Drug Design

Evaluation of ADME properties

- **ADME** is an acronym used in pharmacokinetics and pharmacology for absorption, distribution, metabolism an excretion.

- Ensemble of processes involved in the becoming of a drug after being administered.

- Pharmacokinetics **(**PK**) – "what the body does to the drug"**

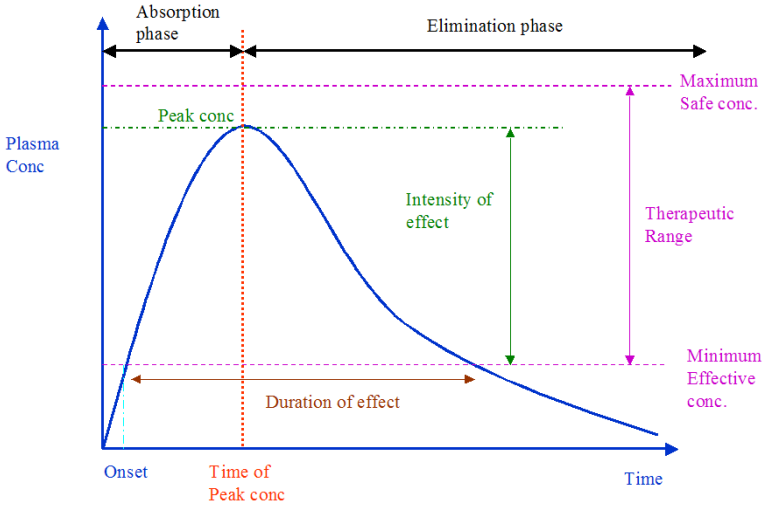
- Non accounting for ADME properties has led to problems when drug candidates were tested in clinical phase.

Evaluation of ADME properties

Pharmacokinetics

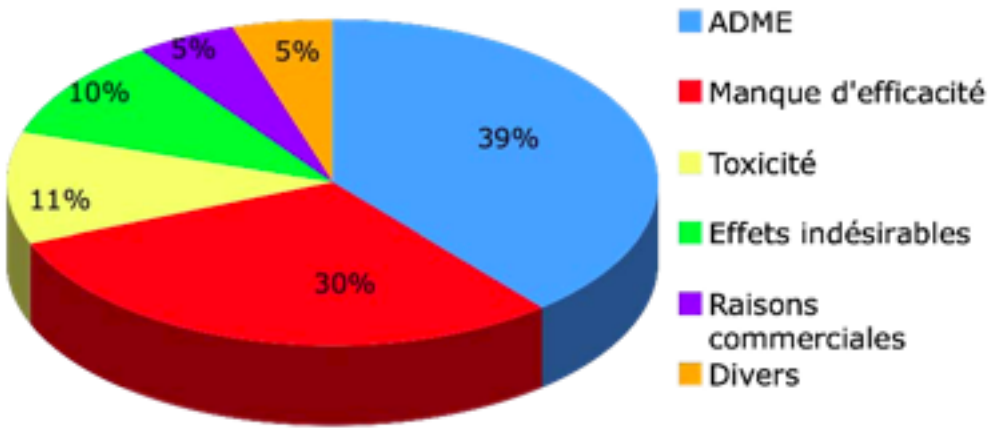
- How do you get it into the body?
- How long does it take to exert its action?
- How long does it stay in the body?
- Where does it go to in the body?
- Is it metabolised to another form?
- How do we analyze and detect it?

