



Lecture 5

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Todays Aims...

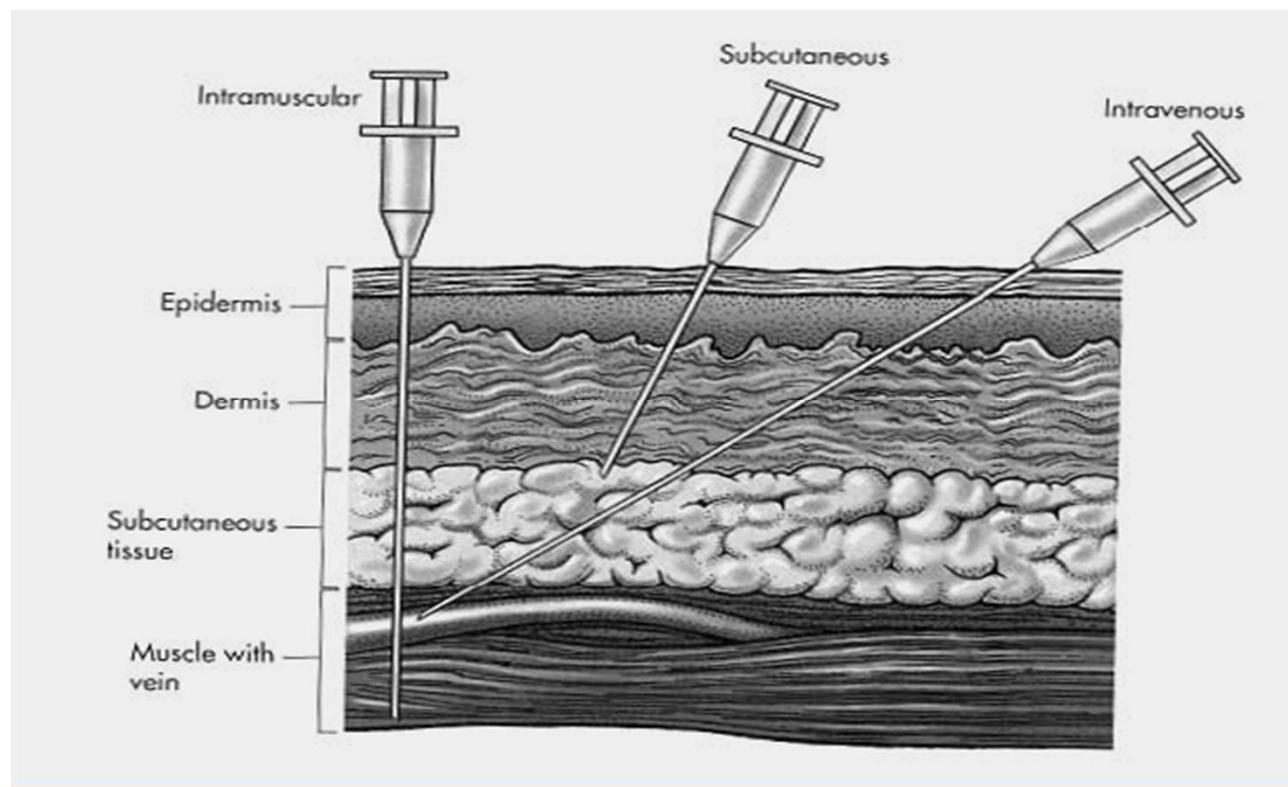


Drug delivery routes cont



Drug concentration models

Parenteral route:

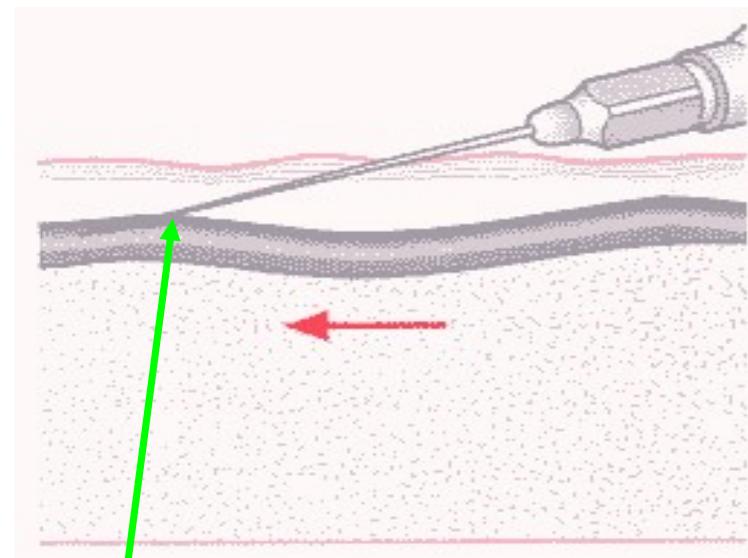


Parenteral route – Intravascular (IV/IA)

- placing a drug directly into blood stream.
- May be -intravenous (into a vein) or - intraarterial (into an artery).
- This route is of prime importance in emergency.
- this is the only route for giving large volume of drugs e.g. blood transfusion.
- However, there are certain disadvantages of this procedure.
 - Once the drug is injected nothing can be done to prevent its action.
 - I/V injection requires technical skill to minimize the risk of leakage of irritant solution into the surrounding tissues.
 - Air embolism may cause serious problems.



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Intravenous Administration

Parenteral route – Intravascular (IV)

ADVANTAGES

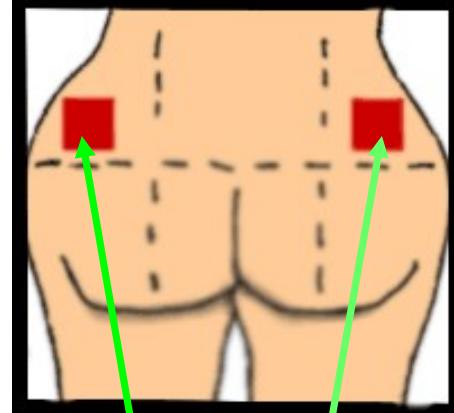
- 1- precise, accurate and immediate onset of action
- 2 - 100% bioavailability.

DISADVANTAGES

- 1- risk of embolism.
- 2- high concentrations attained rapidly leading to greater risk of adverse effects.
- 3- need a trained professional for administration

Parenteral route - Intramuscular

- Into skeletal muscle
- In humans, the best site is deltoid muscle in the shoulder or the gluteus muscle in the buttocks.
- is suitable for the irritating substances that cannot be given by subcutaneous route.
- speed of absorption from site of injection is dependent on the vehicle used
 - absorption is quick from aqueous solutions
 - slow from oily preparations.
- Absorption is complete, predictable and faster than subcutaneous route.



Intramuscular injection in deltoid and gluteal muscles

Parenteral route - Intramuscular

ADVANTAGES

1 - suitable for injection of drug in aqueous solution (rapid action) and drug in suspension or emulsion (sustained release).

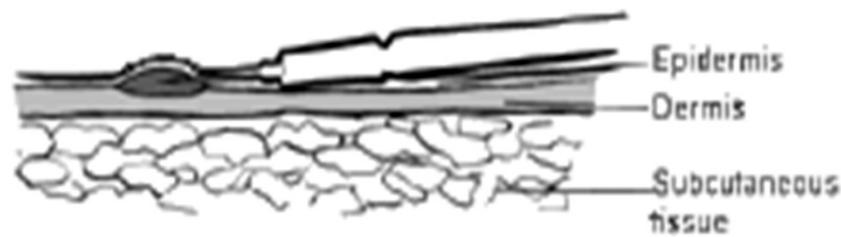
DISADVANTAGES

- 1- Pain at injection sites for certain drugs.
- 2 - Need a trained professional for administration

Parenteral route – Subcutaneous

C- Subcutaneous

- under the skin
- e.g. insulin.
- Includes embedded pellets



Parenteral route – Subcutaneous

ADVANTAGES

Good for skin infections

Safer than IV and IM

Slower than IM and IV

Easier for people to self administer

Can do depot injections

DISADVANTAGES

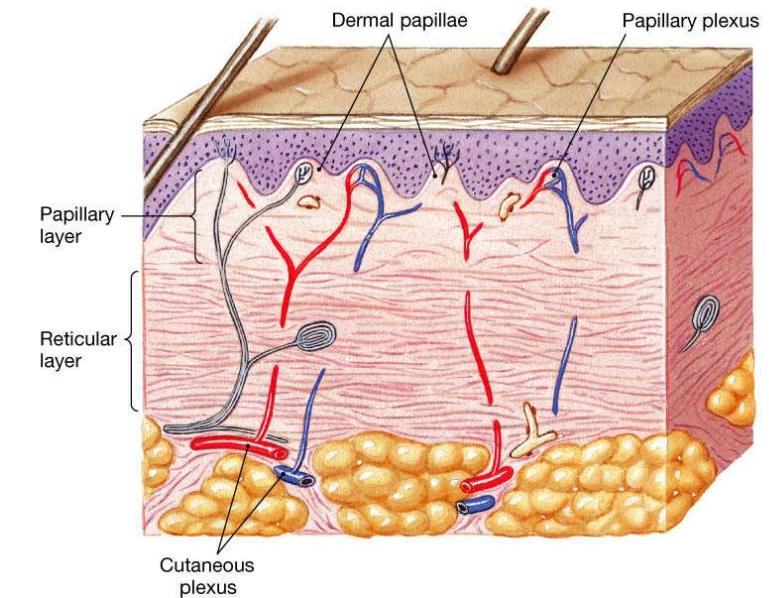
Not good for irritating drugs

Slow absorption

Smaller volumes at once

Parenteral route - Intradermal

- skin testing for some allergens
- drug is injected into papillary layer of skin.
- Tuberculin injection for montoux test
- BCG vaccination for active immunization against tuberculosis.





Intradermal Injection

Parenteral route - Intradermal

ADVANTAGES

- Can give lower dose than sub-cut or IM
- Better response for some vaccines
- Reduced cost
- Better response in immunocompromised or elderly

DISADVANTAGES

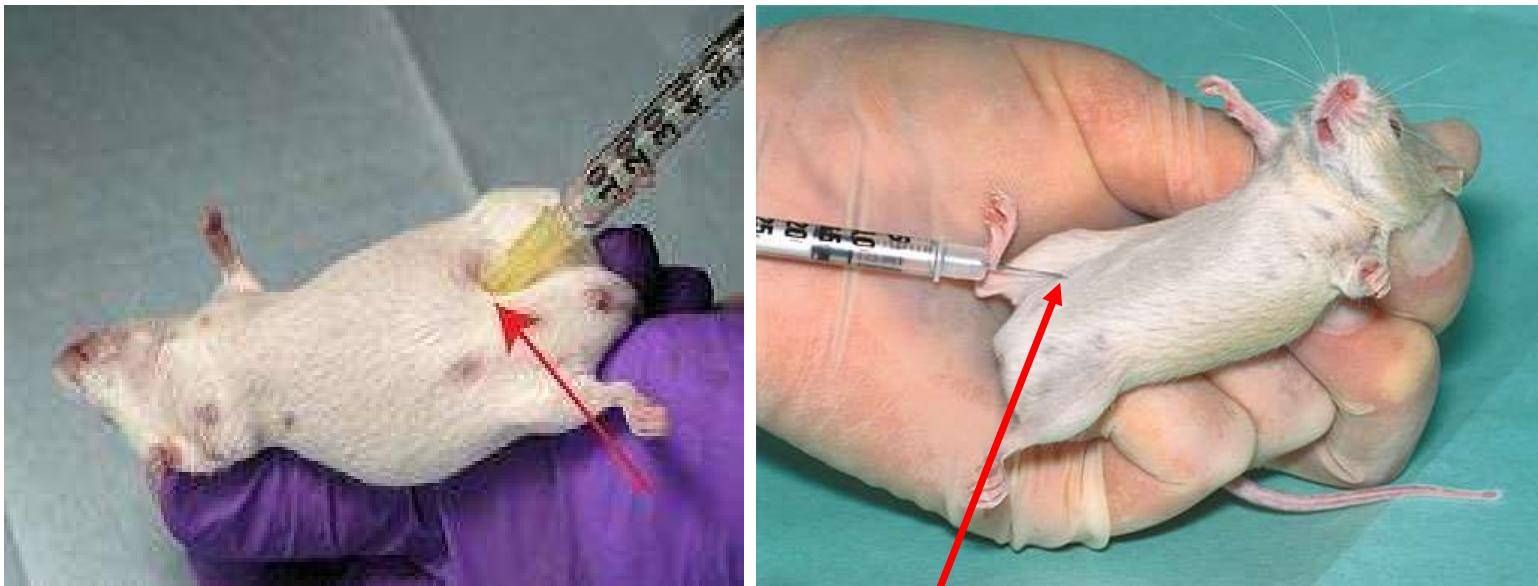
- Small doses
- Trained professional to get needle to correct depth
- Reactions at injection site
- Scarring



Parenteral route - Intraperitoneal

- infusion or injection into the peritoneum
- The peritoneum offers a large absorbing surface area from which drugs enter circulation rapidly but primarily by way of portal vein.
- This is probably the most widely used route of drug administration in laboratory animals.
- In human, it is very rarely employed due to the dangers of infection and injury to viscera and blood vessels.

Parenteral route - Intraperitoneal



Intraperitoneal Injection

Parenteral route - Intrapерitoneal

ADVANTAGES

Easy in mice

Direct targeting of peritoneal cancers

Fluids to infants

Can be used when large amounts of fluids are needed but IV is not an option

Better outcomes for dialysis

DISADVANTAGES

More difficult in humans

Easier ways

Rectal route

Most commonly by suppository or enema.

ADVANTAGES

1. By-pass liver
 - Some of the veins draining the rectum lead directly to the general circulation thus by-passing the liver.
 - Reduced first-pass effect.
2. This route may be most useful for patients unable to take drugs orally
 1. unconscious patients
 2. younger children
 3. patient is nauseous or vomiting

DISADVANTAGES

1. Erratic absorption
 - Absorption is often incomplete and erratic.
2. Not well tolerated by patients.



Inhalation route

- Used for gaseous and volatile agents and aerosols.
- solids and liquids are excluded if larger than 20 micron.

ADVANTAGES

1. Large surface area
2. thin membranes separate alveoli from circulation
3. high blood flow
4. As result of that a rapid onset of action due to rapid access to circulation.

DISADVANTAGES

1. Most addictive route of administration because it reaches the brain so quickly.
2. Difficulties in regulating the exact amount of dosage.
3. Sometimes patients have difficulties in giving themselves a drug by inhaler.



Other Routes

- a) Subcutaneous (S/C)
- b) Intramuscular (I/M)
- c) Intravenous (I/V)
- d) Intraperitoneal (I/P)
- e) Intradermal
- f) Intra Medullary
- g) Intrathecal
- h) Intraarticular
- i) Intra-cardiac
- j) Intra arterial

Intra Medullary

- The needle is introduced into marrow cavity
- effects are similar to those following intravenous injection
- Route is used when veins are not available especially in children.
- In adults the injection is made into marrow cavity of sternum
- Under 3 years of age into tibia or femur.

Intrathecal

- Theca = dura
- Thecal sac surrounds spinal cord and cauda equina
- Blood brain barrier often prevents the entry of certain drugs into the central nervous system
- effects of the drugs are then localized to the spinal nerves and meninges
- injection of local anesthetics for the induction of spinal anesthesia is given by this route.

