2-Distribution

Structure-Distribution relationship

= Structure-Plasma protein binding relationship

= Structure-Albumin binding relationship

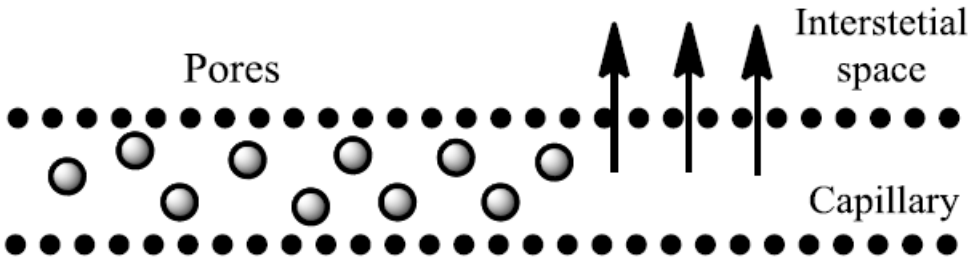
Structure–Distribution Relationship

- The most important factor controlling drug distribution is plasma protein binding.
- Albumin: The primary plasma protein responsible for binding most drugs → “plasma protein binding” essentially means structure–albumin binding relationship.

- Mainly focus on
- Structural factors that control whether a drug binds to albumin.
- Consequences of protein binding on Distribution or Pharmacokinetic or Drug activity and interactions

Consequences of protein binding

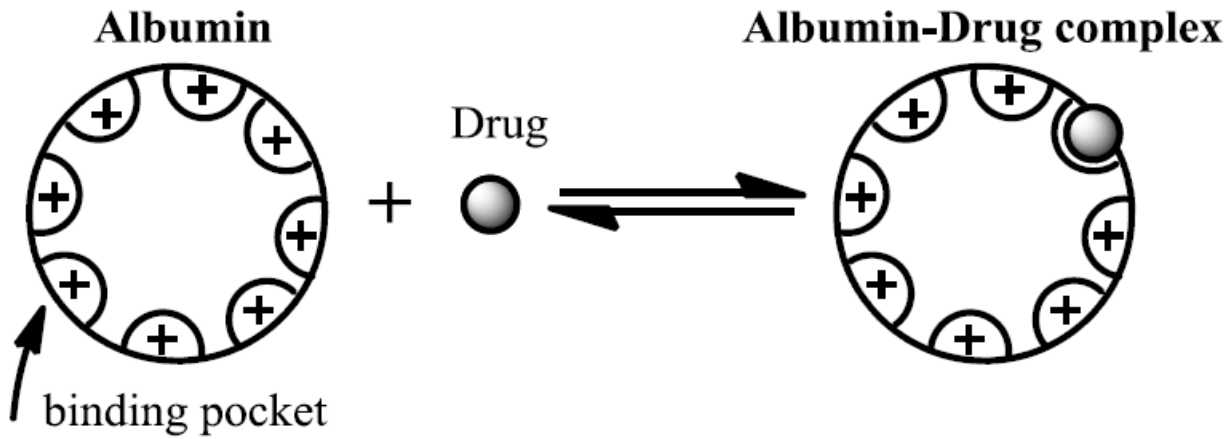
- Protein bindings effects how drugs exit from the plasma to interstitial fluid between cells,
- as you know capillaries are small porous vessels that allow fluids to pass toward interstitial fluid between cells, these pores found in the walls of capillaries allow anything to pass except compounds bound to albumin and albumin itself under normal circumstances.