The [plasma]-time curve after drug administration



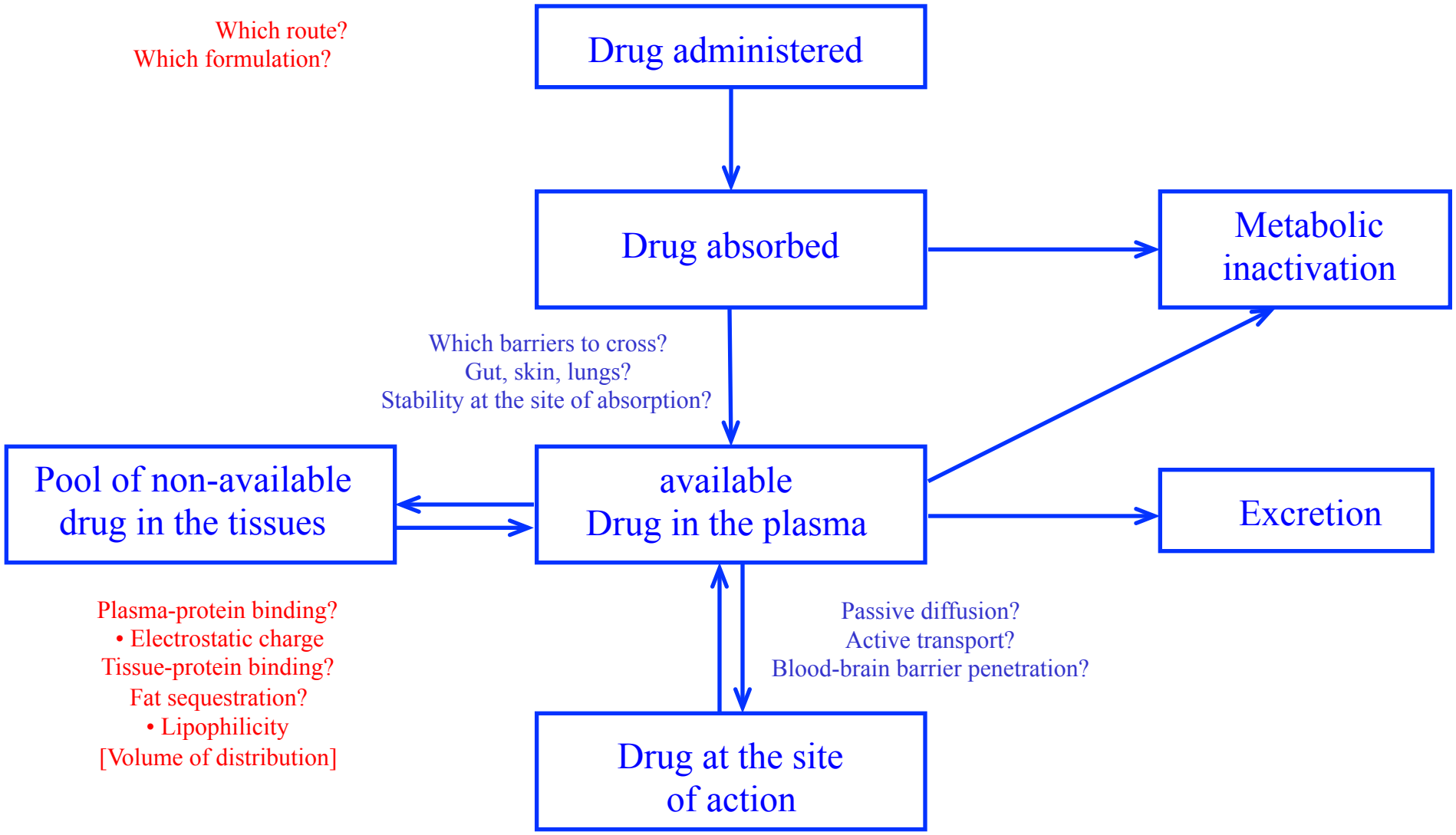
Evaluation of ADME properties

Main causes for rejecting drugs



Evaluation of ADME properties

Pharmacokinetics



Evaluation of ADME properties

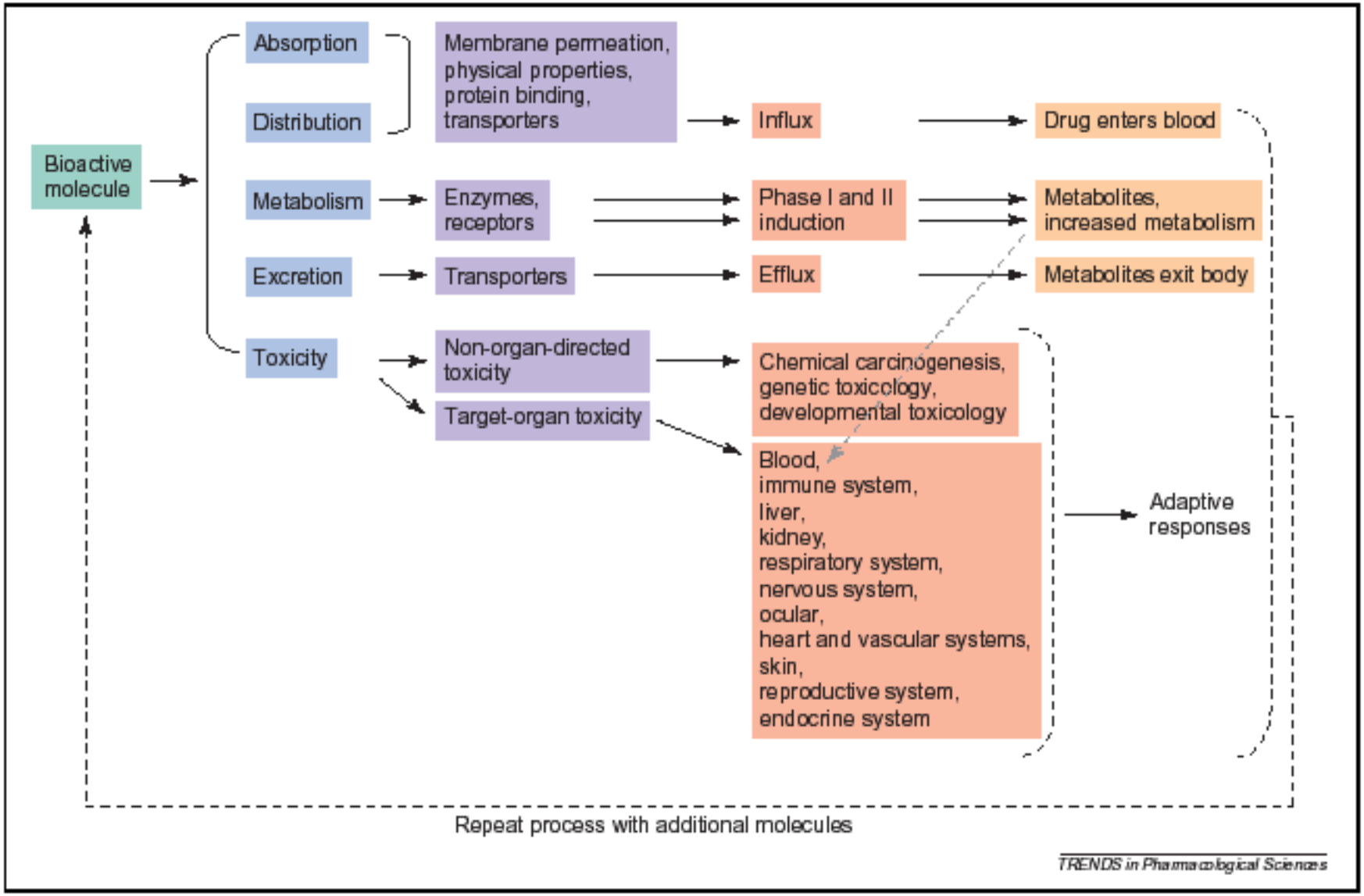


Figure 1. The iterative ADME/Tox optimization process. This figure demonstrates that a bioactive molecule is required to possess many favorable ADME/Tox properties before it can become a drug, and indicates the multidimensional nature of drug discovery. The proteins and endpoint associated with each ADME/Tox function are outlined. Adaptive