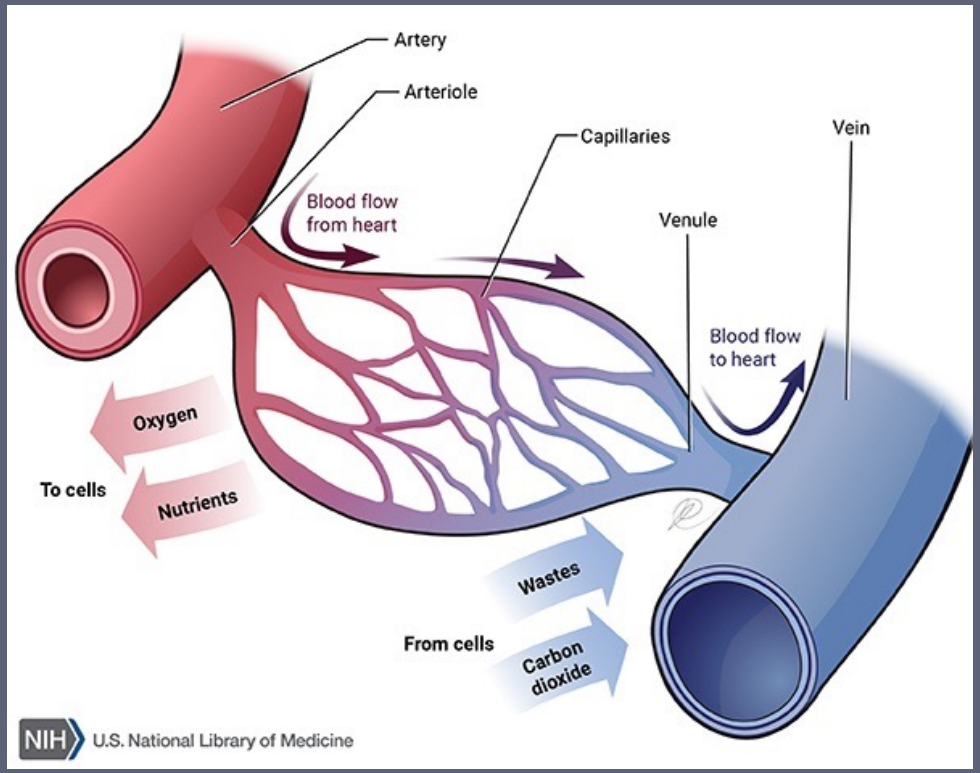
Introduction to tissue perfusion

Quantitative and Functional Imaging
BME 4420/7450
Fall 2022

What is perfusion?

- Volume of blood delivered to a volume of tissue per unit time
- Only delivery to capillaries is included
    - Capillaries are the site of exchange between vascular and interstitial spaces



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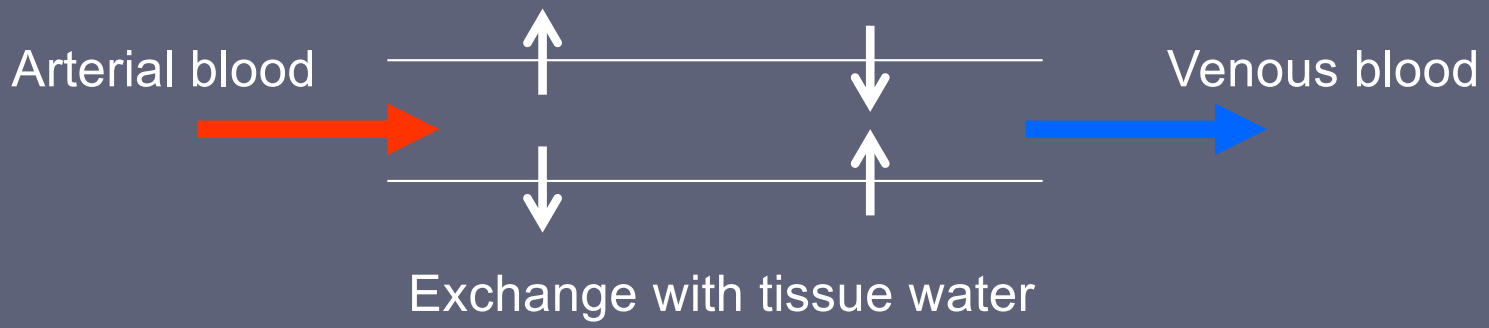