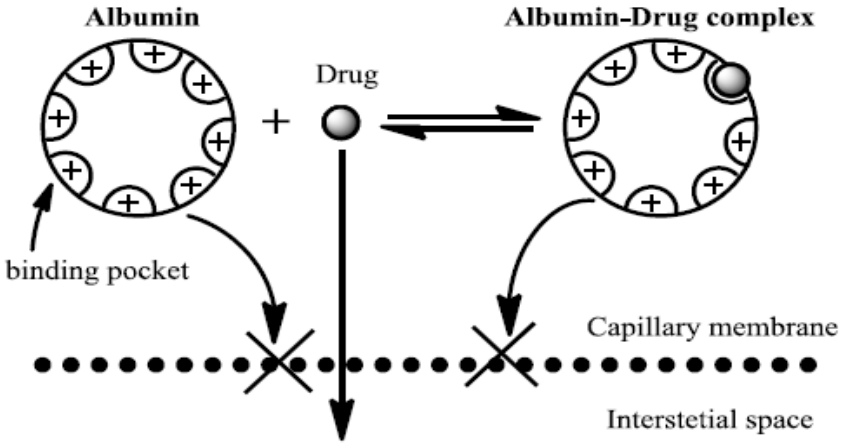


•Molecules **smaller than albumin (≈67,000 Da)** can pass through capillary pores, but **albumin and anything bound to it cannot**.
•Therefore, **drugs tightly bound to albumin remain in the bloodstream** and cannot easily reach tissues.
•Heavily protein-bound drugs have a **low volume of distribution (≈5 L)**, meaning they are mainly confined to blood.
•Drugs that are weakly bound or not bound can distribute throughout body fluids, giving a **larger volume of distribution (up to ~40 L)**.
➢Protein binding is **reversible and dynamic**, creating an equilibrium between:
➢**Bound (inactive) form** – cannot cross membranes
➢**Free (active) form** – crosses membranes and produces biological effects
•Even if a drug is **99% bound**, the remaining **1% free fraction** is responsible for its pharmacological action.

Protein bound form is found only in plasma and is actually biologically inactive but the free form is an active form, and this is very important, leading to the conclusion that protein binding either causes :

- limitation of bioavailability of drugs with low potency, or
- causes prolongation of activity of potent drugs and sustained release effect.





- **Example: Thyroxine**
- Thyroxine is **~95% bound** to plasma proteins.
- Only **~5% is free**, and this free fraction is **biologically active**.
- The free form can cross the **placental membrane**.
- However:
- Thyroxine has **relatively low potency**, so the small free fraction (5%) is **not enough to cause major toxicity to the embryo**.
- Therefore, **protein binding protects the embryo** by limiting the active free concentration.
- Clinical implication:
- In conditions like **liver failure**, protein binding may decrease.
- This increases the **free Thyroxine level**, allowing more drug to cross the placenta.
- Result: potential **embryonic toxicity**.
- So, **low-potency drugs**, excessive protein binding may **limit or suppress biological activity**, while also serving as a protective mechanism.

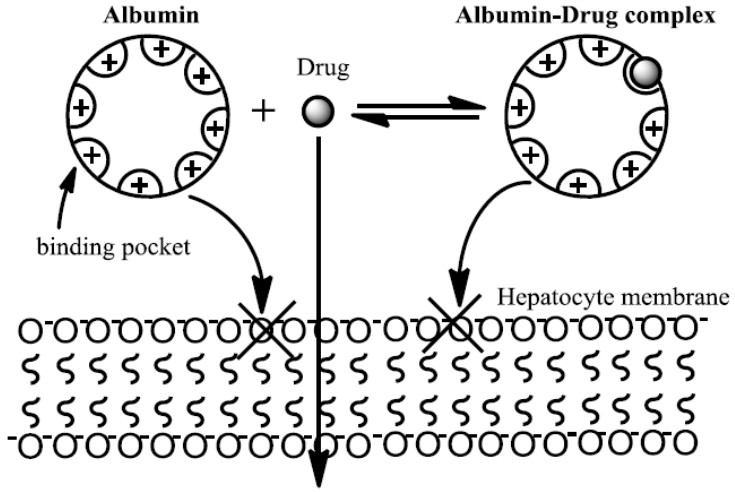
- Example: Suramin
- Suramin is ~99% bound to plasma proteins.
- Only 1% remains free, but this free fraction is highly potent. It is effective against trypanosoma (cause of sleeping sickness).Because of strong protein binding and high potency, a single IV dose can provide protection for up to 3 months.
- Comparison:
- Suramin vs Thyroxine
- Thyroxine: Low potency → protein binding limits activity.
- Suramin: High potency → protein binding prolongs activity.

