution methods

Constant Infusion (Stewart principle)

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



$$j_{in} = j_o$$

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

$$c_0(t)$$

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

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

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

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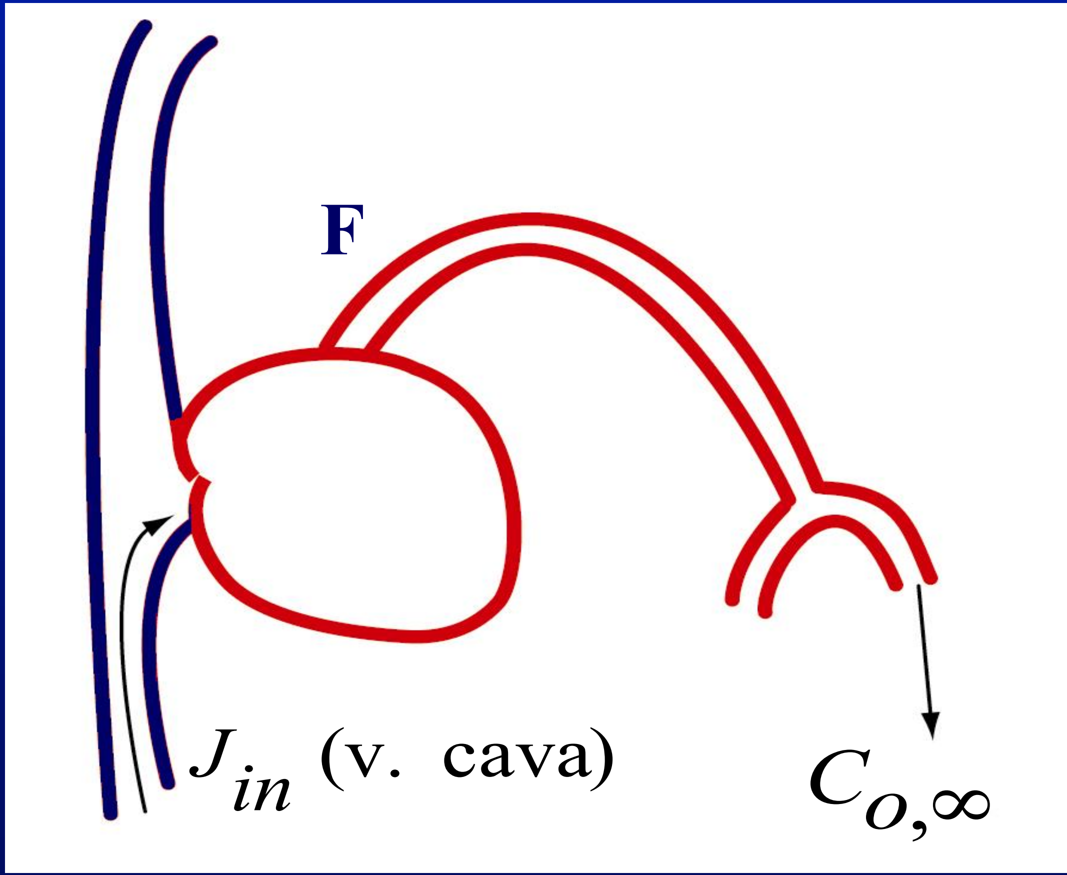
Examples and recirculation



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

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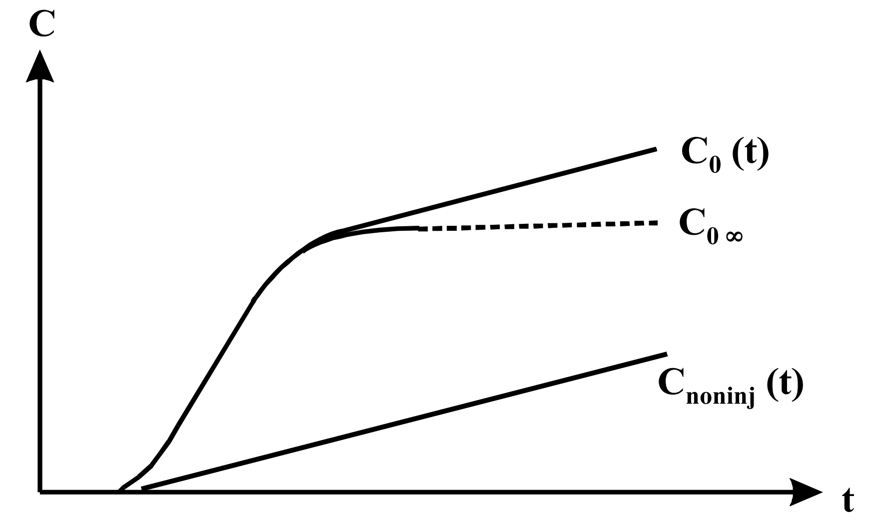

Measurement of concentration at the outlet and the "noninj" side.

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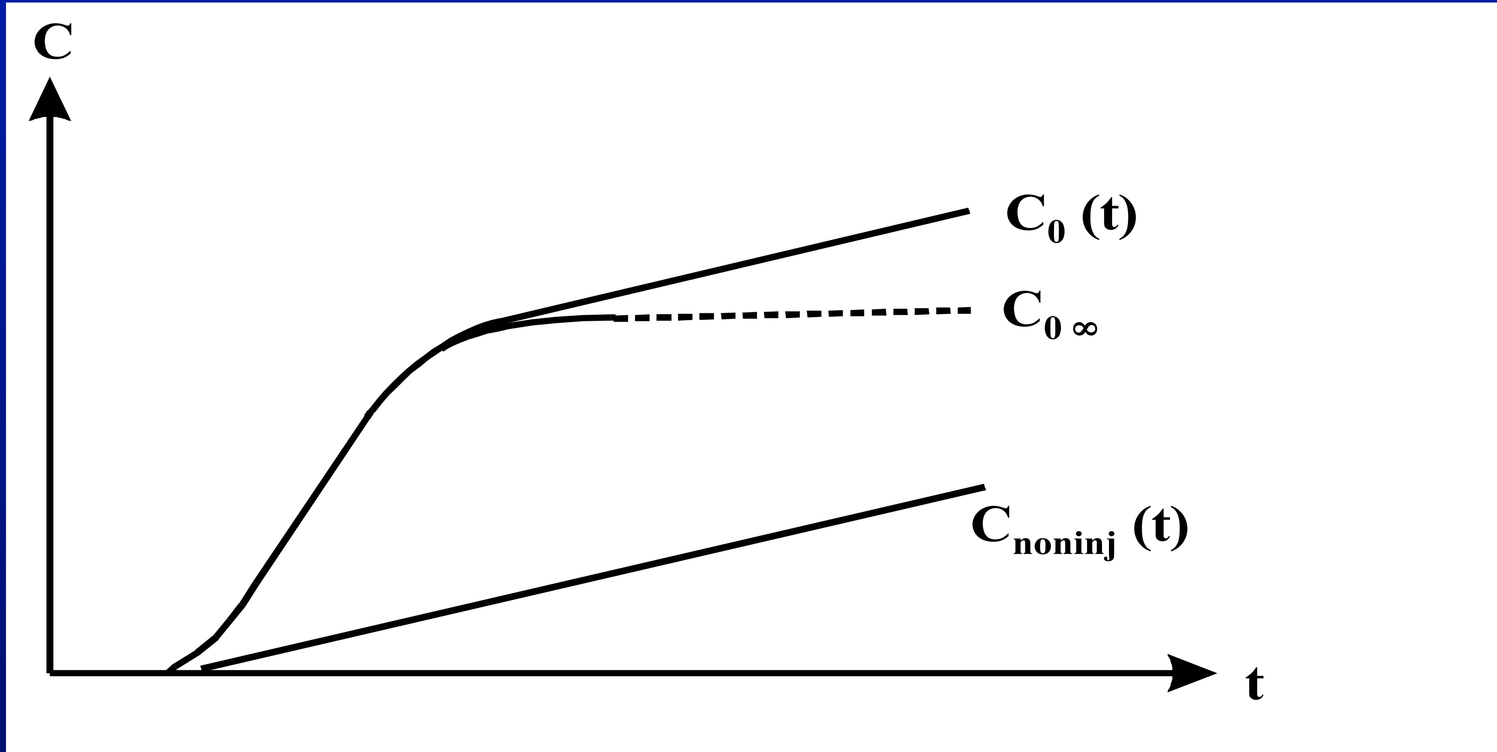

$$J_o = J_{in} + FC_{noninj}(t) \Rightarrow$$

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

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

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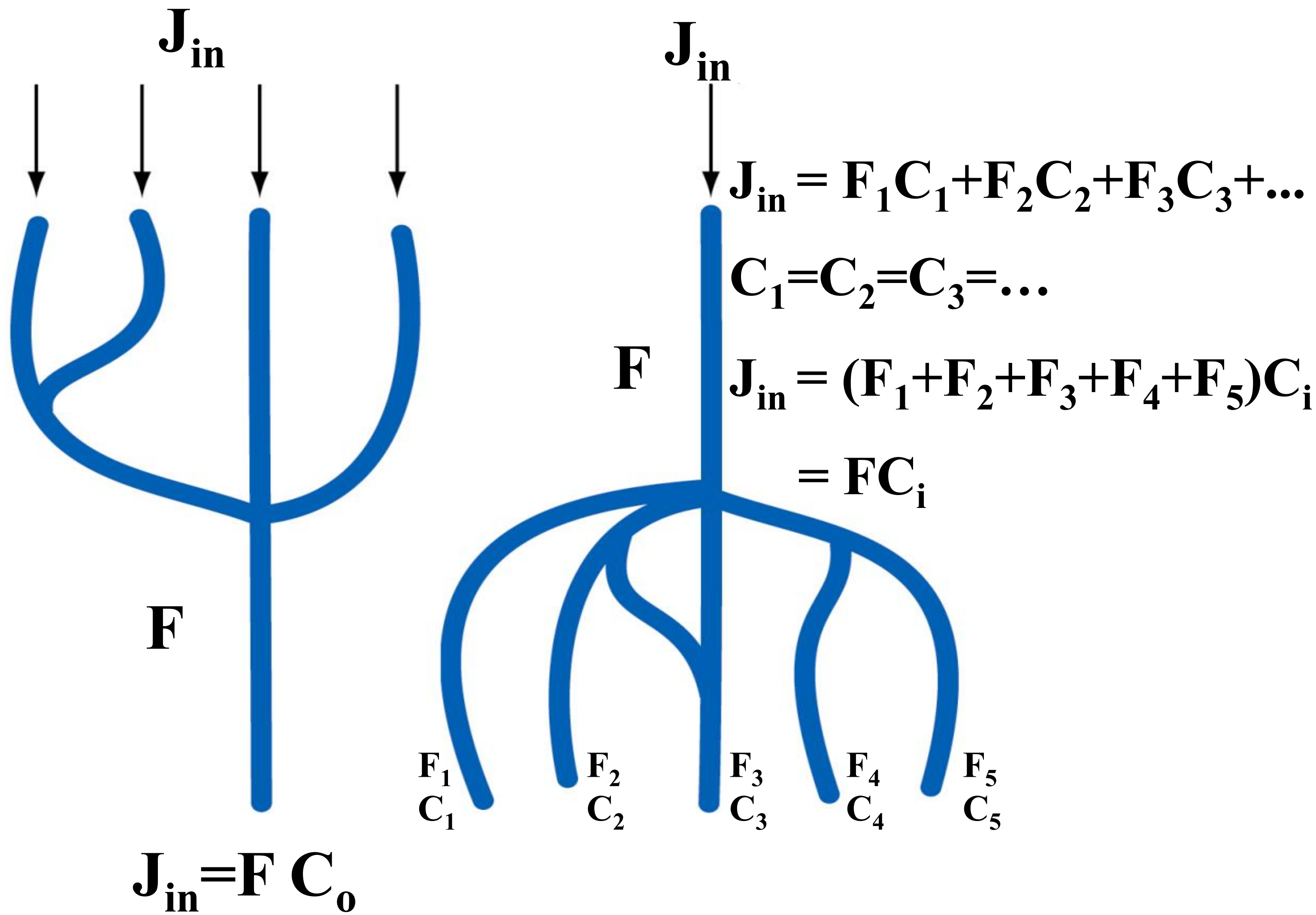
Bolus Fraktion principle - Sapirsteins principle



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Fick's-principle

The conservation of matter

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The principle of Fick

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

$$j_{in} = F \cdot c_{in} \longrightarrow \frac{dc}{dt} = 0 \longrightarrow j_o = F \cdot c_o$$

Convective input by blood entering the tissue

Convective output

$$\downarrow$$

$$j$$

Non-convective uptake of a tissue

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

conservation of mass

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

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

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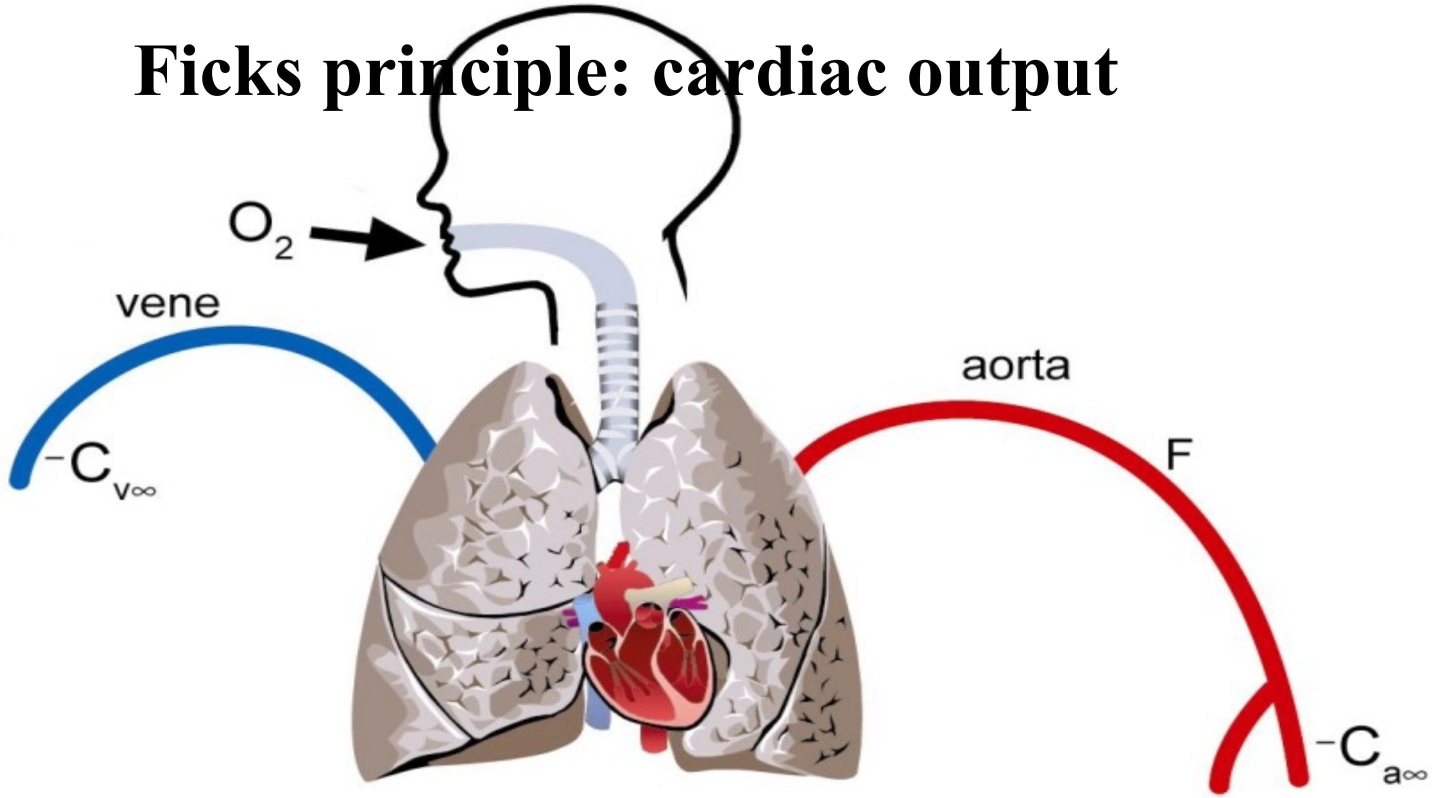
Ficks principle: cardiac output



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

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

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

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Left to right shunt

S_a-pulm=0.85 S_a= 0.98

Optake 300 ml O2 /min

Hb = 150g/l

1.34 mlO_2/g Hb

Ca =150*1.34*0.98=197 mlO_2/l

Ca-Pulm =150*1.34*0.85 =171 mlO_2/l

CO =11.5 l/min

$S_{cava\ sup}$=0.70

$S_{cava\ inf}$ = 0.68

$S_{coronarious}$= 0.15

Average weighted = 0.65

C_v =150*1.34*0.65 =130 mlO_2/l

CO=4.5 l/min

1 mol O2 correspond to 22.4 l

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Cerebral metabolic rate of oxygen $CMRO_2$

- Ficks formel

Bloodsample

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

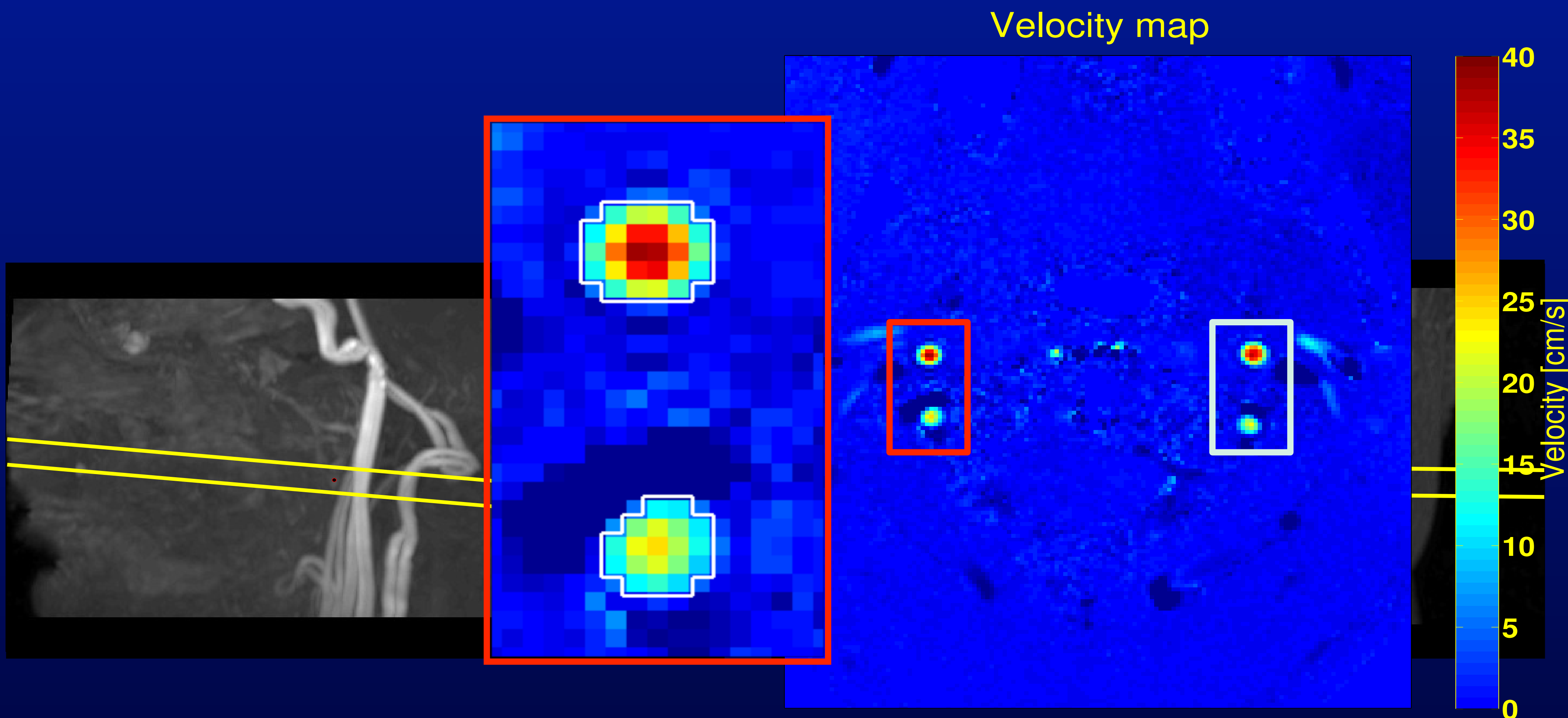
MRI phase contrast mapping

Puls-oximetri (A-cath)

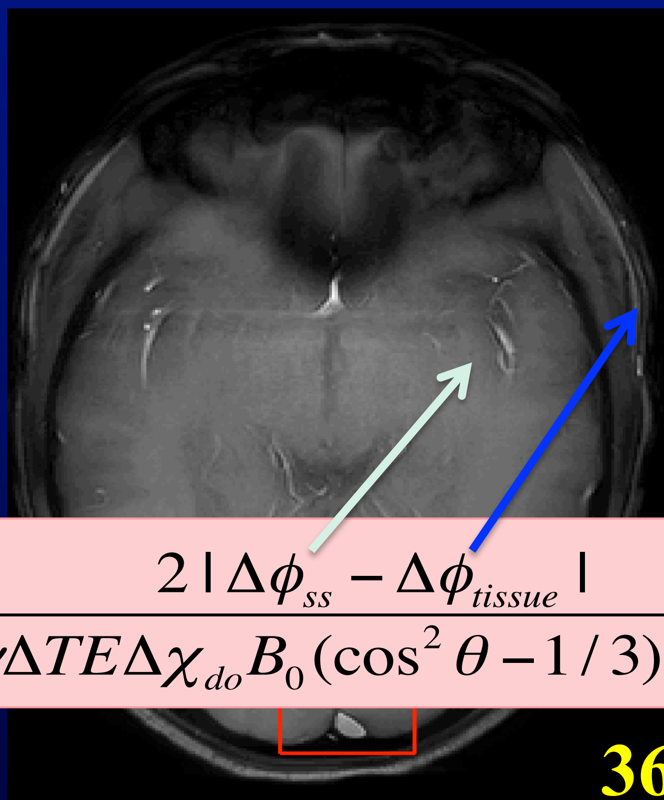
MRI susceptibility-based oximetry from Saggital sinus: venous blood from brain

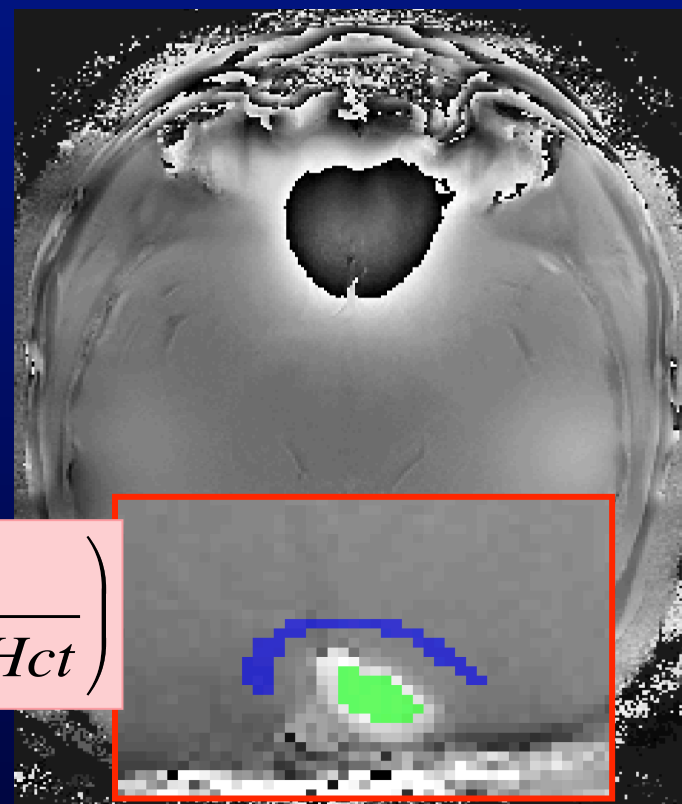
CBF – Fase kontrast MRI

- Velocity through plane (orthogonal the arteries) and area



Susceptibility based oximetry



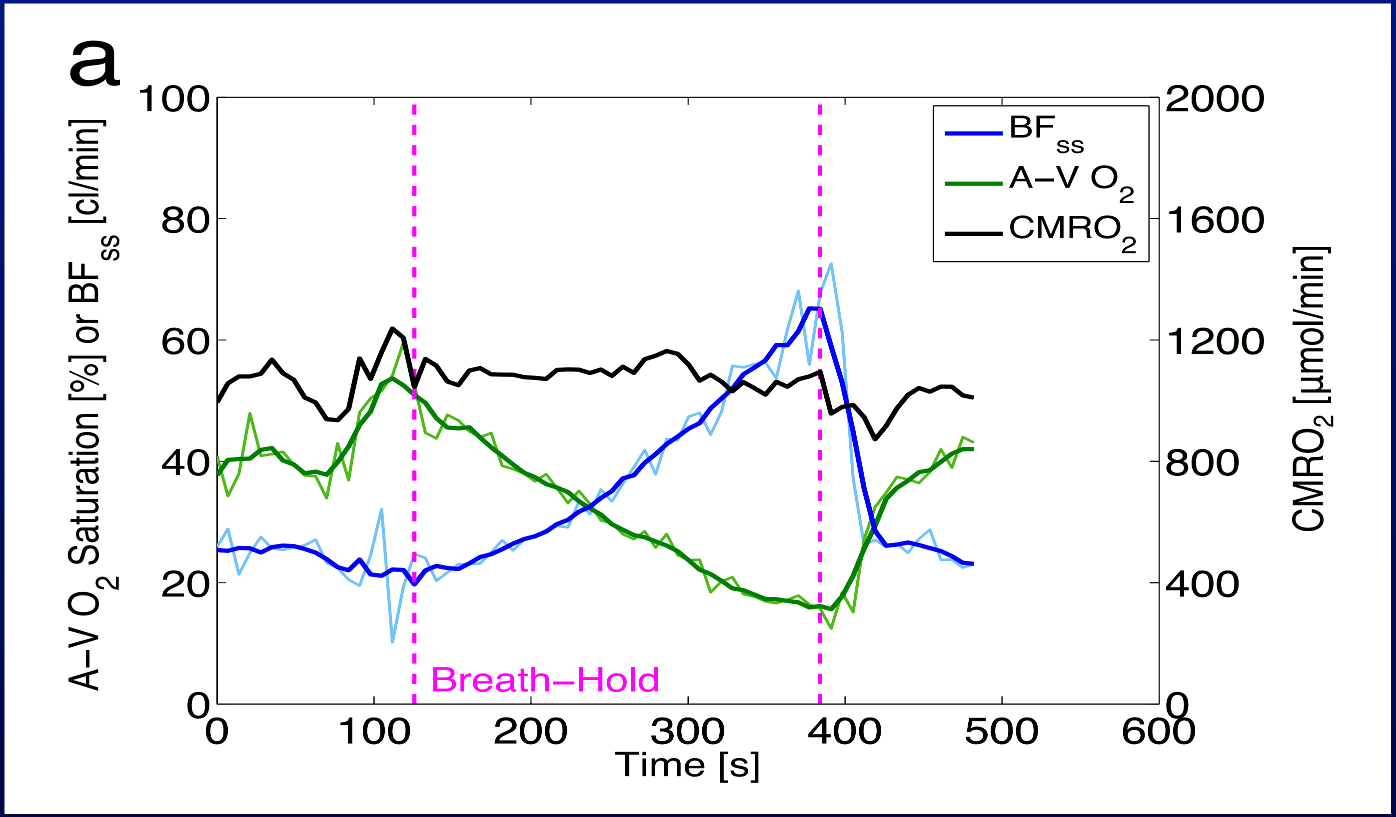


$$SvO_2 = \left(1 - \frac{2\,|\Delta\phi_{ss} - \Delta\phi_{tissue}\,|}{\gamma \Delta TE \Delta\chi_{do} B_0 (\cos^2\theta - 1/3) Hct}\right)$$

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

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

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

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

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

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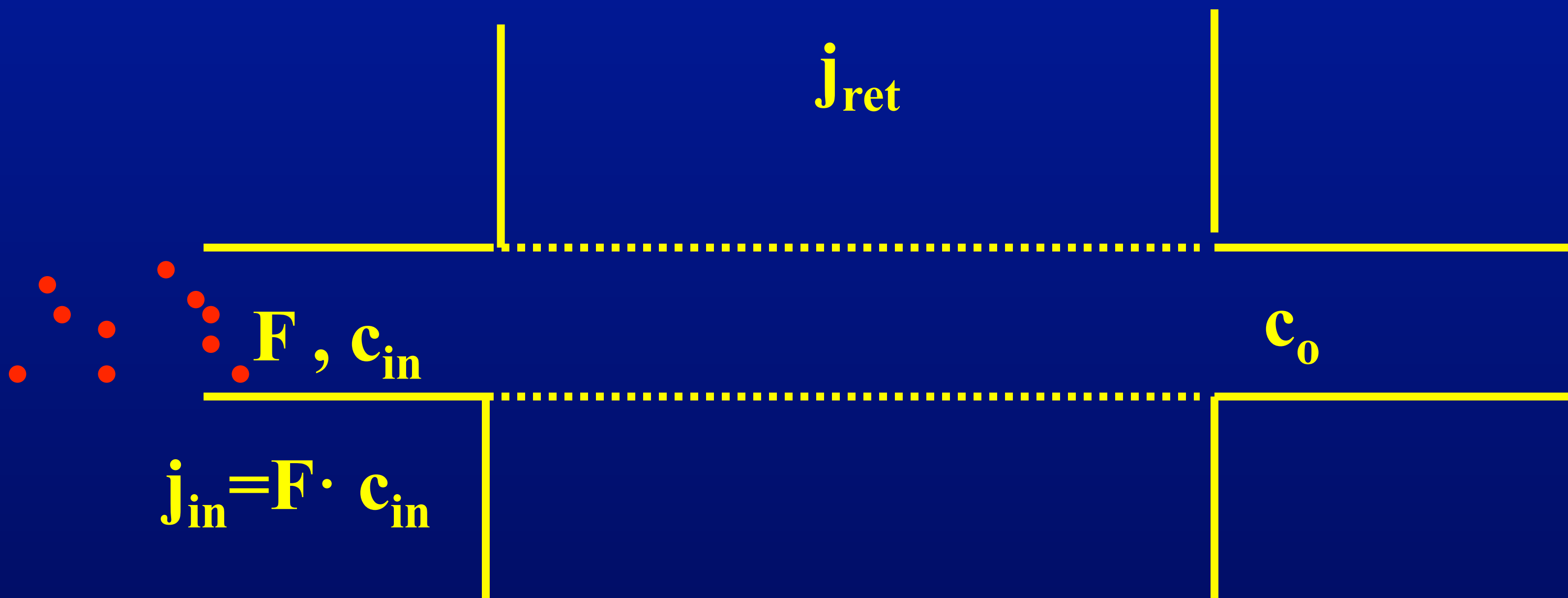
Break

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

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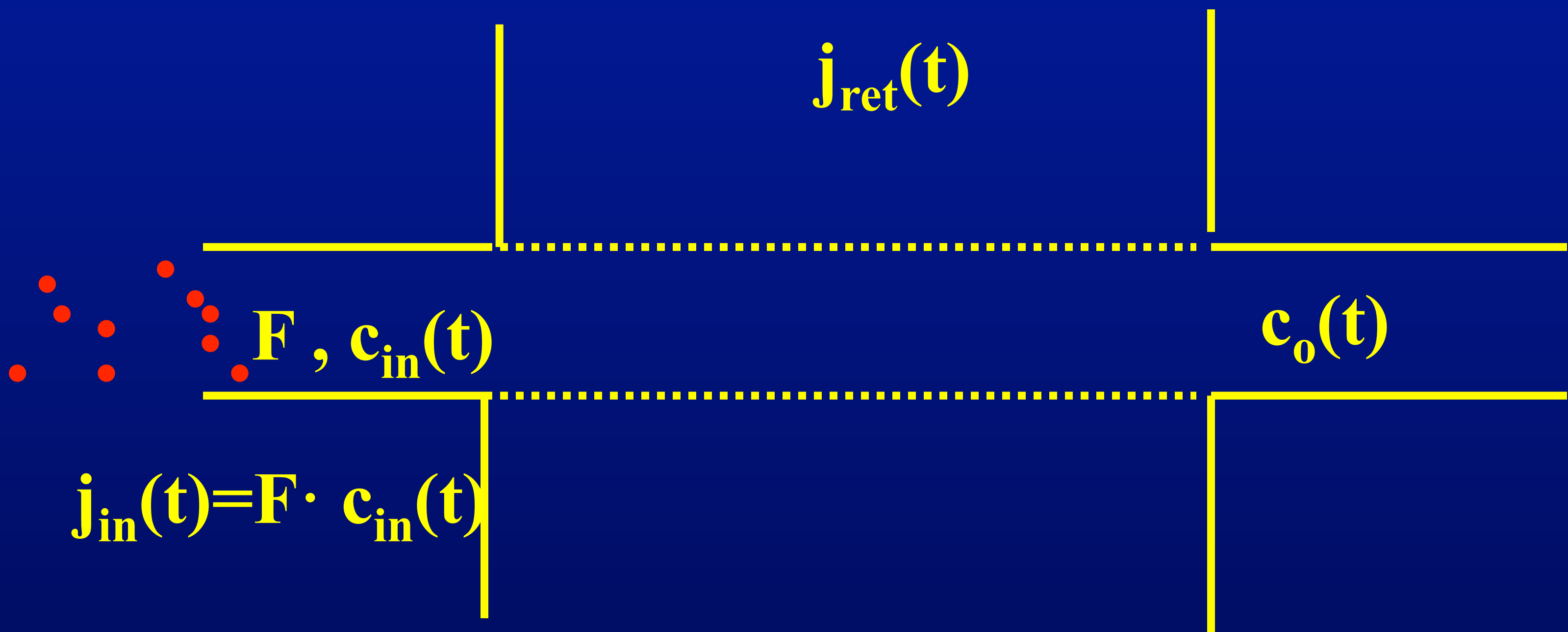
Extraction fraction



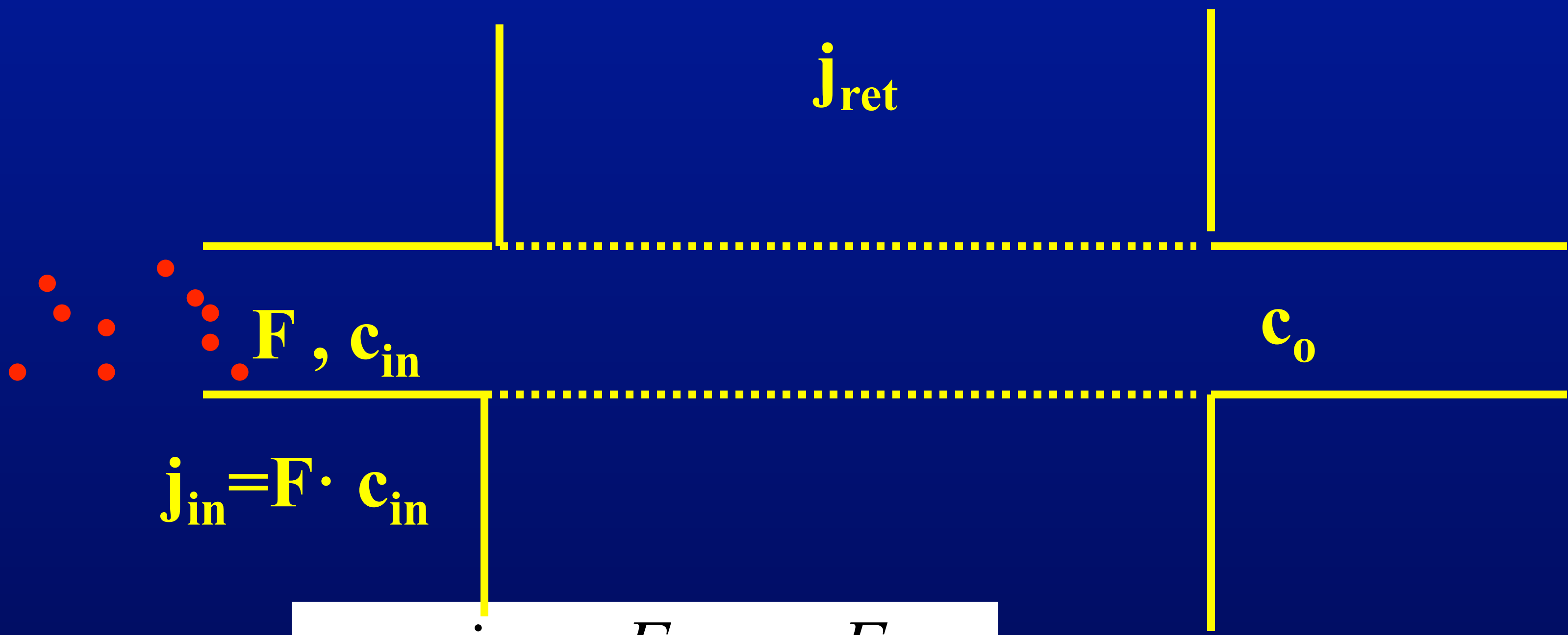
Extraction:

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

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

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Clearence

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

Clearence

clearence:

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

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

HBWL

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

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

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

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

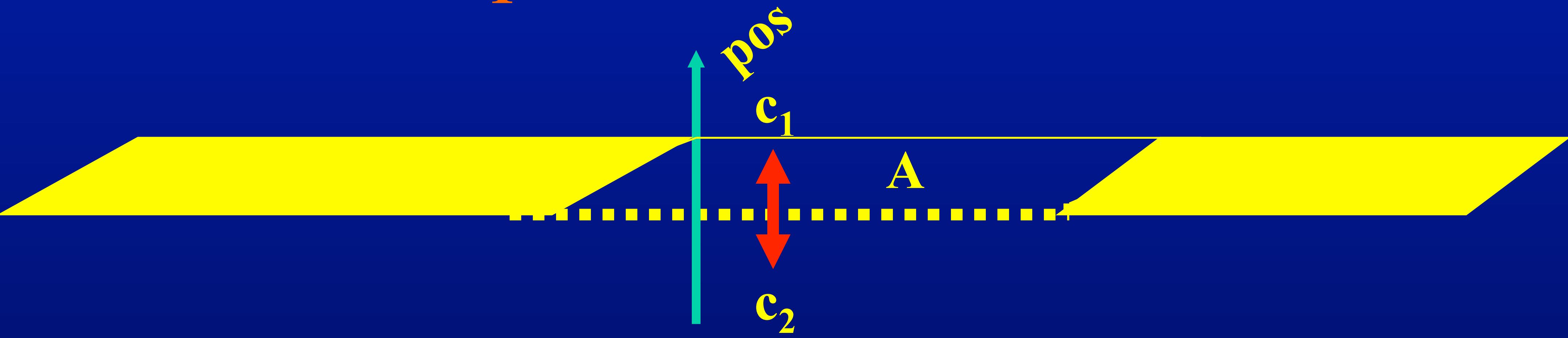
$$v\frac{dc(t)}{dt} = F \cdot c_{in}(t) - F \cdot c_o(t) - K_i \cdot c(t) = F \cdot c_{in}(t) - F \cdot c_o(t) - F \cdot E \cdot c(t)$$

$$c_o(t) = c(t):$$

$$v\frac{dc(t)}{dt} = F \cdot c_{in}(t) - F \cdot c(t) - F \cdot E \cdot c(t) = F \cdot (c_{in}(t) - (1+E) \cdot c(t))$$

Break

Transport over a membrane



$j \quad ? \quad c_2 - c_1$

$j = P(c_2 - c_1)$

$j = -P(c_1 - c_2)$

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

$[P] = \mathrm{cm/s}$

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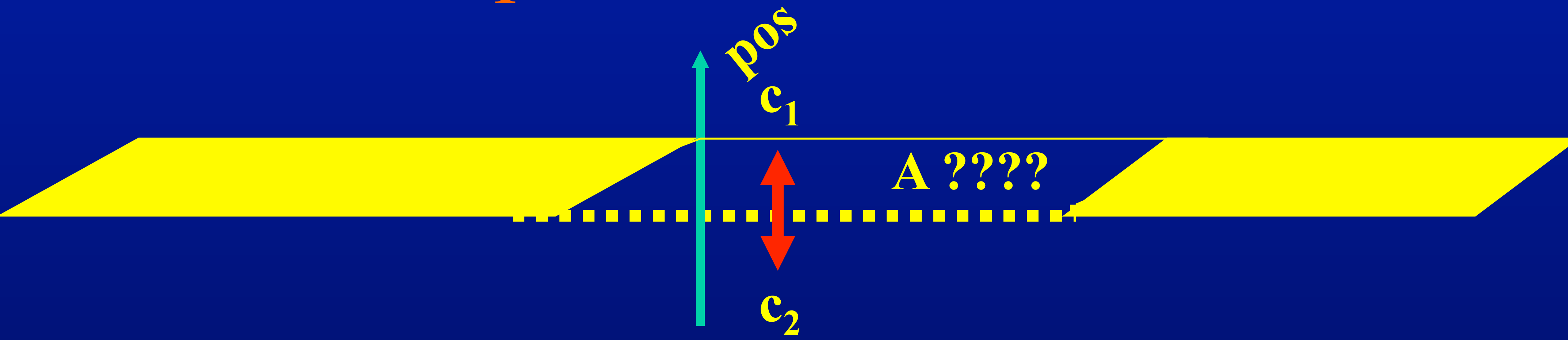
Transport over a membrane



$j = -PS(c_1 - c_2)$ S=surface area

mol/s =[PS] mol/ml

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

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Crone (1963) & Renkin (1959) equation

Transport over the capillary membrane

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

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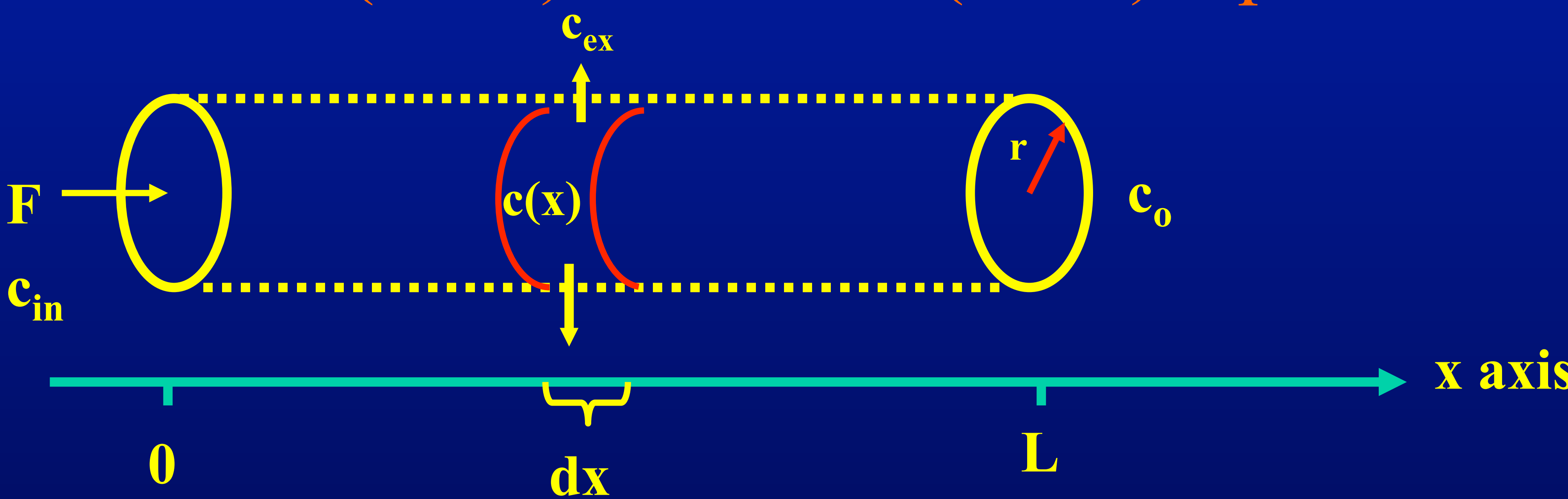
Crone (1963) & Renkin (1959) equation



The flux out of dx :

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

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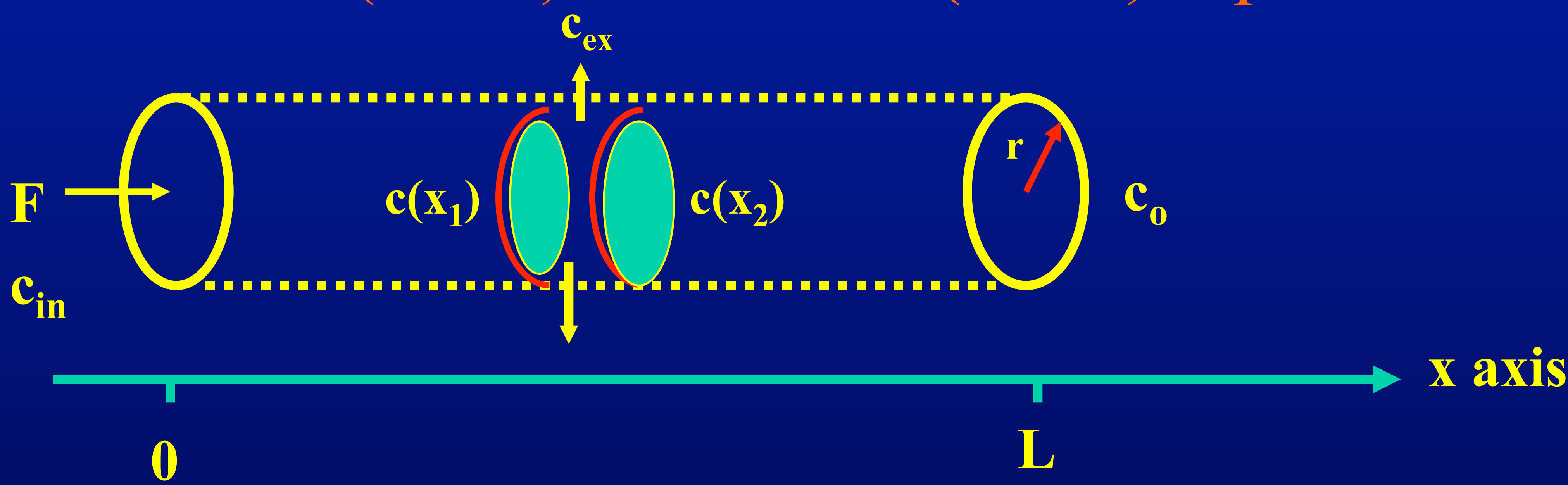
Crone (1963) & Renkin (1959) equation



The loss inside the capillary:

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

Fick's principle

$$dj = -Fdc(x)$$

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Crone (1963) & Renkin (1959) equation

Transport over the capillary membrane

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

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

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

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

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Crone (1963) & Renkin (1959) equation

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

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

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

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Accumulation of tracer in tissue can be

Flow Limited or Diffusion Limited

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

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

$$Cl = F\,E \to F$$

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Accumulation of tracer in tissue can be
Flow Limited or Diffusion Limited

Diffusion limited : PS/F is small

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

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

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

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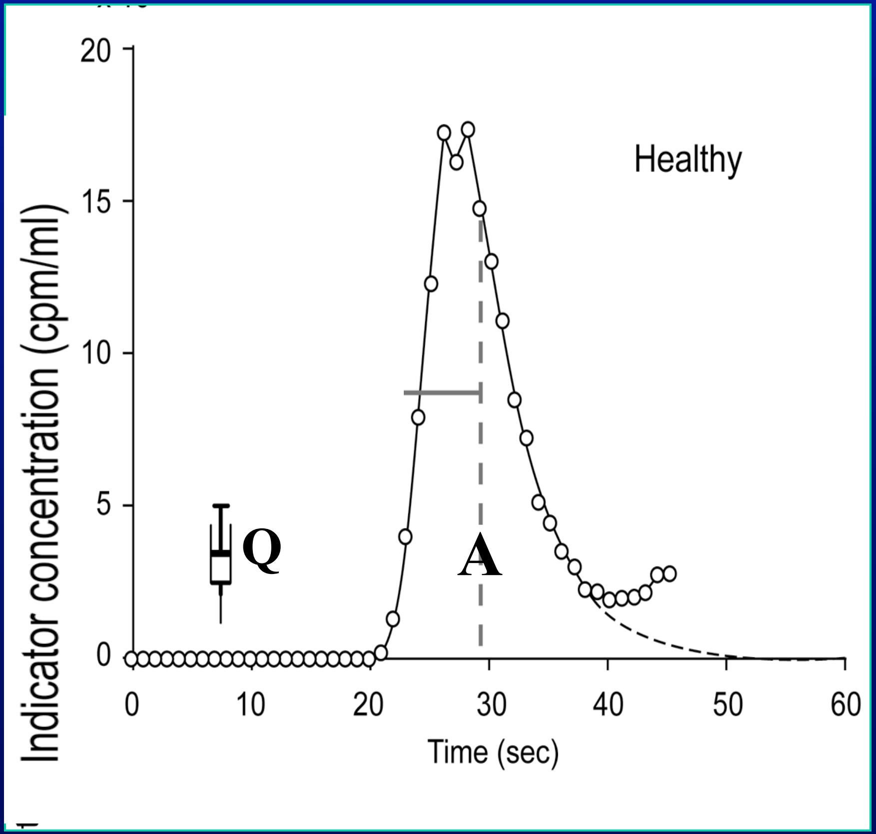
Break

Indicator-technique

Stewart-Henriques-Hamilton

Bolus injection



CO= Q/A

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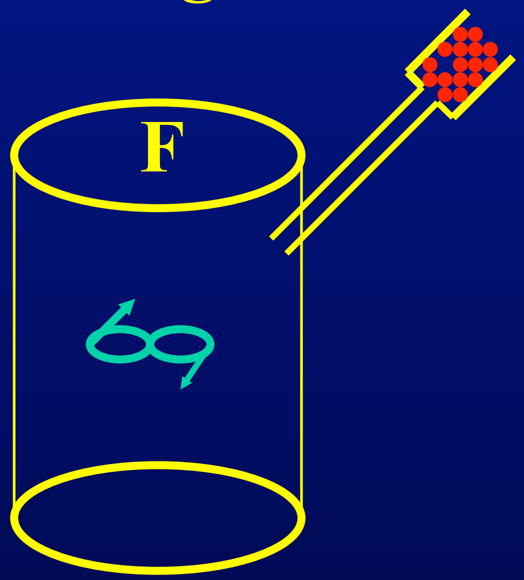
Indicator-dilution methods continued

Bolus injection (Henriques-Hamilton-Bergner principle)

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

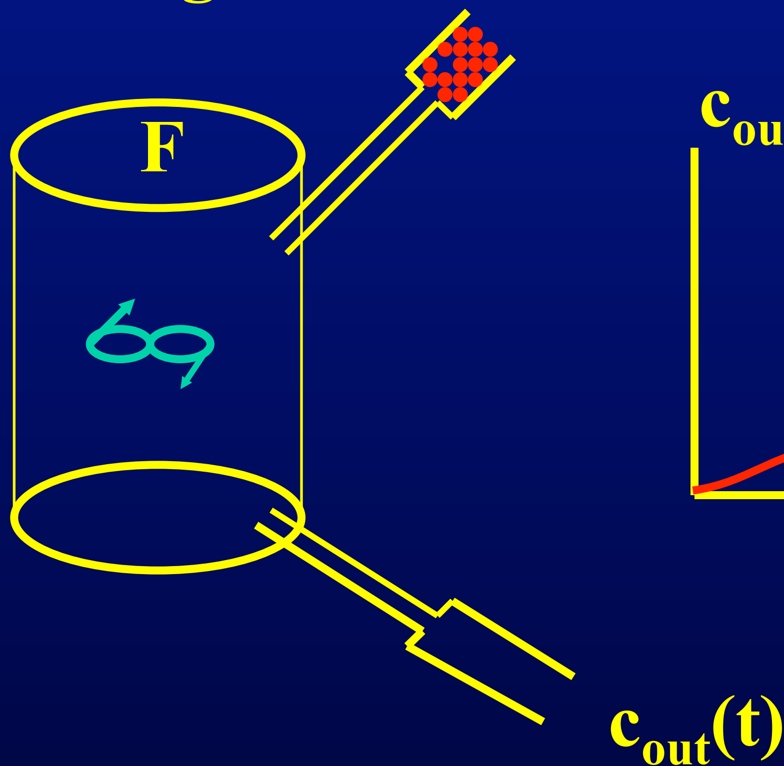


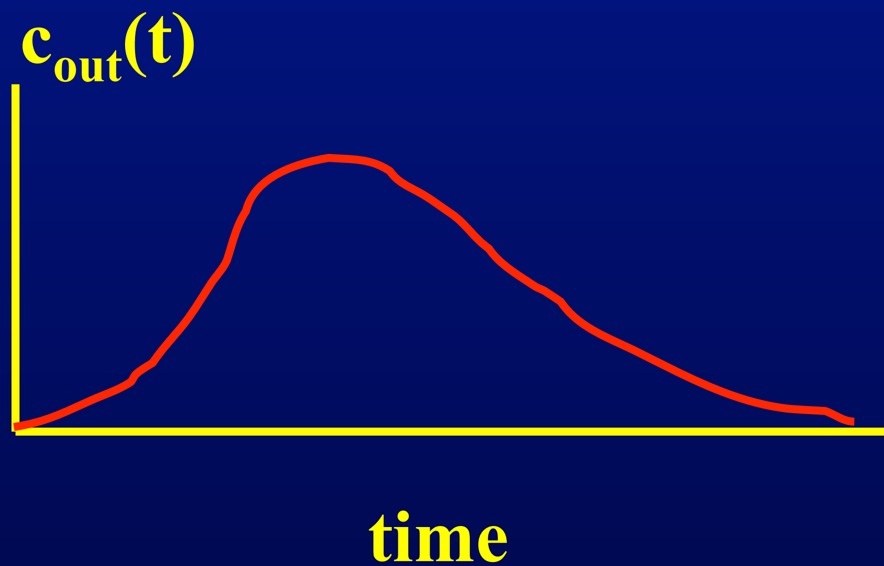
Injection of bolus Q_0 , a known amount of tracer

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





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Indicator-dilution methods continued

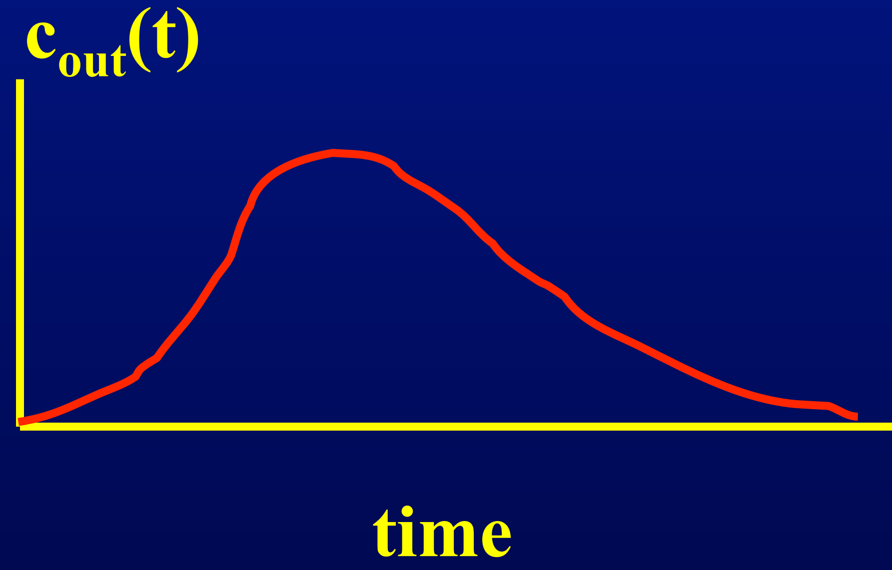
Bolus injection (Henriques-Hamilton-Bergner principle)

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

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

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

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



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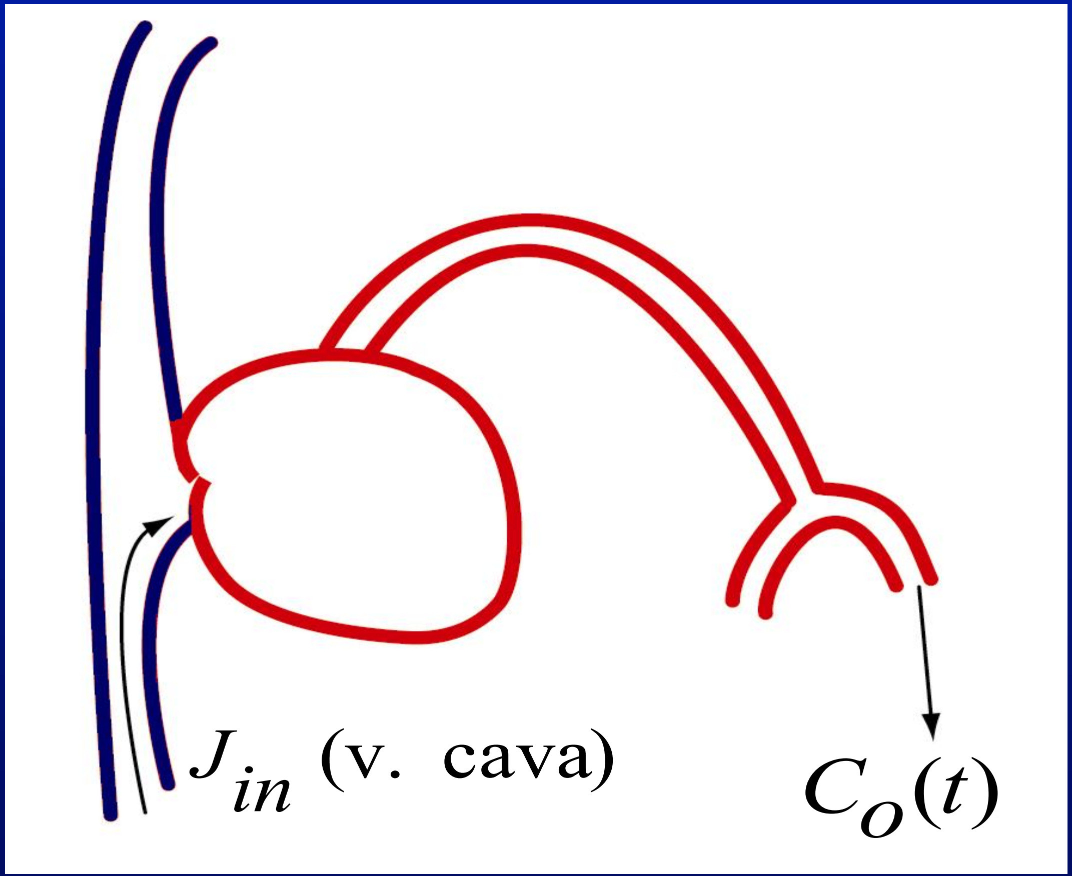

Bolus injection in vena cava/periferal vein, and outlet concentration measurement from a peripheral artery.

