

CLEARANCE, FICK'S PRINCIPLE AND EXTRACTION

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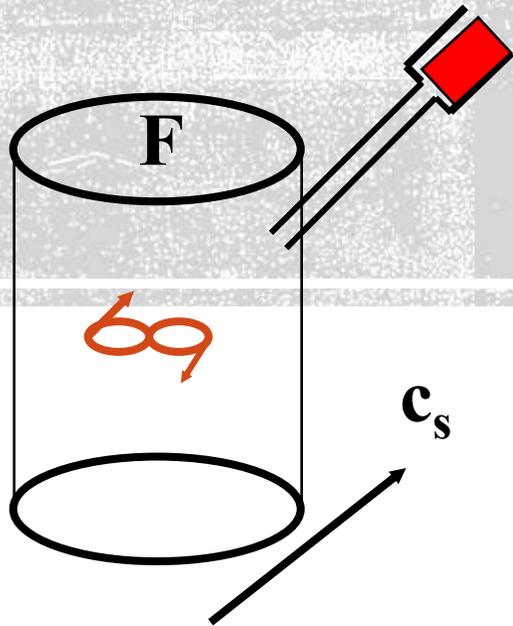
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INDICATOR-DILUTION METHODS

Constant Infusion (Stewart principle)

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



$$[F] = \text{ml/s}$$

[F = volume transport per time unit]
(from conservation of mass)

c_s

$$\cdot F_s = j_{in}$$

flux is
useful!!



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

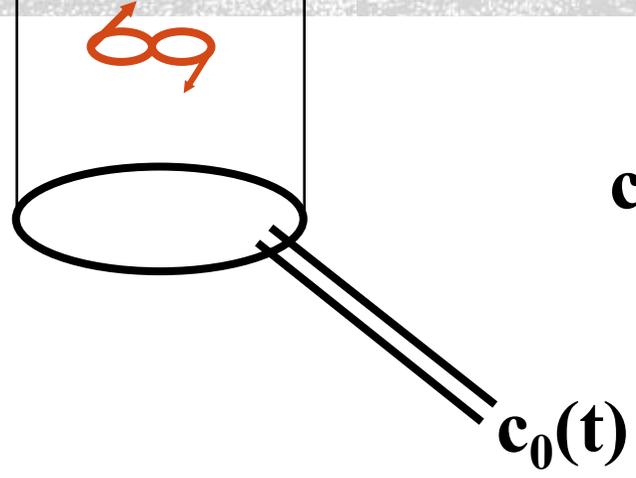
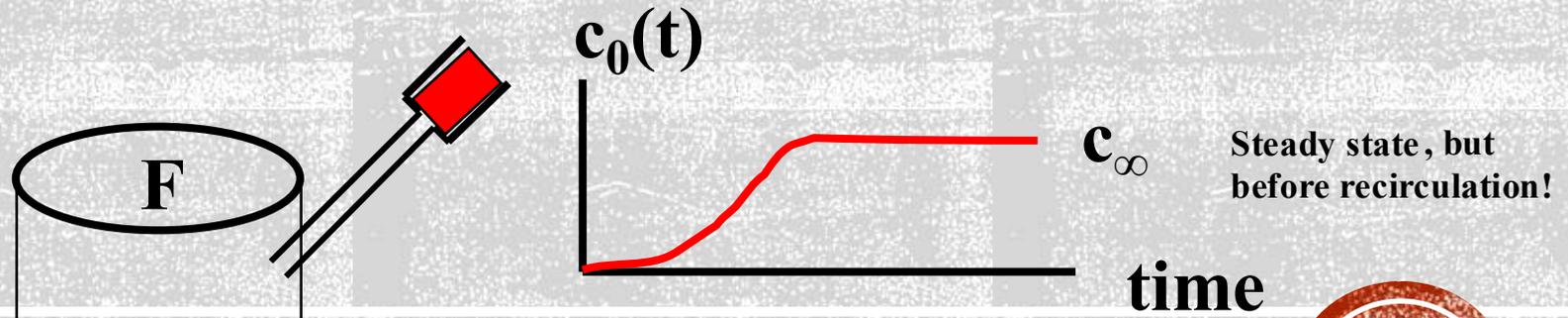
$$[F_s] = \text{ml/s}$$

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

INDICATOR-DILUTION METHODS

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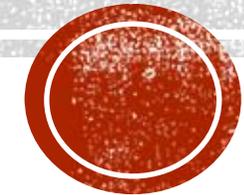


$$j_{in} = j_o$$

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

$$F = \frac{c_s \cdot F_s}{c_\infty}$$

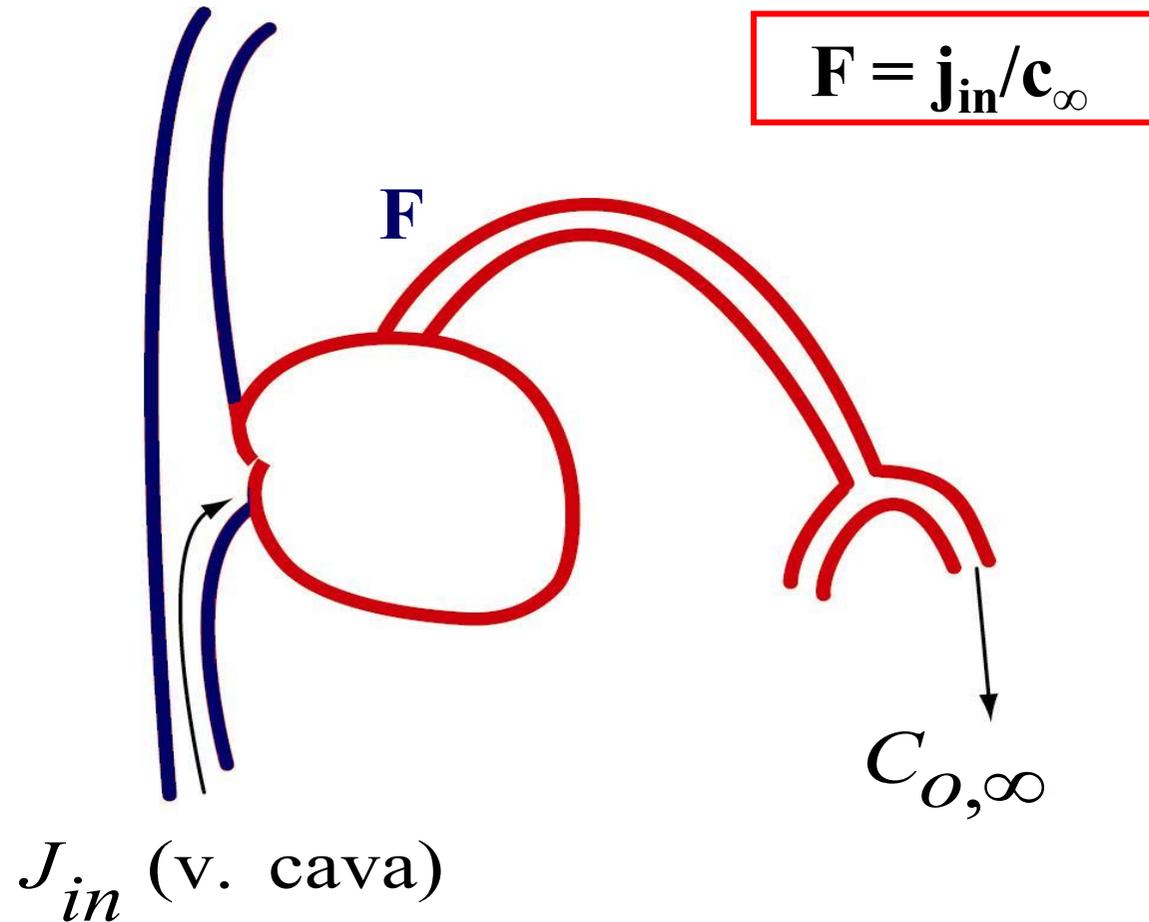
$$F = j_{in} / c_\infty$$



$$F \gg F_s$$

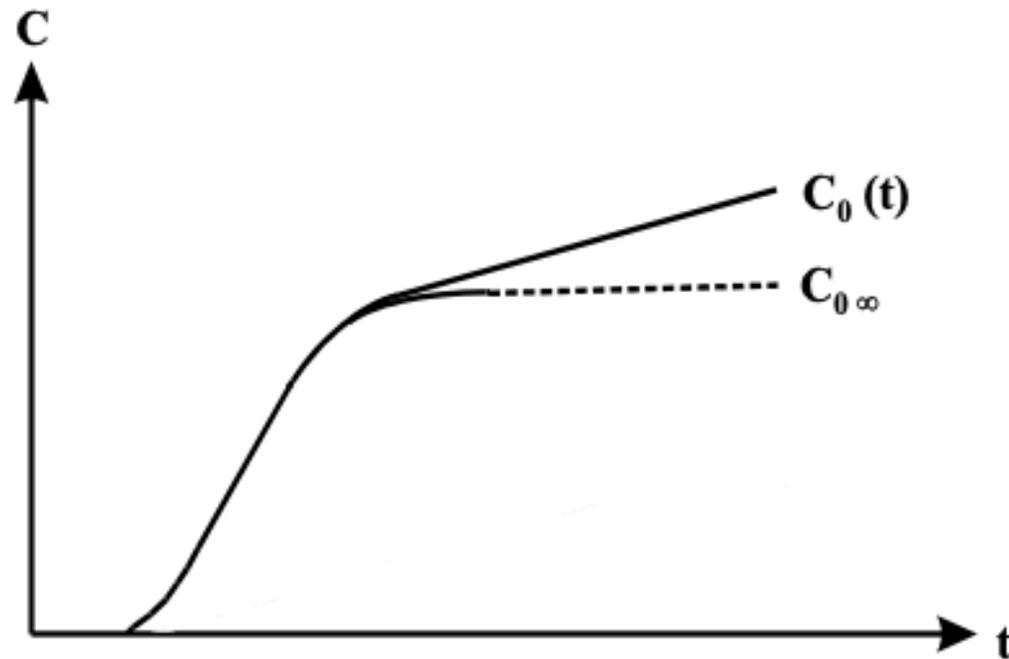
$$[j] = \text{mmol/s}$$

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



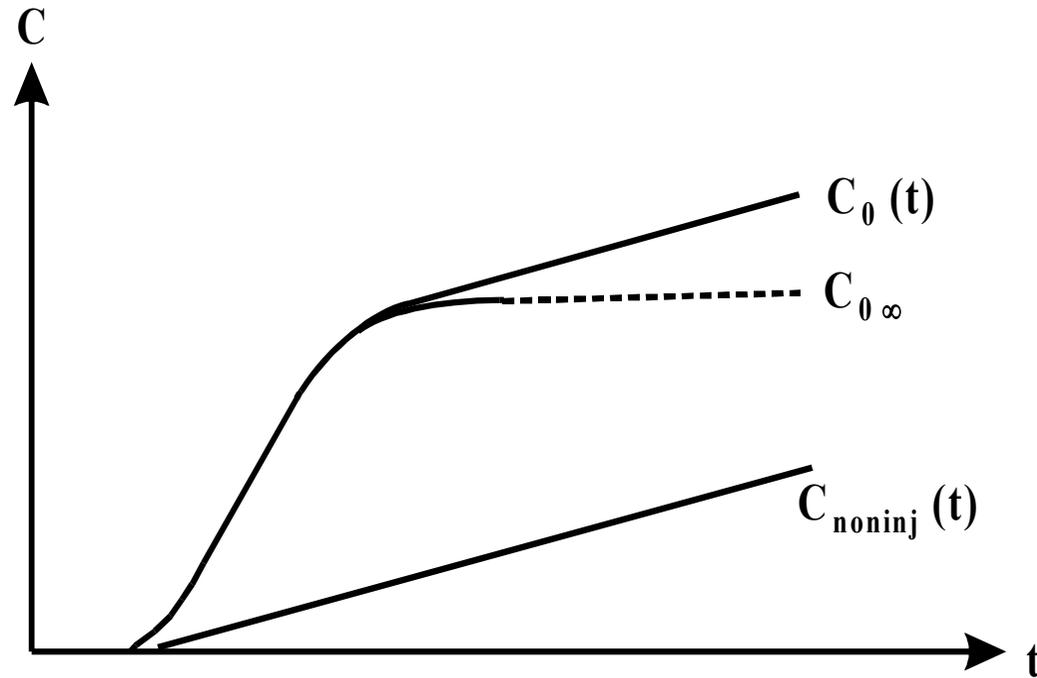
**Stewart's principle: Cardiac output from the left ventricle!
Continuous infusion in vena cava, and outlet concentration
measurement from a peripheral artery.**





In order to use "Stewards Principle" we need to know the **steady state outflow concentration**, but in a physiological system we get recirculation of tracer! How could we correct for this?





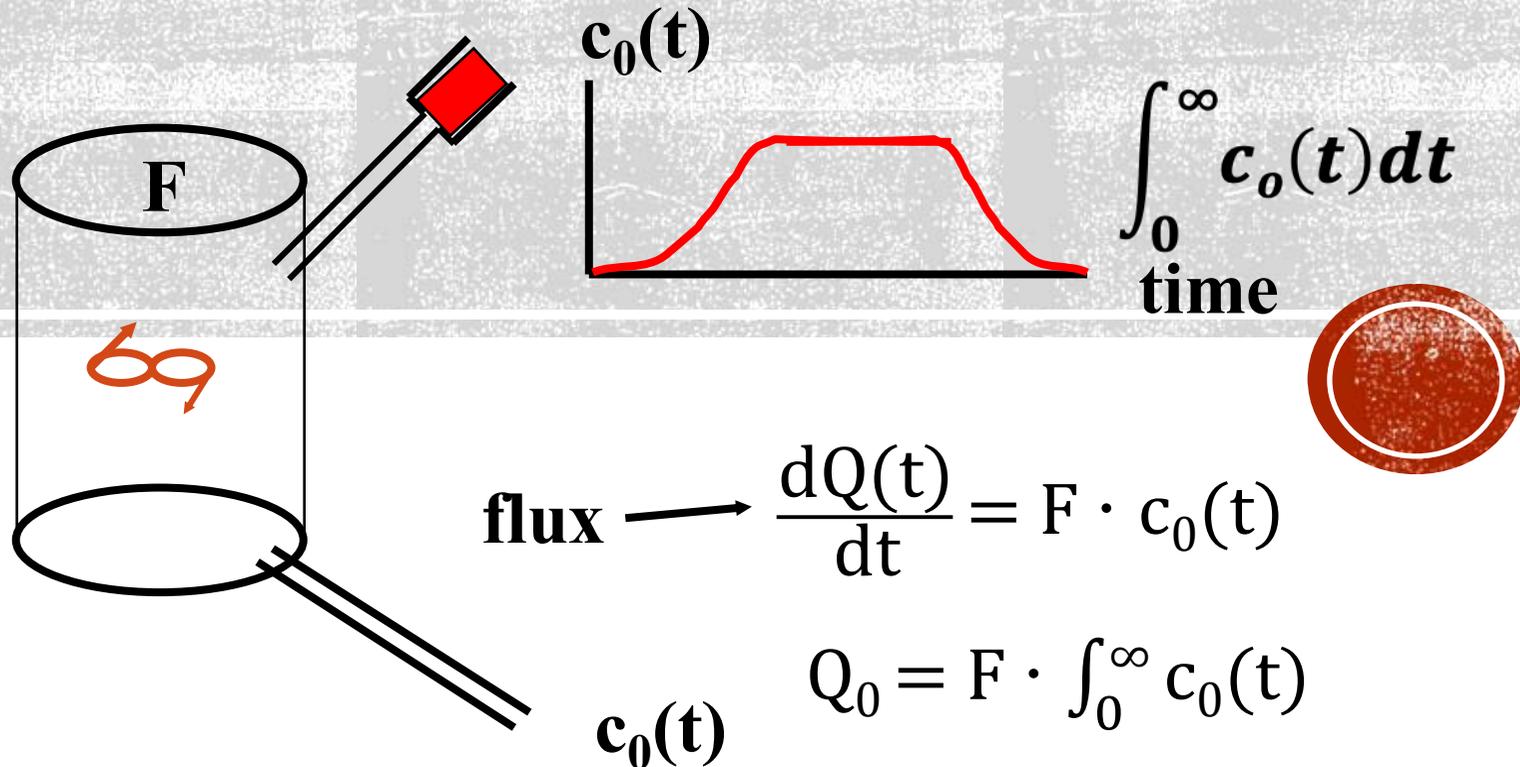
Measurement of concentration at the outlet and the "noninj" venous side.



