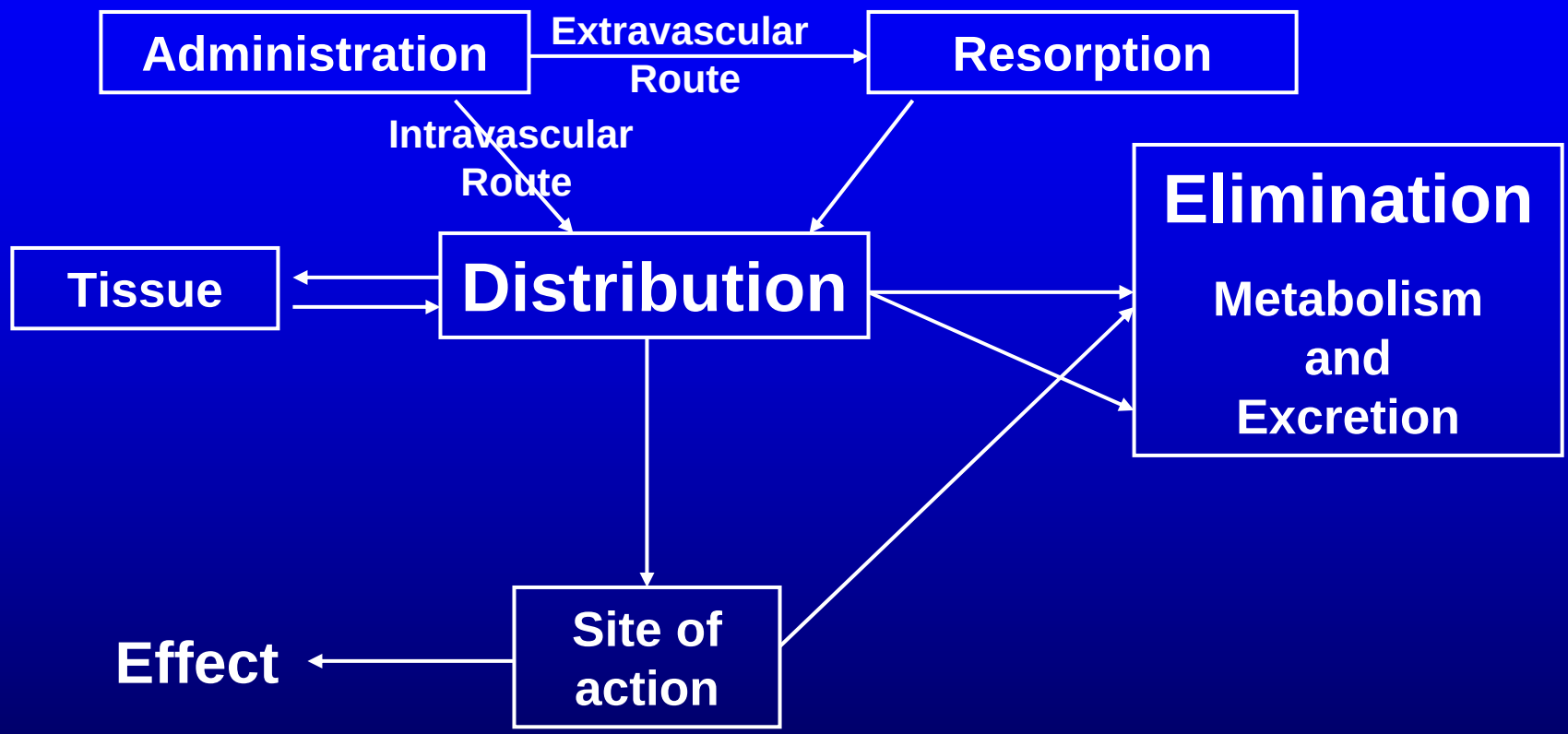
Pharmacokinetics and Drug Release

Pharmacokinetics

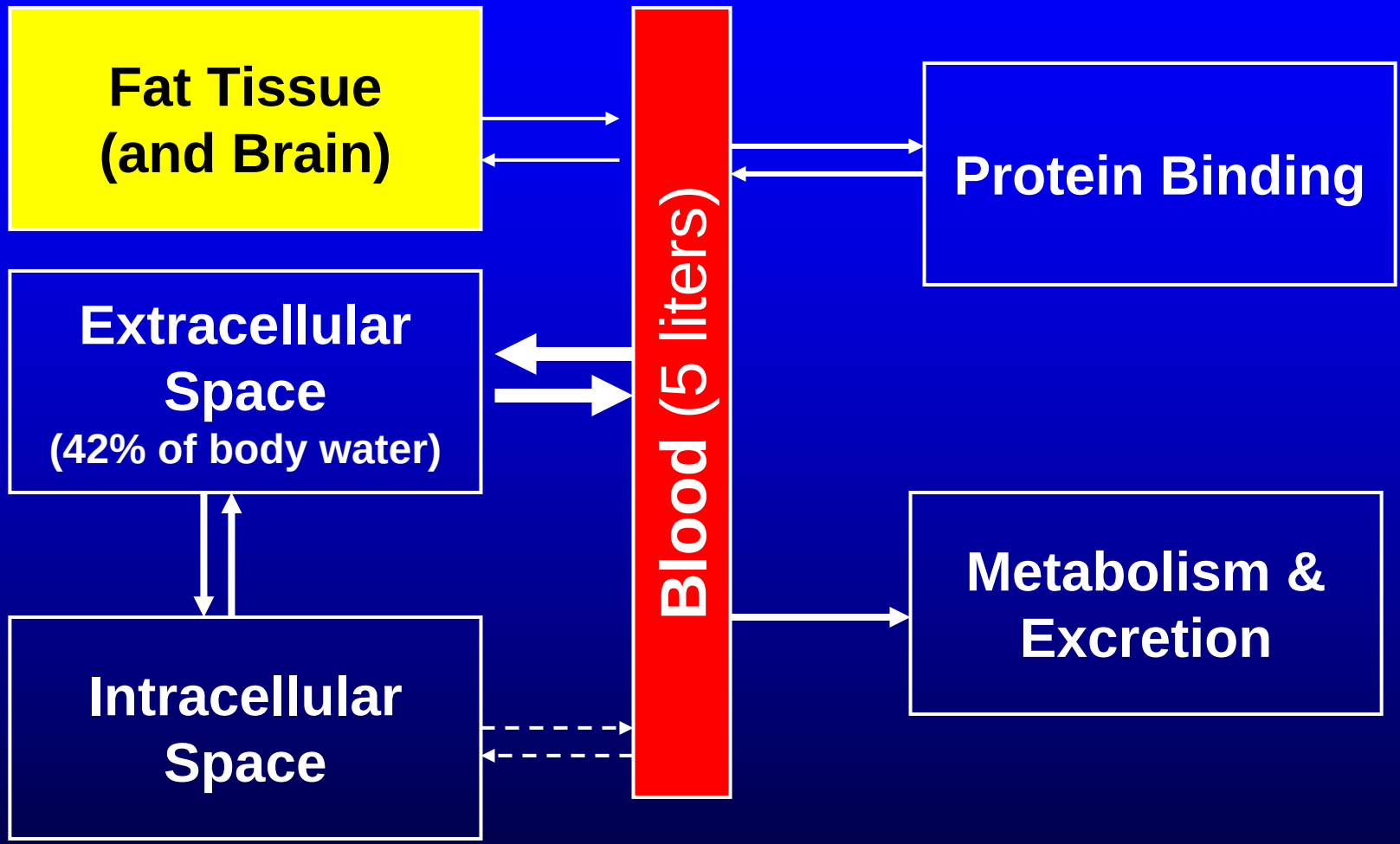
Pharmacokinetics in general is determined by:

- Absorption
- Distribution
  - Solubility
  - Size of compartment
  - Perfusion
- Metabolism
- Elimination

Drug Concentration over Time



Compartments



Compartments

Physical Volumes (L/kg body weight) of some body compartments

Compartment Volume	Example Drug
• Water	
– Total Body water: 0.6 l/kg	small H_2O soluble molecules, e.g. ethanol
– Extracellular water: 0.2 l/kg	larger H_2O soluble molecules, e.g. gentamicin
– Blood: 0.08 l/kg – Plasma: 0.04 l/kg	**Strongly protein-bound molecules or large molecules, e.g. heparin**
• Fat: 0.2-0.35 l/kg	highly lipid soluble molecules, e.g. narcosis gases or DTT
• Bone: 0.07 l/kg	certain ions, e.g. Fluorine, Pb

