Topic 2: Introduction to Drug targets (drug site of actions)

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❖ Pharmacodynamics & Pharmacokinetics

➢ **Pharmacodynamics** is the study of how a drug binds to its target site.

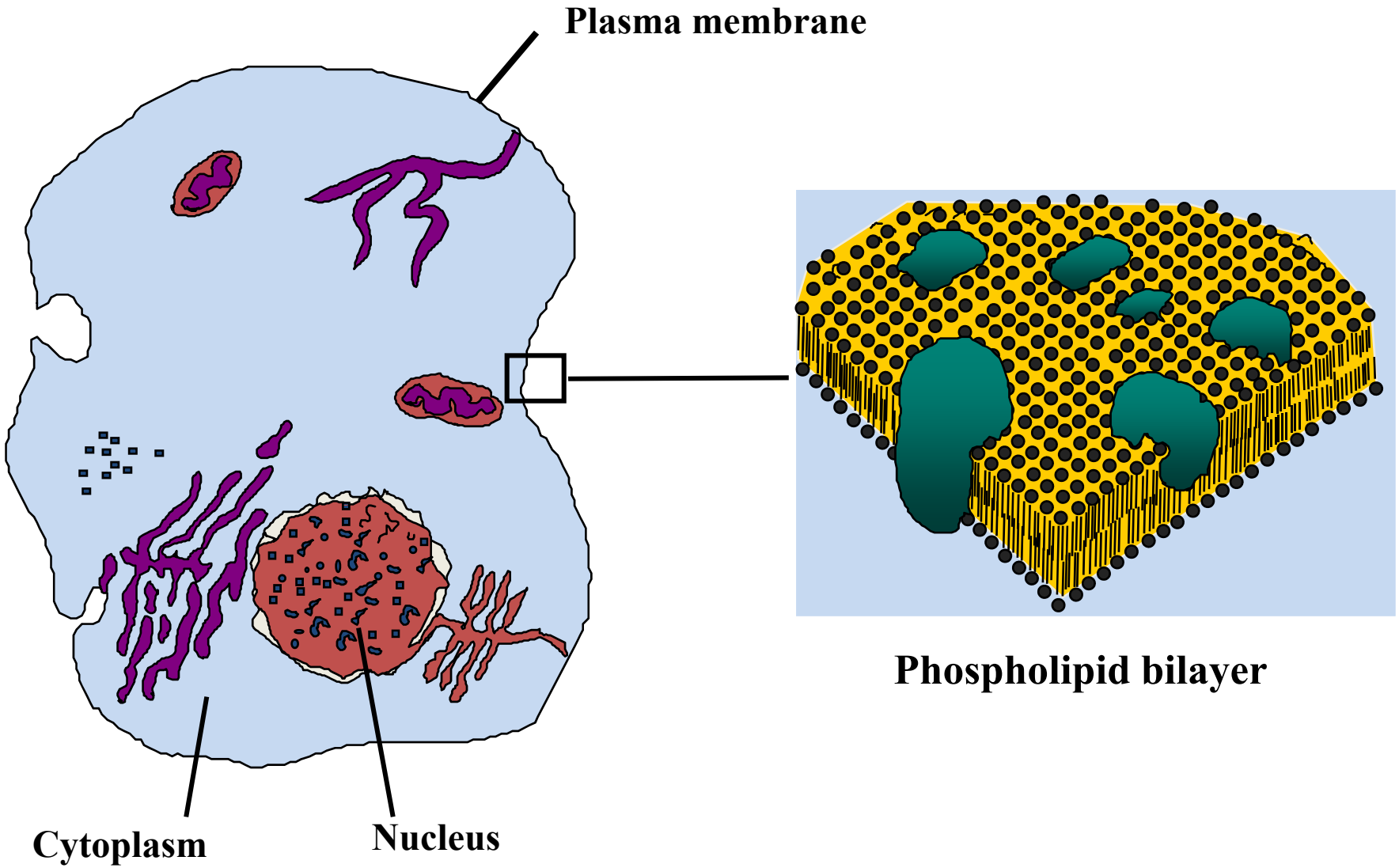
➢ but the drug not only has to bind to its target, it has to reach it in the first place.

➢ **Pharmacokinetic**s is the study of how a drug is absorbed, distributed, metabolized and excreted "ADME".