BOLUS INJECTION

(Henriques and Hamilton)

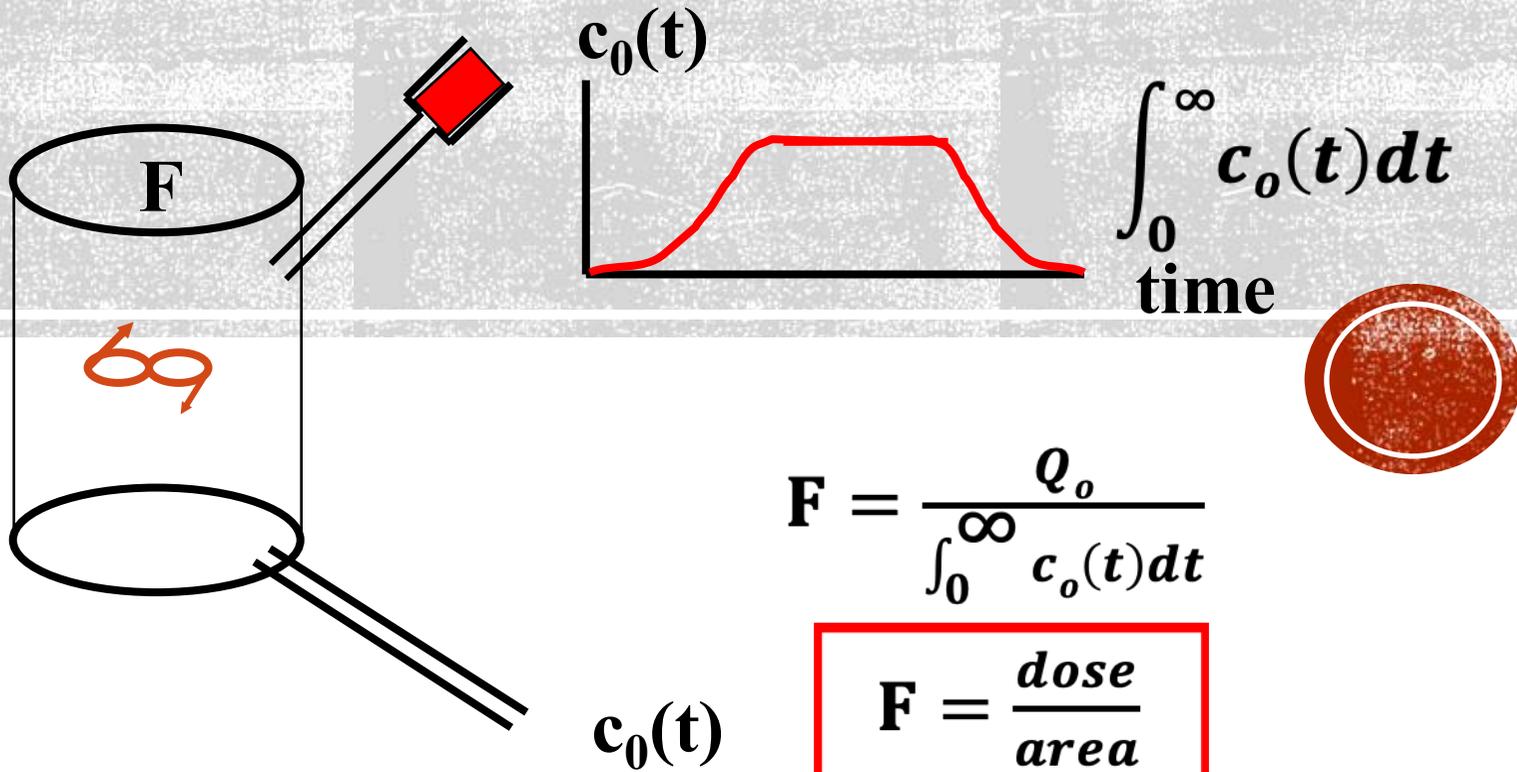
The aim : to measure the flow of an organ or a vessel or a pipeline



BOLUS INJECTION

(Henriques and Hamilton)

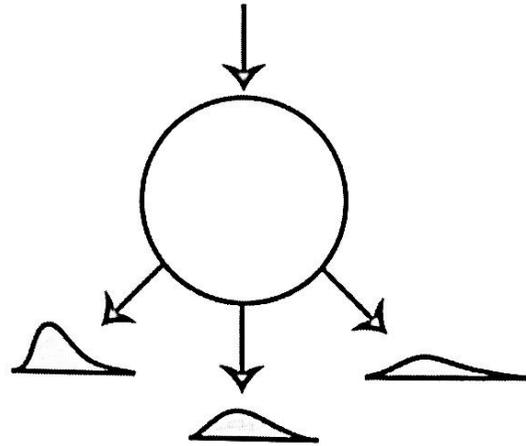
The aim : to measure the flow of an organ or a vessel or a pipeline



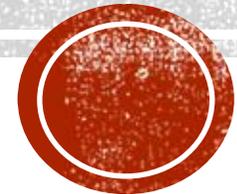
RULE OF EQUIVALENT AREAS

(Sapirstein)

Reglen om ækvivalente arealer:



$$F = \frac{\text{dose}}{\text{area}}$$



- Would we measure different values of F depending on where we measure our outlet concentration?
- No, due to "conservation of matter" the area is the same no matter where we sample the C_0 curve!

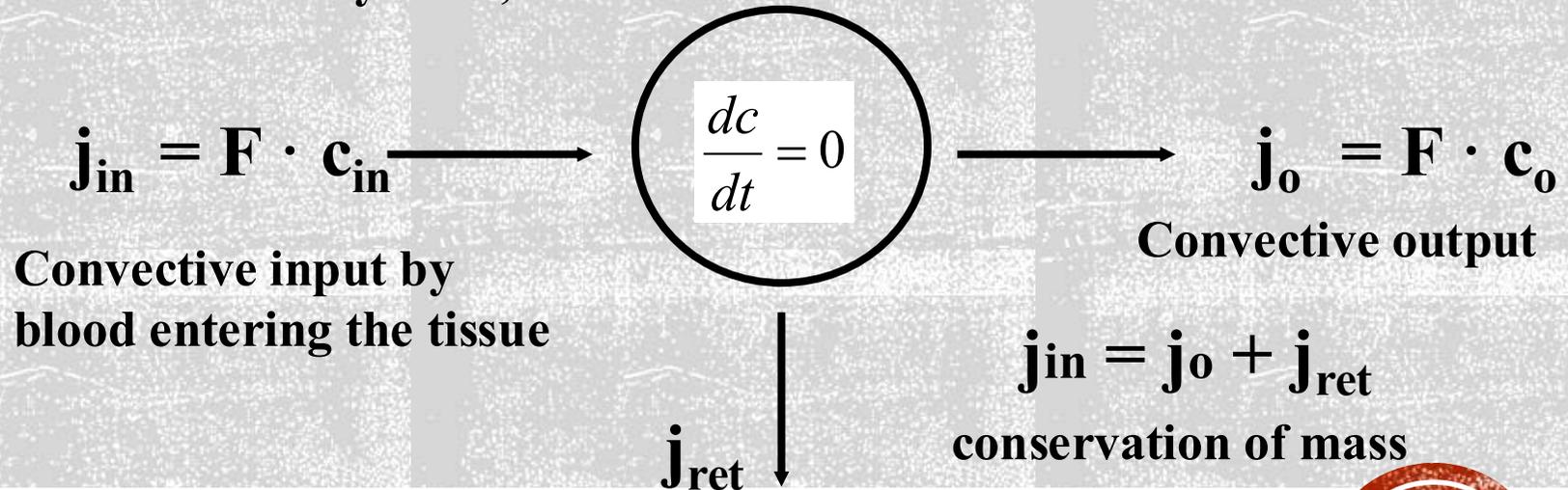
Fick's principle

The conservation of matter



FICK'S PRINCIPLE

Steady state; Concentration and fluxes are constant



Non-convective flux, e.g. tissue uptake

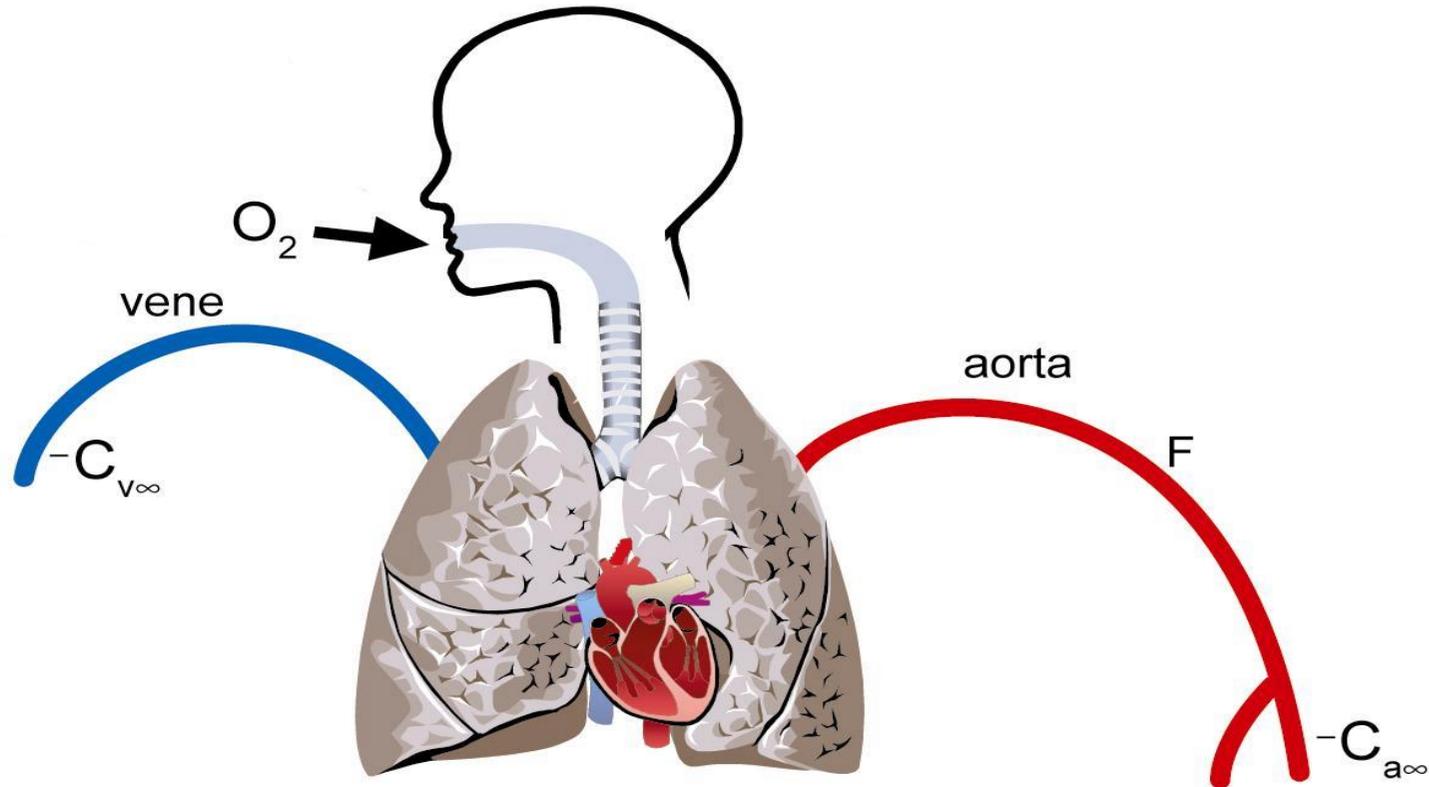
$$F \cdot c_{in} = j_{ret} + F \cdot c_o$$

$$F (c_{in} - c_o) = j_{ret}$$

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



Fick's principle: cardiac output



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

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

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



CEREBRAL METABOLIC RATE OF OXYGEN (CMRO₂)

By Fick's principle

$$\text{CMRO}_2 = [\text{Hgb}] \cdot \text{CBF} \cdot (\text{SaO}_2 - \text{SvO}_2)$$

Haemoglobin (blood sample)

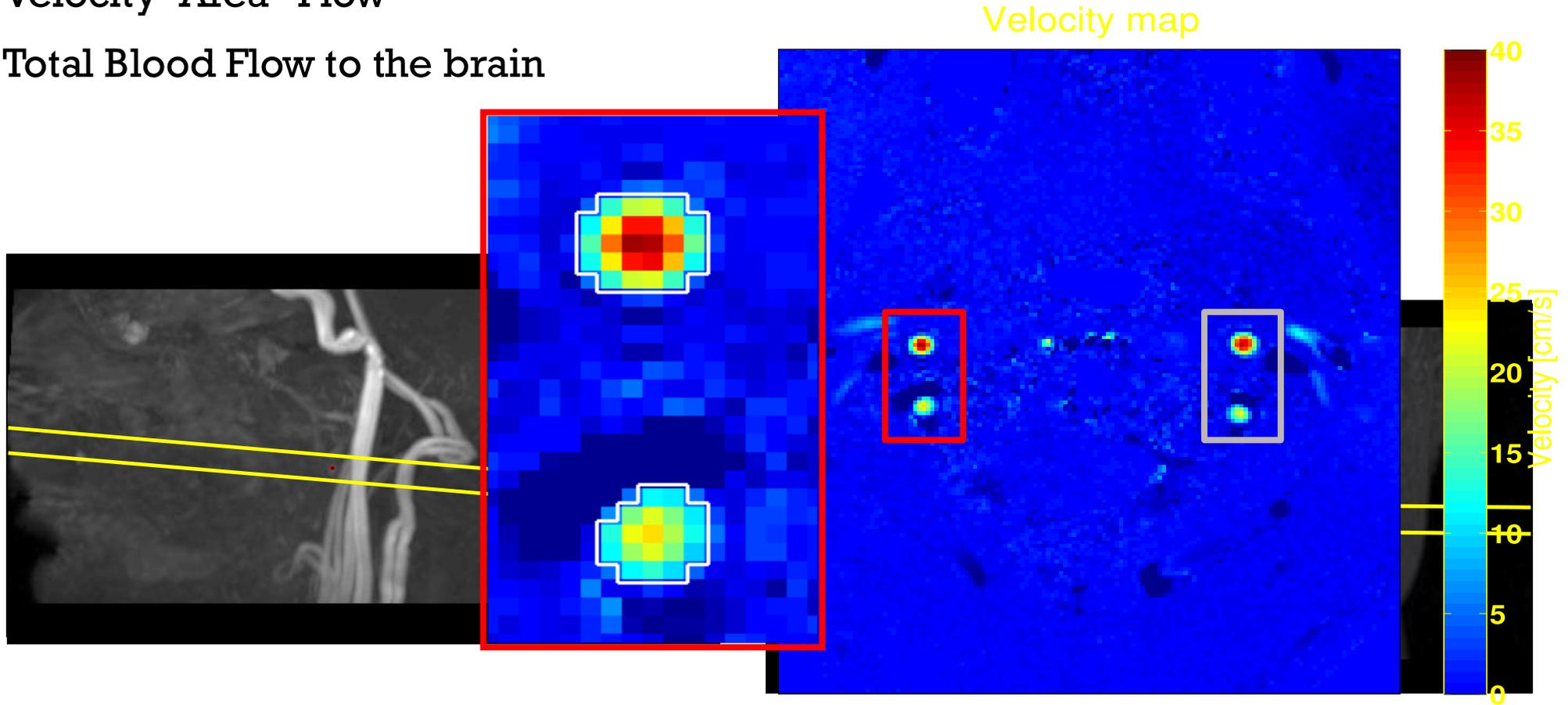
MRI phase contrast
mapping

Pulse-oximetry
(A-cath)