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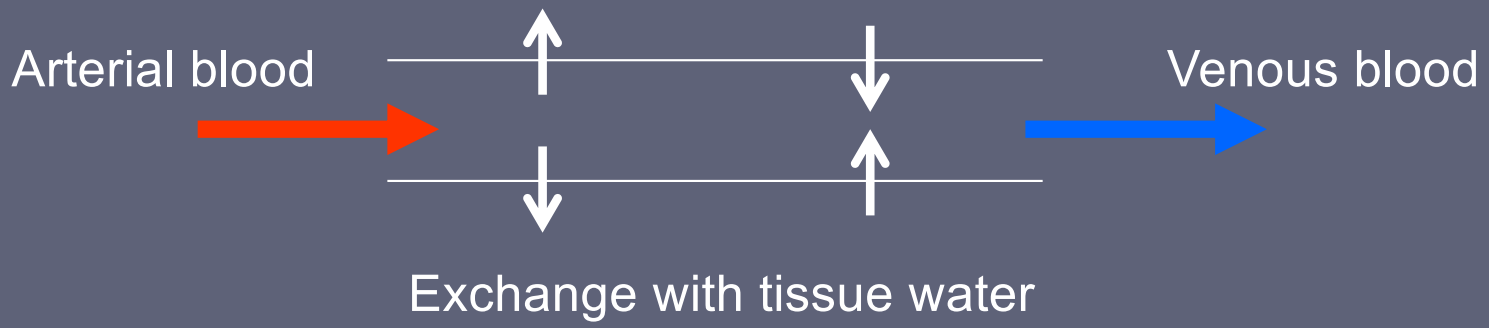


- Perfusion has units of

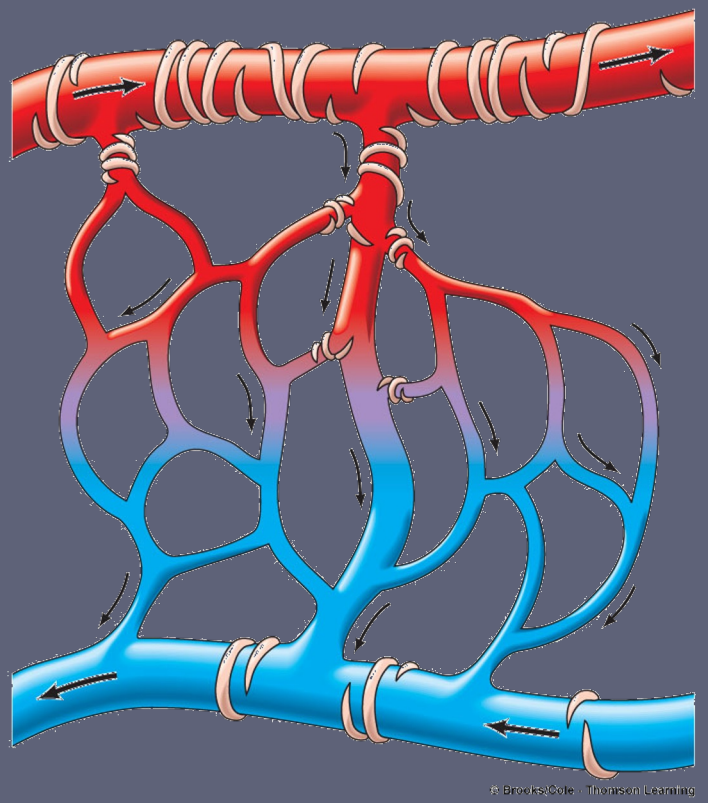
  (ml blood) / [(ml tissue) second] = s^{-1}
- Example: typical value in brain is 0.01 s^{-1}

Why are measurements of perfusion important?

- Perfusion reflects
  - Cardiac output
  - Vascular system conductance
  - Tissue metabolism
- Perfusion can be measured non-invasively with imaging techniques
  - Inject contrast agent
  - Measure signal change in tissue of interest
  - “Time-activity” curve

How is perfusion regulated?