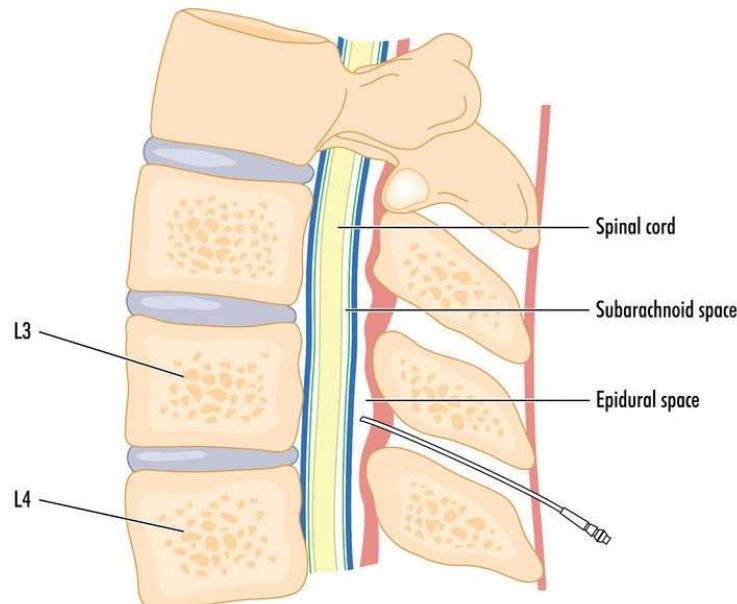
Parenteral route - Intrathecal

ADVANTAGES

- Effective pain relief
- Decrease surgical intervention for nerve pain
- Helps with functional disability due to pain, illness etc

DISADVANTAGES

- Difficult to do
- Painful to administer
- Effects BP
- May induce fever
- Potential o permanent nerve damage



Intra-articular

- also known as intrasynovial
- Sometimes drugs are injected into the joint cavity to localize their action at the site of administration
- e.g. Hydrocortisone acetate in the treatment of rheumatoid arthritis.
- Local anesthetic is added to minimize pain of injection.
- Strict asepsis must be maintained to avoid joint-infection.

Intra Cardiac

- Into the cardiac muscle
- In cardiac arrest intra-cardiac injection of adrenaline is made for resuscitation
 - naloxone for heroin OD

Intra-arterial

- Sometimes a drug is injected directly into an artery to localize its effects in a particular tissue or organ.
- the therapeutic value of such practice is doubtful.

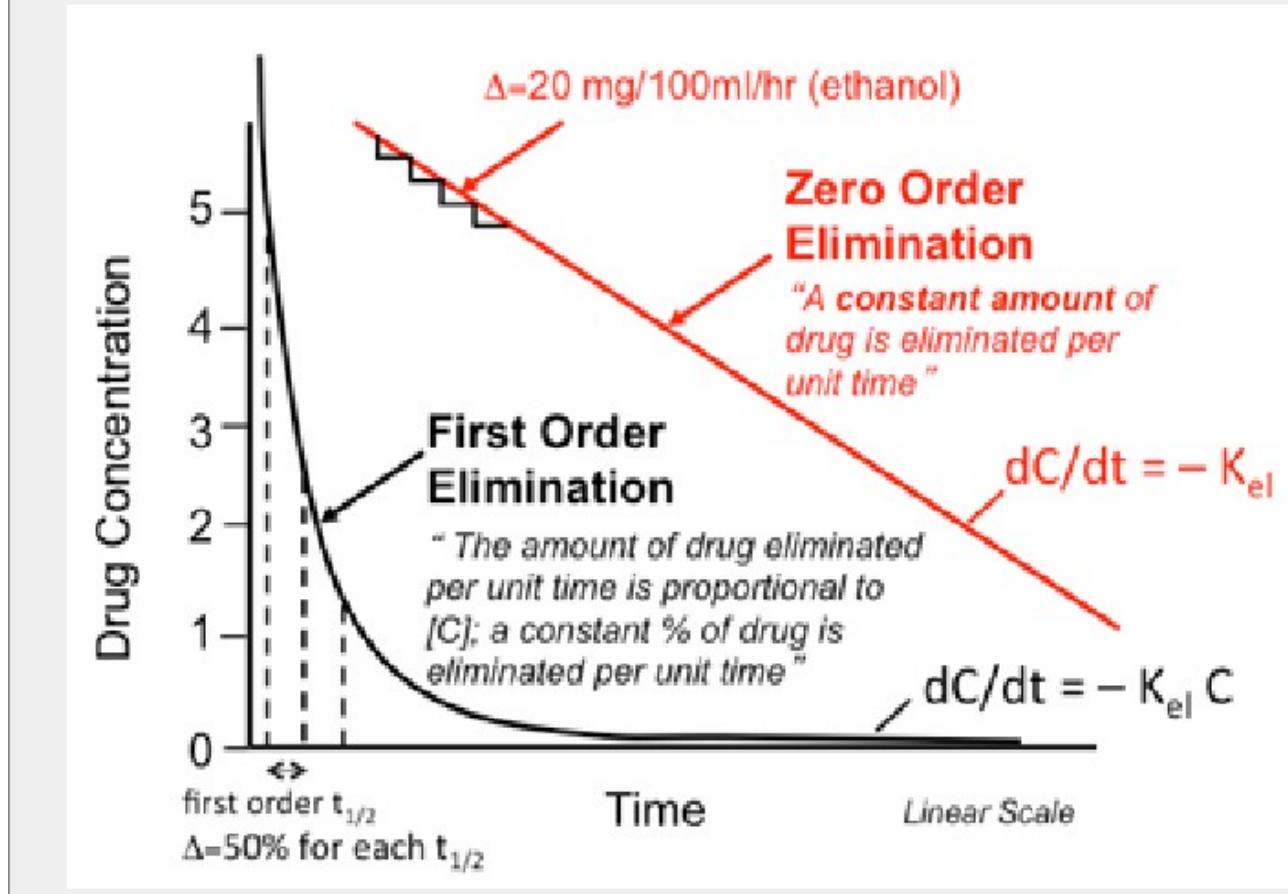
Time-release preparations - Oral

- controlled-release, timed-release, sustained-release
- designed to produce slow, uniform absorption for 8 hours or longer
- better compliance, maintain effect over night, eliminate extreme peaks and troughs

Time-release preparations - Depot

- Depot or reservoir preparations
- parental administration (except IV)
- may be prolonged by using insoluble salts or suspensions in non-aqueous vehicles.

Delivery Kinetics



Region of Action (ROA)

- determined by the physical characteristics of the drug
 - the speed which the drug is absorbed and/ or released
 - the need to bypass hepatic metabolism
 - the need to achieve high conc. at particular sites
-
- No single method of drug administration is ideal for all drugs in all circumstances

Drug Distribution

Dependent upon its route of administration and target area

Tissue is composed of cells which are encompassed within membranes

- Membranes consist of 3 layers
- 2 layers of water-soluble complex lipid molecules (phospholipid)
- a layer of liquid lipid sandwiched within these layers
- Suspended within the layers are large proteins, .

Drug Distribution

- The permeability of a cell membrane, for a specific drug, depends on a ratio of its water to lipid solubility.
- Within the body, drugs may exist as a mixture of two interchangeable forms
 - water (ionized-charged) soluble
 - lipid (non-ionized) soluble
- The concentration of two forms depends on characteristics of the drug molecule

Overview

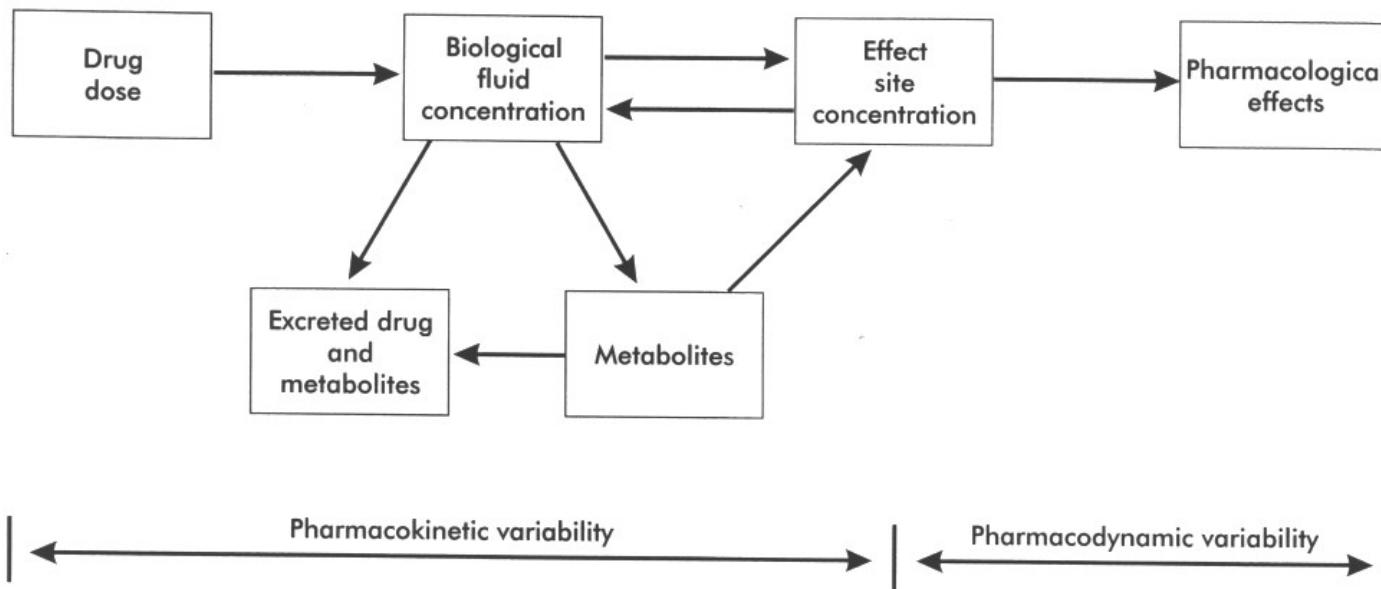


Figure 8-1. Pharmacokinetic and pharmacodynamic variability as determinants of the dose-effect relationship.

Study of drug concentration over time

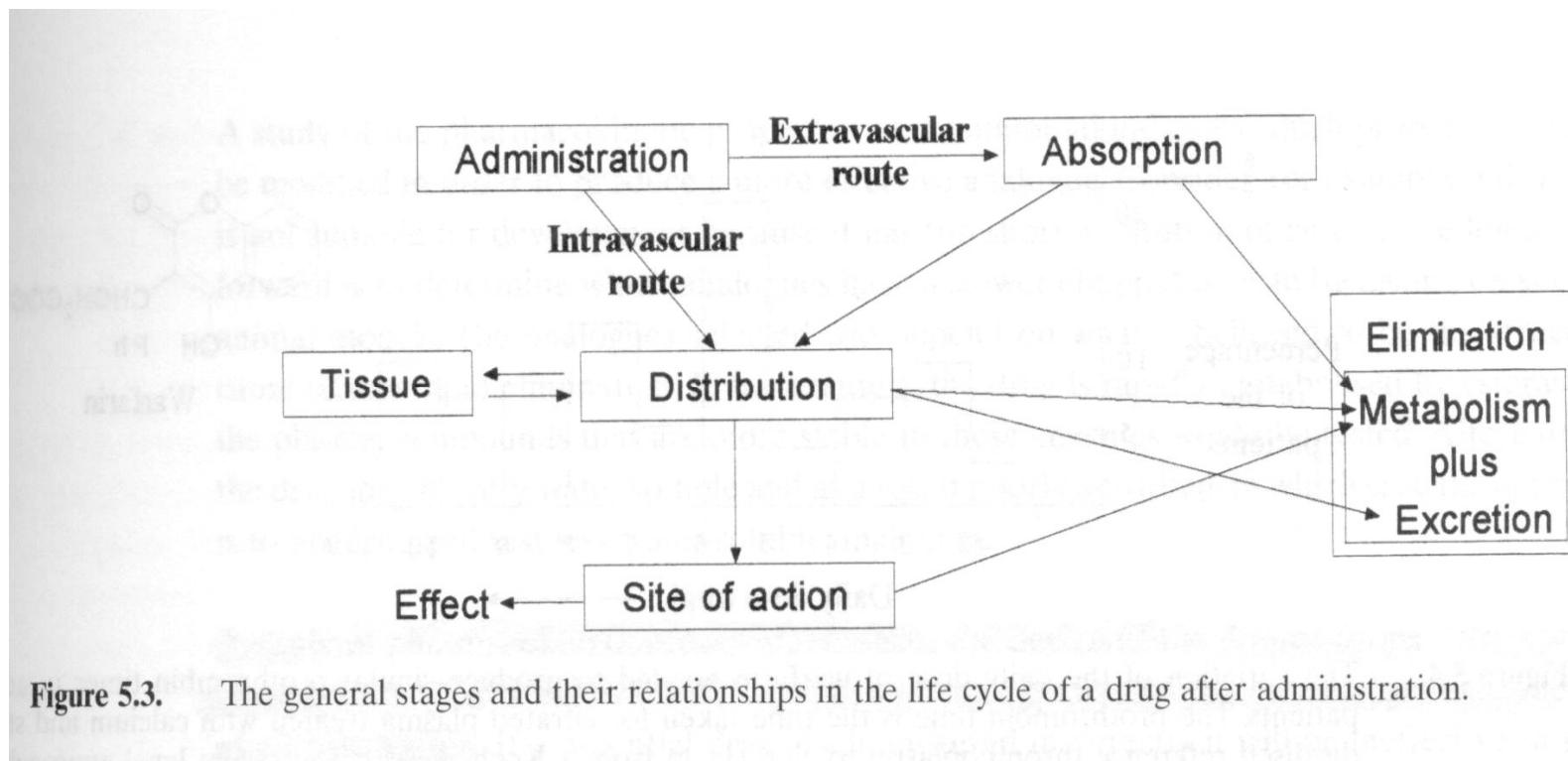


Figure 5.3. The general stages and their relationships in the life cycle of a drug after administration.

Administration Route: Time until effect

Route	Time
intravenous	30-60 seconds
intraosseous	30-60 seconds
endotracheal	2-3 minutes
inhalation	2-3 minutes
sublingual	3-5 minutes
intramuscular	10-20 minutes
subcutaneous	15-30 minutes
rectal	5-30 minutes
ingestion	30-90 minutes
transdermal (topical)	variable (minutes to hours)

Drug Size vs delivery method

- Absorption
 - depends on the route of administration
 - Hydrophobic vs non
 - More lipophilic, more metabolized by gut wall
 - Water soluble are cleared more slowly from the body via kidneys
- Drug distribution
 - depends on how soluble the drug molecule is in fat
 - extent to which the drug binds to blood proteins (albumin)
- Drug elimination
 - Liver
 - Kidney
 - Used up
 - Fat deposits

Reminder on sizes...