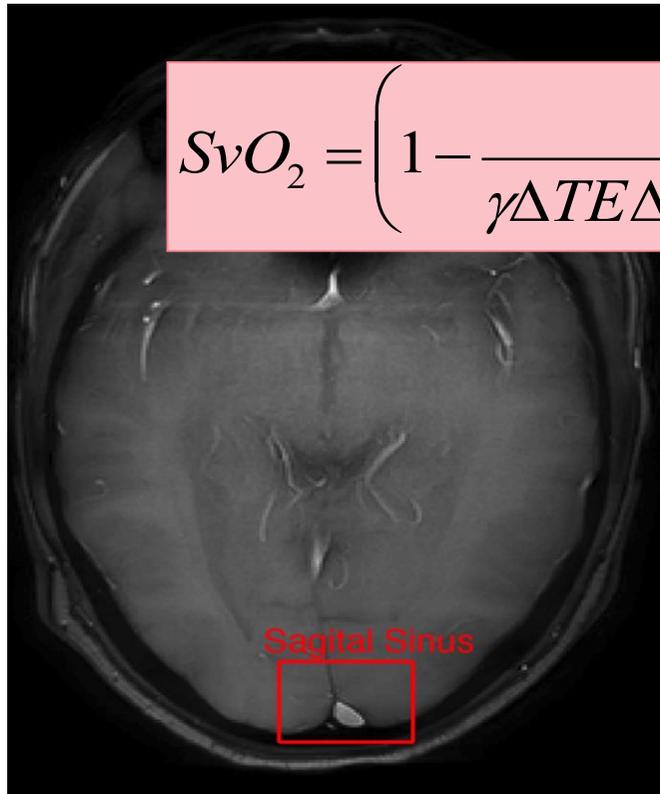
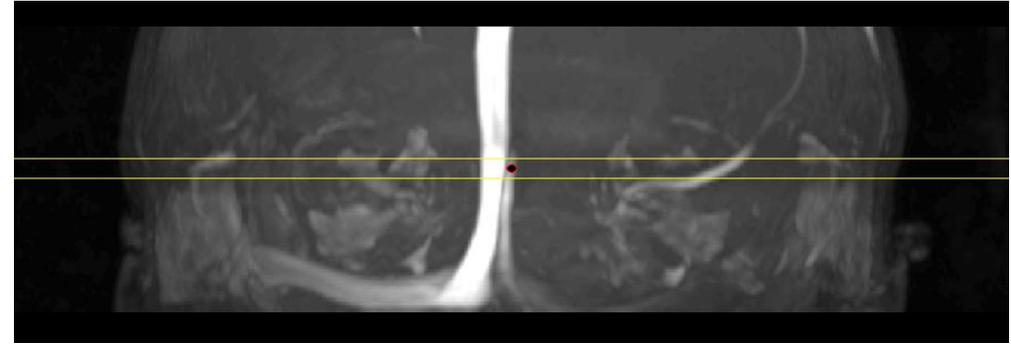
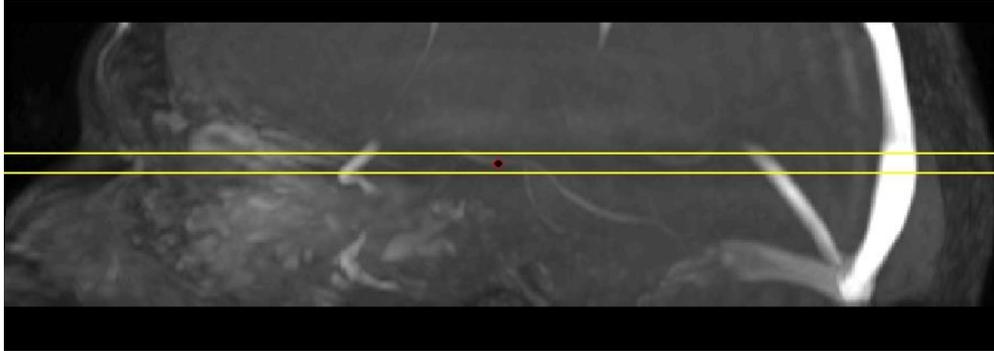
MRI susceptibility-based oximetry from
Sagittal sinus (venous blood from brain)



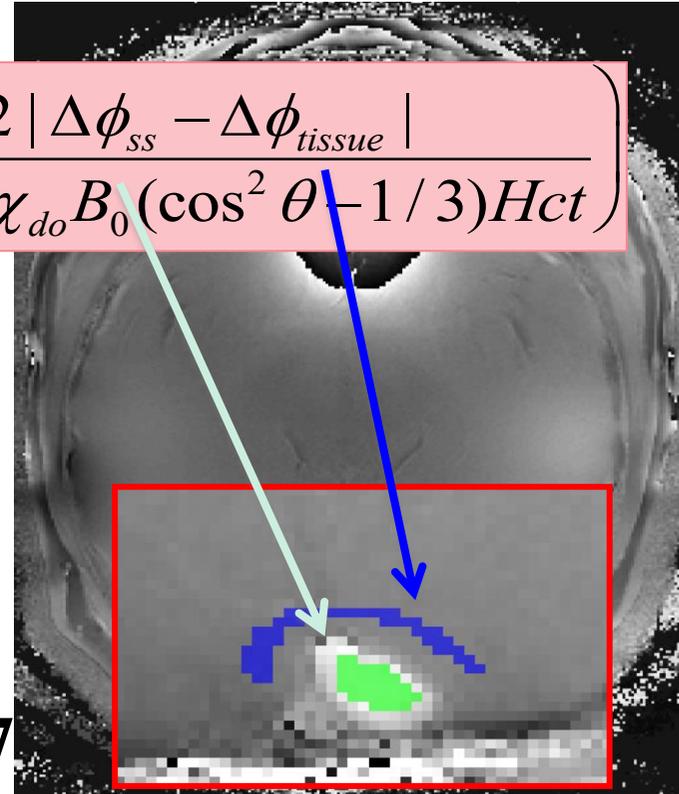
- Velocity through plane (orthogonal the arteries)
- A. carotis interna + a. basilaris:
 $\text{Velocity} * \text{Area} = \text{Flow}$
- Total Blood Flow to the brain



SUSCEPTIBILITY BASED OXIMETRY



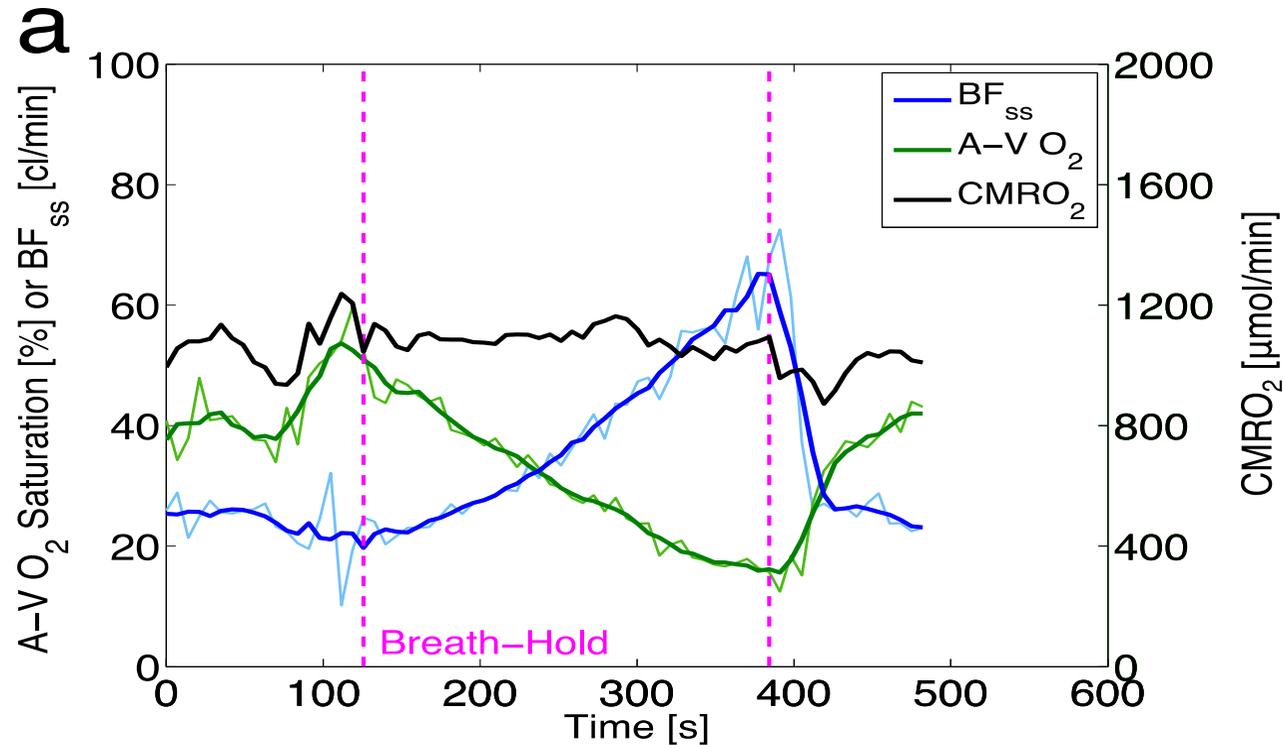
$$SvO_2 = \left(1 - \frac{2 |\Delta\phi_{ss} - \Delta\phi_{tissue}|}{\gamma\Delta TE\Delta\chi_{do}B_0(\cos^2\theta - 1/3)Hct} \right)$$

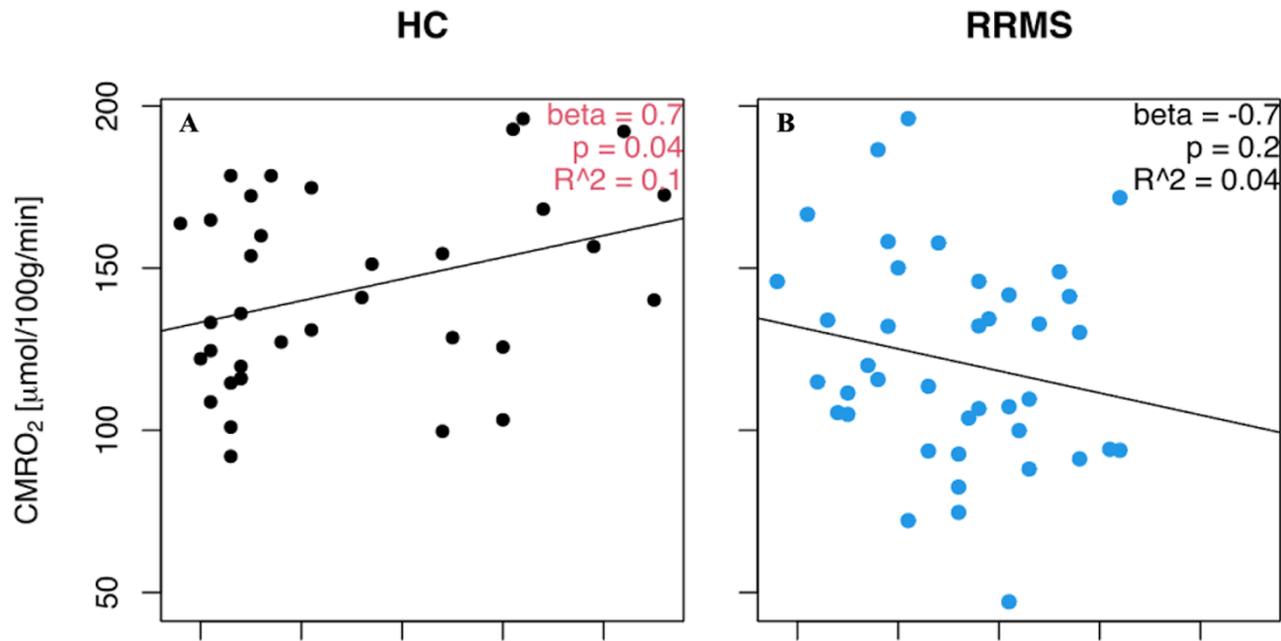


Breathhold: $CMRO_2$

- $CMRO_2 = 4 \cdot [Hgb] \cdot BF_{ss} \cdot (S_a O_2 - S_v O_2)$
- Blood-flow i sagittal sinus (BF_{ss})
- Arteriovenous oxygen-difference ($A-V O_2$)

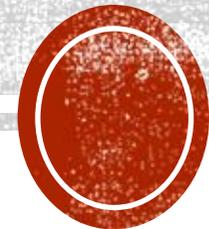
Vestergaard MB, Larsson HBW. Cerebral metabolism and vascular reactivity during breath-hold and hypoxic challenge in freedivers and healthy controls. J Cereb Blood Flow Metab 2017 .