➢ Pharmacokinetics can be viewed as "what the body does to the drug" as opposed to pharmacodynamics "what the drug does to the body".

1. Cell Structure

Since life is made up of cells, then clearly drugs must act on cells.

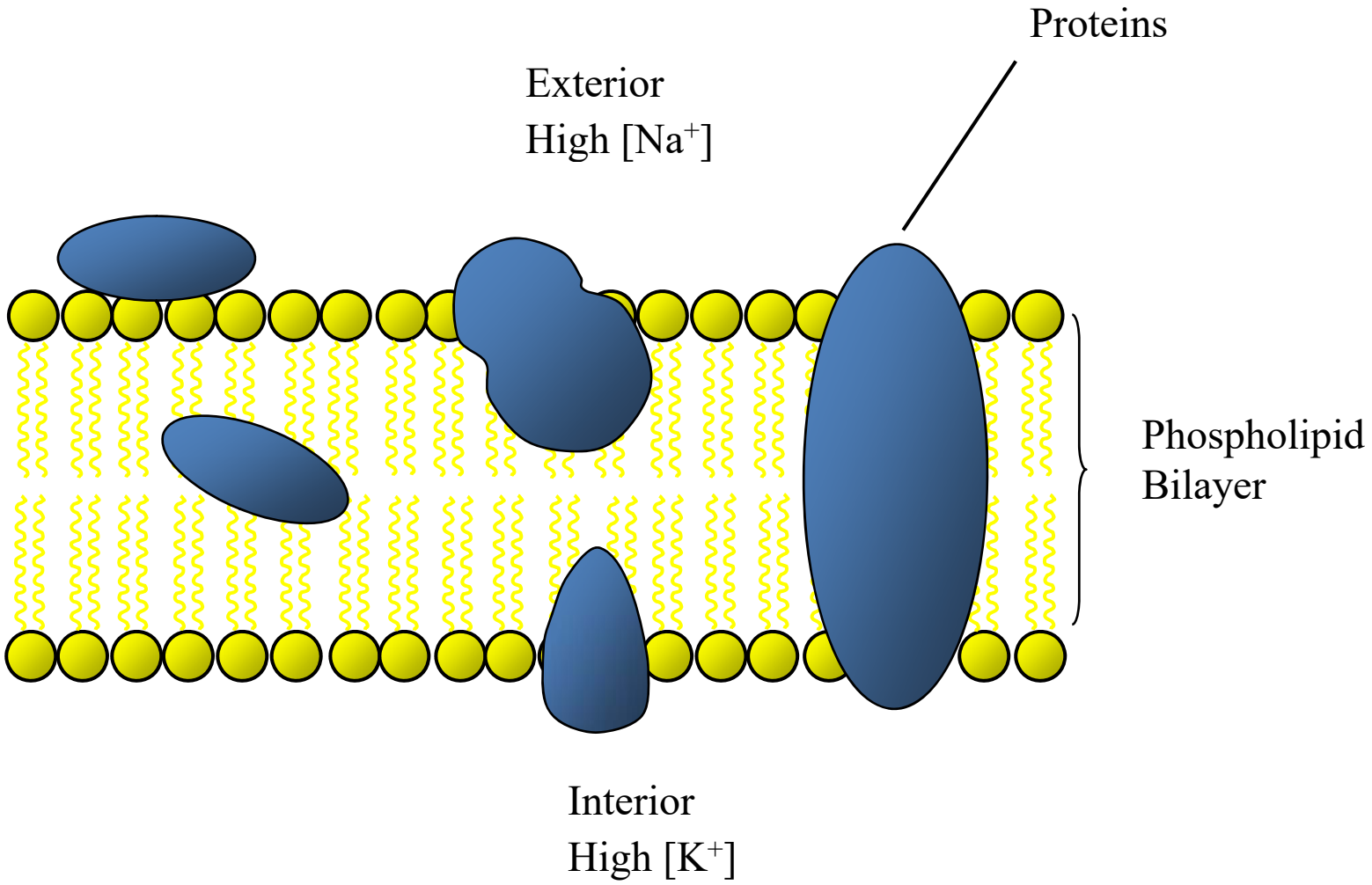


1. Cell Structure

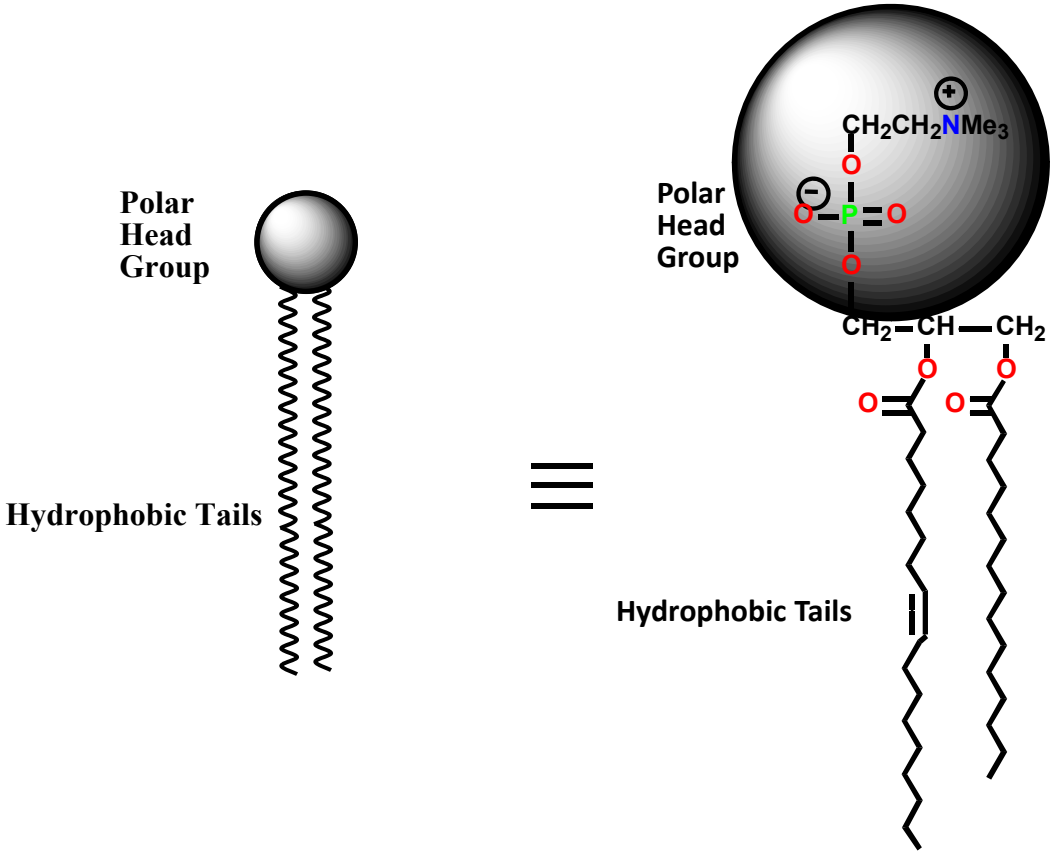
Notes:

- **Human, animal and plant cells are eukaryotic cells**
- **The nucleus contains the genetic blueprint for life (DNA)**
- **The fluid contents of the cell are known as the cytoplasm**
- **Structures within the cell are known as organelles**
- **Mitochondria are the source of energy production**
- **Ribosomes are the cell's protein 'factories'**
- **Rough endoplasmic reticulum is the location for protein synthesis**

2. Cell Membrane



2. Cell Membrane



2. Cell Membrane

Notes:

- **The cell membrane is made up of a phospholipid bilayer**

- **The hydrophobic tails interact with each other by van der Waals interactions and are hidden from the aqueous media**

- **The polar head groups interact with water at the inner and outer surfaces of the membrane**

- **The cell membrane provides a hydrophobic barrier around the cell, preventing the passage of water and polar molecules**

- **Proteins are embedded in the cell membrane (ion channels, receptors, enzymes and transport proteins)**

3. Drug targets

Lipids

- Cell membrane lipids

Proteins

- Receptors
- Enzymes
- Transport proteins
- Structural proteins (tubulin)

Nucleic acids

- DNA
- RNA

Carbohydrates

- Cell surface carbohydrates
- Antigens and recognition molecules

• Drug targets are large molecules – **macromolecules**, and drugs are generally much smaller than their targets

• Drugs interact with their targets by binding to **binding sites**. Binding sites are typically hydrophobic hollows or clefts on the surface of macromolecules