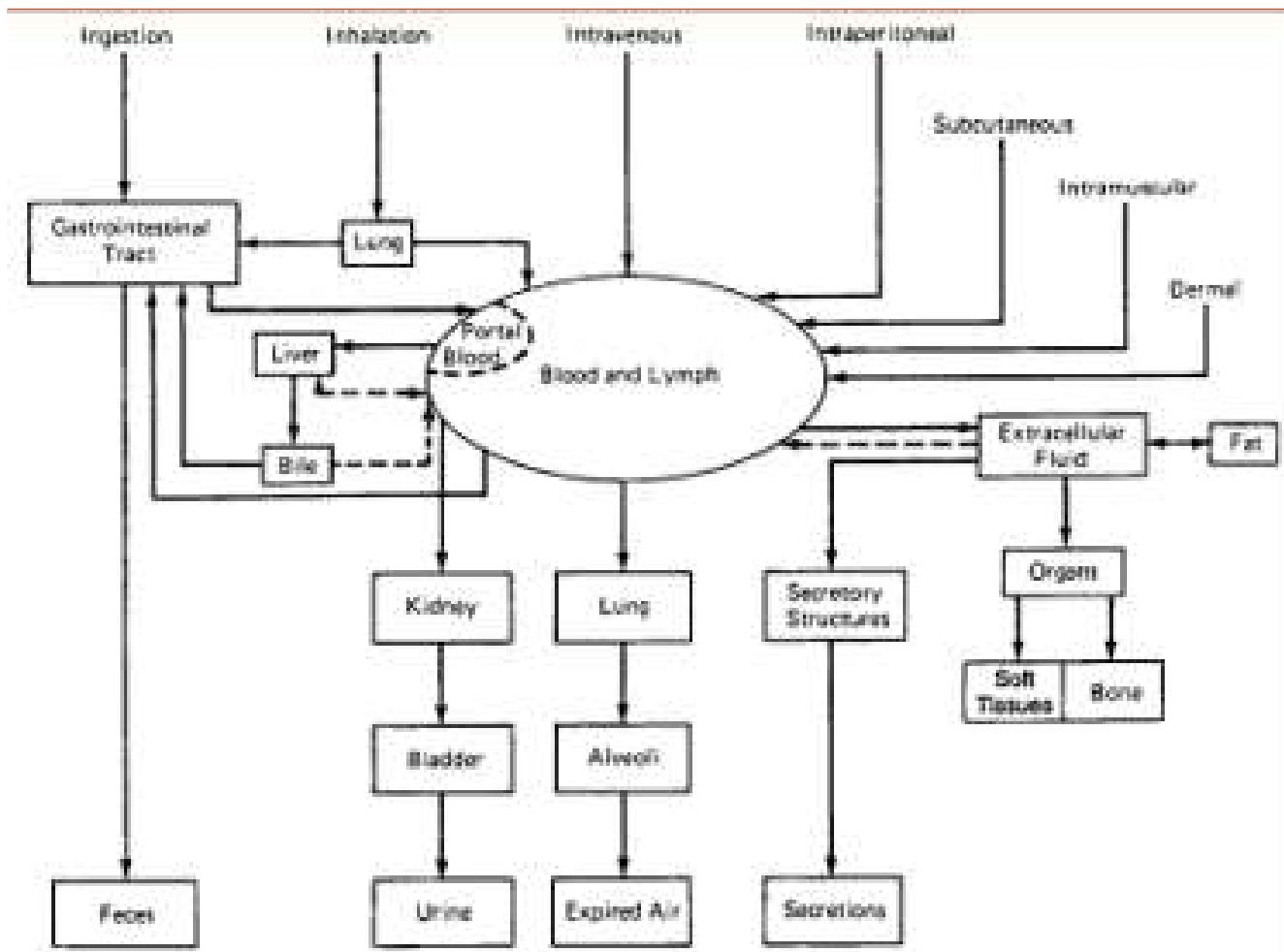
Cell Membranes: Small pores, 8 angstroms, permit small molecules such as alcohol and water to pass through.

Walls of Capillaries: Pores between the cells are larger than most drug molecules, allowing them to pass freely, without lipid solubility being a factor.

Blood/Brain Barrier: This barrier provides a protective environment for the brain. Speed of transport across this barrier is limited by the lipid solubility of the psychoactive molecule.

Placental Barrier: This barrier separates two distinct human beings but is very permeable to lipid soluble drugs.

DEPOSITION OF DRUGS



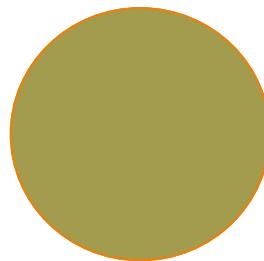
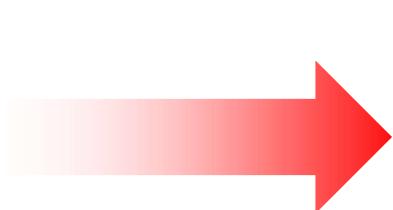
The disposition of chemicals entering the body (from C.D. Klaassen, *Casarett and Doull's Toxicology*, 5th ed., New York: McGraw-Hill, 1996).

Particle Dynamics

Maxwell-Boltzmann Equation

Before we look at diffusion in biological systems, need to examine underlying principles.

The Maxwell-Boltzmann equation governs the motion of small molecules in a gas.



$$E = \frac{mv^2}{2}$$

Maxwell-Boltzmann Equation

From the research of Boltzmann, the energy of a molecule in a gas is known to be proportional to temperature (T) and the Boltzmann constant (k_B):

$$P(\text{m}_i \text{ has energy } E_i) \approx \exp\left(-\frac{E_i}{k_B T}\right) \approx \exp\left(-\frac{mv^2}{2k_B T}\right)$$

Using above relationship it is possible to calculate the normalized distribution for velocity:

$$n(v)dv = 4\pi\left(\frac{m}{2\pi k_B T}\right)^{3/2} v^2 \exp\left(-\frac{mv^2}{2k_B T}\right) dv$$

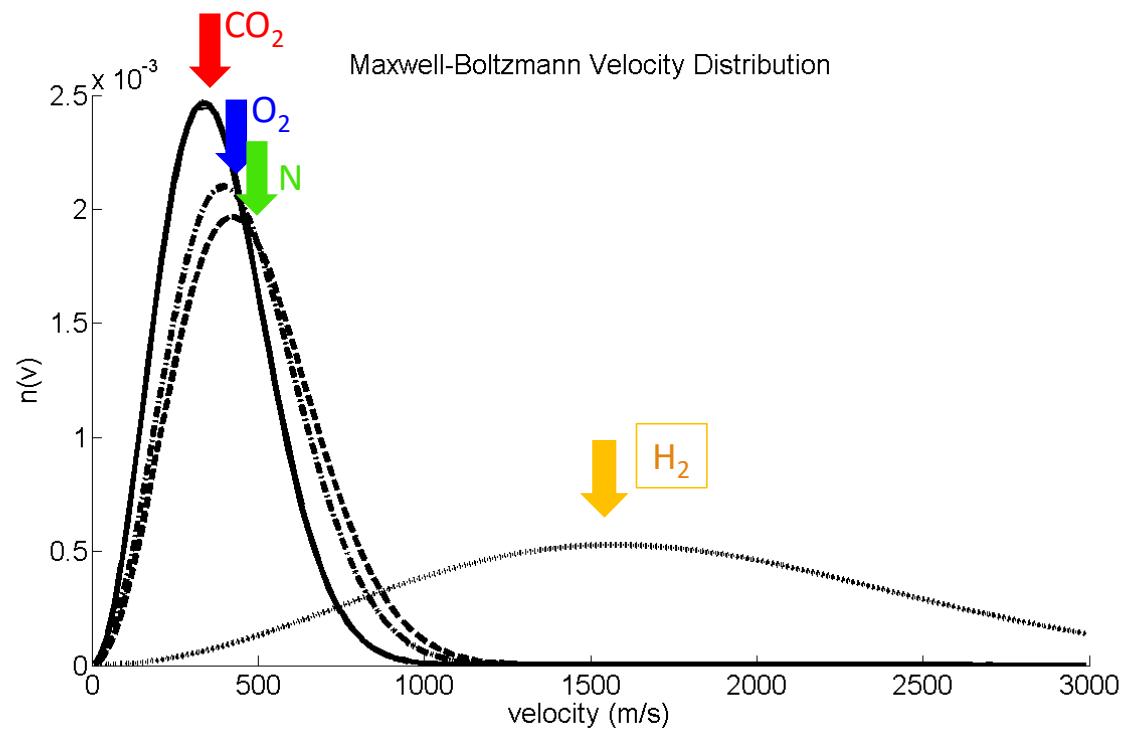
Maxwell-Boltzmann Equation

The average velocities can be calculated:

Root mean square and most probable velocity:

Maxwell-Boltzmann Distributions

The Maxwell-Boltzmann distributions vary heaviest to lightest

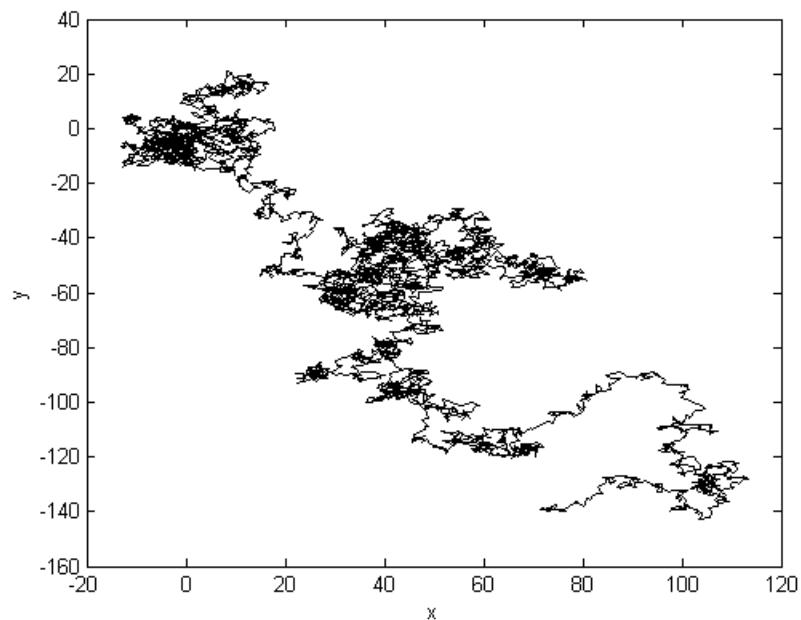


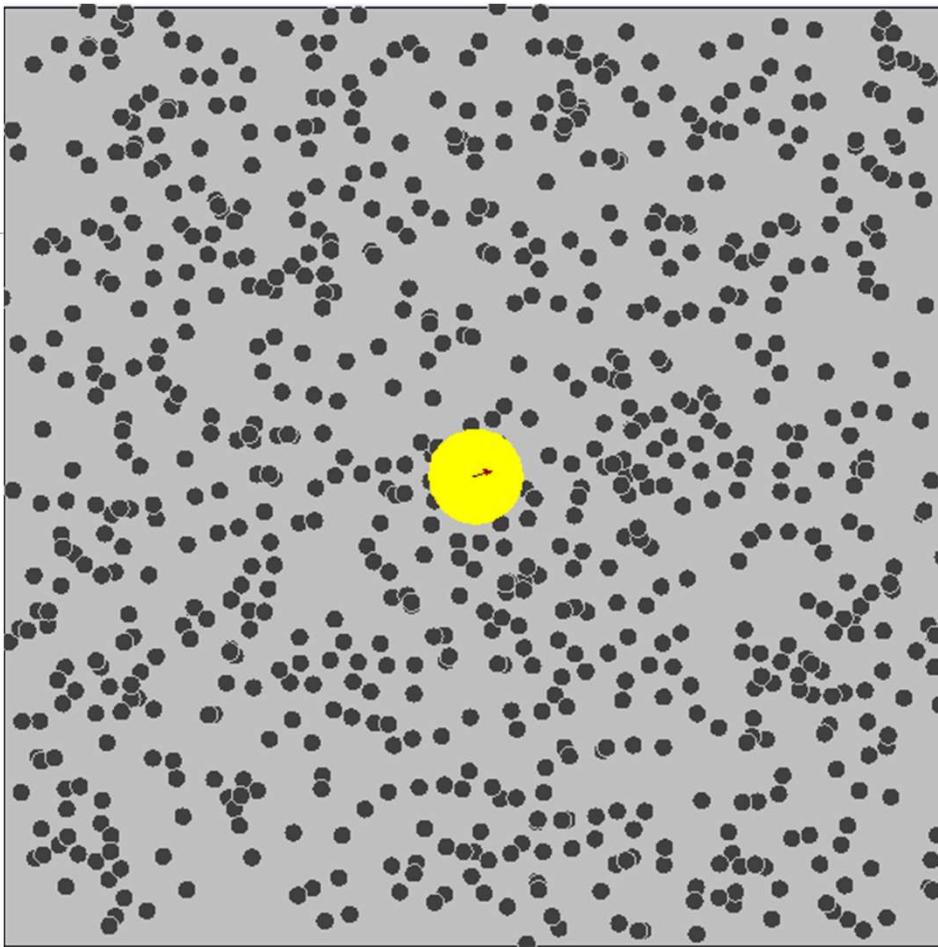
Brownian Motion

Random motion of particles suspended in a medium

Robert Brown noted in 1828 that small particles and organisms appeared to move randomly or appear to jiggle.

In 1905, Albert Einstein finally managed to find an explanation from his work on the photoelectric effect.





Diffusion

Most Brownian motion is too weak to result in diffusion.

However, when particles with very high velocity $v >> v_{rms}$ collide with small molecules, particles or organisms they appear to move in a random pattern $x(t)$.

$$R_{RMS-1D} = \left[x(t)^2 \right]^{\frac{1}{2}} \quad R_{RMS-2D} = \left[x(t)^2 + y(t)^2 \right] \\ = \sqrt{2Dt} \qquad \qquad \qquad = \sqrt{4Dt}$$

$$R_{RMS-3D} = \sqrt{6Dt}$$

Diffusion and Drag

Diffusion is determined using Einstein relation:

η is viscosity and l is the length of the object.

Can also define coefficient of drag according to viscosity:

The force is proportional to speed:

Diffusion Across Energy Membrane

If diffusion requires activation energy (E_a), such as near a barrier. The diffusion is:

$$D = D_0 \exp\left(-\frac{E_a}{k_B T}\right)$$

Diffusion and Perfusion

Blood flow model constructs a paradigm/model for perfusion

Perfusion is the delivery of blood to the capillary bed

In human it is a largely actively driven mechanism driven by the heart

Compartment models simply modeled the movement of pharmacological agents without considering mechanism

Fick's Laws

Fick's Laws were developed in 1855 to describe diffusion in a liquid. Laws are also applicable in gases and solids. They relate diffusion to concentration gradients.