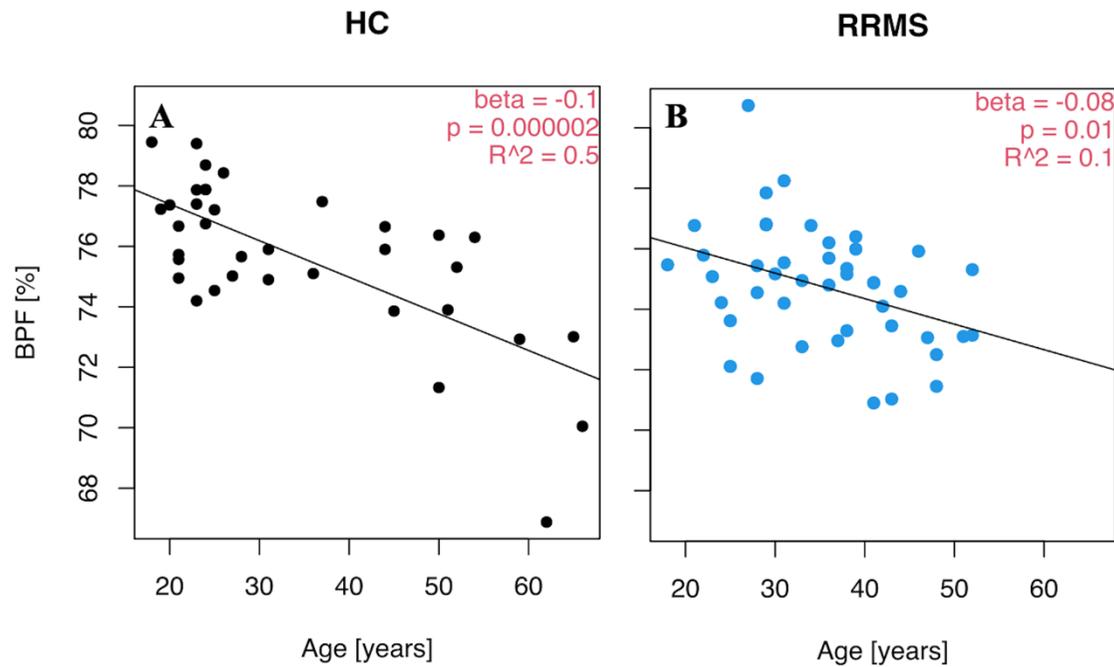




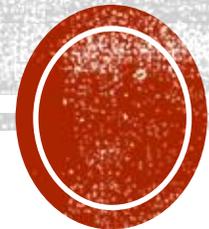
**CMRO₂
INCREASES
WITH AGE**

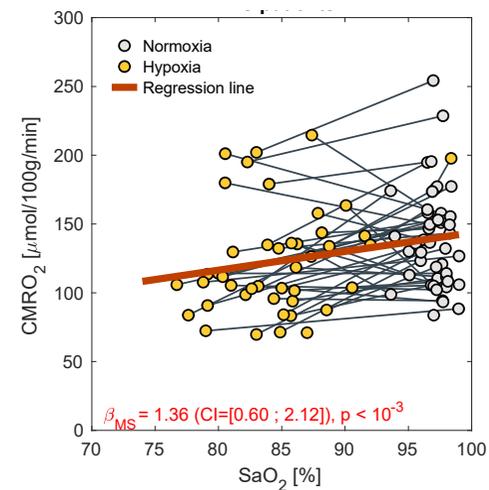
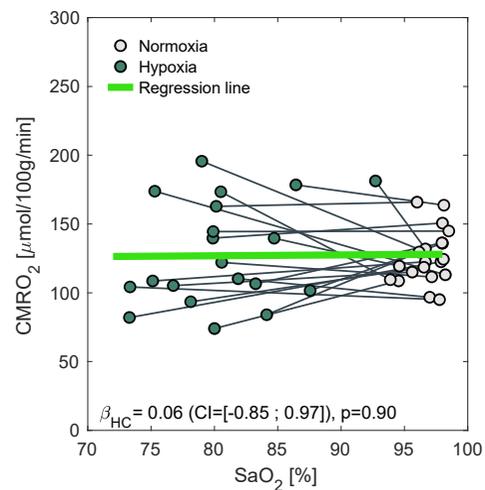
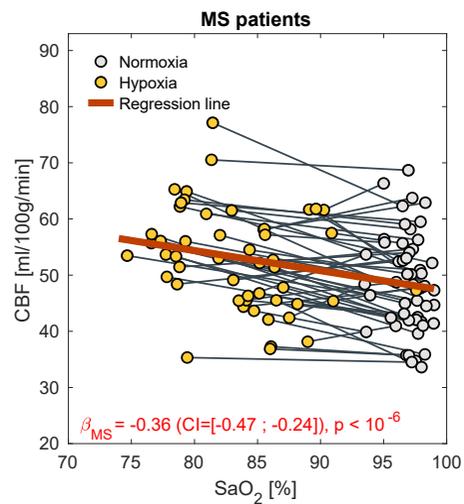
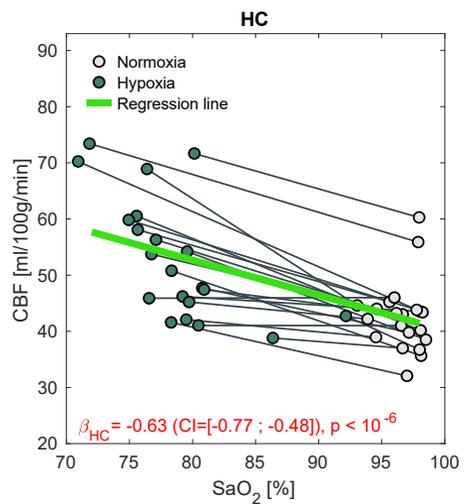
Multiple sclerosis:
Autoimmune disease of the CNS \rightarrow myelin sheaths \rightarrow loss
of brain tissue \rightarrow reduced metabolic demand





CMRO2 AND BRAIN ATROPHY





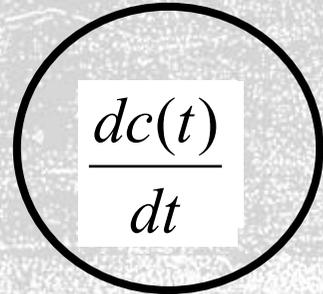
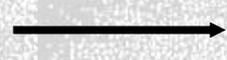
HYPOXIC CHALLENGE IN MS CBF AND CMRO2.

EXTENDING THE PRINCIPLE OF FICK

What if the fluxes are not constant, as in a bolus injection

The concentration here is not constant

$$j_{in}(t) = F \cdot c_{in}(t)$$



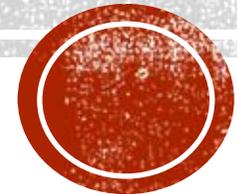
$$j_o(t) = F \cdot c_o(t)$$

conservation of mass

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

$$v \frac{dc(t)}{dt} = j_{in}(t) - j_o(t) - j(t)$$

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



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

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



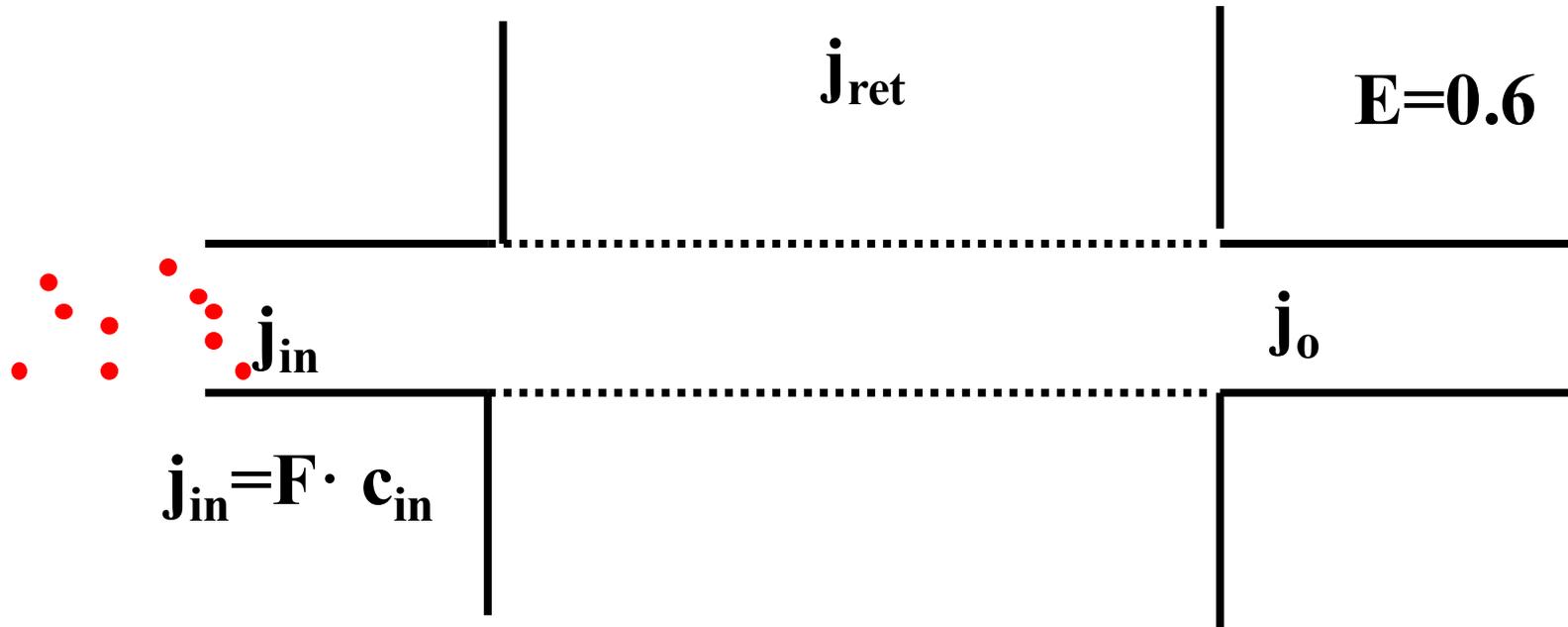
EXTRACTION FRACTION

[The fraction of incoming flux that is taken up or retained in the tissue]

Dimensionless!

EXTRACTION FRACTION

Is E constant??



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

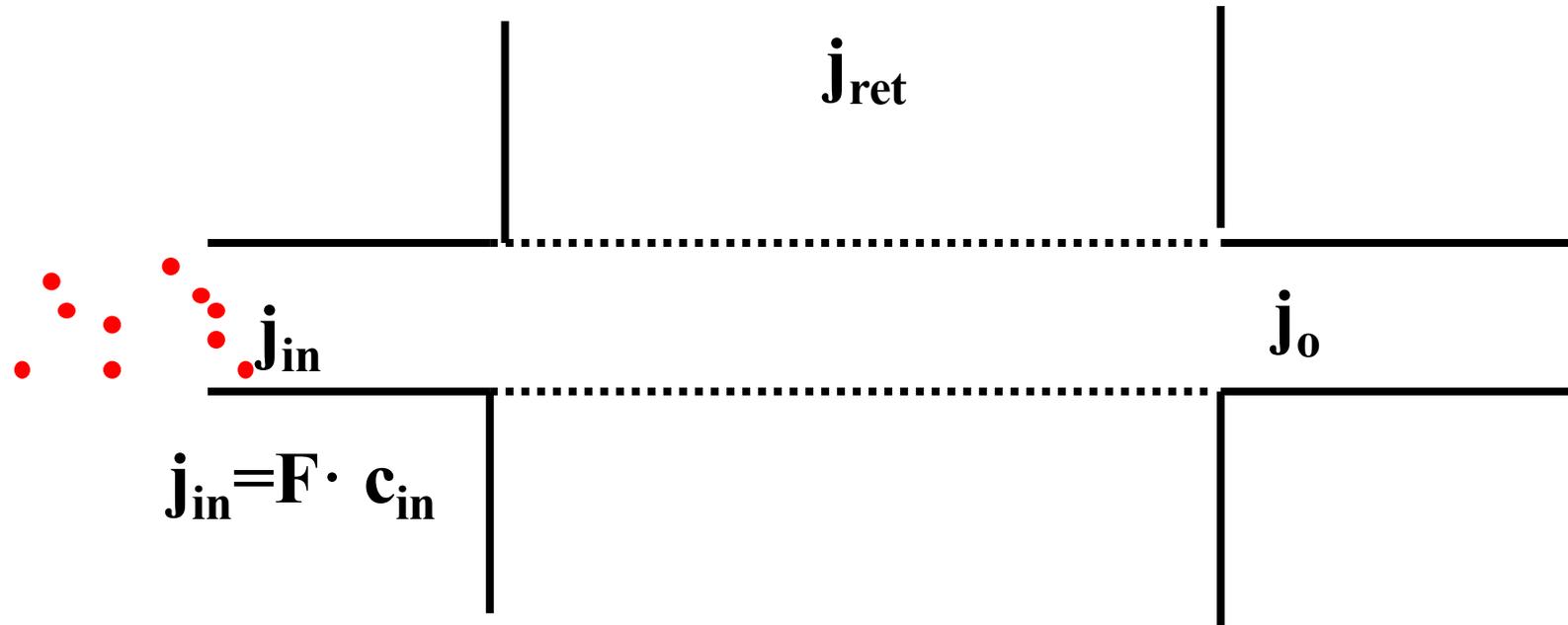


WHAT DETERMINES EXTRACTION FRACTION?

- Depends on the tracer used
 - Molecular size, protein binding, passive diffusion/active transport, receptor uptake
 - Concentration differences, barrier properties (surface area,)
- Depends on the time we measure
 - Backdiffusion or permanent trapping, and second pass!
 - Literature values for extraction fraction of specific tracers are related to the first pass!
- What happens when flow increases?



EXTRACTION FRACTION AND FLOW



With higher flow \rightarrow lower extraction!

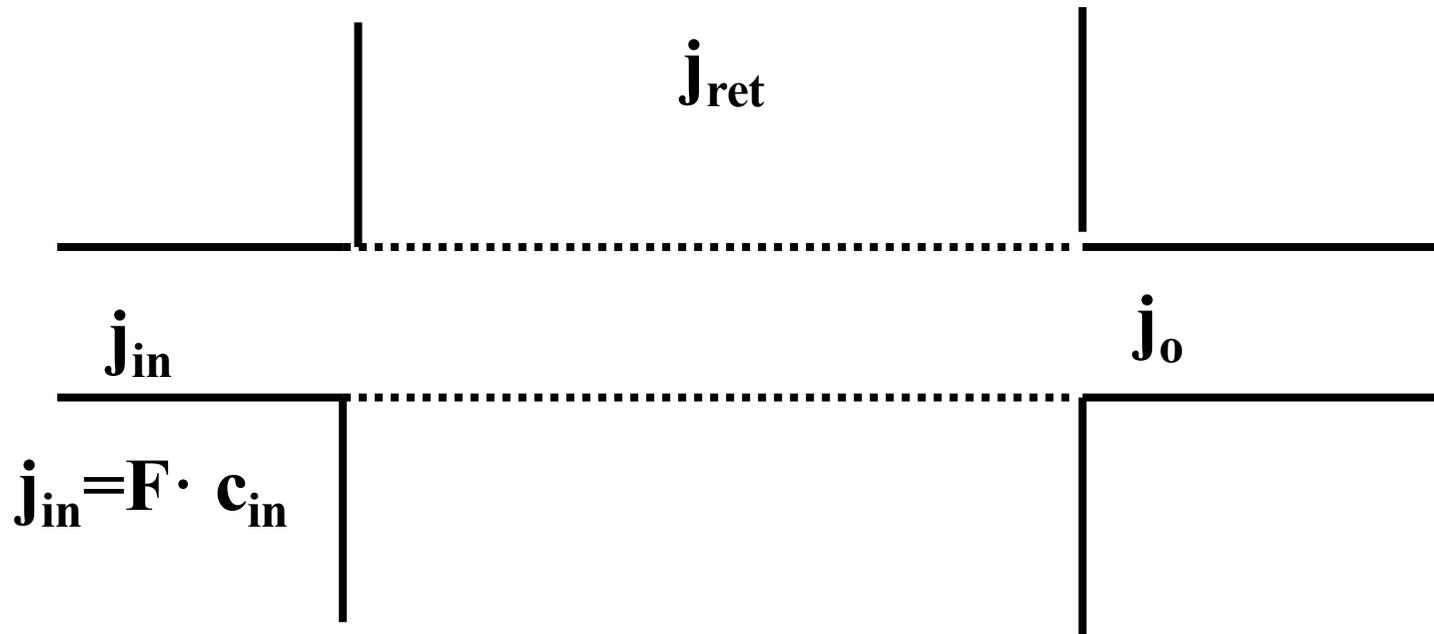


CLEARANCE

[The volume of reference fluid (typically blood) that is cleared of a given tracer per unit time]