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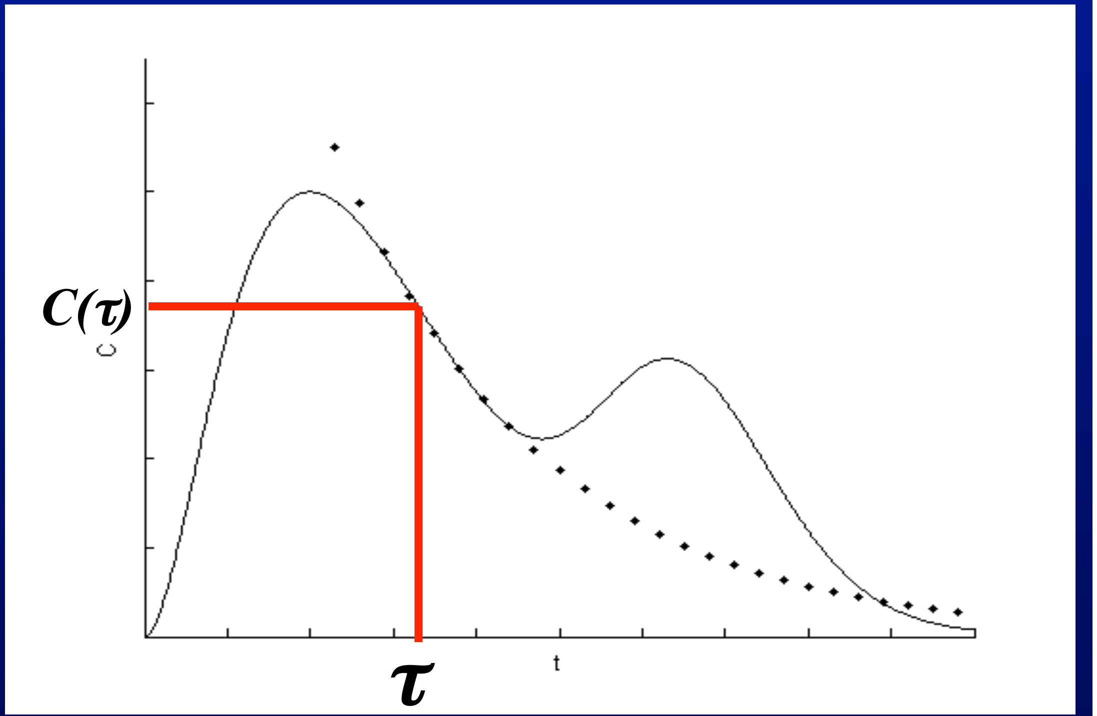

$$\int_{o}^{\infty} C_o(t)dt = \int_{o}^{\tau} C_o(t)dt + \int_{\tau}^{\infty} C(\tau)e^{-k(t-\tau)}dt =$$

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

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

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

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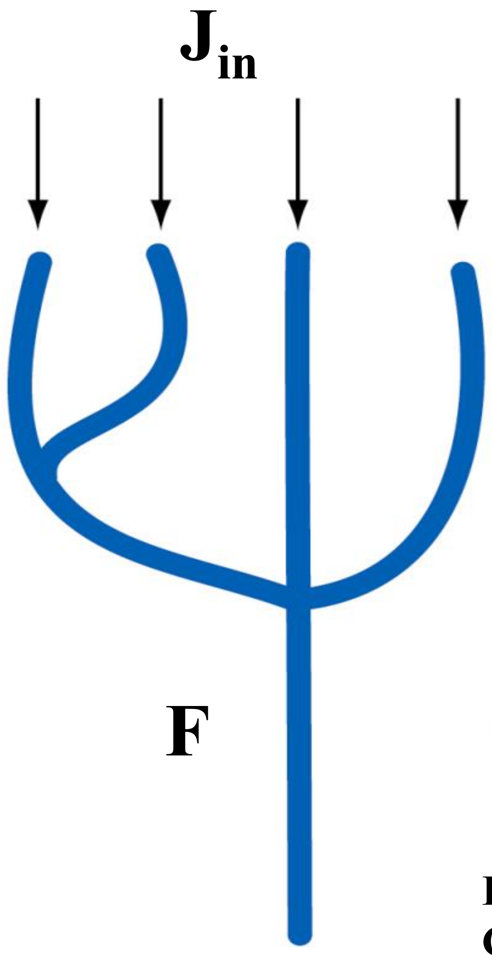
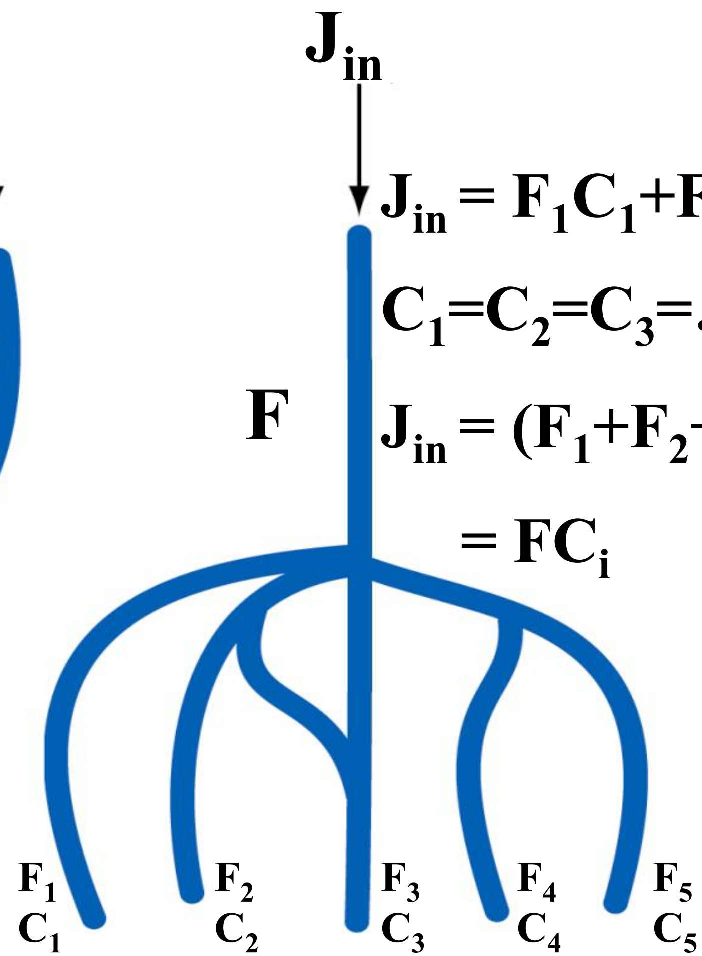
Bolus Fraktion principle - Sapirsteins principle



$J_{in} = F\ C_o$



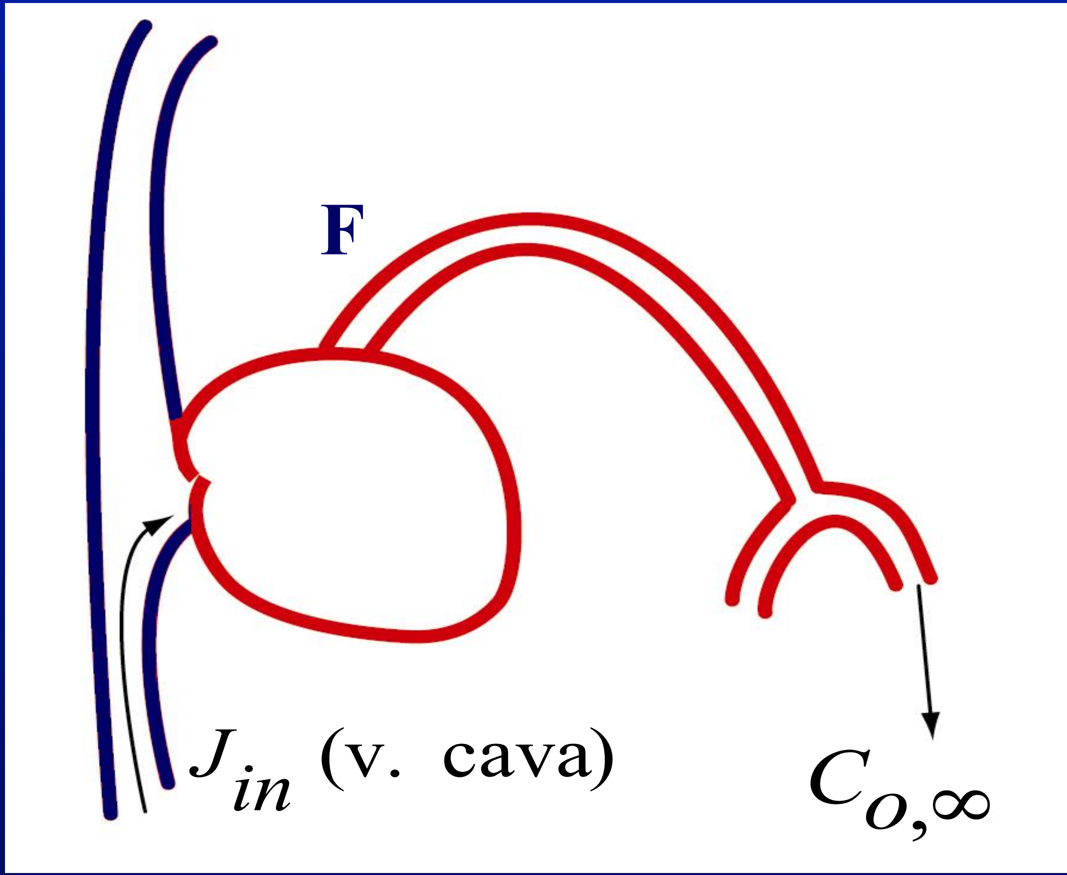
$J_{in} = F_1C_1 + F_2C_2 + F_3C_3 + \ldots$

$C_1 = C_2 = C_3 = \ldots$

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

$= FC_i$

HBWL

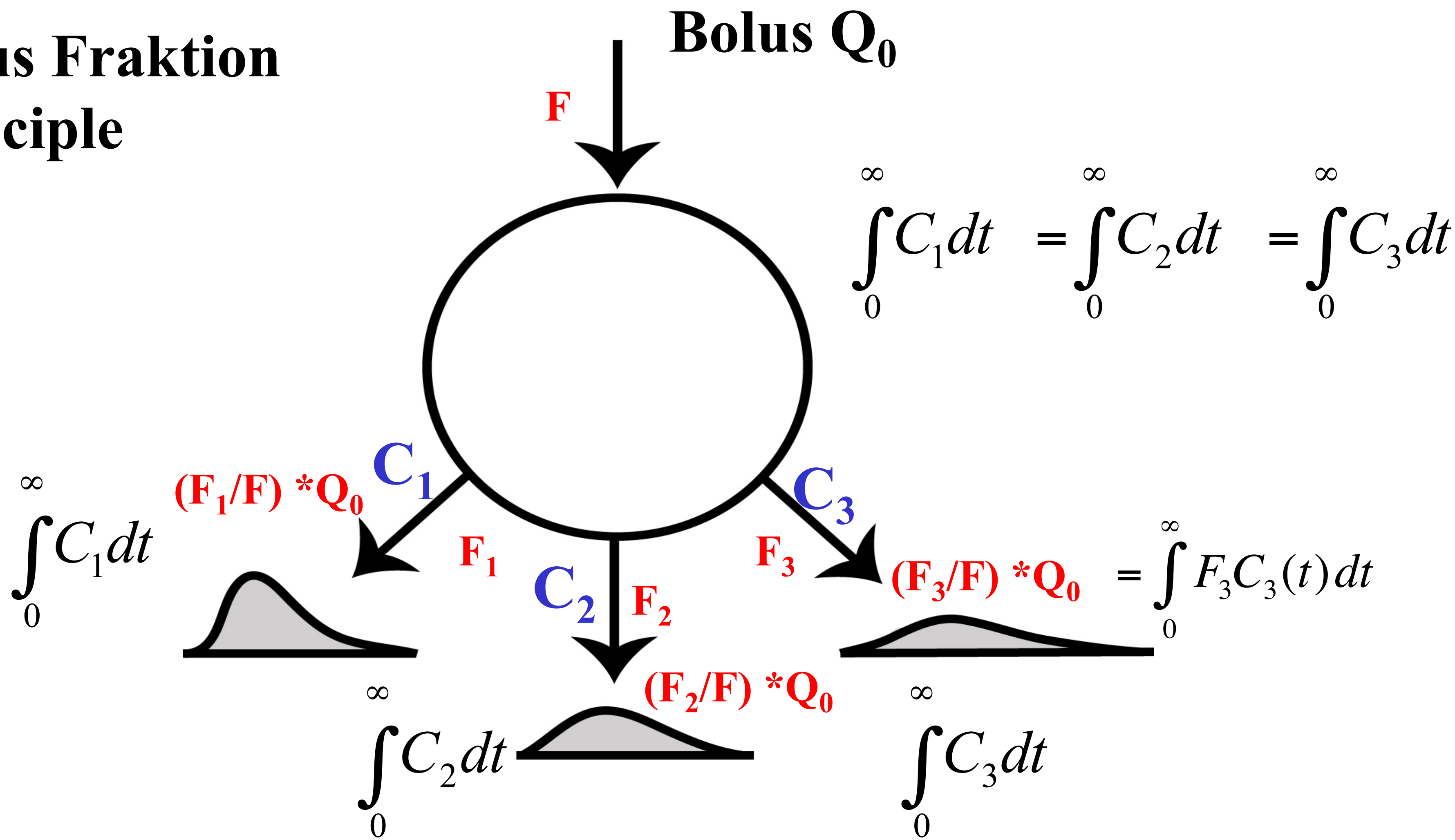


So the outlet concentration can be measured from a convenient artery

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

HBWL

Bolus Fraktion principle

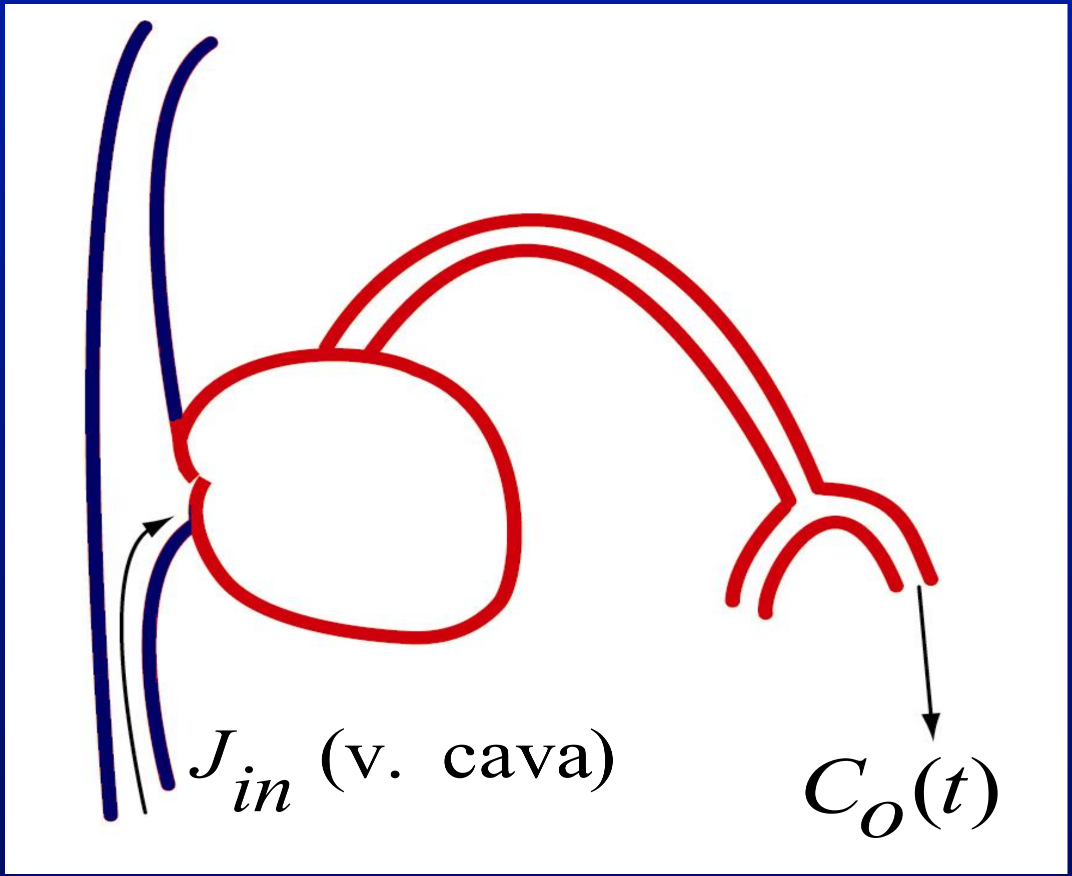


Equal area rule. The shape is different but the areas of the different outles are equal. This allows us to choose freely the most appropriate sampling point with regards the outlet concentration measurement.

HBWL

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

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

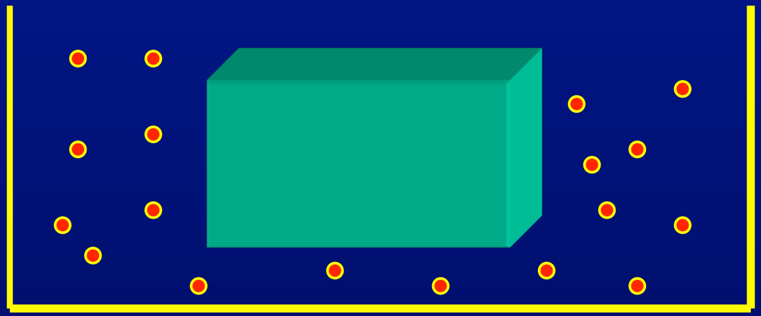


So the outlet concentration can be measured from a convenient artery

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}

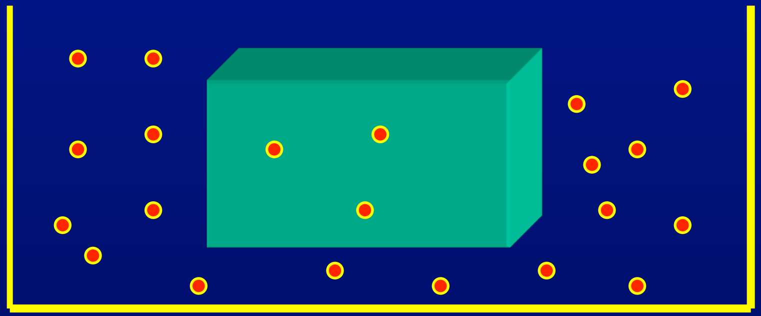
$$V_d \equiv Q/c_{ref}$$

$$[V_d] = \text{mmol/mmol/ml} = \text{ml}$$

HBWL

The volume of distribution: V_d

A tissue element



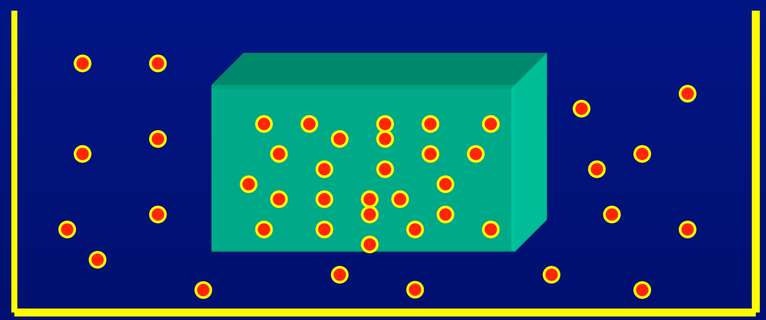
$V_d \equiv Q/c_{ref}$

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 : $[\lambda]$ = ml/g

or

V is the (real) volume of the tissue : $[\lambda]$ = ml/ml

HBWL

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

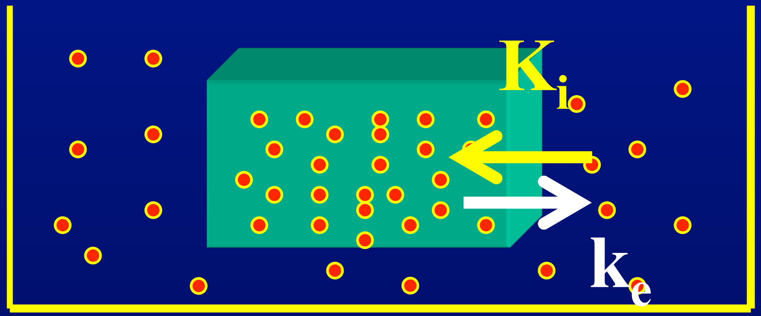
HBWL

The volume of distribution: V_d

$V_d \equiv Q/c_{ref}$

$\lambda = C_{tissue}/C_{ref}$

A tissue element



$$J_{in}(t) = K_i C_{ref}(t)$$

$$J_o(t) = K_i C_{eff}(t) = K_i \frac{C_{tissue}(t)}{\lambda} = k_e C_{tissue}(t) \quad \wedge \quad C_{eff}\lambda = C_{tissue}$$

When equilibration established:

$$J_{in}(\infty) = J_o(\infty) \Leftrightarrow$$

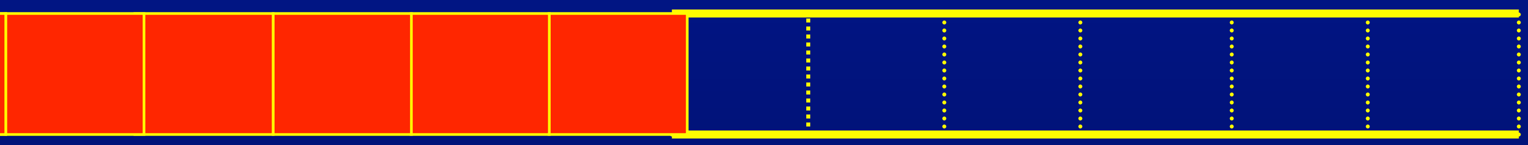
$$K_i C_{ref}(\infty) = k_e C_{tissue}(\infty) \Leftrightarrow \frac{K_i}{k_e} = \frac{C_{tissue}(\infty)}{C_{ref}(\infty)} = \lambda$$

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

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

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

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

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

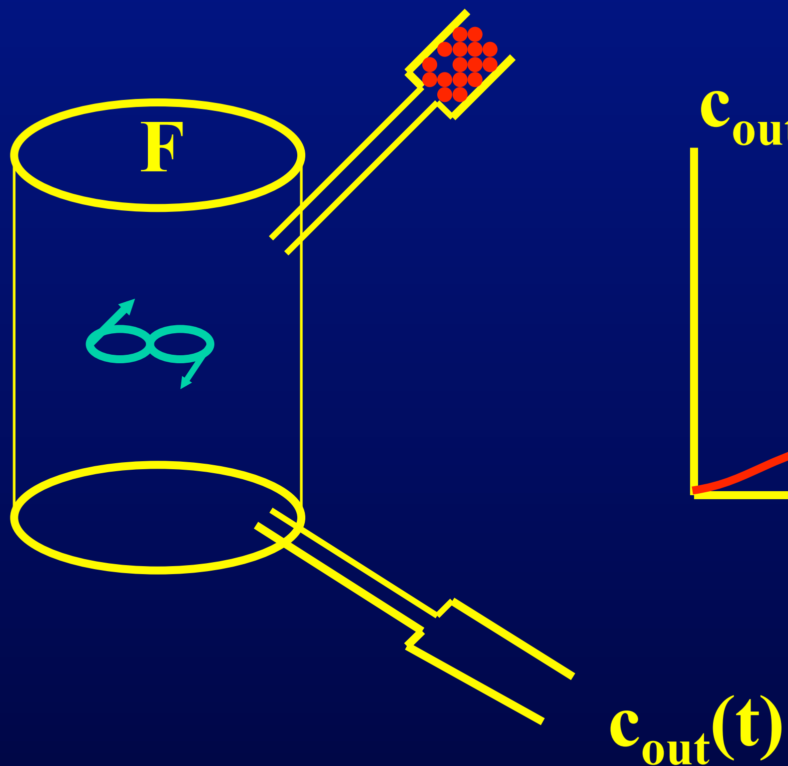
In words : It is the fraction of the dose given as an impuls (a delta function), which leaves the system per unit time !!!! , at time t, (and therefore a function of time)

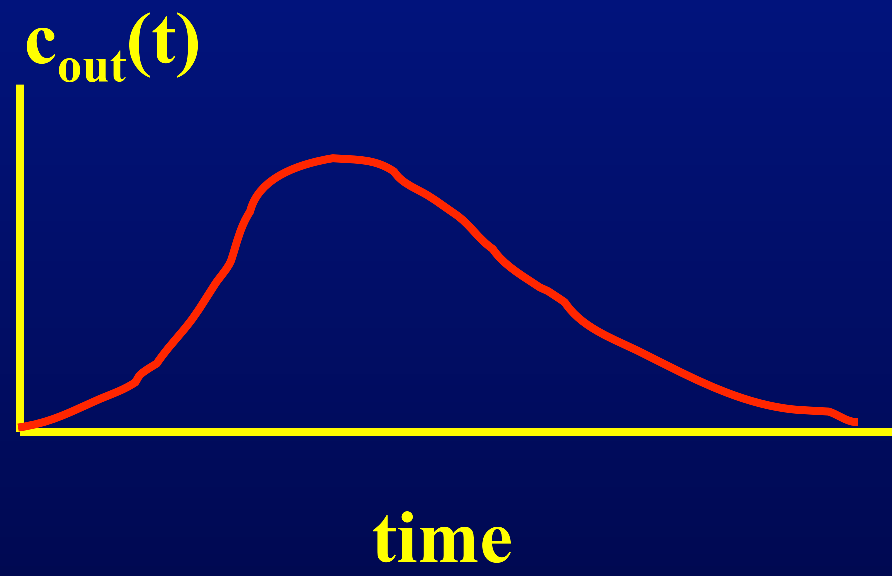
$$\bar{t} = \int_0^\infty t \cdot h(t) \cdot dt$$

Finding h(t)

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

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

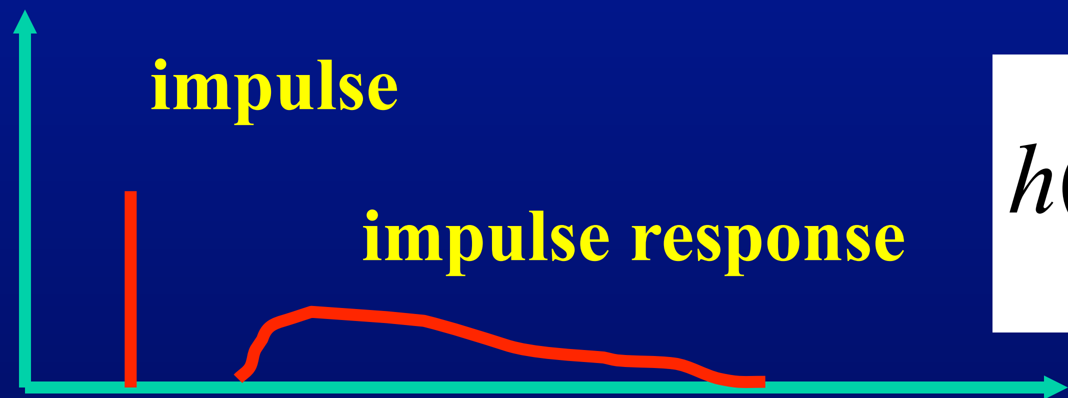




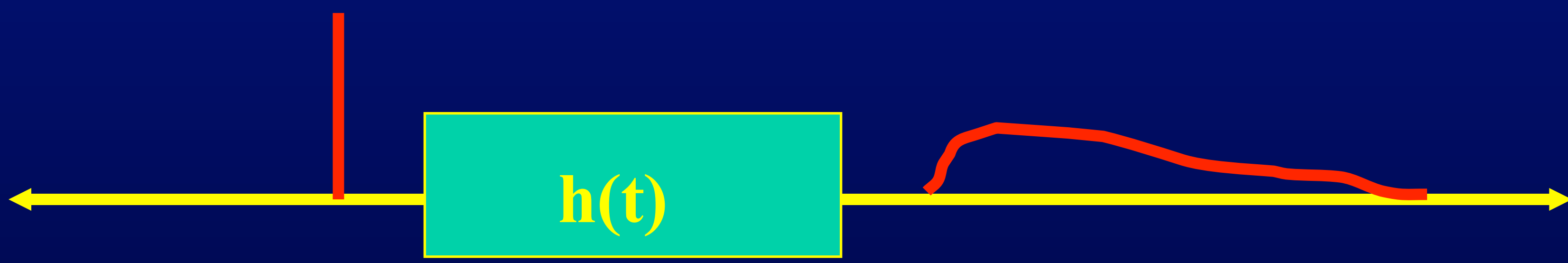
HBWL

Break

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



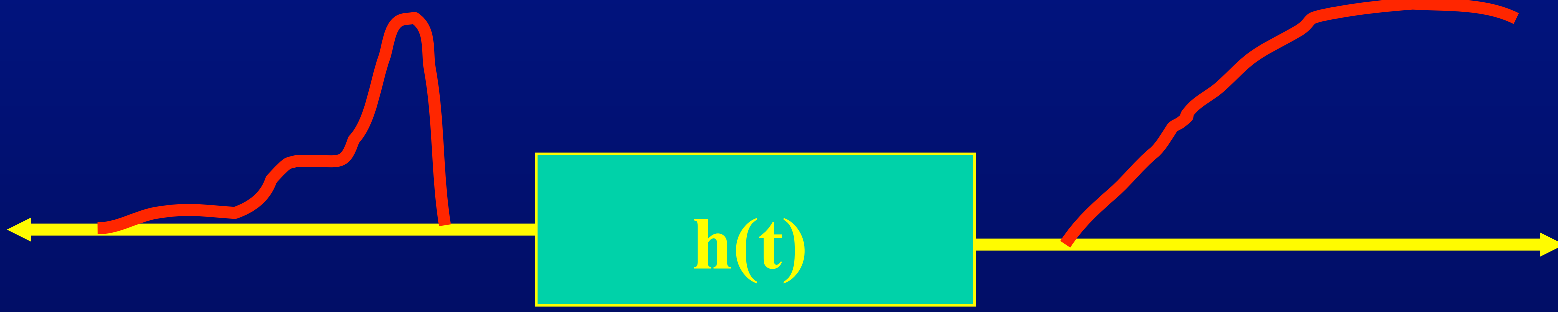
$$h(t) = \frac{dQ(t)}{Q_0 dt}$$



HBWL

Why is h(t) interesting ?

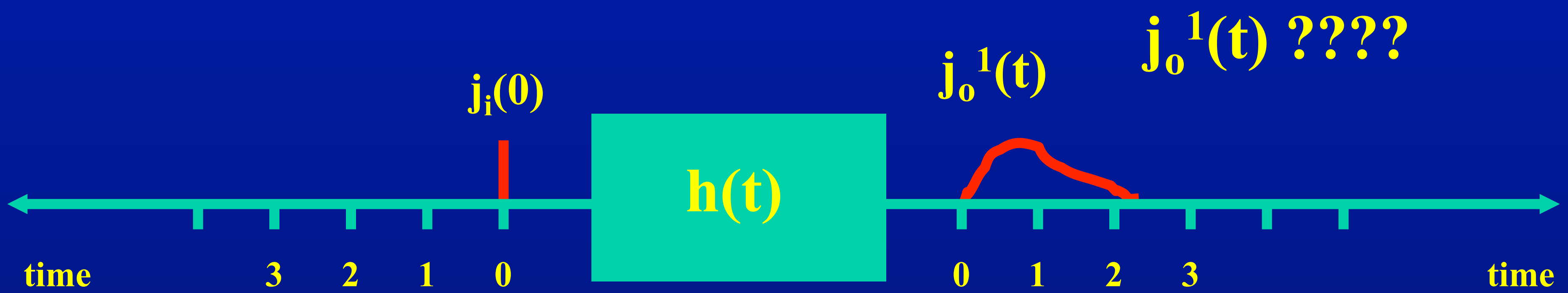
Because it relates input to an output in the case of the input not being a bolus (a deltafunction) !



j_i : input **j_o : output**

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

HBWL

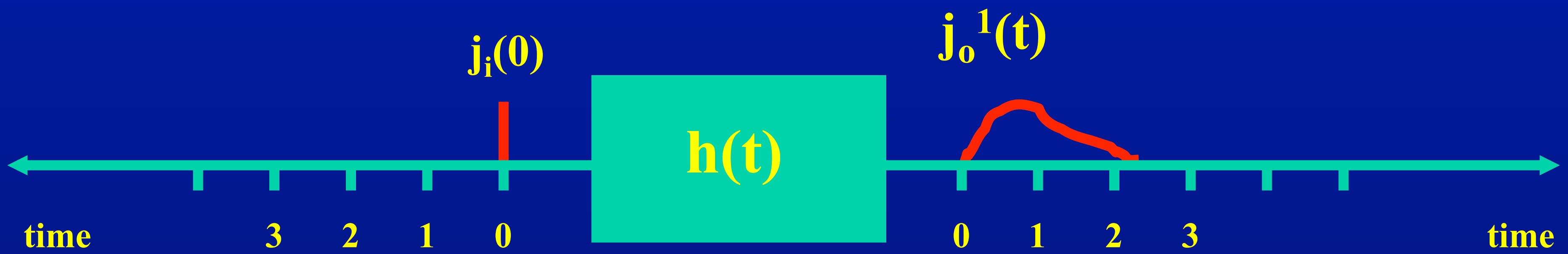


e.g $j_i(0) = 1$ mmol / 0.01s

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

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

HBWL

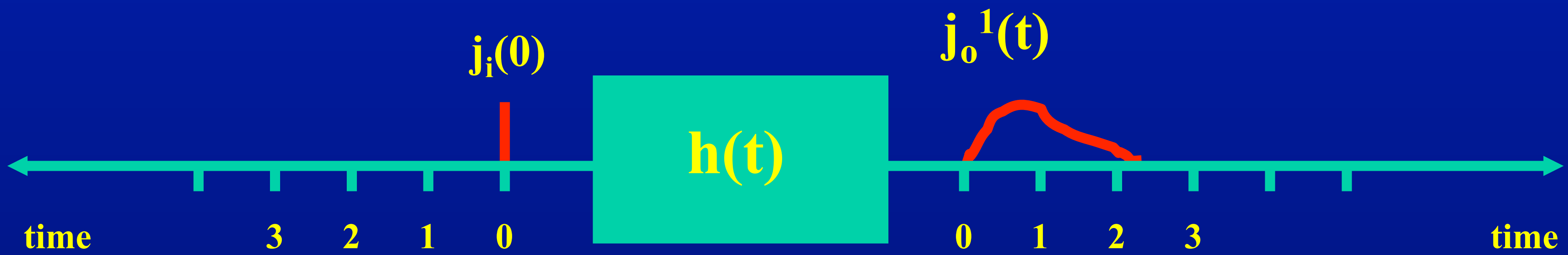


$$\text{e.g } j_i(0) = 1 \text{ mmol} / 0.01\text{s}$$

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

Flux entering the system at time zero

HBWL

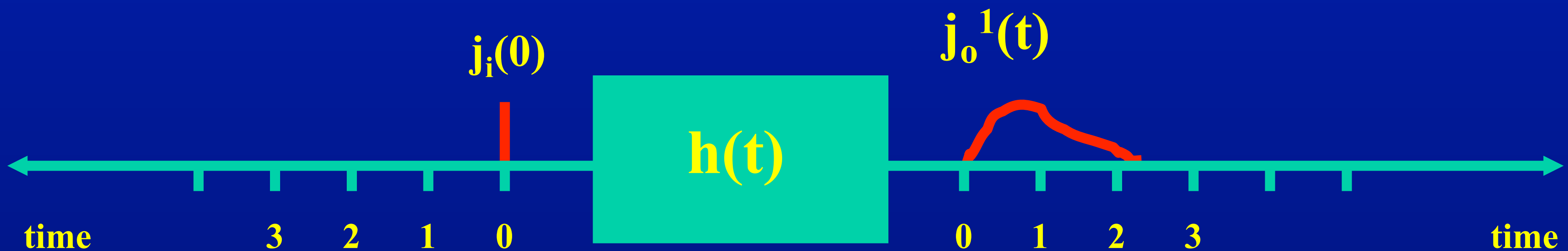


e.g $j_i(0) = 1$ mmol / 0.01s

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

A small time interval

HBWL

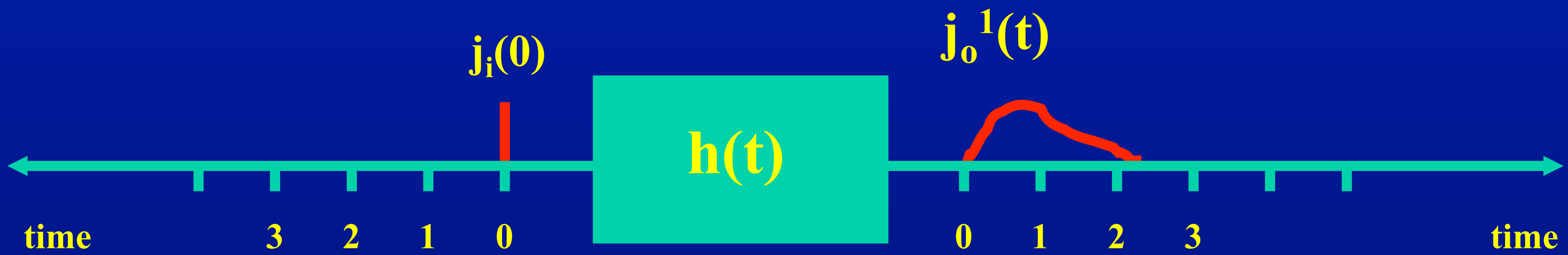


e.g $j_i(0) = 1$ mmol / 0.01s

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

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

HBWL

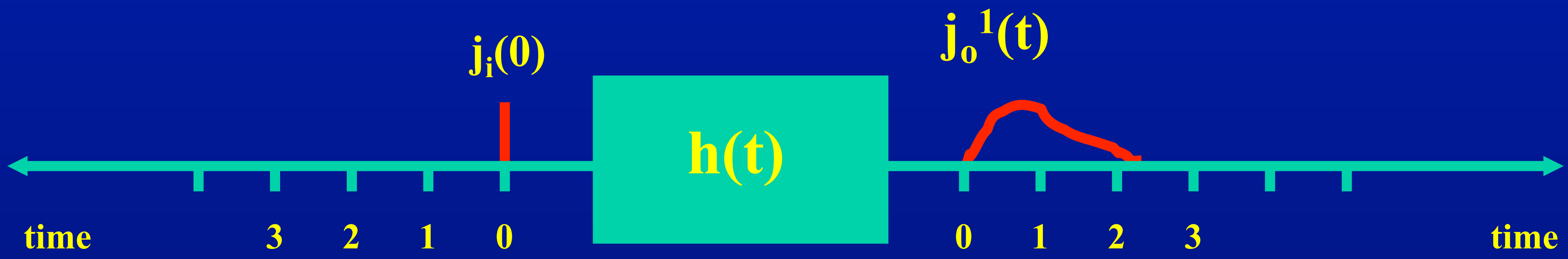


e.g $j_i(0)$ = 1 mmol / 0.01s

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

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

HBWL

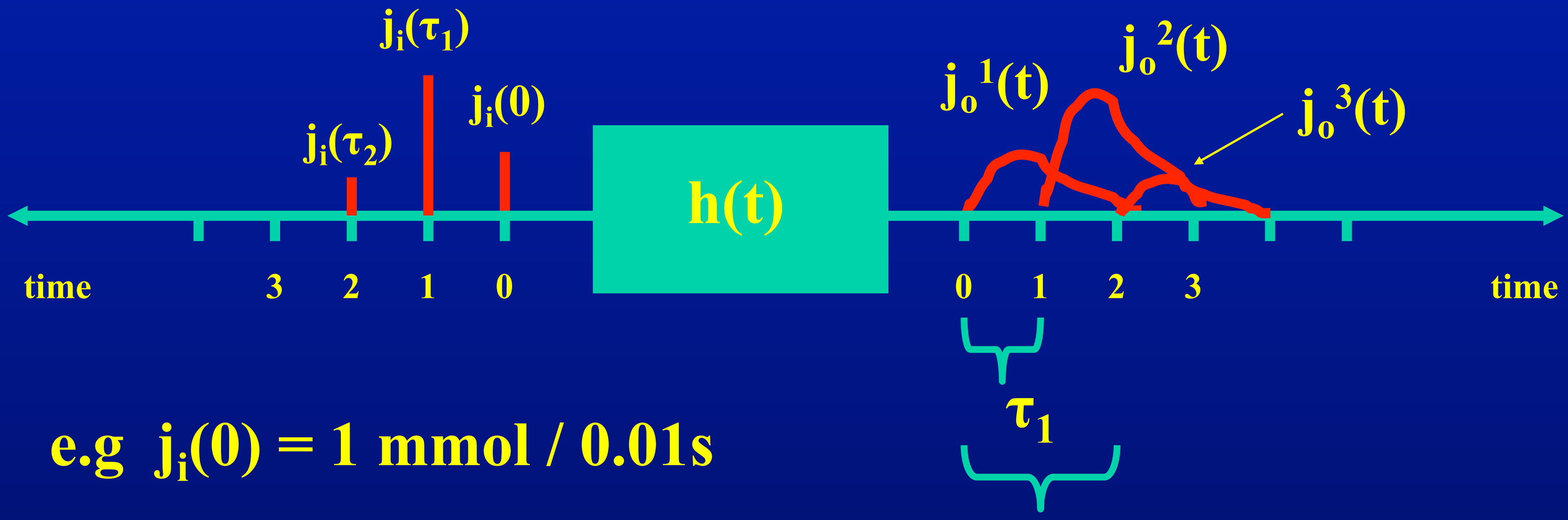


e.g $j_i(0) = 1$ mmol / 0.01s

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

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

HBWL



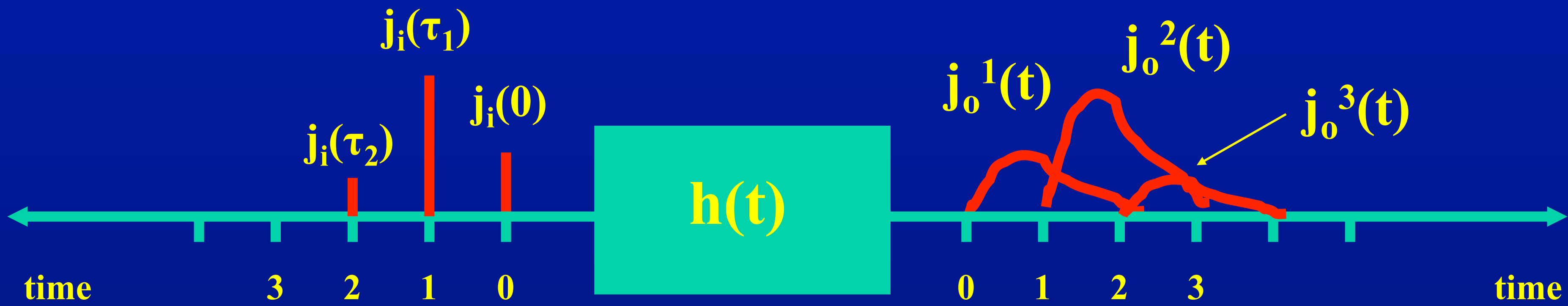
e.g $j_i(0)$ = 1 mmol / 0.01s

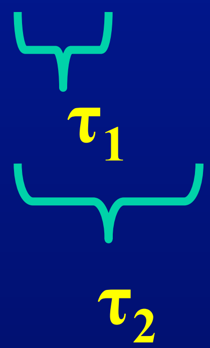
$$j_o^1(t) = j_i(0)\,\Delta\tau\, h(t)$$

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

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

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) !!

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

$$\int_0^{+\infty} h(t)\,dt = \frac{1}{\int_0^{\infty} c_o(t)\,dt} \int_0^{\infty} c_o(t)\,dt = 1$$

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

HBWL

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

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

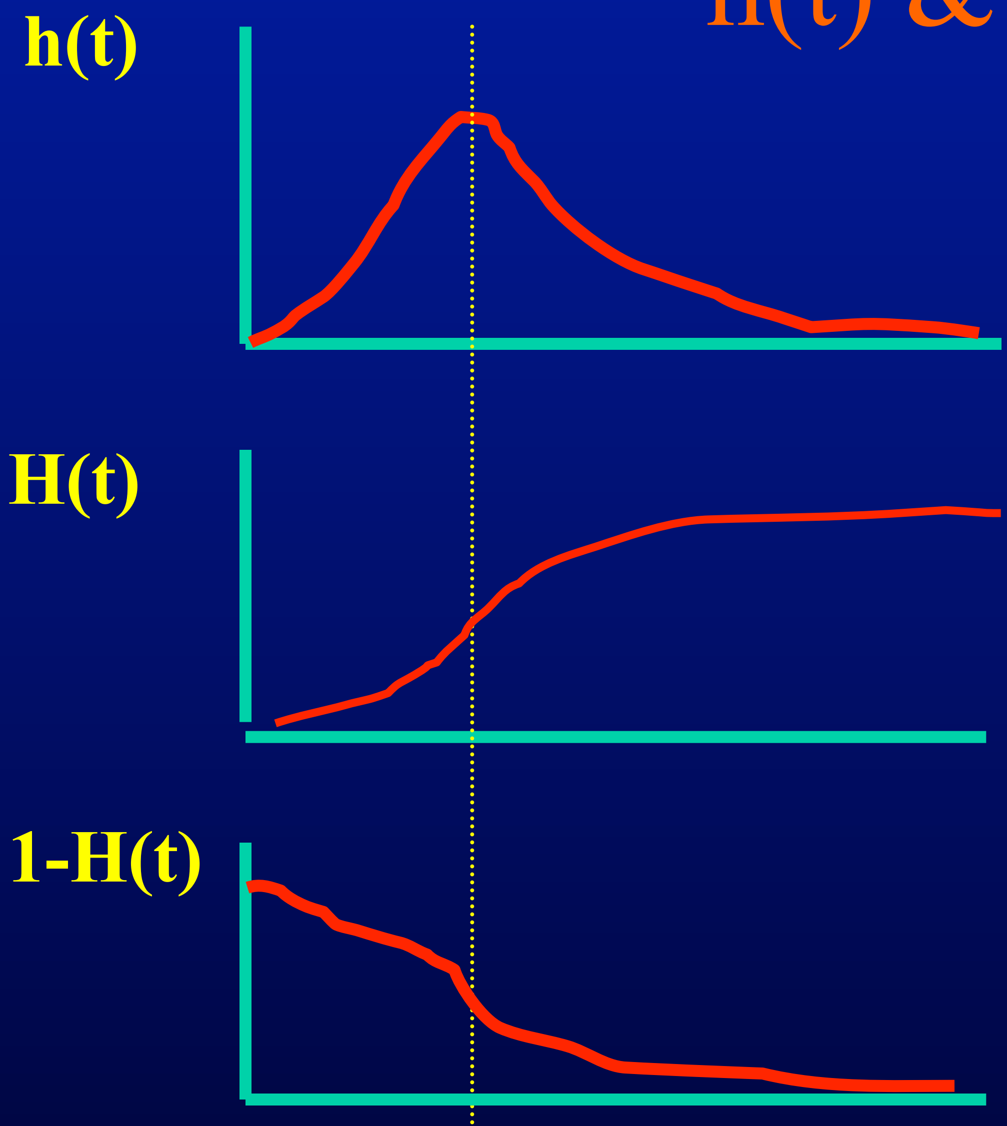
h(t) & H(t) !!

The residue impulse response function

$$\boxed{1 - H(t)}$$

HBWL

h(t) & H(t) !!

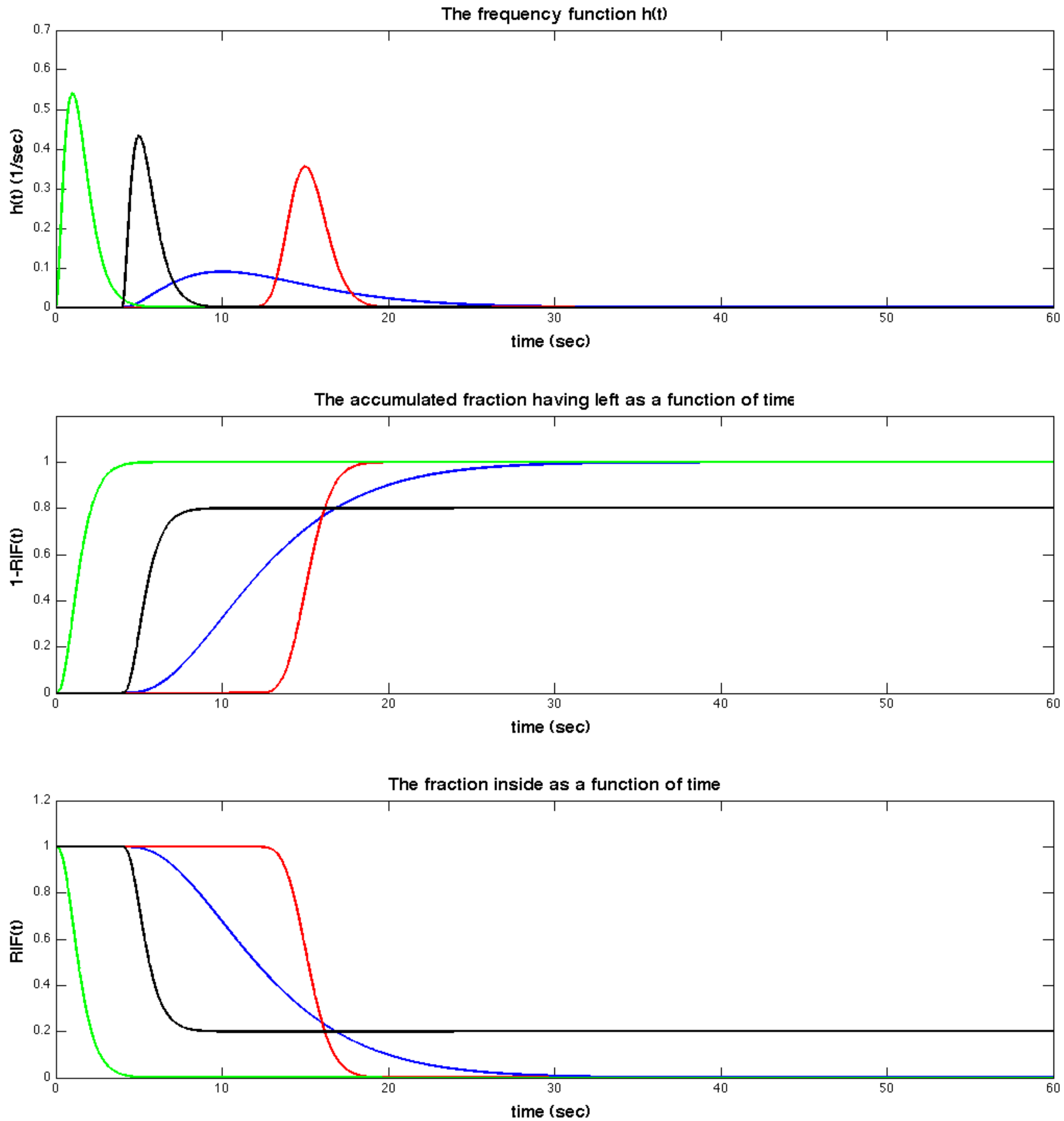


$$h(t) = \frac{dH(t)}{dt}$$

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

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

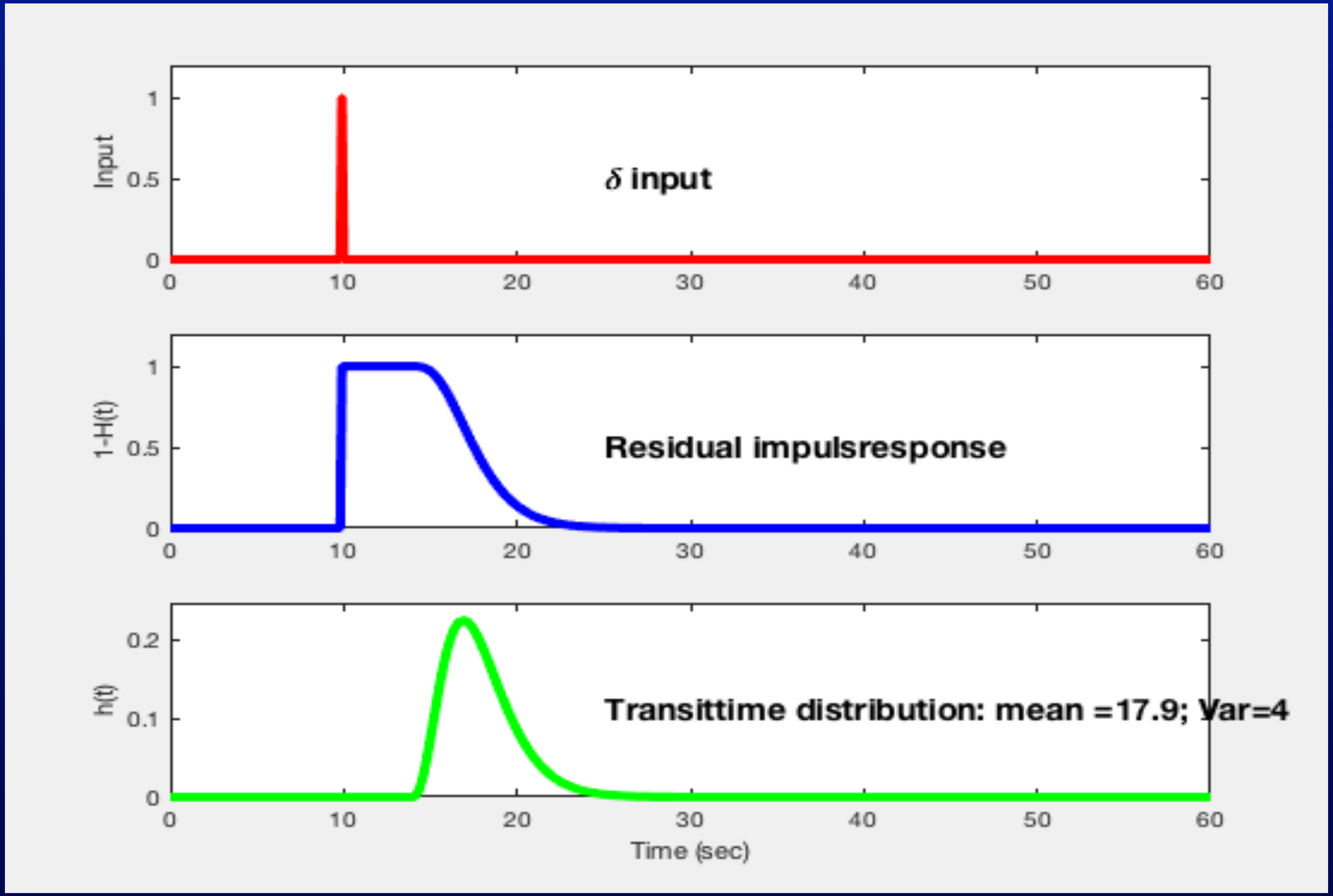
HBWL



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

outpu
t

h(t) & H(t) !!

$$\bar{t} = \int_{0}^{\infty} [1 - H(t)]\, dt$$

HBWL

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

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

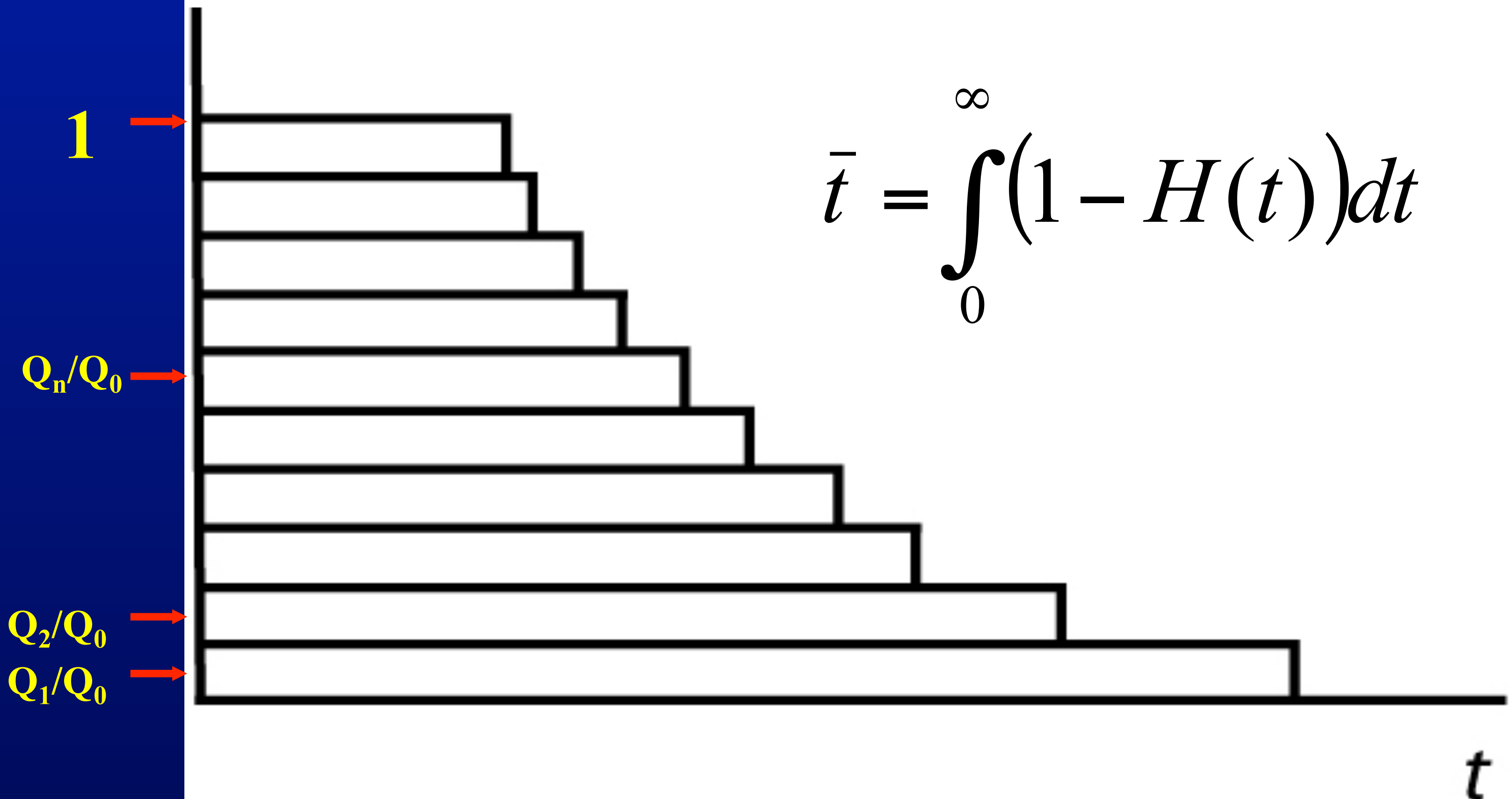


Illustration of transittimes and mean transittime estimated by residual measurement.