Fick's 1st Law:

J Diffusion Flux/Amount of Substance $\left(\frac{mol}{m^2 s} \right)$

Fick's 2nd Law:

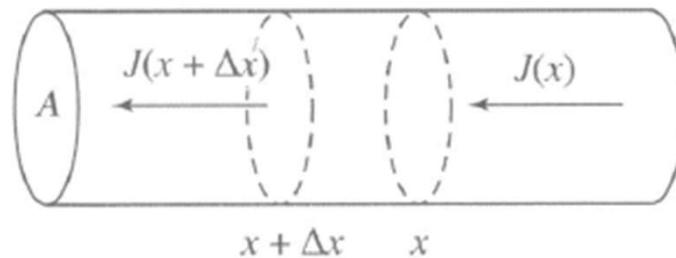
D Diffusion Constant (ie. Rate) $\left(\frac{mol}{s} \right)$

C Concentration $\left(\frac{mol}{m^3} \right)$

Fick's Second Law

Fick's second law arises from conservation of mass. Take Fick's first law and derive with respect to x :

$$\frac{dJ}{dx} = -D \frac{\partial^2 C}{\partial x^2}$$



If material diffuses, then concentration must change

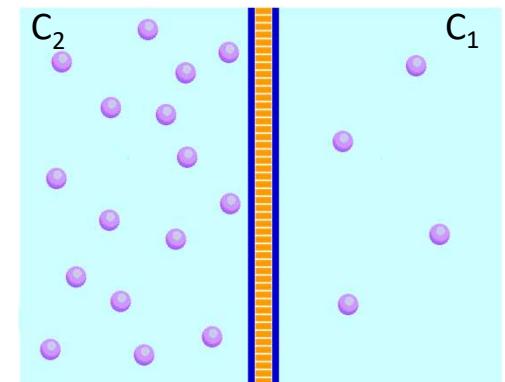
$$\frac{dJ}{dx} = -\frac{\partial C}{\partial t} \quad \text{in 3D} \rightarrow \frac{dC}{dt} = D \nabla^2 C$$

Diffusion Between Compartments

2 compartments are separated by a barrier

The rate of solute diffusion from one compartment to the other is proportional to the difference in concentration of the two compartments, C_1 and C_2

Thus in a short time interval Δt the amount of solute Q that will cross the barrier will be:



<https://year12biologyatsmc.wikispaces.com/Diffusion>

Where K is a constant that depends on the nature of the barrier (e.g. geometry, charge, pores, etc.), and the solute.

Diffusion Between Compartments (Cont.)

Therefore:

where V_1 and V_2 are the volumes of the two compartments, which are assumed constant. In the limit as Δt goes to zero:

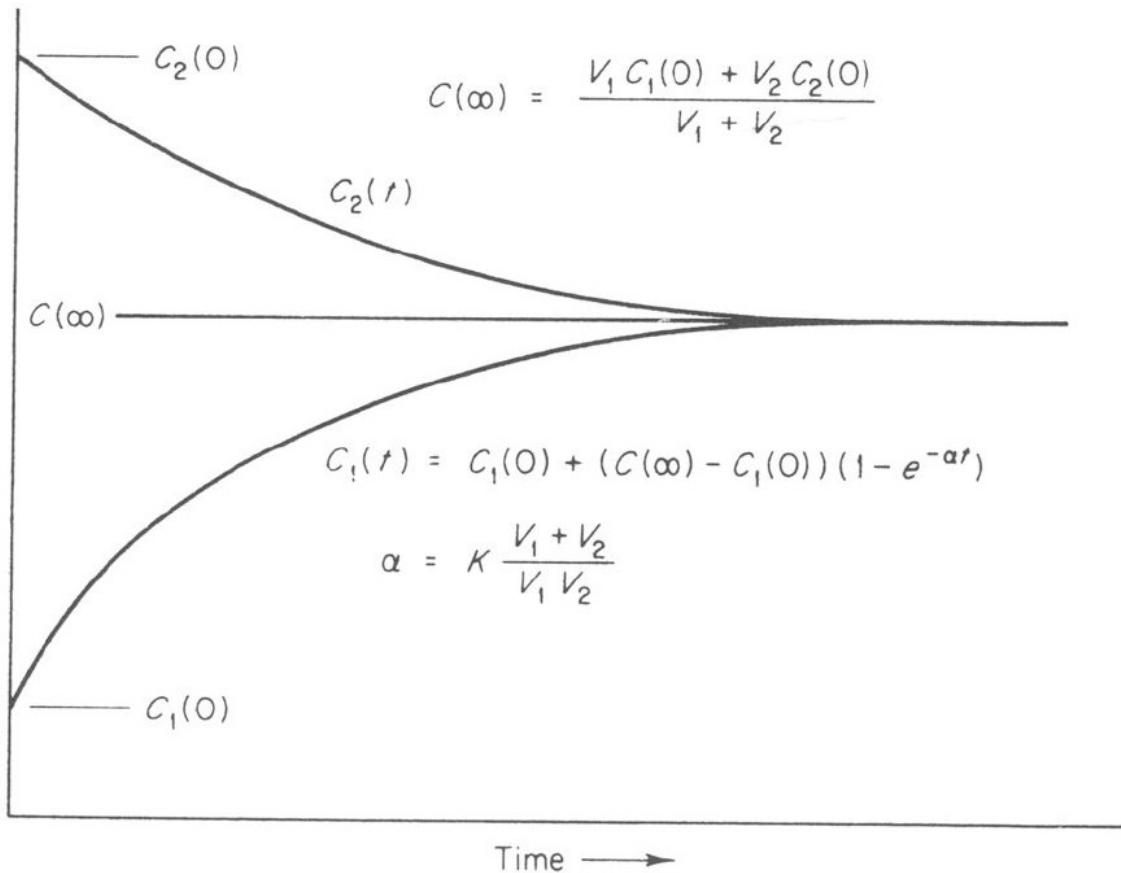
Diffusion Between Compartments (Cont.)

Let the initial concentrations in the two compartments be $C_1(0)$ and $C_2(0)$.

Thus in the initial state, the total amount of solute present is:

At some time= t an equilibrium condition is reached in which the concentrations in the two compartments are equal. i.e. the solute is distributed throughout a volume $V_1 + V_2$

Therefore the concentration at equilibrium is given by:



C(t) graph – 2 compartment

Result is independent of the nature of the diffusion process.

If the initial concentrations and volumes are known, the concentration at infinite time is also known

Diffusion Between Compartments (Cont.)

Reasonable initial educated guess of a model:

$$C_1 = C_1(0) + (1 - e^{-\alpha t}) [C(\infty) - C_1(0)]$$

$$C_2 = C_2(0) + (1 - e^{-\beta t}) [C(\infty) - C_2(0)]$$

The derivatives are:

$$\frac{\partial C_1}{\partial t} = \alpha e^{-\alpha t} [C(\infty) - C_1(0)]$$

$$\frac{\partial C_2}{\partial t} = \beta e^{-\beta t} [C(\infty) - C_2(0)]$$

Diffusion Between Compartments (Cont.)

$$C_1(t) = C_1(0) + (1 - e^{-\alpha t}) [C(\infty) - C_1(0)]$$

$$C_2(t) = C_2(0) + (1 - e^{-\beta t}) [C(\infty) - C_2(0)]$$

From previous slide. So $C_2 - C_1$, with some algebra, equals:

Diffusion Between Compartments (Cont.)

$$C_2(t) - C_1(t) = C(\infty)(e^{-\alpha t} - e^{-\beta t}) + C_2(0)e^{-\beta t} - C_1(0)e^{-\alpha t}$$

If one takes this result and inserts into previous differential equations:

$$\frac{dC_1}{dt} = \alpha e^{-\alpha t}(C(\infty) - C_1(0))$$

$$\frac{dC_2}{dt} = \beta e^{-\beta t}(C(\infty) - C_2(0))$$

Diffusion Between Compartments (Cont.)

SI 58

$$C_2(t) - C_1(t) = e^{-\alpha t}(C_2(0) - C_1(0))$$

SI 53

$$V_2 \frac{dC_2}{dt} = K(C_1 - C_2) = -V_1 \frac{dC_1}{dt}$$

Therefore:

From previous:



Multiply both sides by V_1 ,

$$\frac{dC_1}{dt} = \alpha e^{-\alpha t}(C(\infty) - C_1(0)) \quad V_1 \frac{dC_1}{dt} = \alpha V_1 e^{-\alpha t}(C(\infty) - C_1(0))$$

Diffusion Between Compartments (Cont.)

$$V_1 \frac{dC_1}{dt} = \alpha V_1 e^{-\alpha t} (C(\infty) - C_1(0)) \quad \text{SI 59}$$

Using above solve for α :

$$\alpha = \frac{K}{V_1} \frac{C_2(0) - C_1(0)}{C(\infty) - C_1(0)}$$

This can be simplified by observing that:

$$C(\infty) - C_1(0) = \frac{V_1 C_1(0) + V_2 C_2(0) - (V_1 + V_2) C_1(0)}{V_1 + V_2} = \frac{V_2 (C_2(0) - C_1(0))}{V_1 + V_2}$$

Therefore:

Diffusion Between Compartments (Cont.)

Back to these ugly equations:

$$C_1 = C_1(0) + (1 - e^{-\alpha t}) [C(\infty) - C_1(0)]$$

$$C_2 = C_2(0) + (1 - e^{-\beta t}) [C(\infty) - C_2(0)]$$

put into a nicer form by replacing $C(\infty)$ - $C_1(0)$ by its value from:

$$C(\infty) - C_1(0) = \frac{V_1 C_1(0) + V_2 C_2(0) - (V_1 + V_2) C_1(0)}{V_1 + V_2} = \frac{V_2 (C_2(0) - C_1(0))}{V_1 + V_2}$$

Diffusion Between Compartments (Cont.)

$$C_1 = C_1(0) + (1 - e^{-\alpha t}) [C(\infty) - C_1(0)]$$

$$C_2 = C_2(0) + (1 - e^{-\beta t}) [C(\infty) - C_2(0)]$$

Also, replace $C(\infty)$ - $C_2(0)$ by the analogous form:

$$C_1(t) = C_1(0) + (1 - e^{-\alpha t}) [C_2(0) - C_1(0)] \frac{V_2}{V_1 + V_2}$$

$$C_2(t) = C_2(0) + (1 - e^{-\beta t}) [C_1(0) - C_2(0)] \frac{V_1}{V_1 + V_2}$$

Recap of all this math:

1. Relate the derivatives of concentration of each side to each other
2. Model the equilibrium concentration as a function of the concentration of both sides at time zero
3. Create the model for the equilibrium concentration in terms of the exponentials of each side
4. Link everything together by assume alpha = beta
5. Solve for alpha and use 2) to have alpha in terms of volumes and initial concentrations
6. Model C₁ and C₂ in terms of initial concentrations, and volumes

$$V_2 \frac{dC_2}{dt} = K(C_1 - C_2) = -V_1 \frac{dC_1}{dt}$$

$$C(\infty) = \frac{V_1 C_1(0) + V_2 C_2(0)}{V_1 + V_2}$$

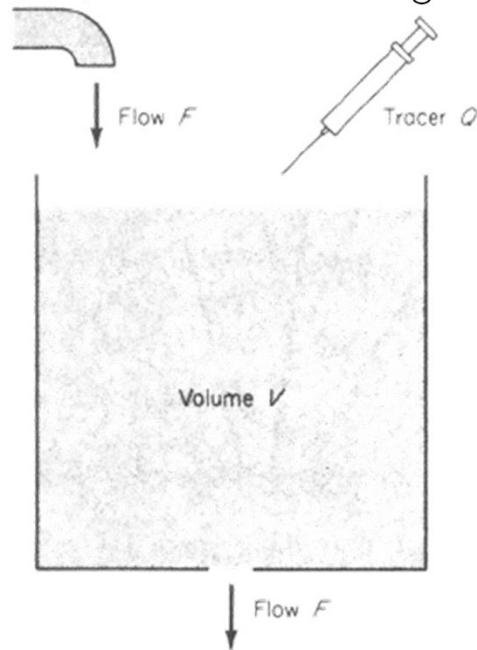
$$C_2(t) - C_1(t) = C(\infty)(e^{-\alpha t} - e^{-\beta t}) + C_2(0)e^{-\beta t} - C_1(0)e^{-\alpha t}$$

$$C_2(t) - C_1(t) = e^{-\alpha t}(C_2(0) - C_1(0))$$

$$\alpha = \frac{K(V_1 + V_2)}{V_1 V_2}$$

Model #1: The basic 1 compartment continuous dilution process

The idealized one-compartment dilution problem consists of a single continuously mixed chamber through which a fluid is flowing at a constant rate.



Say:

$V = 10 \text{ Litres (constant)}$

$F_{\text{in}} = 2 \text{ Litres/min}$

At $t(0)$ 3 Moles of dye is injected

- assume dye is injected instantly
- assume dye is instantly mixed

Therefore at $t=0$, concentration = 0.3 moles/liter

Model 1

- 1) The concentration of dye immediately begins to fall (i.e. being lost in the effluent while water is replacing the lost volume of solution).
- 2) At very long times, which we designate $t(\infty)$, all of the dye has been flushed out.
- 3) To find the concentration of dye at any time following its injection, we must calculate instantaneous description of a continuous process.

Note minus sign indicates
[tracer] is decreasing

Model 1

ΔQ is a quantity, not a concentration:

We're interested in concentration at time=t (i.e. $C(t)$). So, divide both sides of the equation by Δt and take the limit as $\Delta t \rightarrow 0$

Therefore:

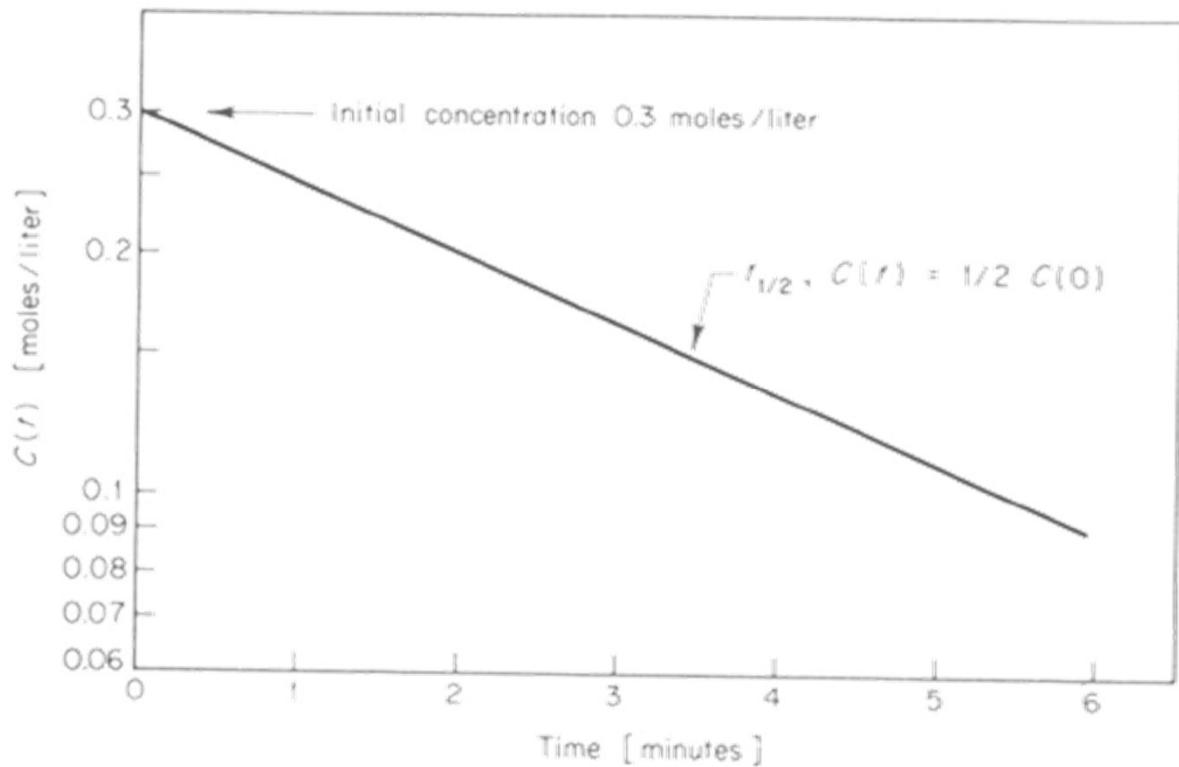
Model 1

Check units:

$$\frac{\text{moles}}{\text{liter}} = \frac{\text{moles}}{\text{liter}}$$

Exponent units:

$$\frac{F}{V} t = \frac{\text{liters}}{\frac{\text{min}}{\text{liters}}} \text{ min}$$



Model #2: One compartment with metabolic turnover

- same mathematical form as dilution process.
- 1) To this pool is added a small quantity $q(0)$ moles of a metabolite.
- 2) The rate of disappearance of the metabolite is analogous to the rate of disappearance of the tracer in the one-compartment dilution process.
- 3) Here the total pool ($Q + q$) is analogous to volume [model 1] and rate of metabolite turnover is analogous to flow [model 1].
- assume addition of the metabolite does not change its rate of utilization.