CLEARANCE

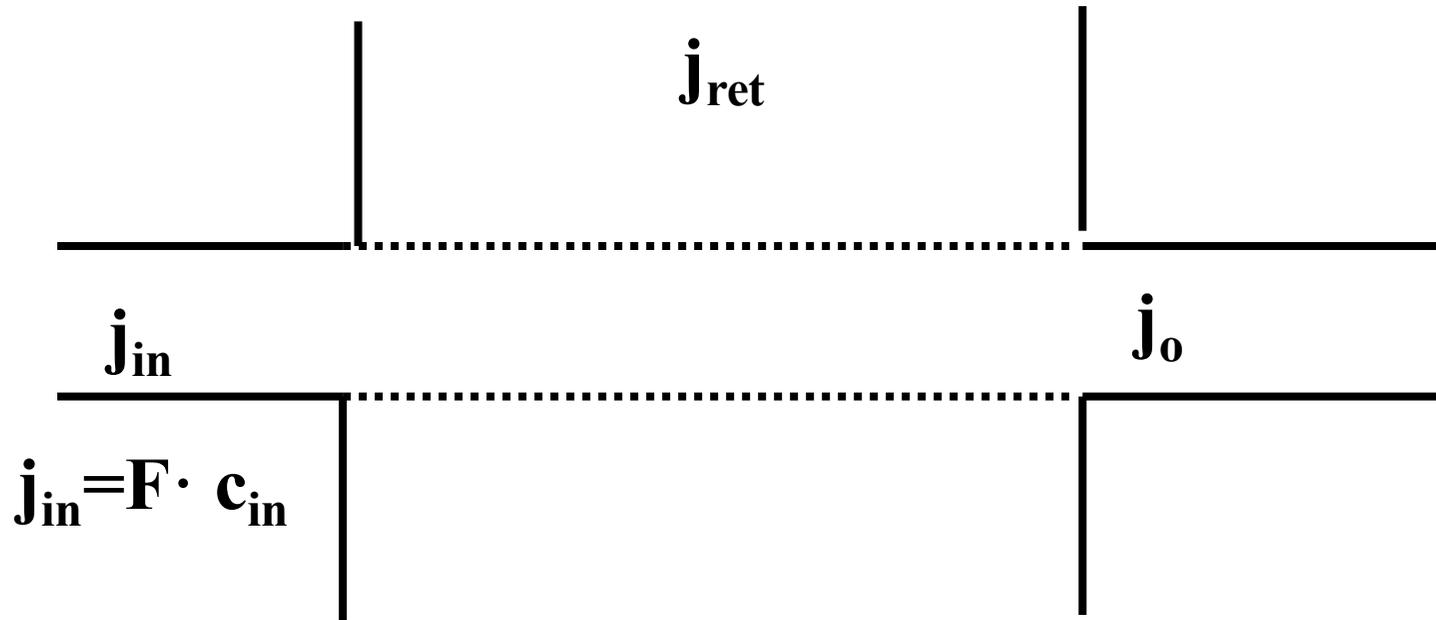


clearance: $Cl = \frac{j_{ret}}{c_{ref}} = \frac{F \cdot c_{in} - F \cdot c_o}{c_{ref}} \quad [Cl] = \text{ml/s}$

Thus clearance is a fictive flow!



CLEARANCE



clearance: $Cl = \frac{j_{ret}}{c_{ref}}$

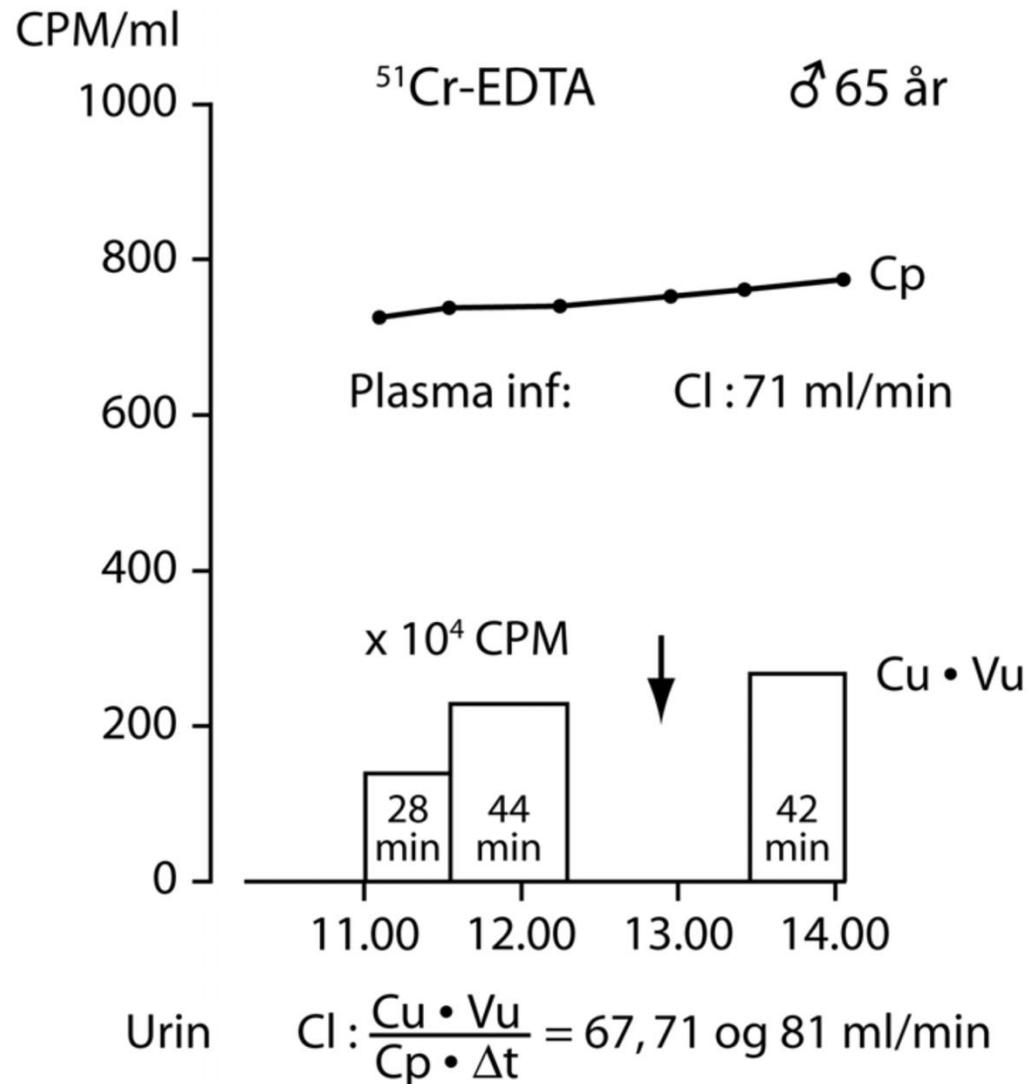
If we choose
 $C_{ref} = C_{in}$

$Cl = F \cdot E$; thus when $E=1$, Clearance = Flow

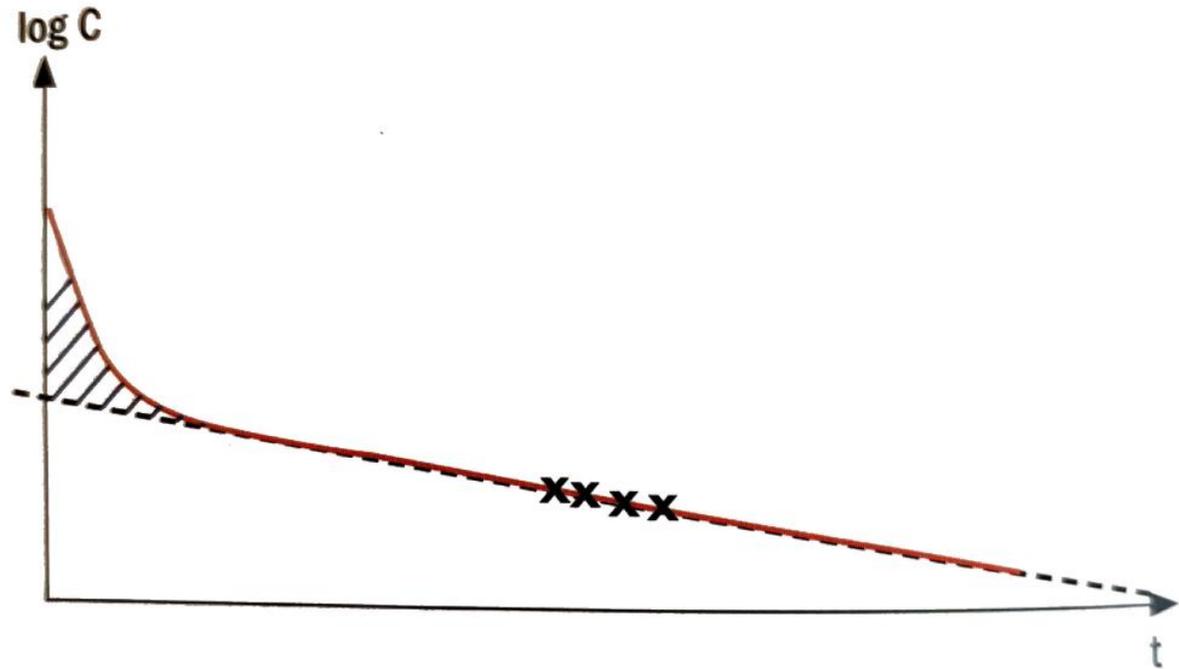


CLEARANCE IS A CLINICAL TERM USED TO DESCRIBE RENAL FUNCTION (GFR)

- $^{51}\text{Cr-EDTA}$, $^{99\text{m}}\text{Tc-DTPA}$, inulin (freely filtered over the glomerulus membrane, is not bound to plasmakolloids, and is not actively secreted or reabsorbed)
- C_{ref} =renal plasma clearance (C_p)
- $Cl = J_{\text{ret}}/C_{\text{ref}} = C_u/C_p$
- $Cl = \text{GFR}$



RENAL CLEARANCE IN THE CLINICAL SETTING

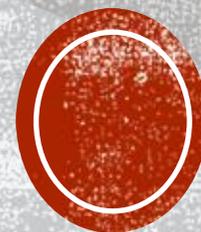


- Plasma concentration as a function of time.
- After a while, the plasma decay curve becomes a monoexponential function (straight line with logarithmic y-axis)
- Note that the area under the full curve is slightly larger than the straight line (correction factor)
- Clearance = Q_0/AUC





BREAK





CRONE-RENKIN & PERMEABILITY

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CRONE (1963) & RENKIN (1959) EQUATION

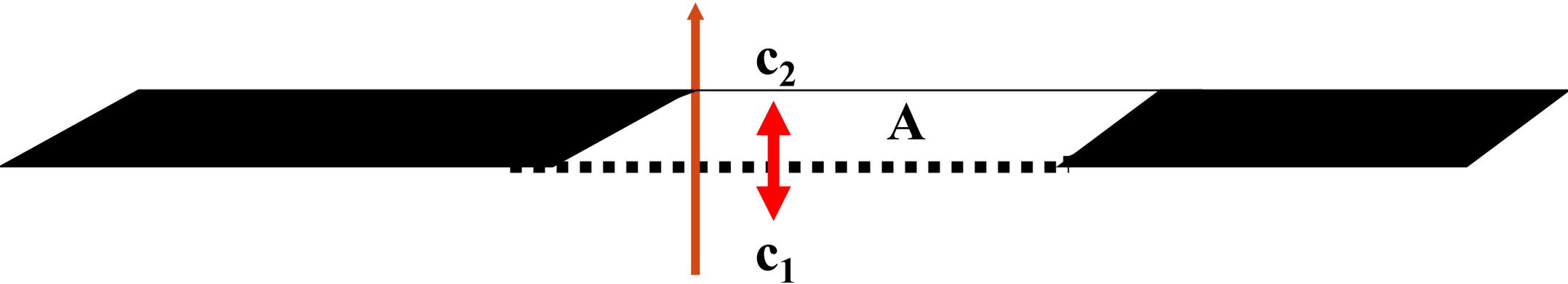
TRANSPORT OVER THE CAPILLARY MEMBRANE



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



TRANSPORT OVER A MEMBRANE (PS DEFINITION)



$$J_{1 \rightarrow 2} = PS(c_1 - c_2) \quad PS = \frac{J_{1 \rightarrow 2}}{c_1 - c_2} \quad \frac{\text{mmol/min}}{\text{mmol/ml}}$$

Thus, a high value of PS means that a small difference in concentration can drive a large flux from capillary to extravascular space.

$$[PS] = \text{ml/min}$$



CRONE (1963) & RENKIN (1959) EQUATION

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

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

$$E = 1 - e^{-\frac{PS}{F}}$$

From earlier:
Cl = F · E

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



ACCUMULATION OF TRACER IN TISSUE CAN BE **FLOW LIMITED OR DIFFUSION LIMITED**

**Freely diffusible: $PS \gg F \rightarrow PS/F$ is large
(flow limited)**

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

$$E \rightarrow 1 \text{ for } PS/F \rightarrow \infty$$

$$CI = F E \rightarrow F$$

Tracer examples?

- 1) Xenon
- 2) Oxygen-15 labeled water



ACCUMULATION OF TRACER IN TISSUE CAN BE FLOW LIMITED OR DIFFUSION LIMITED

Diffusion limited: $PS \ll F \rightarrow PS/F$ small
(intravascular)

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

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

Tracer examples?

- 1) MRI contrast
- 2) FET, Albumin tracers, etc.

$$Cl = F \cdot E = F \cdot PS/F \rightarrow PS$$





FLOW AND CLEARANCE

You have to design an experimental setup to measure flow in an organ:

- Which tracer do we choose?
- Flow-limited (freely diffusible, e.g. Xenon, ^{15}O -marked H_2O)
- The tracer manufacturer reports that $E=0,90$
 - What does this mean?
- Resting flow in the organ is $F=50$ ml/100g/min
 - How can we then calculate PS?
 - Crone & Renkin:
 $E=1-\exp(-PS/F) \rightarrow 0,9=1-\exp(-PS/50) \rightarrow$
 $PS = -\ln(0,1)*50$ ml/100g/min =
115 ml/100g/min

FLOW AND CLEARANCE

Experimental setup: PS is constant, while F and clearance is measured e.g. during stimulation – what can we derive?

F ml/100g/min	PS ml/100g/min	PS/F	E	Cl ml/min/100g
10	115	11,5	1,00	10
25	115	4,6	0,99	24
30	114,9	3,8	0,98	29
50	115	2,3	0,90	45
75	114,8	1,5	0,78	59
100	115	1,2	0,68	68
200	116	0,58	0,44	88
300	114	0,38	0,32	96

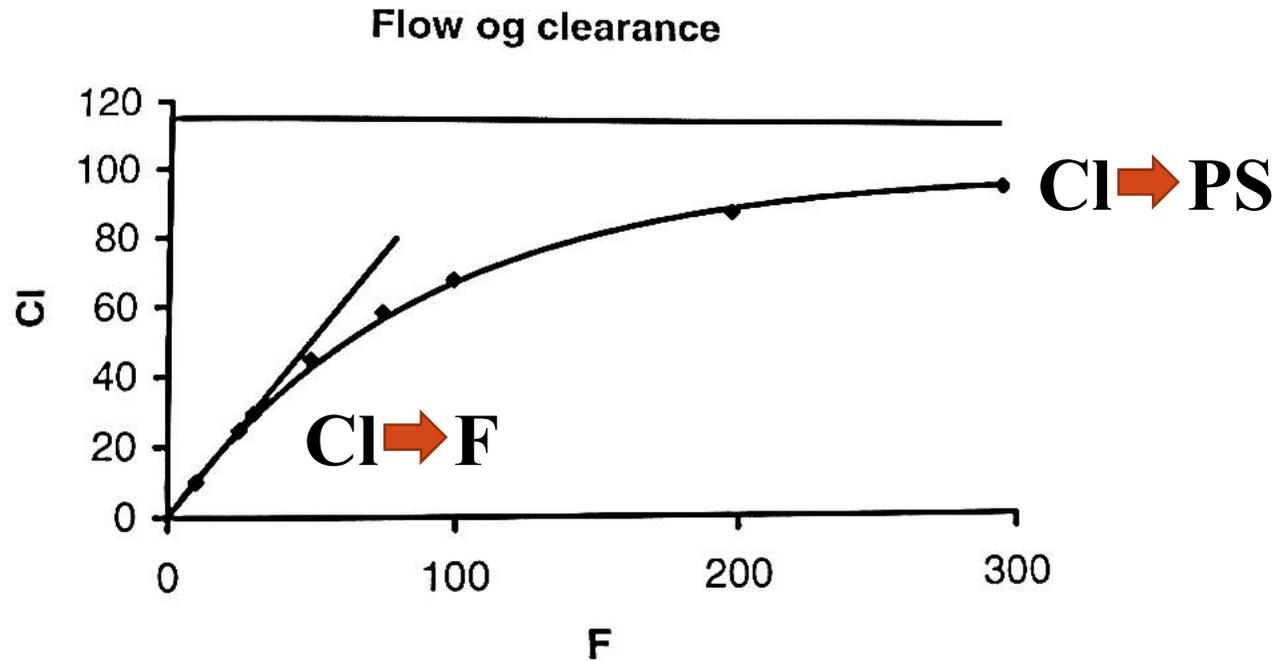
1. Extraction goes down with increasing flow → e.g. E is not constant!