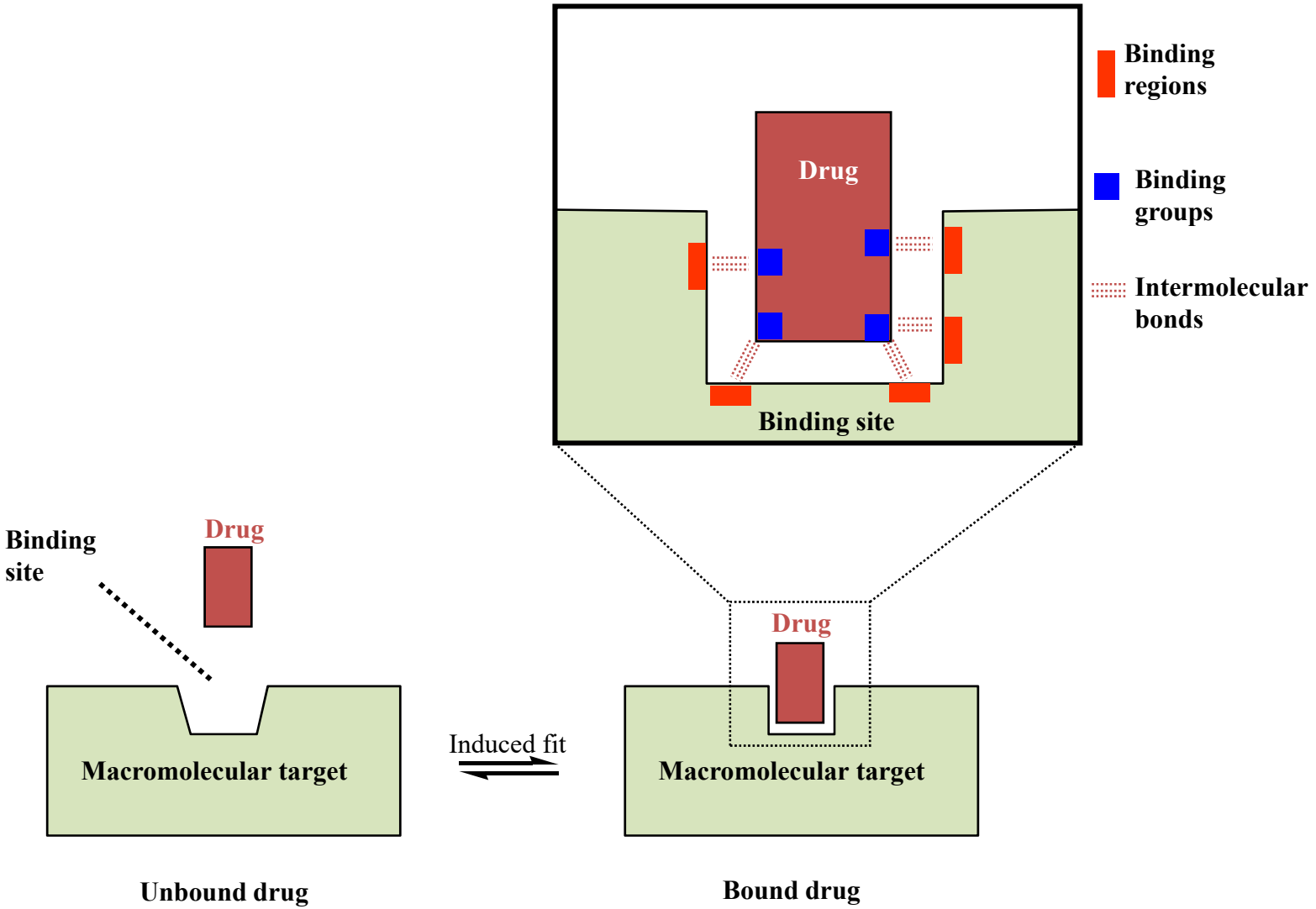
• Binding interactions typically involve **intermolecular bonds**

• Most drugs are in equilibrium between being bound and unbound to their target

• Functional groups on the drug are involved in binding interactions and are called **binding group**

• Specific regions within the binding site that are involved in binding interactions are called **binding regions**

3. Drug targets



Notes

• Binding interactions usually result in an induced fit where the binding site changes shape to accommodate the drug

• The induced fit may also alter the overall shape of the drug target

• Important to the pharmacological effect of the drug

• Some drugs react with the binding site & be become permanently attached via a **covalent bond** that has a bond strength of 200-400 KJ/mol.