- **Summary**
- **Protien Binding Controls Volume of Distribution (Vd)**
- Heavily bound drugs → stay in blood → **Low Vd (~5 L)**
- Poorly bound drugs → distribute widely → **High Vd (~40 L)**
- **Protien Binding Controls Bioactivity**
- If free drug is **highly potent** → binding prolongs action.
- If free drug is **low potency** → binding limits activity.

❖ **Protein-bound drugs resist metabolism and elimination.**

•For a drug to be metabolized, it must cross the **hepatocyte membrane** (phospholipid bilayer).

•The **protein-bound form cannot cross** this membrane.



Why?

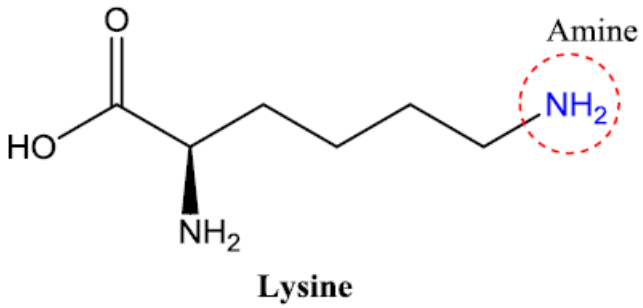
•**Albumin**:

- •Large molecular weight (~67,000 Da)
- •Positively charged surface
- •Rich in lysine and arginine (both strongly basic and positively charged)
- •Water soluble

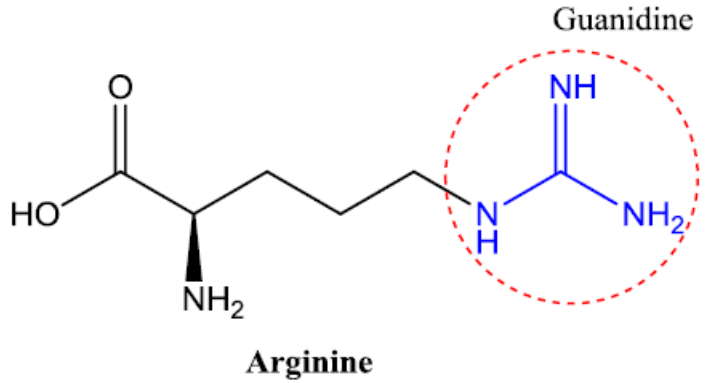
•Because albumin is:

- •Very large
- •Positively charged
- •Unable to permeate lipid membranes

➡ Any drug bound to albumin **cannot enter liver cells**, so it cannot undergo metabolism.



Lysine



Arginine

protein Binding and Renal Elimination

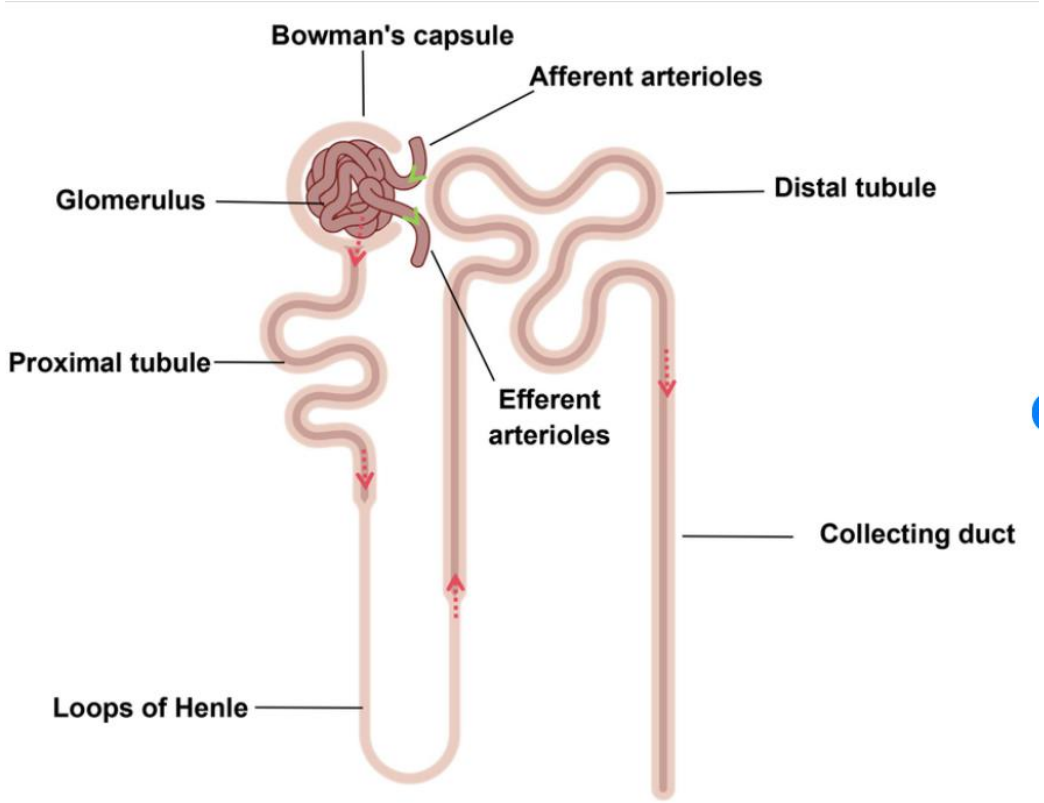
•The functional unit of the kidney is the **nephron** (Bowman capsule, glomerulus, afferent & efferent arterioles).
•During **glomerular filtration**, substances smaller than albumin are filtered:

- Amino acids
- Glucose
- Ions (Na^+, Cl^-, K^+)
- Water

•**Albumin is normally NOT filtered** because of its large size.
•If albumin appears in urine, it indicates **kidney dysfunction**.

Relation to Drugs

•**Free drug** → filtered through glomerulus → can be eliminated.
•**Protein-bound drug** → cannot be filtered → remains in bloodstream.



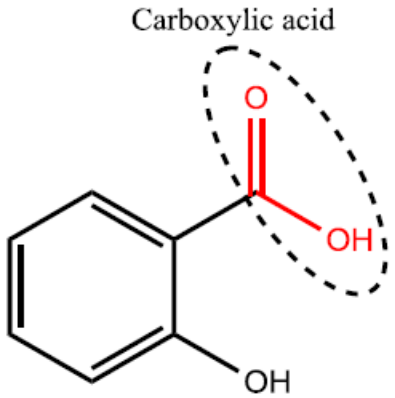
- So far protein binding contributed to 3 consequences:
- 1. Protein bound drugs tend to accumulate in the blood so they tend to have little or limited volume of distribution.
- 2. Protein bound drugs tend to have little access to their target so if they're potent, protein binding causes prolongation of biological activity like Suramine given IV providing 3 months protection even though IV is not designed for sustained release; while if they're not potent like Thyroxine, protein binding causes limitation of activity.
- 3. Protein bound drugs resist metabolism and resist renal elimination.

Structural factors that control protein binding

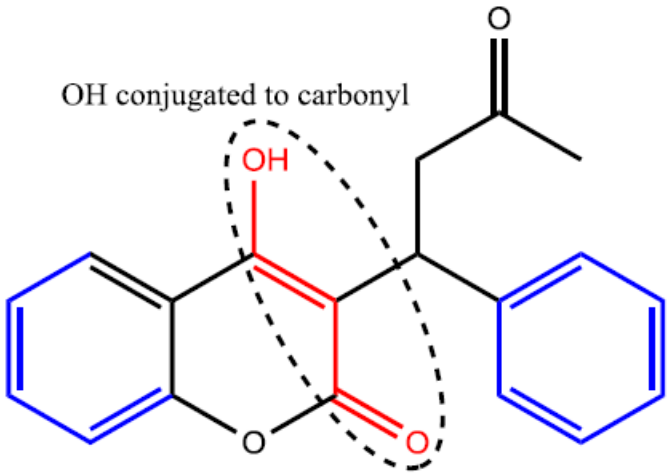
- what makes a chemical structure protein bound or not?
- **1- The charge of drug molecules**
- Negatively charged drugs bind more strongly to plasma proteins (especially albumin).
- Drugs containing **carboxylic acid groups** (pKa ≈ 3–4.5) are negatively charged at physiological pH (7.4).
- Example: Salicylic acid and many NSAIDs.
- These drugs tend to show high plasma protein binding.
- Drugs with similar structures (e.g., carboxylic acid group) compete for the same albumin binding sites.
- Albumin binding sites are relatively **nonspecific** (unlike stereospecific receptors).
- Competition may increase the free (unbound) fraction of one drug.
- This can alter pharmacokinetics and lead to **drug–drug interactions**.