- Increased metabolism triggers release of vasodilators
- Arteriolar smooth muscle relaxes
  - Most of the resistance of vascular system is due to arterioles
  - Perfusion is normally regulated by arteriolar smooth muscle



Sherwood, 2004

Flow depends on resistance

- If ΔP is the arterial-to-venous pressure drop, then flow is

$$f = \frac{\Delta P}{R}$$

where the resistance, R, depends on the radius, r, of the vessel (for laminar flow):

$$R \propto \frac{1}{r^4}$$

- Hence flow varies as

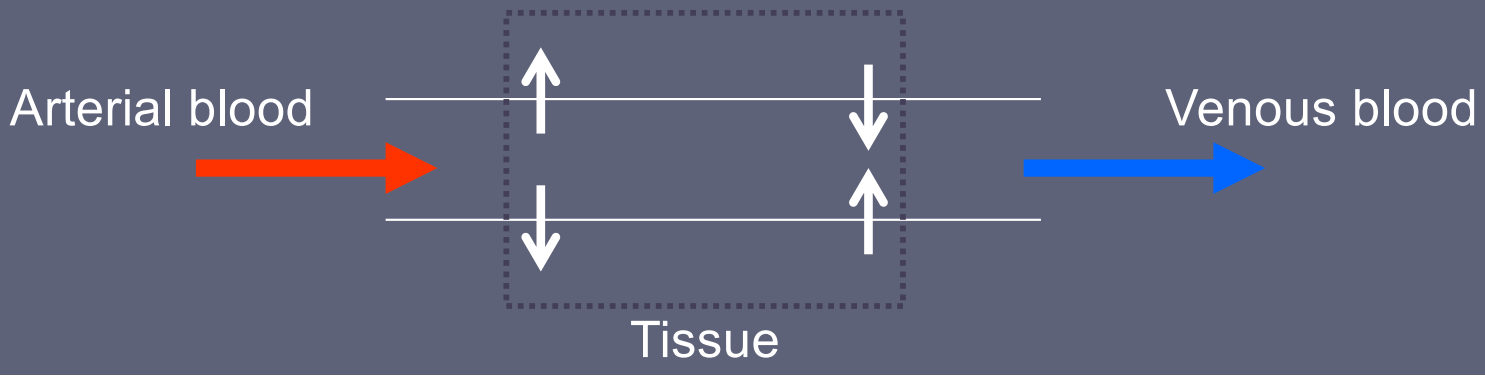
$$f \propto r^4$$

Overview of tracer measurements of perfusion

- What is a tracer?
- How can perfusion be measured using tracers?
- Tissue tracer concentration for three cases
  - Constant arterial input
  - Square function arterial input 
  - General case—arbitrary input function

What is a tracer?

- A substance
  - Introduced in one part of the body
  - Detected in another part
- Transport can be measured quantitatively
- Due to exchange across capillary wall,
  - Tracer leaks into interstitial space
  - Remains in extravascular space for some time
  - Leaks back into capillary
  - Passes into venous circulation



Tissue tracer concentration

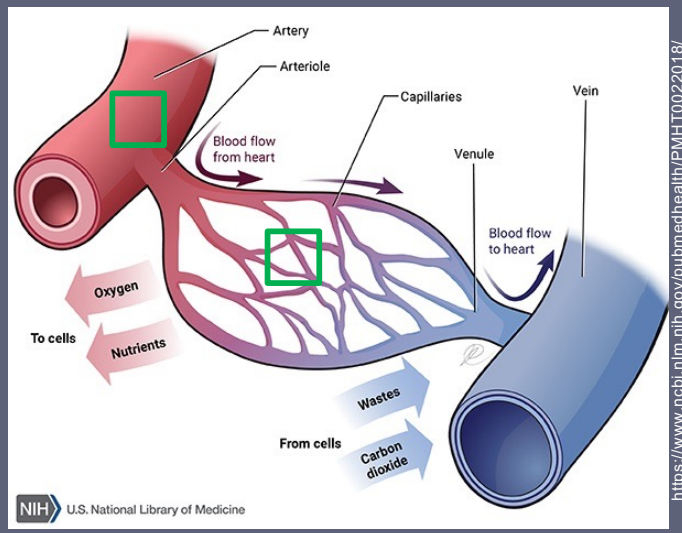
- 'Tissue' compartment includes
  - Intracellular space
  - Interstitial space
  - Capillary space
- Tissue tracer concentration varies with time: $C_T(t)$
- Depends on
  - Arterial tracer concentration, $C_A(t)$
  - Exchange between arterial and tissue "compartments"
- Goal of tracer studies: given $C_A(t)$,
  - Measure $C_T(t)$
  - Determine exchange properties