• Most drugs interact through weaker forms of interactions known **intermolecular bonds**. These include ionic bonds, hydrogen bonds, van der waals interactions, dipole-dipole interactions & hydrophobic interactions.

4. Intermolecular bonding forces

4.1 Electrostatic or ionic bonds

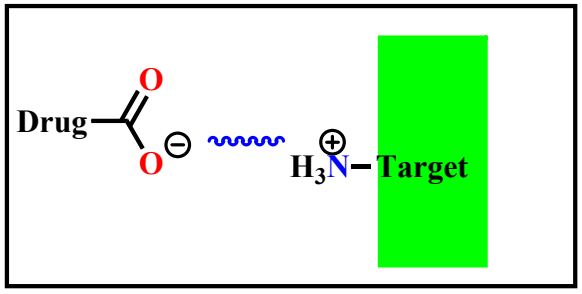
• Strongest of the intermolecular bonds (20-40 kJ mol^{-1})

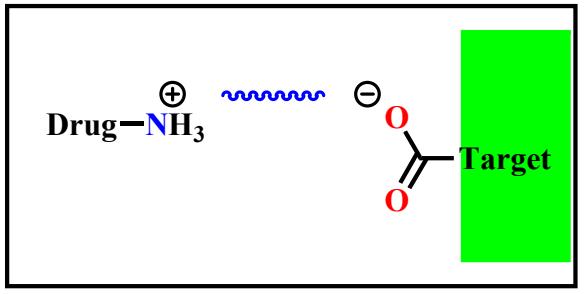
• Takes place between groups of opposite charge

• The strength of the ionic interaction is inversely proportional to the distance between the two charged groups

• Stronger interactions occur in hydrophobic environments

•Ionic bonds are the most important initial interactions as a drug enters the binding site





4.2 Hydrogen bonds

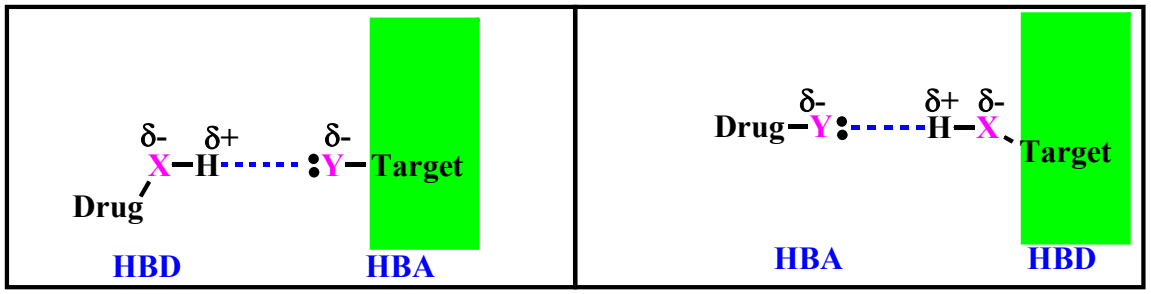
• Vary in strength, weaker than electrostatic interactions but stronger than van der Waals interactions

• A hydrogen bond takes place between an electron-deficient hydrogen and an electron-rich heteroatom (N or O)