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

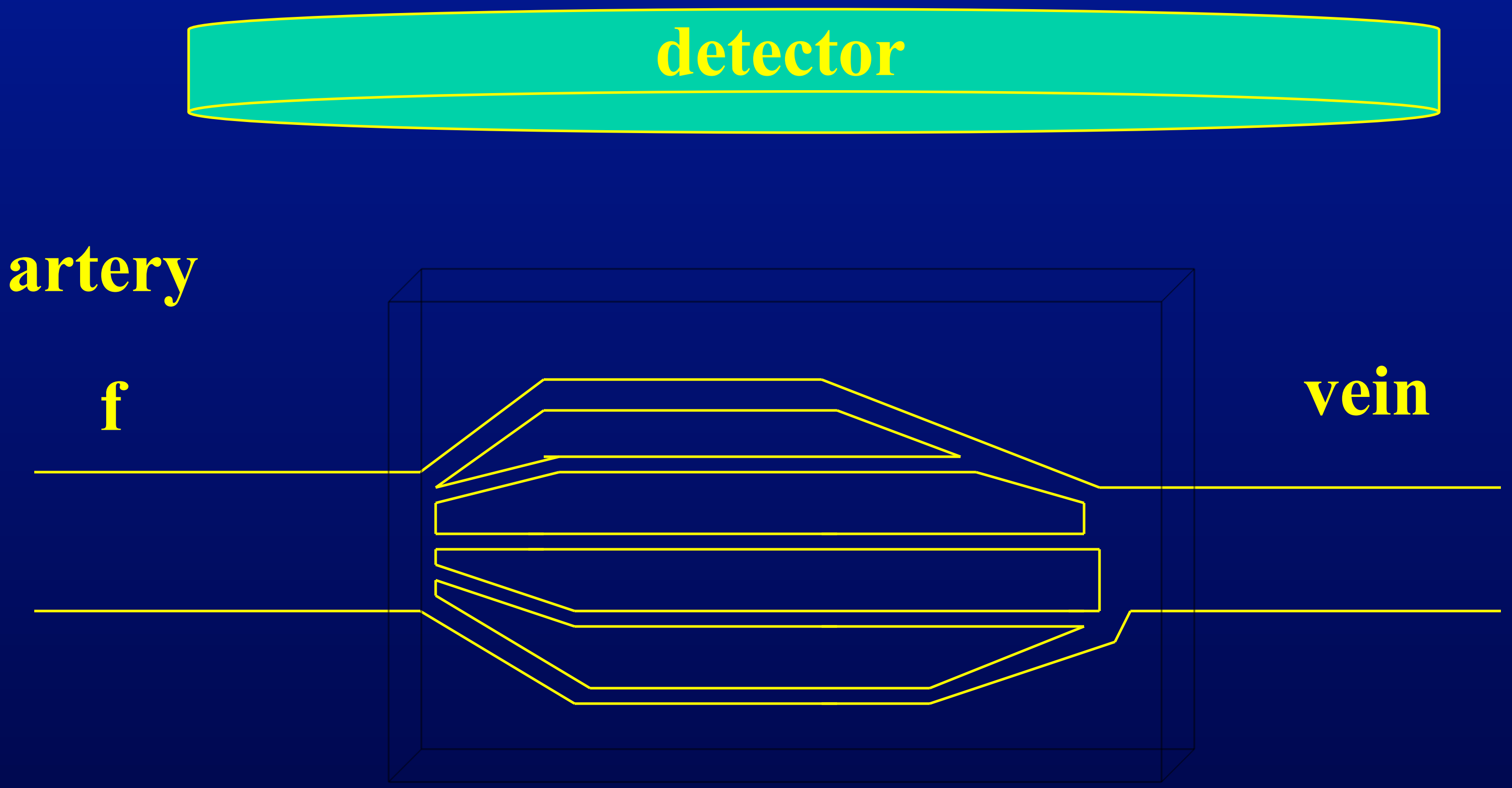
Residue detection in CT-PET- SPECT-MRI

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

$$1 - H(t)$$

HBWL

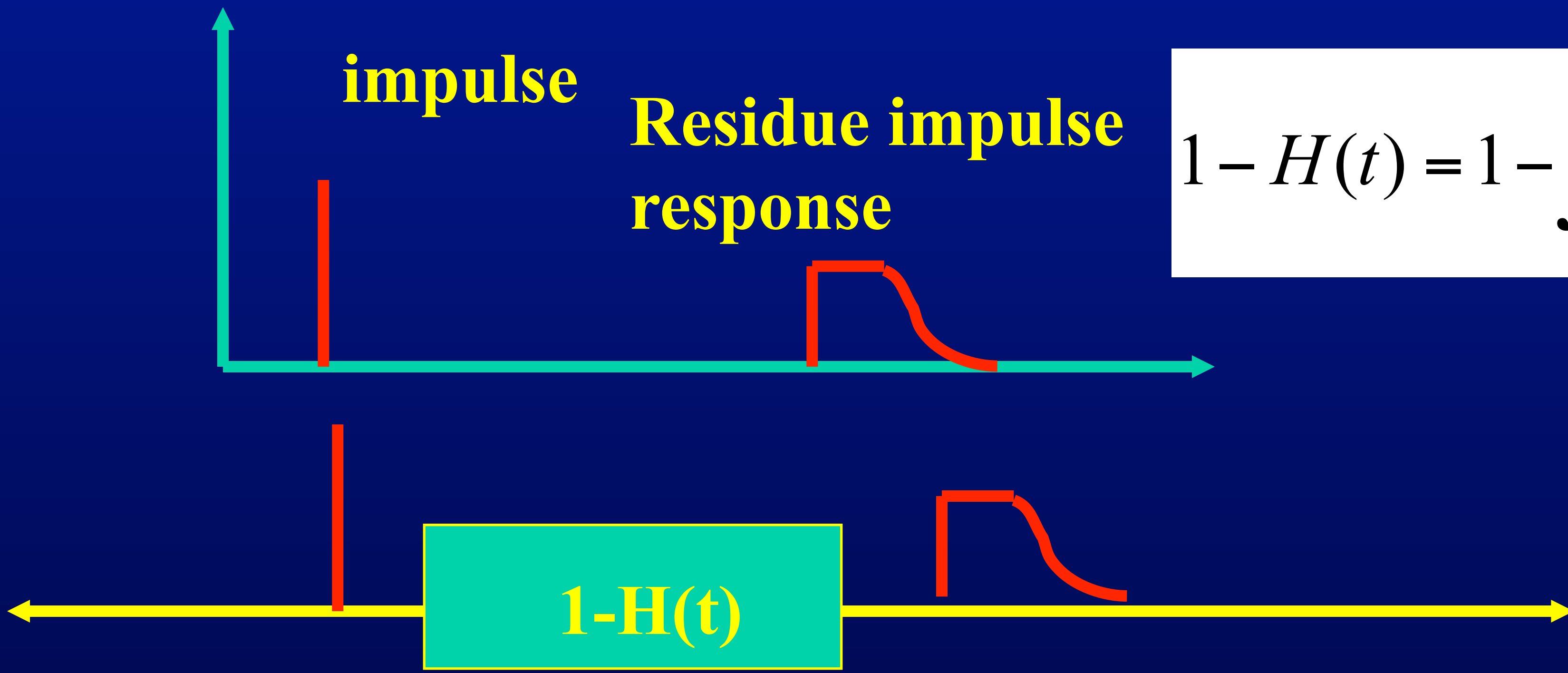
Measuring perfusion by an external registration: CT,SPECT,PET,MRI



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**

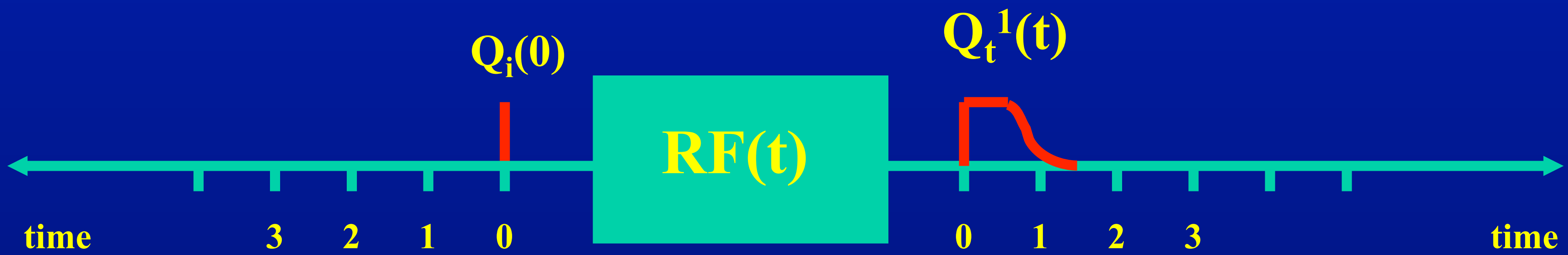
$$C_t(t) = f\, C_a(t) \otimes RF(t) = f \int_0^t C_i(\tau) RF(t-\tau)\, d\tau$$

HBWL

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

The number which enters the system at time zero

HBWL



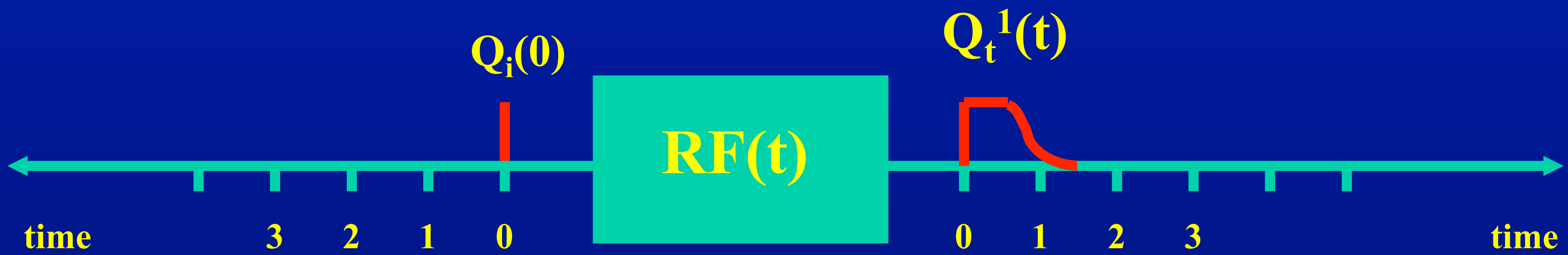
$$Q_i(0) = F\ C_i(0)\ \Delta\tau$$

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

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

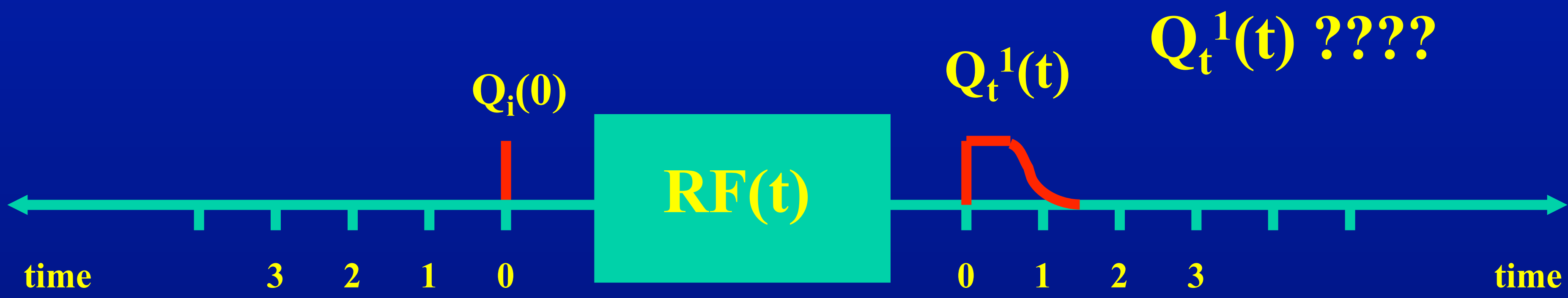
The flux which enters the system at time zero

HBWL

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

The number which enters the system at time zero

HBWL

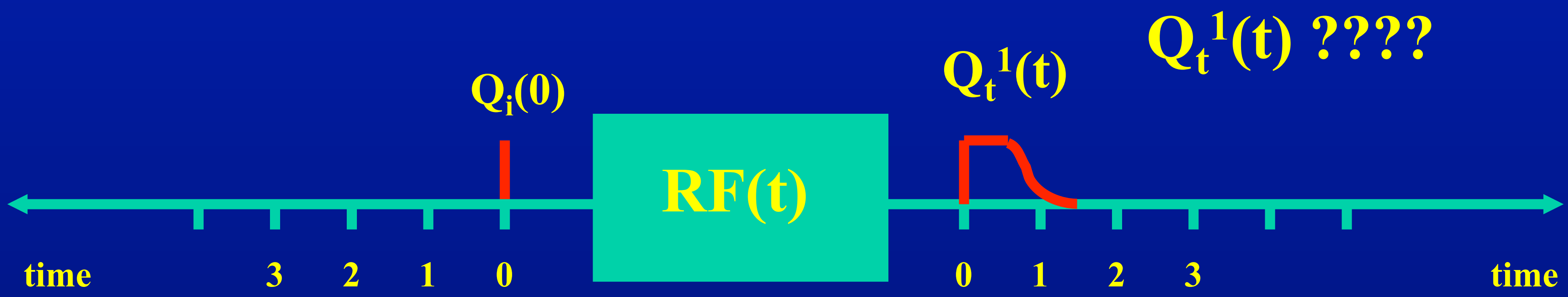


$$Q_i(0) = F\,C_i(0)\,\Delta\tau$$

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

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

HBWL

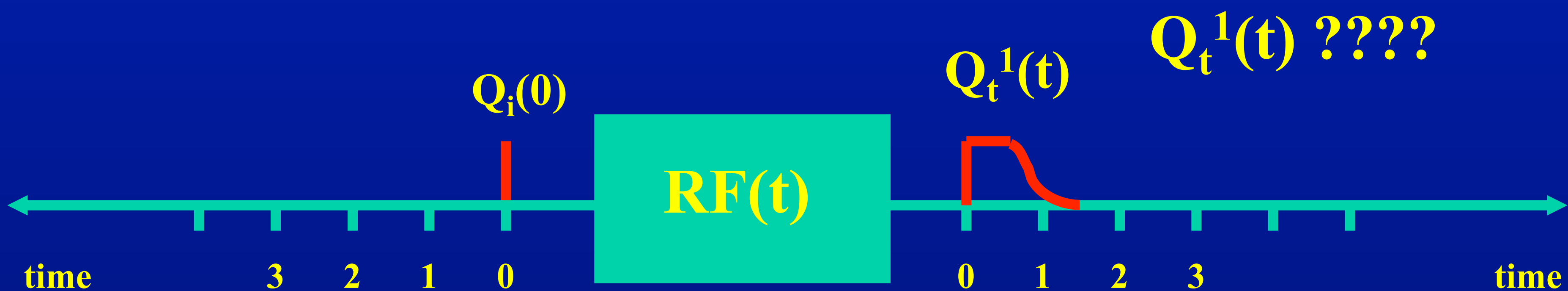


$$Q_i(0) = F\, C_i(0)\, \Delta\tau$$

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

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

HBWL

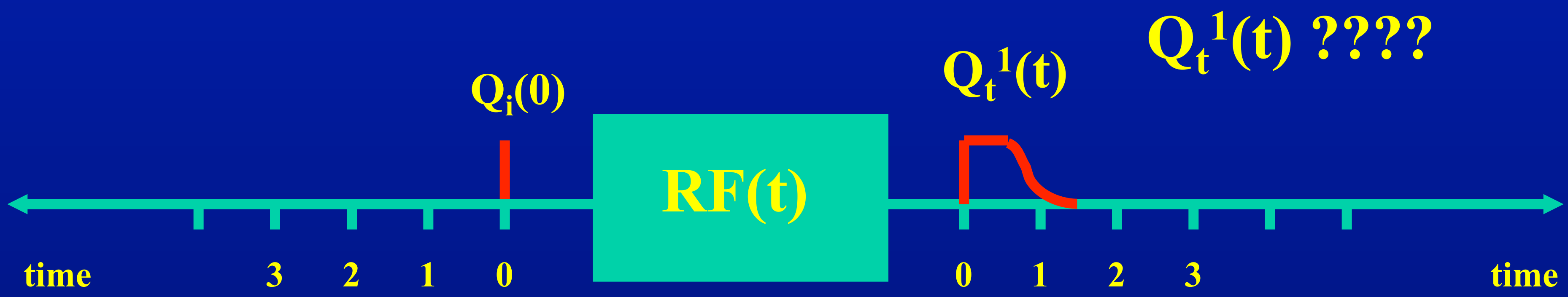


$$Q_i(0) = F\, C_i(0)\, \Delta\tau$$

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

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

HBWL



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

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

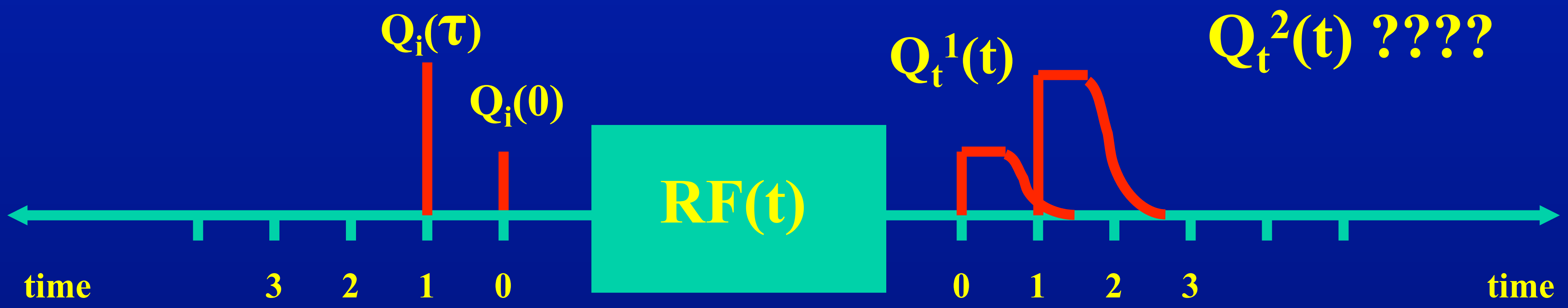
The number (amount) of tracer in tissue as a function of time due to an input at time zero

HBWL

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

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

HBWL



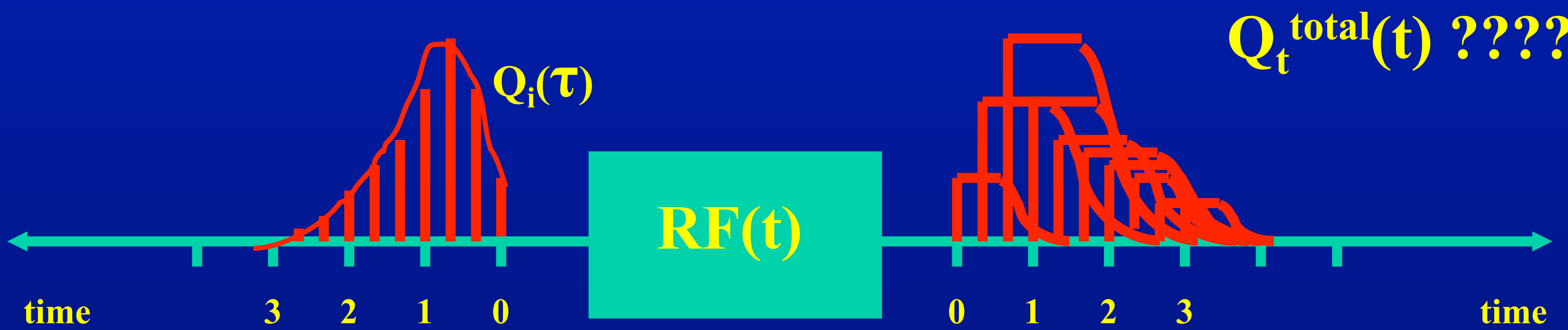
$$Q_i(0) = F\,C_i(0)\,\Delta\tau$$

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

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

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:

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

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

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

HBWL

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

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

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

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

HBWL

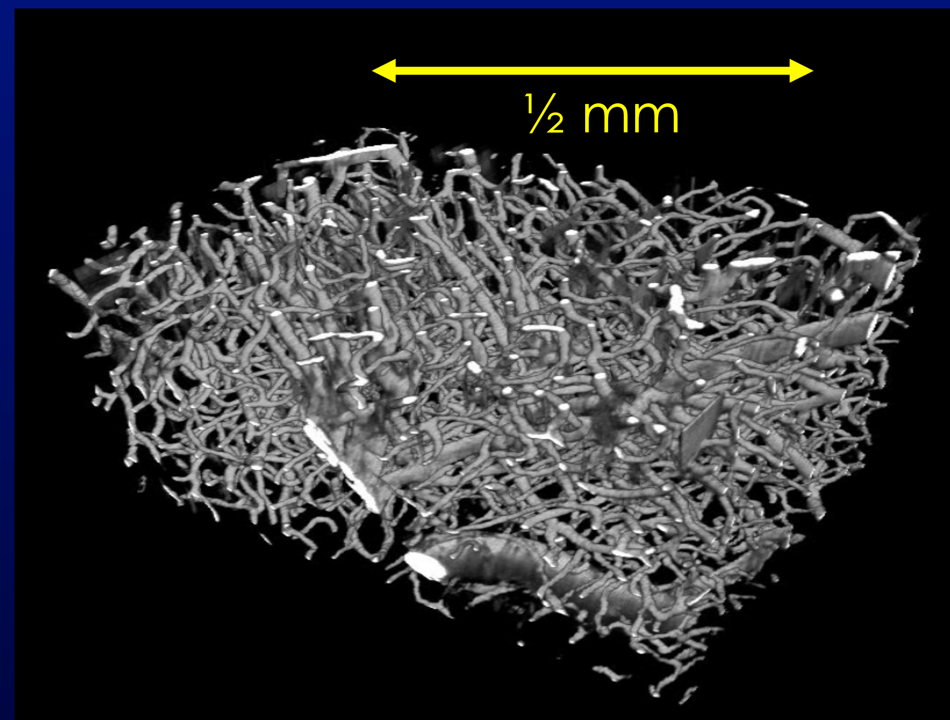
Convolution from the MAT point

- MATLAB

Break

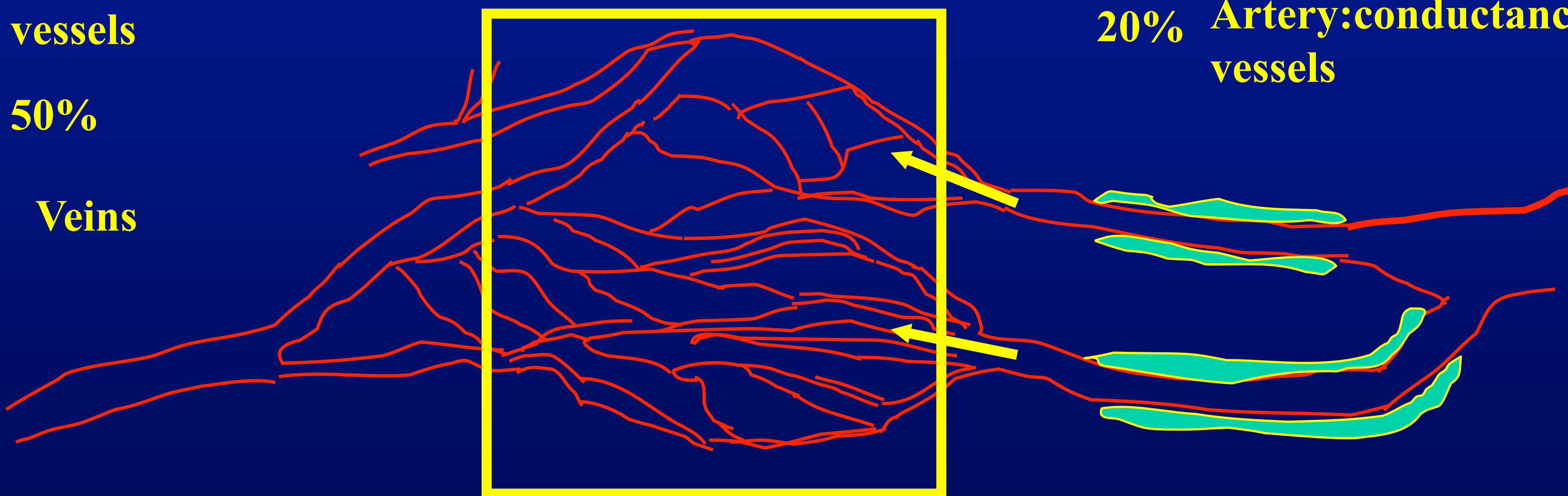
What is perfusion?

Large vessels : flow



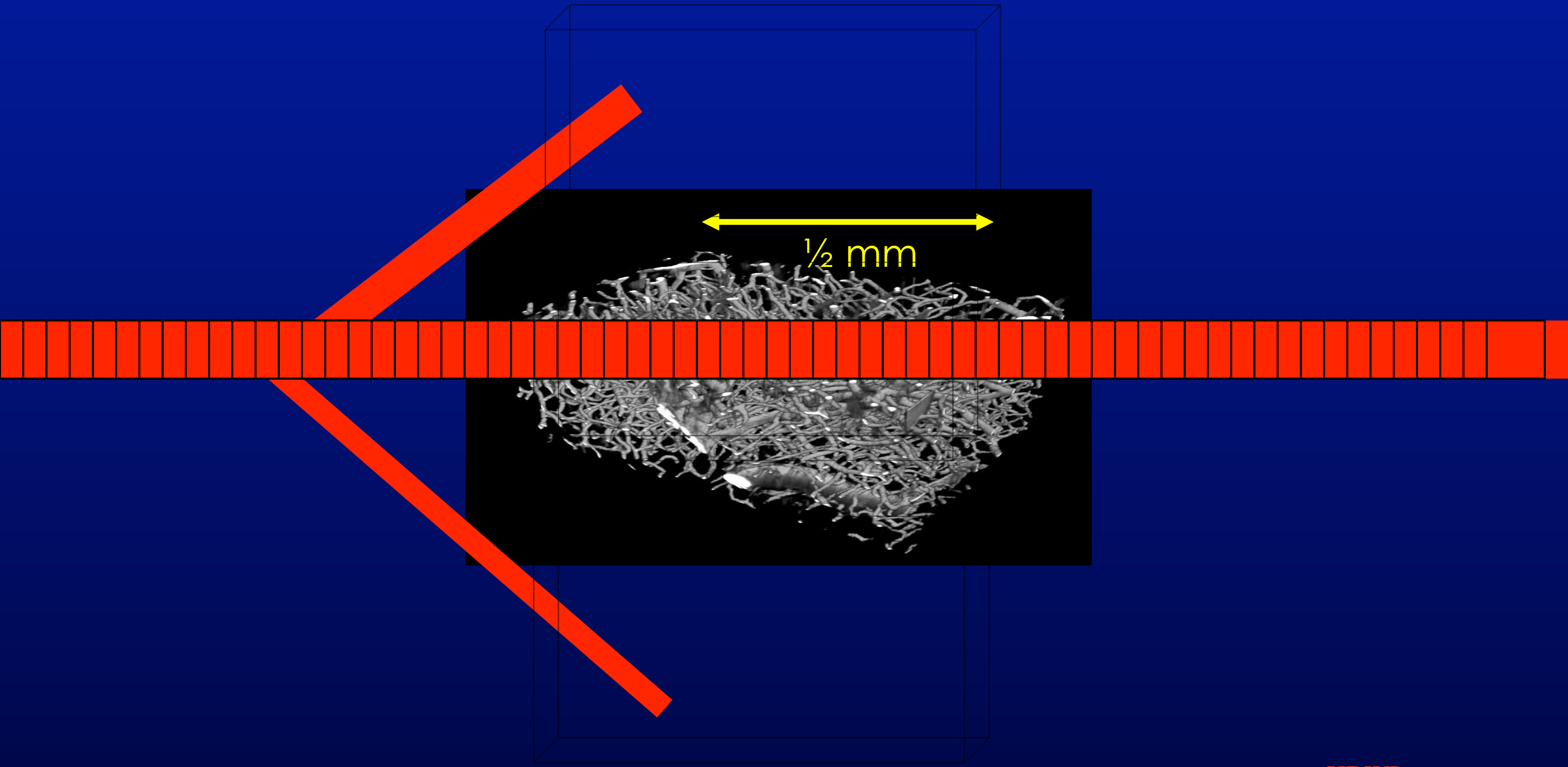
Perfusion: related to the microvascular system ~ the capillaries

The vascular system of the brain and perfusion

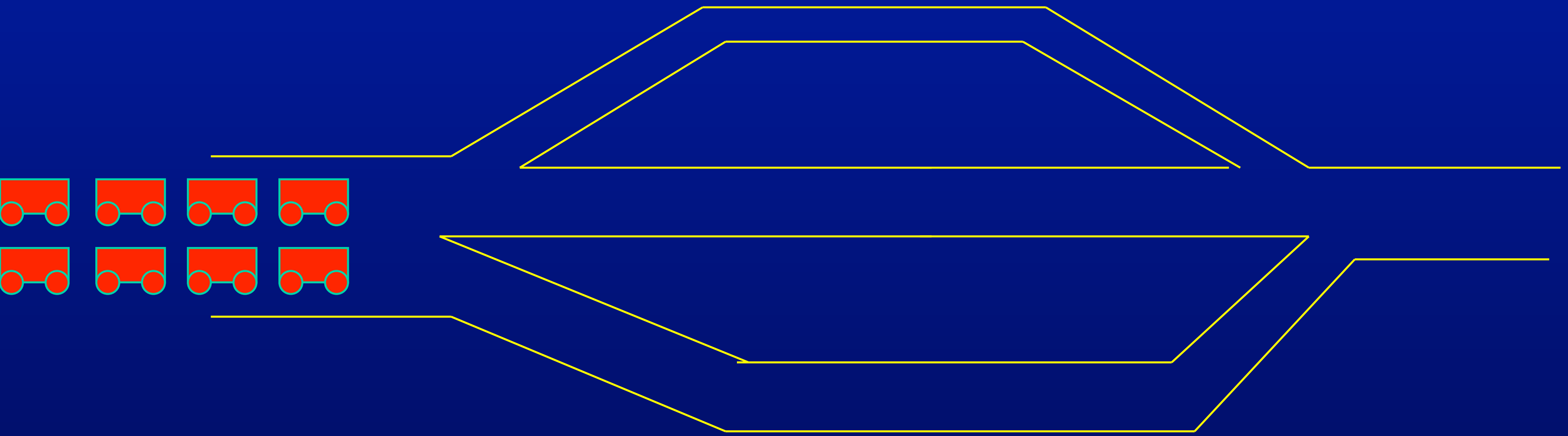


HBWL

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



HBWL

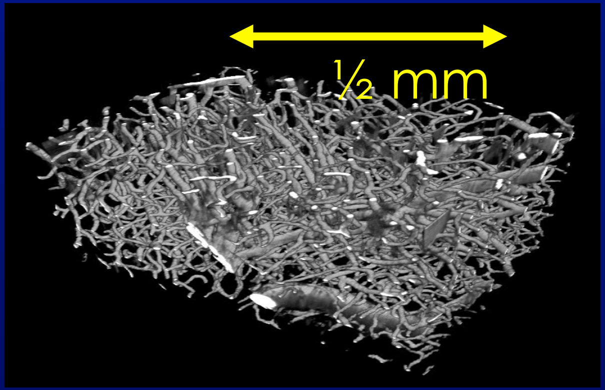


Number of transport (ml) vehicles entering 100 ml tissue pr. time unit::
20 - 80 ml/min/100 ml tissue volume

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]



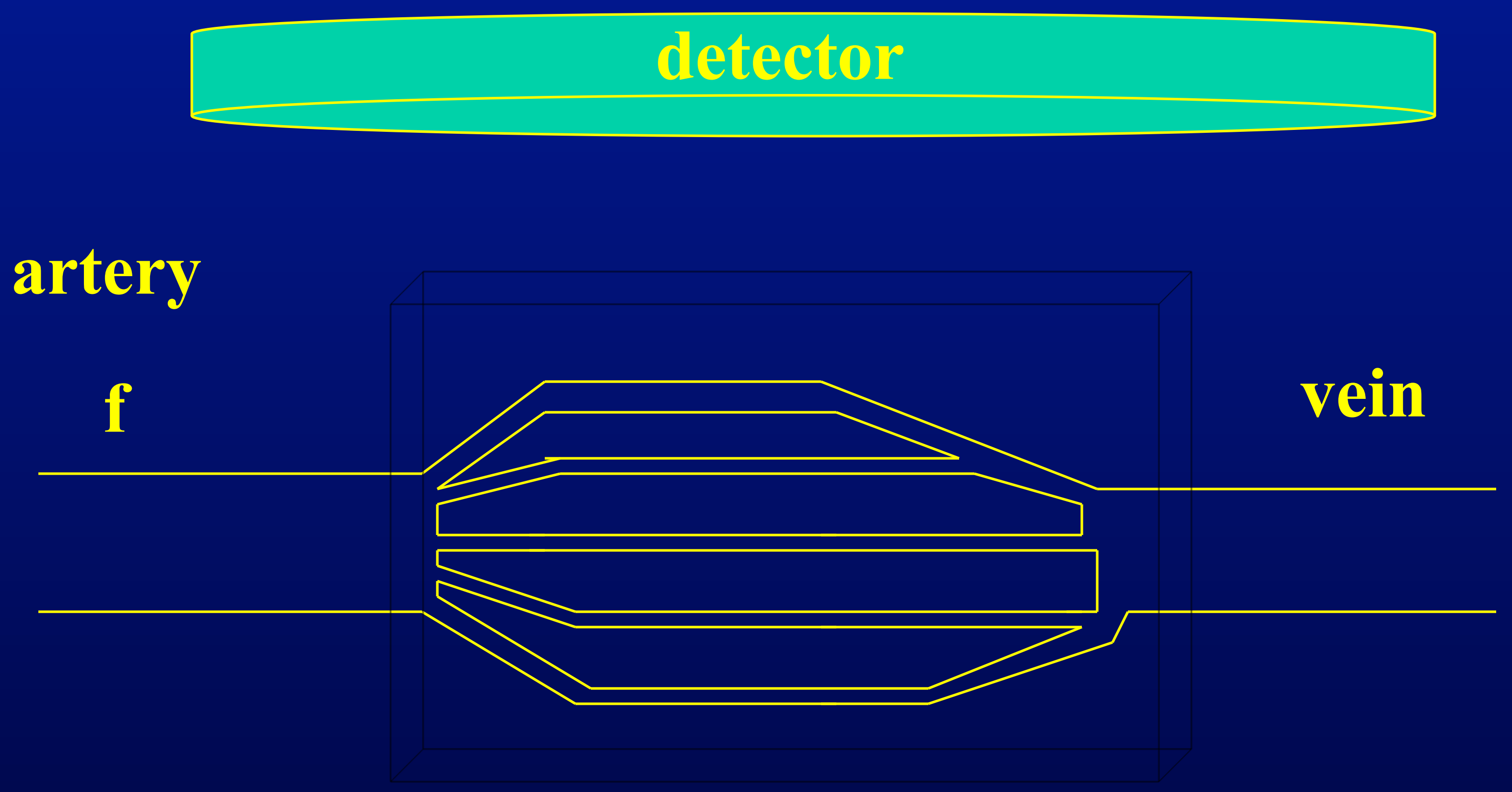
- Mean transit time: MTT [s]
- Blood brain permeability: PS product [ml/100g/min]

HBWL

Non-invasive perfusion:
What to do
and
the easy part

HBWL

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

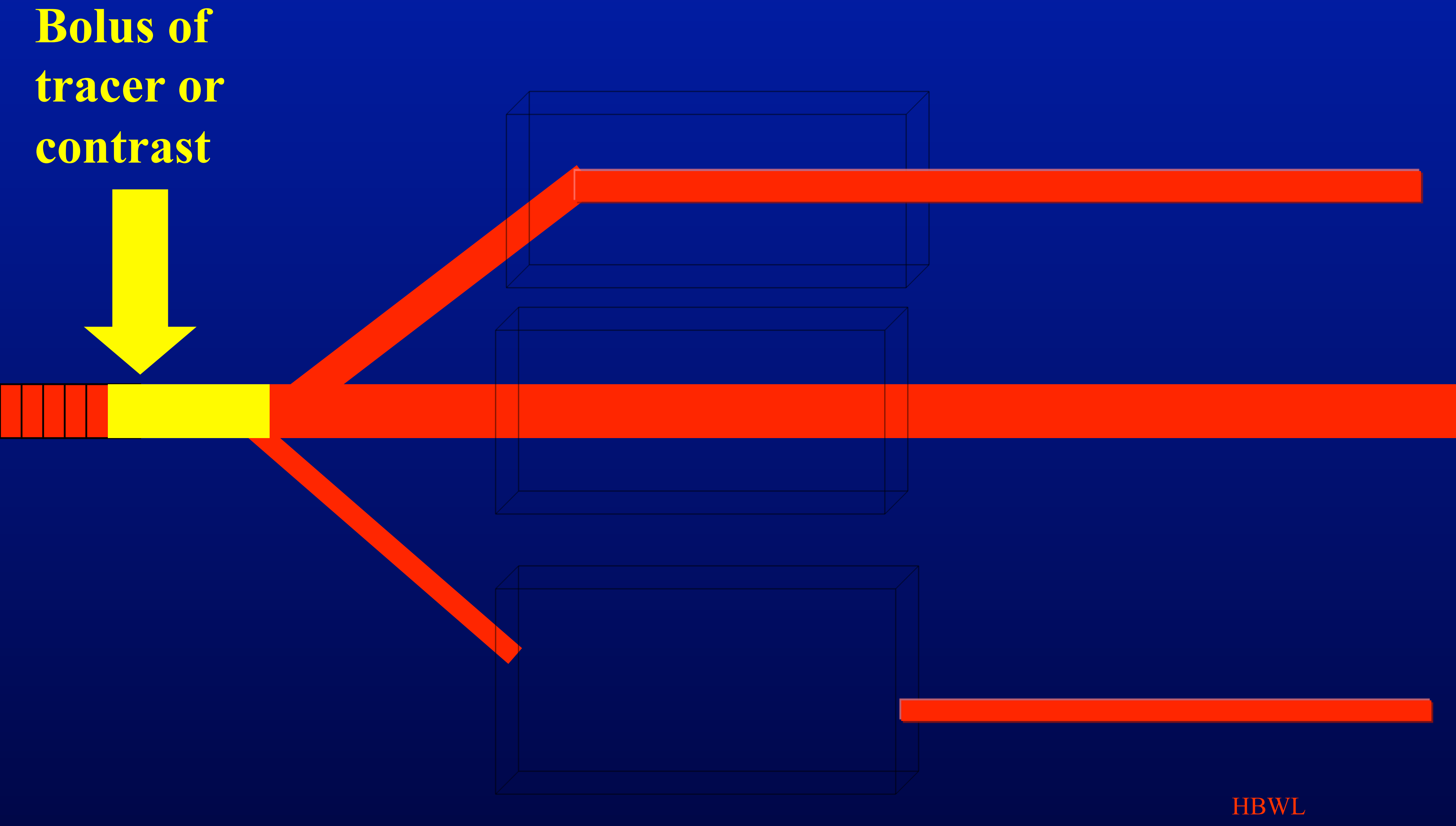


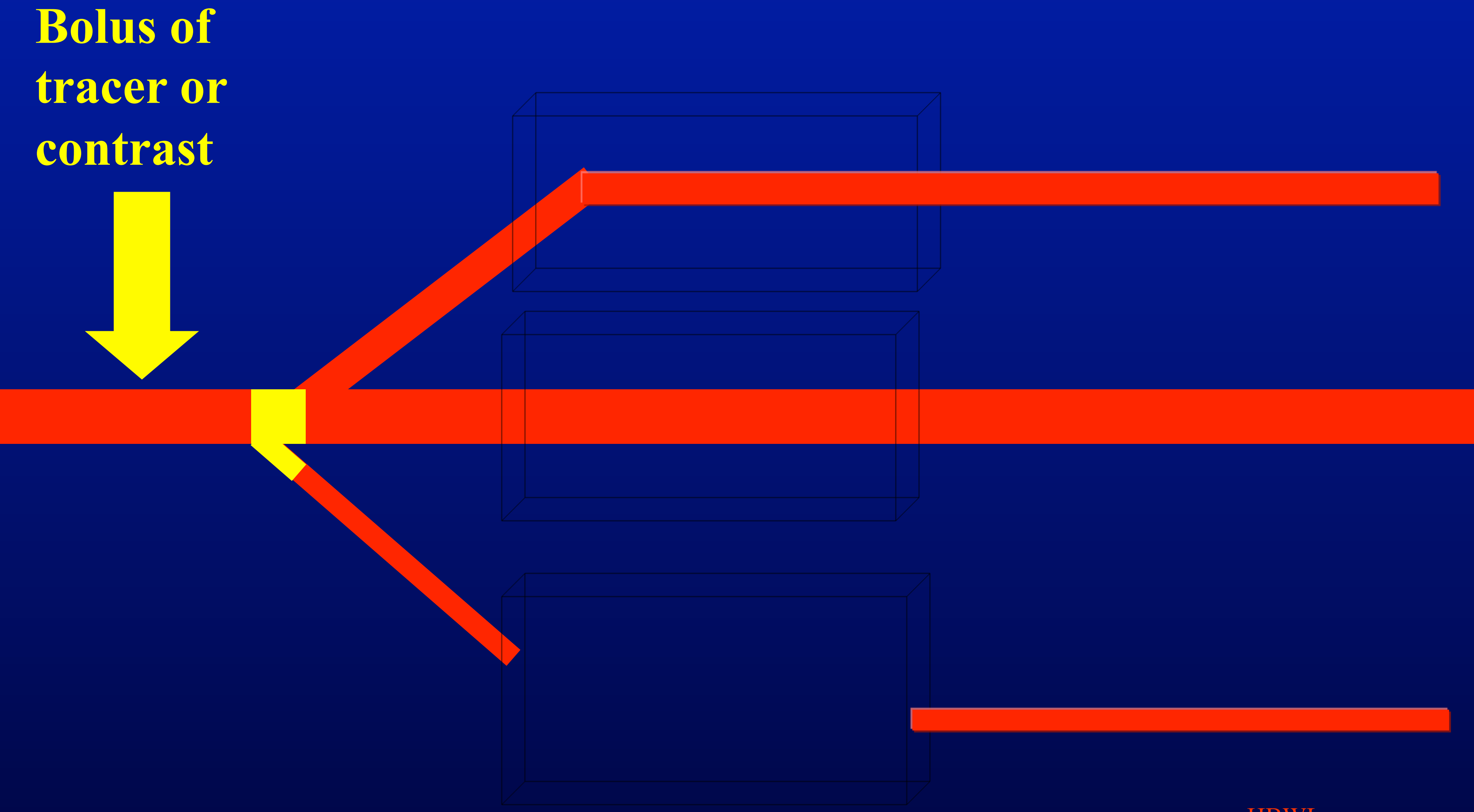
f: perfusion in [ml/min /100g]

HBWL

How can it be measured ?

Add a contrast agent carried by the blood to the tissue


Bolus of
tracer or
contrast
HBWL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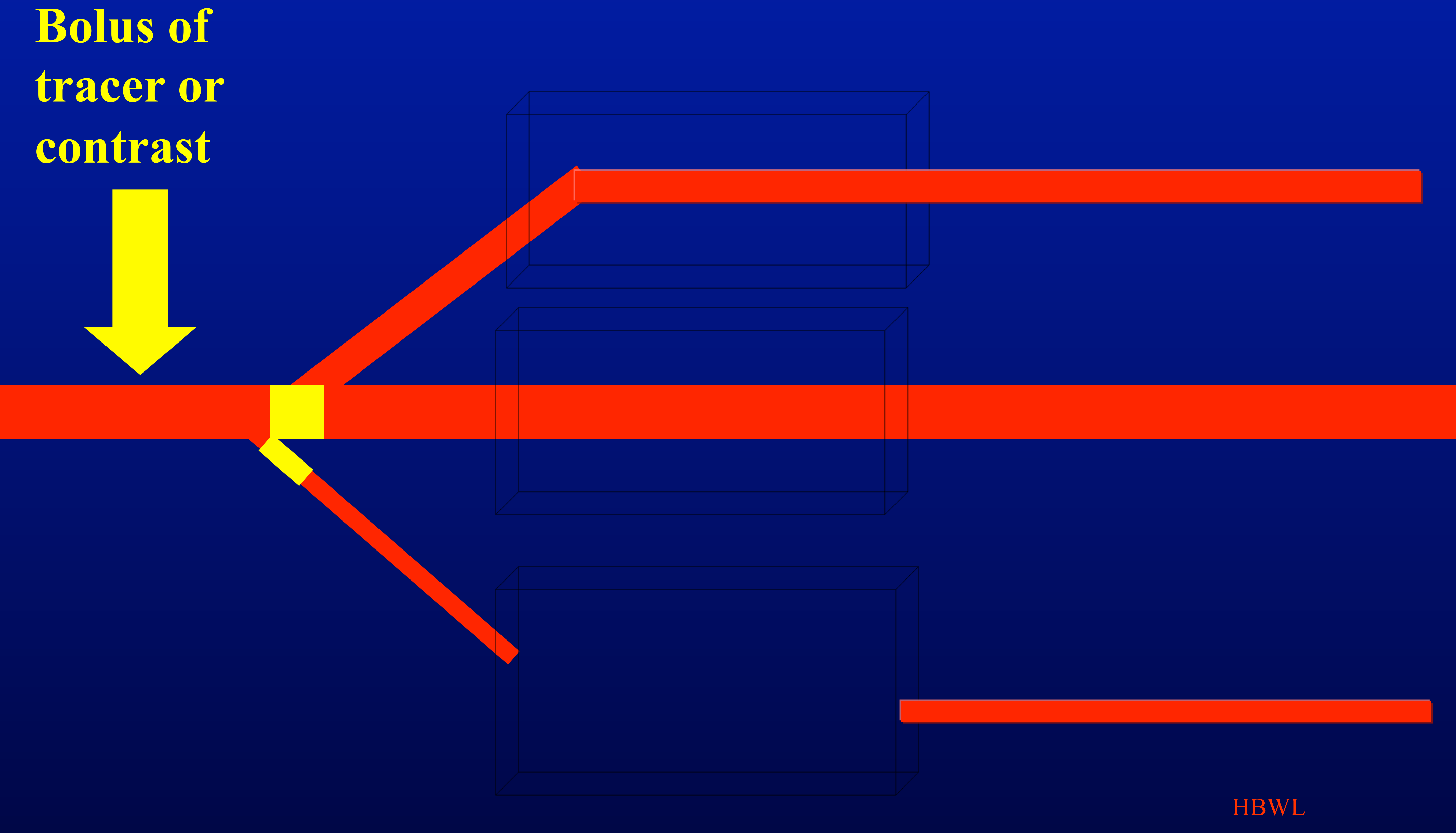
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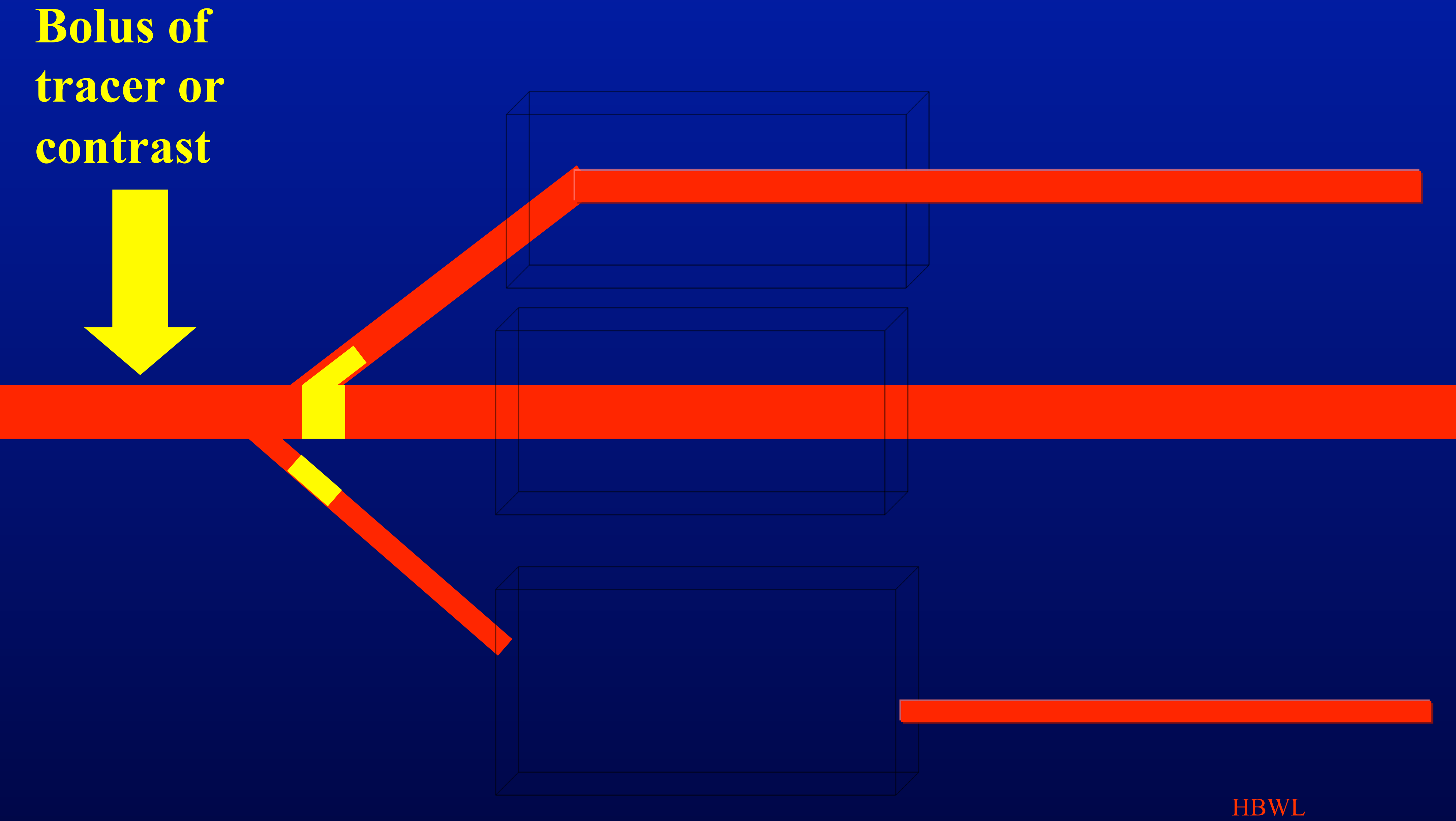
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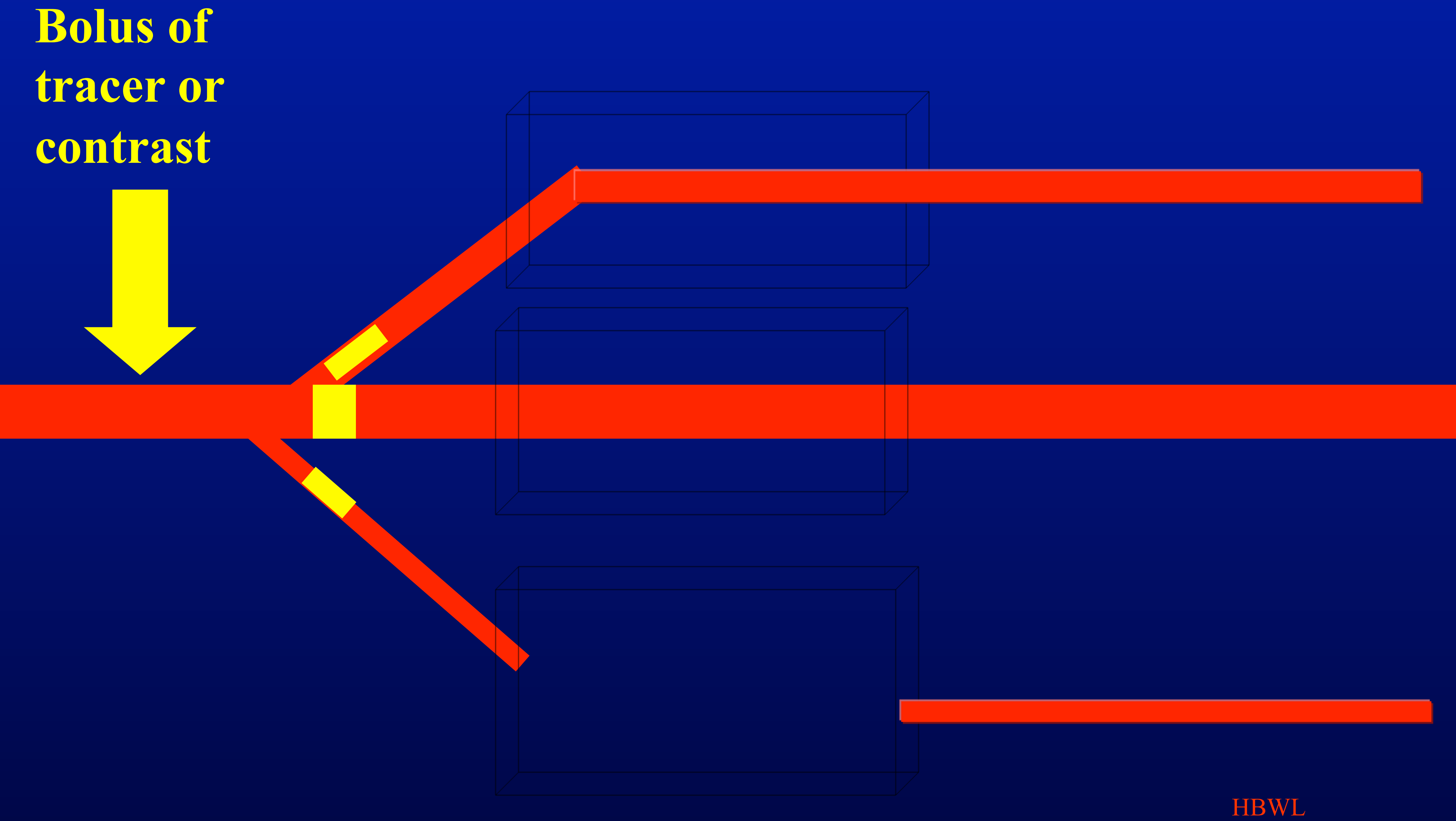
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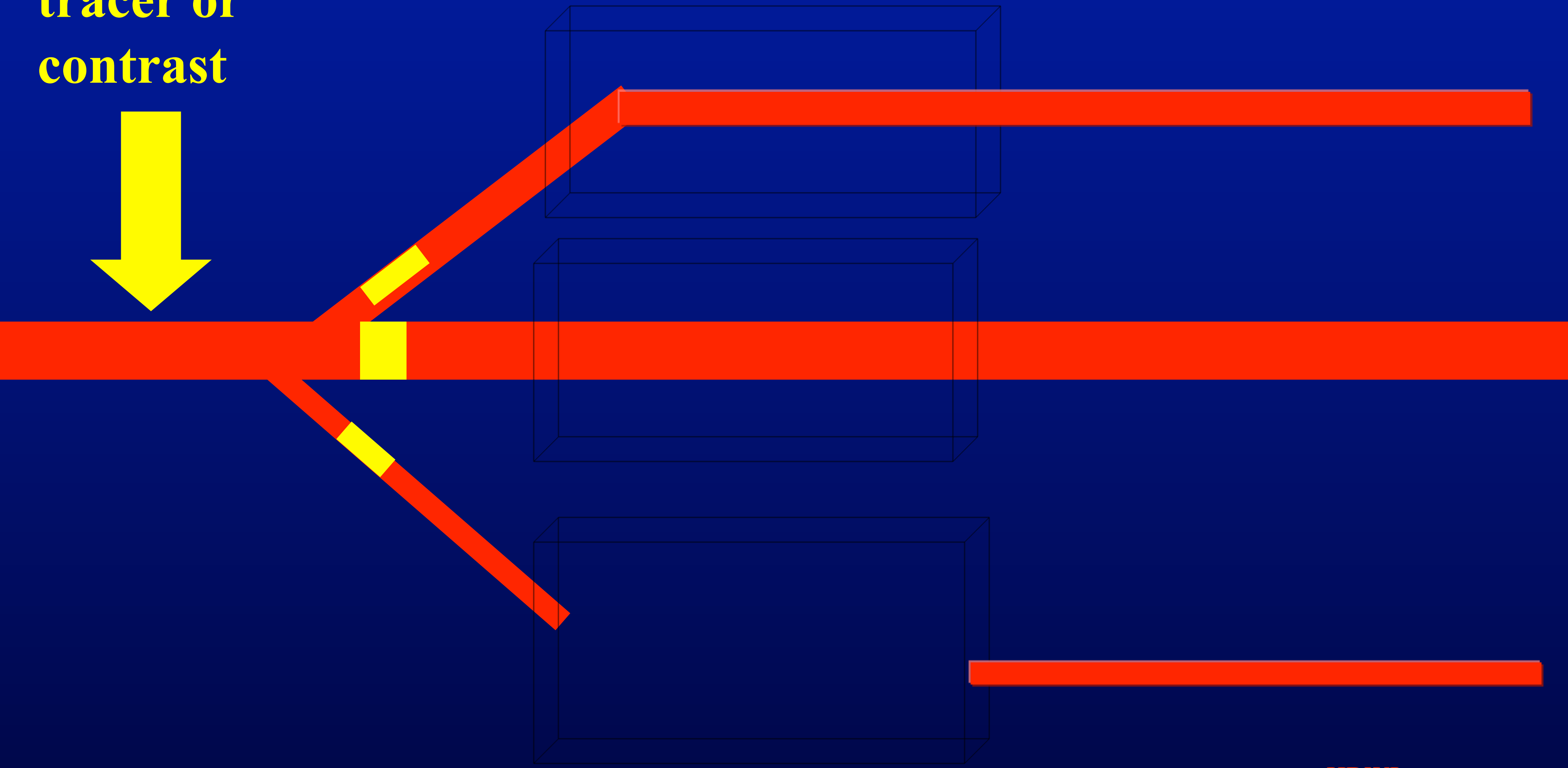
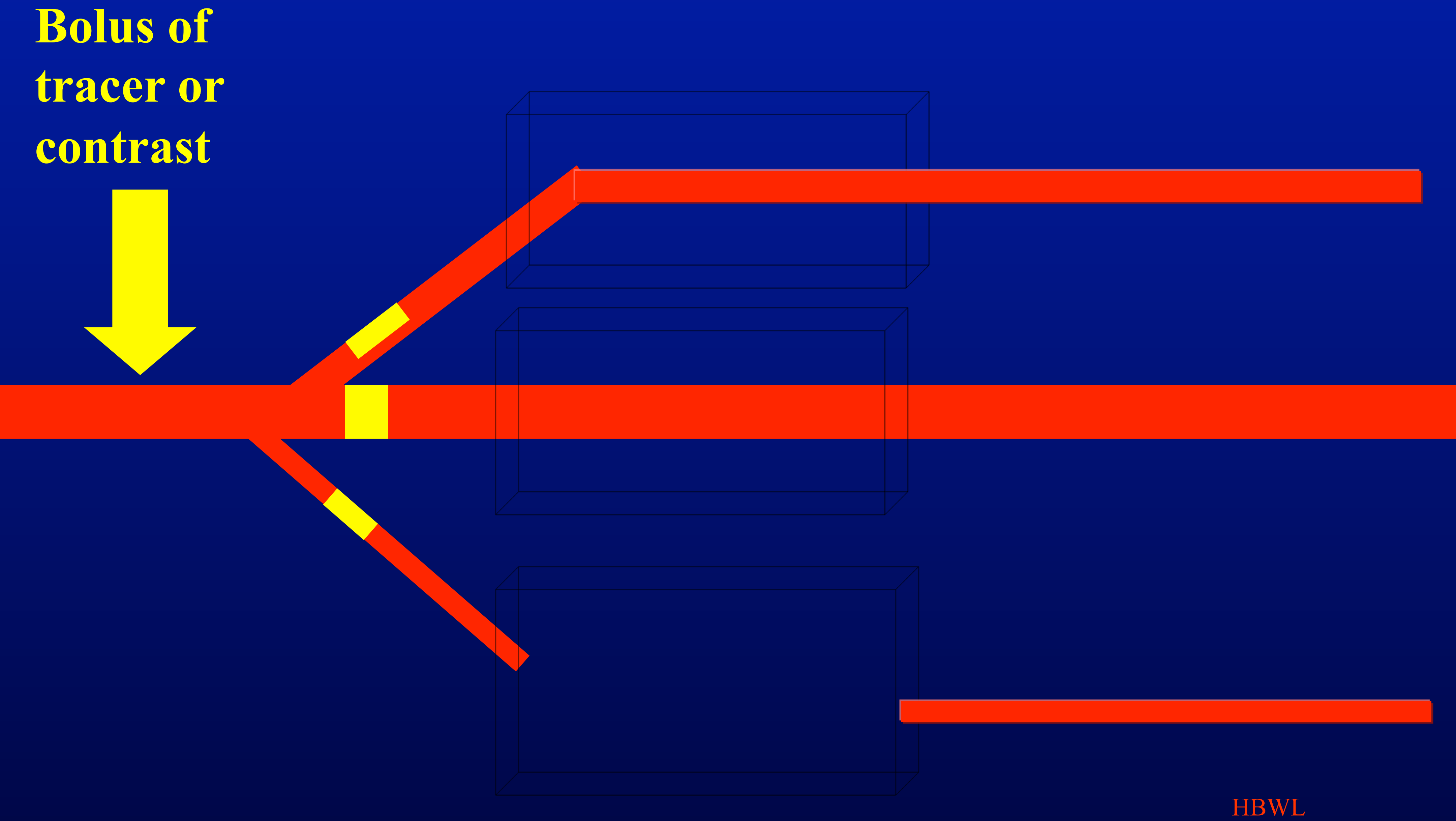


HBWL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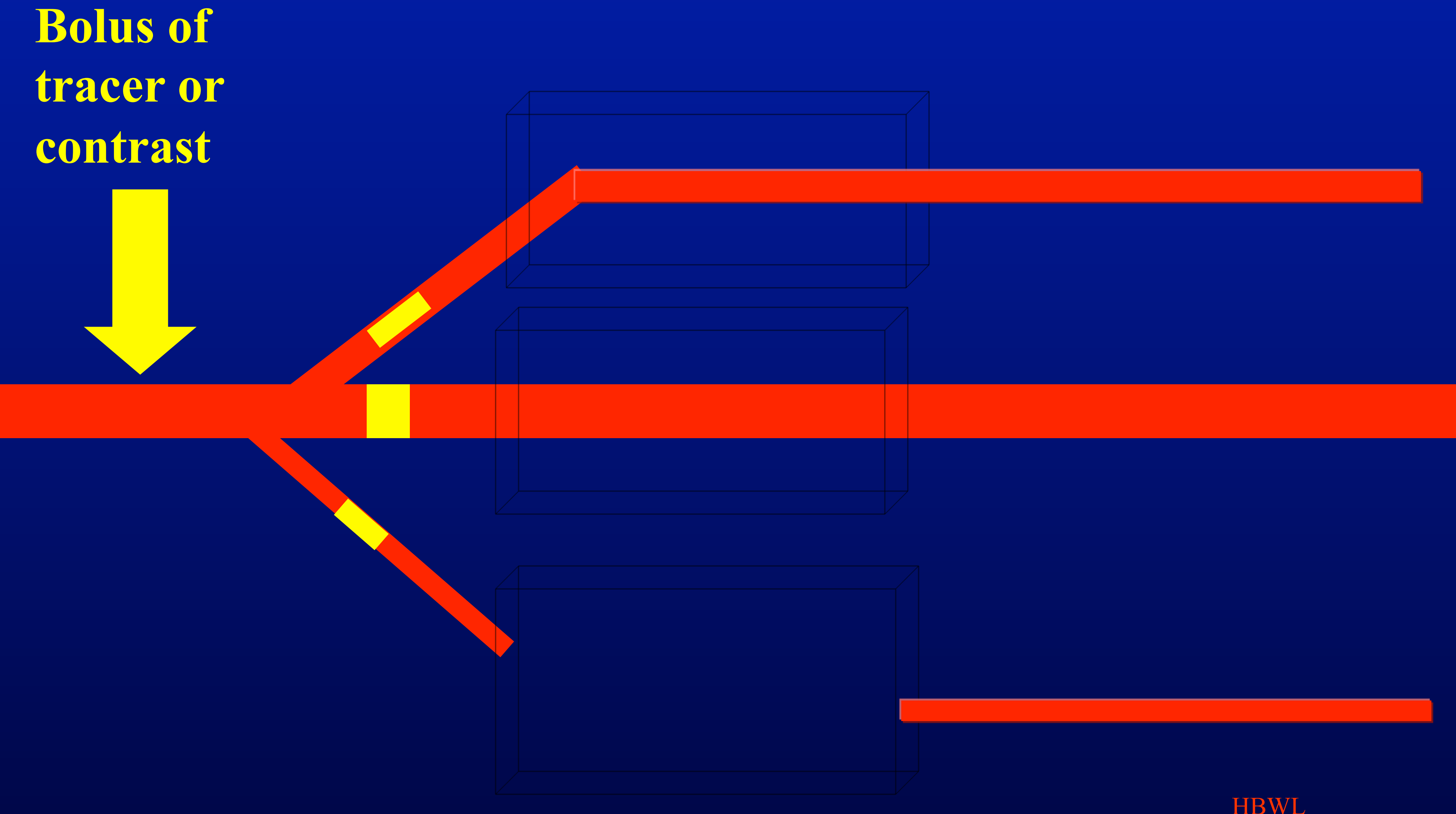
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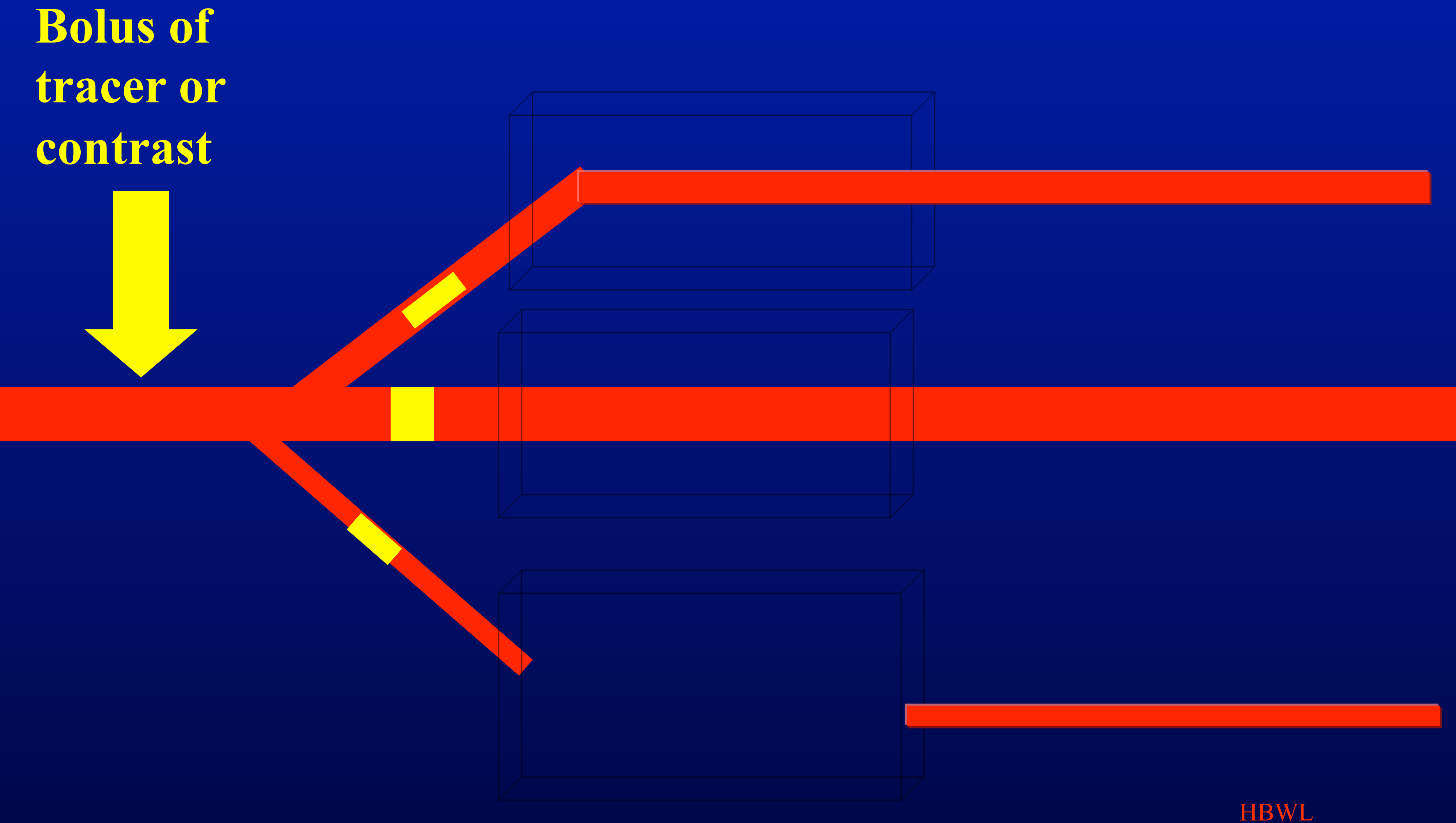
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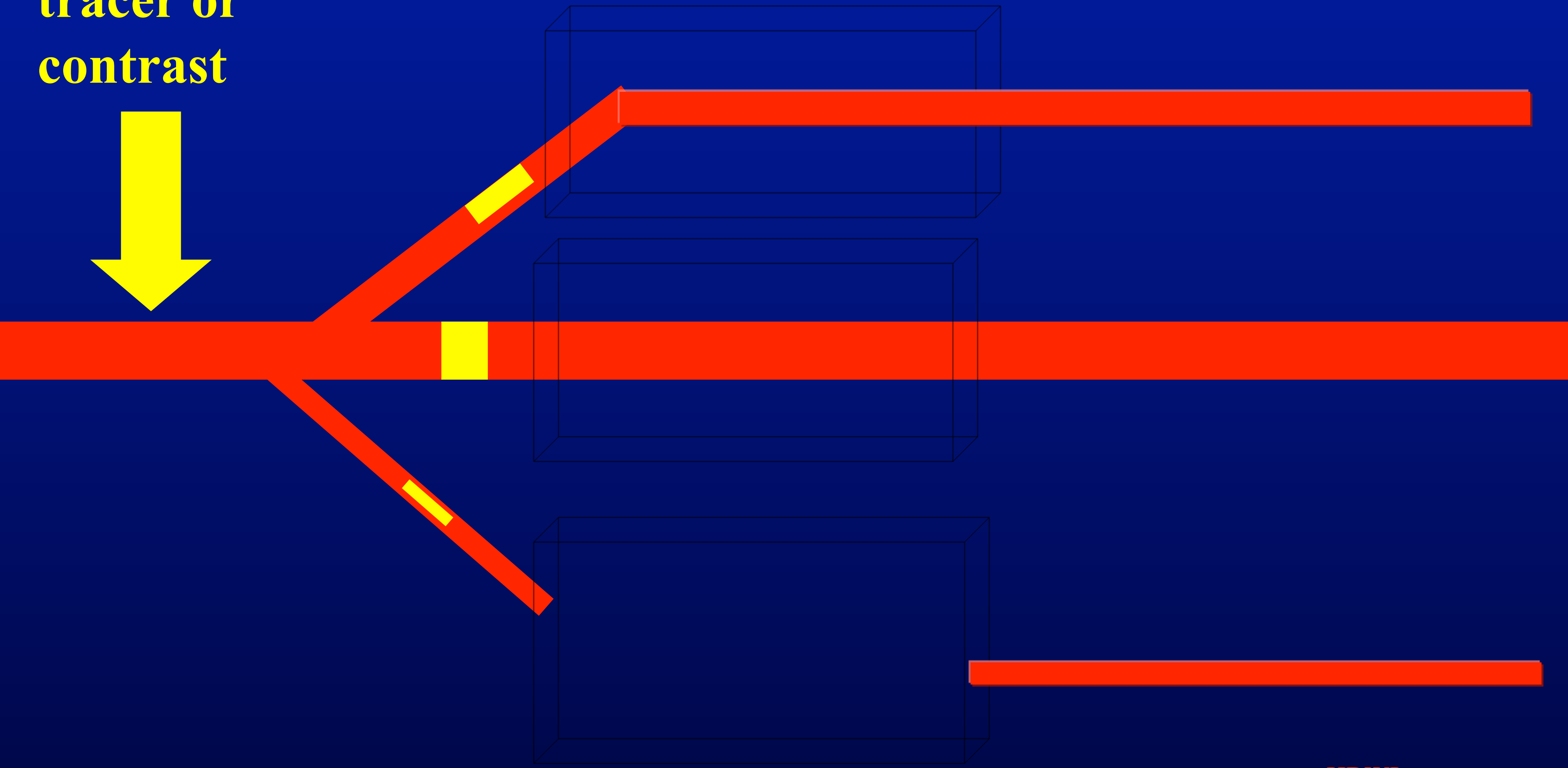
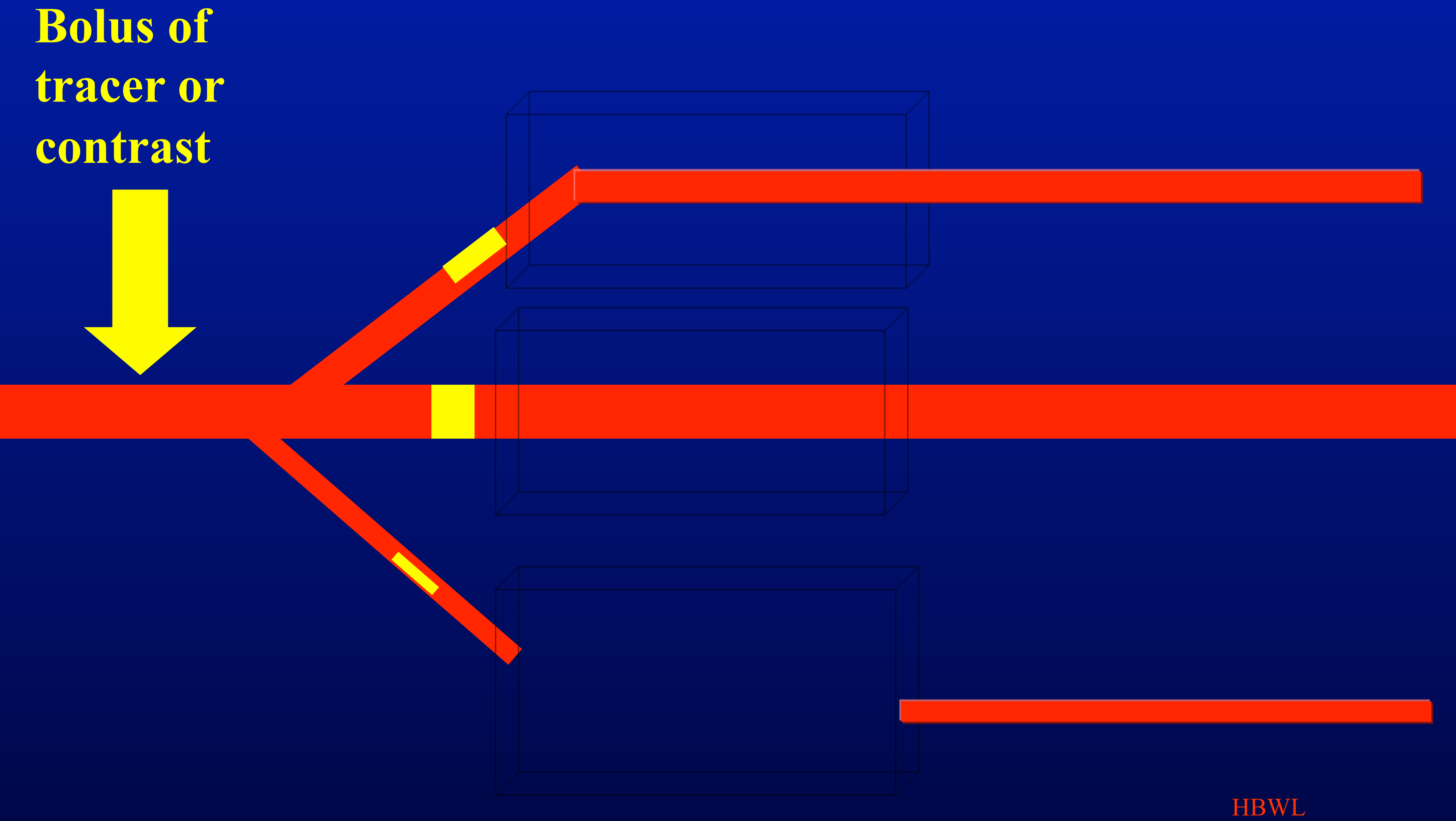