Case 1: constant arterial input

- For constant arterial input: $C_A(t) = C_A$
- Tissue tracer concentration reaches an equilibrium value:

$$C_T(\infty) = \lambda \cdot C_A$$

The proportionality constant (λ) is called the *partition coefficient*



https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0022018/

The tissue partition coefficient

- Depends on tracer properties
- Examples
  1. An intravascular agent (e.g., Gd-DTPA in the brain)

$$\lambda = \frac{C_T(\infty)}{C_A}$$

$$= \text{capillary volume fraction}$$

$$= \text{cerebral blood volume (CBV) in the brain}$$

CBV in the brain is typically ~4%

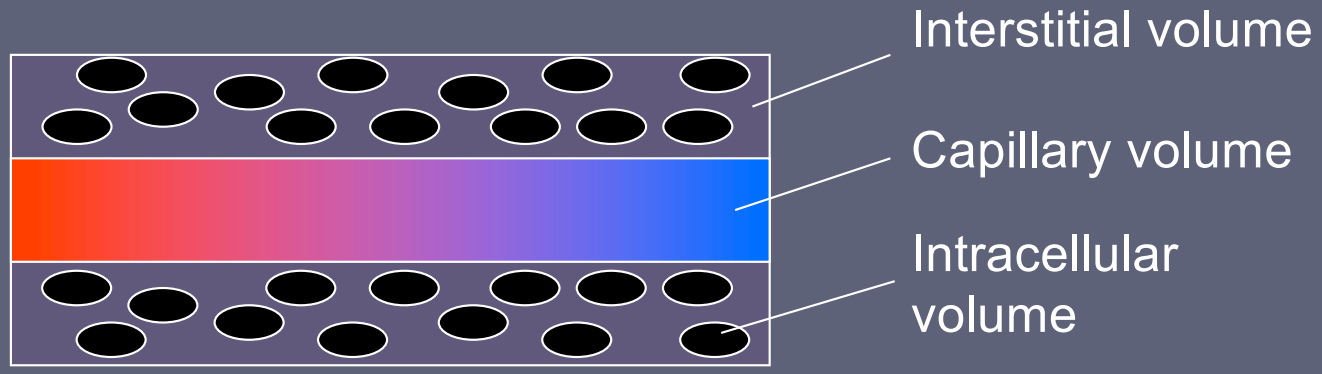
Examples

2. An agent that diffuses into the interstitial, but not intracellular space

$$\lambda = \frac{\text{interstitial + capillary volume}}{\text{interstitial + capillary + intracellular volume}}$$

$$\cong 0.2 \quad \text{(in brain)}$$

For a diffusible tracer, λ is also called the 'volume of distribution'



Examples

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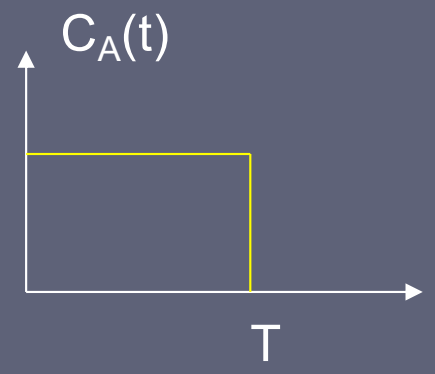
4. An agent with high extravascular affinity (e.g., a lipophilic tracer)

$$\lambda > 1$$

Case 2: arterial input is a square function

- Suppose

$$C_A(t) = \begin{cases} 0, & t < 0 \\ C_A, & 0 \le t < T \\ 0, & t \ge T \end{cases}$$



where *T* is long enough that the tissue reaches equilibrium with the arteries.

Short time solution

- Assume time *t* is so short that no tracer has *left* the tissue
- Number of moles of tracer entering a tissue volume V_T in time Δt is

$$N_T = C_A \cdot f \cdot V_T \cdot \Delta t$$

where *f* is the flow (perfusion) rate.

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- The initial slope of the tissue "time-activity" curve, $C_T(t)$, depends only on arterial concentration and flow.

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- At this point,

$$C_T = \lambda \cdot C_A \qquad \text{(steady state)}$$

independent of flow.