1. The charge of the drug molecule.

- Example interaction: Salicylic acid (Aspirin) with Warfarin.
- Both drugs compete for the same albumin binding site.
- Warfarin contains an **acidic OH group** stabilized by an adjacent carbonyl group (electron-withdrawing effect).
- This makes warfarin sufficiently acidic to bind strongly to albumin.
- When salicylic acid is co-administered, it displaces warfarin from albumin.
- Result → Increased free (unbound) warfarin.
- Clinical outcome → Increased anticoagulant effect → Risk of bleeding.
- Therefore, patients are advised to avoid Aspirin while taking warfarin.



Salicylic acid

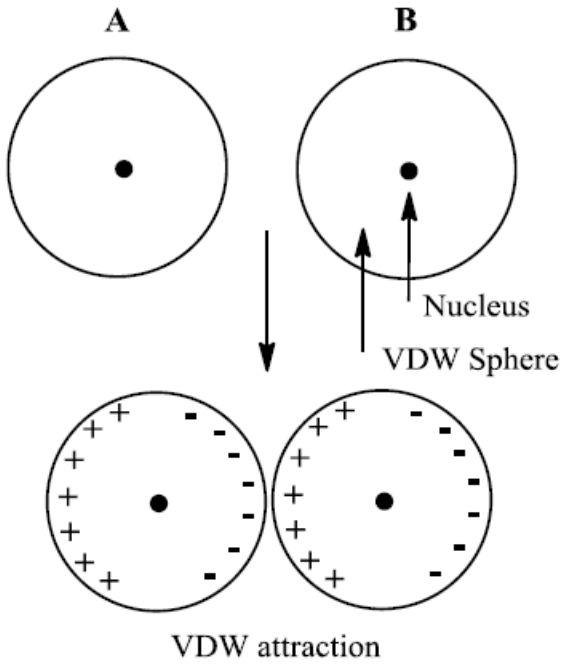


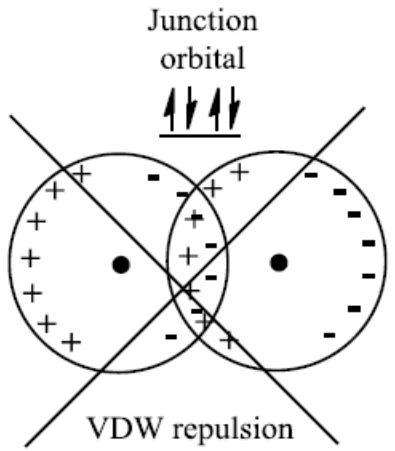
warfarin

2. Van Der Waal's attraction in the ligand's structure.

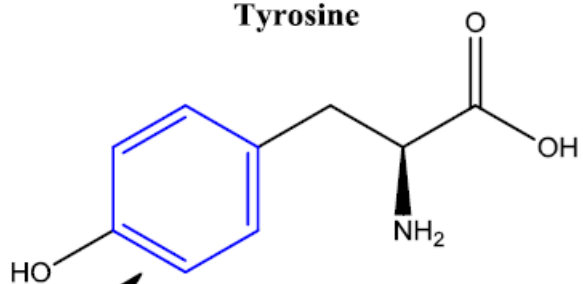
- Albumin contains tyrosine and phenylalanine on its surface.
- Both have aromatic rings capable of Pi-Pi stacking, a type of Van der Waals attraction.
- VDW attraction occurs between atoms or molecular fragments with large electron clouds.
- Van der Waals sphere: volume occupied by electrons around the nucleus.
  - Large atoms → large VDW sphere → electrons are far from the nucleus → highly polarizable.
  - Small atoms → small VDW sphere → less polarizable.
- Polarizable atoms can spontaneously create partial positive and negative charges.
- These temporary charges can induce polarization in neighboring atoms, leading to weak, short-range attractions.