2. Clearance goes up with increasing flow, why is that?

→ For low values of F, Clearance reflects F, while for higher values of F, clearance → PS



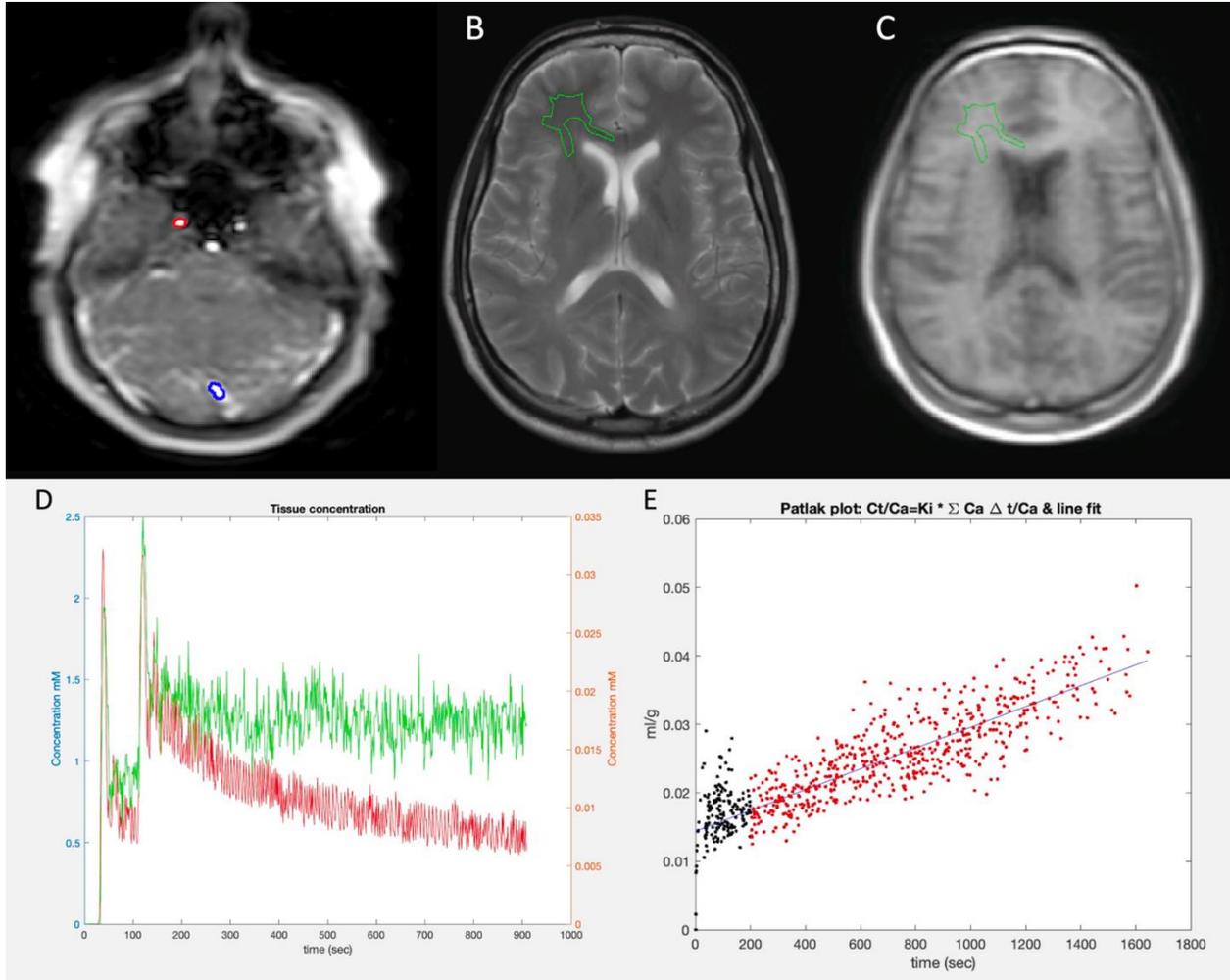
FLOW AND CLEARANCE



Flow or diffusion limited?



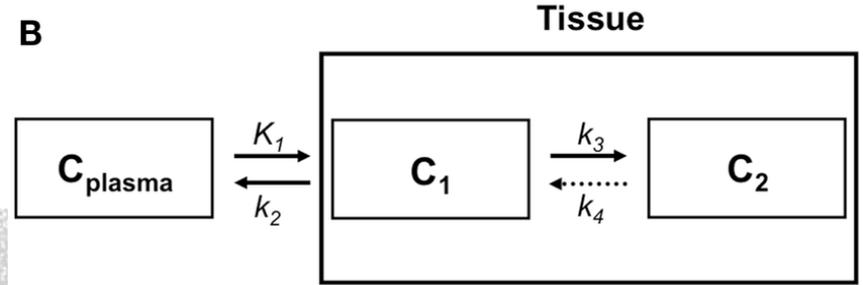
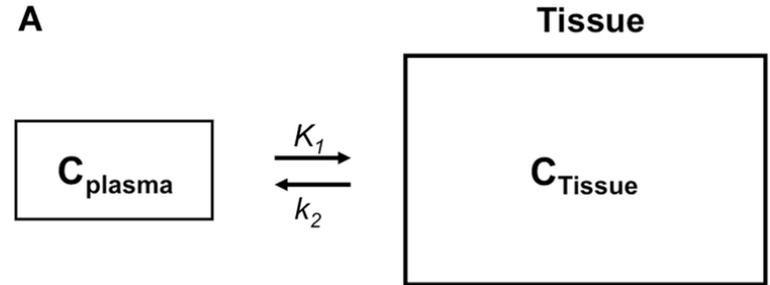
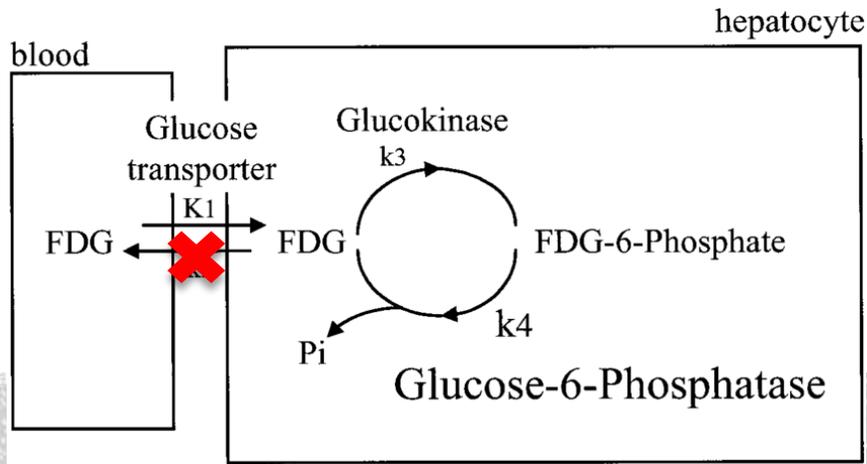
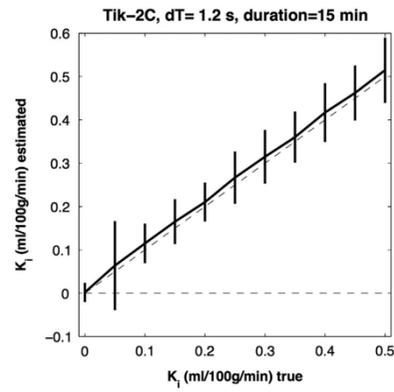
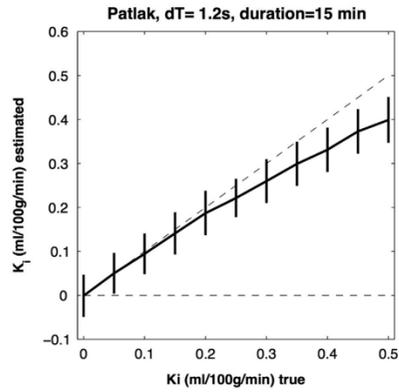
PATLAK MODEL — ESTIMATION OF PERMEABILITY



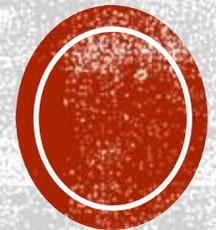
- Originally from FDG-PET
- Model assumes no back diffusion, e.g. no K_2
- Diffusion limited tracer, e.g. gadolinium-DTPA; $K_i \rightarrow PS$
- Slope = K_i (ml/100g/min)
- Intersect = V_b (ml/100g)

$$\frac{C_t(t)}{C_a(t)} = K_i \frac{\int_0^t C_a(\tau) d\tau}{C_a(t)} + V_b$$

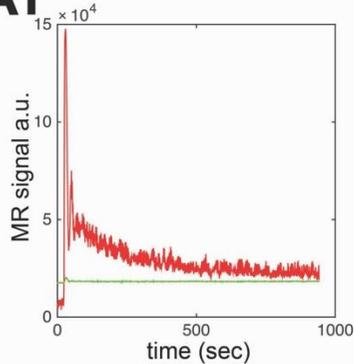




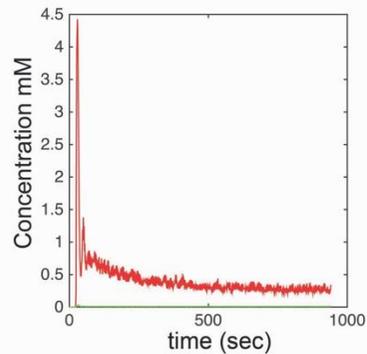
COMPARTMENT MODELLING



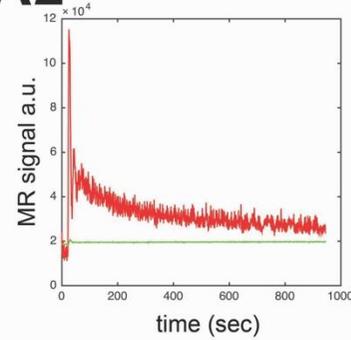
A1 Tissue & Inputfunction



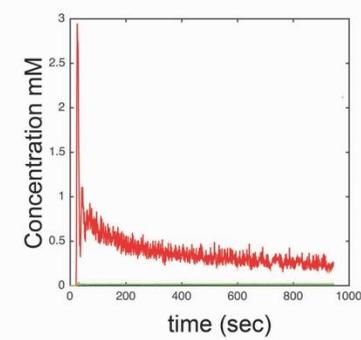
Tissue & Inputfunction



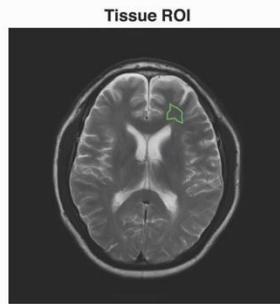
A2 Tissue & Inputfunction



Tissue & Inputfunction

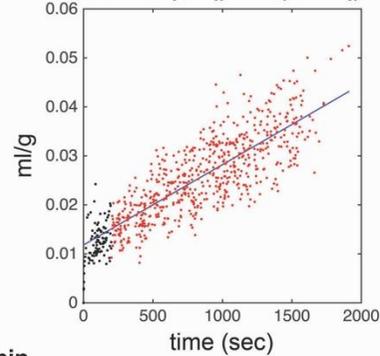


B1

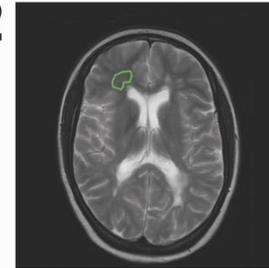


Ki = 0.0984 ml/100g/min
SD of Ki = 0.0029 ml/100g/min
Intercept: λ = 1.18 ml/100g; SD λ = 0.047ml/100g
pixels-tissue = 142

Patlak plot: $C_t/C_a = K_i \times \Sigma C_a dt / C_a$

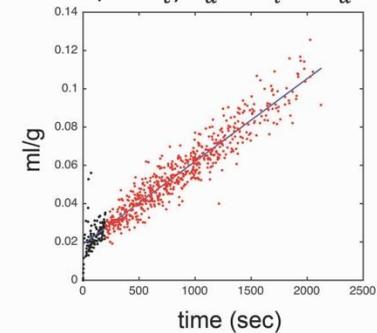


B2

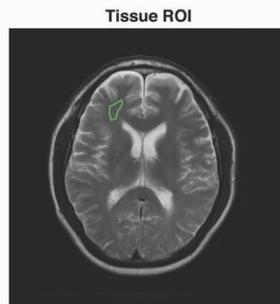


Ki = 0.260 ml/100g/min
SD of Ki = 0.0036 ml/100g/min
Intercept: λ = 1.88 ml/100g; SD λ = 0.058 ml/100g
pixels-tissue = 208

Patlak plot: $C_t/C_a = K_i \times \Sigma C_a dt / C_a$

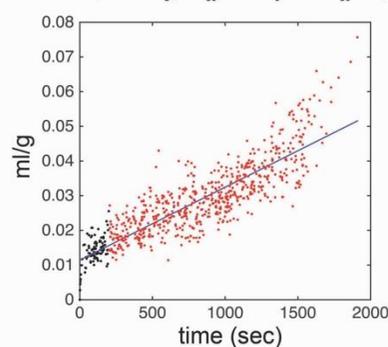


C1

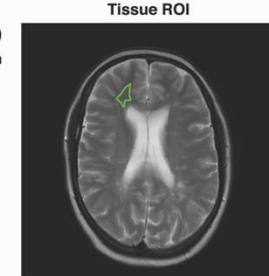


Ki = 0.126 ml/100g/min
SD of Ki = 0.0034 ml/100g/min
Intercept: λ = 1.14 ml/100g; SD λ = 0.055 ml/100g
pixels-tissue = 129

Patlak plot: $C_t/C_a = K_i \times \Sigma C_a dt / C_a$

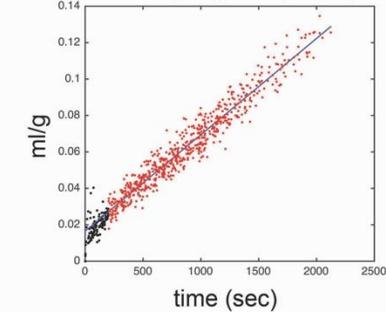


C2



Ki = 0.317 ml/100g/min
SD of Ki = 0.0032 ml/100g/min
Intercept: λ = 1.66 ml/100g; SD λ = 0.052 ml/100g
pixels-tissue = 147