•is usually attached to a heteroatom (O or N) The electron-deficient hydrogen

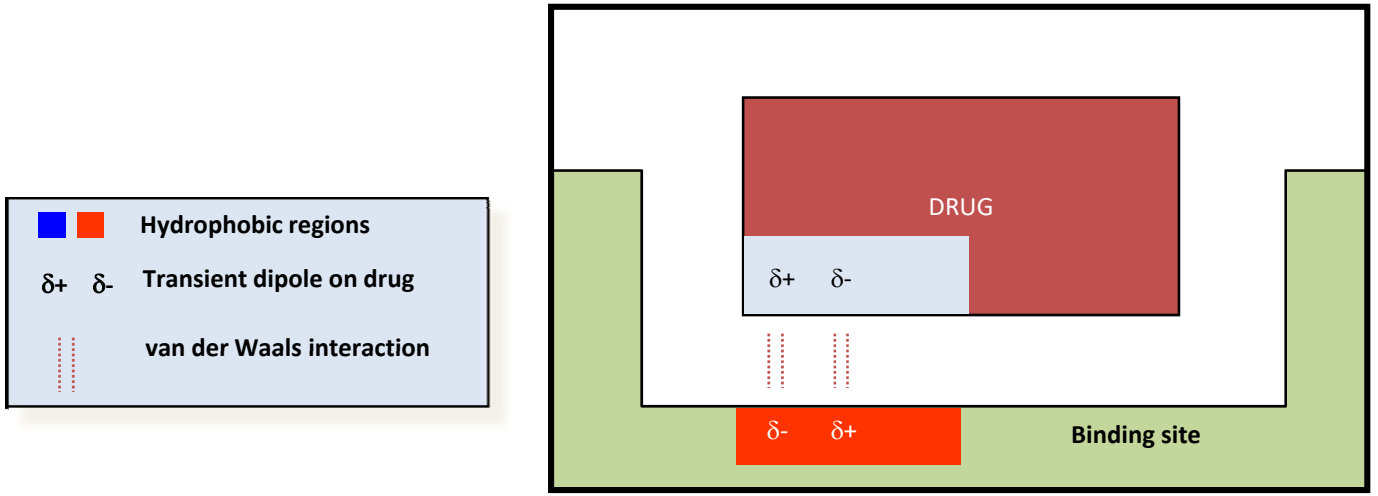
• The electron-deficient hydrogen is called a hydrogen bond donor

• The electron-rich heteroatom is called a hydrogen bond acceptor



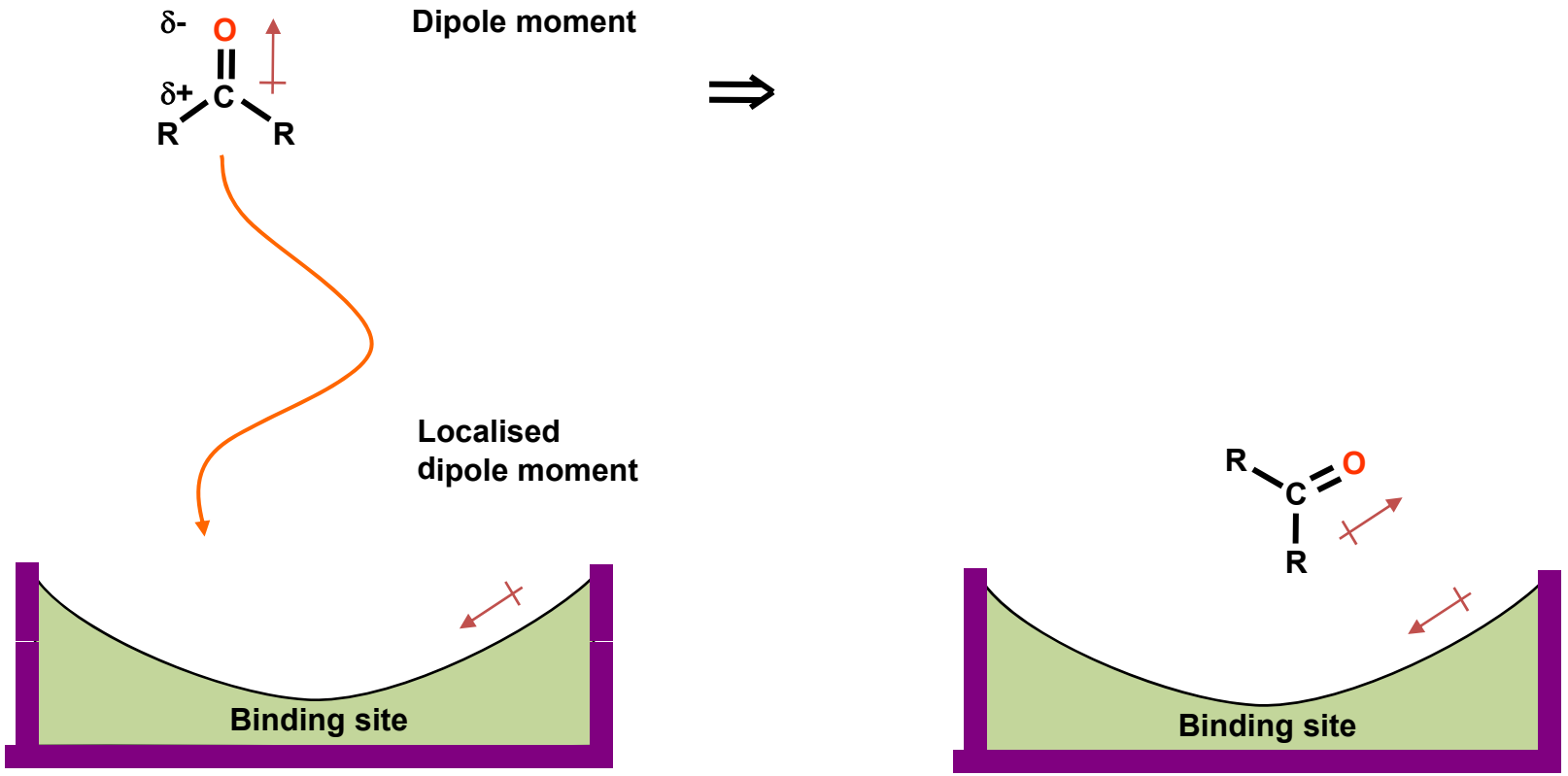
4.3 London forces (Van Der Waals interaction) (hydrophobic interaction)