Model 2

Since $q(t) \ll Q$ we can make the approximation:

Therefore:



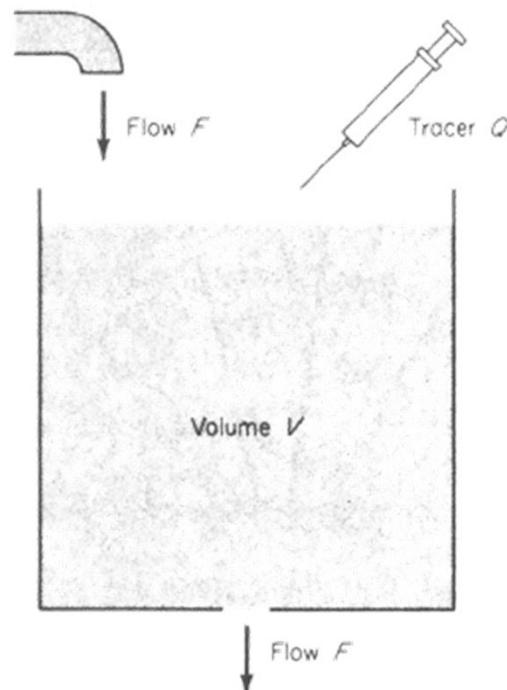
R = metabolism of metabolite
(moles/sec)
Q = moles

Model #3: Radioactive Decay

Again, same mathematical form is given by the decay of a radioactive isotope.

Here, # of atoms that decay per unit time is proportional to the number of remaining radioactive atoms:

Model #4: One compartment with Constant Injection



Constant Injection
rate = R moles/sec

As previously, amount of tracer lost from the tank in a small unit of time Δt is:

Model 4

- but at the same time tracer is entering the tank at a rate R
- Thus, in the interval Δt the net change in quantity of tracer in the tank is given by:

- with same logic as previously (i.e. Q is moles and want a concentration, so divide by volume):

Model 4

- divide by Δt and take the limit as $\Delta t \rightarrow 0$

$$\frac{\Delta C}{\Delta t} = \frac{R - FC(t)}{V} \quad \longrightarrow$$

Units Check:

$$\frac{\text{moles}}{\text{liter sec}} = \frac{\text{moles}}{\text{sec liters}} - \frac{\text{liter}}{\text{sec liters}} \frac{\text{moles}}{\text{liter}}$$

Solution:



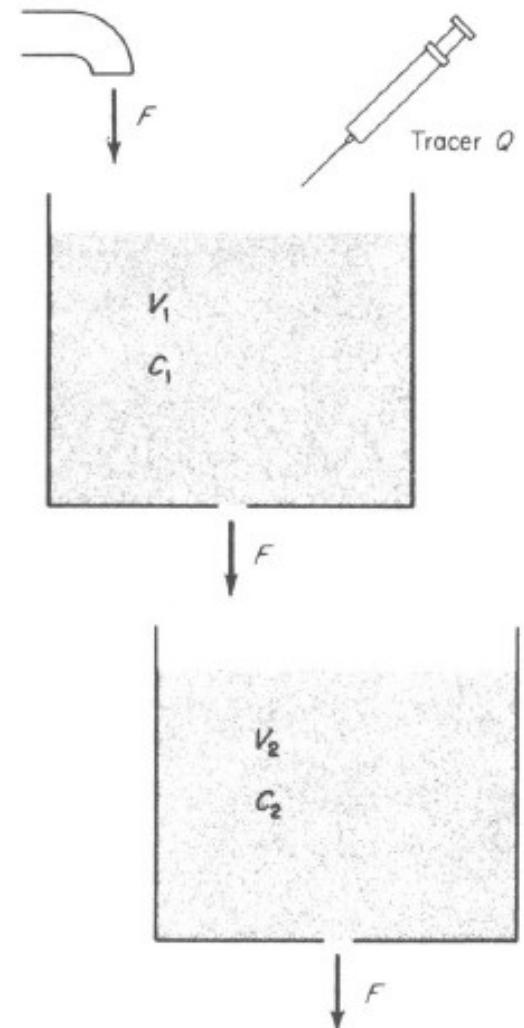
Model 5

- 1) First compartment is identical to Model 1.

$$C_1(t) = C_1(0)e^{-(F/V_1) \cdot t}$$

- 2) Second compartment (V_2), is filled by the effluent from the first compartment

- 3) V_2 is a flow-through-type compartment, losing solution at a rate F .



Model 5

- 1) Need to calculate concentration (C_2) in compartment 2 as a function of time
- 2) find total amount of tracer that enters and leaves the compartment in a small interval of time Δt .
- 3) Amount leaving will be the rate of flow F multiplied by the concentration in 2nd compartment (C_2) multiplied by a small time interval Δt .
- 4) Amount entering during that time will be flow rate, $F \times \Delta t \times C_1$.

Model 5

Net change in tracer in compartment 2 is:

this is converted to a change of concentration
by dividing by the volume, V_2 :

Again divide by Δt and take the limit as $\Delta t \rightarrow 0$:

$$\Delta Q_2 = -\Delta t C_2(t)F + \Delta t C_1(t)F$$

$$\Delta C_2 = \frac{F}{V_2} C_1(t) \Delta t - C_2(t) \frac{F}{V_2} \Delta t$$

$$\frac{dC_2}{dt} = \frac{F}{V_2} [C_1(t) - C_2(t)]$$

$$= \frac{F}{V_2} [C_1(0)e^{-(F/V_1)t} - C_2(t)]$$

Solution:

$$C_2(t) = \frac{V_1 C_1(0)}{V_1 - V_2} [e^{-(F/V_1)t} - e^{-(F/V_2)t}]$$

Model 5

This is a complicated problem!

- usually wish to visualize it by plotting $C_2(t)$ as a function of time. BUT
- confronted with the fact that V_1 V_2 C_1 and F can all take on wide ranges of values in practical problems
- making plots for wide ranges of four different parameters is prohibitive.
- therefore examine function to see if it is possible to reduce number of parameters

$$C_2(t) = \frac{V_1 C_1(0)}{V_1 - V_2} \left[e^{-(F/V_1) \cdot t} - e^{-(F/V_2) \cdot t} \right]$$

Model 5

F*t?

$$C_2(t) = \frac{V_1 C_1(0)}{V_1 - V_2} \left[e^{-(F/V_1) \cdot t} - e^{-(F/V_2) \cdot t} \right]$$

Exponents?

Model 5

$$C_2(t) = \frac{V_1 C_1(0)}{V_1 - V_2} [e^{-p} - e^{-Kp}]$$

- It would be nice to express the leading fraction in terms of the same dimensionless quantities.
- easily done by dividing through by V_1 and thus we find :

Where: $K = \frac{V_1}{V_2}$

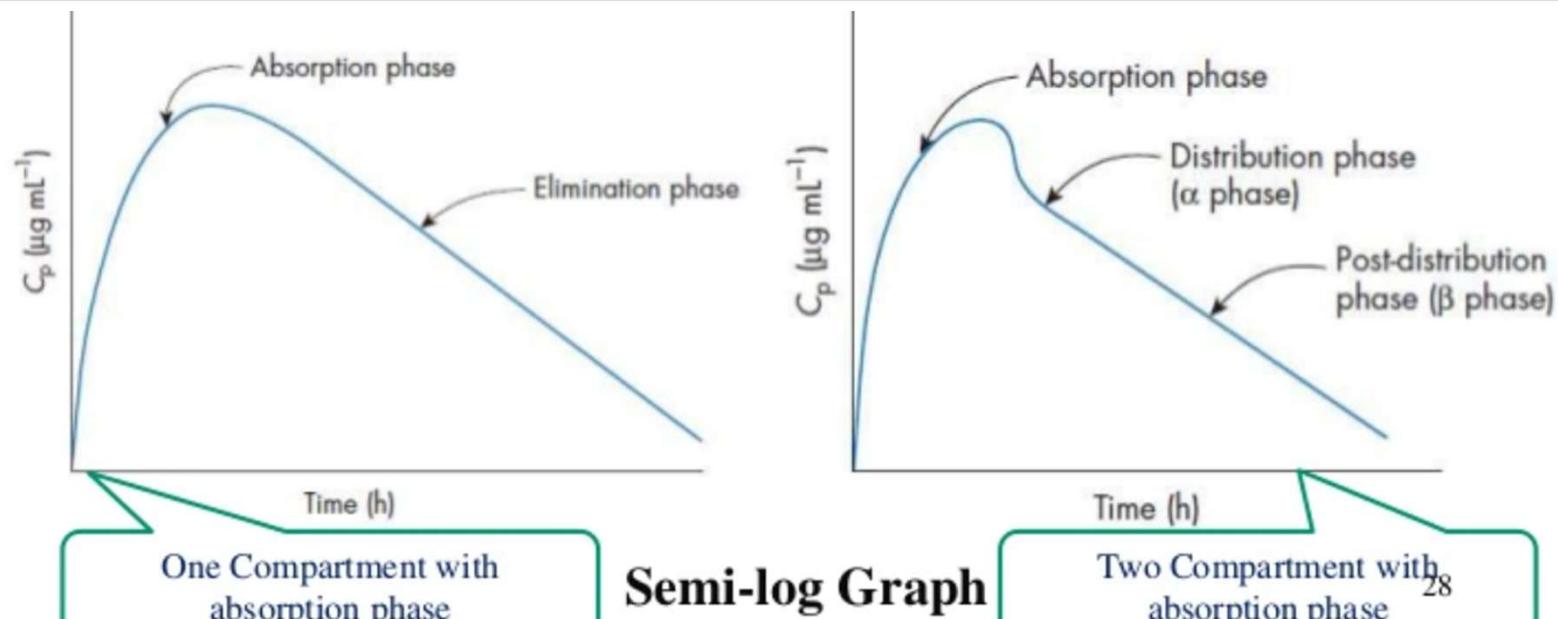
- This function, which is a ratio of concentrations and is therefore dimensionless, is expressed in terms of only two dimensionless variables p and K .

Model 5

$$\frac{C_2(t)}{C_1(0)} = \frac{1}{1 - K^{-1}} \left[e^{-p} - e^{-Kp} \right] \quad \text{Where: } K = \frac{V_1}{V_2}$$

Thus a problem that initially had 4 independent variables is reduced to one of only 2 independent dimensionless variables!

Model 5



Anas Bahnassi PhD 2011

$$V_1 > V_2$$

$$V_1 < V_2$$

Getting to more complicated Models

Homogeneous and Inhomogeneous Equations

When the dependent variable appears exactly once in every term of the equation, the equation is said to be homogeneous:

$$\frac{d^2C(t)}{dt^2} + t \frac{dC(t)}{dt} + 4C(t) = 0 \quad \sin \omega t \frac{dC(t)}{dt} + C(t) \cos \omega t = 0$$

If there are terms that do not contain the dependent variable,
the equations are called inhomogeneous:

$$\frac{dC(t)}{dt} + C(t) = 4 \quad \frac{d^2C(t)}{dt^2} + \frac{dC(t)}{dt} + t = 0$$

Homogeneous and Inhomogeneous Equations

Linear homogeneous equations with constant coefficients have a solution that can be expressed as a sum of exponentials

The number of such exponential terms required for a solution is the same as the order of the differential equation:

$$\frac{d^2C(t)}{dt^2} + B \frac{dC(t)}{dt} + DC(t) = 0$$

This is a 2nd order linear homogeneous differential equation with solution:

where the constants A1 and A2 are arbitrary and α_1 and α_2 are solutions of the quadratic algebraic equation:

Homogeneous and Inhomogeneous Equations

Now consider a similar differential equation but with the addition of an inhomogeneous term:

$$\frac{d^2C(t)}{dt^2} + B \frac{dC(t)}{dt} + DC(t) = 4$$

The solution is given by:

The solution of an inhomogeneous linear equation will always consist of the solution to the homogeneous equation plus the addition of a constant or a function of the independent variable.

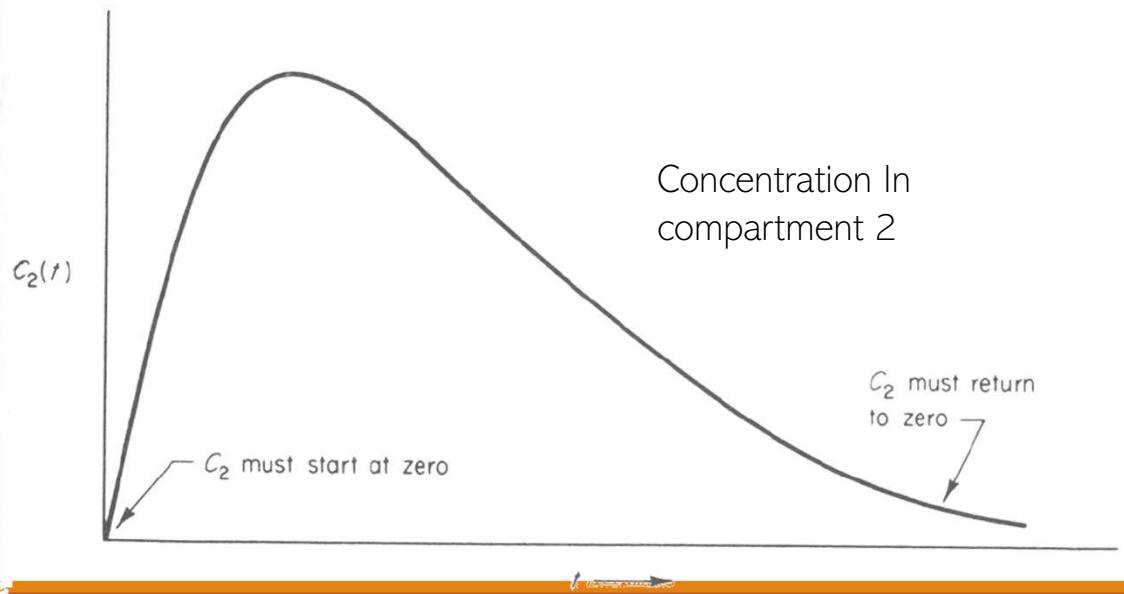
The arbitrary constants A1 and A2 cannot be determined from the differential equation and must be determined by other means.

Let's go back to the 2 compartment series dilution:

$$\frac{dC_2}{dt} = \frac{F}{V_2} [C_1(t) - C_2(t)] = \frac{F}{V_2} [e^{-(F/V_1)t} - e^{-(F/V_2)t}]$$

This is an example of an inhomogeneous linear differential equation

- cannot be a single exponential, since a single exponential cannot both start and end at 0
- sum of 2 exponentials?



Let's go back to the 2 compartment series dilution:

$$C_2(t) = A_1 \exp(-\alpha_1 t) + A_2 \exp(-\alpha_2 t)$$

2 conditions must be true:

- 1) Both exponentials must have negative exponents, since a positive exponent would imply a concentration that becomes infinite at infinite time.
- 2) The constants A_1 and A_2 must be equal to each other but of opposite signs, so that their sum will be zero at zero time.