responses represent the transcriptional and post-transcriptional effects following a toxic insult. Solid arrows represent the links between ADME/Tox properties, functions and endpoints. The grey dashed line represents reactive metabolites that can cause toxicity.

Drug Metabolism

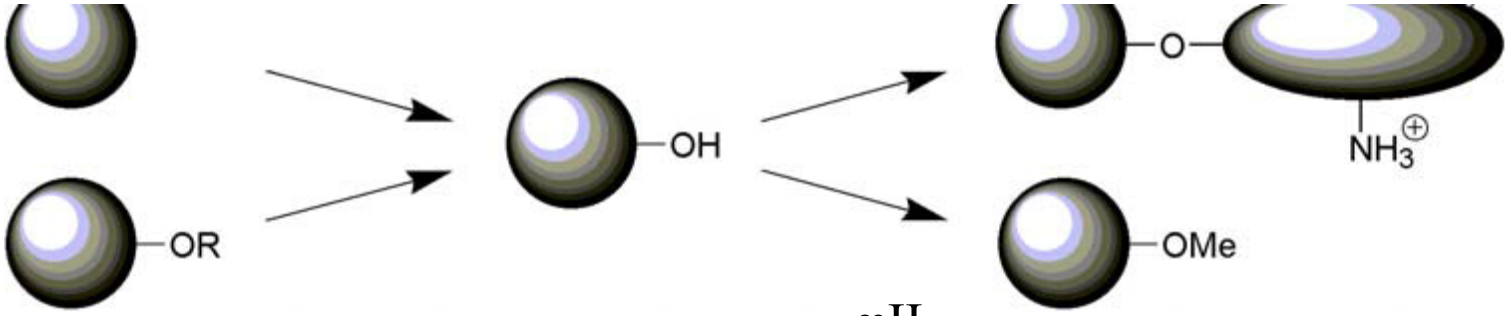
- **Drug molecules are processed by enzymes** evolved to cope with natural compounds
- May be several routes of metabolism
- May not be what terminates drug action
- May take place anywhere BUT liver is prime site
- Not constant - can be changed by other drugs; basic of many drug-drug interactions