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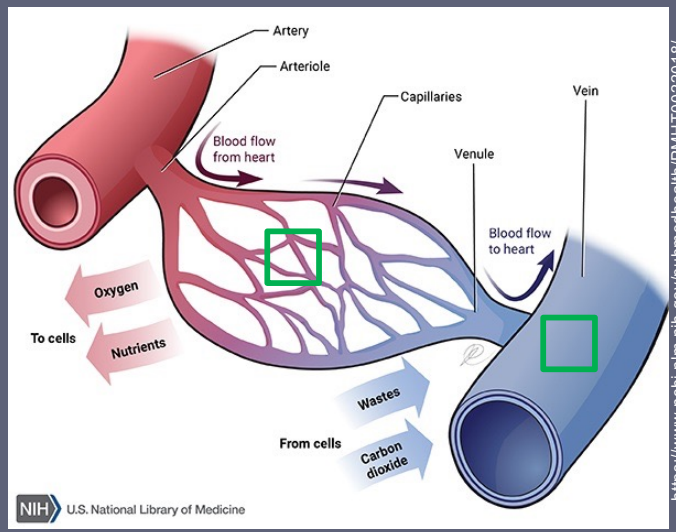
  - Depends on details of tracer exchange between compartments
- To make predictions, use a simple model…

The ‘fast exchange’ model

- Venous and tissue compartments exchange rapidly
- The two compartments are always in equilibrium
  - Both are changing with time
  - In equilibrium: $C_T = \lambda C_V$



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Solving for C_T,

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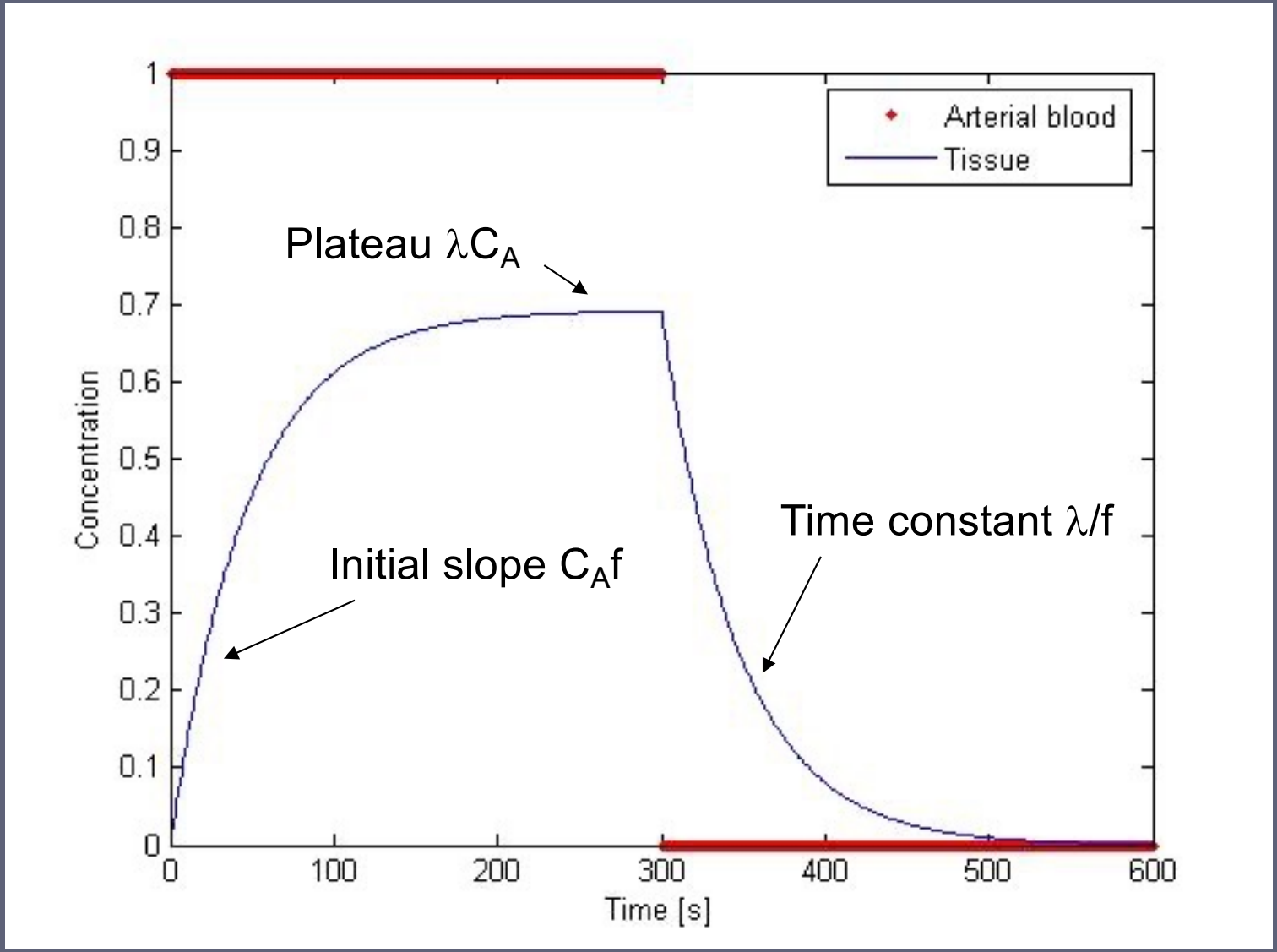
where