Thus, this must be of the form:

Differentiate:

$$\frac{dC_2}{dt} = A \left[\exp(-\alpha_1 t) - \exp(-\alpha_2 t) \right]$$

From previous:

$$\frac{dC_2}{dt} = \frac{F}{V_2} [C_1(t) - C_2(t)] = \frac{F}{V_2} [C_1(0)e^{-(F/V_1)t} - C_2(t)]$$

$$A\alpha_2 e^{-\alpha_2 t} - A\alpha_1 e^{-\alpha_1 t} = \frac{F}{V_2} C_1(0) e^{-(F/V_1)t} - \frac{F}{V_2} A e^{-\alpha_1 t} - \frac{F}{V_2} A e^{-\alpha_2 t}$$

Or:

$$A \left(\frac{F}{V_2} - \alpha_1 \right) e^{-\alpha_1 t} + A \left(\alpha_2 - \frac{F}{V_2} \right) e^{-\alpha_2 t} = \frac{F}{V_2} C_1(0) e^{-(F/V_1)t}$$

2 compartment model cont

$$\alpha_1 = \frac{F}{V_2}, \quad \alpha_2 = \frac{F}{V_1}$$

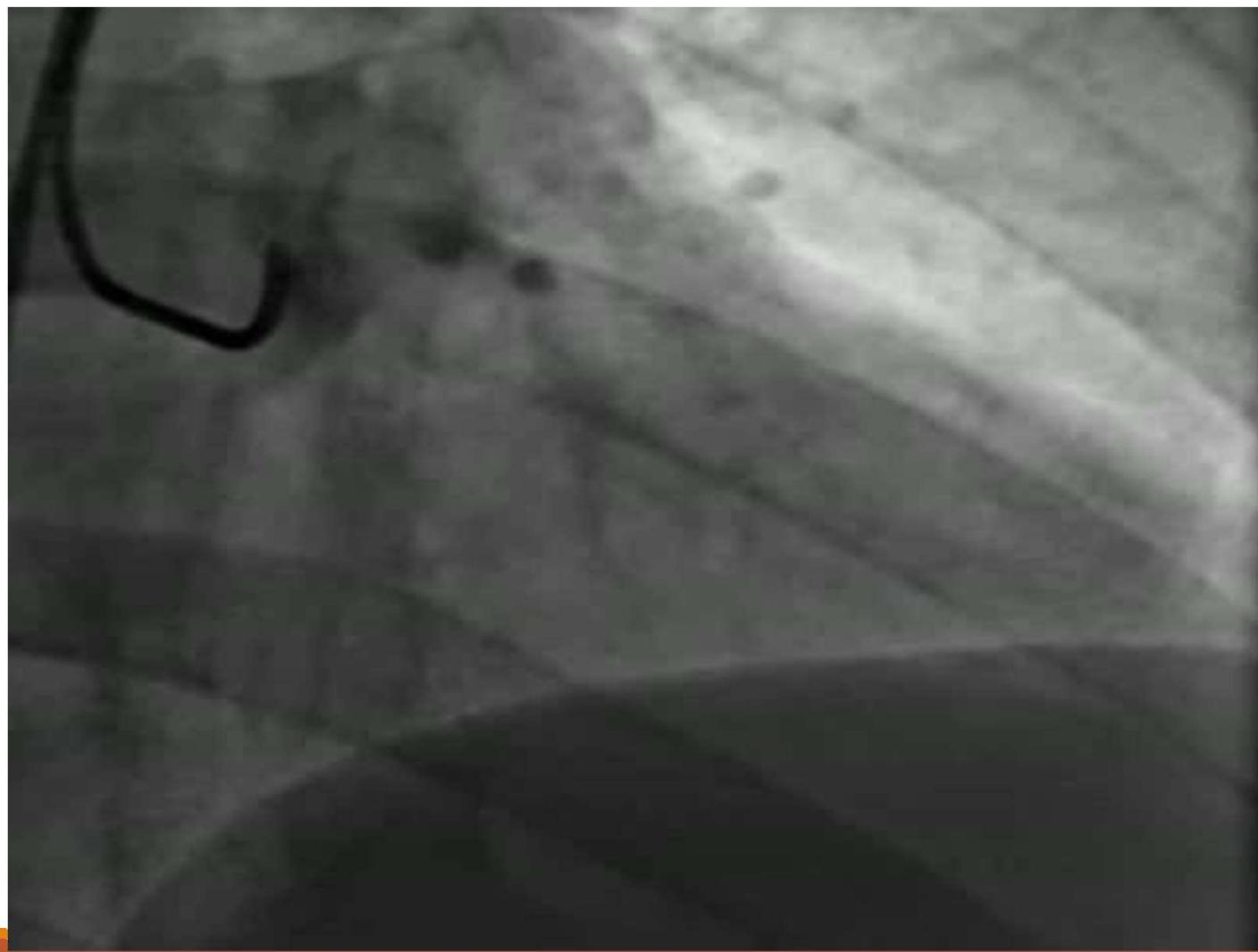
Based on mathematics of exponentials either α_1 , or α_2 must equal F/V_2 and the other α must be F/V_1

$$A = \frac{(F/V_2)C_1(0)}{(F/V_1) - (F/V_2)}$$

Therefore our model can be derived 2 ways

$$C_2(t) = \frac{V_1}{V_1 - V_2} C_1(0) (e^{-(F/V_1)t} - e^{-(F/V_2)t})$$

Imaging and Pharmacokinetic Modeling of Tracers



GE MEDICAL SYSTEMS
SIGNA HDx SJMROCO
Ex: 3197
Se: 1000
Im: 1+C
COL OCor A 48.6
DFOV 14.0cm

DT:1.00
Ph:1/17

ET:1

R
S
A

SAL

St Josephs Hosp
tricks
M47V
AW1188584572.301.1177100917
Apr 18 2007
02:08:45 PM
Mag = 1.00

FL:
ROT:

3D/TRICKS/30
TR:8.1
TE:3.1/Fr
EC:1 /1 31.2kHz

HRWRIST
FOV:14x9.8/W
1.4thk/-0.7ov
408/01:56
320X192/0.75 NEX
MP/Z2

IPR

WW: 4845 WL: 3520

Modeling Imaging Tracers

1). Dynamic susceptibility weighted MRI (dscMRI)

- See decreased signal intensity

2). Dynamic contrast enhanced MRI (dceMRI)

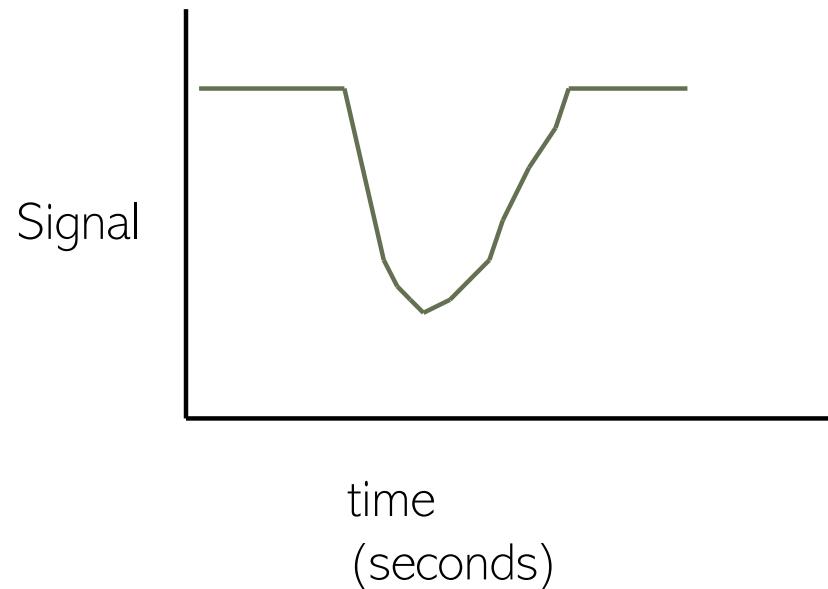
- see increased signal intensity

Using MRI these are almost exclusively done with Gadolinium (Gd) contrast agents

APPLICATIONS:

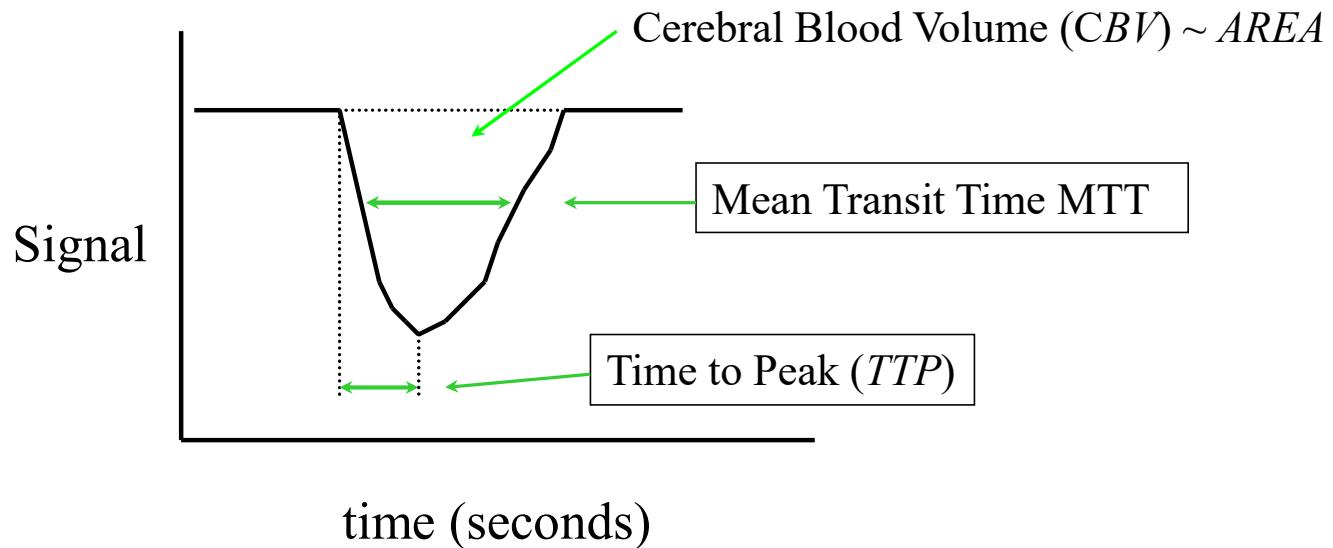
- stroke assessment
- tumour vascularity
- many other possibilities

MRI Model #1: dscMRI

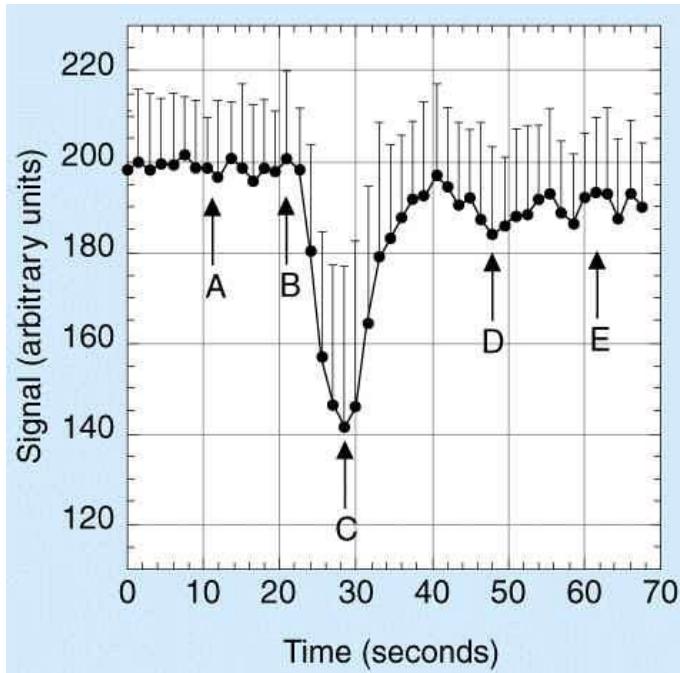


MRI Model #1: dscMRI

- Looking at 'raw data' of signal vs. time
- Want to model blood flow and blood volume
- This approach is most often for brain.
- Cerebral blood flow (CBF) and cerebral blood volume (CBV)



Sample Brain Data:



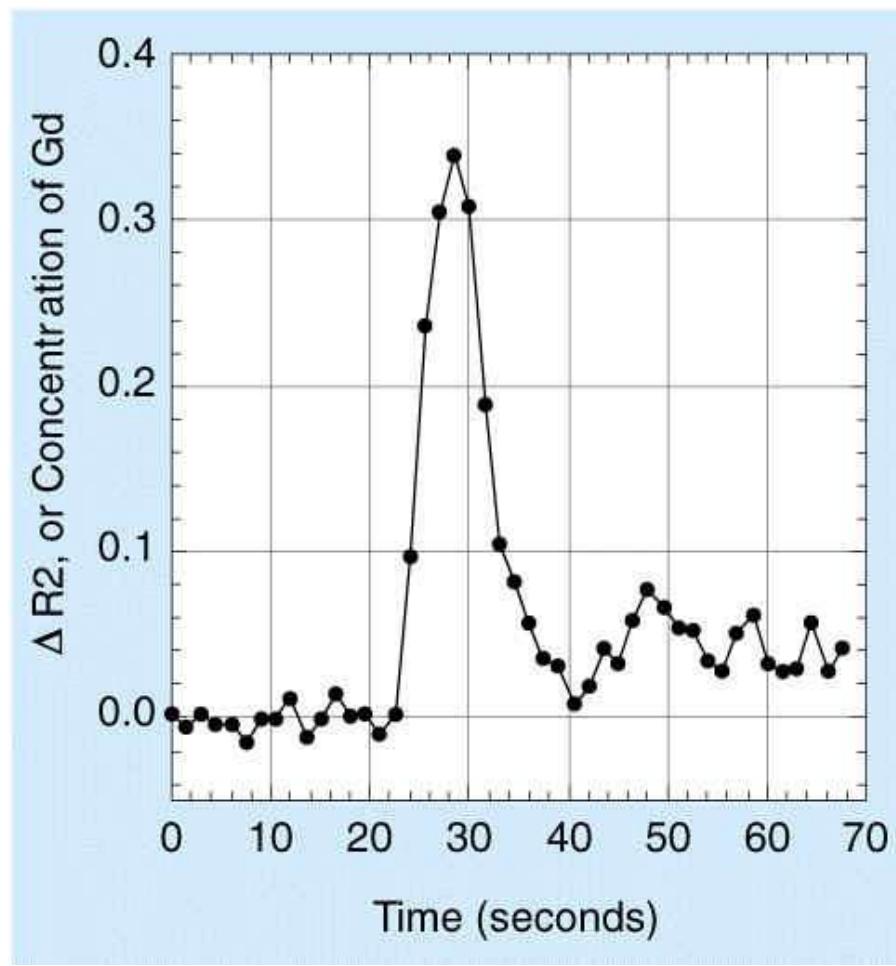
A = baseline

B = bolus time of arrival

C = Time to Peak (TTP)