Drug Metabolism

Modify the chemical nature of the molecule to facilitate its elimination
(metabolism ---> excretion)

Transformations in phase I
• introduce functional groups

Transformations in phase II
• produce polar derivatives or block functional groups by coupling (conjugaison).



φI φII

Elimination
– kidneys
– gall-bladder

Drug Metabolism

Transformations in phase I
Oxydation reactions

Cytochrome P450 is a superfamily of heme proteins which use a large number of exogenous and endogenous compounds as substrates in enzymatic reactions.

Cytochrome P450 catalyses oxydations that introduce a new chemical function (-OH, -NH2, -COOH) in xenobiotic molecules making the molecules more polar.

Drug Metabolism

Molecular modelling of drug metabolizing enzymes

To understand the interaction of drugs with drug metabolizing enzymes, their 3D structures have been determined by comparative modelling using the Xray structures of bacterial **P450**s as templates.

Fifty specific and nonspecific substrates were docked into the active site of their metabolizing enzyme by automatic **rigid body docking program** DOCK.

It was found that substrate binding was favoured mainly **by hydrogen bonding and electrostatic interactions** between the substrates and protein residues.

More recently the crystal structure of a human P450 cytochrome in the absence and presence of warfarin was determined.

Drug Distribution

Pharmacophore models for analysis of substrate specificity

The first step in oral absorption of medically important **peptide-based drugs** is mediated by an intestinal proton-dependent peptide transporter.

This transporter facilitates the oral absorption of di- and tri-peptides resulting from the digestion of dietary proteins.

Peptidomimetics: **Penicillins, cephalosporins, ACE inhibitors** and other drugs are substrates of the intestinal peptide transporter.

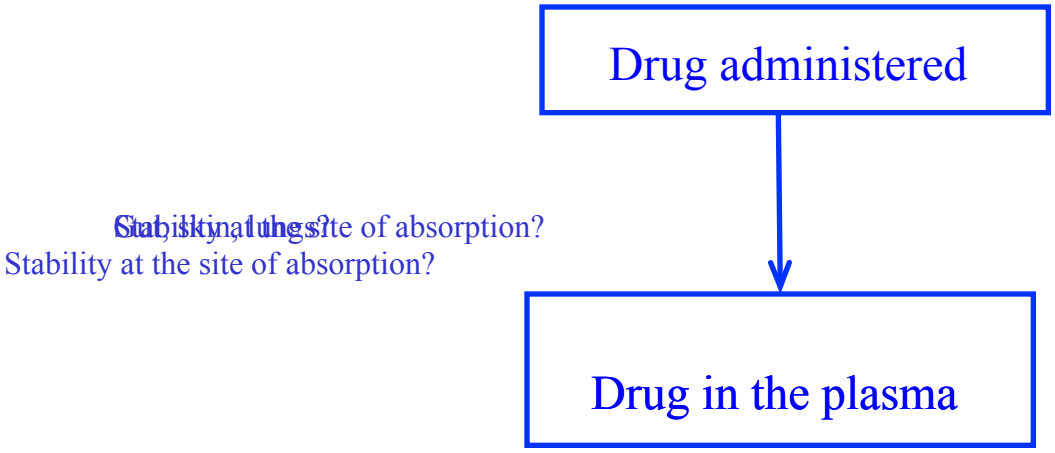
They were subjected to a **pharmacophore** analysis.

It was found that the affinity for the peptide transporter could be diminished either by:

Esterification of the free carboxylic moiety
Introduction of a second negative group

Evaluation of ADME properties

This is an essential tool in pharmacokinetics as bioavailability must be accounted for calculating doses.