Drug Distribution

In the equilibrium state situation:

- The drug has the same **partial pressure** in every compartment

- The partial pressure depends on the **solubility** and **concentration** (= amount / volume)

- The time to reach the steady state situation depends also on the diffusion properties and the perfusion of the compartment

Drug Distribution

Exchange between Compartments depends upon

- Chemical structure of drug
- Rate of blood flow
- Ease of transport through membrane
- Binding of drug to proteins in blood
- Elimination processes

Distribution in Compartments

- Solubility
  - Ionidized (charged) molecules (and polar molecules) are more soluble in aqueous solutions
    - Blood
    - Extracellular space
    - Intracellular space
  - neutral molecules are more soluble in fat
    - Adipose tissue
    - Brain
    - Cell membranes
- Ion Trapping
  - Low pH: weak acids accept one proton $\Rightarrow$ neutral
  - High pH: weak bases give off one proton $\Rightarrow$ neutral

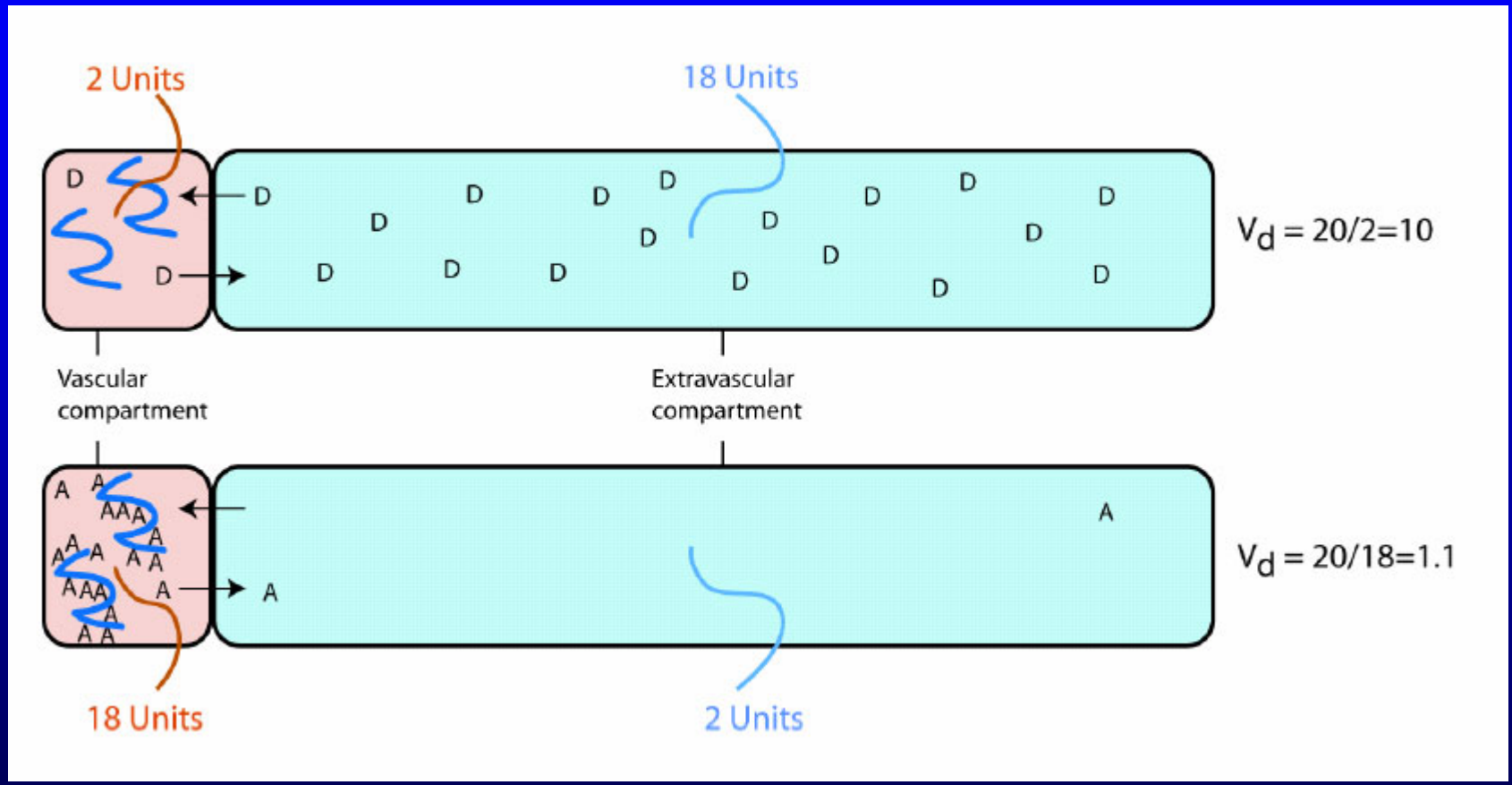
Effects of pH Partitioning

- Urinary acidification
  - accelerates the excretion of weak bases and retard that of weak acids
  - alkalination has the opposite effects
- Increasing plasma pH (by addition of $NaHCO_3$)
  - weakly acidic drugs will be extracted from the CNS into the plasma