HBWL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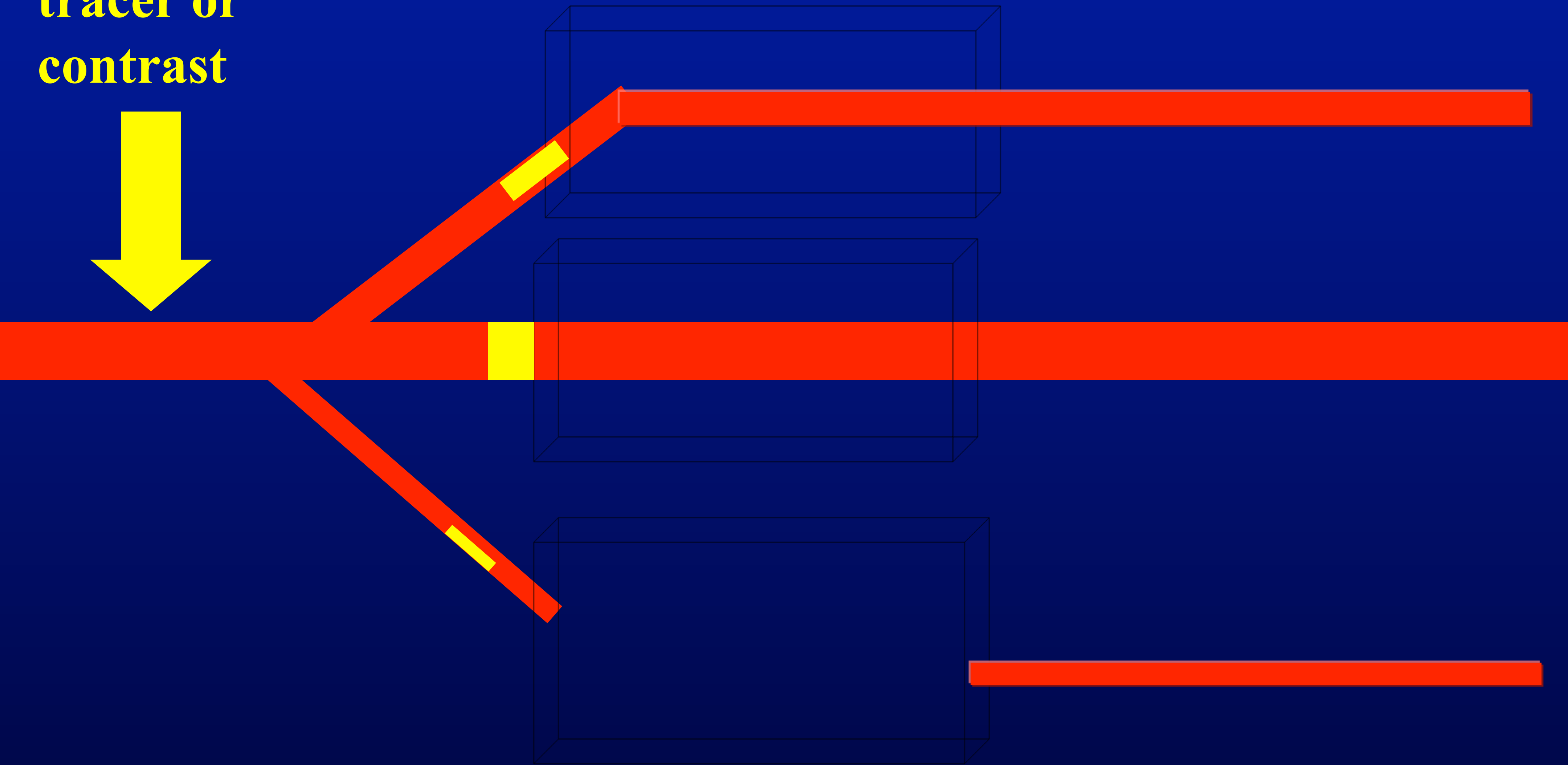

HBWL

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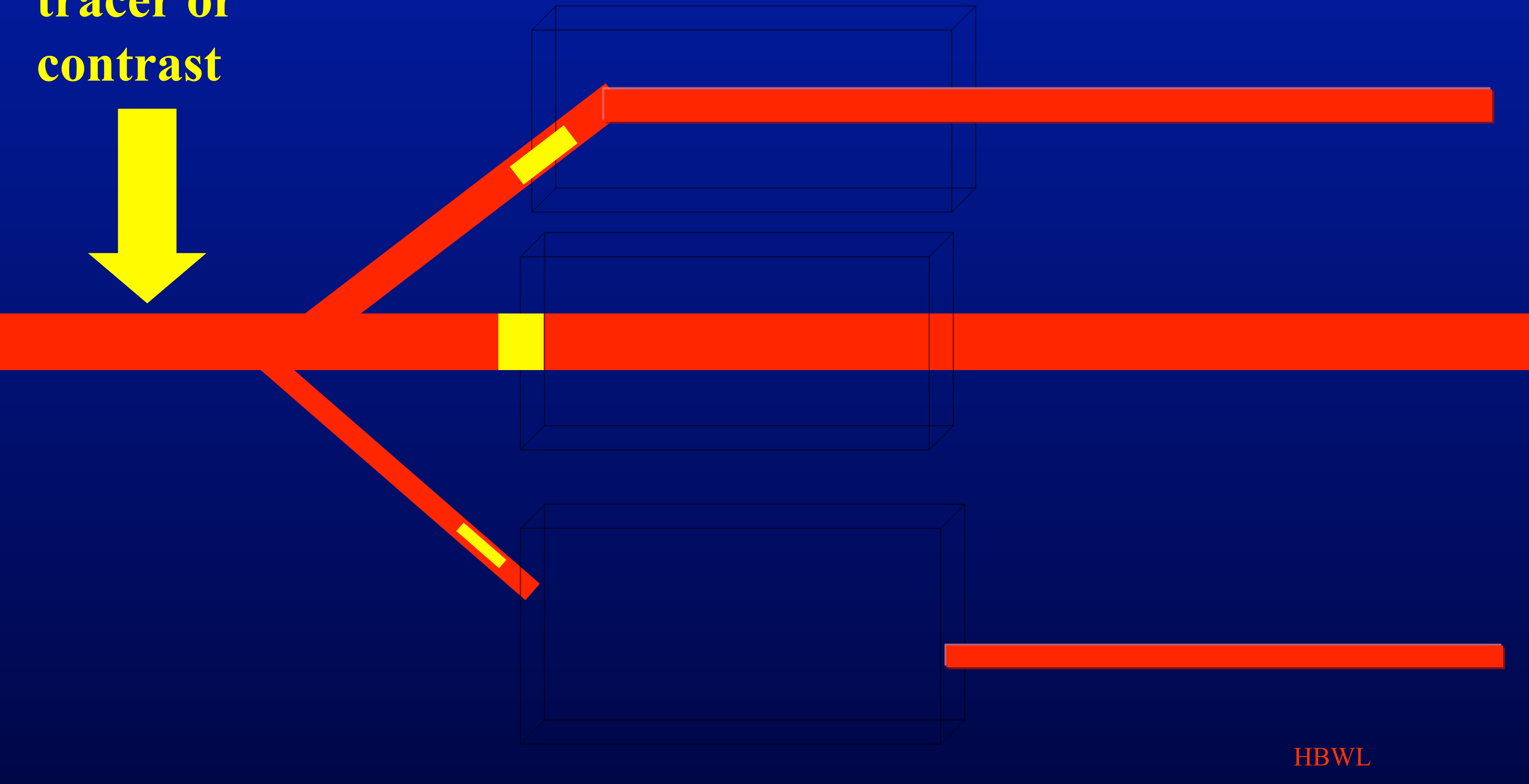

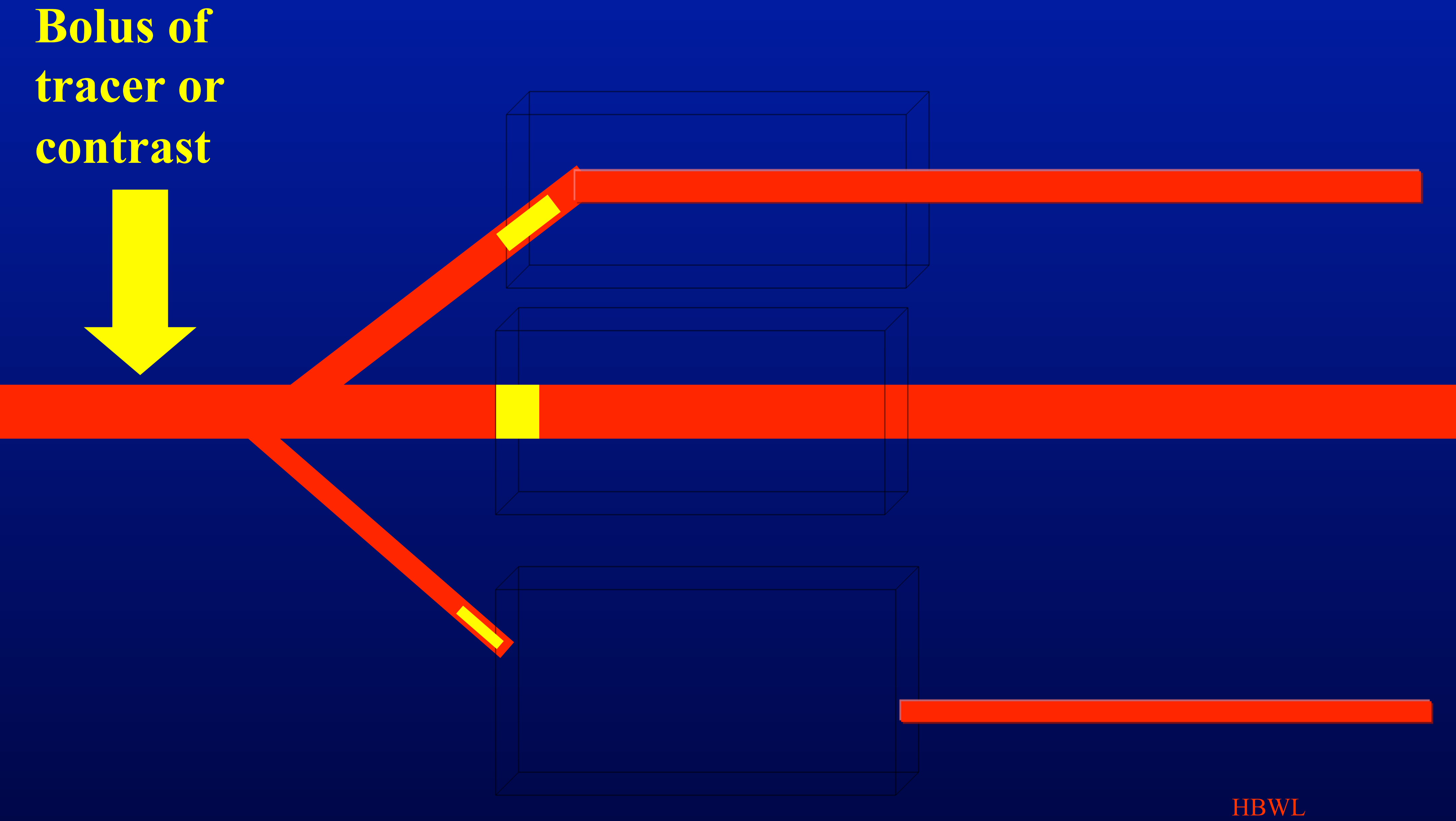
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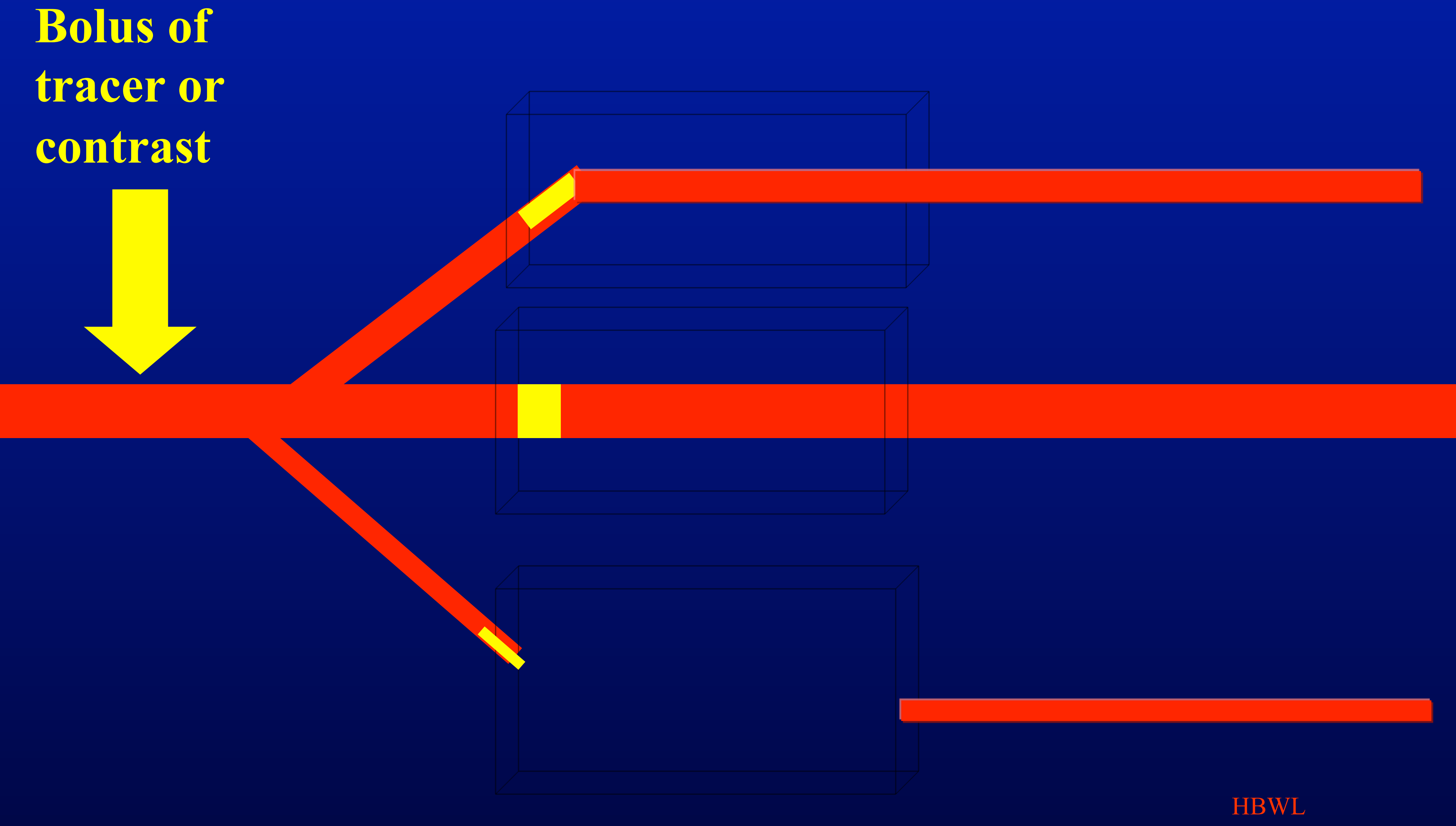
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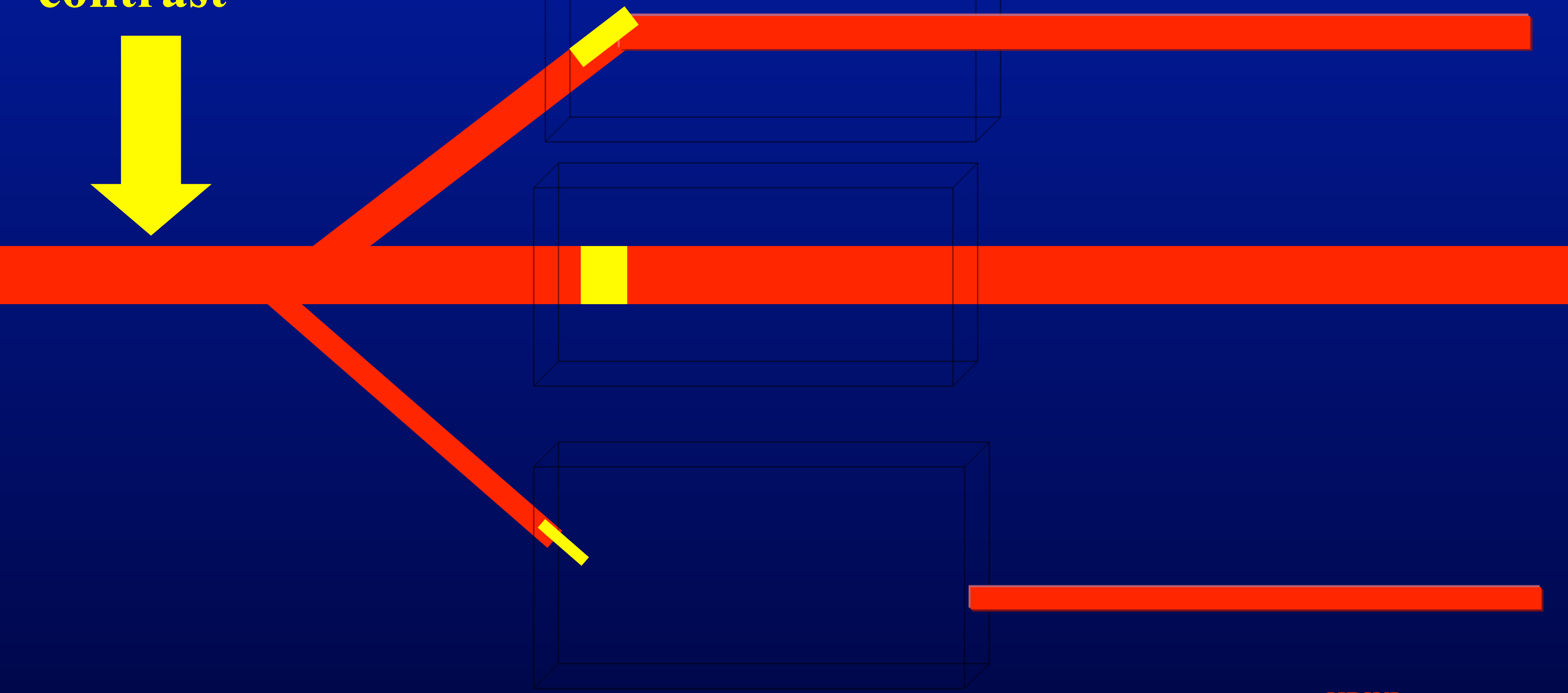
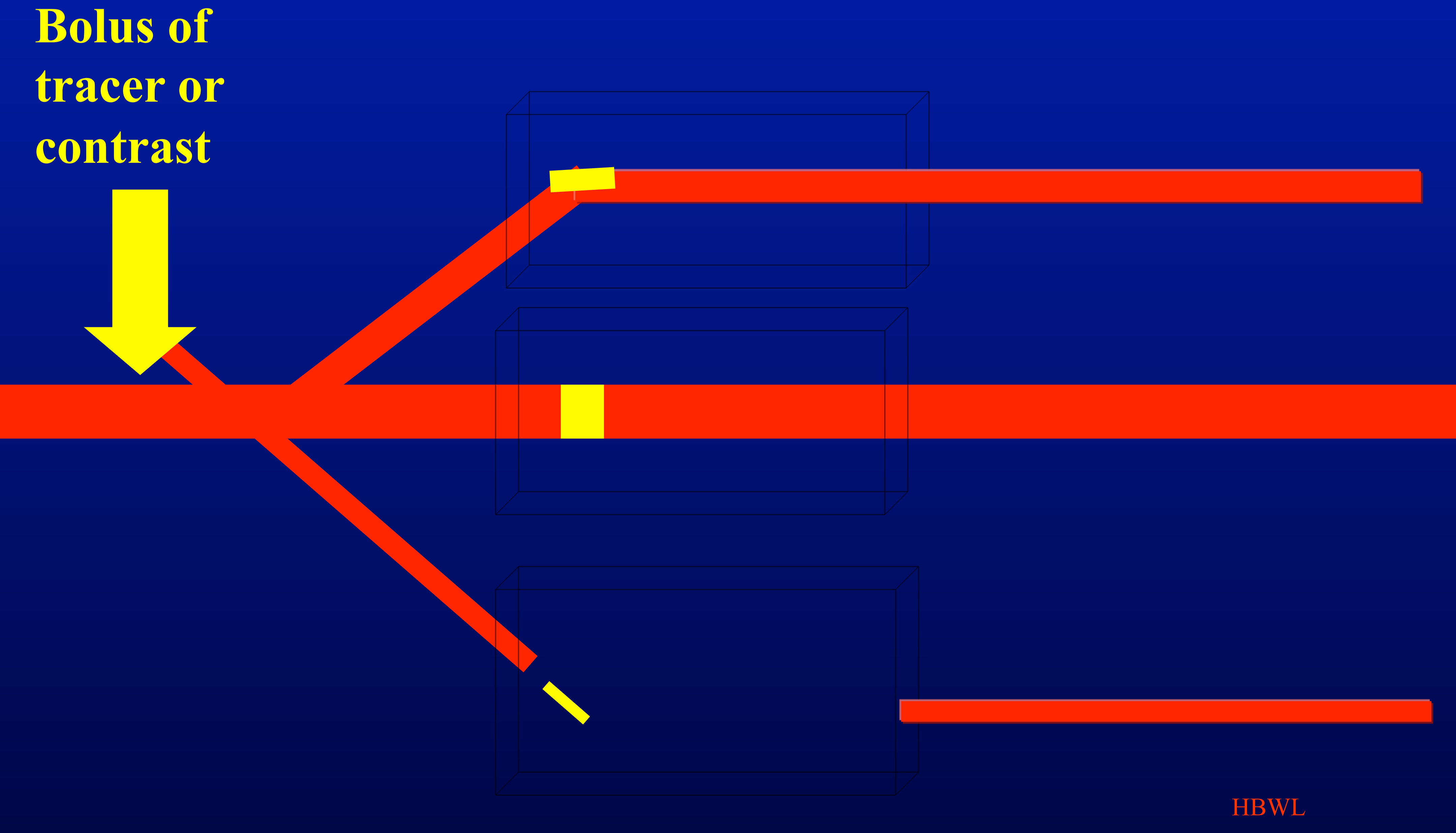


HBWL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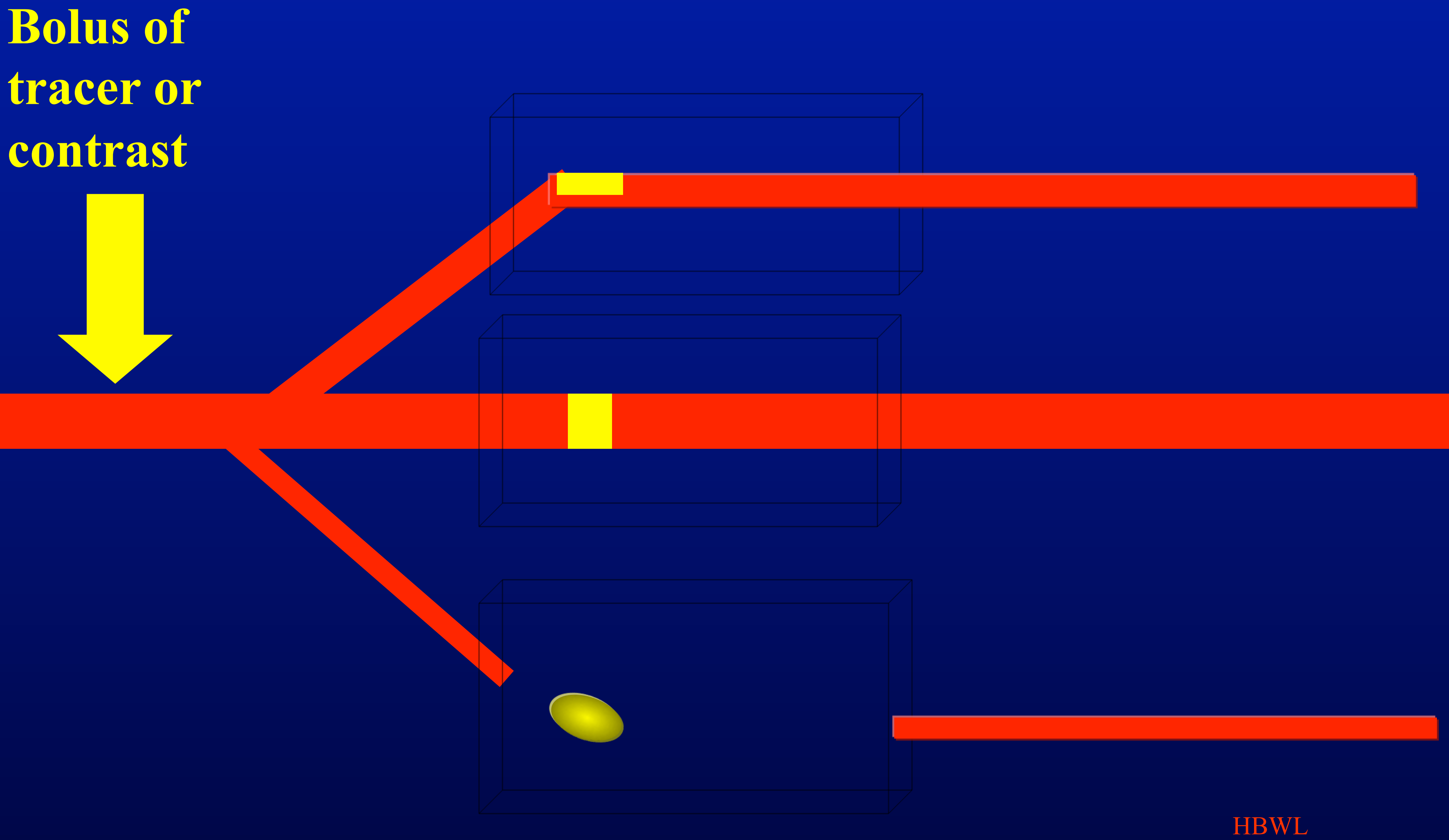
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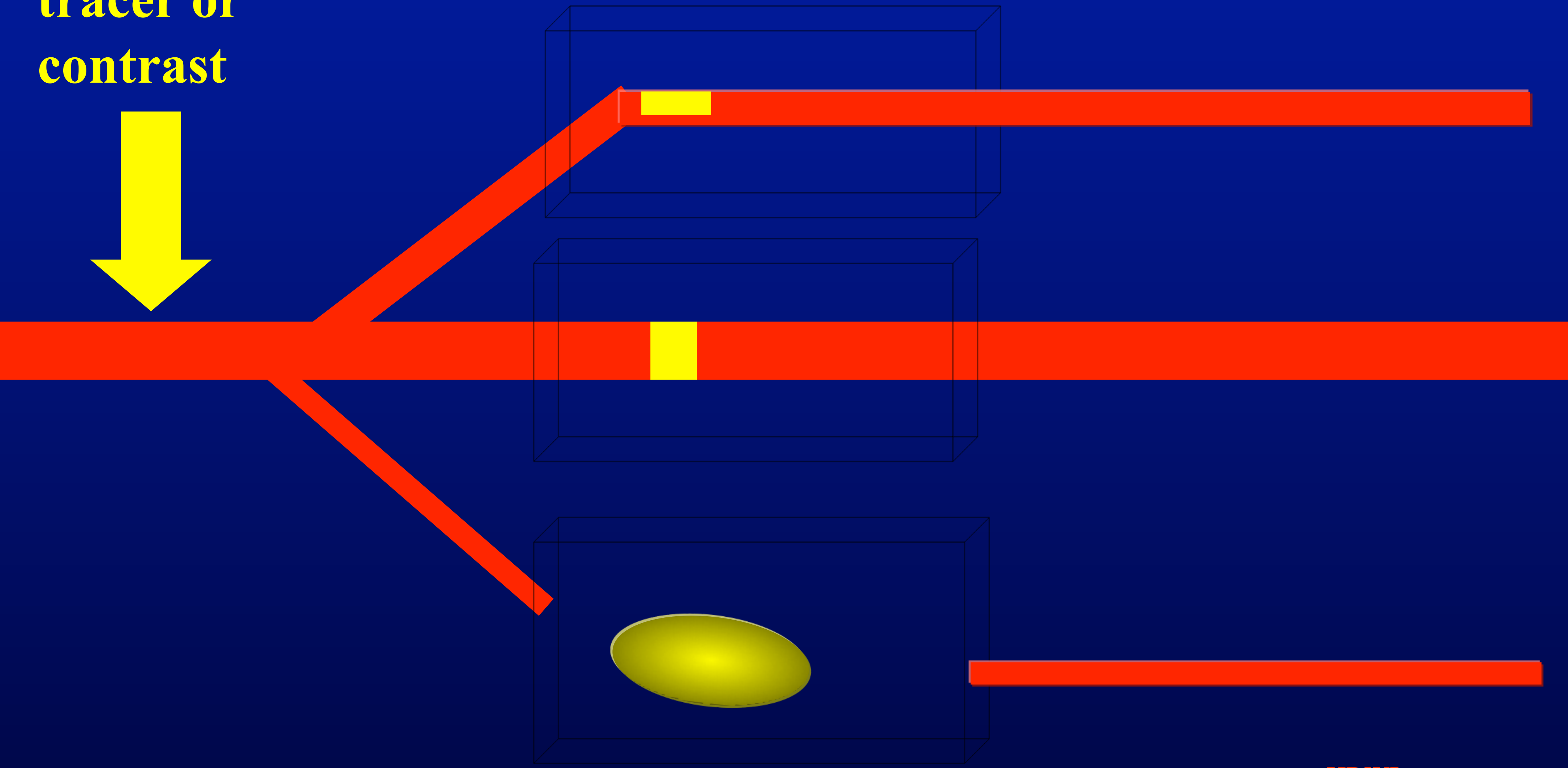
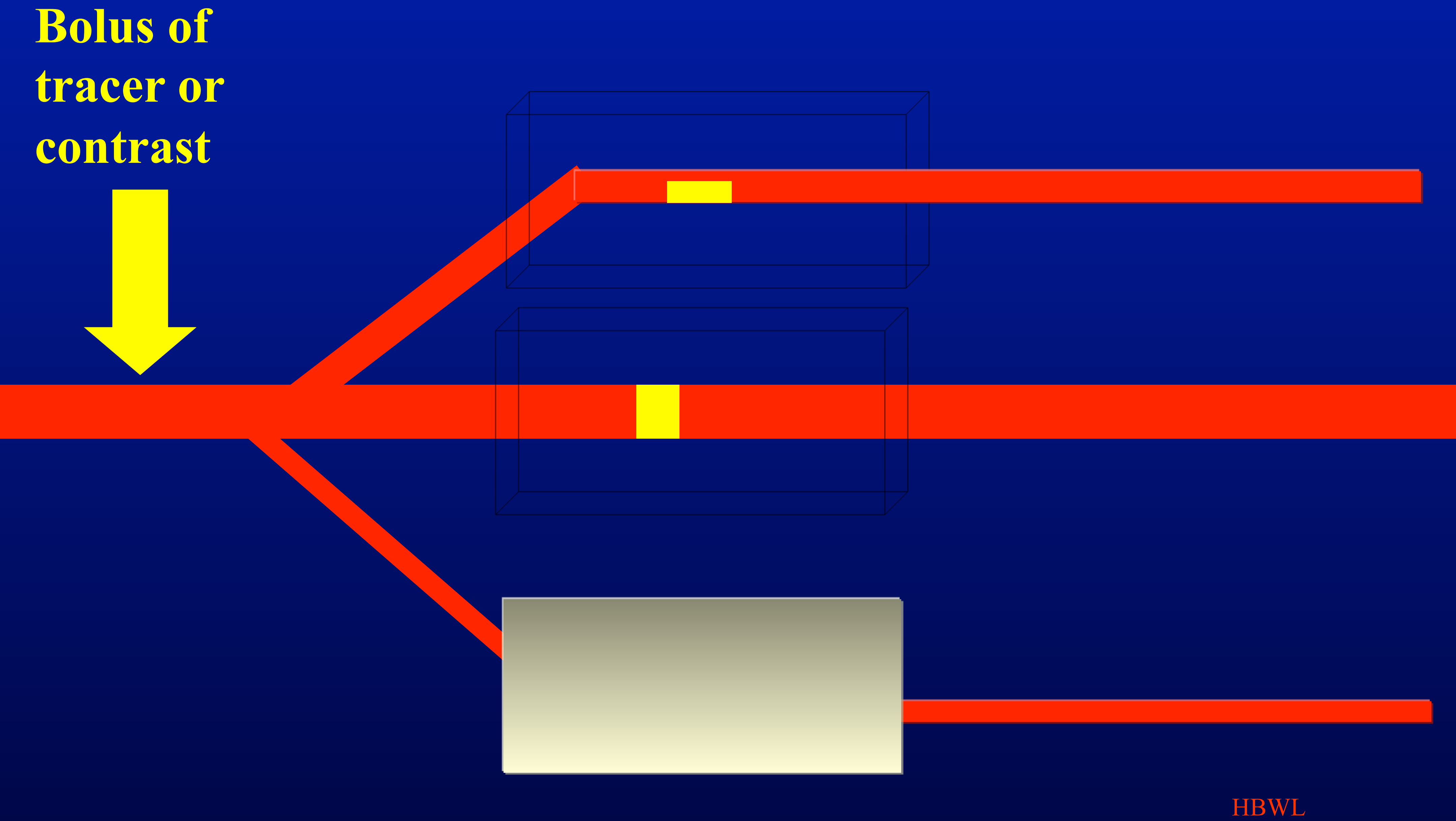


HBWL



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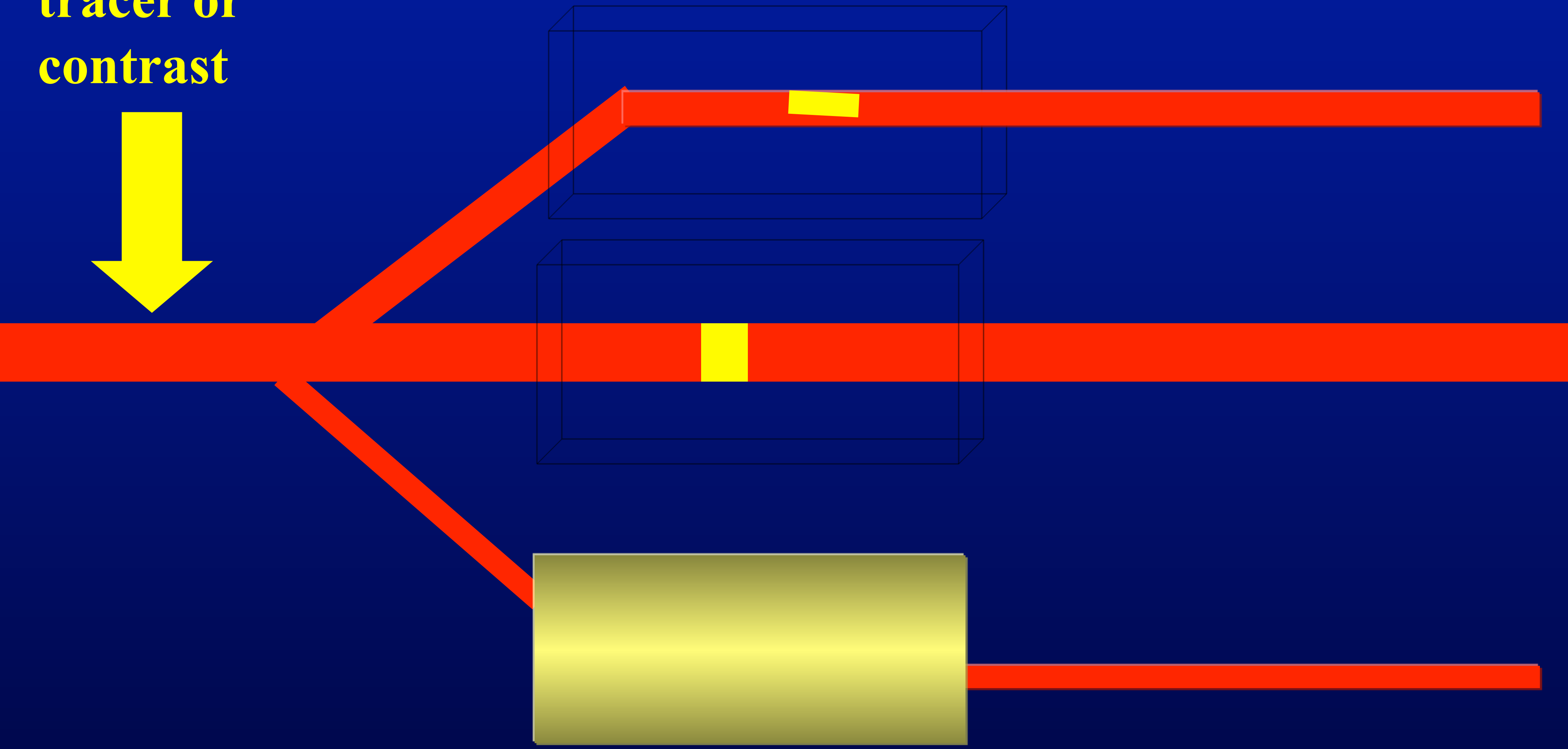
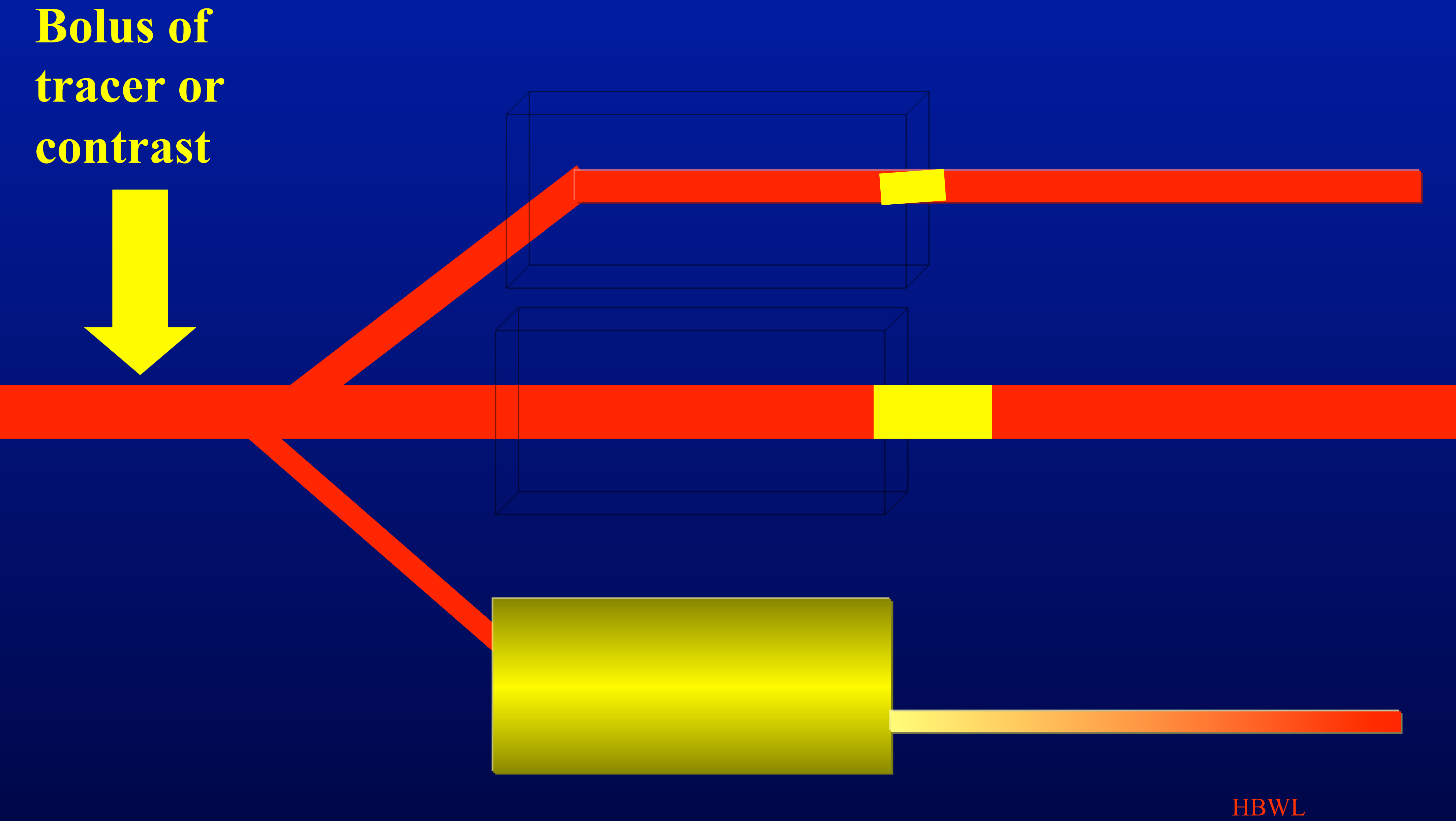