•**VDW Attraction :**
•Occurs between large, polarizable atoms or molecular fragments.
•Electrons can shift easily, creating temporary partial charges.
•Attraction happens when VDW spheres touch but do not overlap.
•**VDW Repulsion:**
•If spheres overlap, electrons repel due to Pauli exclusion principle → called steric repulsion.
•Ligand-receptor binding and protein-drug interactions rely on **VDW attractions.**
•Requires large, polarizable atoms/groups: I, Br, Cl, S, aliphatic chains (propyl, butyl, etc.), aromatic rings.
•**Pi-Pi Stacking:**
•Special case of VDW attraction between aromatic rings.
•Rings approach closely without overlapping, interacting via electron clouds above and below the ring plane.

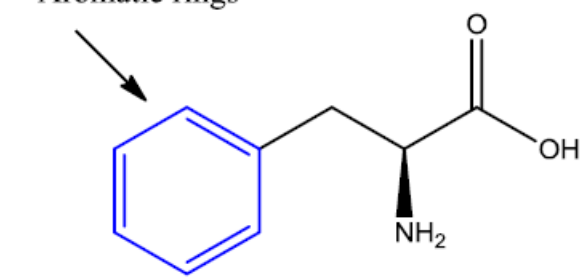




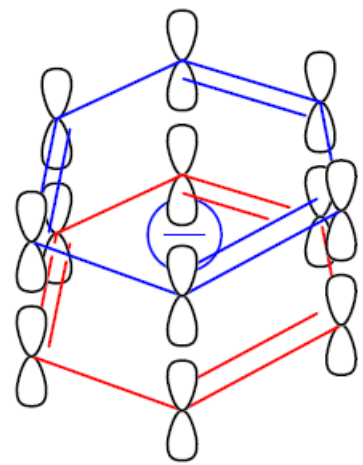
Tyrosine



Aromatic rings

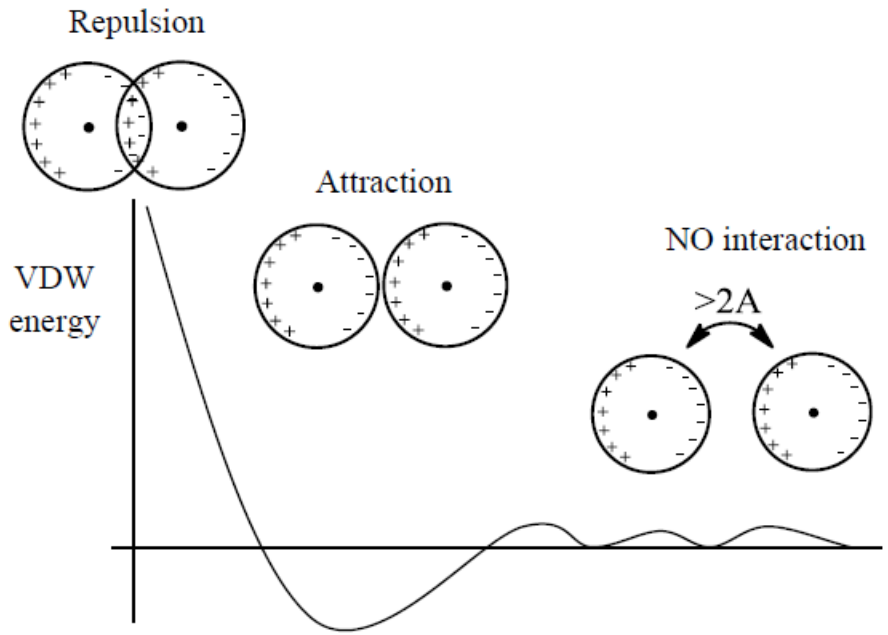


Phenylalanine

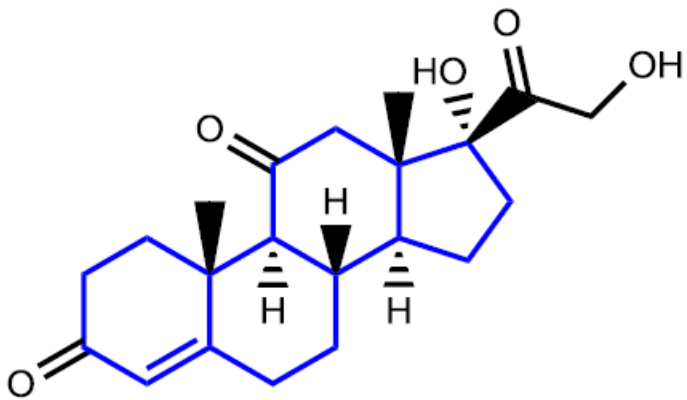


Pi-Pi Staching

If we draw Van Der waals' forces plotting VDW energy against distance, we'll notice that at very close distance overlapping and repulsion happen represented by positive energy, but when they get away until they only touch each others' spheres, an attractive interaction occur represented by negative energy, while if they get more away from each other around 2A, no attraction nor repulsion happen.



- **EXAMPLE**
- **Cortisone**
- the corticosteroid Cortisone is a hydrophobic
- backbone without charges; in general steroidal
- hormone backbone which is hydrophobic tend
- to exert significant Van Der Waals interactions
- making the corticosteroids more than 80%
- protein bound.



cortisone

Structure–Protein Binding Relationship

1. **Negative Charge:**