  - reducing plasma pH (by administering a carbonic anhydrase inhibitor) will cause weakly acidic drugs to be concentrated in the CNS, increasing their efficiency
- Inflammatory tissue generally has low pH
  - Acidic drugs (antibiotics, analgetics) do not reach high concentrations there

Partitioning into Fat Tissue

- **A large, non-polar compartment.**
- Fat has low blood supply - less than 2% of cardiac output, so drugs are delivered to and resorbed from fat relatively slowly.
- **Brain is the other non-polar compartment, but blood supply is high.**
- For practical purposes: Partition into body fat important following acute dosing only for a few highly lipid-soluble drugs and environmental contaminants which are poorly metabolized and remain in body for long period of time

Effect of Protein Binding on Distribution



Protein Binding

Protein-bound drugs have no effect!

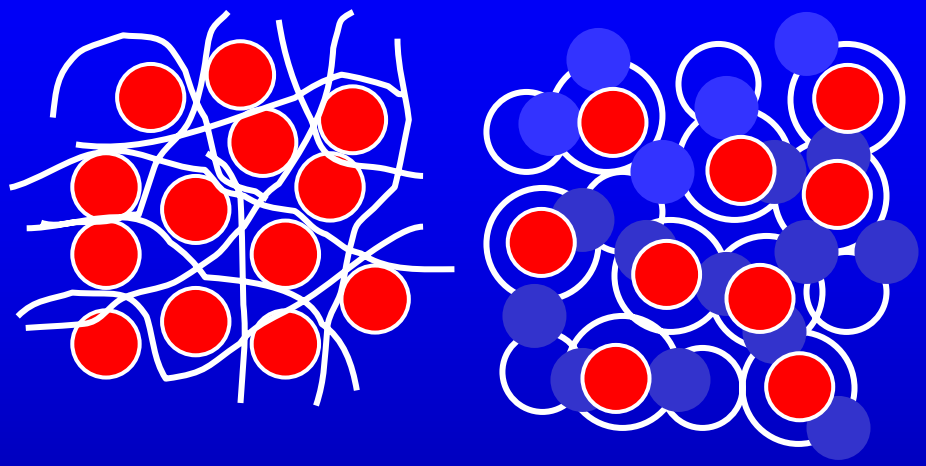
- **Albumin**: binds many acidic drugs and a few basic drugs
- **Beta-globulin** and an α_1**acid glycoprotein** have also been found to bind certain basic drugs
- Protein binding depends on the ionization of the drug $\Rightarrow$ pH dependence
- Renal failure, inflammation, fasting, malnutrition can have effect on plasma protein binding.
- Competition from other drugs can also affect protein binding.