HBWL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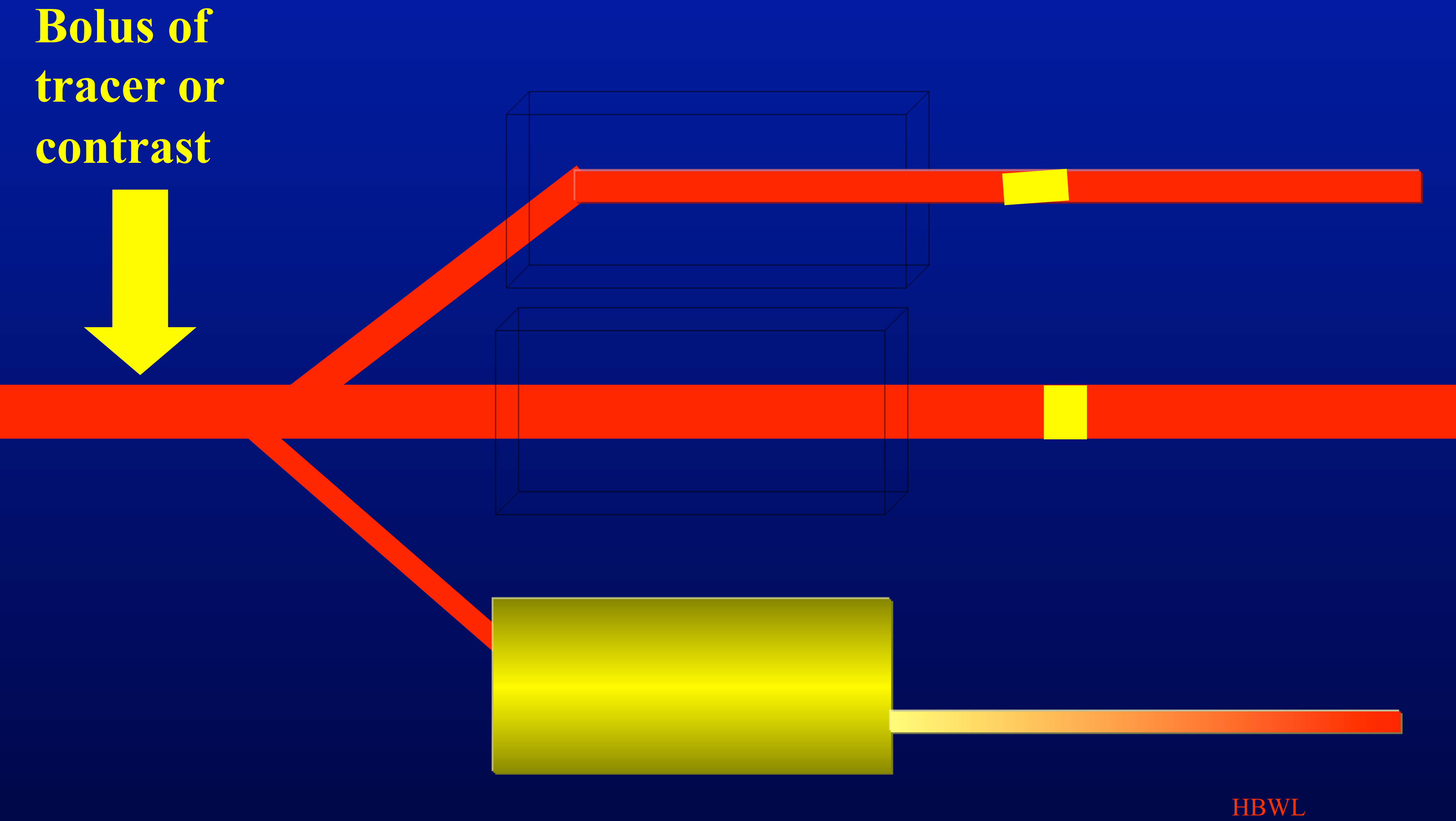
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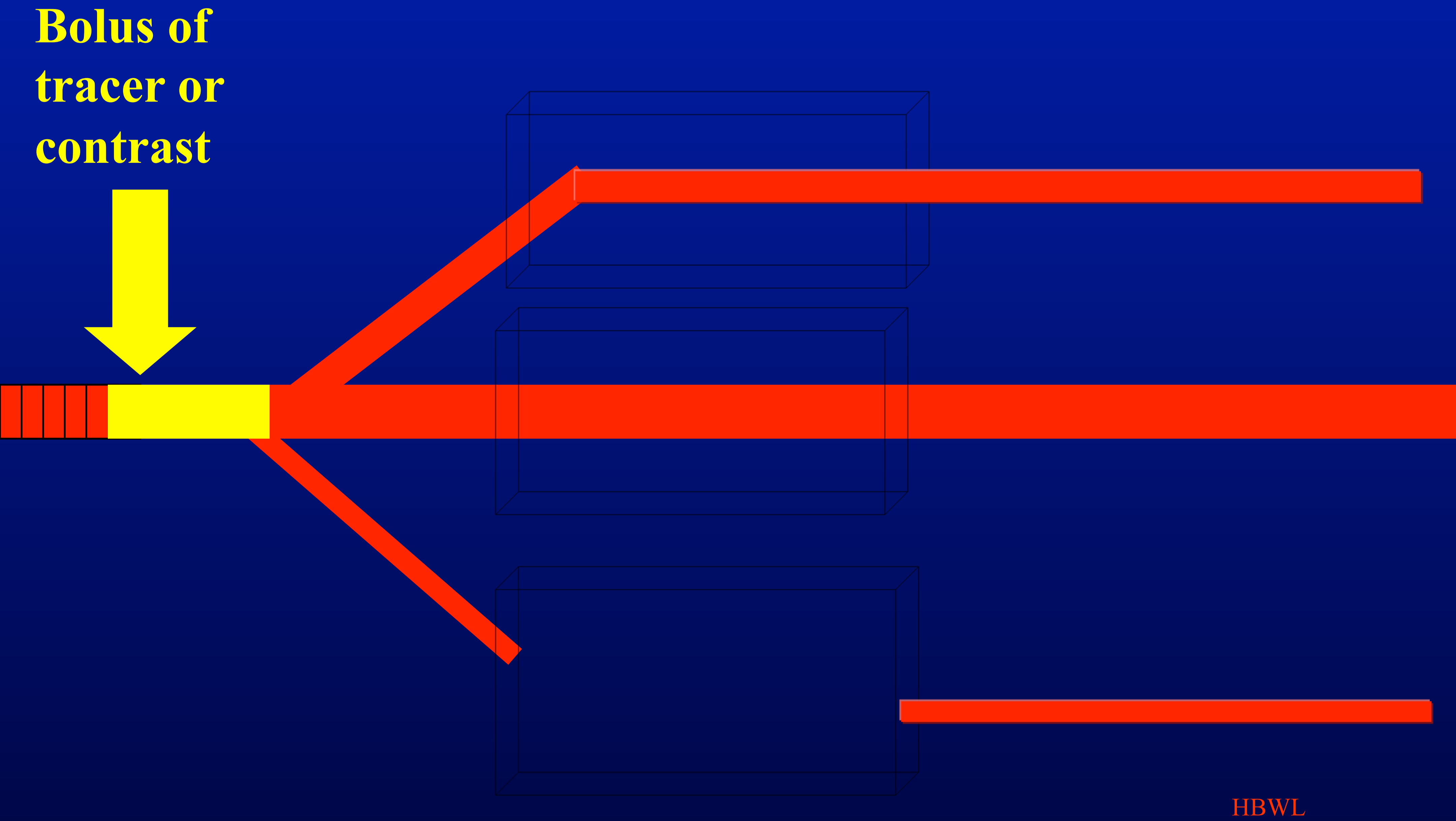
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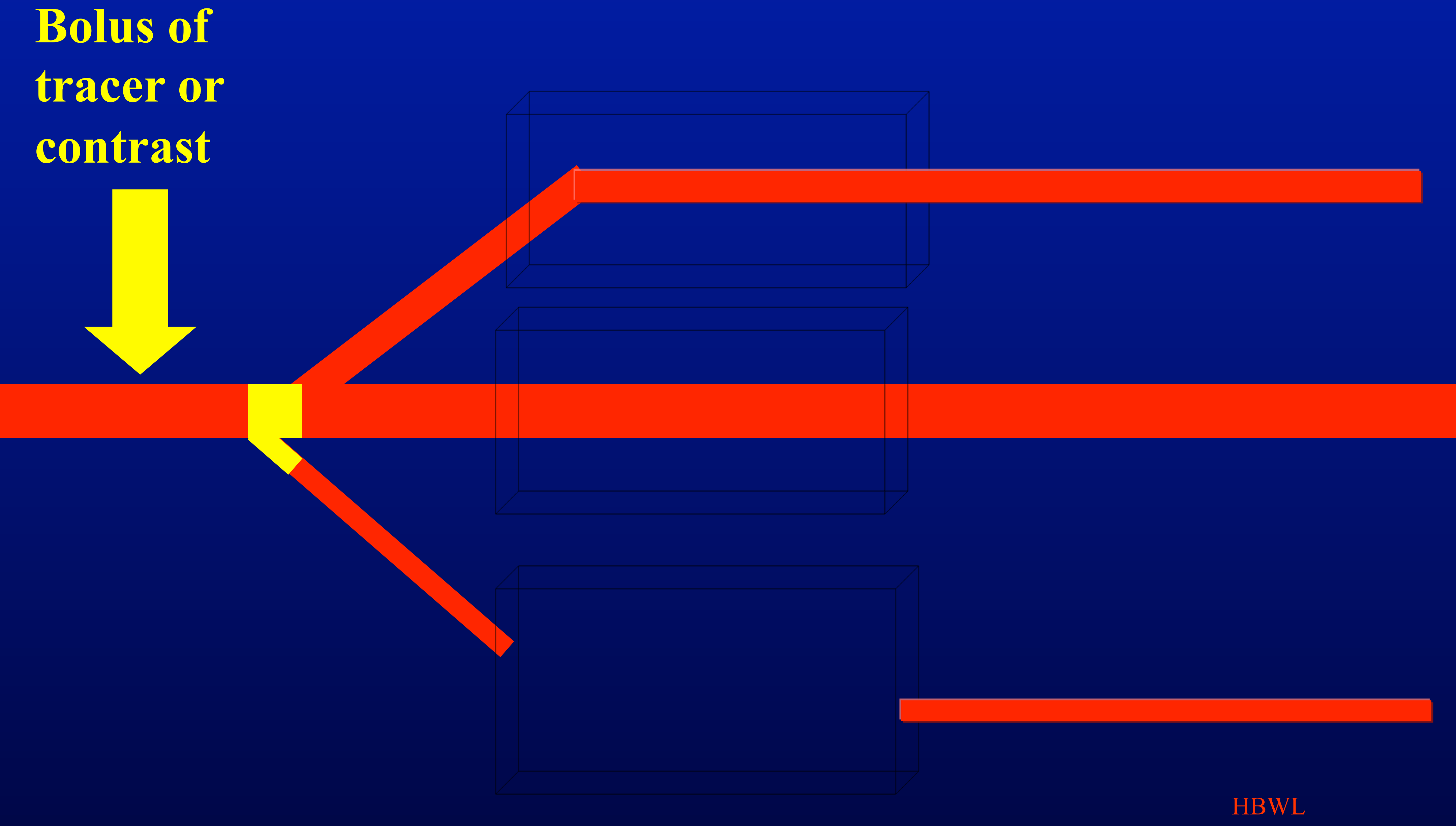
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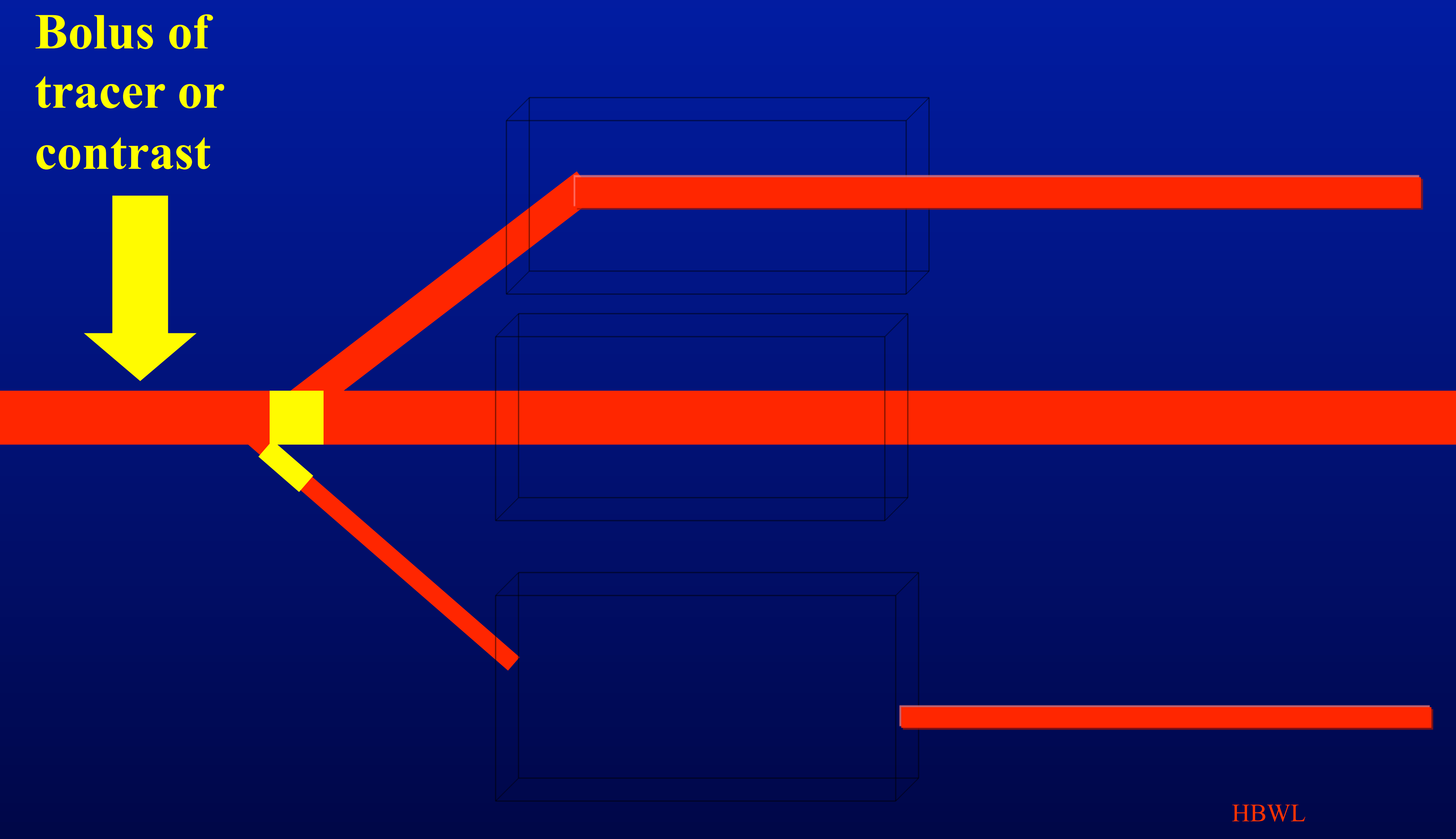
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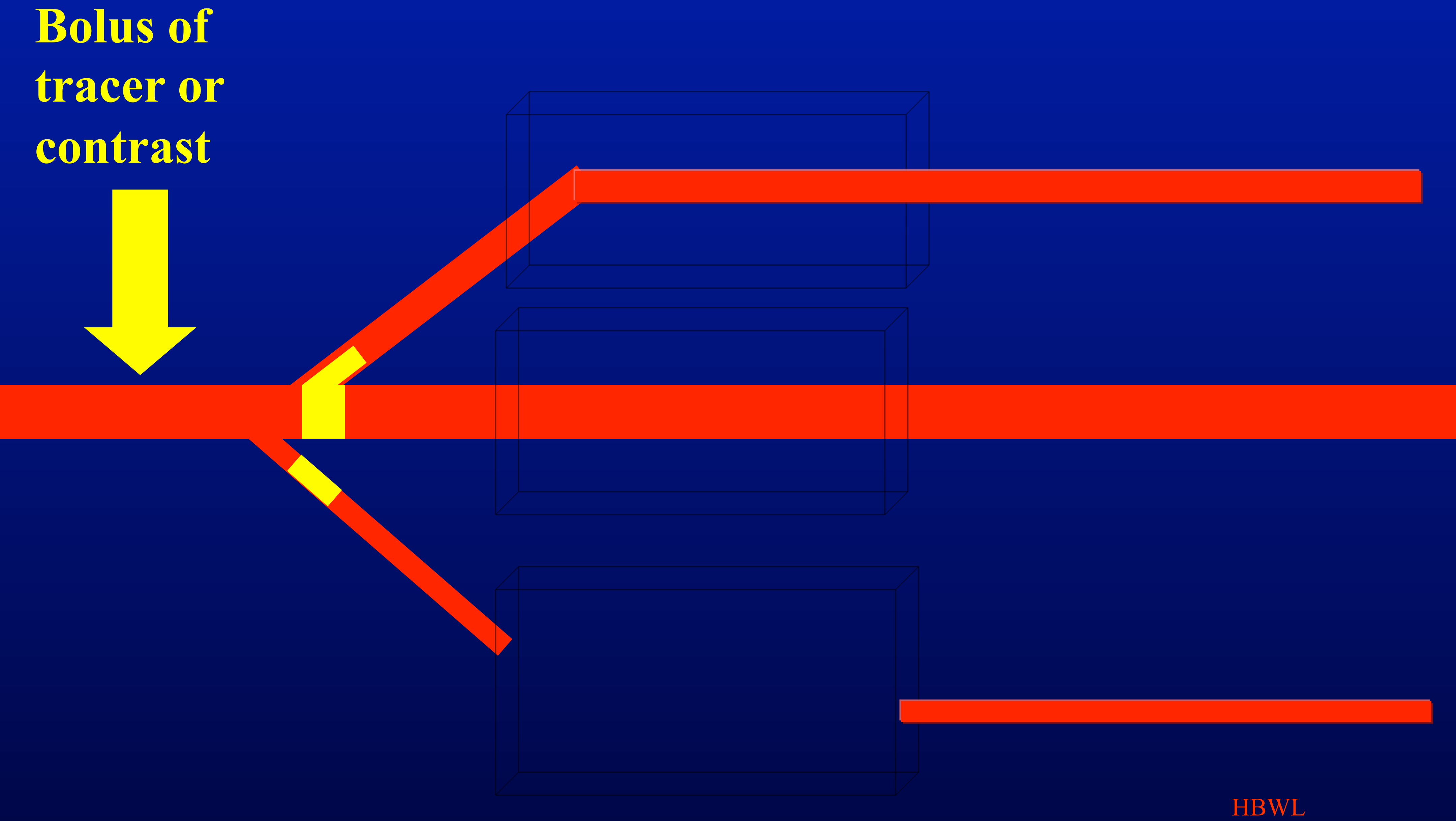
Bolus of tracer or contrast
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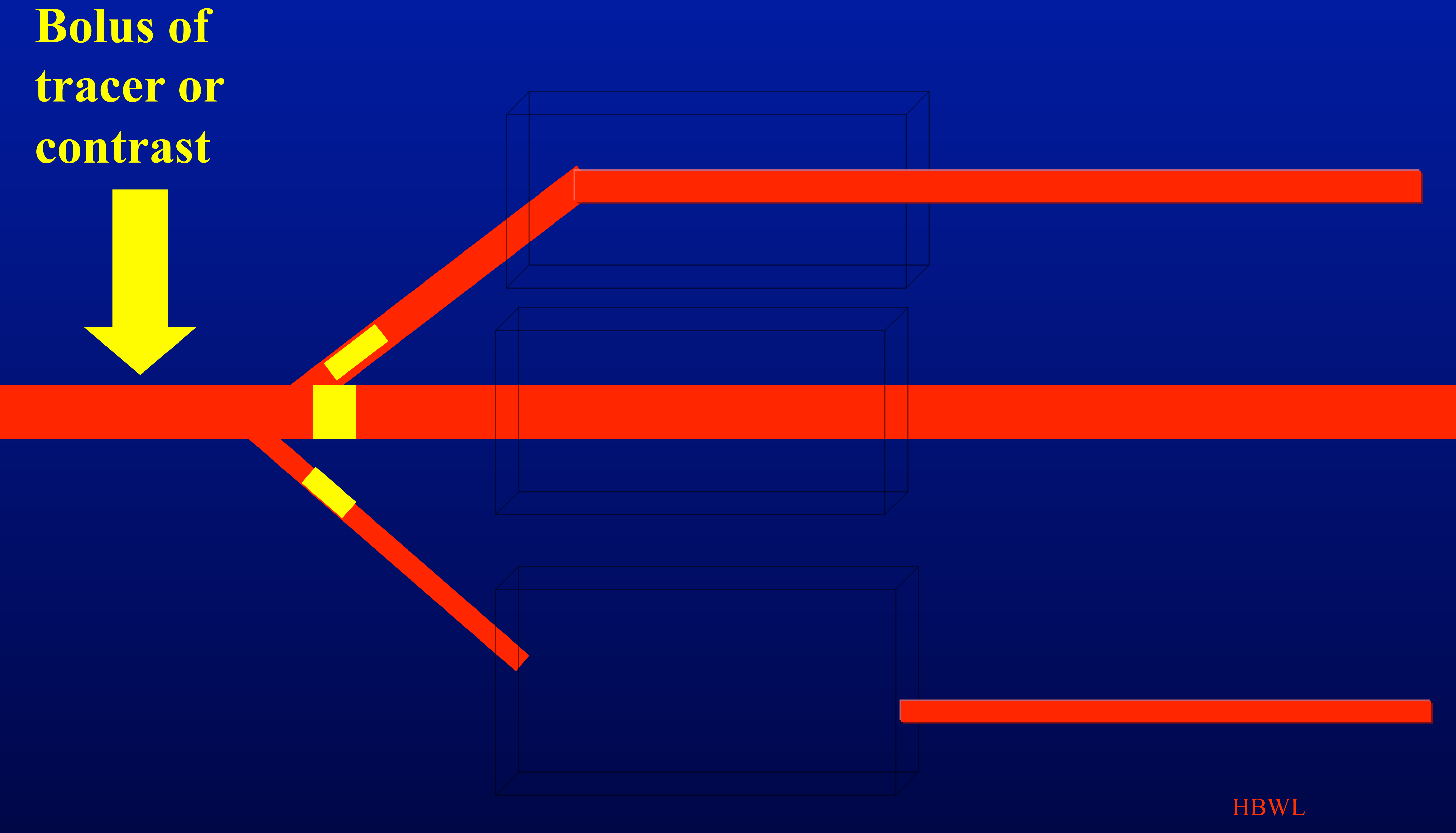
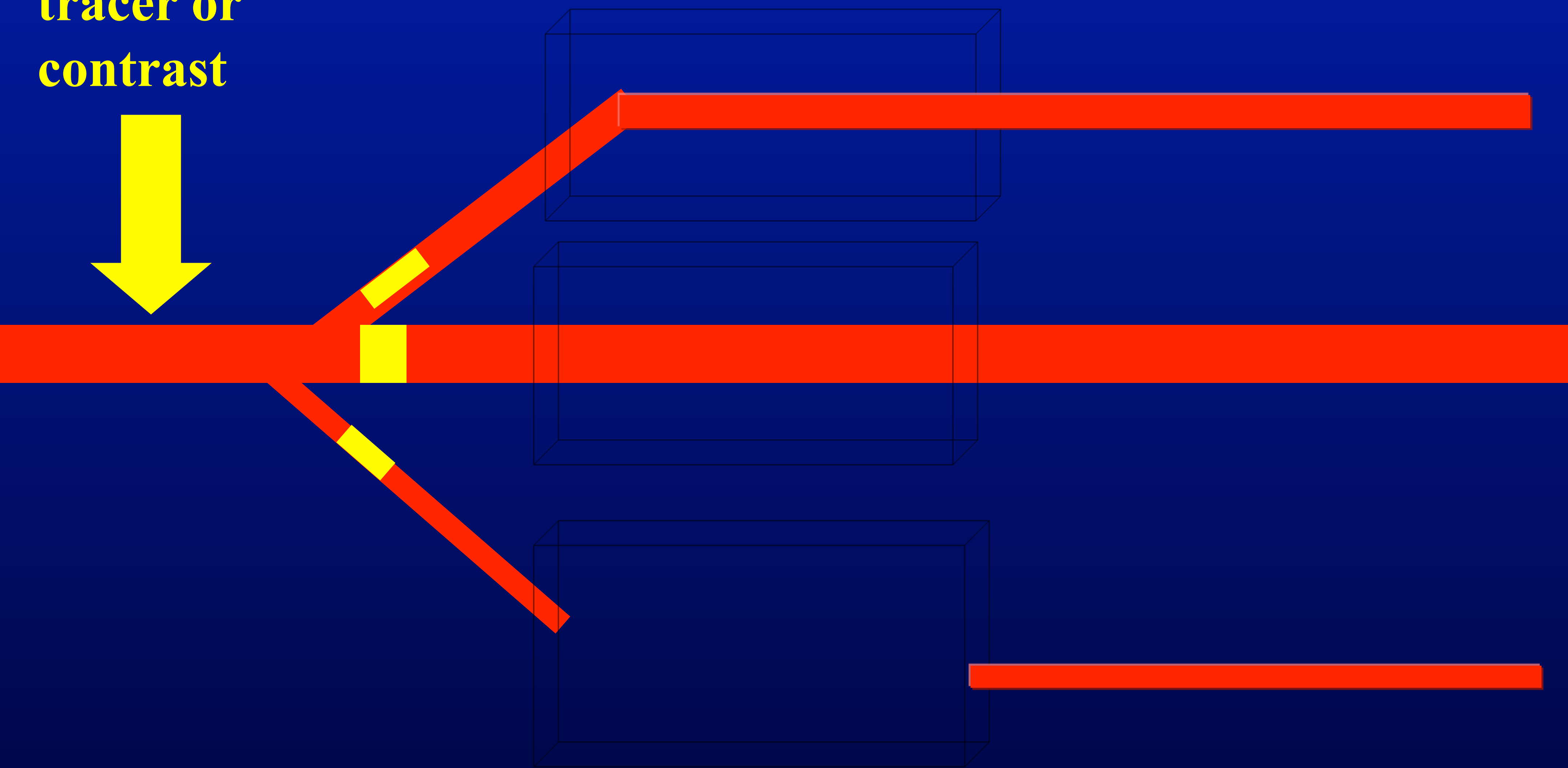
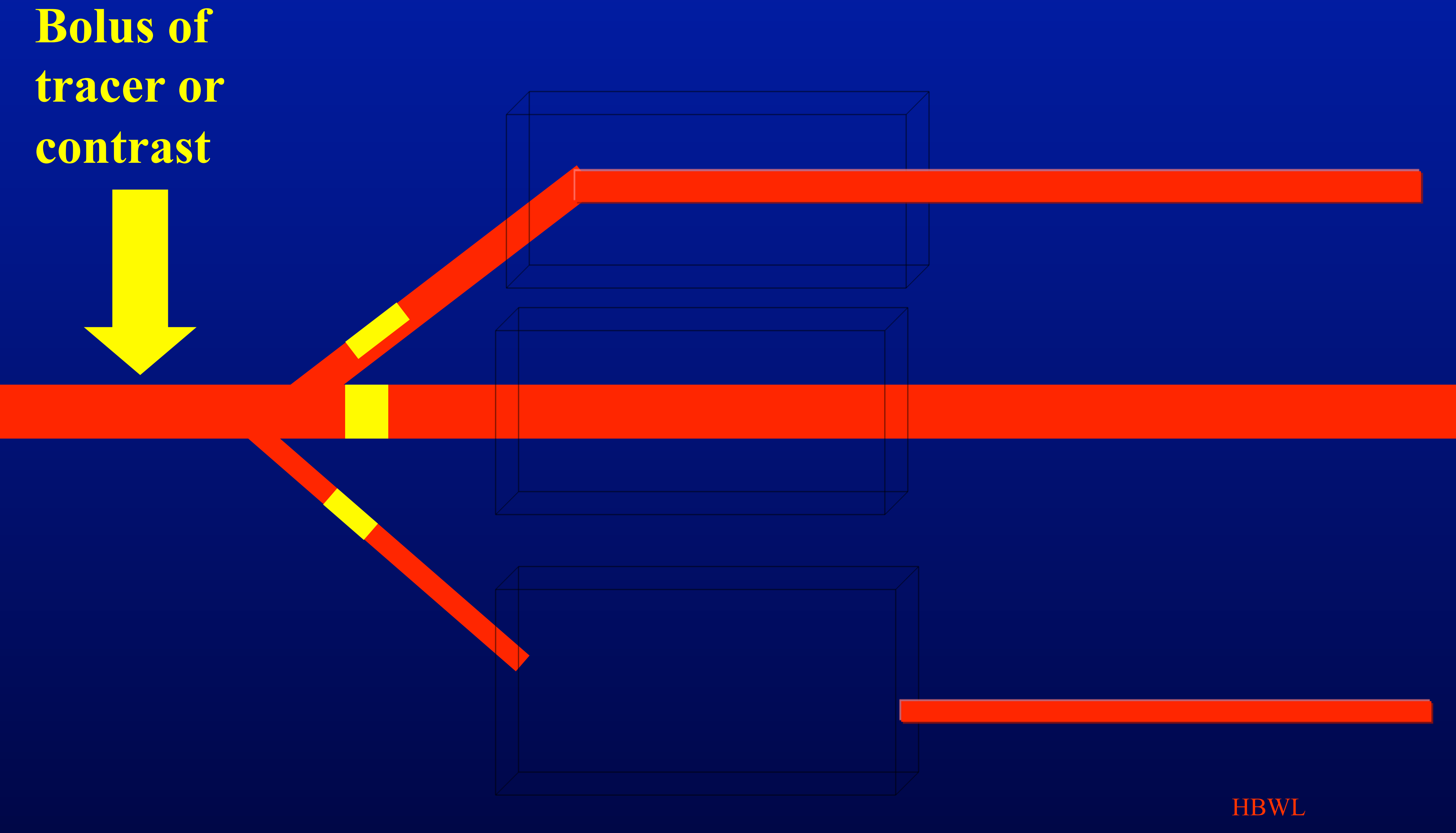

Bolus of tracer or contrast
HBWL

Bolus of tracer or contrast



HBWL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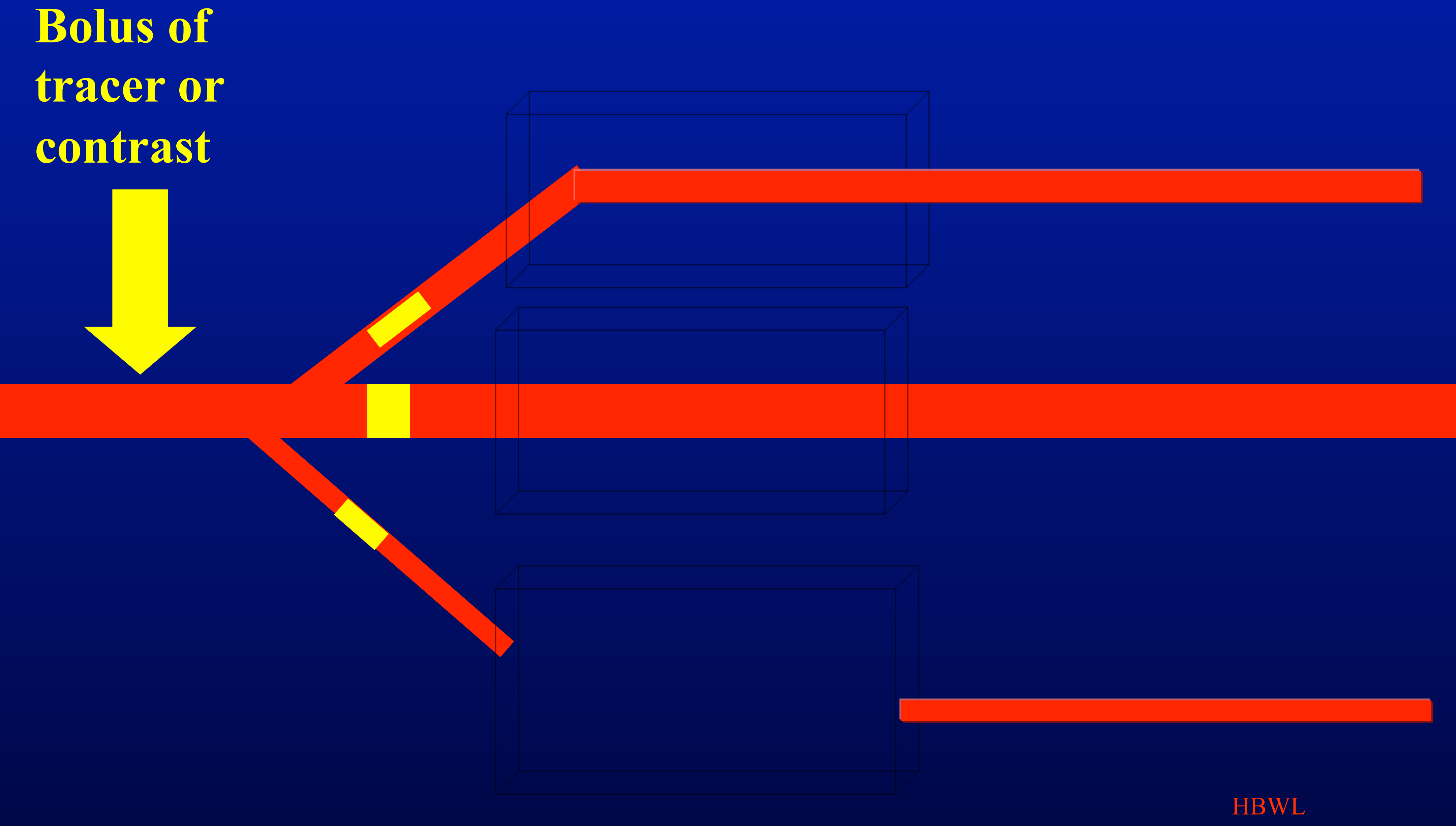
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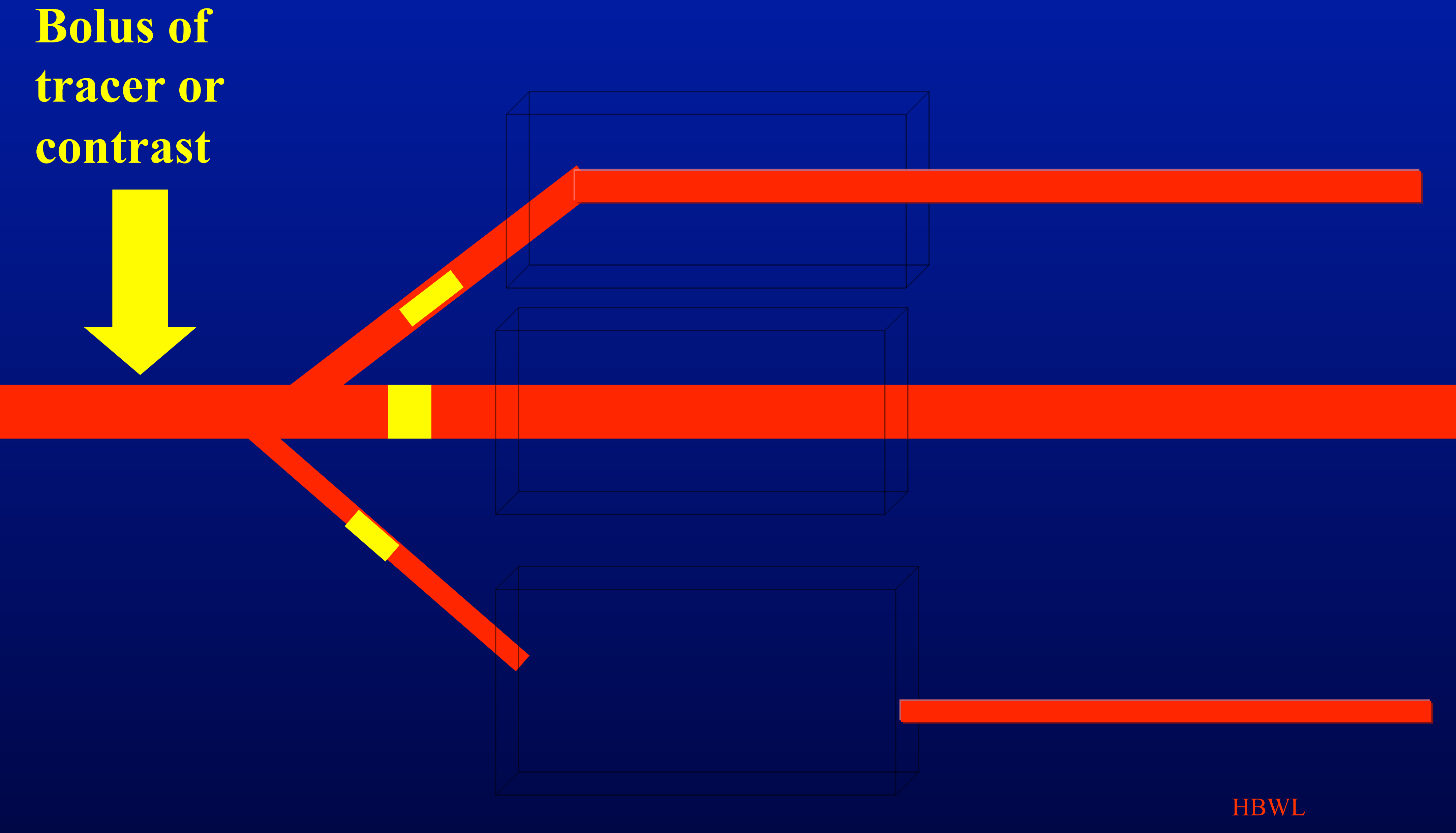
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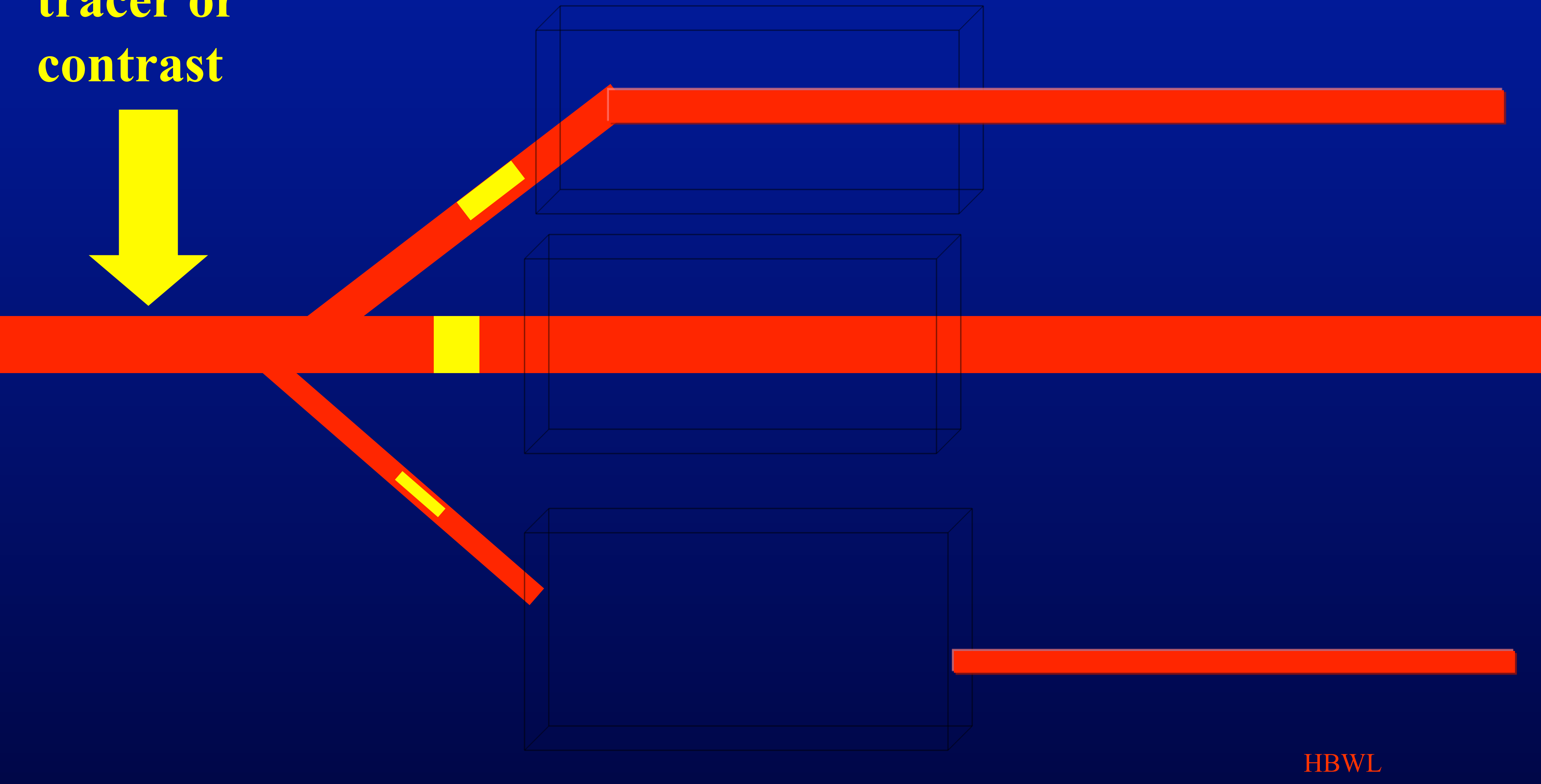

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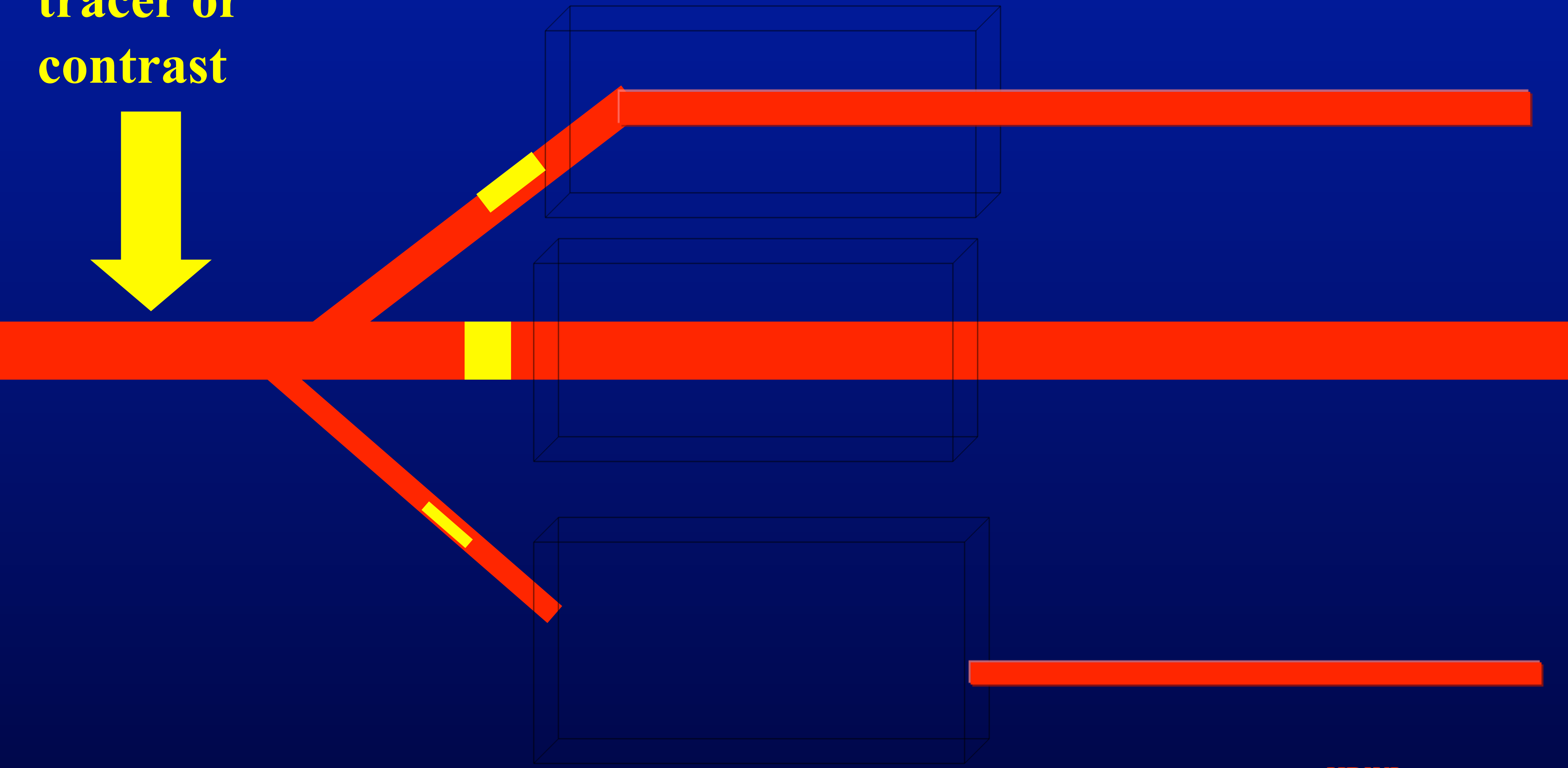
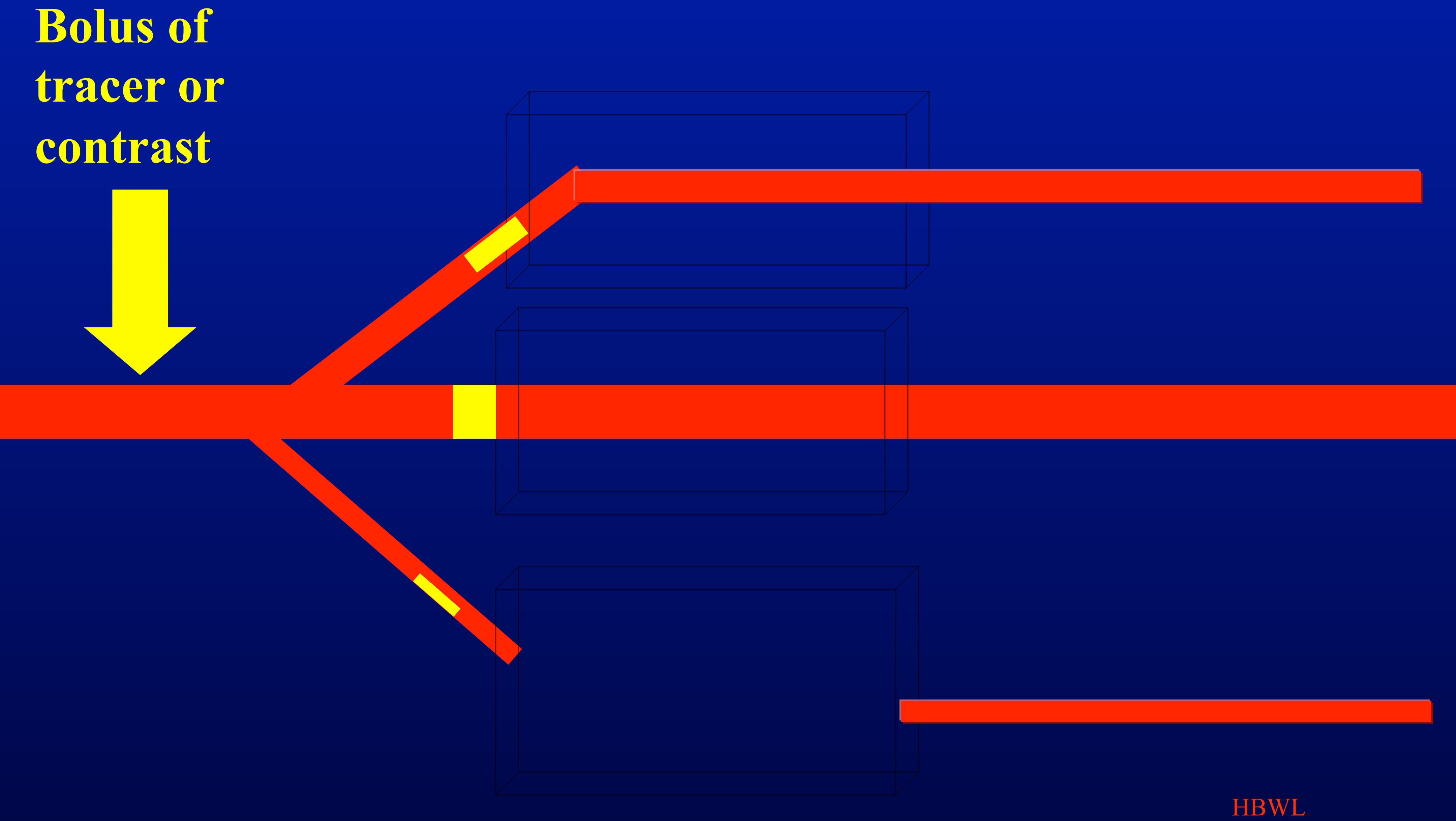


HBWL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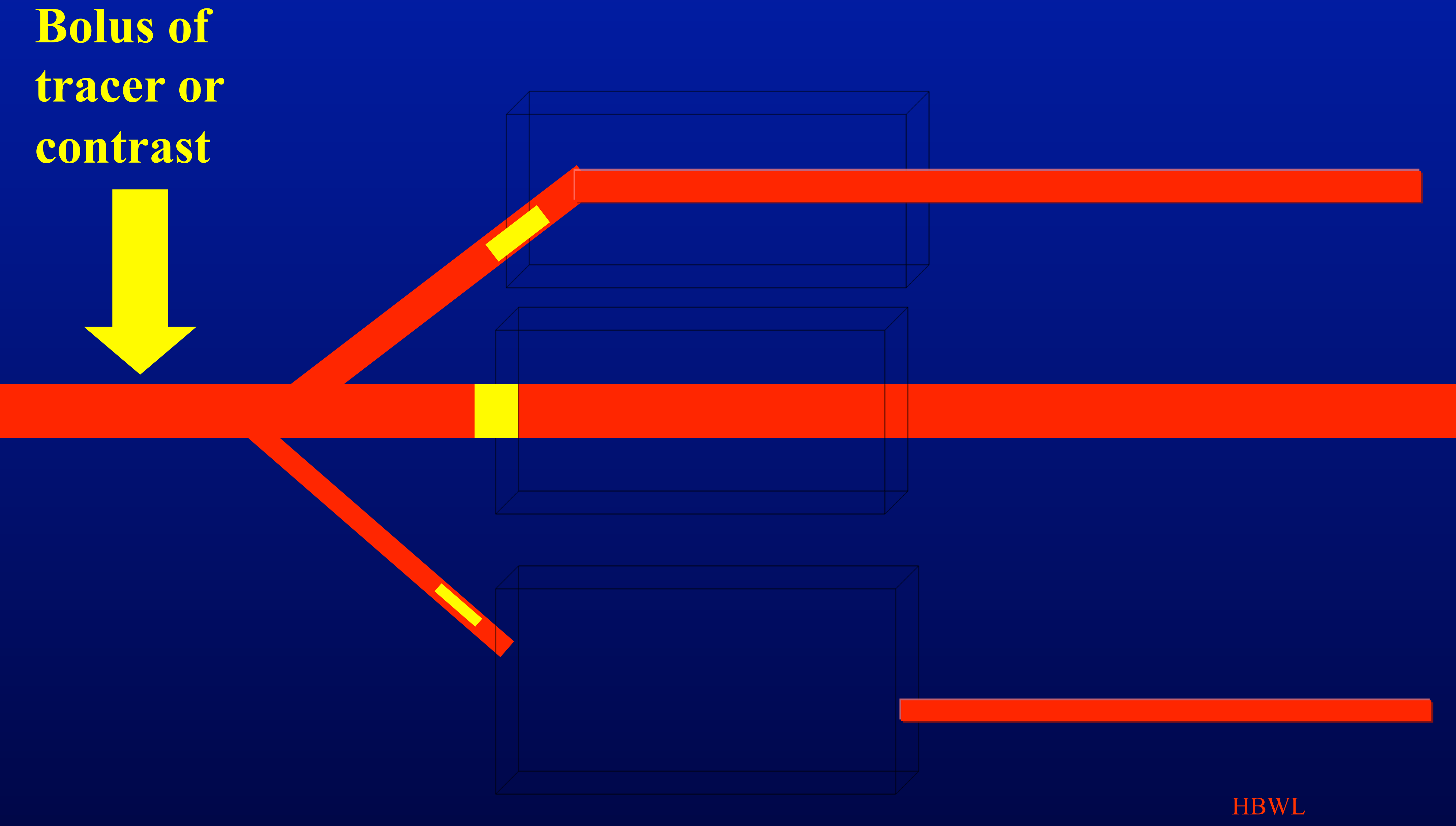
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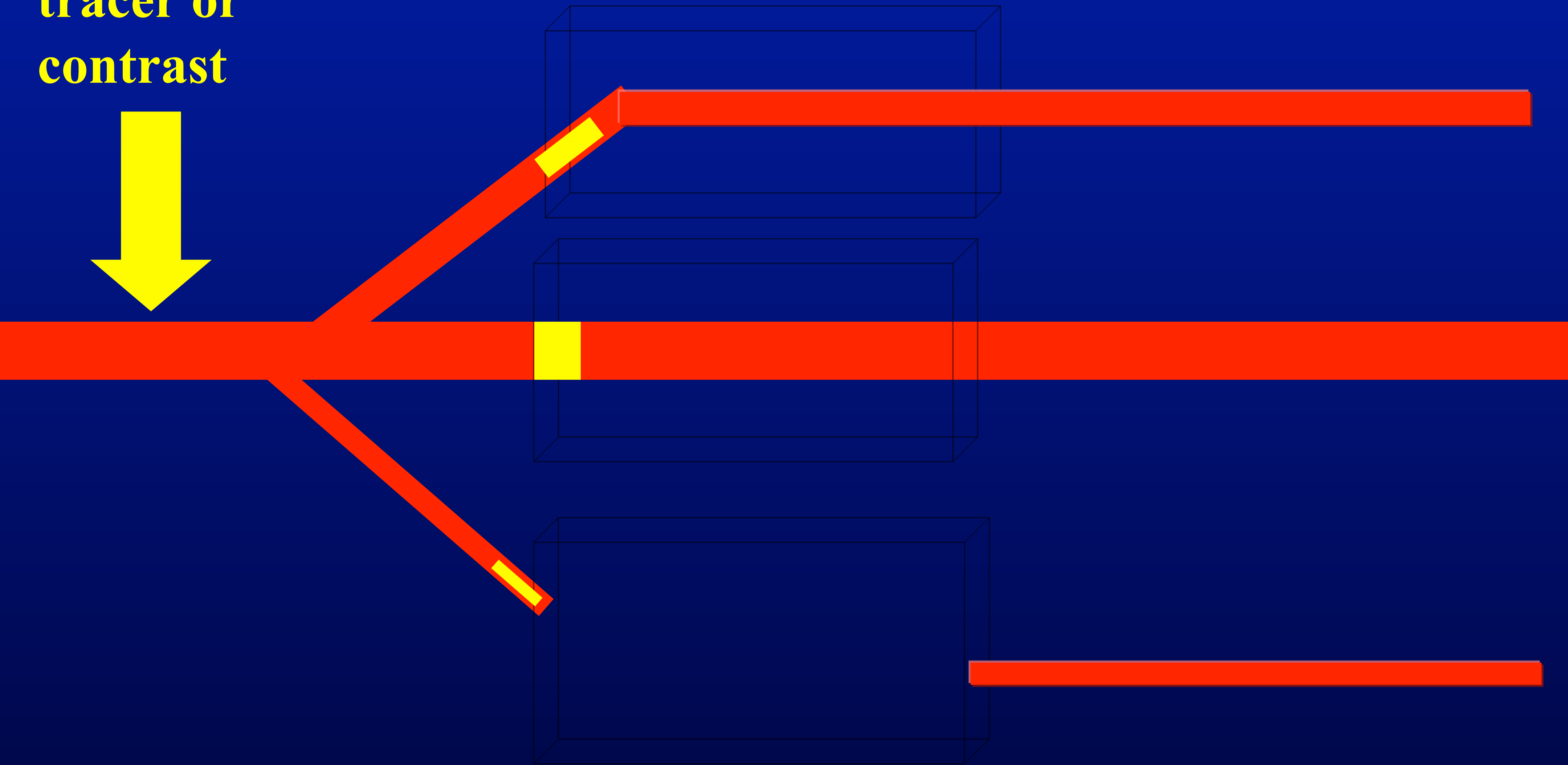
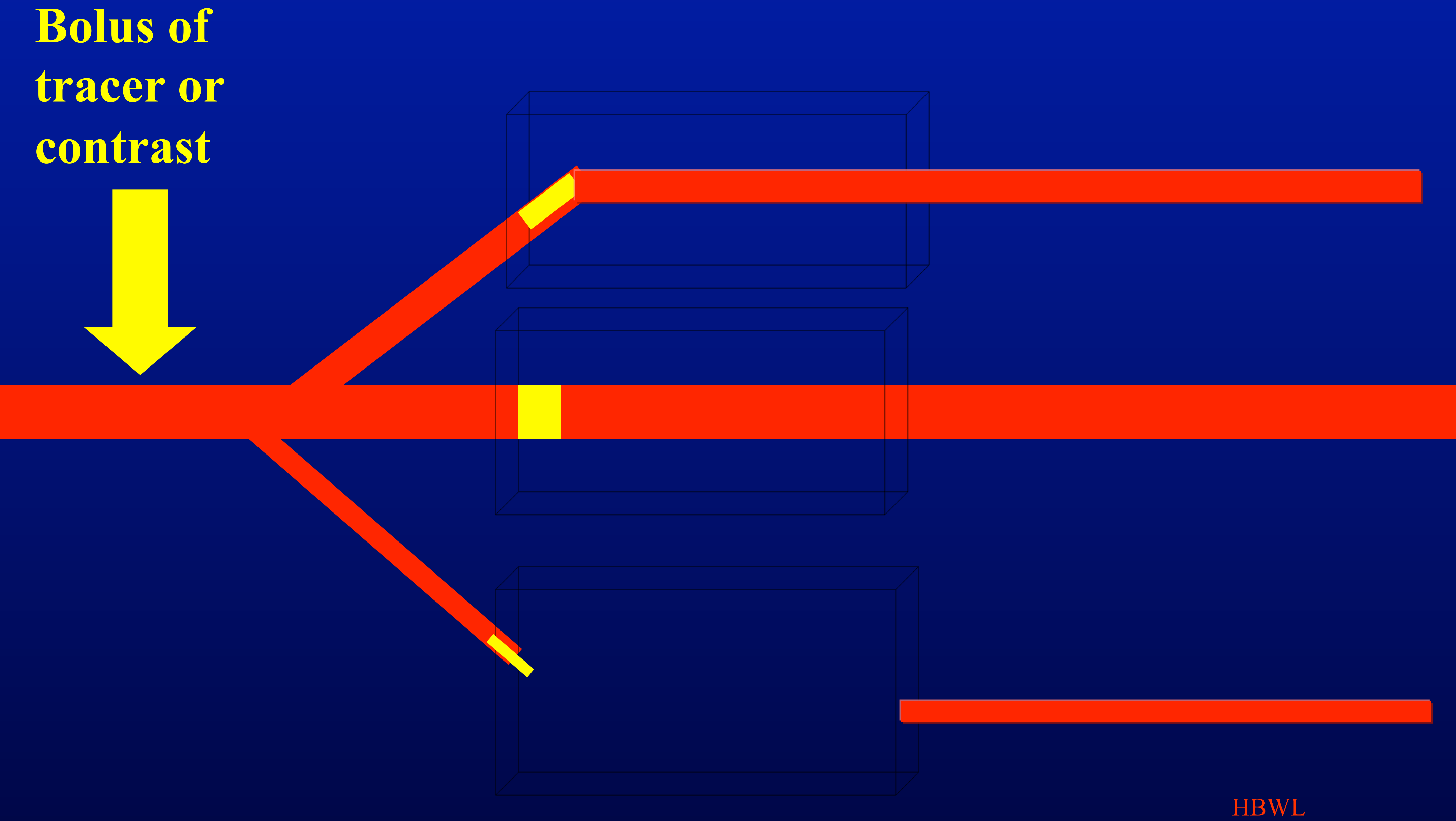


HBWL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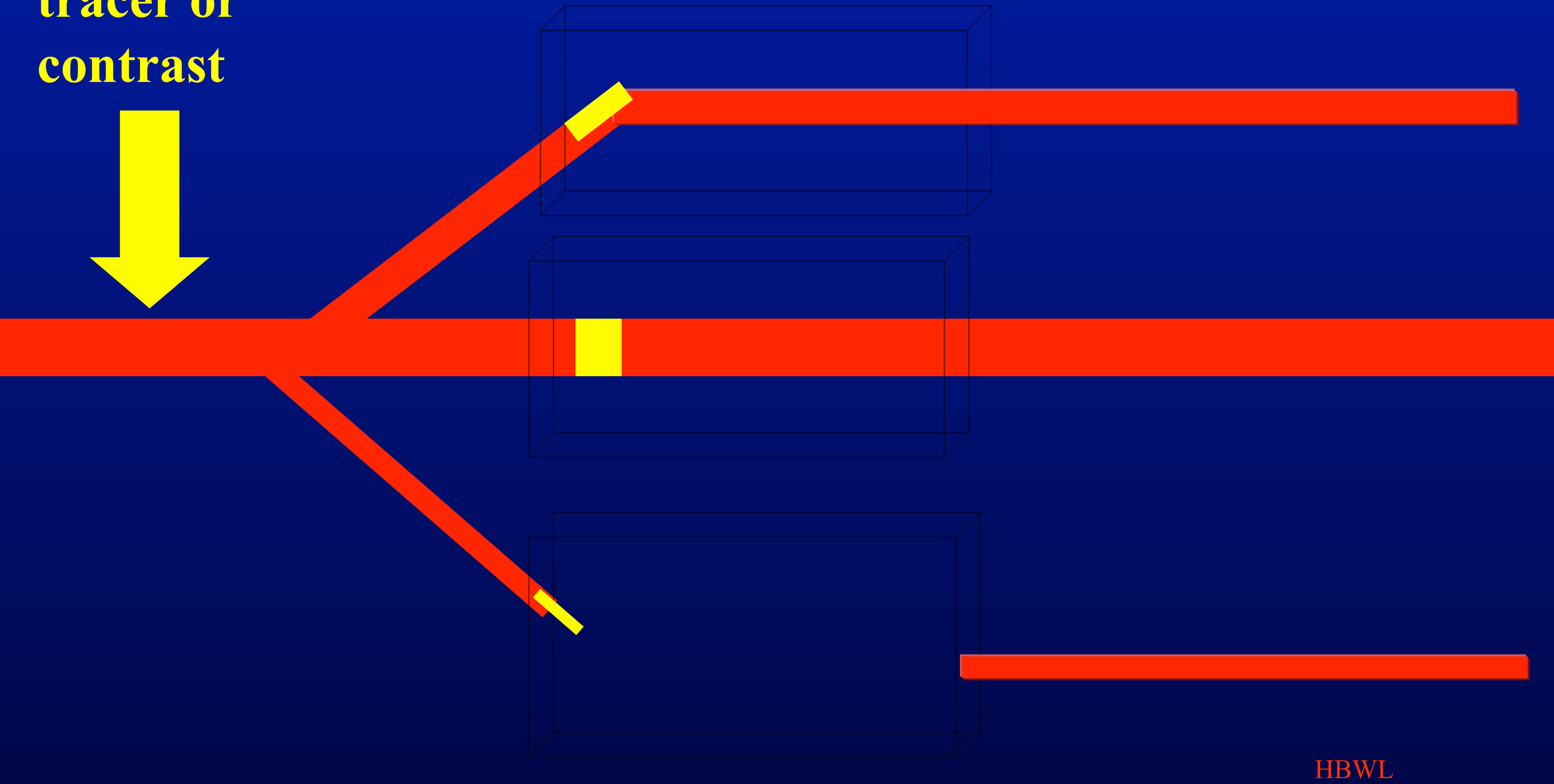

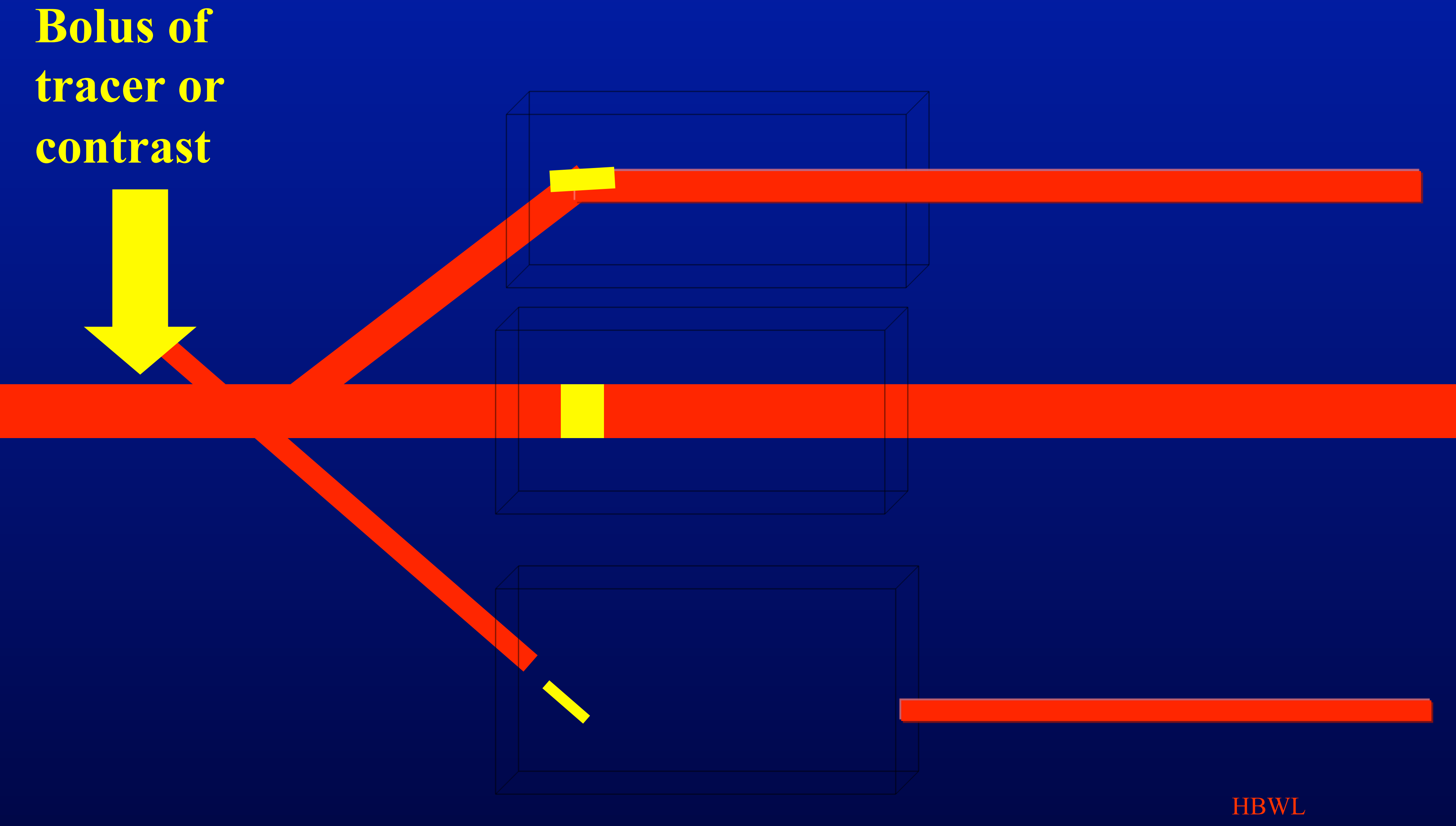
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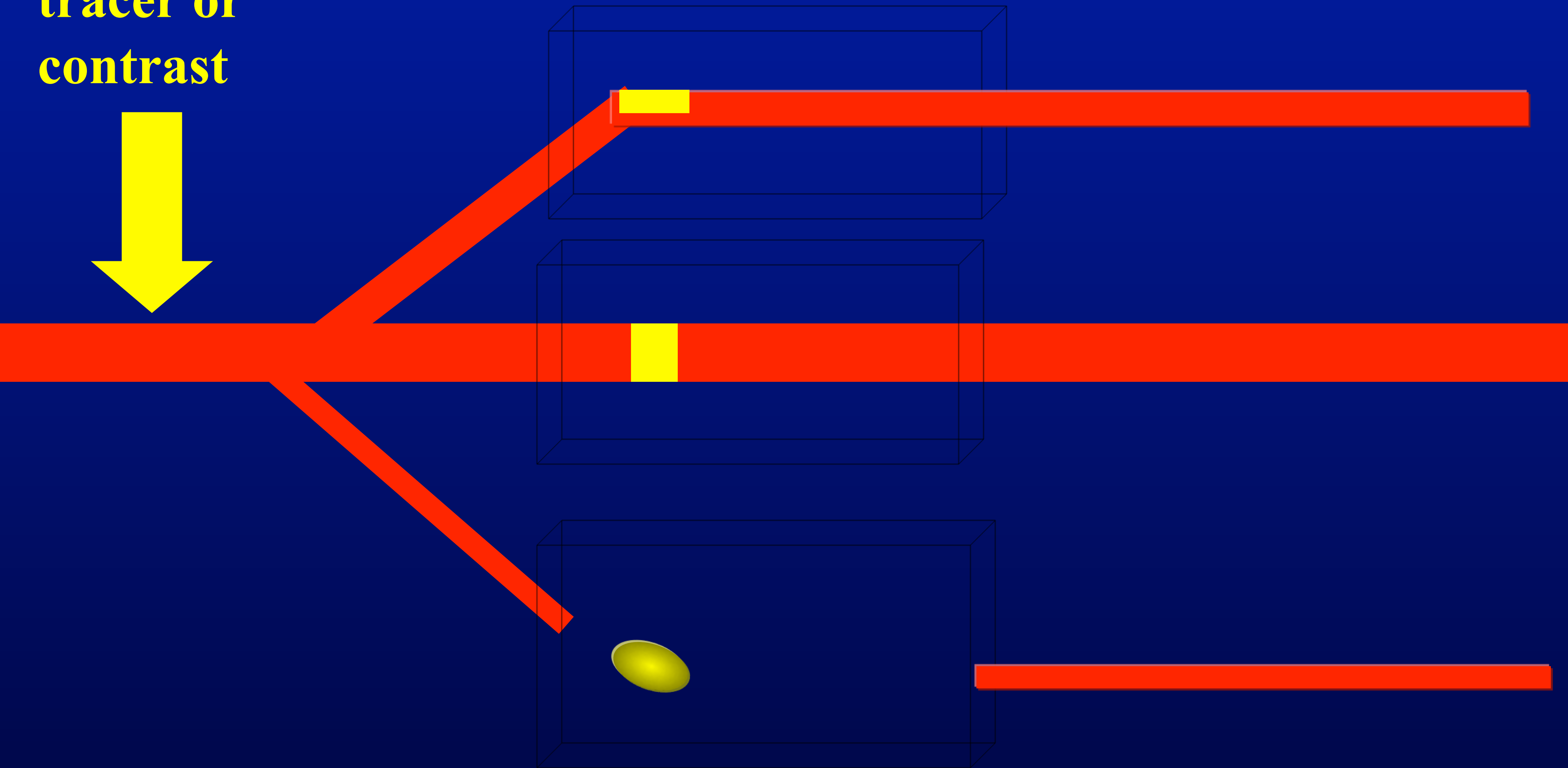

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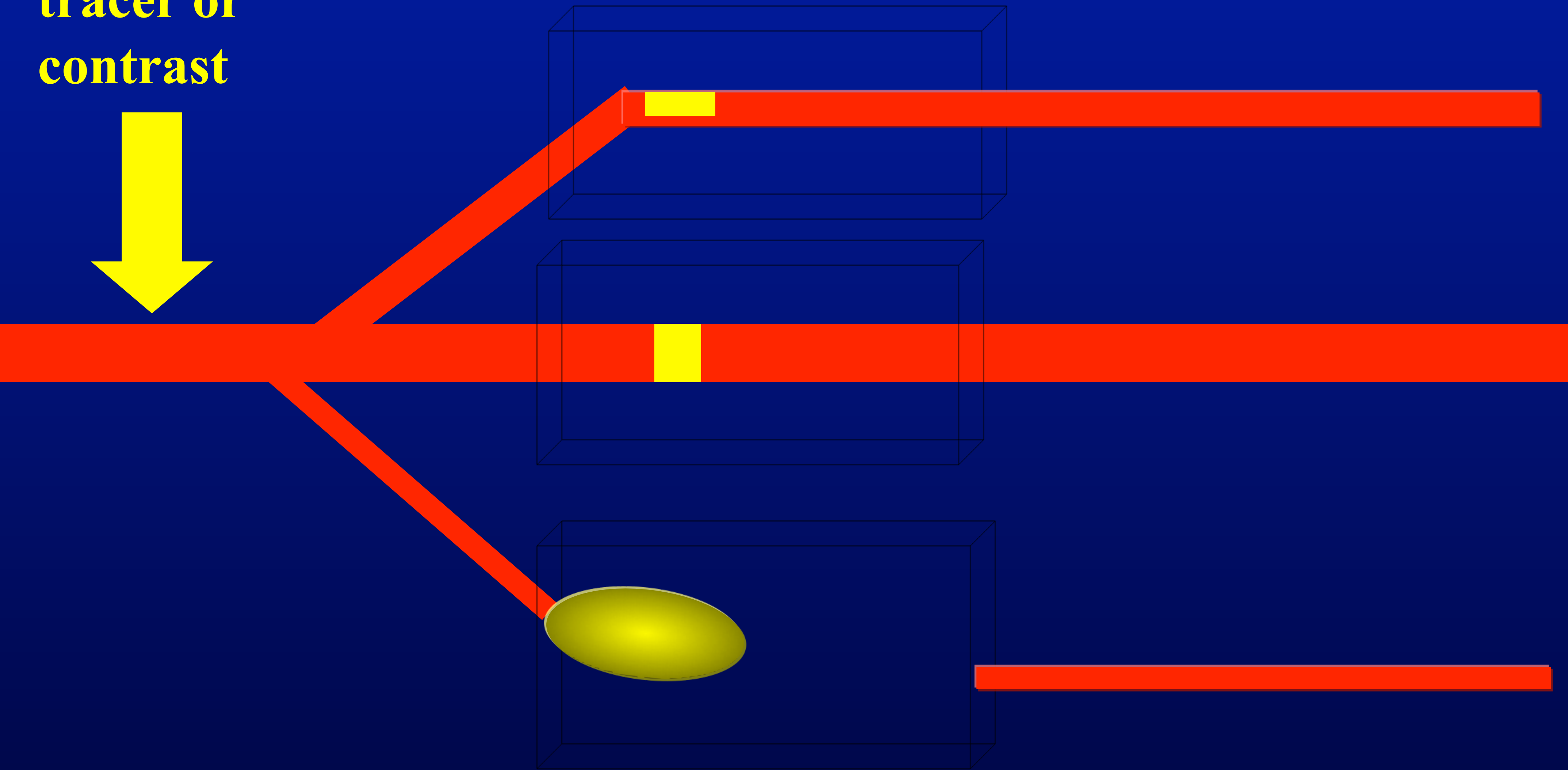