D = second pass

E = third pass



$$\Delta R_2 = \frac{-\ln(S / S_o)}{TE}$$

$$C_T(t) = \Delta R_2(\text{tissue})$$

$$C_A(t) = \Delta R_2(\text{artery})$$

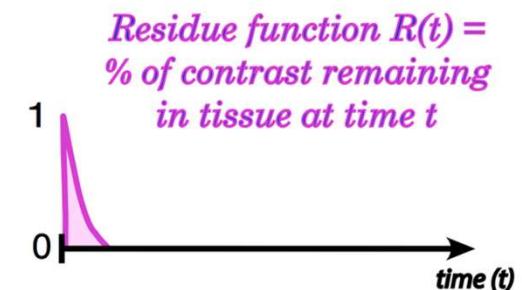
$$CBV = \frac{\int_0^{\infty} C_T(t) dt}{\int_0^{\infty} C_A(t) dt}$$

Note: TE = MRI parameter called “echo time”; set by MRI operator

Arterial Input Function (AIF):

The linear system here is the tissue capillary bed

- 1). Tissue response to a Dirac delta function $\delta(t)$ at $t=0$.
- 2). After injection, see dispersion of the bolus within tissue and a range of particle transit times.
- 3). The fraction of injected particles remaining at time= t after impulse injection is the residue (dimensionless function $R(t)$).
- 4). Immediately after injection $R(t)$ is maximal with value $R(0) = 1$, then $R(t)$ decreases

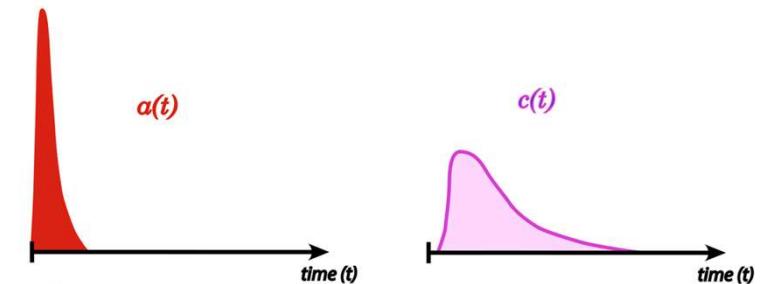


Arterial Input Function (AIF):

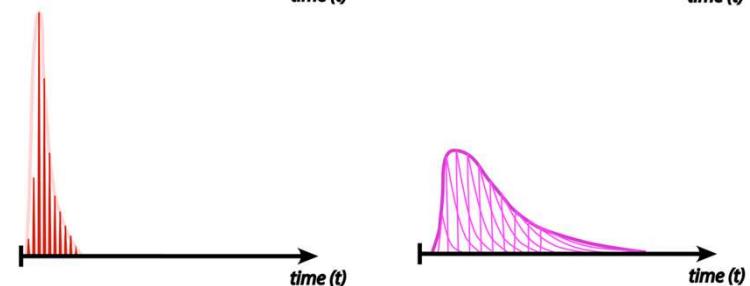
- Width of $R(t)$ reflects the distribution of particle transit times through a tissue.
 - area under $R(t)$ reflects the average time a particle spends transitioning through a tissue vascular bed (mean transit time, MTT):
-
- Instantaneous bolus is only hypothetical. The arterial input function, $CA(t)$, is thus always temporally dispersed.
 - broad $CA(t)$ can be represented as a set of Dirac delta functions at different time delays (τ), each producing an independent response.

Model vs Real life AIF

a real-life arterial input function (AIF)
with corresponding resultant tissue
concentration curve $C_T(t)$



Modeling the tissue response by a set of
Dirac delta functions



CBF (FT) requires AIF!

Blood Flow (CBF)

- require AIF (arterial input function)

$$C_T(t) = F_T \cdot C_A(t) \otimes R(t) = F_T \int_0^t C_A(\tau) R(t-\tau) d\tau$$

$C_T(t)$ = [Gd] in tissue at time = t

$C_A(t)$ = arterial [Gd] concentration at time = t

$R(t)$ = vascular residue function

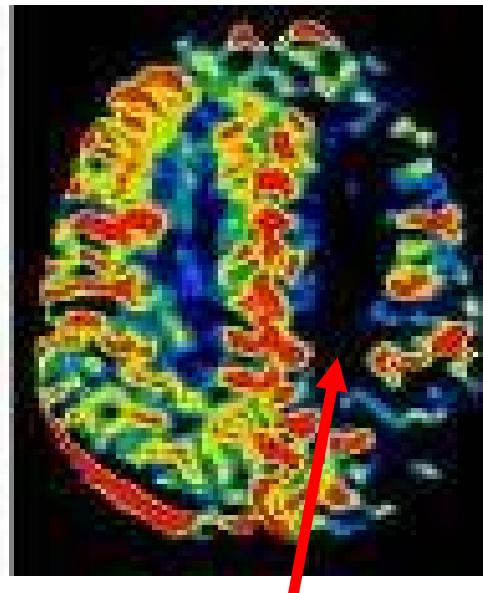
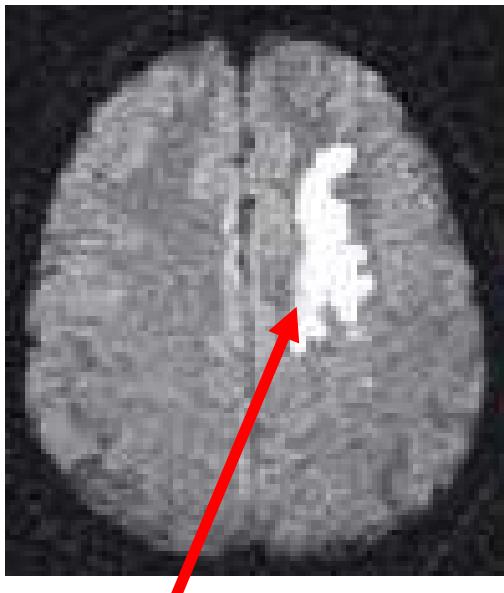
F_T = tissue blood flow

NOTE: Some versions of this equation contain a constant (ρ/h) preceding FT, where ρ = tissue density (g/mL) and h = fraction accounting for difference in hematocrit between capillaries and larger vessels.

CBF Model Assumptions...

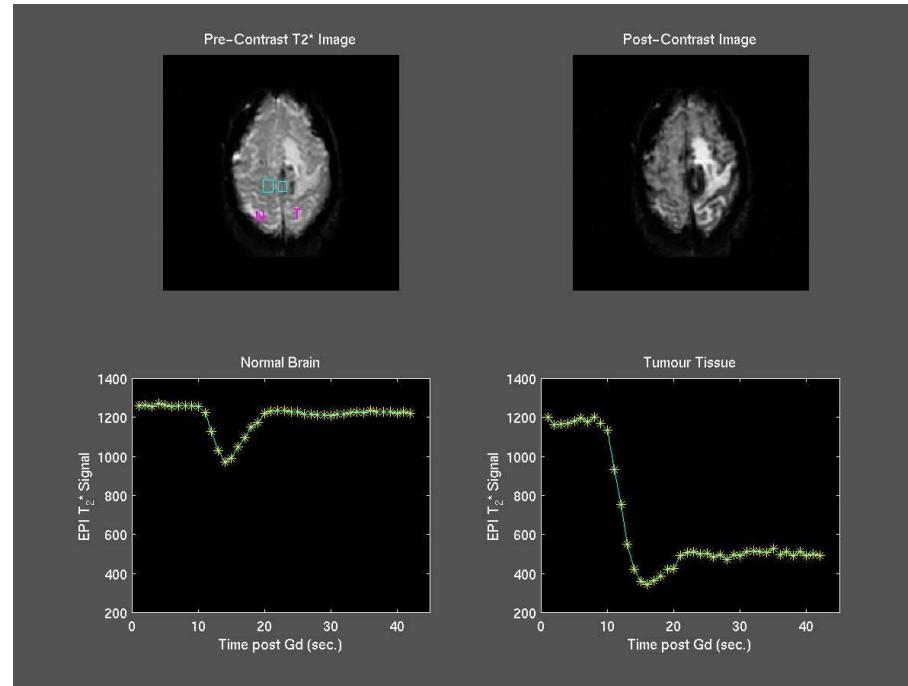
- 1) Cerebral blood flow (CBF) and cerebral blood volume (CBV) remain constant during the measurement period.
- 2) All injected tracer molecules eventually leave the system (i.e. there is nothing that stays around in the tissue for great lengths of time, lost within the tissue).
- 3) The system has a linear response to inputs

MRI Diffusion-Perfusion mismatch: Acute ischemic stroke

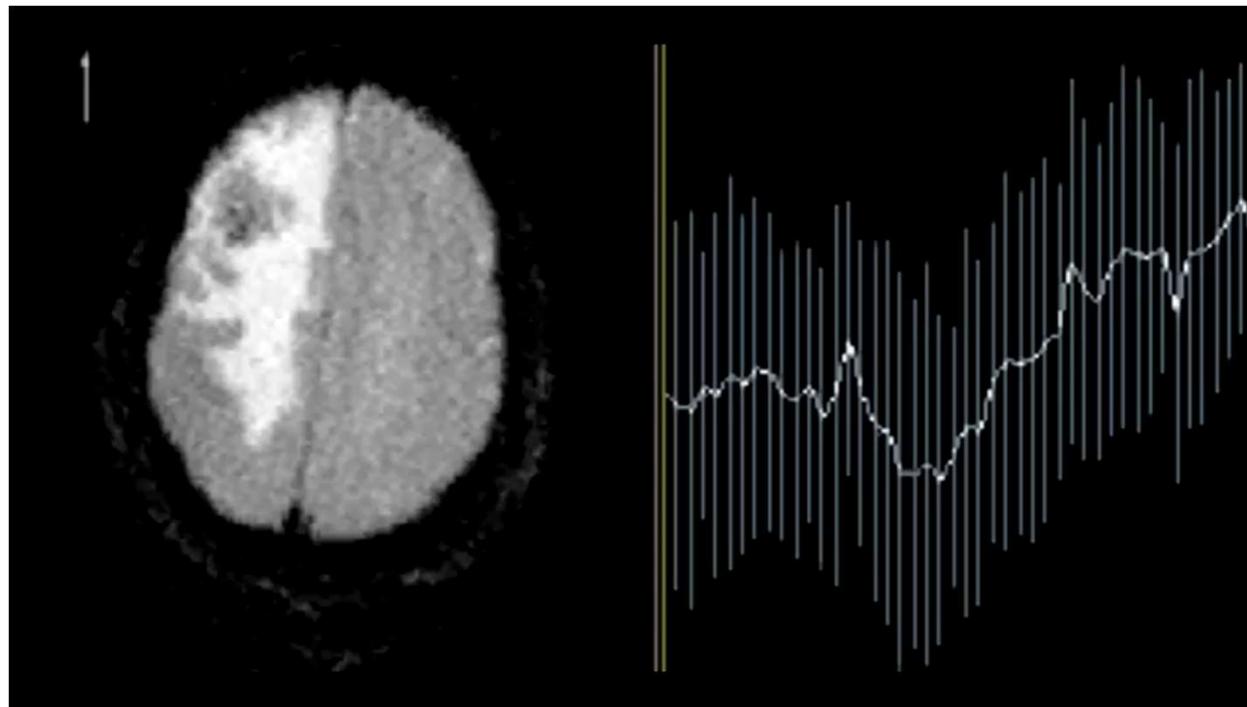


Diffusion (DWI) abnormality < perfusion (CBF) abnormality
= ischemic penumbra (risk of infarction)

Brain Tumour: Example of FAILED model!

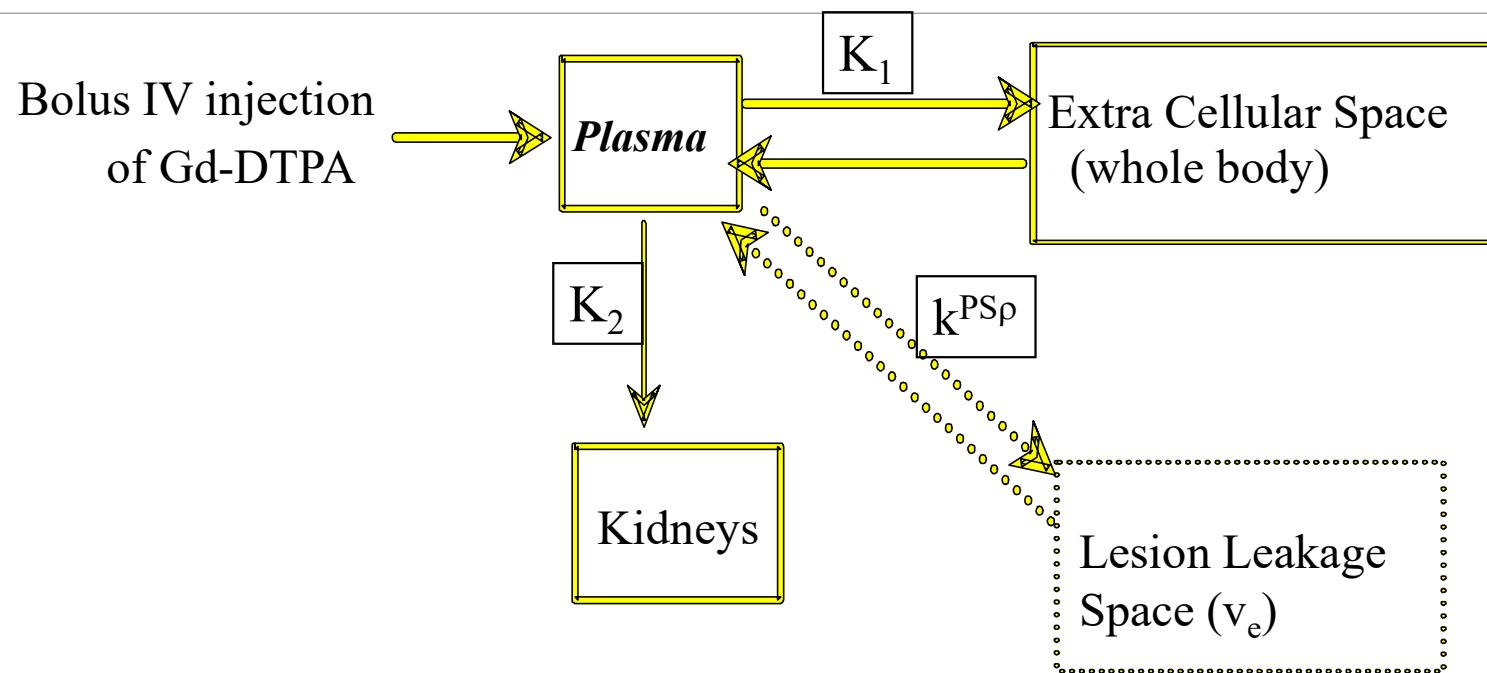


BBB Breakdown: FAILED model!