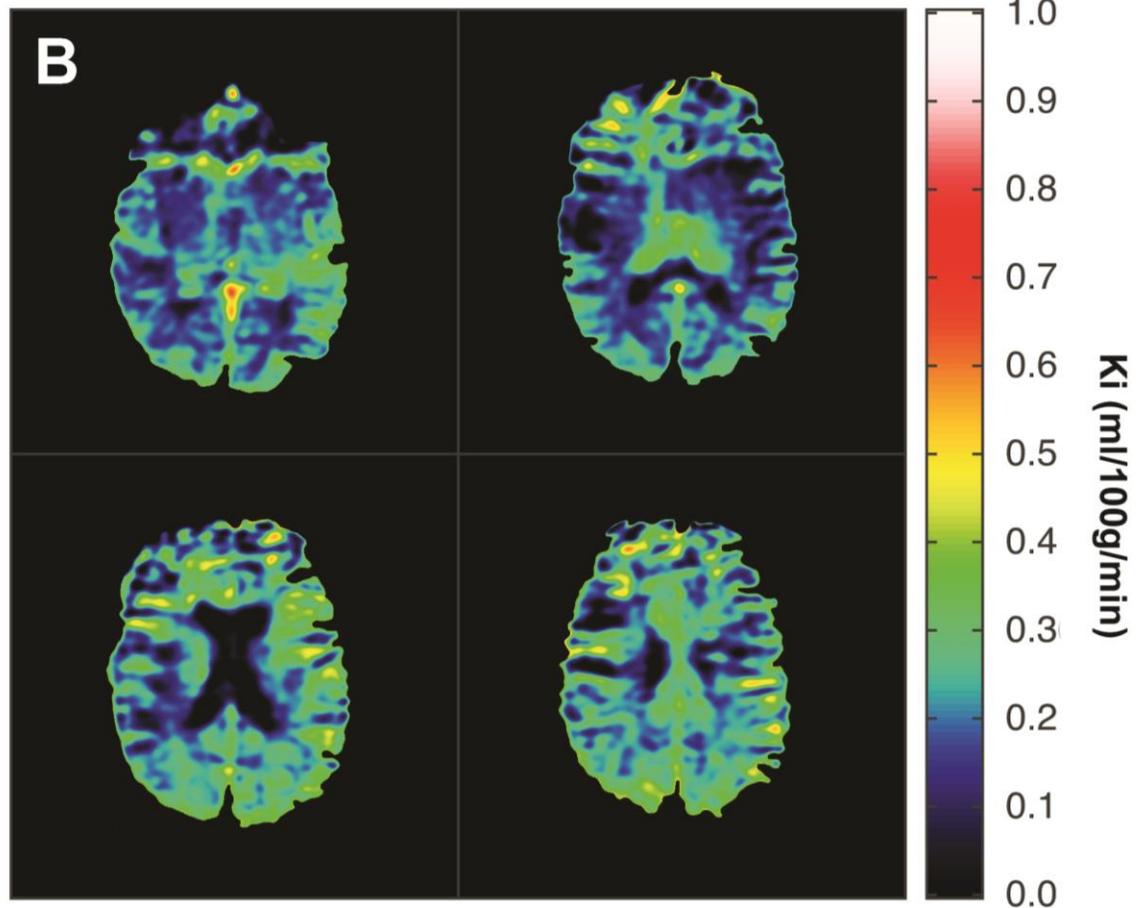
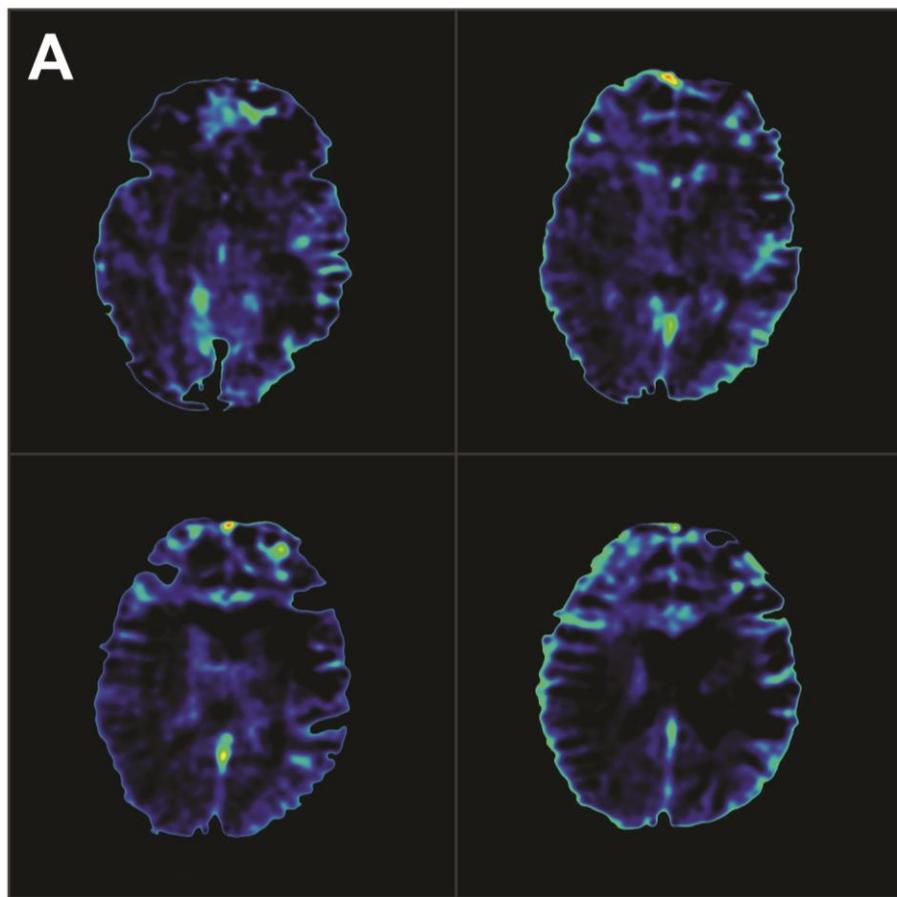
Patlak plot: $C_t/C_a = K_i \times \Sigma C_a dt / C_a$