HBWL

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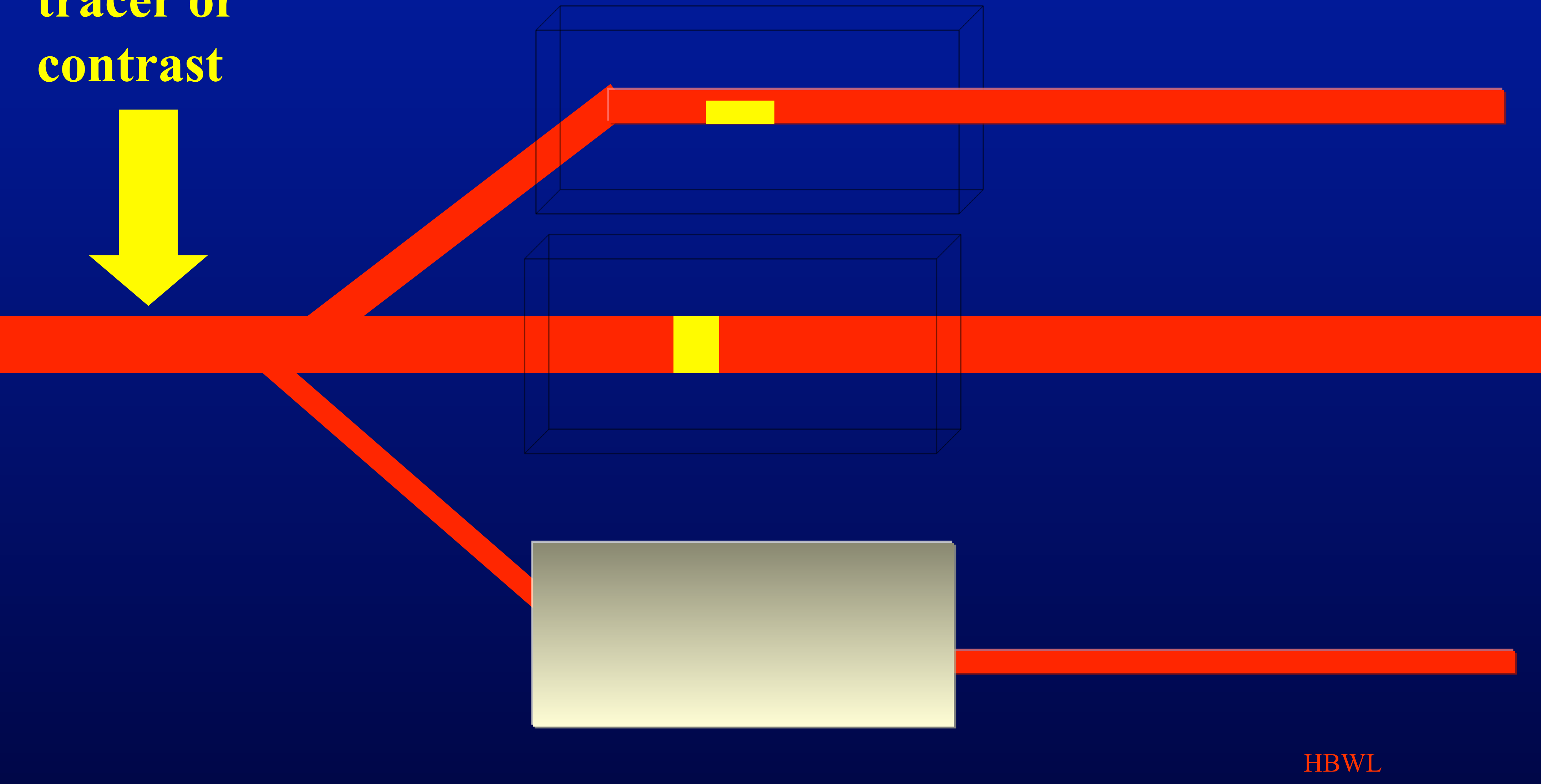

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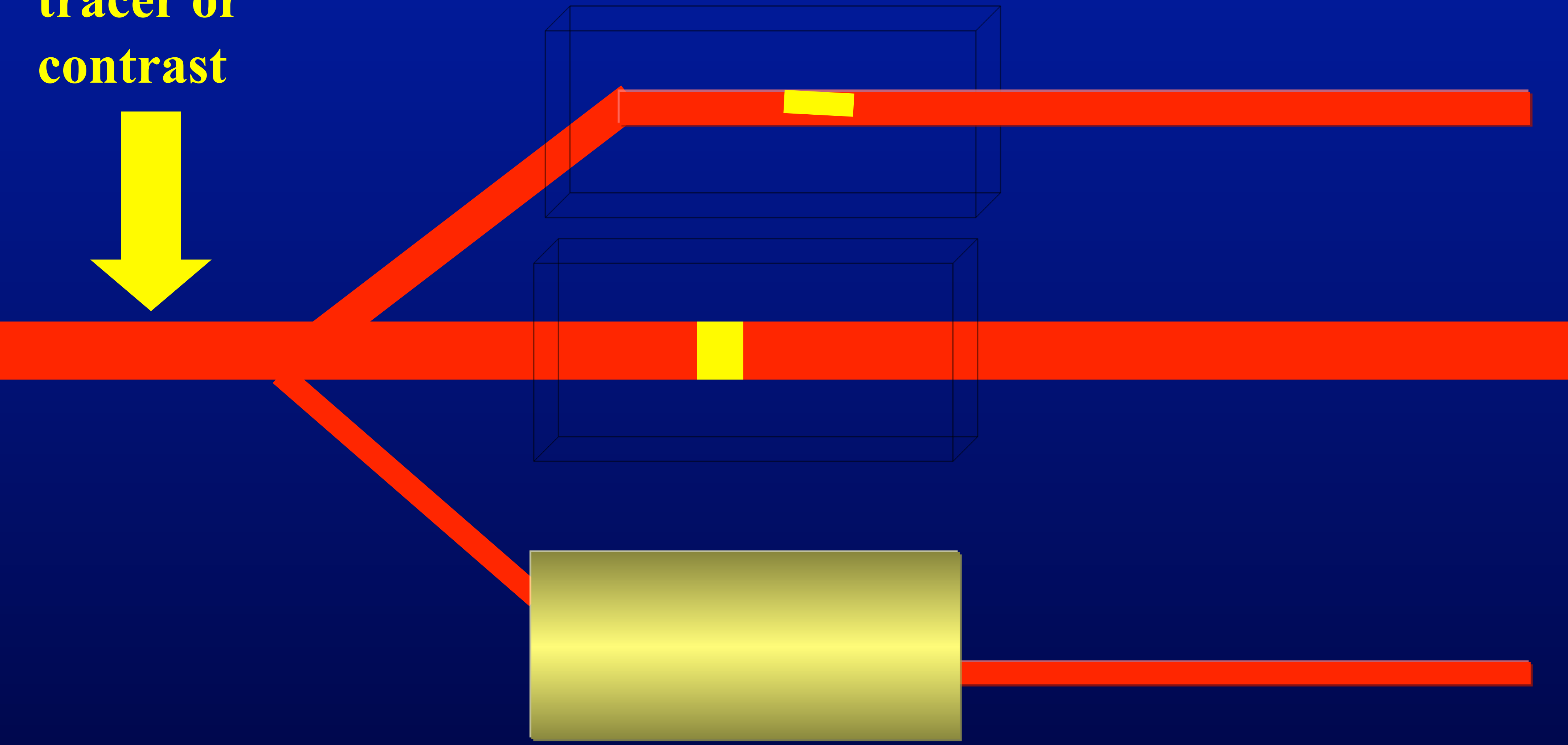
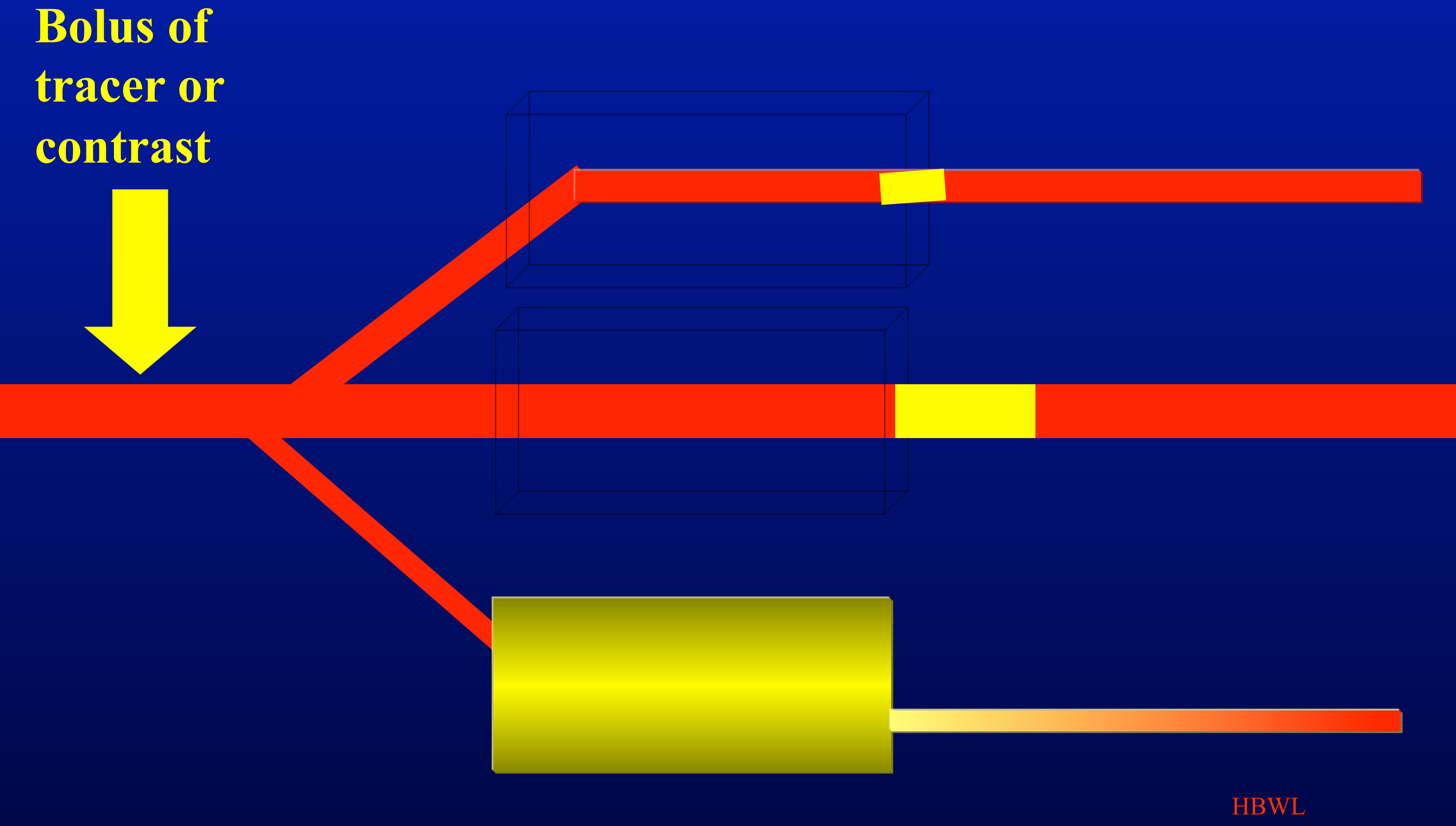


HBWL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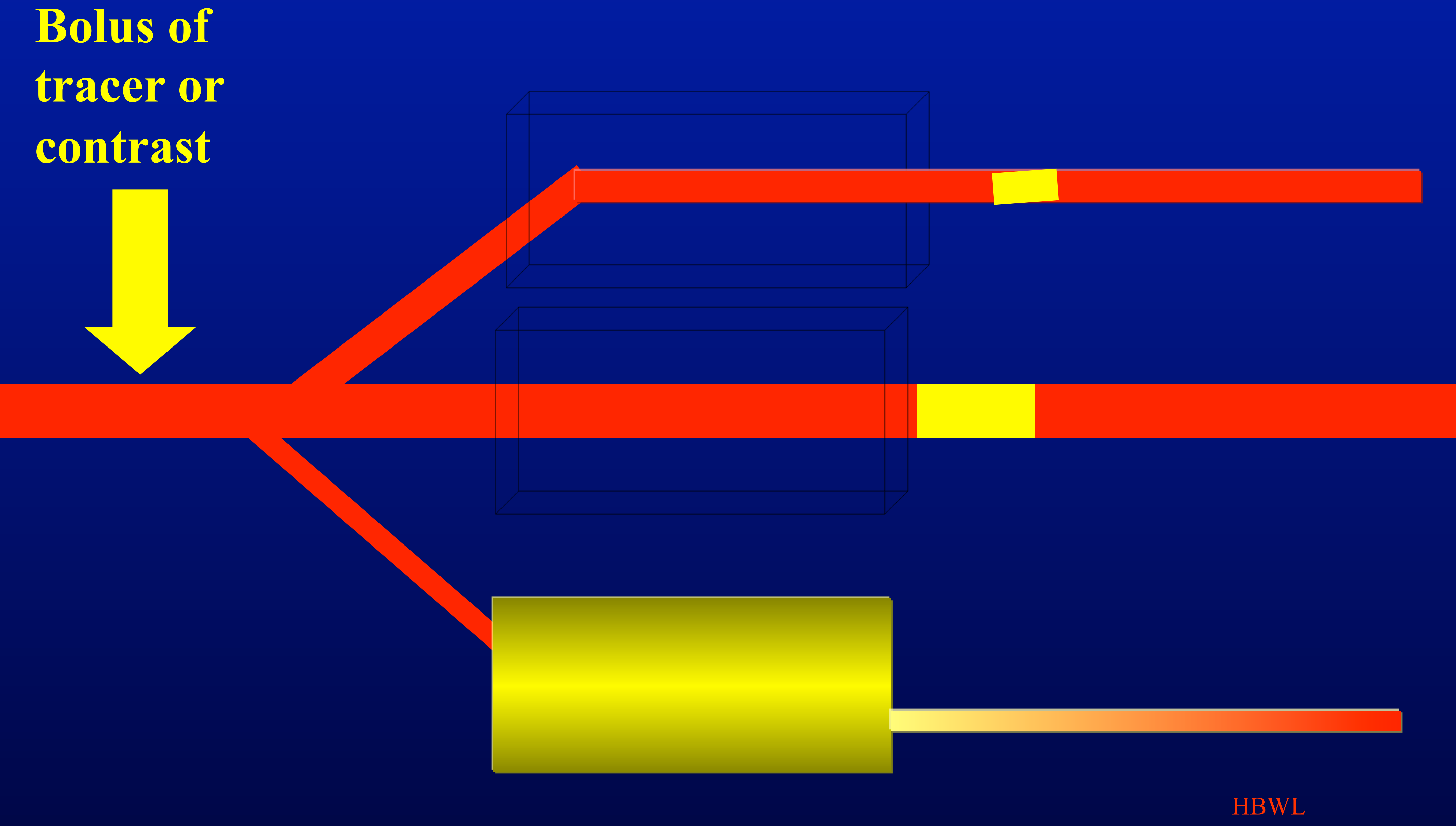

Bolus of tracer or contrast
HBWL

How can it be measured ?

Add a contrast agent carried by the blood to the tissue

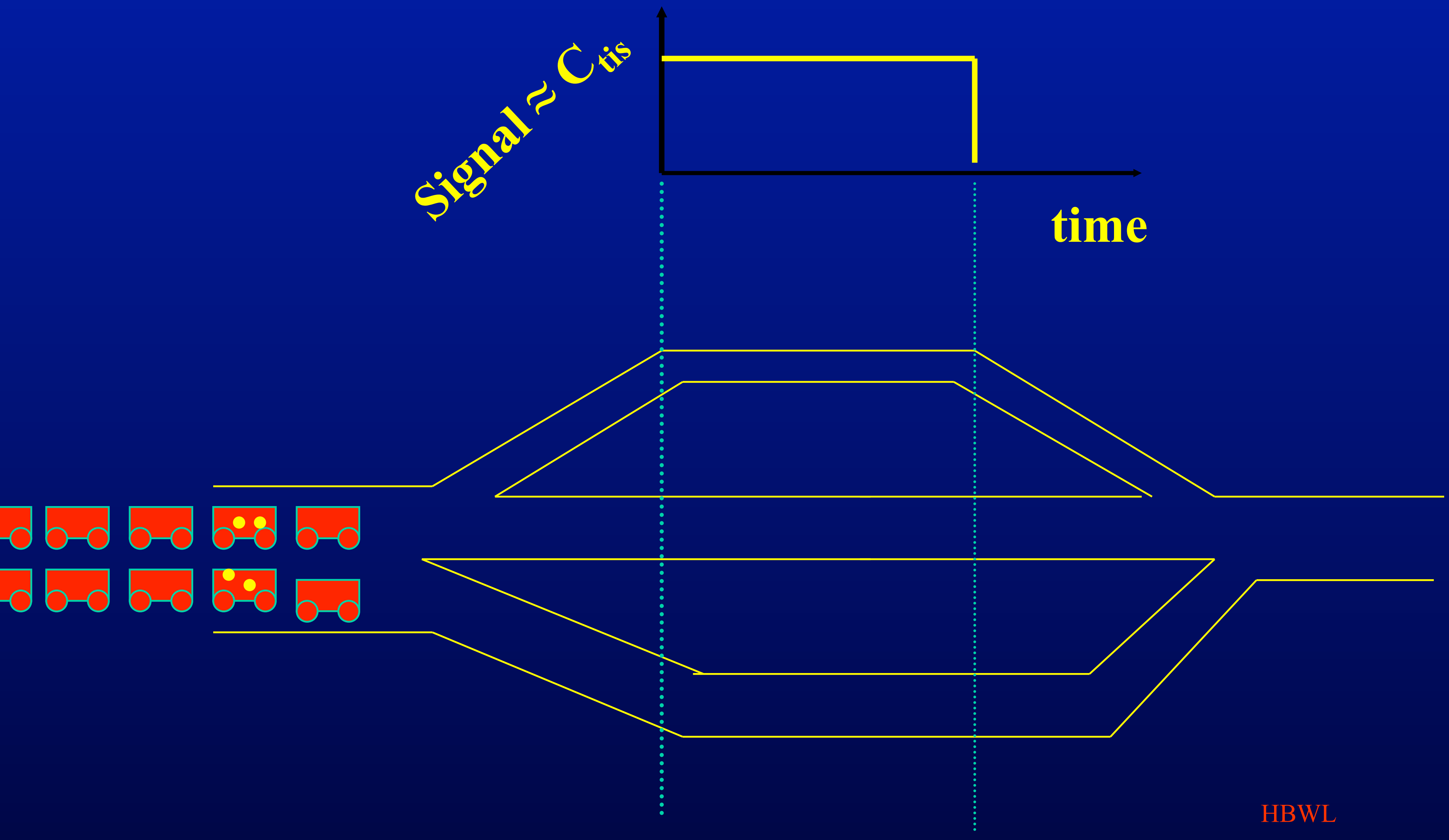
Contrast agent → **exogent**

Contrast agent → **endogent**

HBWL

The complicated part: Single bolus injection and external registration

HBWL



Signal ≈ C tis
time
HBWL

$$\text{Signal} \approx C_{tis}(0) : \; f\, C_a(0)$$

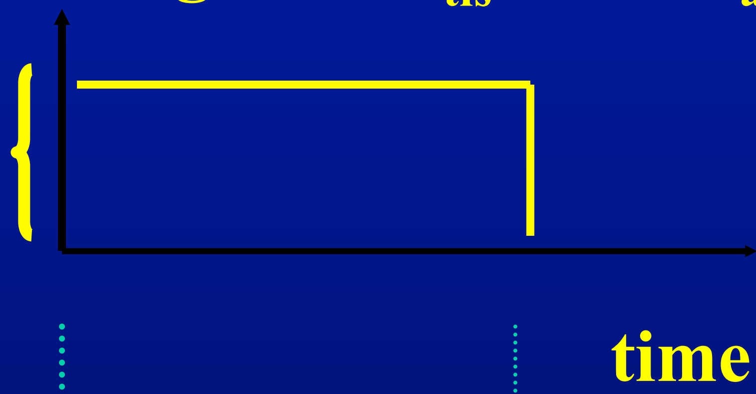
Perfusion (f) = vehicles/min

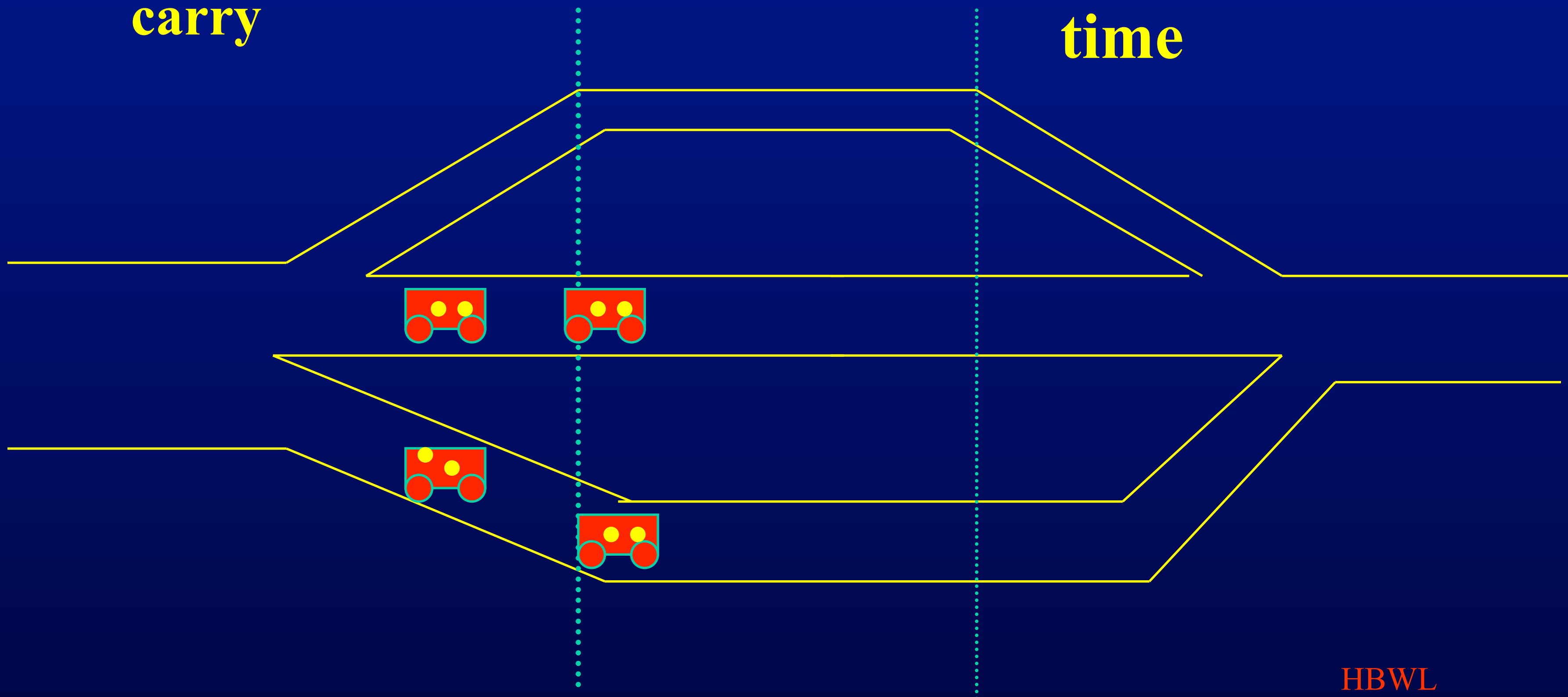
ml/min

x

Conc (C_a) = the cargo they carry

mmol/ml

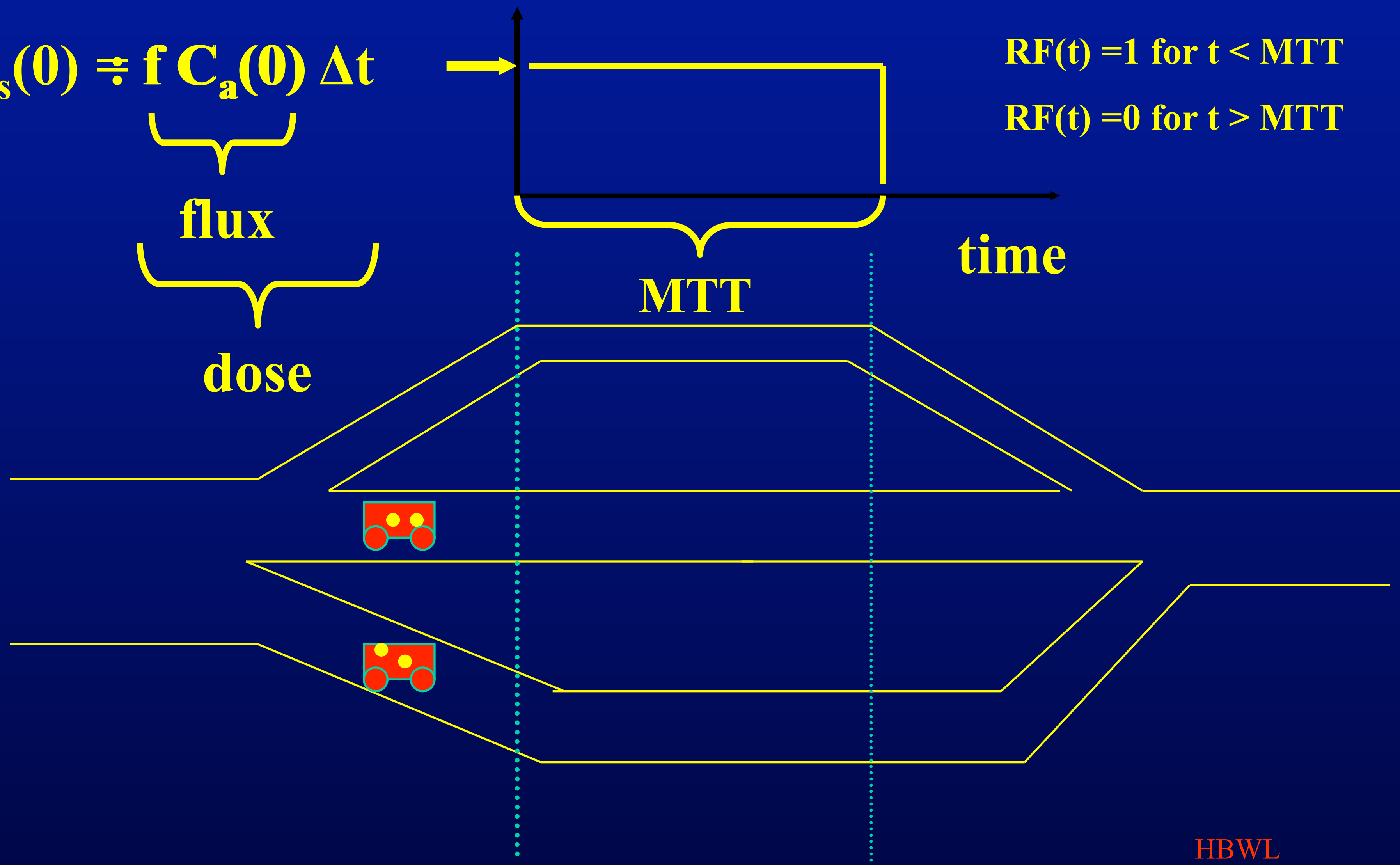




HBWL

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

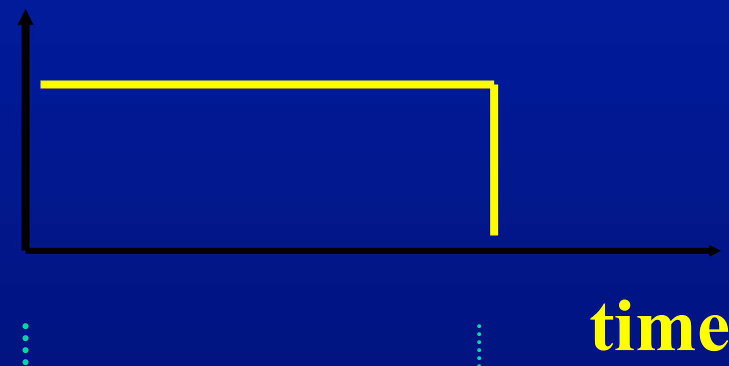
$$C_{tis}(0) \doteq \underbrace{\underbrace{f\,C_a(0)}_{\text{flux}}\,\Delta t}_{\text{dose}}$$



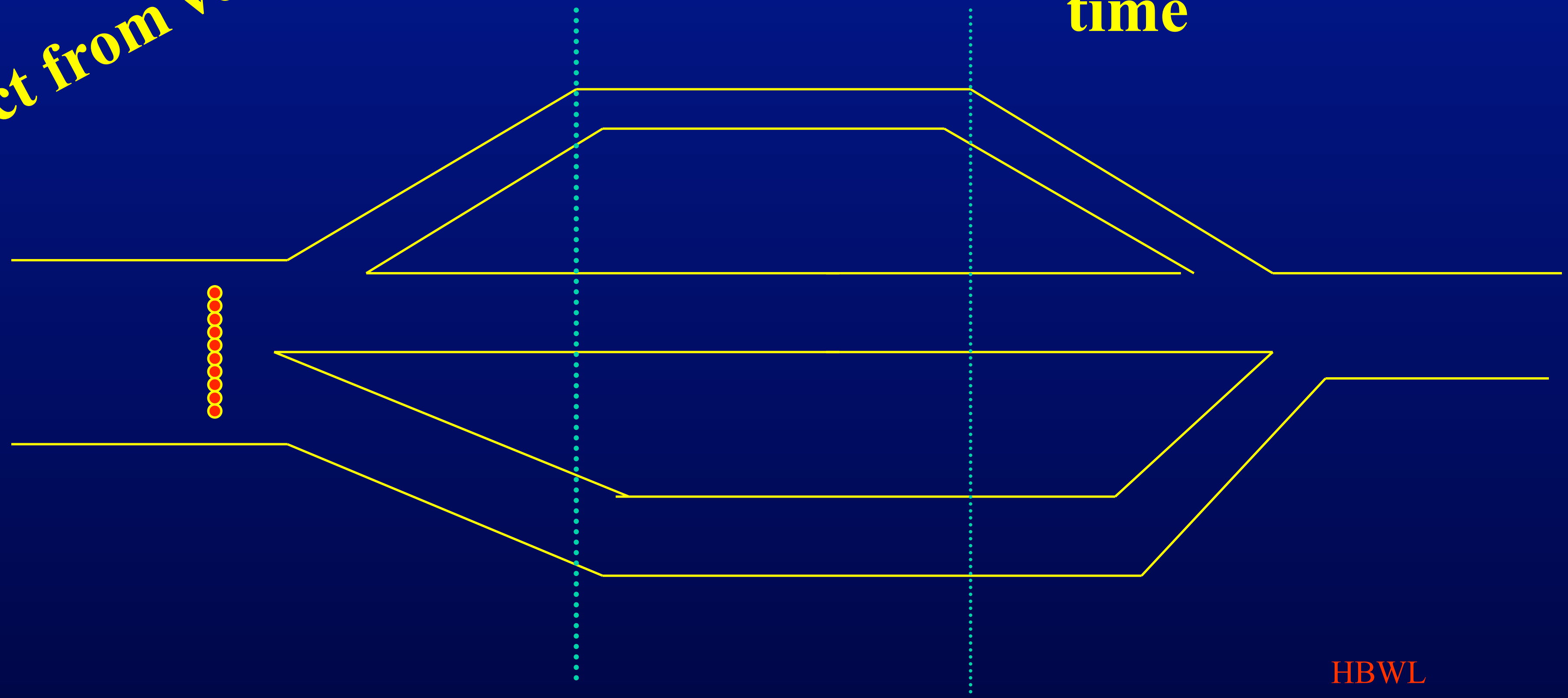
HBWL

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

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



Abstract from vehicles



HBWL

Summing up: direct short bolus

Measure the tissue conc

Measure the input conc i.e. input function

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

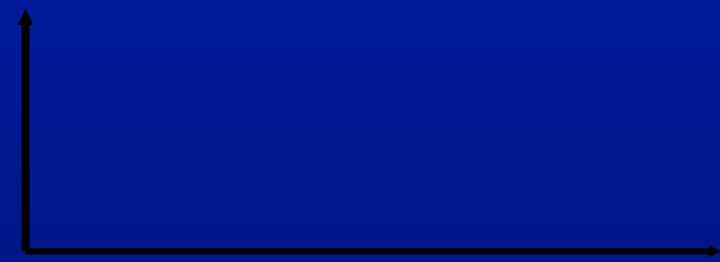
Estimate f and RF(t)

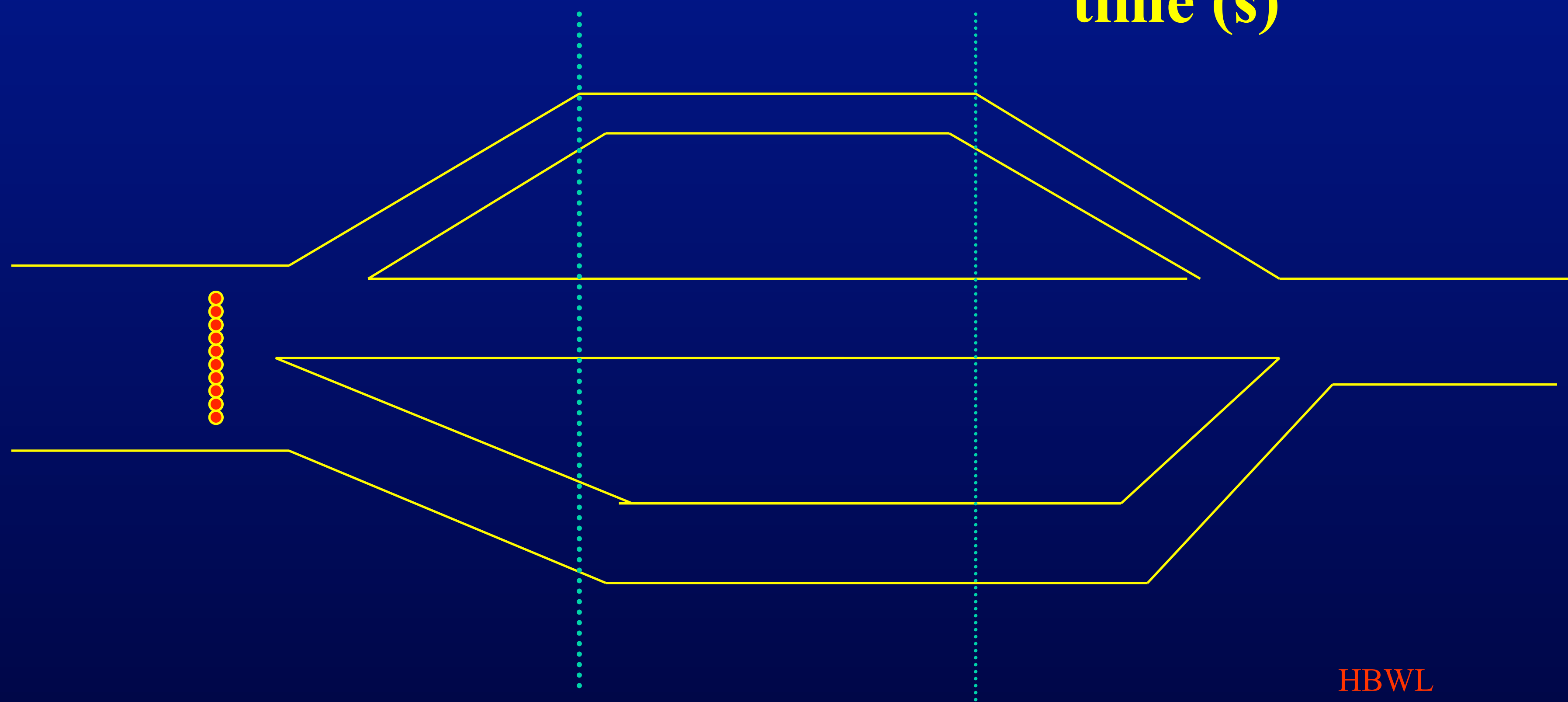
HBWL

Different perfusion tracers behaves differently

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

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

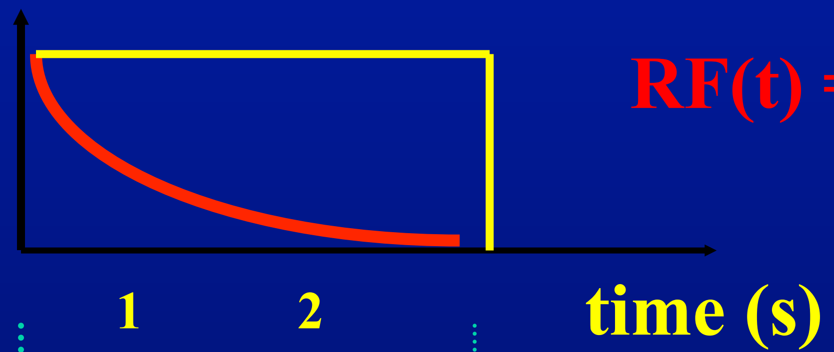




HBWL

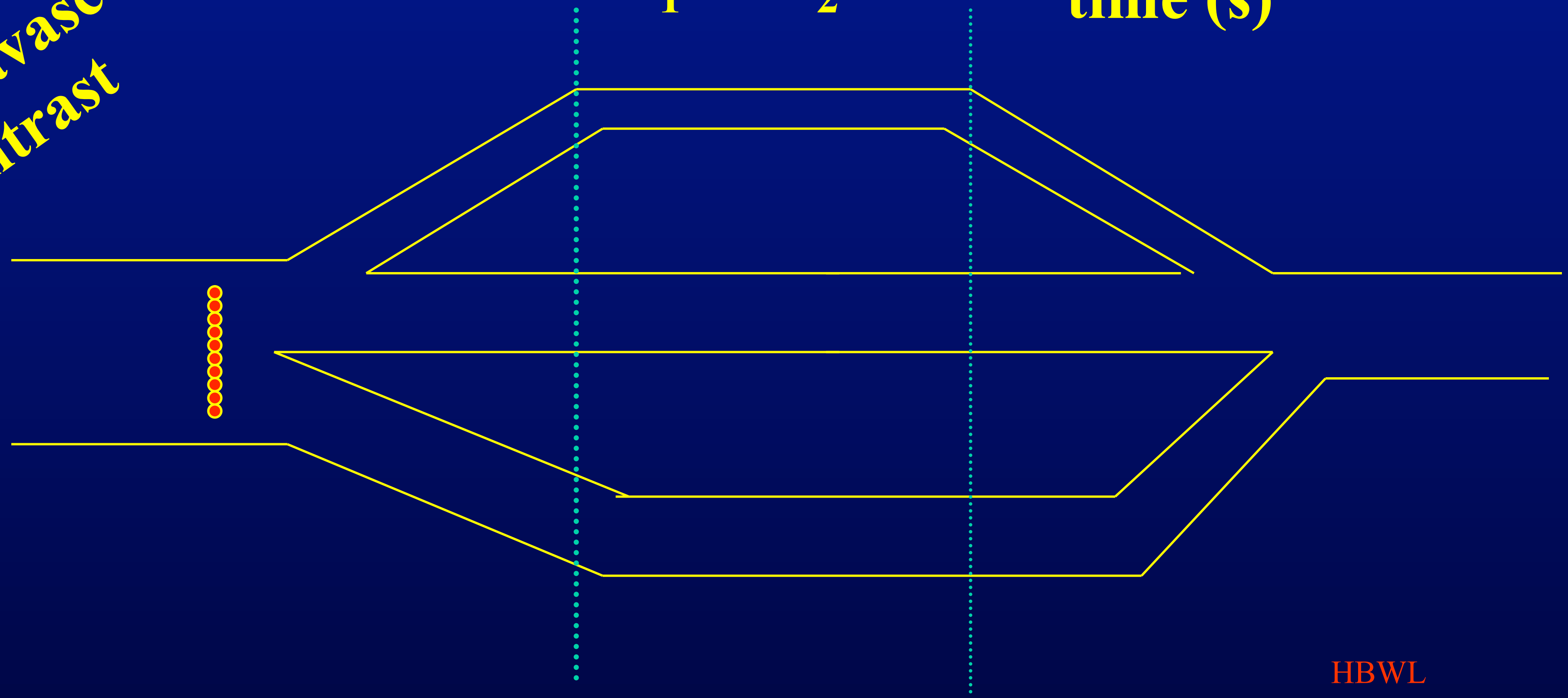
$$C_{tis}(t) = f\,C_a(0)\,\Delta t\,RF(t)$$

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



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

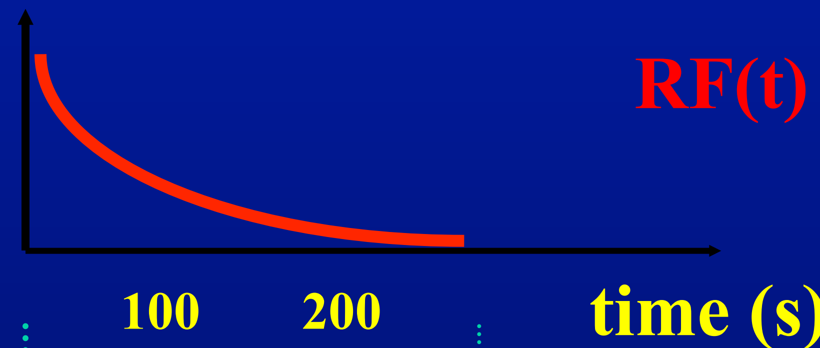
Intravascular contrast



HBWL

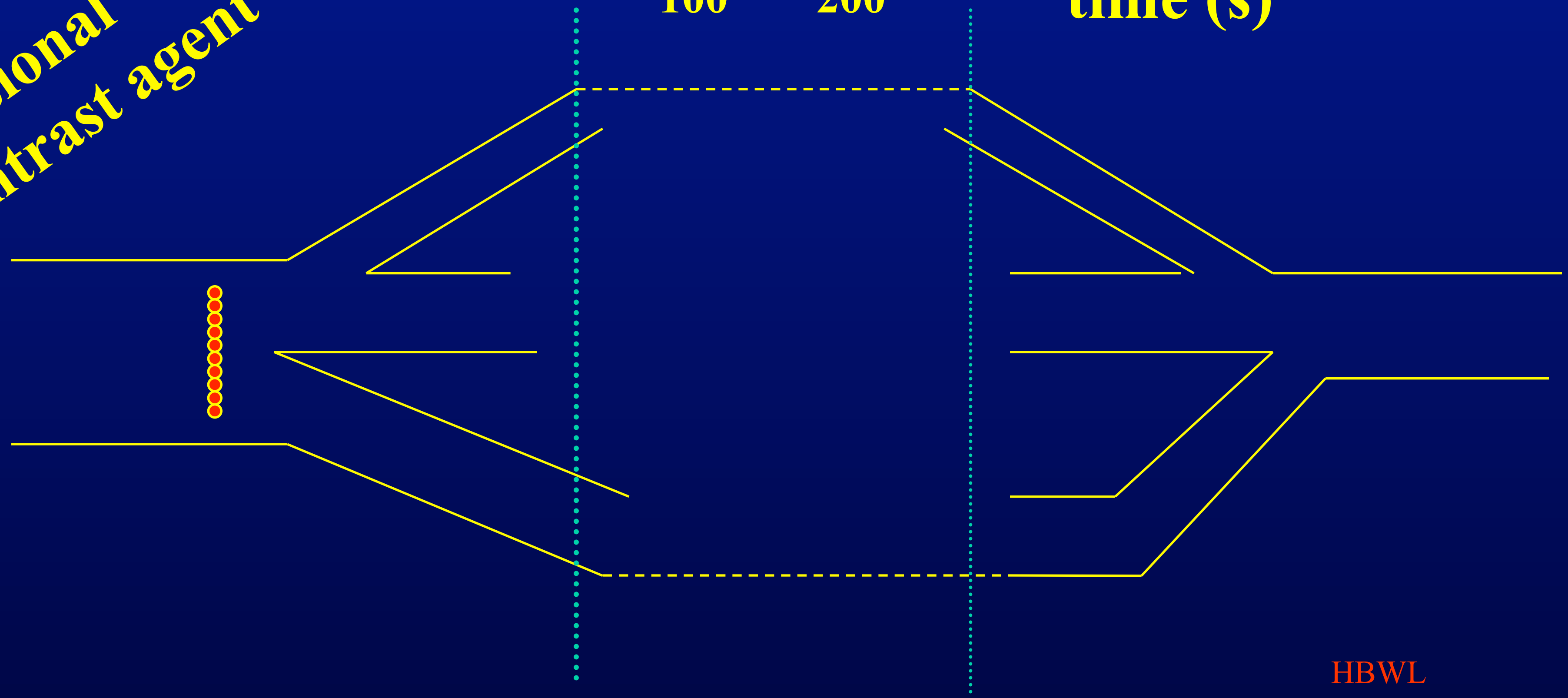
$$C_{tis}(t) = f\, C_a(0)\, \Delta t\, RF(t)$$

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



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

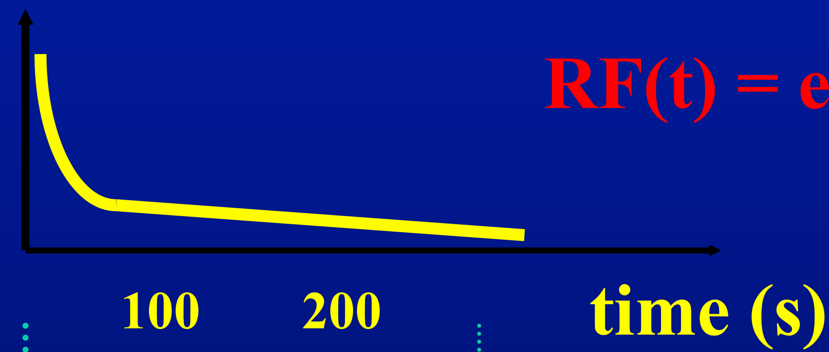
Freely difusional contrast agent



HBWL

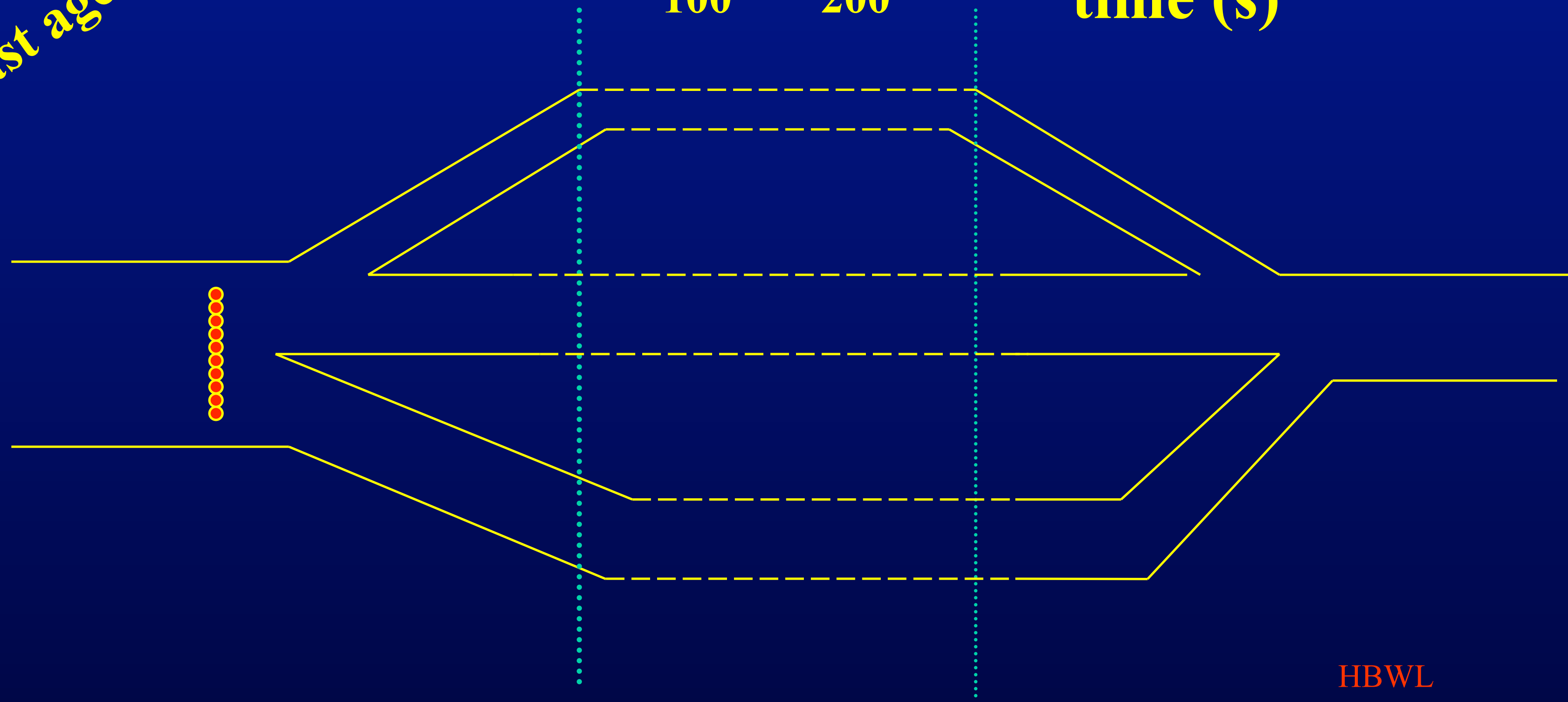
$$C_{tis}(t) = f\, C_a(0)\, \Delta t\, RF(t)$$

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

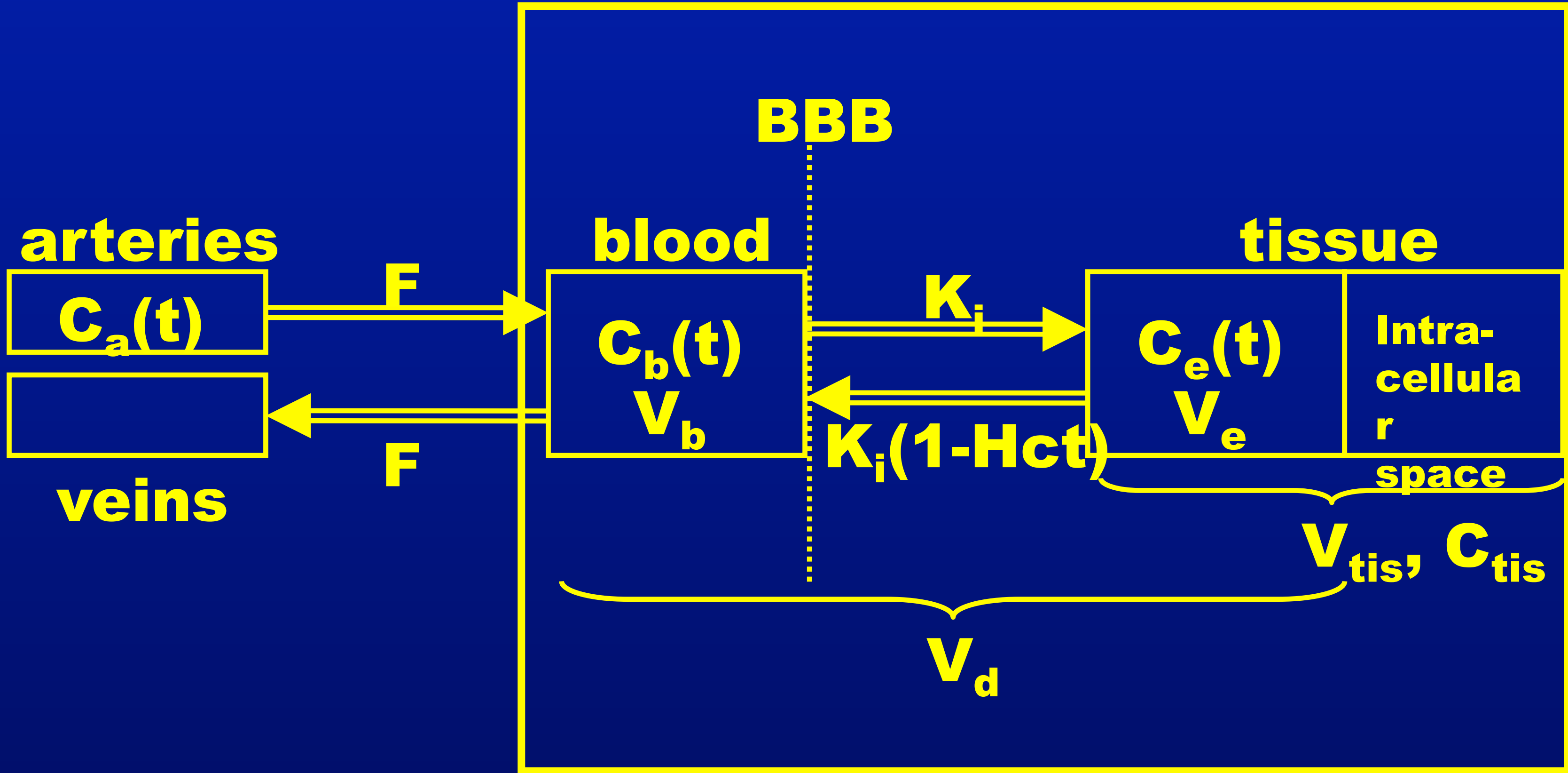


$$RF(t) = e^{-k2t} + e^{-k3t}$$

Extravascular contrast agent



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

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

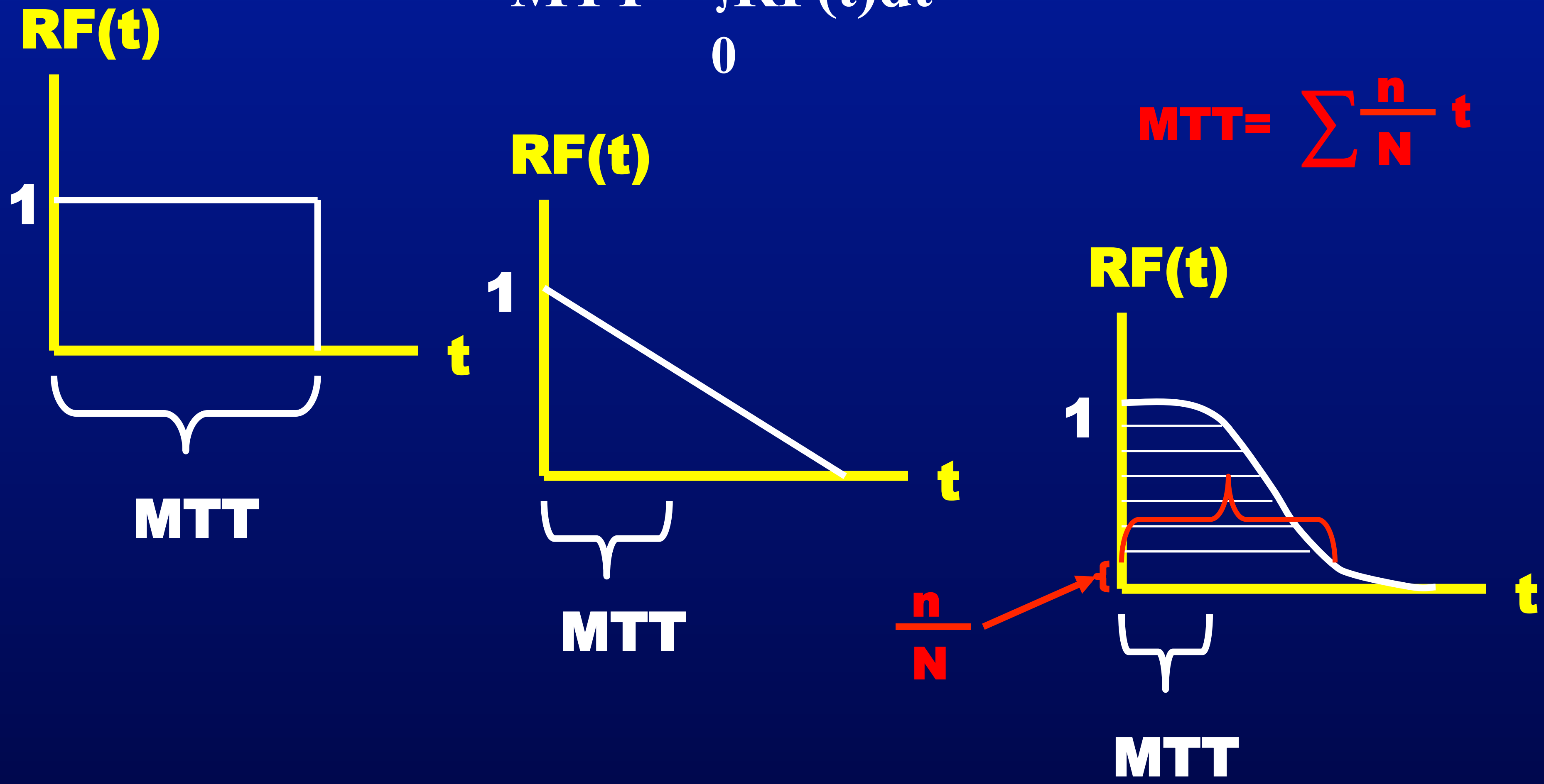
$$MTT = \int_0^\infty RF(t)$$

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, the case in brain MRI we have:

Brain perfusion: CBF

Brain blood volume: CBV

Mean transit time: MTT

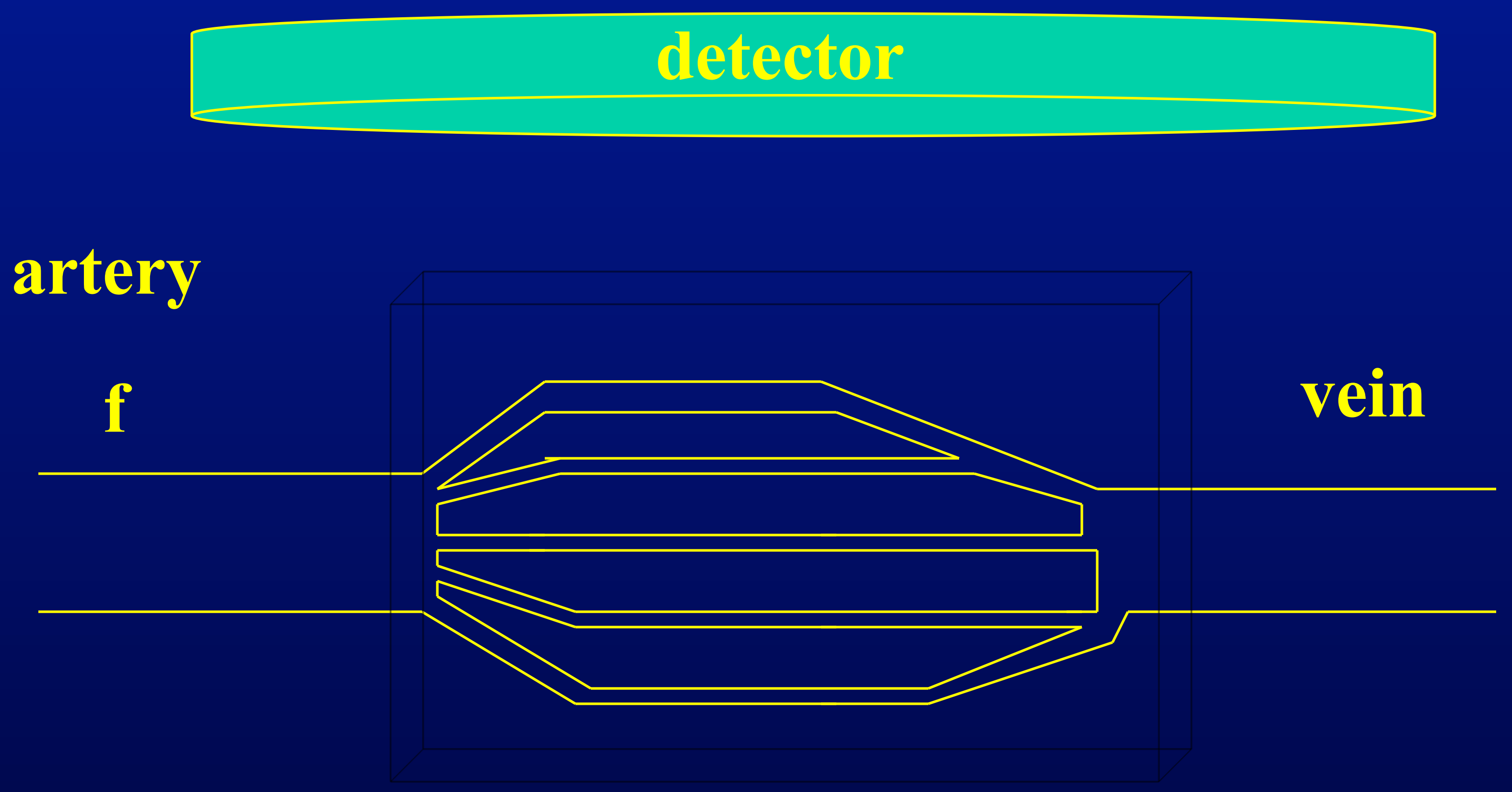
$$CBF = \frac{CBV}{MTT}$$

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 !