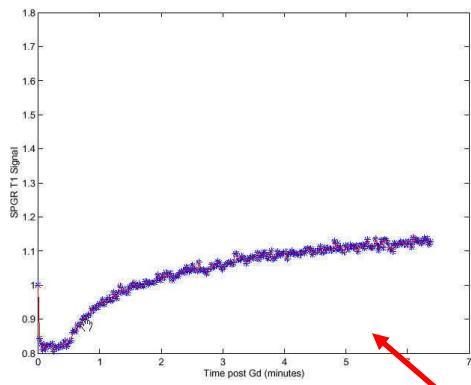
Tissue $\Delta R_2 \pm \text{std}$

Pharmacokinetic Model:

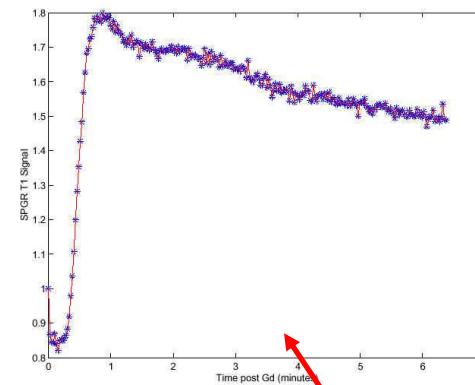


MRI Model #2: dceMRI

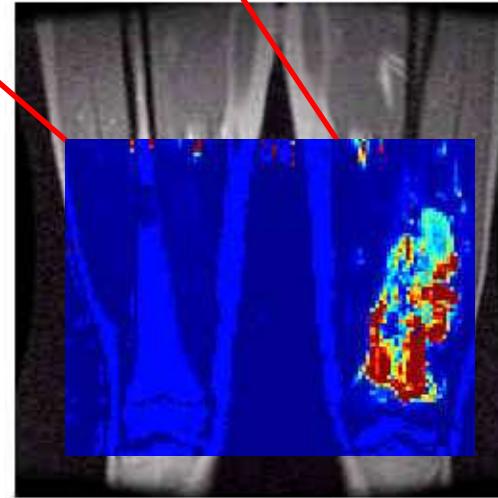




Initial SPGR image



SPGR at 50 seconds



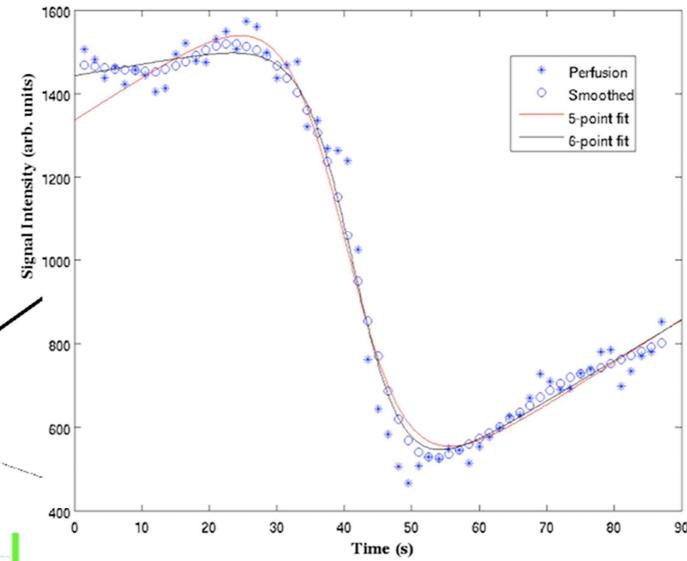
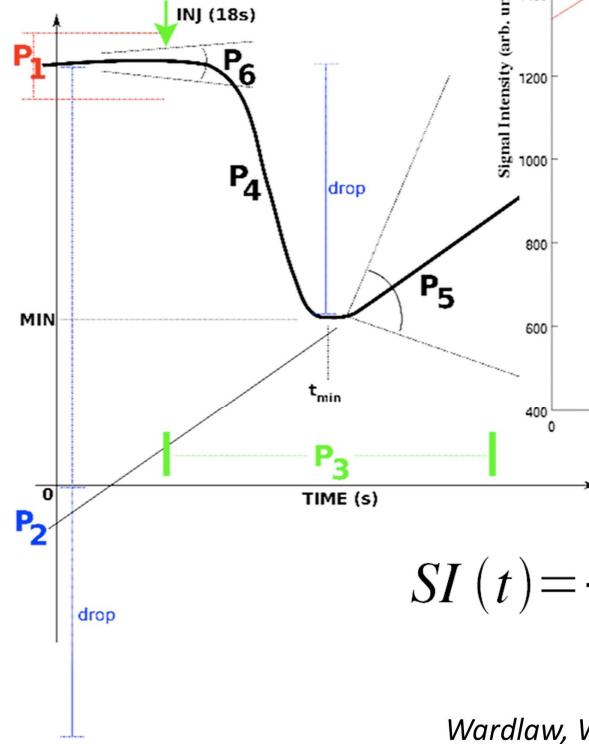
Caveats of Dynamic Contrast Enhanced MRI

Need an IV injection of contrast agent (typically Gadolinium based). A potential problem with patients who have reduced GFR and shouldn't be injected with this

Mathematical modeling requires fast injection (3-5cc per second). This is a problem for children, chemotherapy patients, and others.

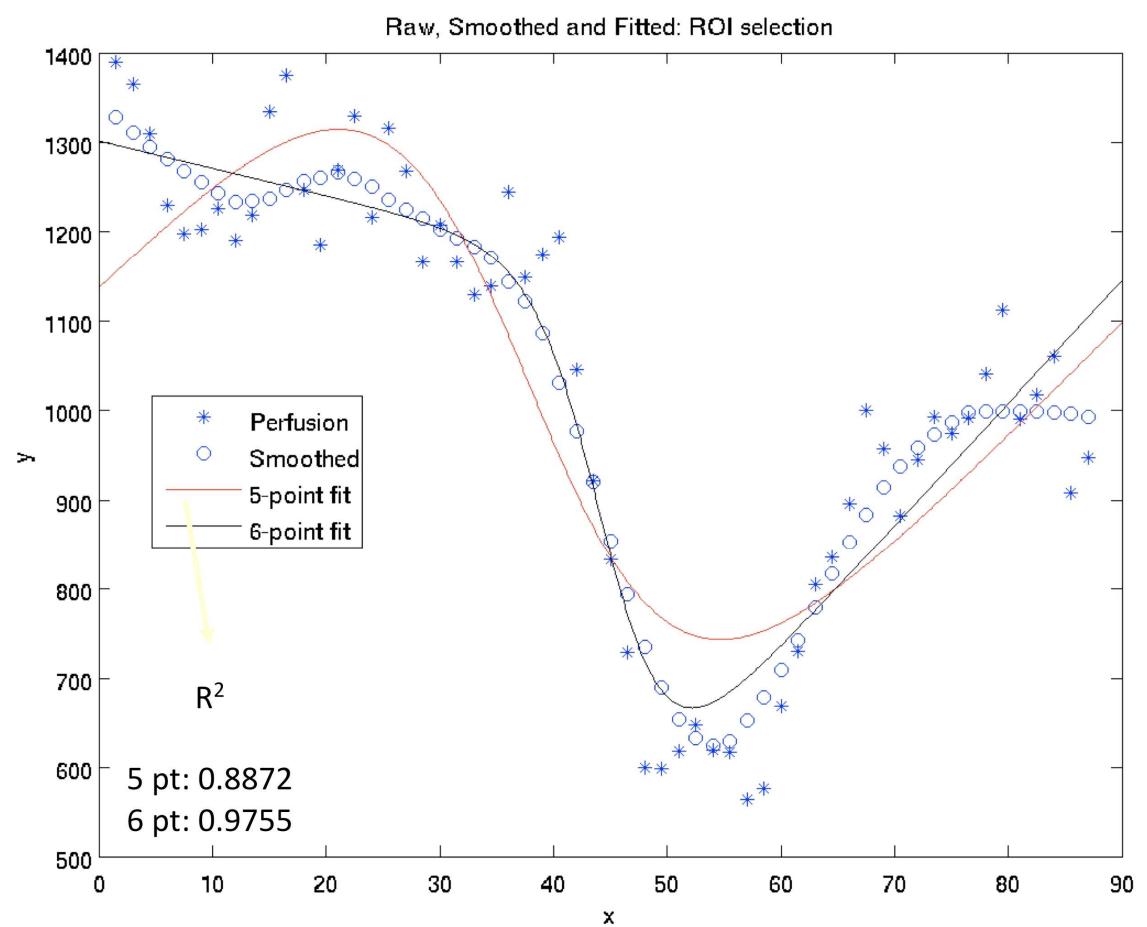
What is the appropriate mathematical model? What should be the 'initial conditions' of the model?

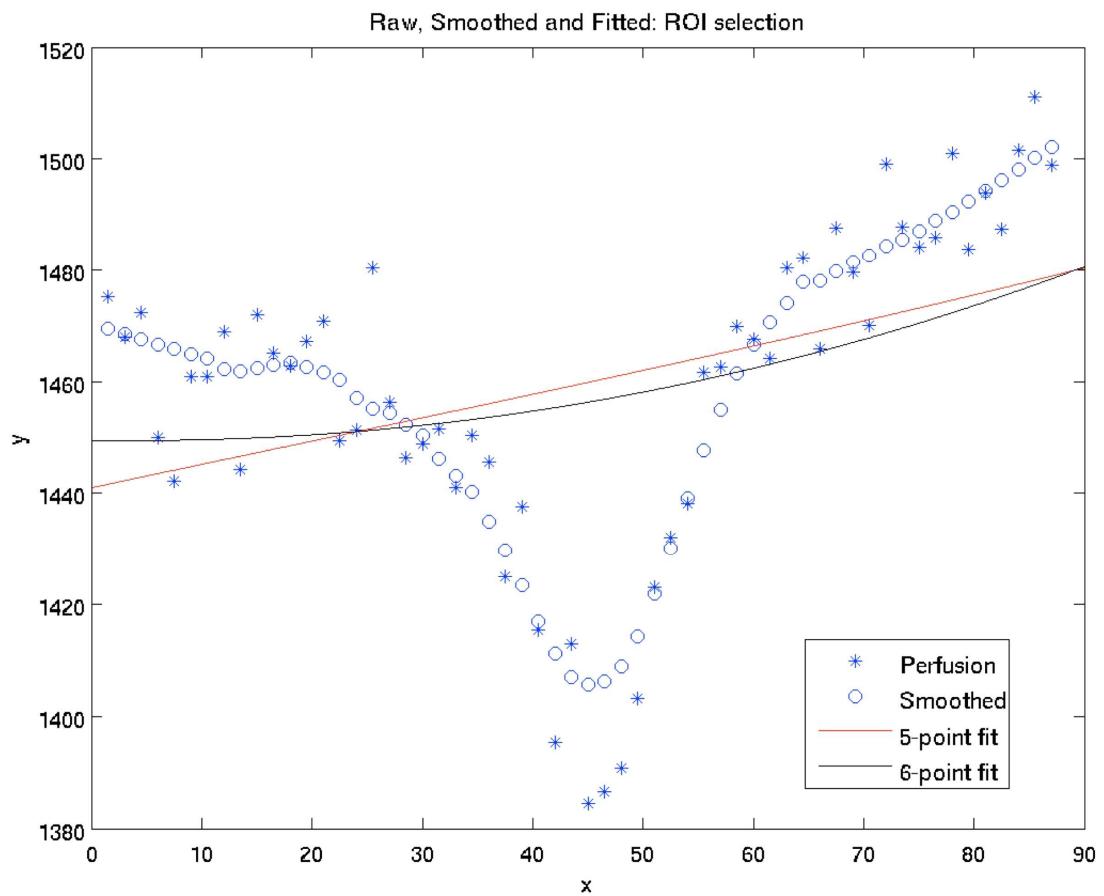
T2* Logistic Model



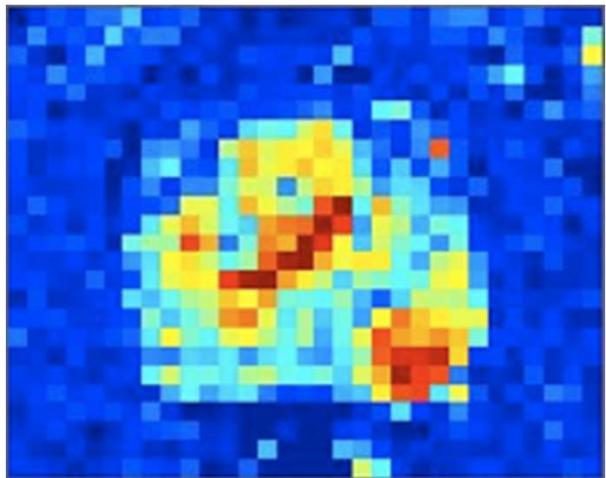
$$SI(t) = \frac{P_1 + P_6 t}{1 + e^{P_4(t - P_3)}} + (P_2 + P_5 t)$$

Wardlaw, Wong, Noseworthy (2009) Submitted



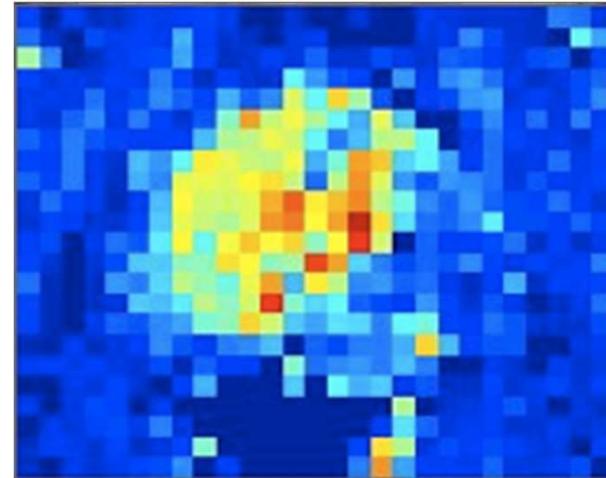


dceMRI of Prostate Cancer



Perfusion:

- Appropriate Model
- hypervasculär peripheral zone



Perfusion:

- inappropriate model
- now what ?

Tensor Math

Tensors are a mathematical construct that allows for the simple representation of vectors and directional fields. In some sense, tensors can be thought of as matrices.

For example a scalar for temperature can be a real number.

	Normal Notation	Tensor Notation
Scalar:	a	a

Vectors are directional values.

	Normal Notation	Tensor Notation
Vector:	$v_x i + v_y j + v_z k$	\vec{v}

When are Tensors Necessary?

Consider Fick's law in elementary form:

$$J = -D \frac{\partial C}{\partial x}$$

- flux, J , of a diffusing species flows opposite the gradient in concentration
- magnitude of the flux is proportional to the steepness of the gradient.
- adequate for diffusion across a slab or membrane

$$\vec{J} = -D \vec{\nabla} C$$

$$\vec{\nabla} = (\partial / \partial x, \partial / \partial y, \partial / \partial z)$$

Diffusion in 3d

$$J_x = -D \frac{\partial C}{\partial x}$$

$$J_y = -D \frac{\partial C}{\partial y}$$

$$J_z = -D \frac{\partial C}{\partial z}$$

This can be used to describe a great number of situations as long as the material in question is isotropic.

$$J_x = -D_{xx} \frac{\partial C}{\partial x} - D_{xy} \frac{\partial C}{\partial y} - D_{xz} \frac{\partial C}{\partial z}$$

$$J_y = -D_{yx} \frac{\partial C}{\partial x} - D_{yy} \frac{\partial C}{\partial y} - D_{yz} \frac{\partial C}{\partial z}.$$

$$J_z = -D_{zx} \frac{\partial C}{\partial x} - D_{zy} \frac{\partial C}{\partial y} - D_{zz} \frac{\partial C}{\partial z}$$

$$\begin{bmatrix} J_x \\ J_y \\ J_z \end{bmatrix} = - \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \begin{bmatrix} \partial C / \partial x \\ \partial C / \partial y \\ \partial C / \partial z \end{bmatrix}$$



<https://youtu.be/f5liqUk0ZTw/>