   - Promotes strong binding to albumin (which has positively charged amino acids: lysine, arginine).
   - Examples:
     - Salicylic acid → negatively charged → good protein binding.
     - Warfarin → hydroxyl conjugated to carbonyl → negatively charged → strong binding.
   - Negative charge alone → >95% binding.
2. **Van der Waals Attraction / Pi-Pi Stacking:**
   - Weak attractions between large, polarizable atoms or groups: I, Br, Cl, S, propyl, butyl, isopropyl, isobutyl.
   - Aromatic rings: planar, electron-rich → Pi-Pi stacking with albumin's tyrosine and phenylalanine.
   - Enhances binding further; combined with negative charge → >99% binding.

- **3-Hydrogen Bonding & Dipole Interactions promote protein binding.**
  - Examples: -OH, C=O groups.
  - Dipole–dipole interactions arise from electronegativity differences.
  - Examples:
    - C=O → δ+ on carbon, δ– on oxygen
    - CN → δ– on N, δ+ on C

4- Hydrophobic Interactions

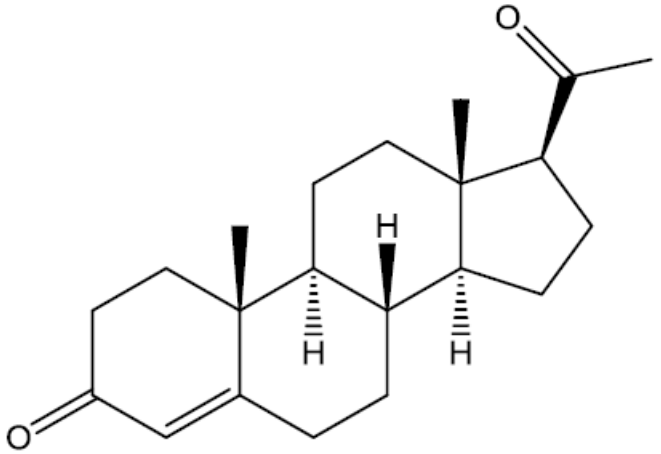
- **Hydrophobic fragments** (aliphatic chains) avoid water and **cluster together**.
- Interaction is **entropically driven**, not enthalpic (no bonds formed/broken).
- Adds to protein binding when drugs contain **multiple hydrophobic groups**.

- Consequences of Protein Binding
- Limited volume of distribution → drug mostly stays in plasma.
- Resistance to metabolism and renal elimination → slower clearance.
- Effect on biological activity:
  - Potent drugs → prolonged activity.
  - Low-potency drugs → limited activity.
- **Drug–drug interactions:**
  - Drugs compete for the same protein binding sites.
  - Example: **Aspirin** vs **Warfarin**

✓Molecules with negative charge + aromatic rings have the strongest albumin binding, leveraging electrostatic and Van der Waals interactions.