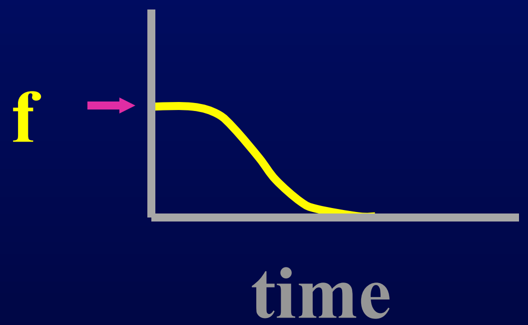
Input :

$C_a(t)$

Tissue enhancement :

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

Deconvolution :
find f RF(t)

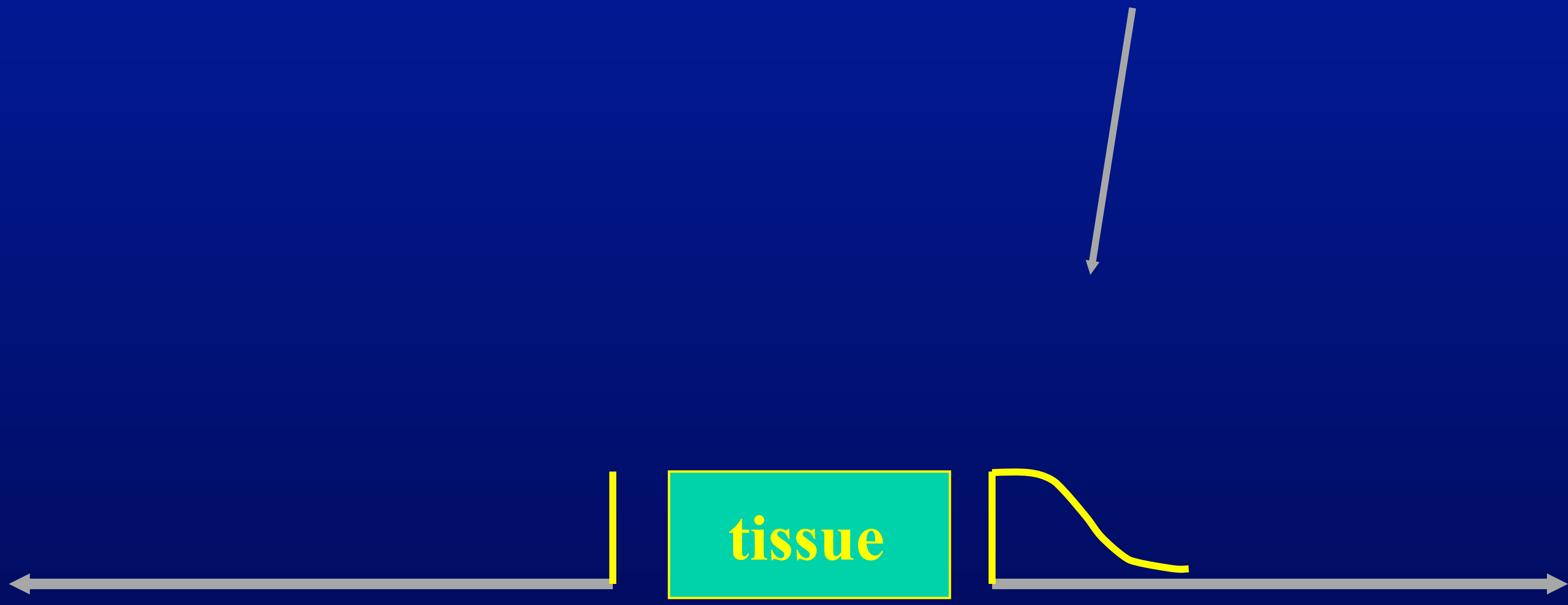


HBWL

Input : $C_a(t)$

Tissue enhancement :

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



HBWL

Input : $C_a(t)$

Tissue enhancement :

$C_{tis}(t) = ?$

HBWL

Input : $C_a(t)$

composed of many
small input

Tissue enhancement :

$C_{tis}(t) = ?$

If the linearity of the system exist

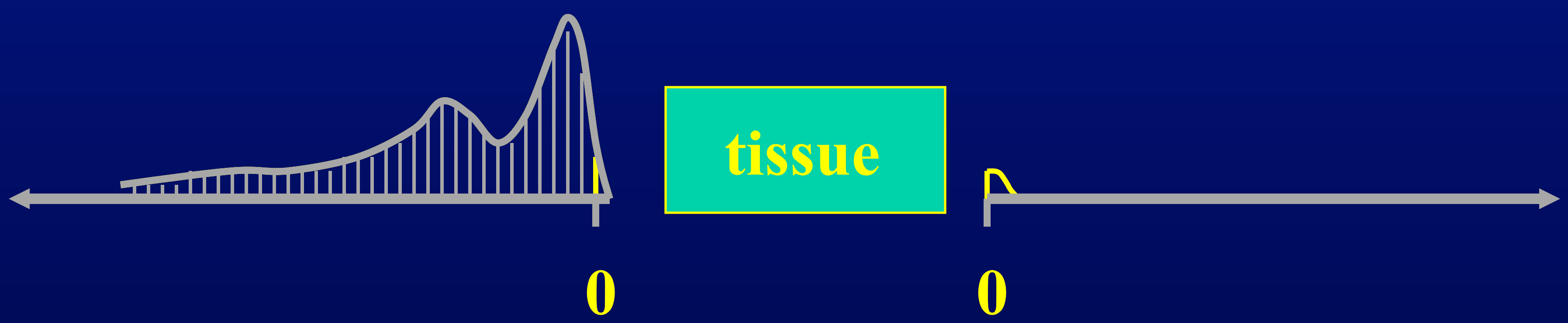
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



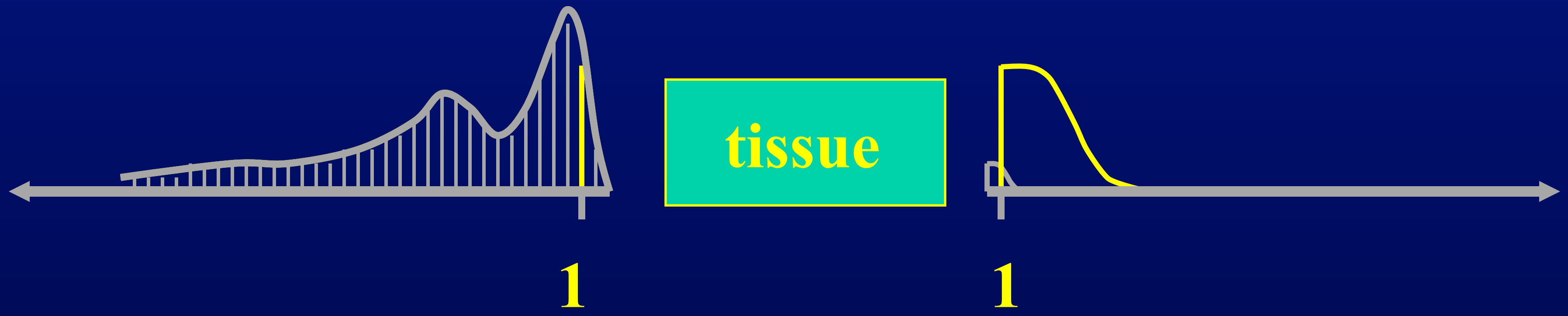
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



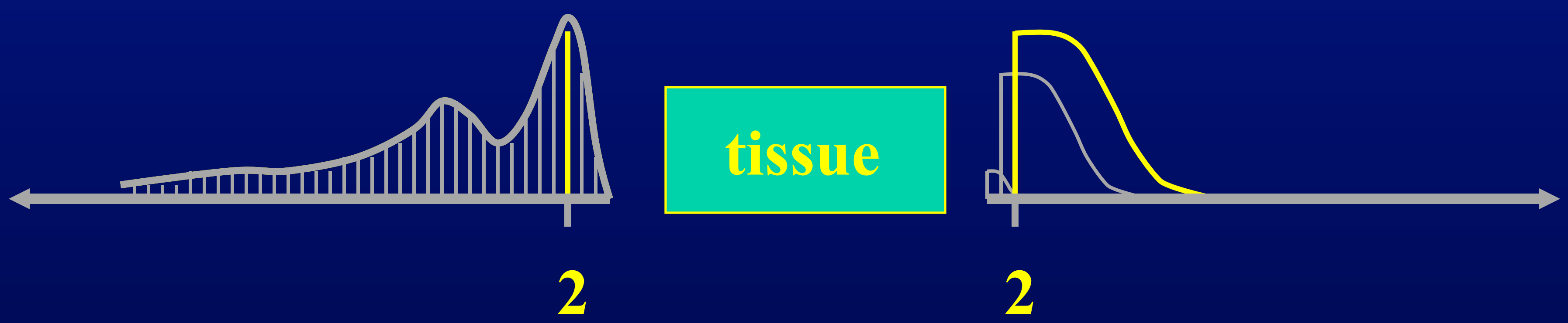
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



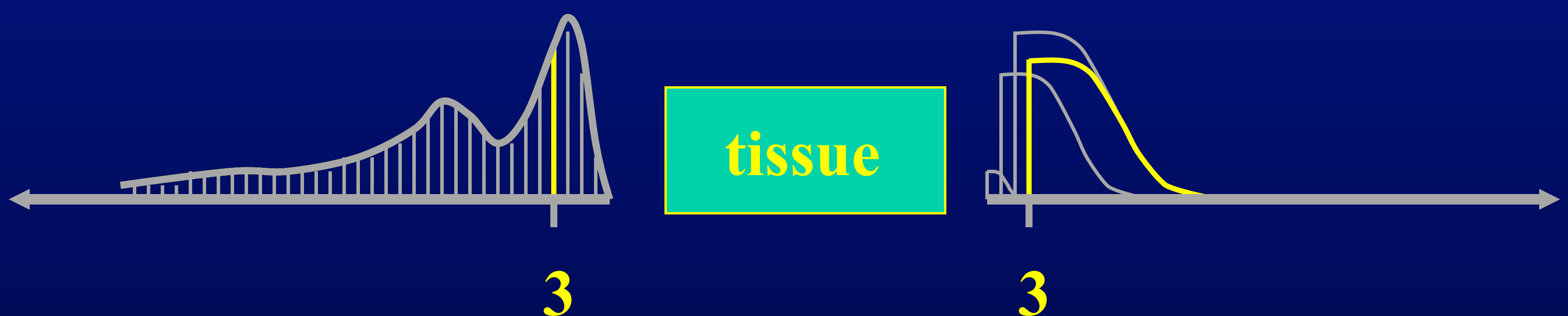
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



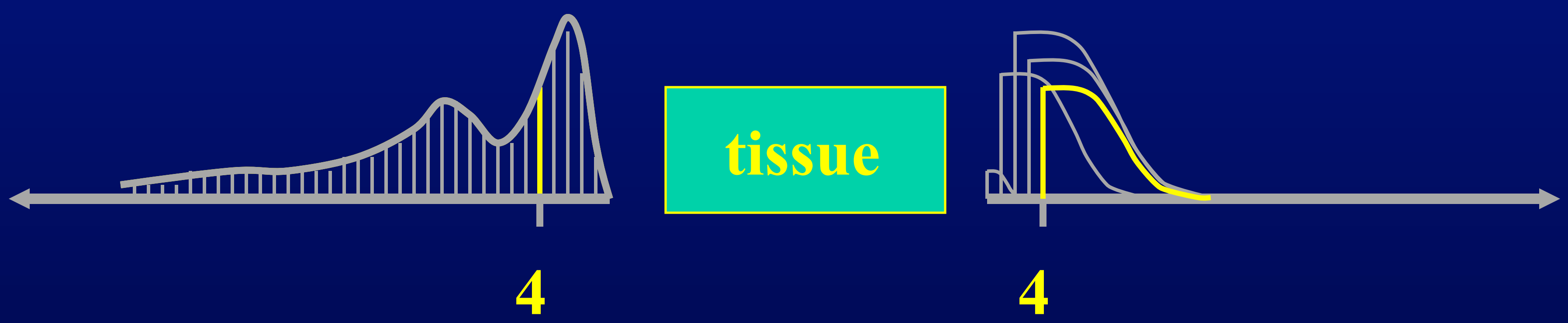
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



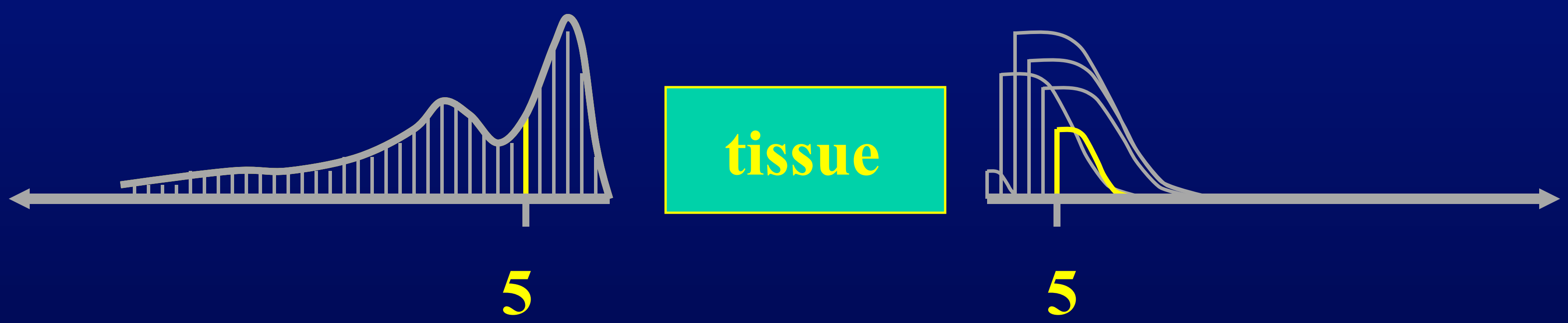
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



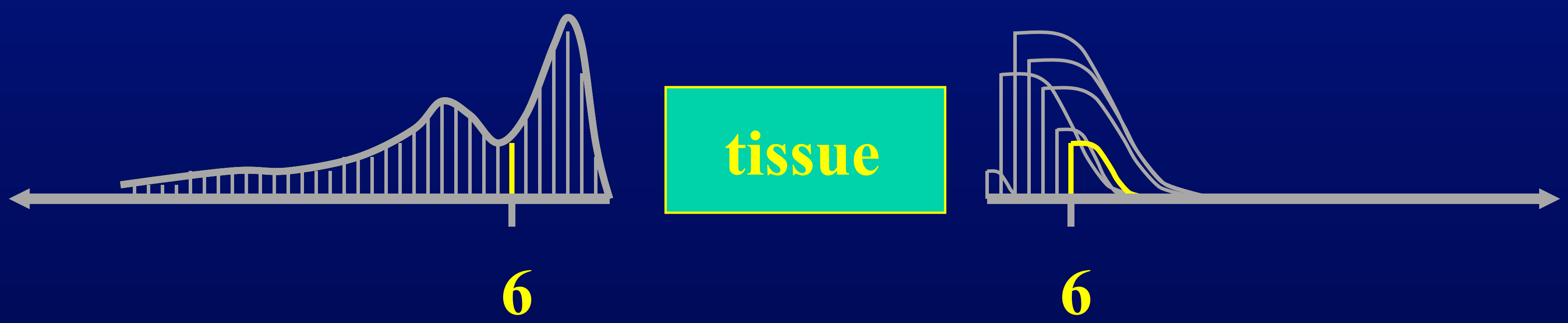
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



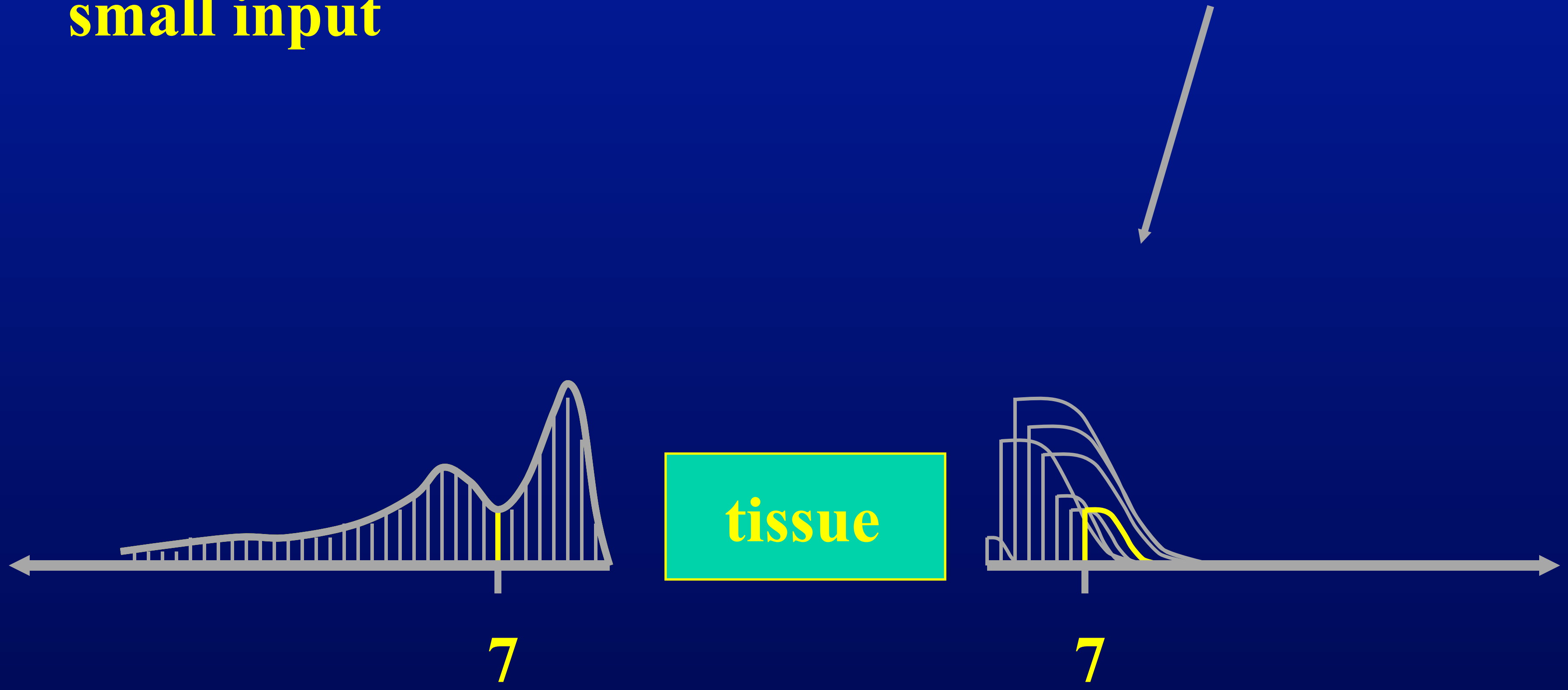
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



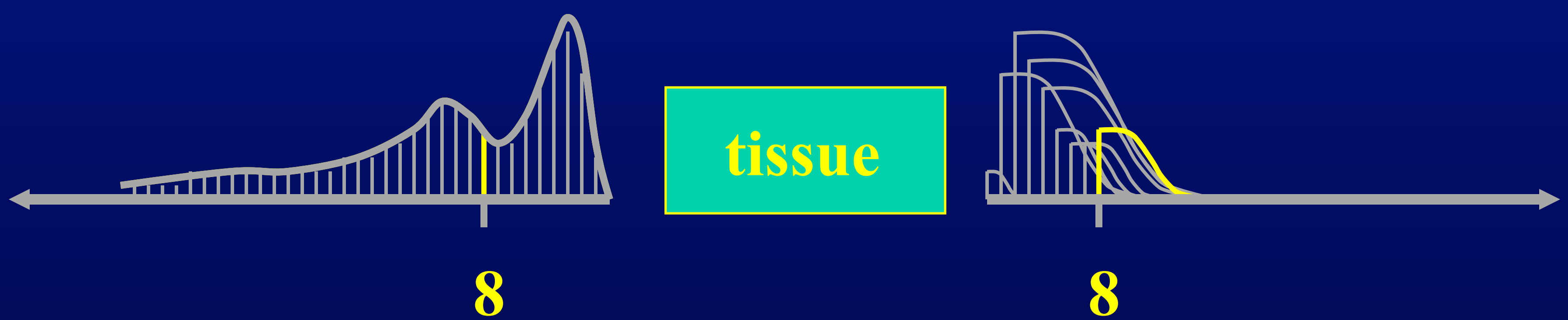
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



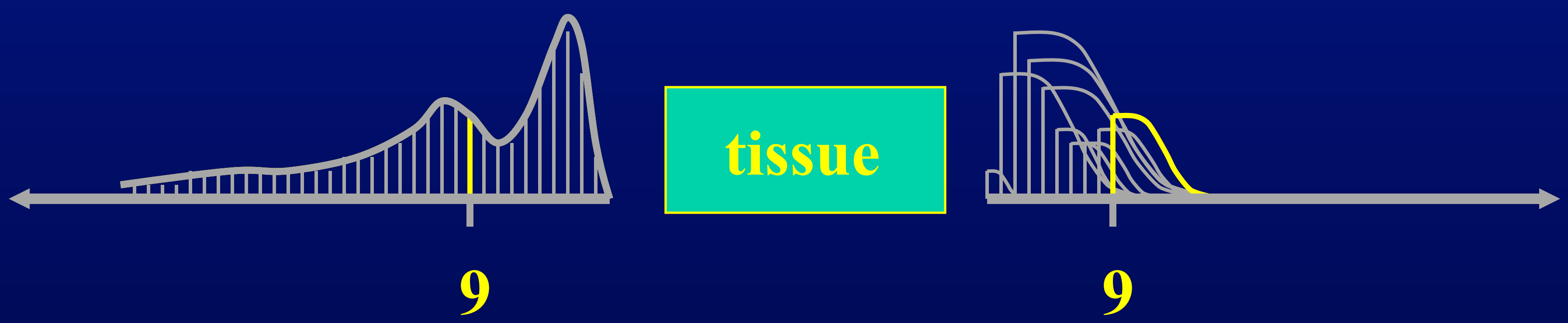
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



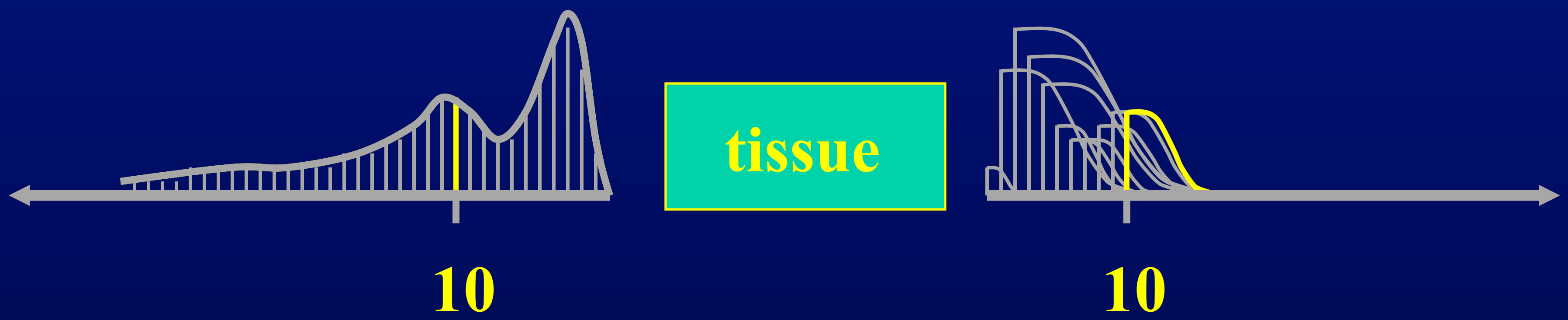
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



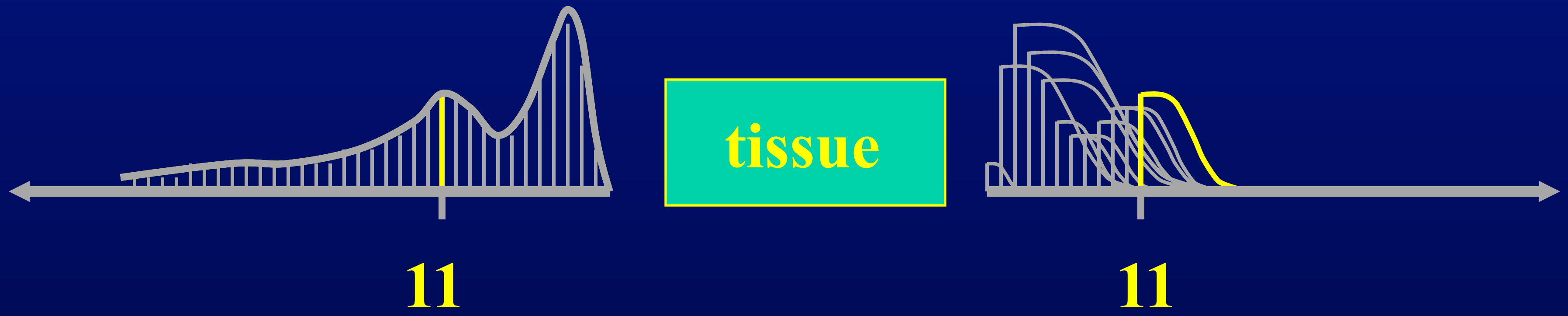
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



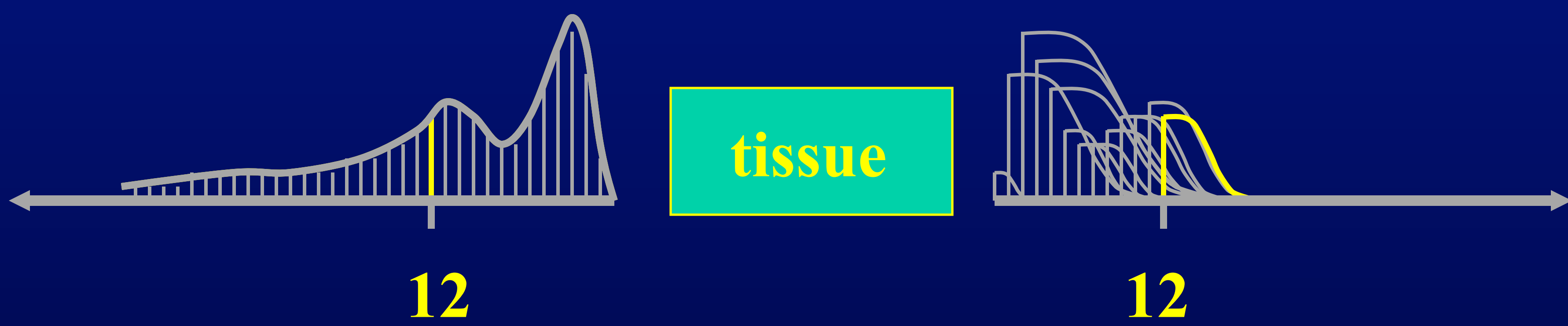
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



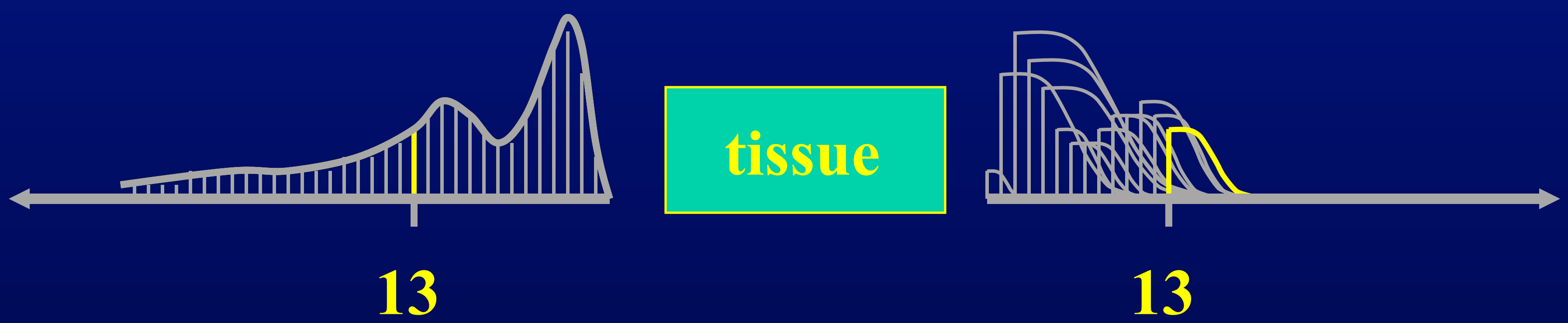
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



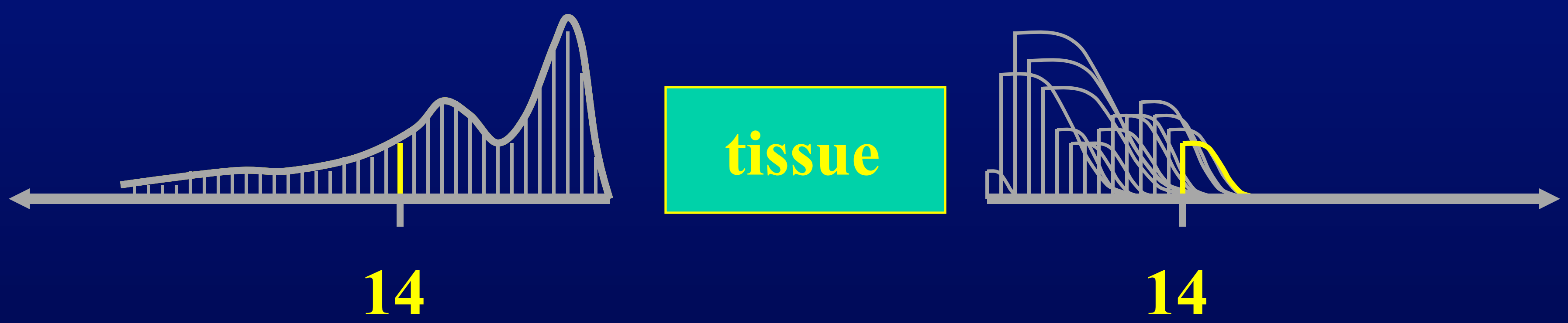
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



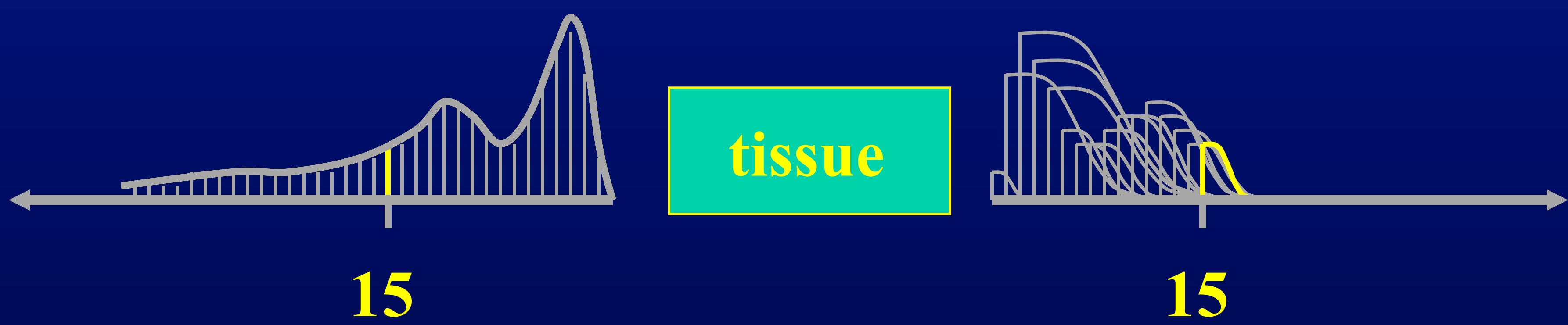
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



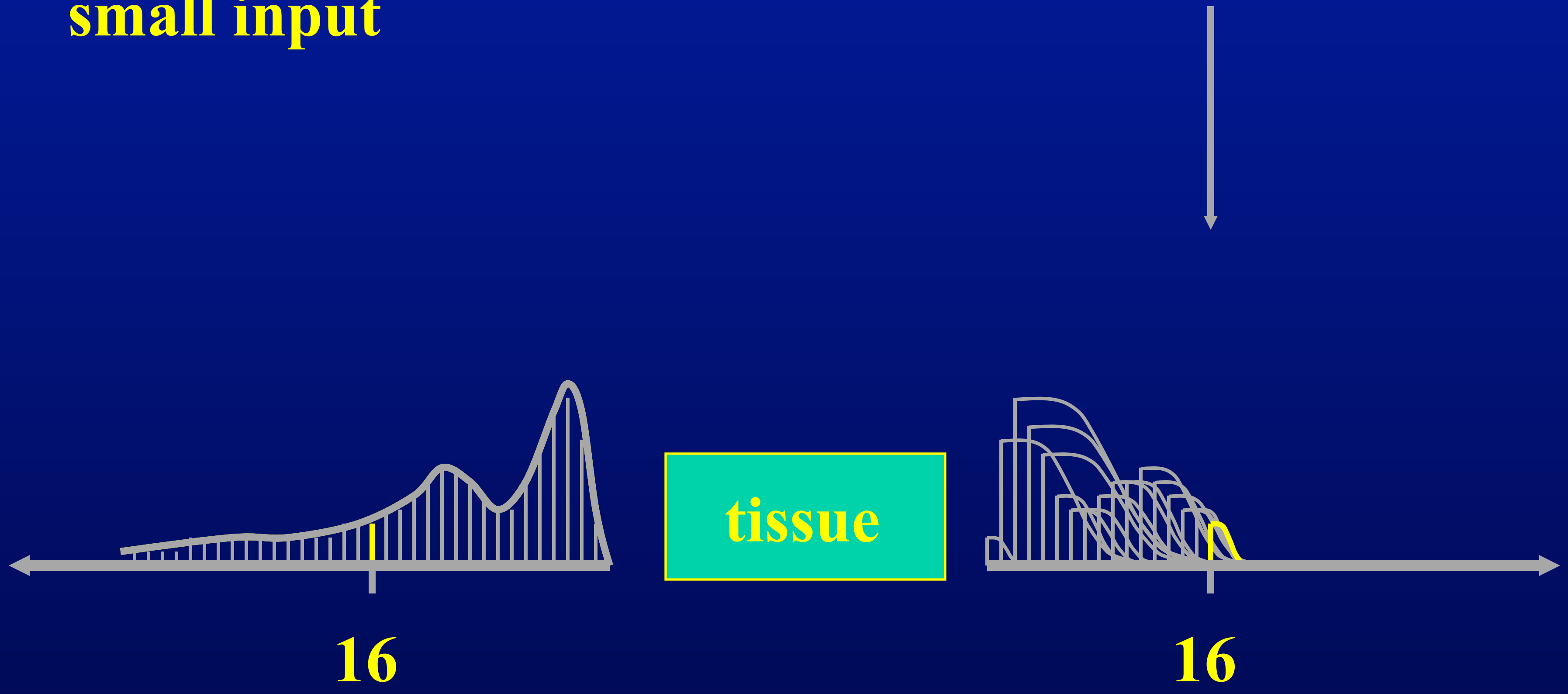
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



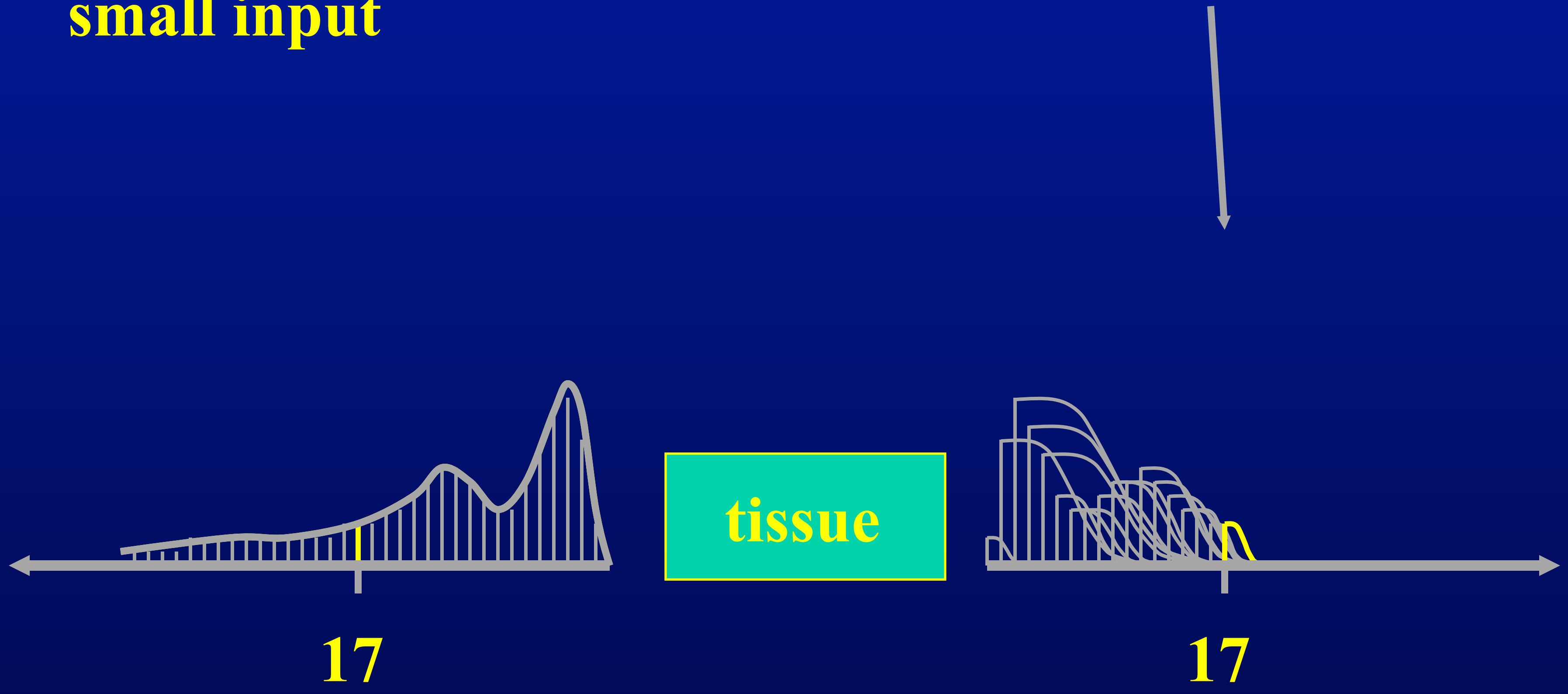
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



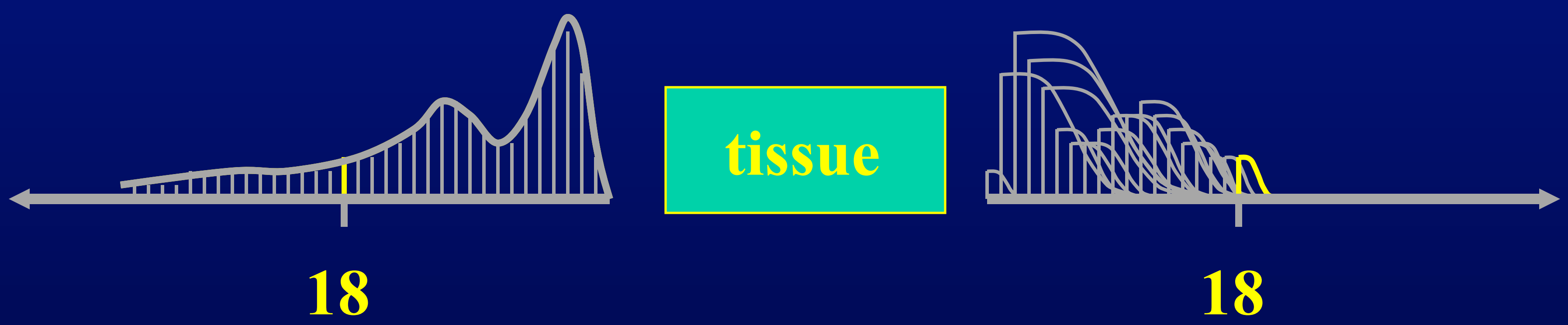
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



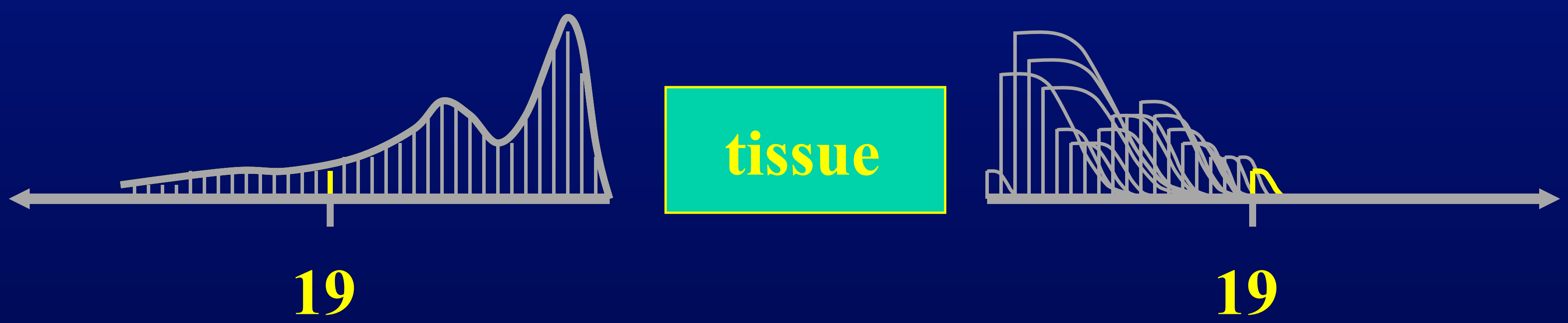
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



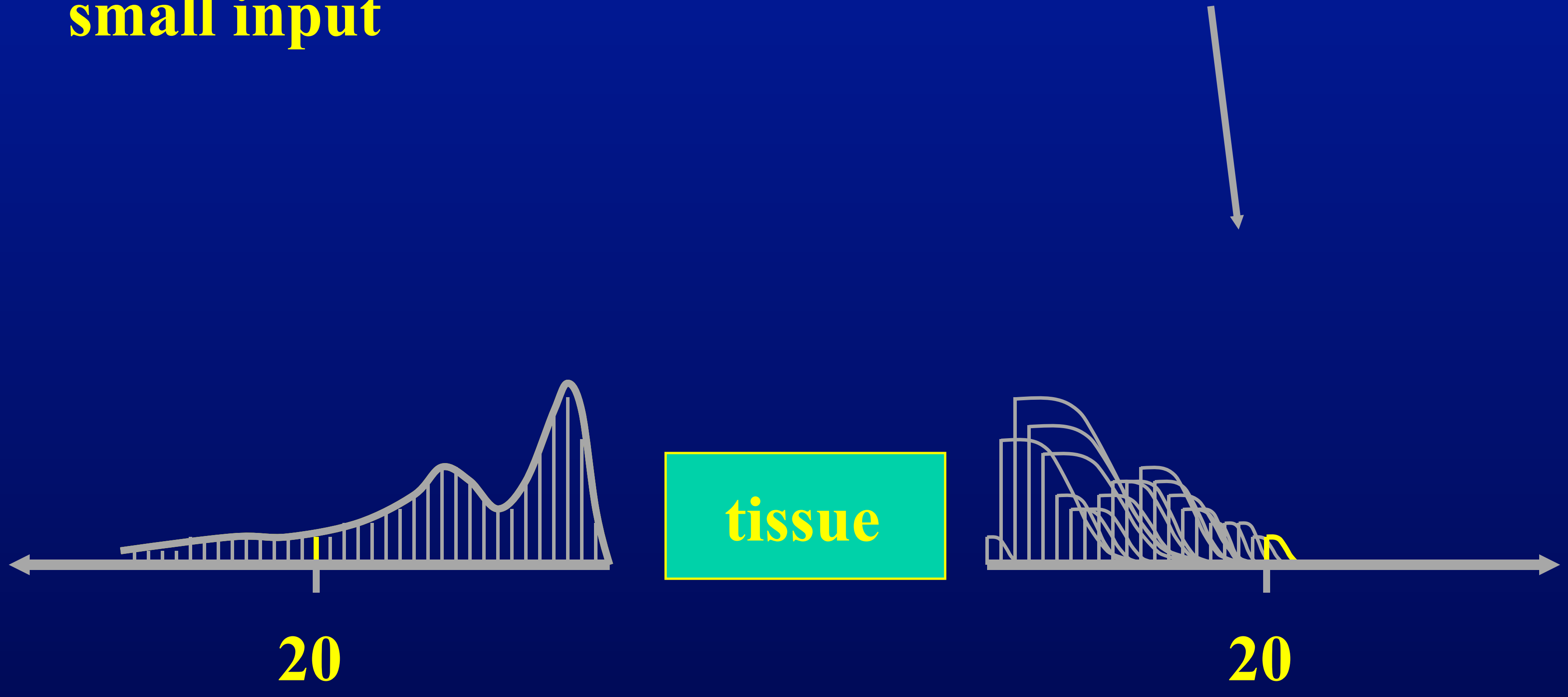
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



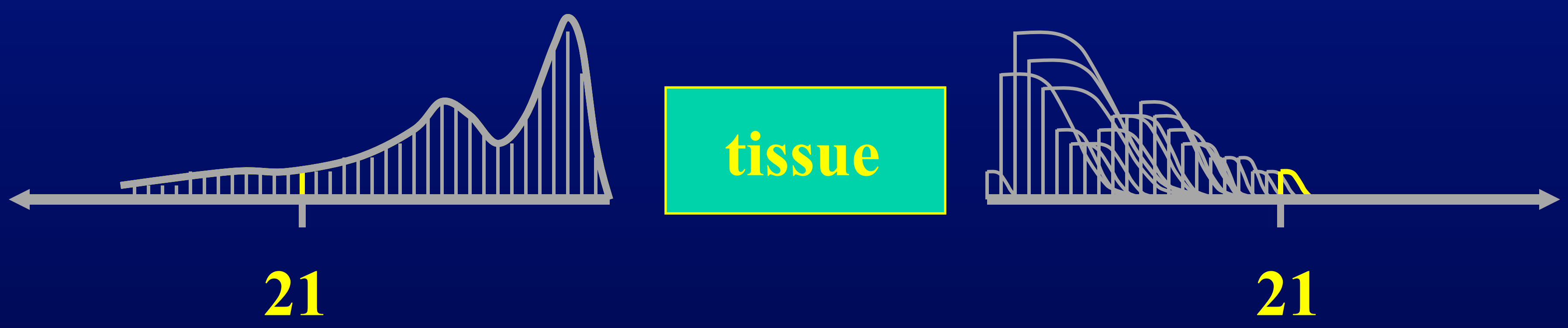
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



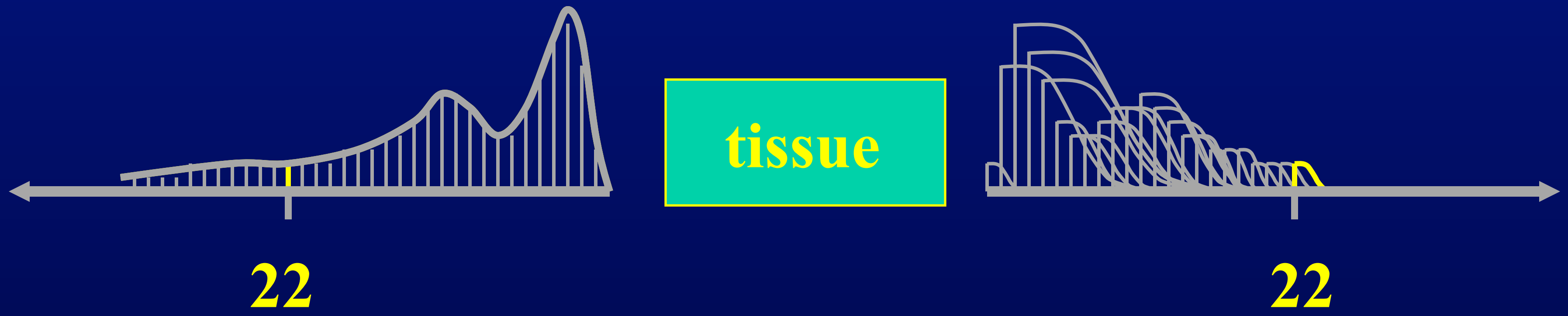
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



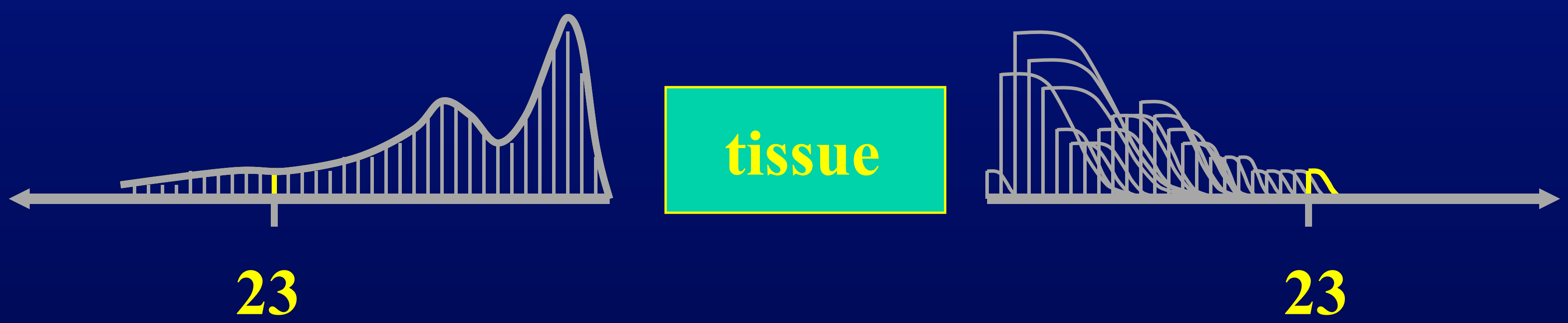
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



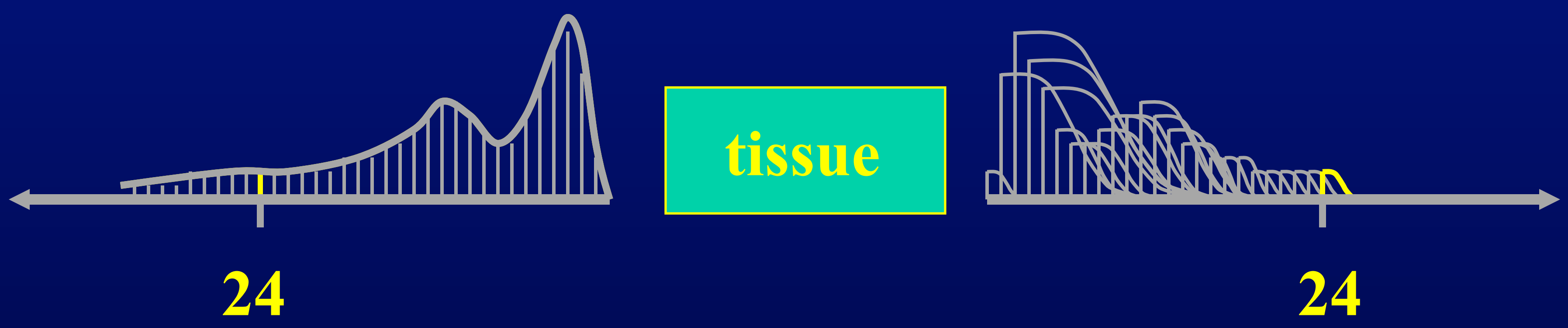
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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

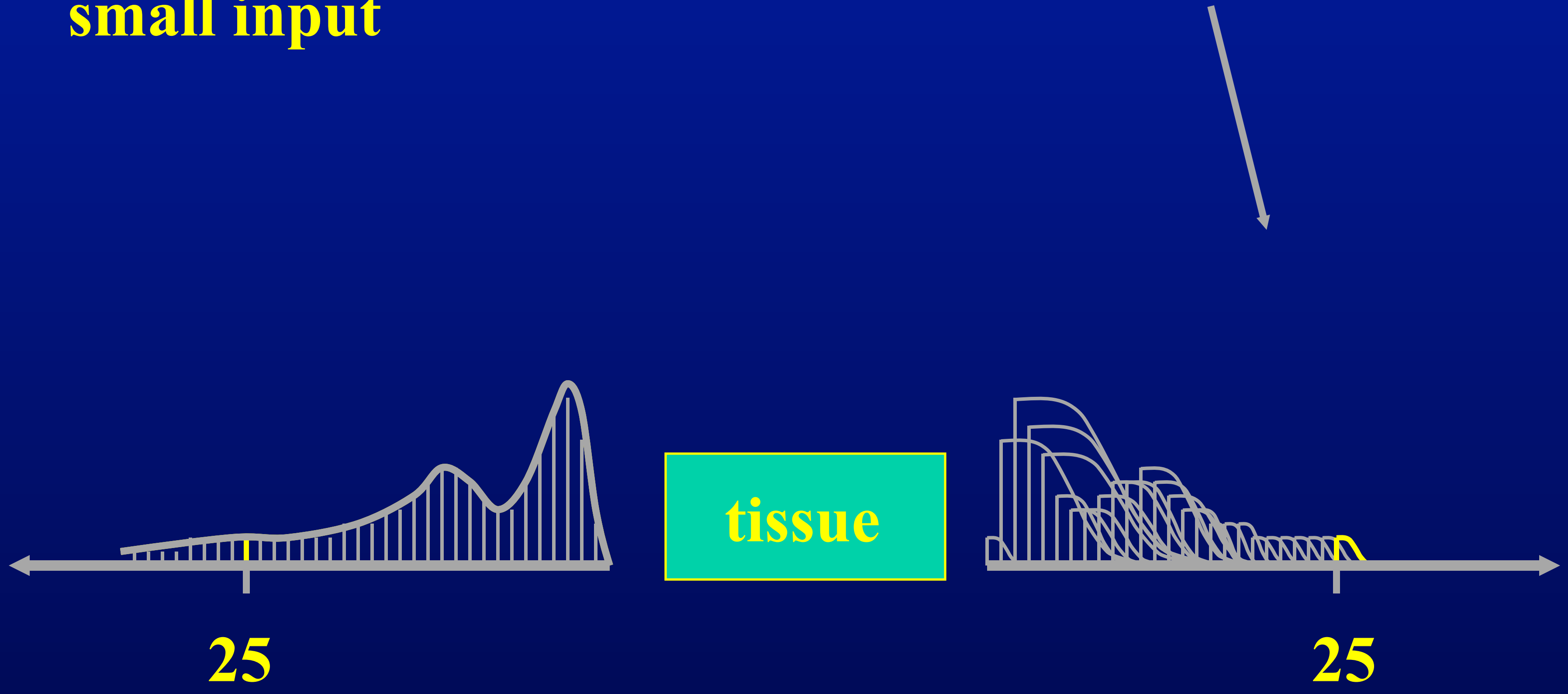


Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



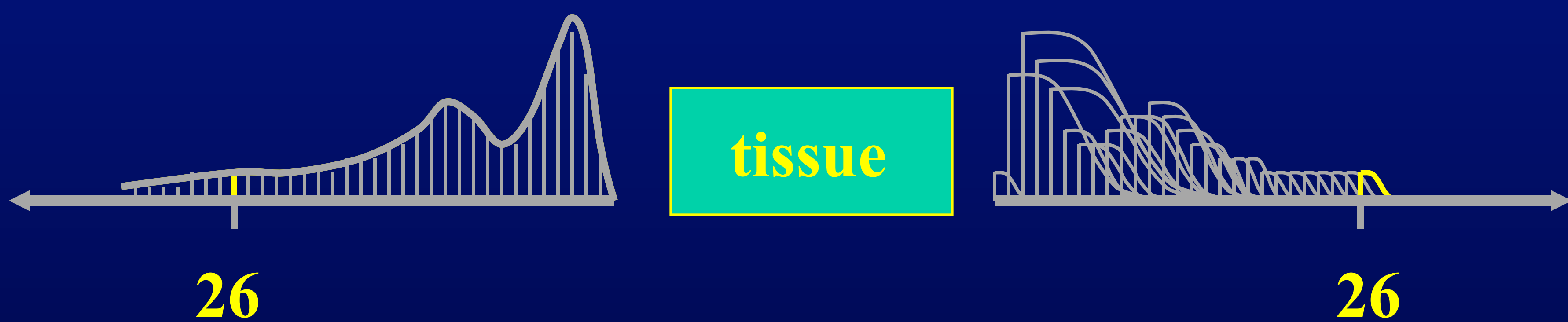
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



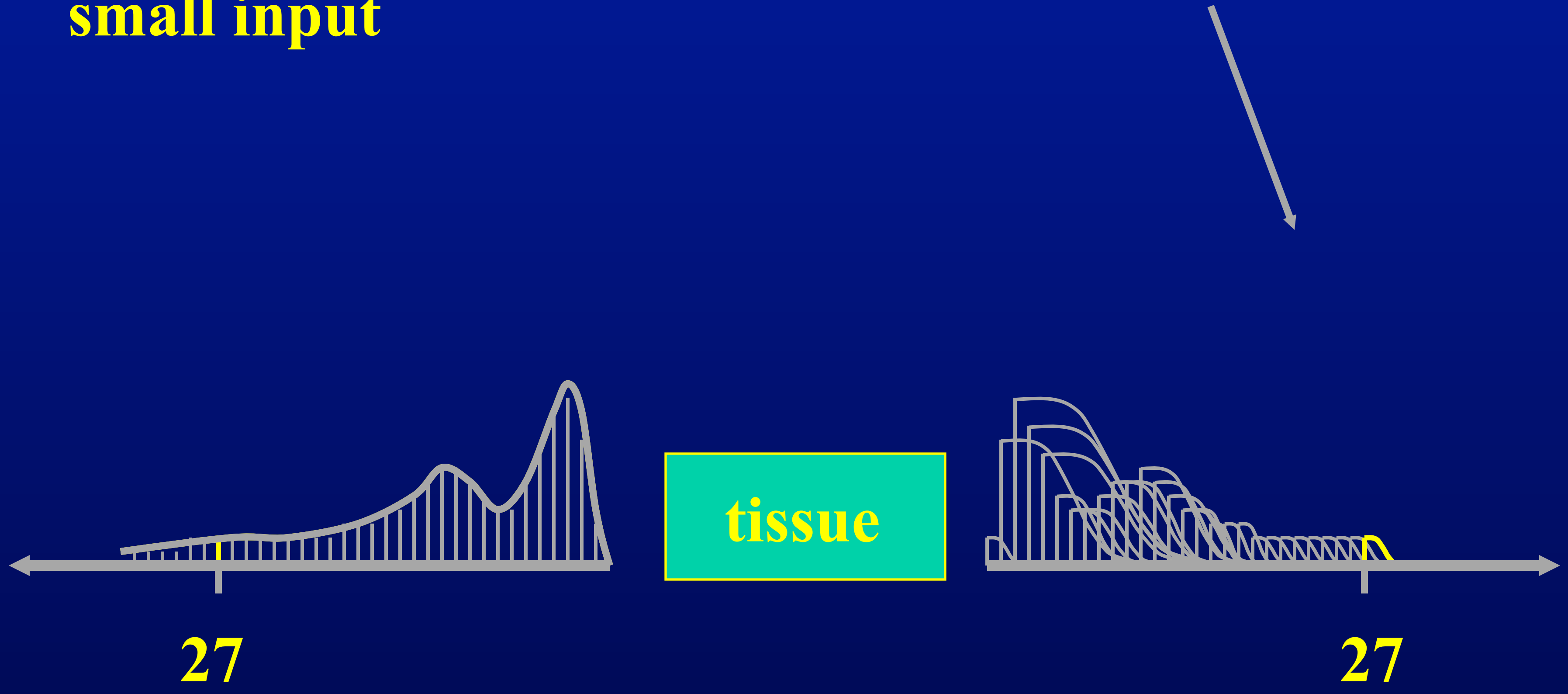
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



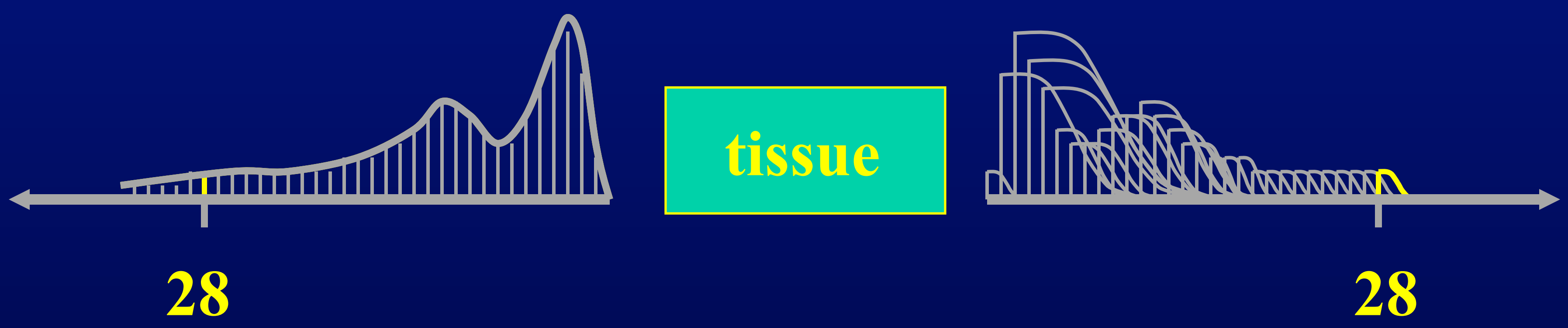
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



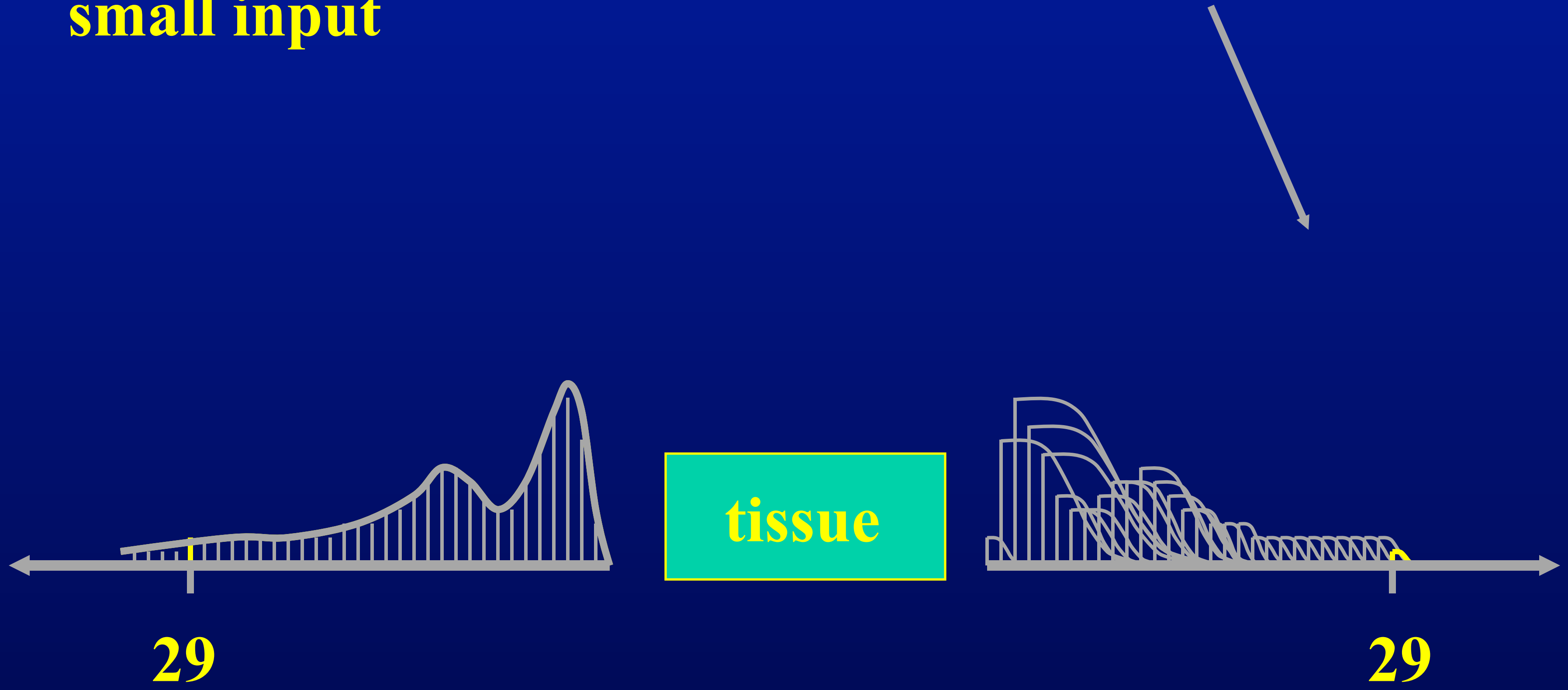
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