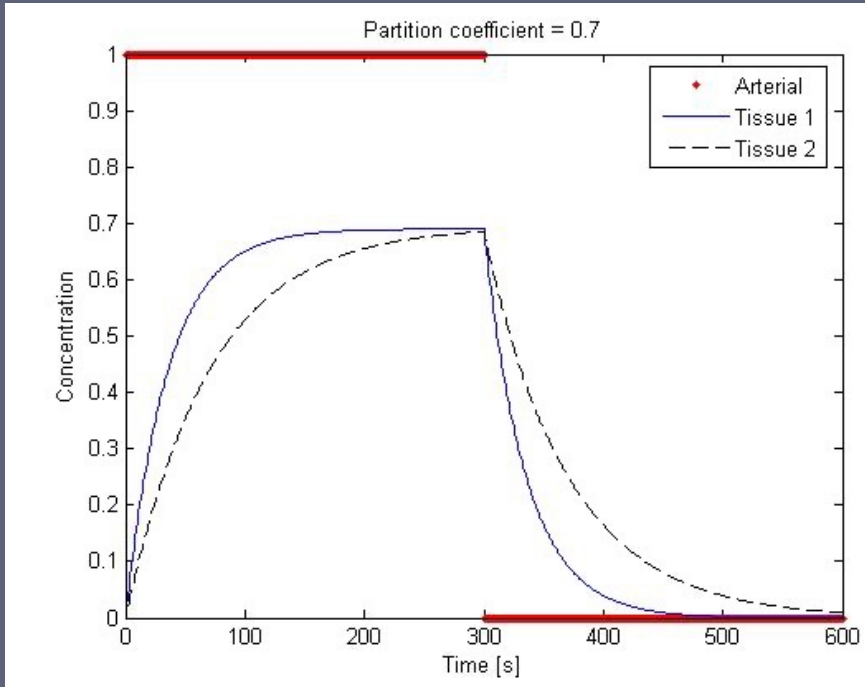
$$\tau_{FE} = \frac{\lambda}{f}$$

=> Clearance depends only on the ratio of λ to *f*

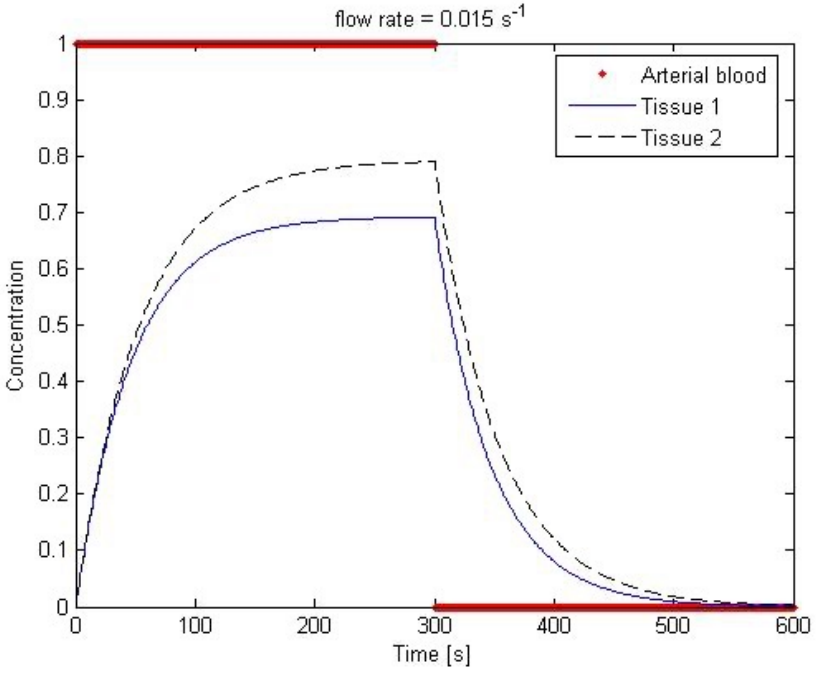
Time/activity curve



In-class exercise: which tissue has greater flow? Which has greater λ?



Same λ, different flow



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Implications of time constants

1. Intravascular tracer in the brain

$$\tau_{FE} = \frac{\lambda}{f} = \frac{CBV}{f} \approx \frac{0.04}{0.01\ \mathrm{s}^{-1}}$$
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2. Freely diffusible tracer

$$\tau_{FE} = \frac{\lambda}{f} \approx \frac{1}{0.01\ \mathrm{s}^{-1}}$$
$$\approx 100\ \mathrm{s}$$

$\Rightarrow$Long ramp—good for flow measurements

Generalize the model

- In reality, $C_A(t)$ is not a square function
- Define a "residue" function, r(t-t')
  - Probability that a tracer molecule that entered the tissue at time t' is still there at time t.
  - Assume no physiological changes during measurement, so residue function depends only on the time difference, t-t'.

- The number of moles of the agent delivered between t’ and t’+dt’ is

$$N_T = C_A(t') \cdot f \cdot V_T \cdot dt'$$

- The number of moles of the agent delivered between t' and t'+dt' is

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The fraction of these still in the tissue at time t is r(t-t').

- The net concentration at time t is the sum of the contributions at all previous times:

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$$= \int_{-\infty}^{\infty} f \cdot C_A(t') \cdot r(t-t')\,dt' \qquad \text{since } r(t-t') = 0 \text{ for } t' > t$$

$$= f \cdot C_A(t) * r(t)$$

=>Tissue concentration depends on the convolution of the $C_A(t)$ with the residue function.

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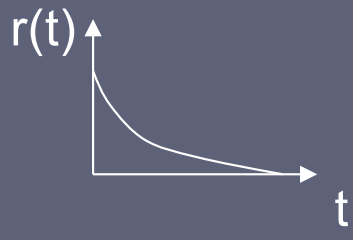
- r(t) cannot have positive slope
  - Probability that a molecule is still present cannot increase with time.



Transit time distribution function, h(t)

- The fraction of tracer molecules entering the tissue voxel at t=0 that exits between time t and t+dt is h(t)dt.
  - Also equals the change in *r(t)* over that interval

$$h(t) \cdot dt = -dr$$

$$\frac{dr}{dt} = -h(t)$$

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- The mean transit time (mean time molecules spend in the tissue) is

$$\tau_{MT} = \int_0^\infty t\cdot h(t)\cdot dt = -\int_0^\infty t\cdot\frac{dr}{dt}\cdot dt = -t\cdot r\Big|_0^\infty + \int_0^\infty r(t)\cdot dt$$

$$= \int_0^\infty r(t)\cdot dt$$

=> Integral of residue function is mean transit time

The Central Volume Principle

- Suppose that $C_A(t)$ is
  - Equal to zero for t<0
  - Equal to C_A from t=0 up to some large time

$$C_T(t \to \infty) = f \cdot \int_0^\infty C_A(t') \cdot r(t - t') \cdot dt' = f \cdot C_A \cdot \int_0^\infty r(t - t') \cdot dt'$$