- Very weak interactions (2-4 kJ mol^{-1})
- Occur between hydrophobic regions of the drug and the target
- Transient areas of high and low electron densities cause temporary dipoles
- Interactions drop off rapidly with distance
- Drug must be close to the binding region for interactions to occur



4.4 Dipole-dipole interactions

- Can occur if the drug and the binding site have dipole moments
- Dipoles align with each other as the drug enters the binding site
- Dipole alignment orientates the molecule in the binding site

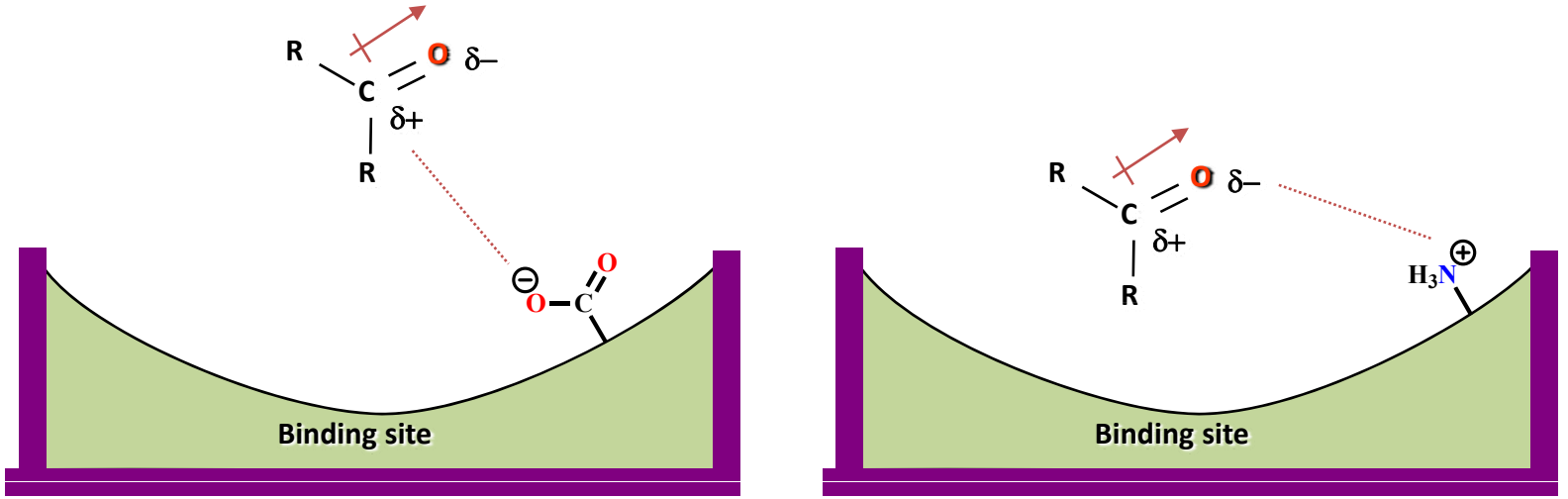


4.5 Ion-dipole interactions

• Occur where the charge on one molecule interacts with the dipole moment of another

• Stronger than a dipole-dipole interaction

• Strength of interaction falls off less rapidly with distance than for a dipole-dipole interaction



4.6 Induced dipole interactions

- Occur where the charge on one molecule induces a dipole on another
- Occur between a quaternary ammonium ion and an aromatic ring