Example: Progesterone

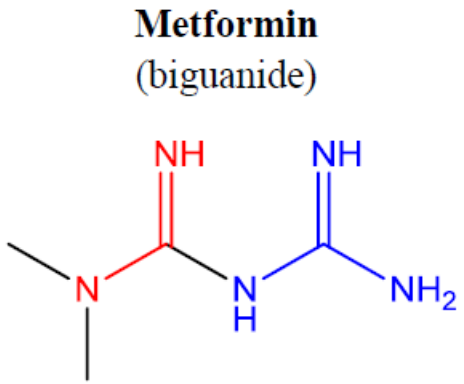
- **Mostly hydrophobic steroid** → large nonpolar surface.
- **Few polar groups**: carbonyls (dipoles) → minor hydrogen bonding.
- **Water insoluble** → cannot freely circulate in plasma.
- **Result:** strongly binds to **albumin** (**>90% protein binding**).
  - E.g., 100 mg dose → ~90 mg bound to plasma proteins.
- **Key Points on Hydrophobic & VDW Interactions**
- **Van der Waals + Hydrophobic clustering** often occur togethe
  - Example: **Aromatic rings** → Pi-Pi stacking driven by VDW **and** tendency to avoid water.
- **Extremely hydrophobic drugs** bind extensively even **without negative charge**.



Progesterone

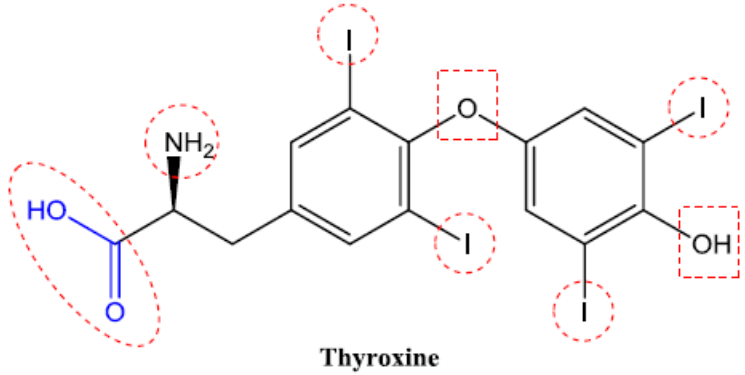
Example: Metformin (Glucophage)

- **Class:** Biguanide, antidiabetic
- **Charge:** Positively charged (guanidine, pKa >12) → repels albumin (+ charge)
- **Hydrophobicity:** None → no tendency to cluster away from water
- **Van der Waals groups:** None (no aromatic rings, no I, Br, Cl, S, no aliphatic chains >3C)
- **Water solubility:** Very high → highly hydrated
- **Result:**
- Limited protein binding **<20%**
- Well-distributed in body → not restricted by albumin
- Rapid renal elimination → minimal metabolism
- Minimal drug–drug interactions via protein binding
- **Key Concept:**
- **Hydrophilic, positively charged molecules** generally **avoid protein binding**.



Example: Thyroxine (Tetraiodothyronine) – Highly Protein Bound

- **Structural Features Promoting Protein Binding:**
- **Charge:**
  - Contains amino acid with negatively charged carboxyl and positively charged amine → strong electrostatic interactions with albumin.
- **Van der Waals / Pi-Pi Stacking:**
  - 2 aromatic rings → planar, electron-rich → interact with albumin's tyrosine and phenylalanine via Pi-Pi stacking.
- **Large Polarizable Atoms:**
  - 4 iodine atoms → polarizable → Van der Waals attraction.
- **Hydrogen Bonding:**
  - OH groups and ether oxygens → additional binding support.
- **Result:**
- **Extensive protein binding: >99%**
- Functional significance: protects embryo from thyroid hormone toxicity.



Thyroxine

Example: Suramin – Extremely Protein Bound

- **Structural Features Promoting Binding:**
- **Negative Charge:**
  - **6 sulfonate groups (-SO_3^-)** → very strong acidic groups (pKa <1) → strongly bind albumin.
- **Van der Waals / Pi-Pi Stacking:**
  - **8 aromatic rings** → planar, electron-rich → interact with albumin's aromatic residues.
- **Hydrogen Bonding:**
  - O, NH, OH groups → further support binding.
- **Result:**
- **Extensive protein binding: >99%**
- Highly potent → **1% free drug sufficient to kill trypanosomes**
- Not orally bioavailable → administered parenterally for prophylaxis.