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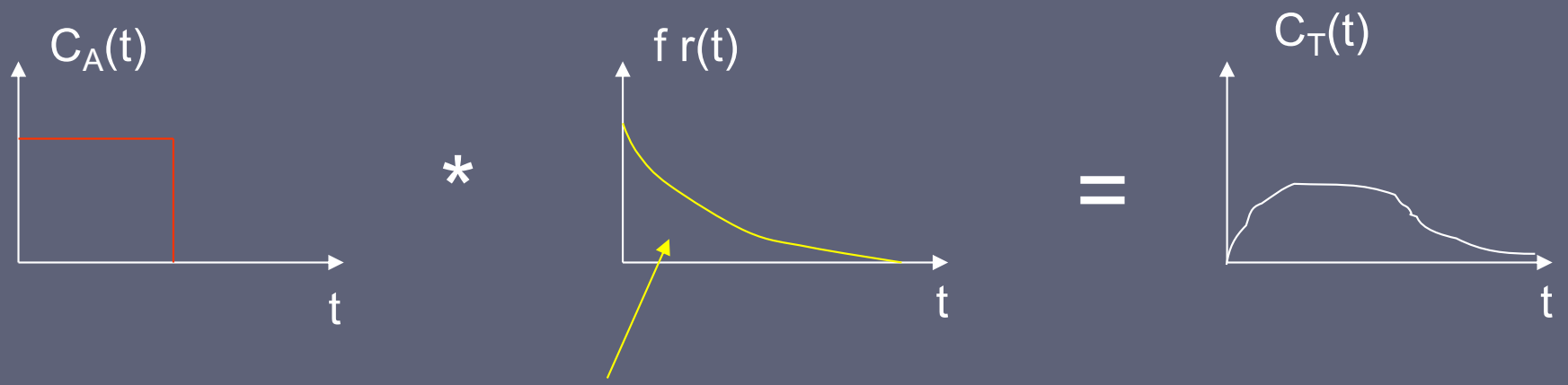
Solving for the mean transit time,

$$\lambda = f \cdot \tau_{MT}$$

$$\tau_{MT} = \frac{\lambda}{f}$$ => The integral of *r(t)* is λ / *f*.

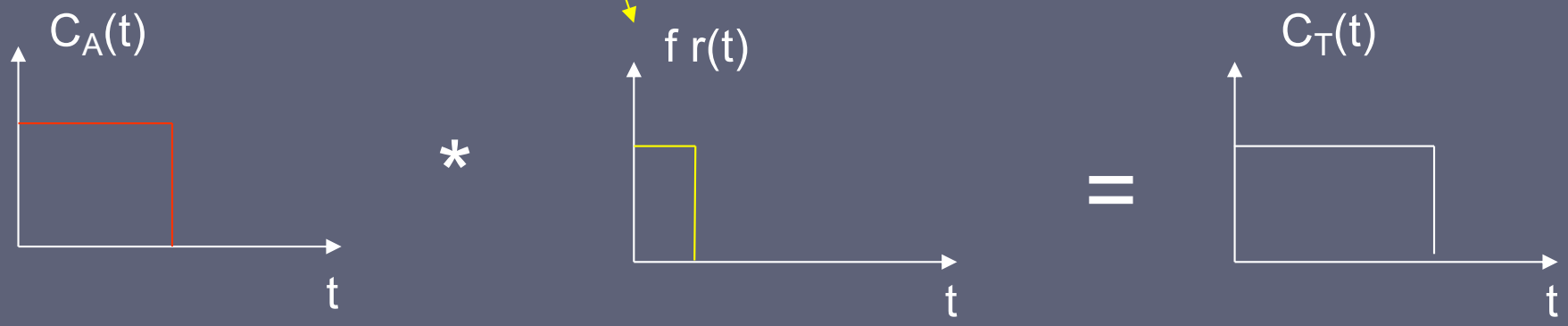
Examples

Fast exchange:



Area under the curve is λ

Plug flow:



Summary

- Perfusion tells us a lot about the state of a tissue
- We can measure perfusion, *f*, in a dynamic contrast imaging study
- The change in image intensity is proportional to the concentration of tracer in the tissue
- The tissue time-activity curve is given by

$$C_T(t) = f \cdot \left[C_A(t) * r(t) \right]$$

- The mean transit time of the agent is

$$\tau_{MT} = \frac{\lambda}{f}$$

Next week

- Dynamic contrast studies in practice
- Project 5: Stroke detection with dynamic contrast enhancement

References

- R.B. Buxton, Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques (Cambridge Univ., 2002).
- L. Sherwood, Human Physiology: From Cells to Systems, 5th ed. (Brooks Cole, 2004).