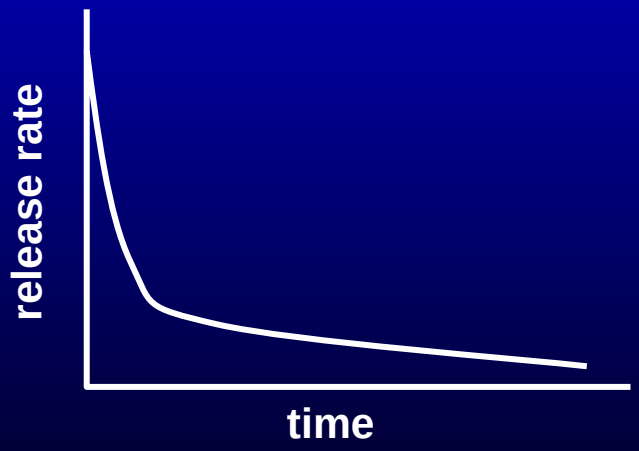
(Local) Drug Release Systems

Drug Release Systems

- Intention
  - Prolonged release of the drug
  - Provide a highly active drug at locally sufficient concentration but no effect on other organs/ the body as a whole
    (local effect but no systemic effect)
  - No first pass effect (degradation in the liver)
- Requirements
  - System with continuous slow release
    - Release rate and duration adjusted to the local requirements
  - Drug should stay locally and not flow away
    - No flow conditions
    - Non-soluble/ lipophilic drug

Standard Drug Release System





- **Drug molecules**
  - embedded in the pores of a foam/ sponge
  - in a polymer
  - Adsorbed on a meshwork/ non-woven
- **Drug release by diffusion processes**
- **Initially very high release rates**
  - Higher concentration available
  - Shorter diffusion ways
  - Active push-out by invading water

⇒ **Generally very inconstant release rates**

Standard Drug Release System

More constant release kinetics by

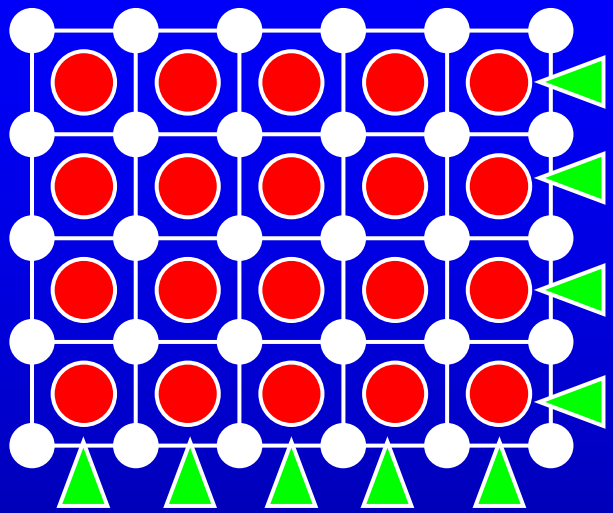
- Drug-free cover layer
- Formation of multilayer systems with different diffusion rates
- (ion implantation into the surface)
  - Destroys the drug in the surface layer
  - Carbonizes the surfaces: lower diffusion rate

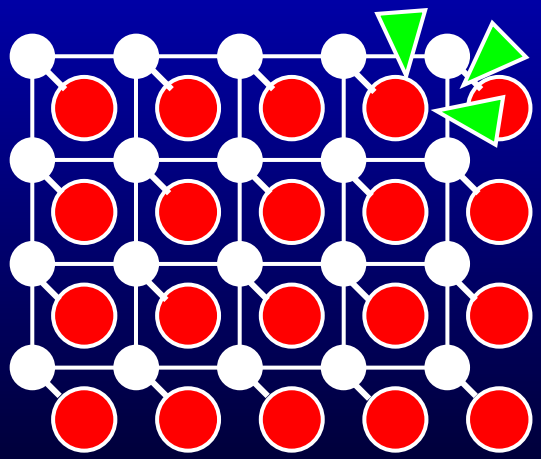
Standard Drug Release System

Polymers as Drug Release System

- Drug incorporation by diffusion will result in highest concentrations outside and lower concentrations inside ⇒ Release will be more inhomogeneous
- Drug incorporation during polymerization ⇒ Reactive monomers may destroy the drug

Advanced (Proposed) Release Systems





Drug

Polymer/ Carrier

Enzyme (e.g. Esterase)

Drug release by enzymatic degradation of the matrix

- Release of the drug then by diffusion
- Enzymatic release of the drug

- Most constant release profile (dependent mainly on surface)
- Release rate individually different
- Compatibility of the degradation products?