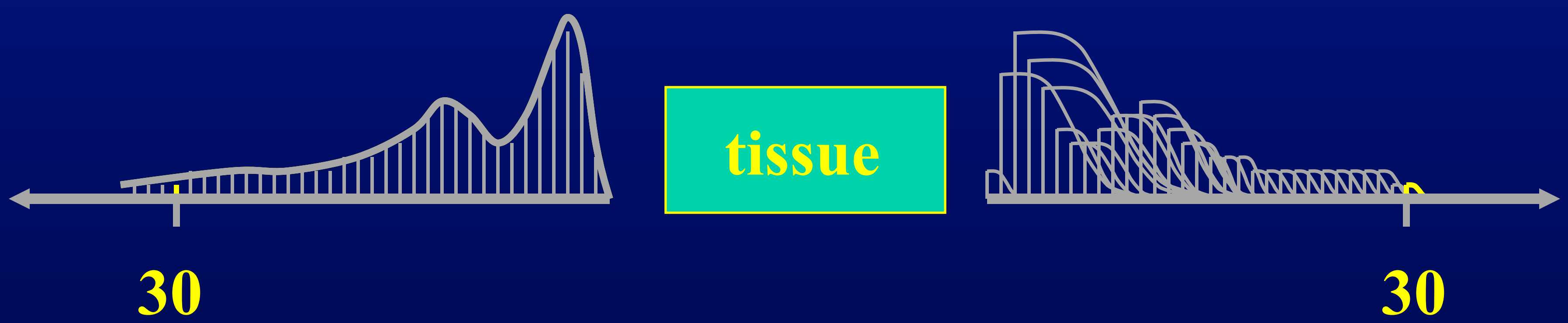
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



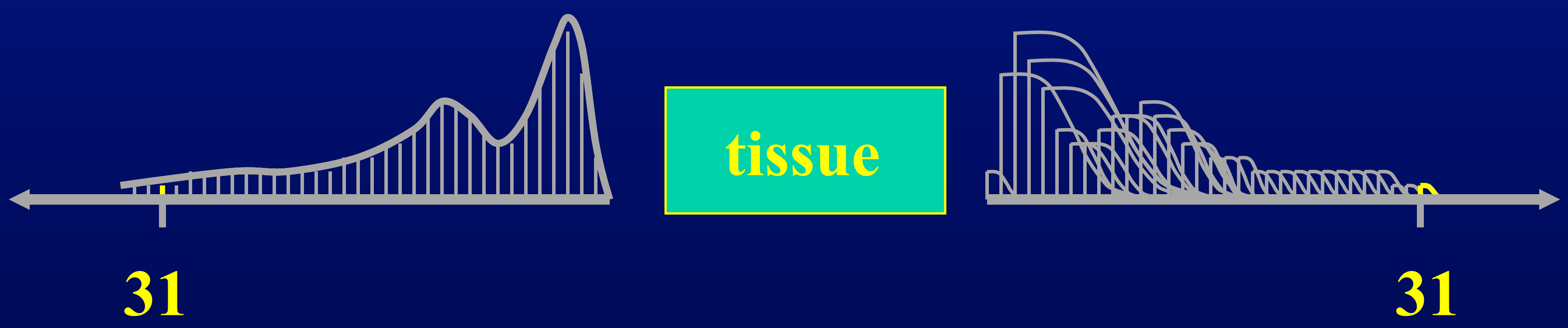
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



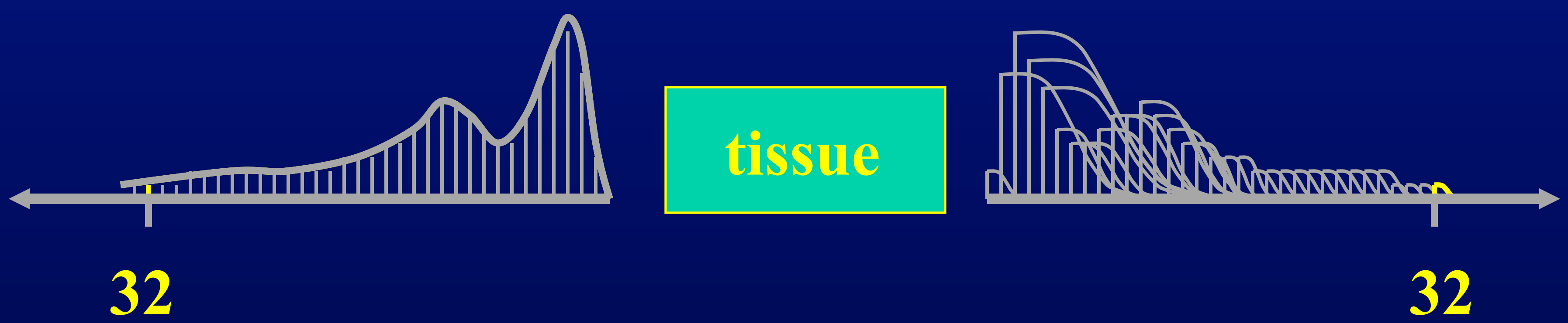
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



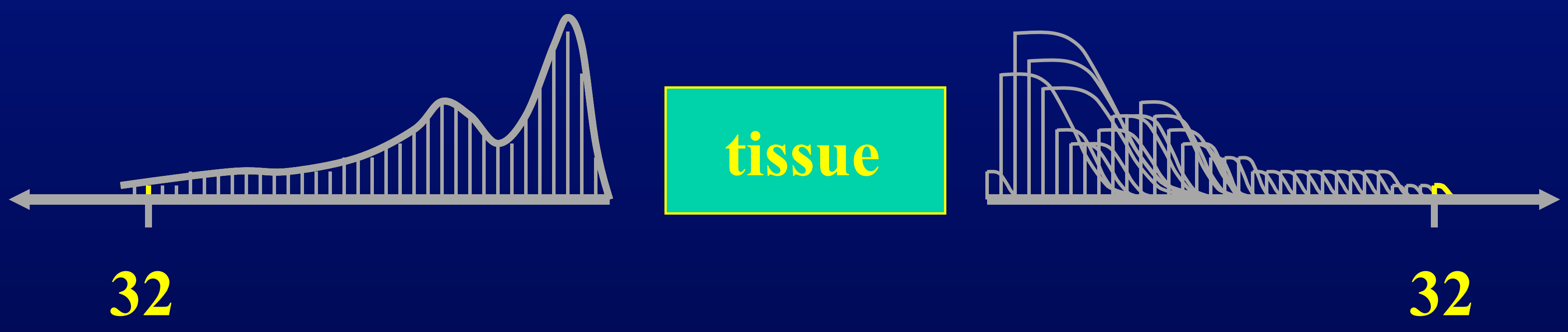
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

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



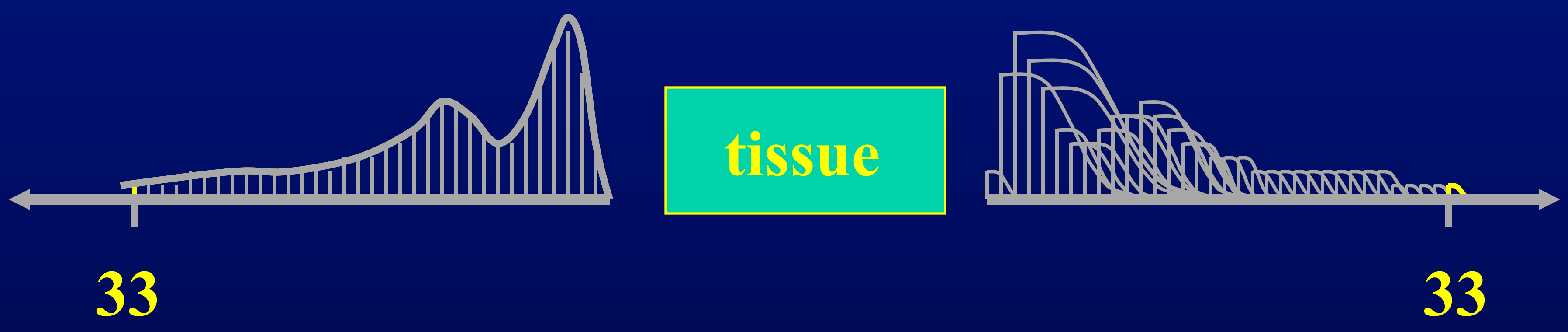
HBWL

Input : $C_a(t)$

composed of many small input

Tissue enhancement :

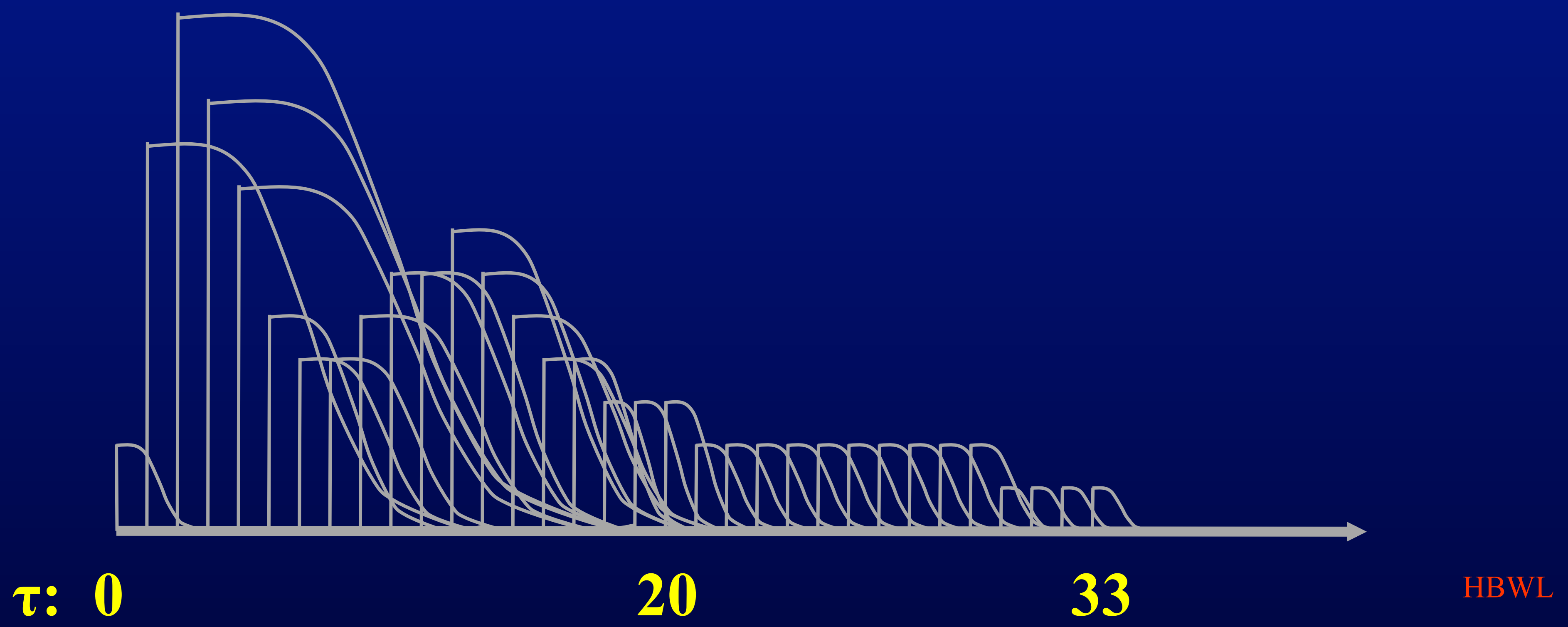
$C_{tis}(t) = f\ C_a(33)\ RF(t - 33)\ \Delta\tau$



HBWL

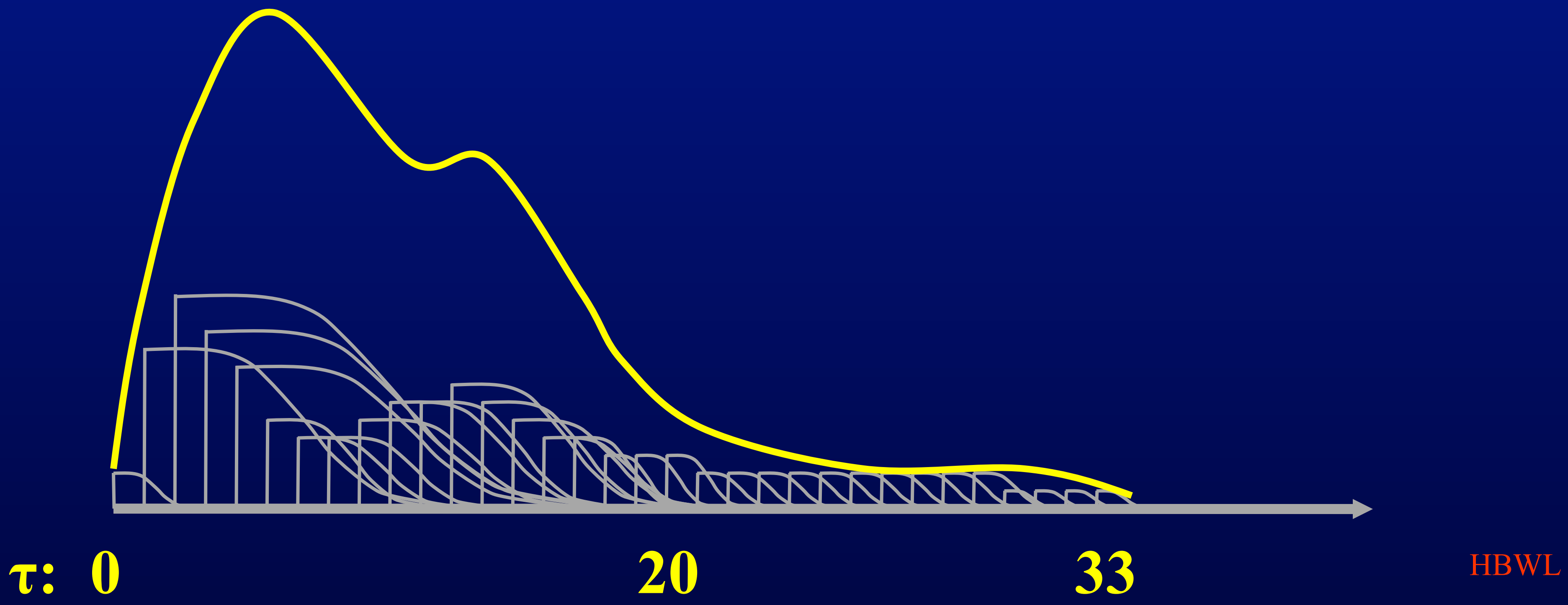
Tissue enhancement :

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



Total tissue enhancement :

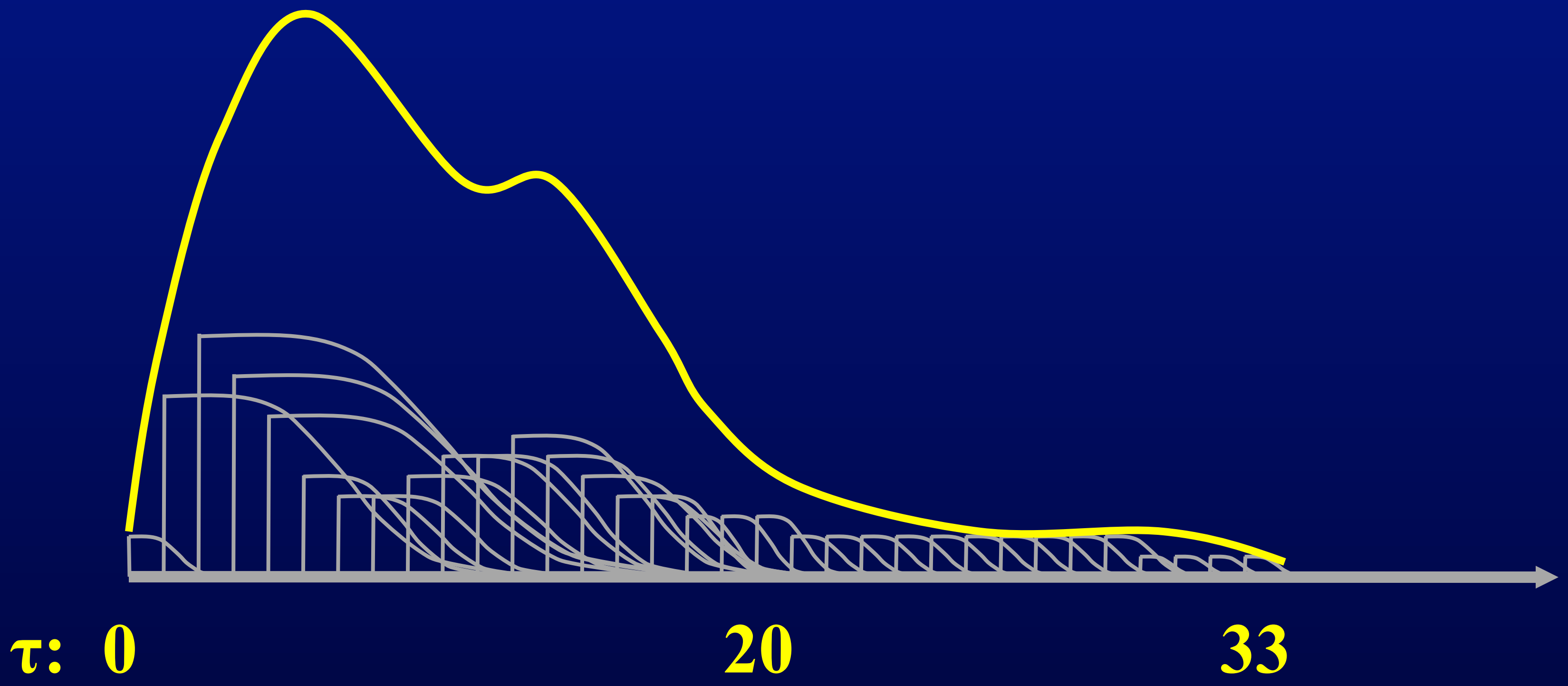
$$C_{tis}(t) = \sum f\, C_a(\tau)\, RF(t - \tau)\, \Delta\tau \; ; \; \tau = 0:33$$



Total tissue enhancement :

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

The convolution integral



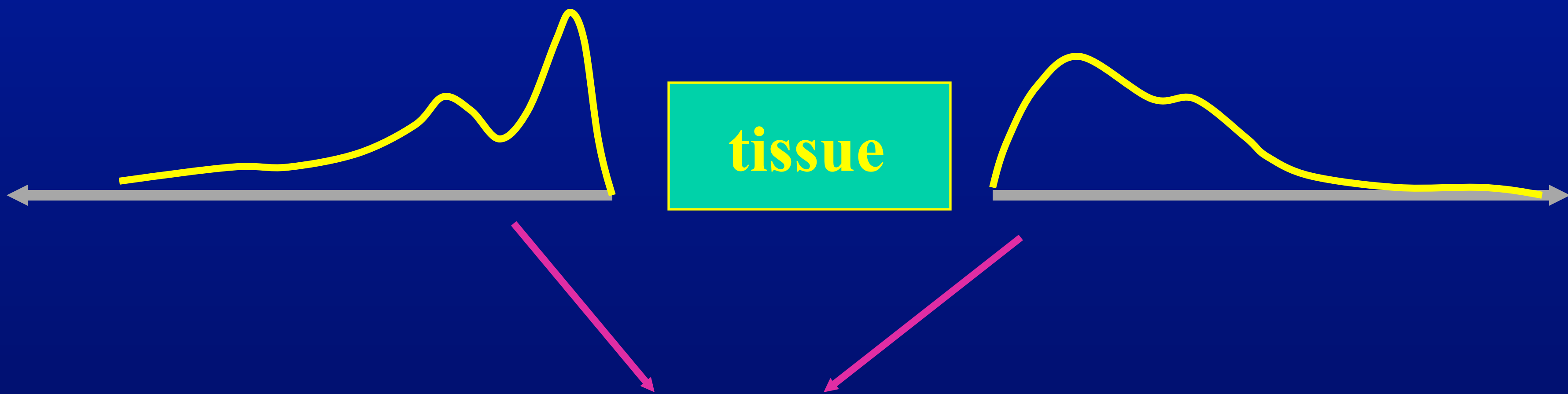
HBWL

Input :

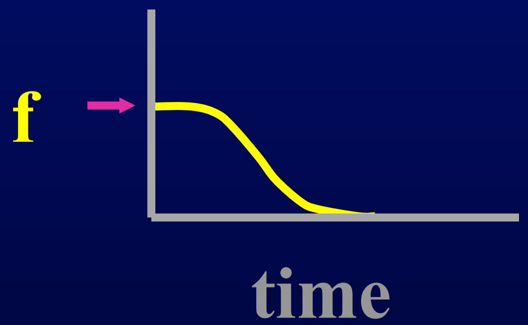
$C_a(t)$

Tissue enhancement :

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



Deconvolution :
find f and RF(t)



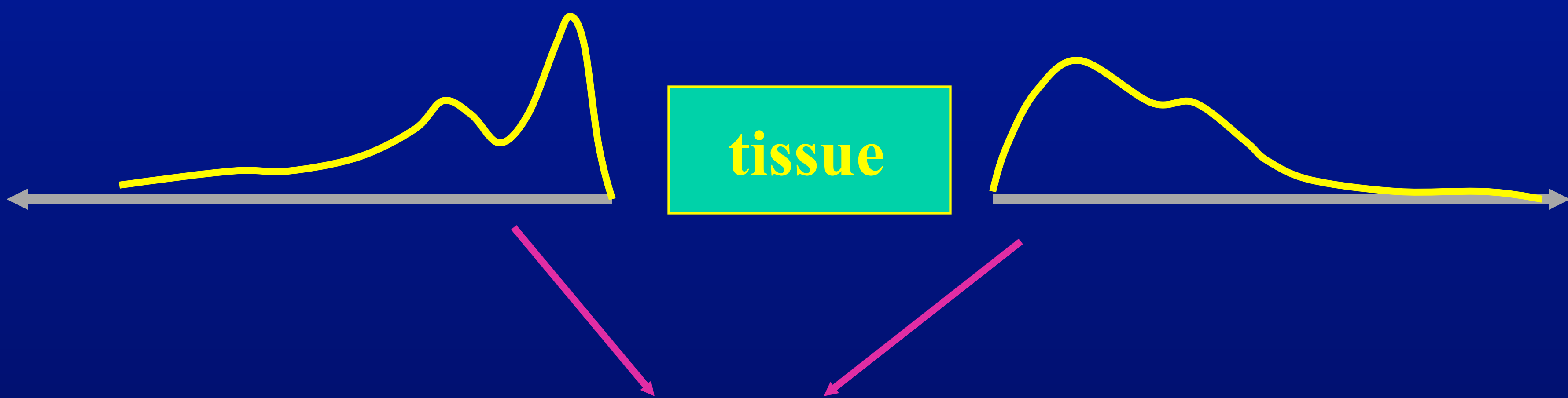
HBWL

Input :

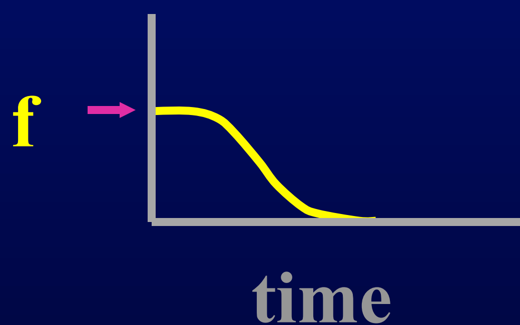
$C_a(t)$

Tissue enhancement :

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



Deconvolution :
find f and RF(t)



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Conclusion

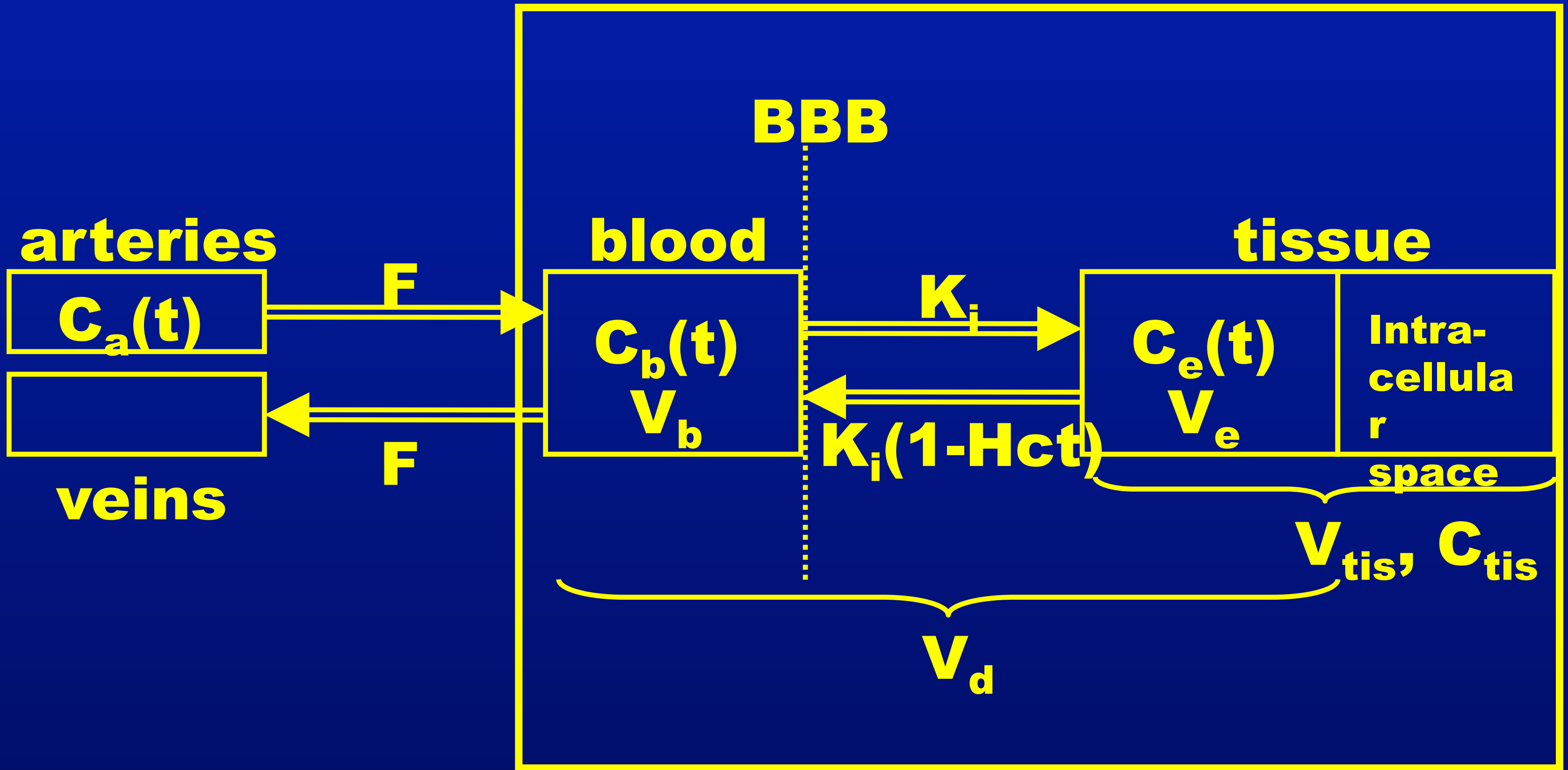
Measure the tissue conc

Measure the input conc i.e. input function

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

Estimate f and RF(t)

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



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

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

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

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

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

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

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

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

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

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

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

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

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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

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

Yes we can !!!!

HBWL

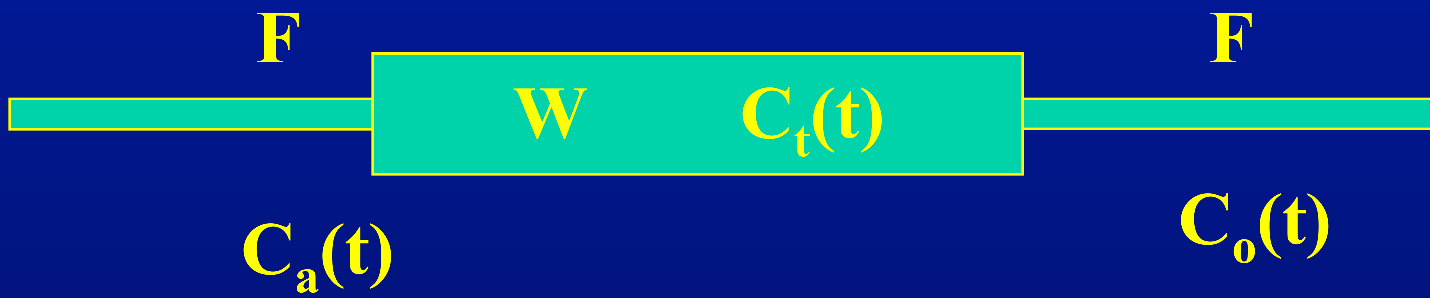
Kety's methods
The inventor of classic tracer kinetic theory

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

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

HBWL

Kety's methods (Residue detection)



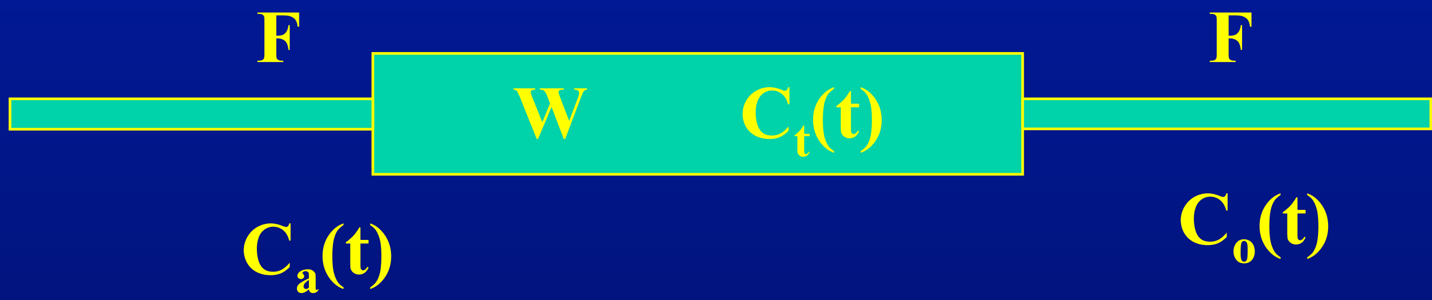
$$C_t(t) \equiv \frac{n(t)}{W_{eight}}$$

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)

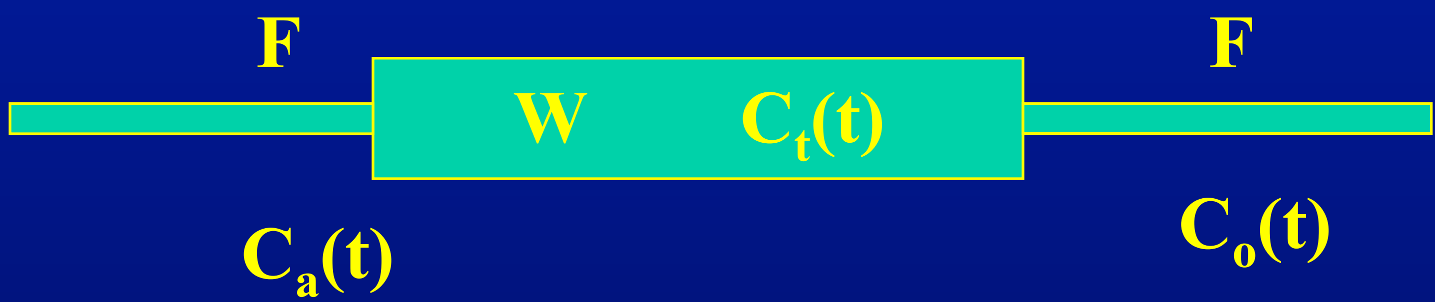


$$\frac{dn(t)}{dt} = j_i(t) - j_o(t)$$

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

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

Kety's methods (Residue detection)



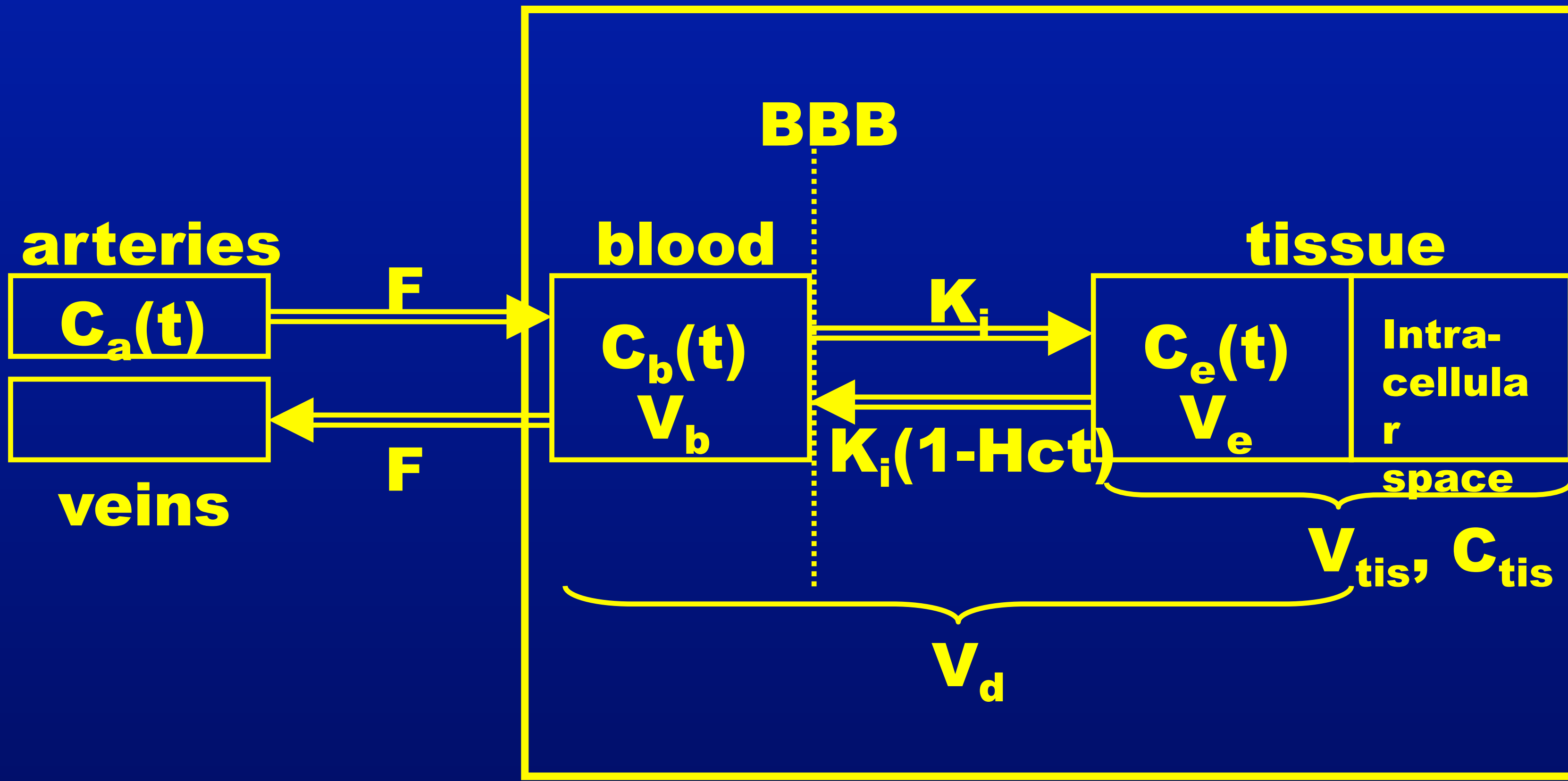
$$\frac{dC_t(t)}{dt} = \frac{F}{W} C_a(t) - \frac{F}{W\lambda} C_t(t)$$

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

Solution:

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

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



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

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

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

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

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

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

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

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

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

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

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

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

HBWL

Kety's methods (Residue detection and no outflow)

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

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

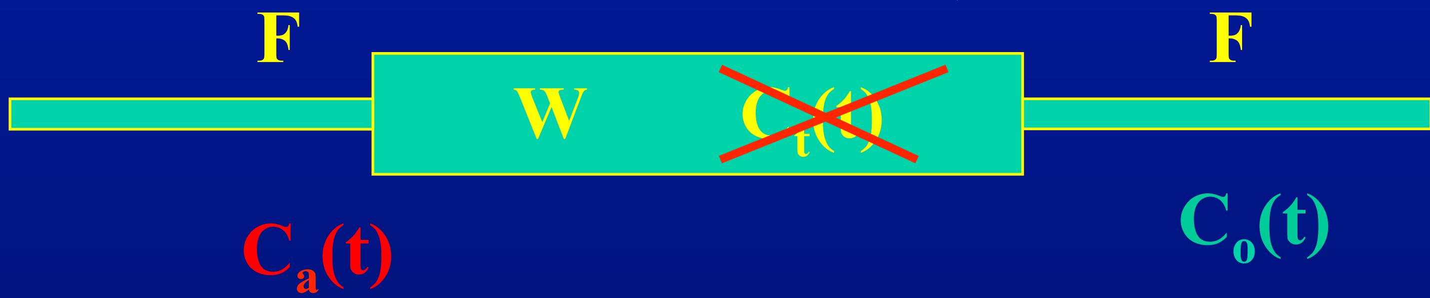
$$\Leftrightarrow dC_t(t) = \frac{F}{W}\,C_a(t)\,dt$$

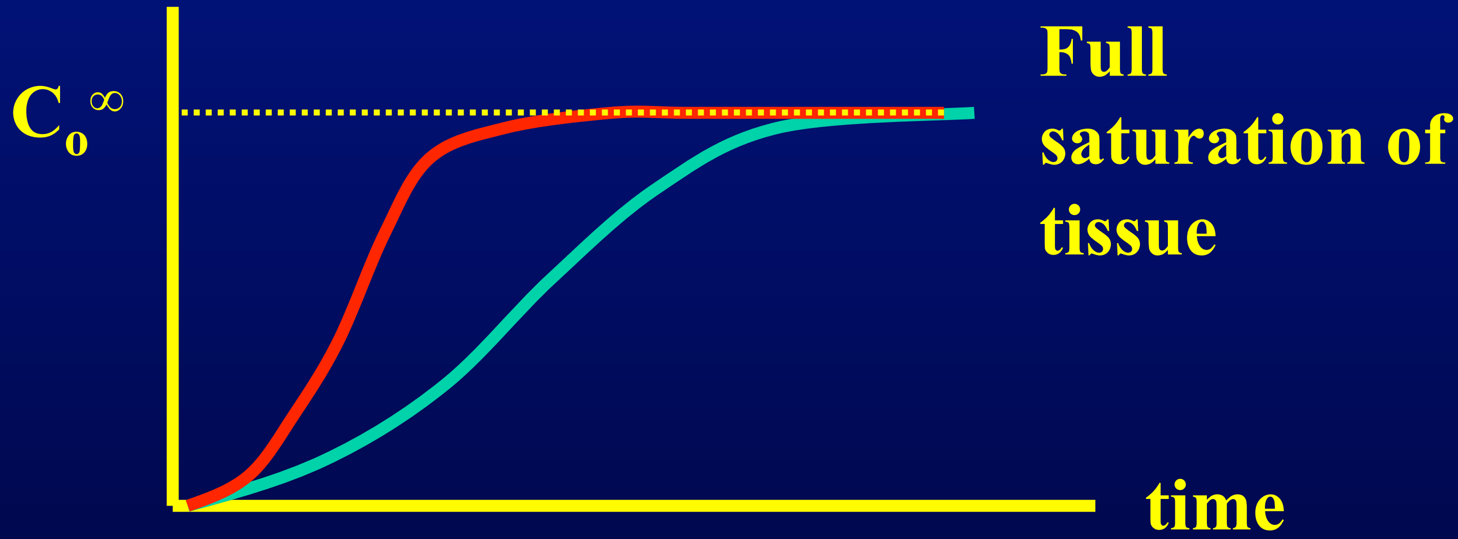
$$\Rightarrow \int_0^T dC_t(t) = \int_0^T \frac{F}{W}\,C_a(t)\,dt$$

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

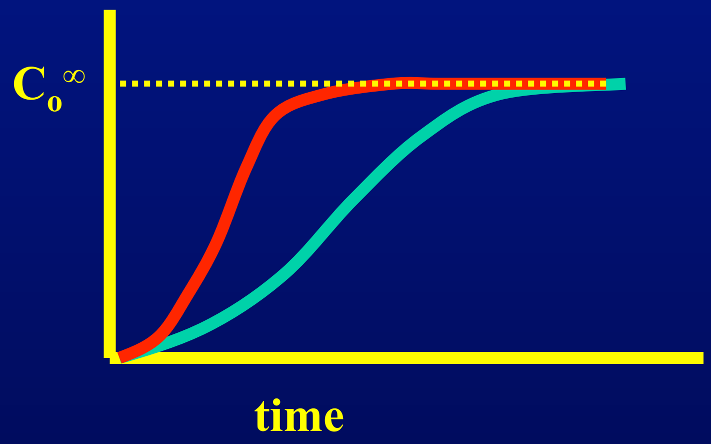
HBWL

Kety's methods (Inflow & outflow detection)





Kety's methods (Inflow & outflow detection)

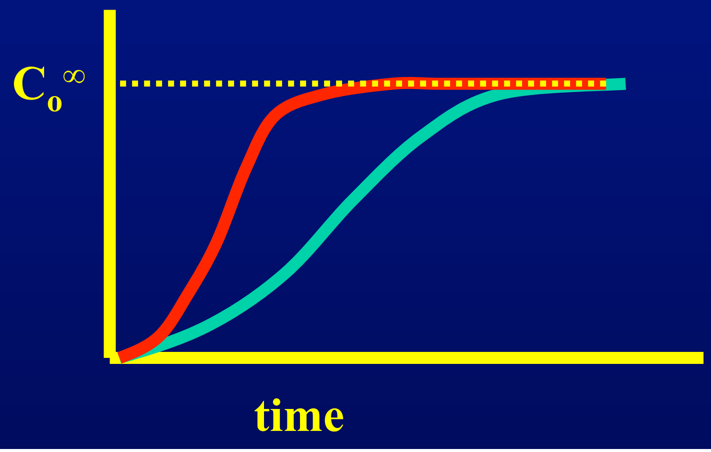


$$\frac{dn(t)}{dt} = j_i(t) - j_o(t)$$

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

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

Kety's methods (Inflow & outflow detection)



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

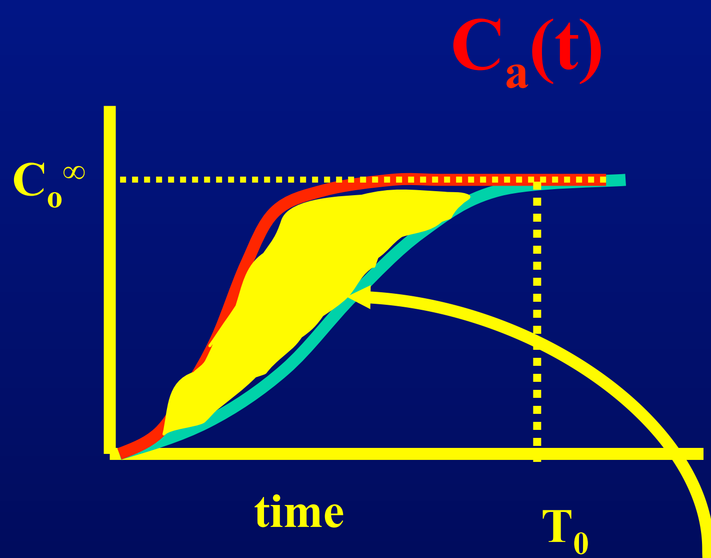
$$\Leftrightarrow dC_t(t) = \frac{F}{W}\left(C_a(t) - C_o(t) \right) dt$$

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

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

HBWL

Kety's methods (Inflow & outflow detection)



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

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

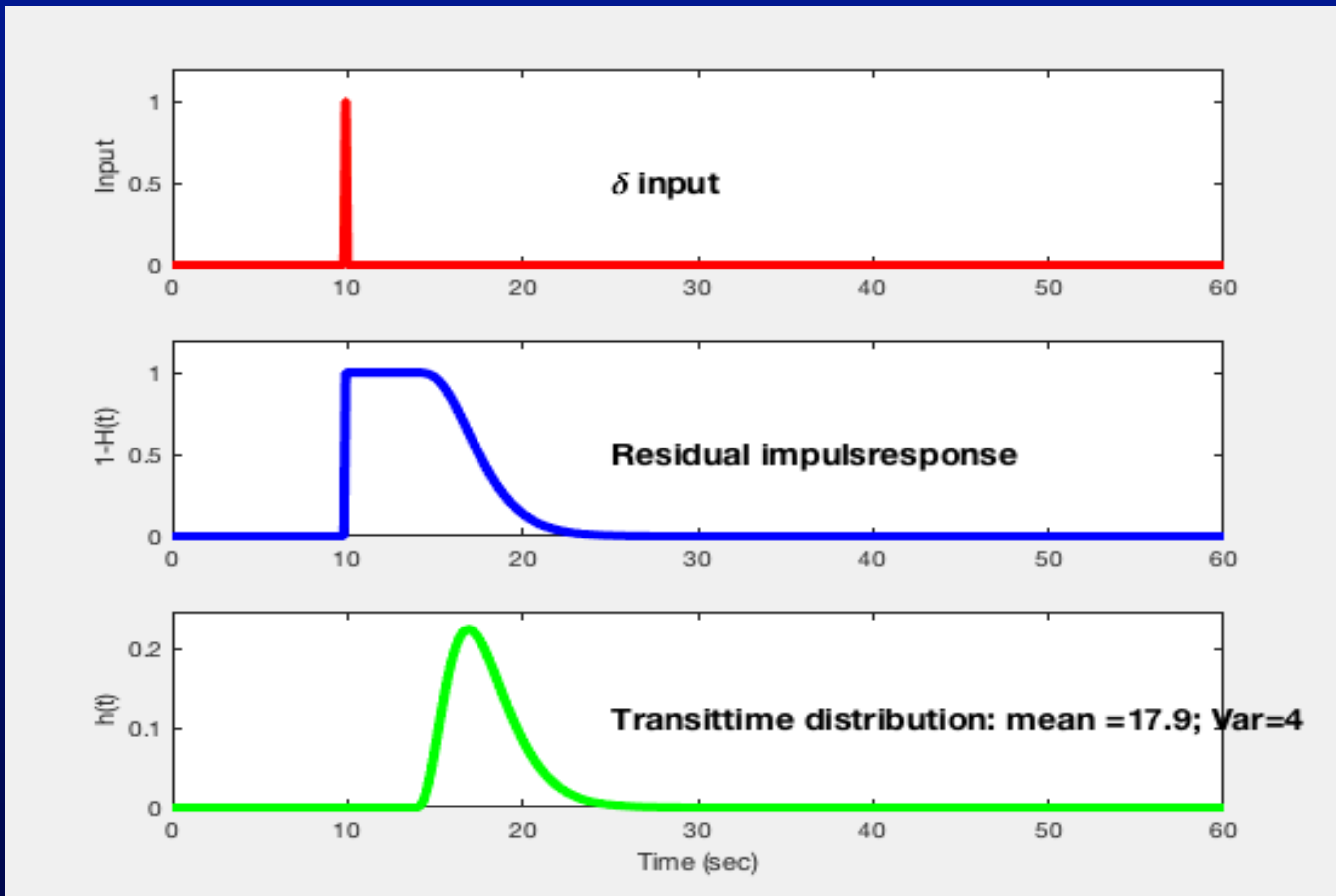
$$\Rightarrow \frac{F}{W} = \frac{\lambda\, C_o^{\infty}}{\int_0^{\infty} \left(C_a(t) - C_o(t) \right) dt}$$

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

outpu
t

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

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

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

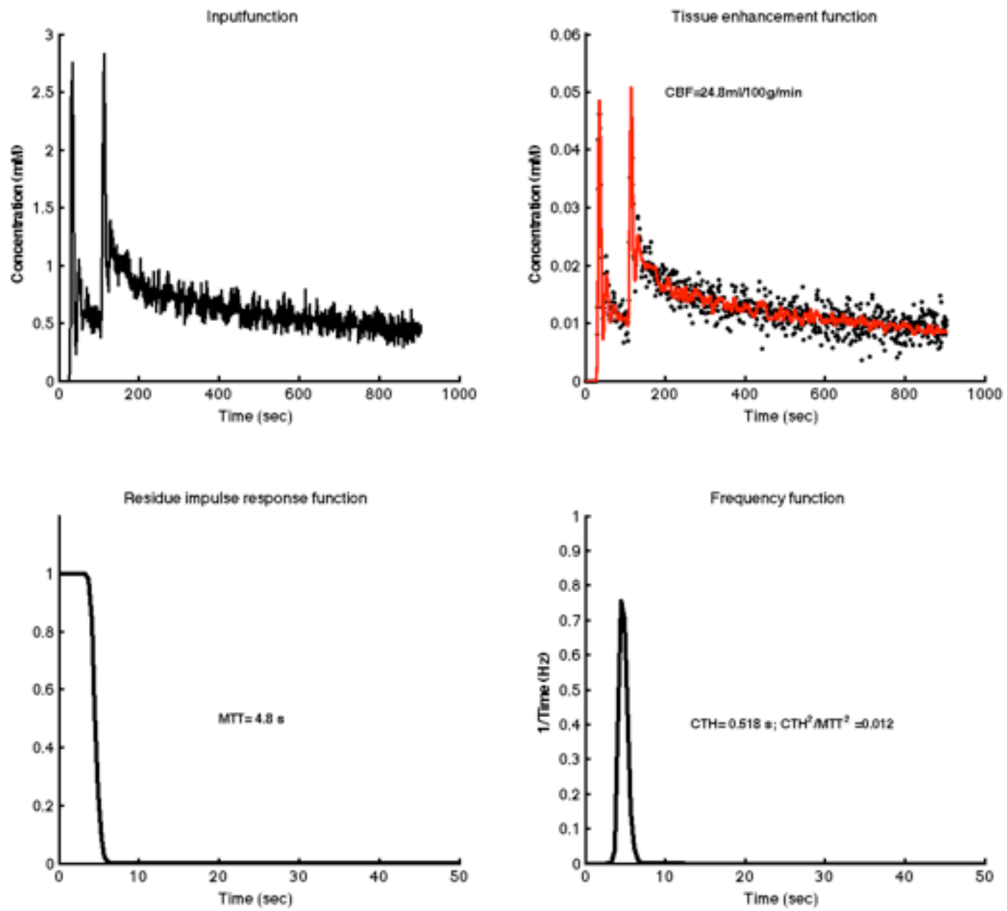


Figure 1. An example of calculation from a ROI placed in thalamus in a young healthy subject. Note the symmetrical shape of the h(t) function. Mean Transit time (MTT), the Capillary Transit time Heterogeneity (CTH) and CTH^2/MTT^2 values are inserted.

HBWL

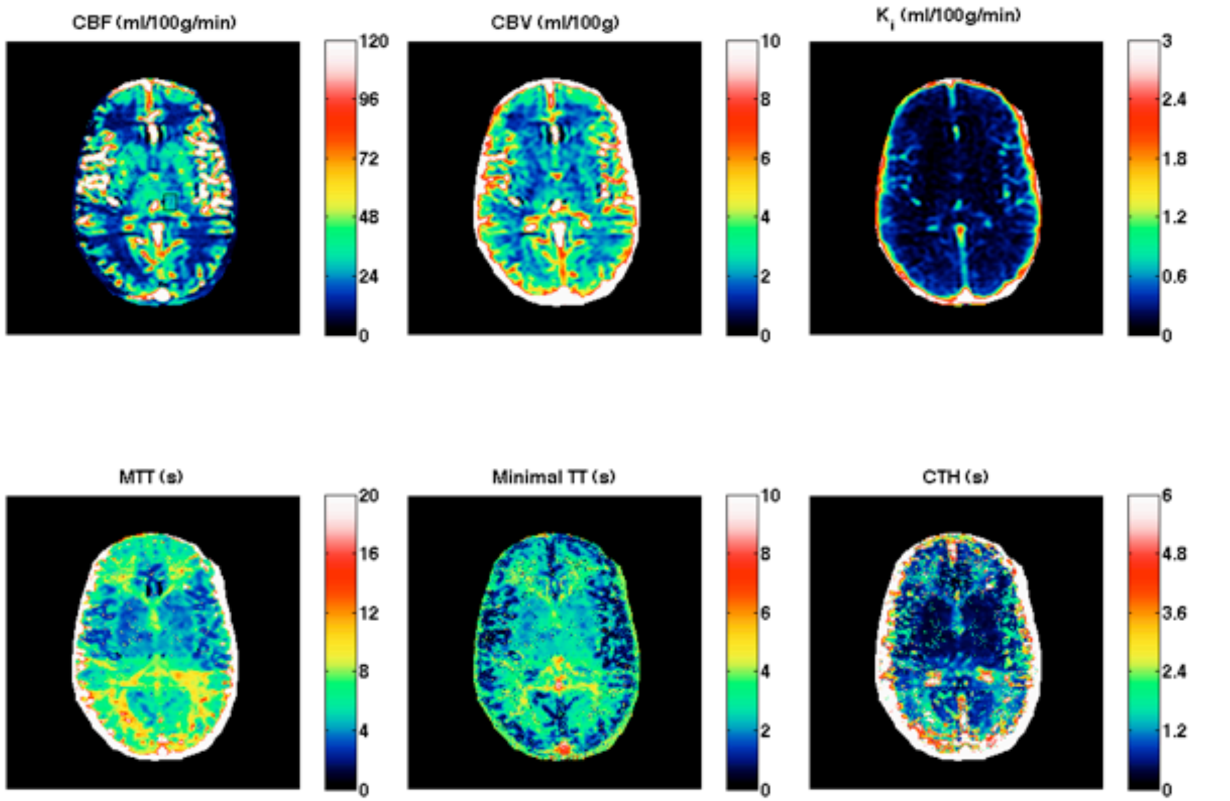


Figure 5. Pixel wise calculated maps of CBF, CBV, permeability K_i, mean transit time (MTT), minimal transit time (Minimal TT), and capillary transit time heterogeneity (CTH), of one healthy subject. The results from the ROI on the CBF map are shown in figure 1.

BWL

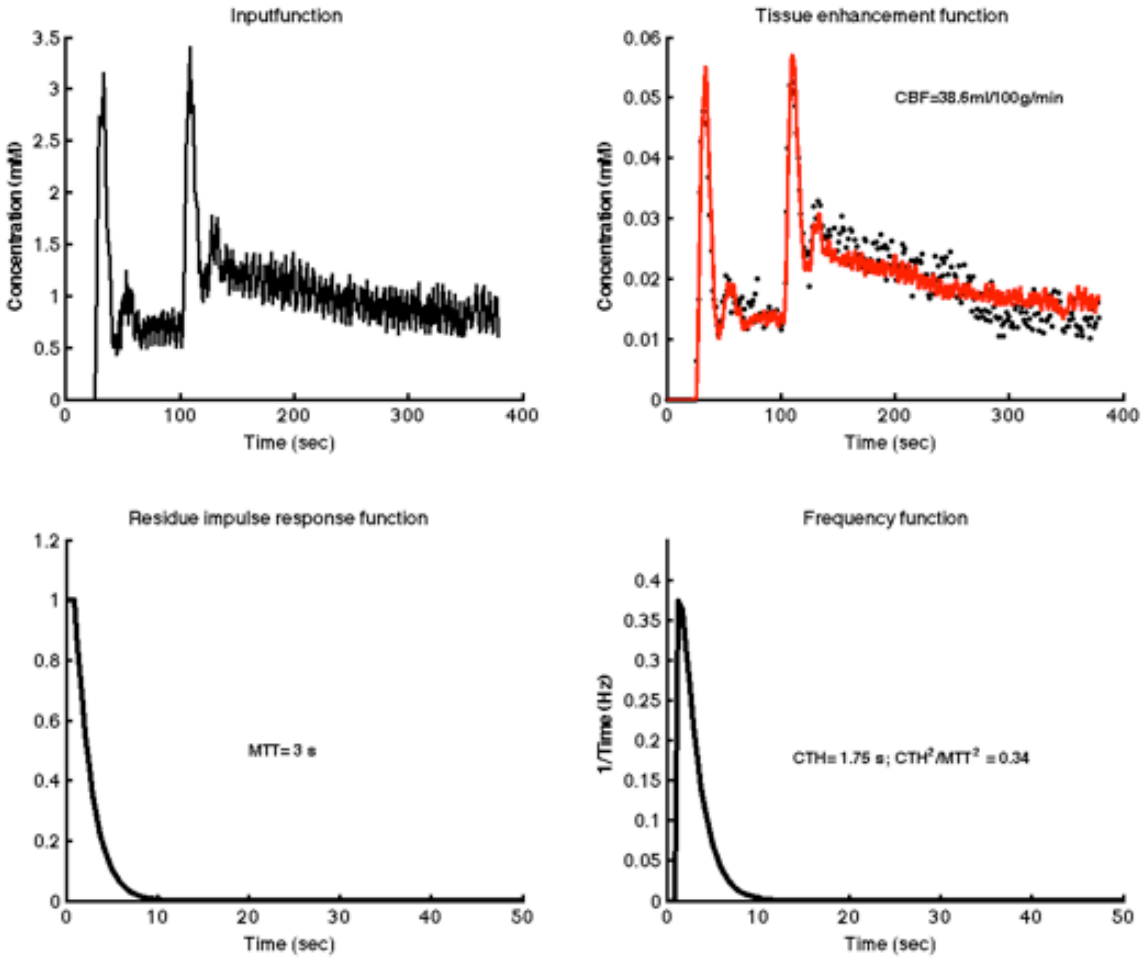


Figure 2. An example of calculation from a ROI placed in frontal WM of a 75-year-old man having internal carotid stenosis contralateral to the ROI placement.

WL

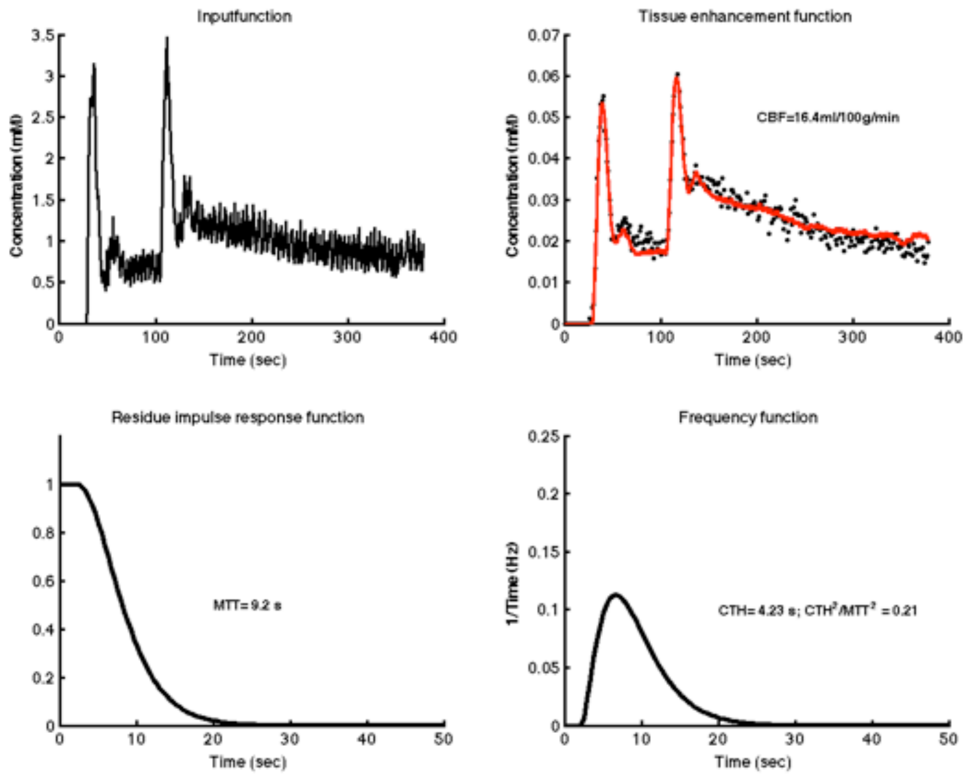


Figure 3. An example of calculation from a ROI placed in parietal WM ipsilateral to an internal carotid stenosis in a 75-year-old man. Mean Transit time (MTT), Capillary Transit time Heterogeneity (CTH) and CTH^2/MTT^2 values are inserted. Note the asymmetry of h(t) signifying a large heterogeneity in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

HBWL

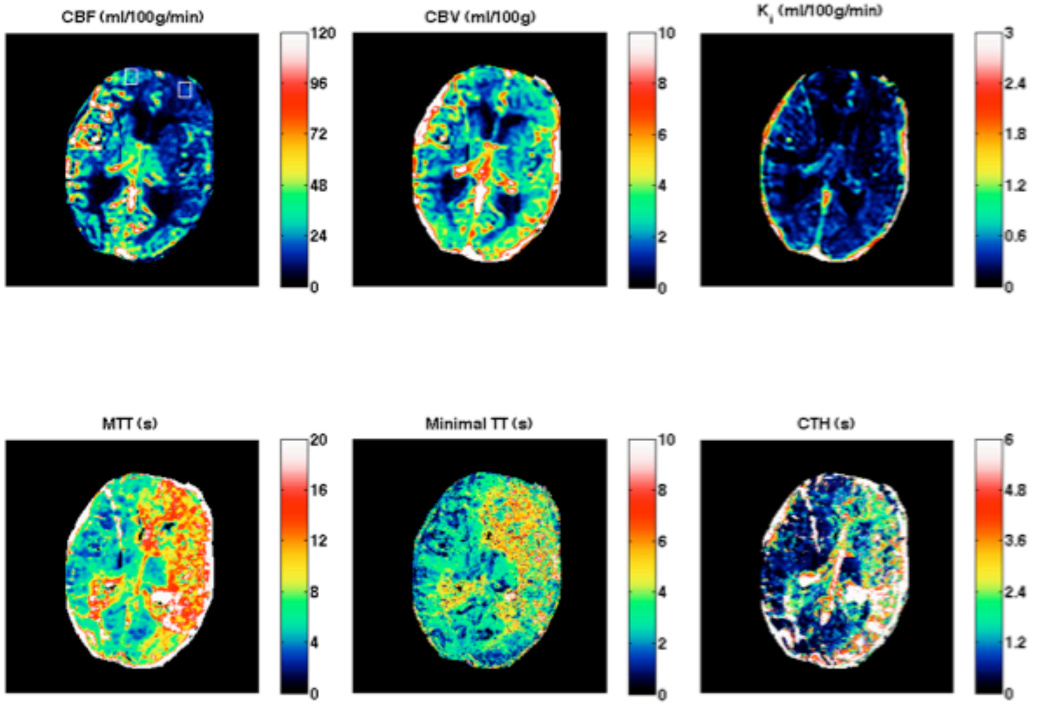


Figure 6. The figure shows results from a patient with left sided internal carotid stenosis, with multiple thrombo-embolic episodes. Perfusion (CBF) is decreased while the cerebral blood volume (CBV) is increased in the fronto-parietal region, but the permeability (K_i) seems relatively normal. The mean 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