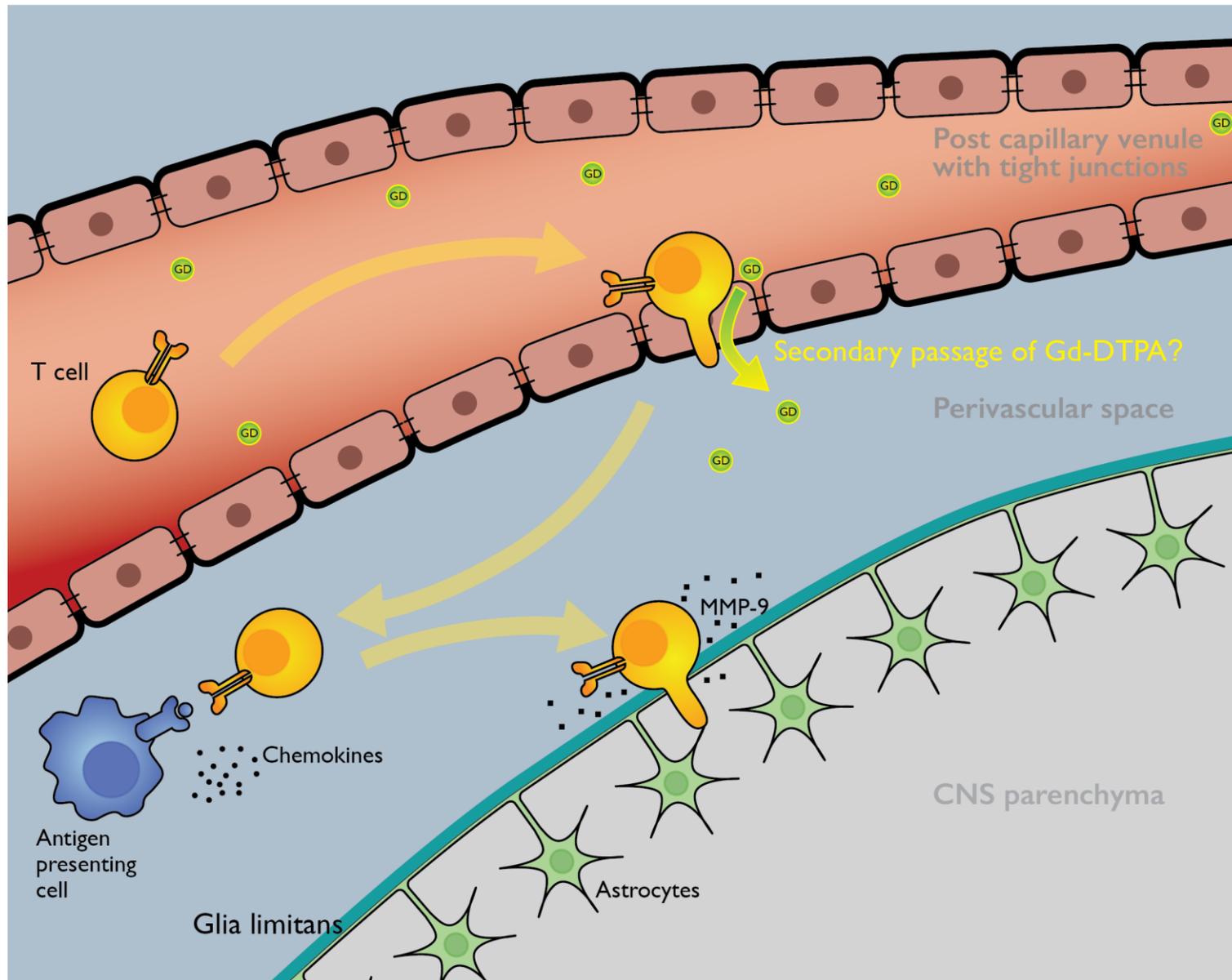


**K_i=slope
(mL/100g/min)**
**V_b=intersect
(mL/min)**

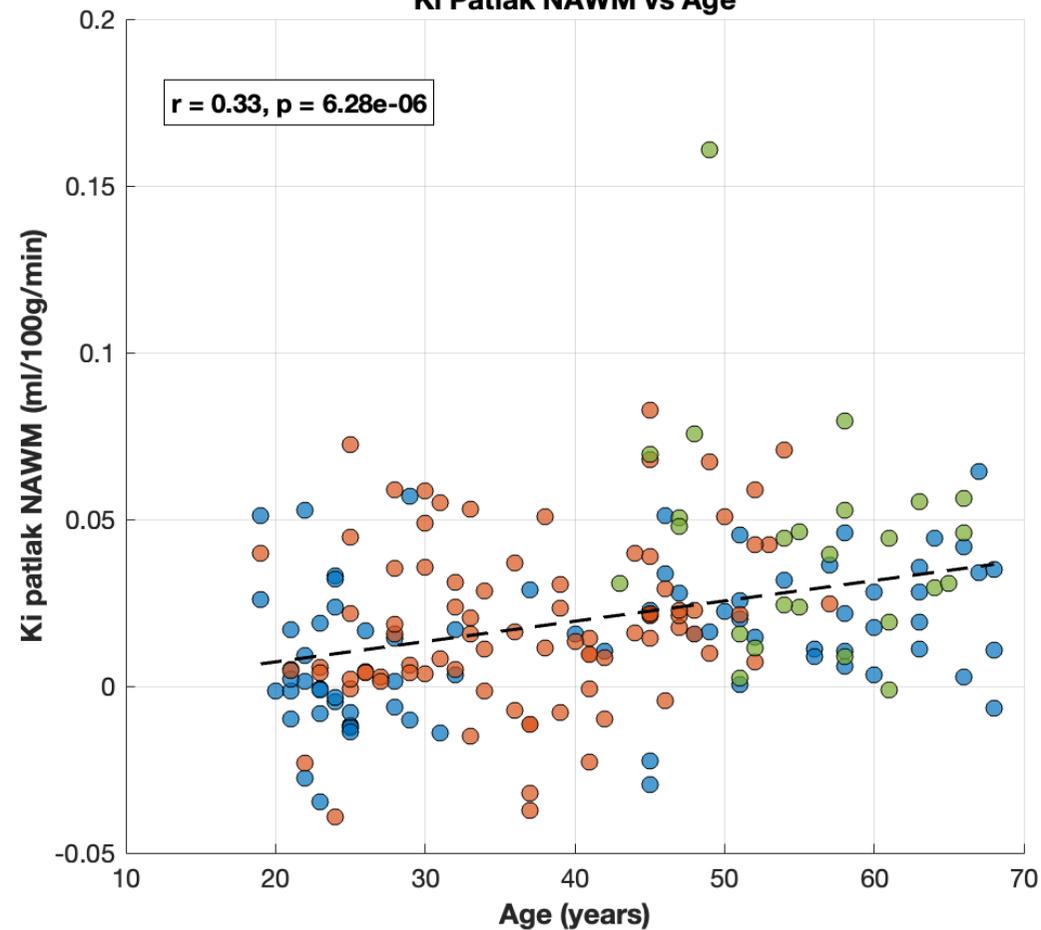


REGIONAL K_i MAPS; OPTIC NEURITIS WITHOUT (A) AND WITH (B) CONVERSION TO MULTIPLE SCLEROSIS

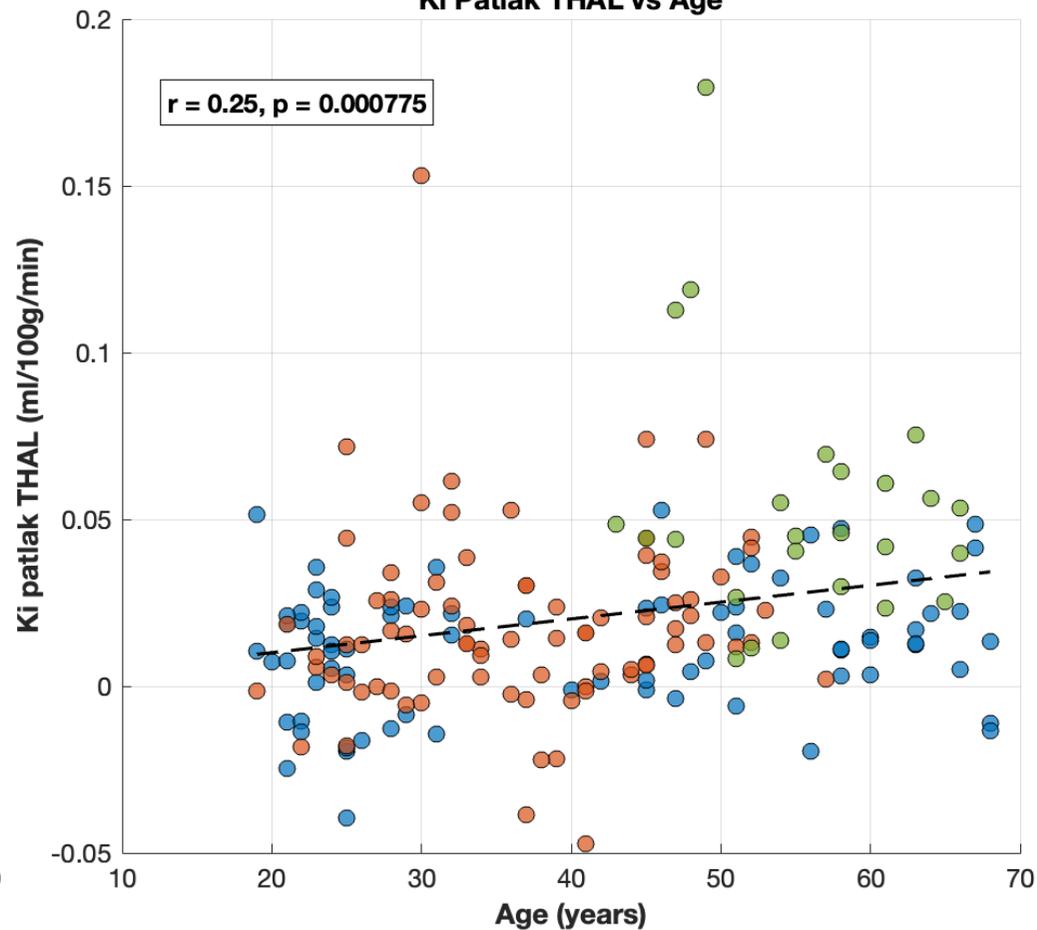




Ki Patlak NAWM vs Age



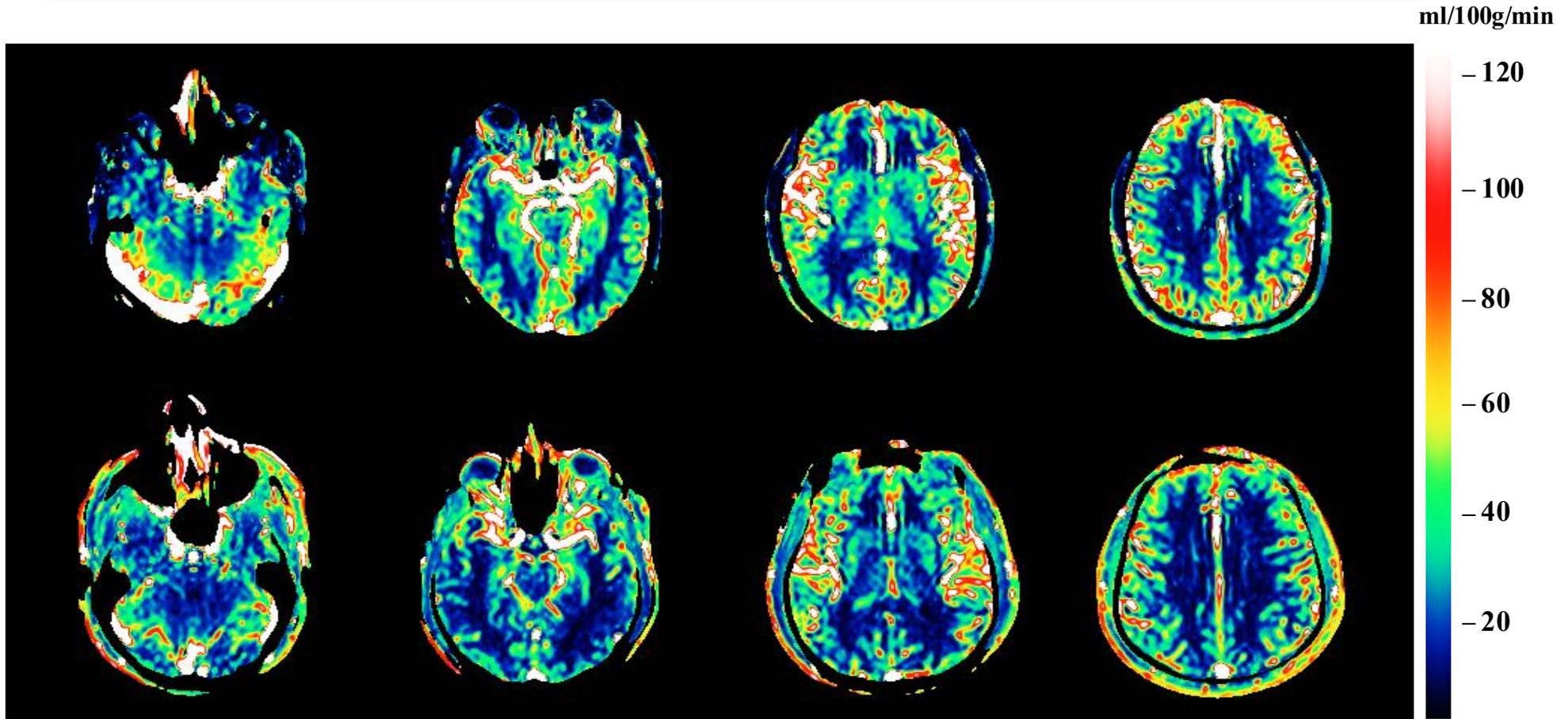
Ki Patlak THAL vs Age



● HC ● RRMS ● PPMS

BBB PERMEABILITY WITH AGE

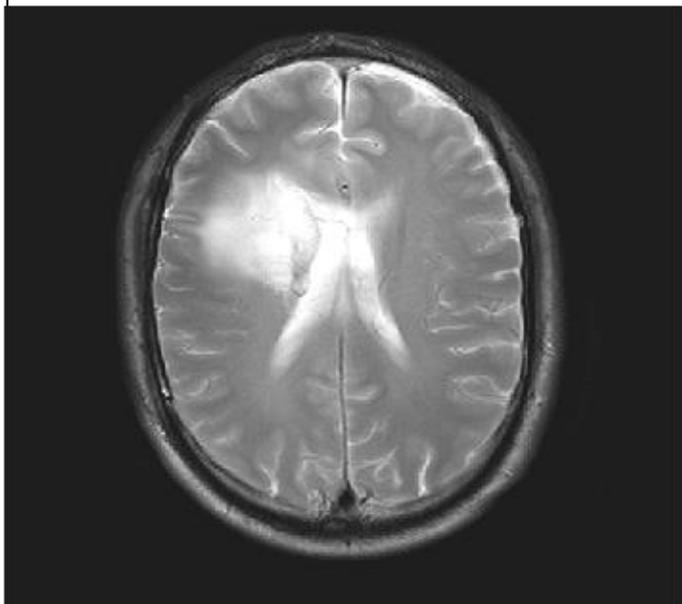
Can CBF be measured with a diffusion limited tracer?



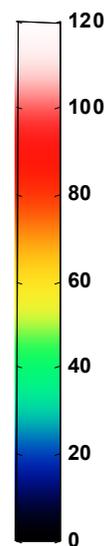
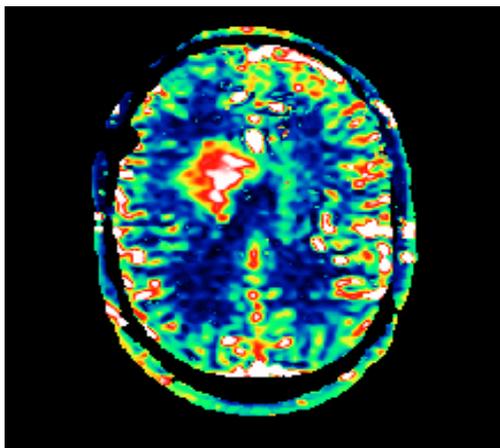
We found perfusion value for ROI's to be **62 ml/100g/min in gray matter** and **21 ml/100g/min in white matter** in 7 patients with acute optic neuritis.



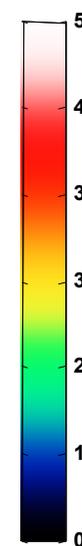
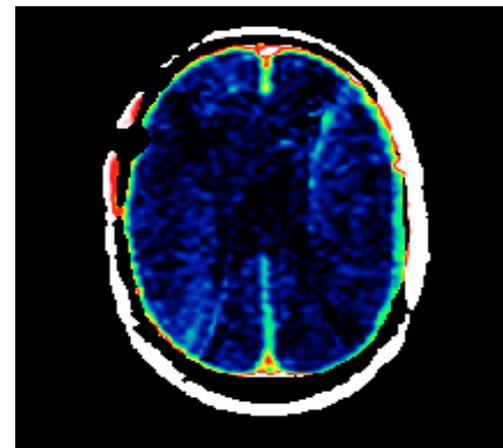
Anatomy, T2w



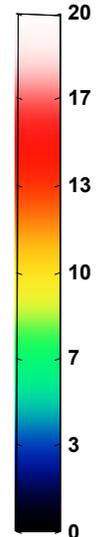
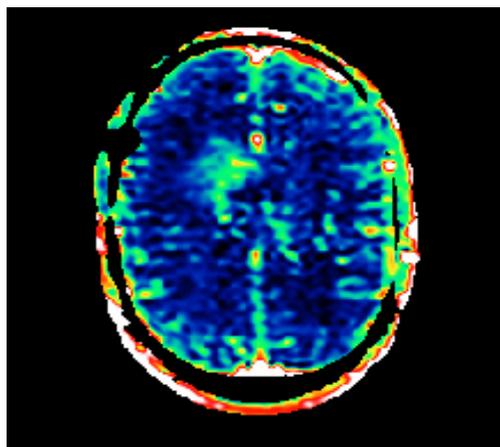
F (ml/100g/min)



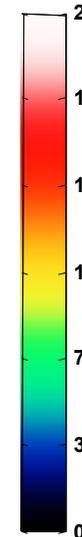
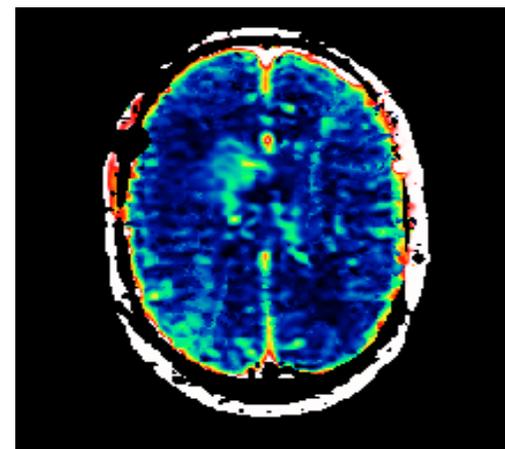
K_i (ml/100g/min)



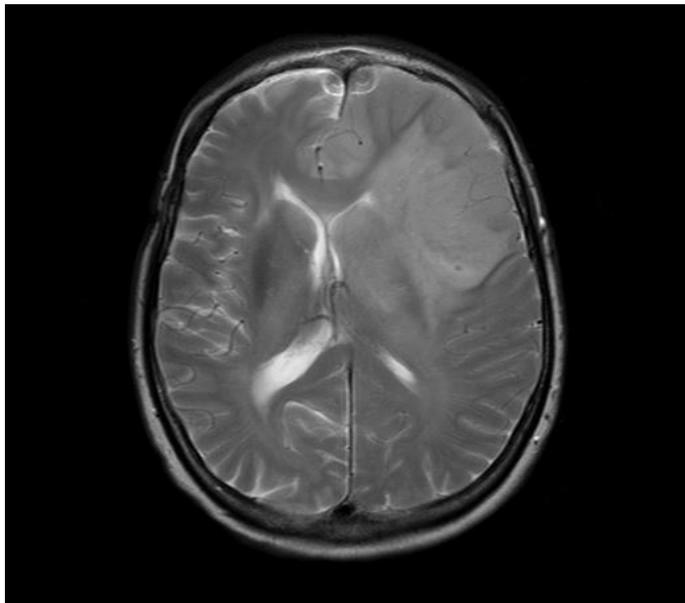
V_b (ml/100g)



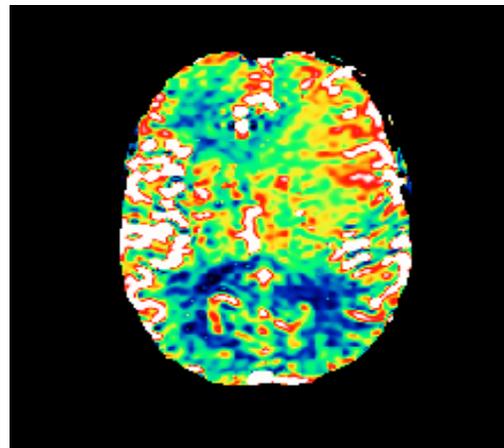
V_d (ml/100g)



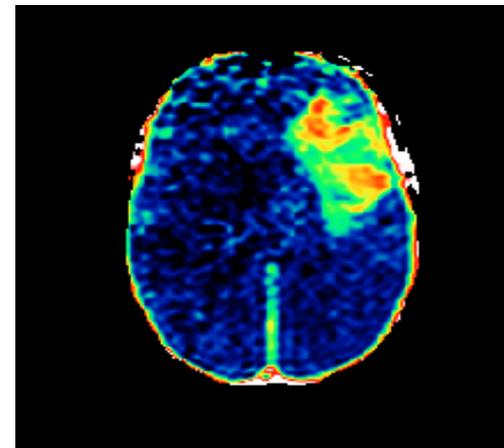
Anatomy, T2w



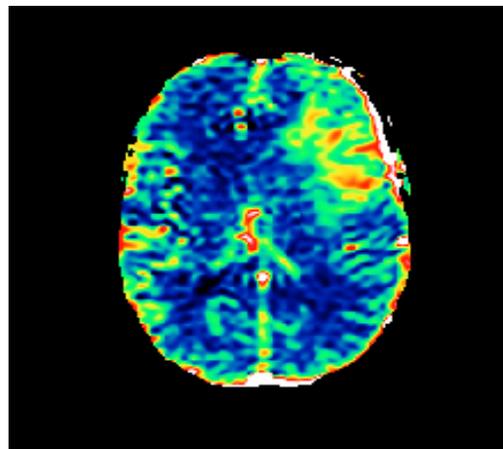
F (ml/100g/min)



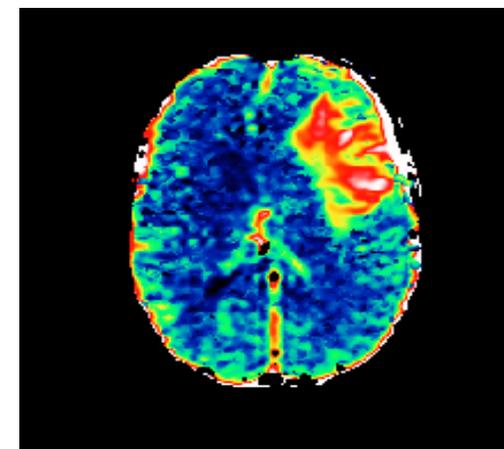
K_i (ml/100g/min)



V_b (ml/100g)



V_d (ml/100g)



SUMMARY

- Flux (mmol/s) = Flow (ml/s) x Concentration (mmol/ml)
- Flow can be estimated by steady infusion or bolus injection, by knowing the injected amount (flux) and measuring the outlet concentration.
- Fick's principle; $F = j_{\text{tissue}} / (c_{\text{in}} - c_{\text{out}})$
- Extraction fraction; The fraction of incoming flux that is taken up or retained in the tissue. $E = (c_{\text{in}} - c_{\text{o}}) / c_{\text{in}}$
- Clearance: The volume of reference tissue cleared per time unit. $Cl = J_{\text{ret}} / c_{\text{ref}}$
If $C_{\text{ref}} = C_{\text{in}}$; $Cl = F * E$
- Crone-Renkin: Transport over the capillary membrane; $c_{\text{o}} = c_{\text{in}} e^{(-PS/F)}$
- PS product= permeability surface area product
- Flow vs. diffusion limited tracers
 - A **flow** limited tracer is good for measuring **flow**
 - A **diffusion** limited tracer is good for measuring diffusion, e.g. **PS product**



THE END