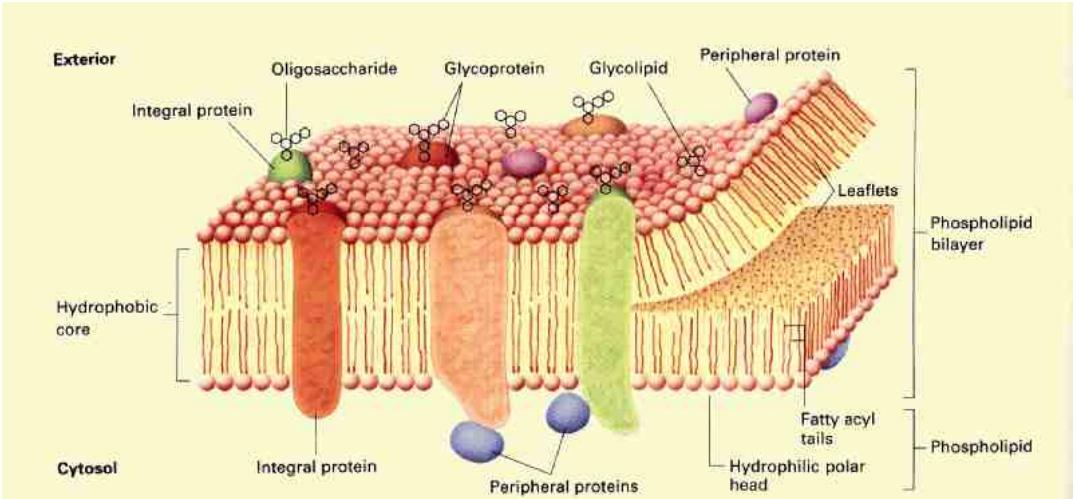


Permeation of drugs across biological membranes

- Biological membrane is essential to the separation of the inside and outside of the cell.

- It is composed of a phospholipid bilayer in which proteins are associated.

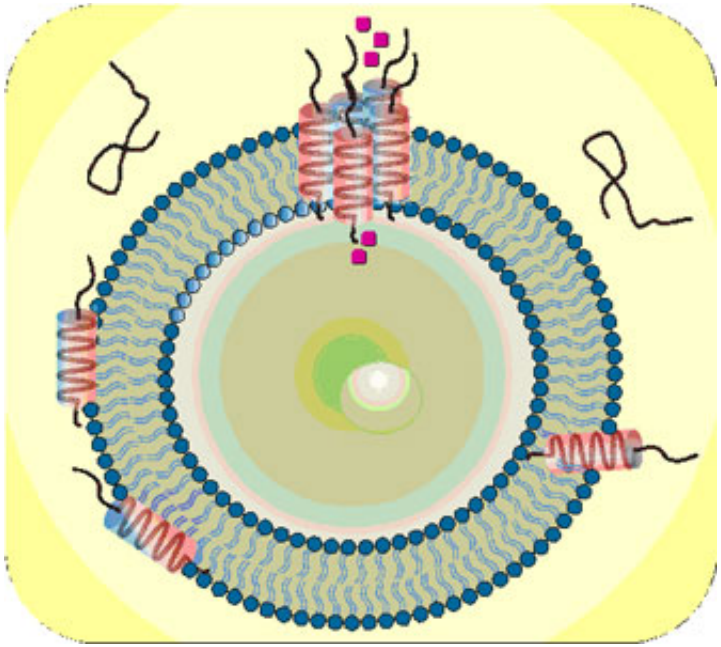
- Biological membranes are made of two main parts with different physicochemical properties: One is hydrophobic and the other hydrophilic.



▲ **Figure 13-1** A phospholipid bilayer constitutes the basic structure of biological membranes. The hydrophobic fatty acyl tails of the phospholipids form the middle of the bilayer; the polar, hydrophilic heads of the phospholipids line both surfaces. Integral proteins have one or more regions embedded in the lipid bilayer. Peripheral proteins are primarily associated with the membrane by specific protein-protein interactions. Oligosaccharides bind mainly to membrane proteins; however, some bind to lipids, forming glycolipids.

Permeation of drugs across biological membranes

- The role of the biological membrane is to define the extent of the cell and to settle a boarder preventing the permeation of undesired compounds to the interior of the cell.

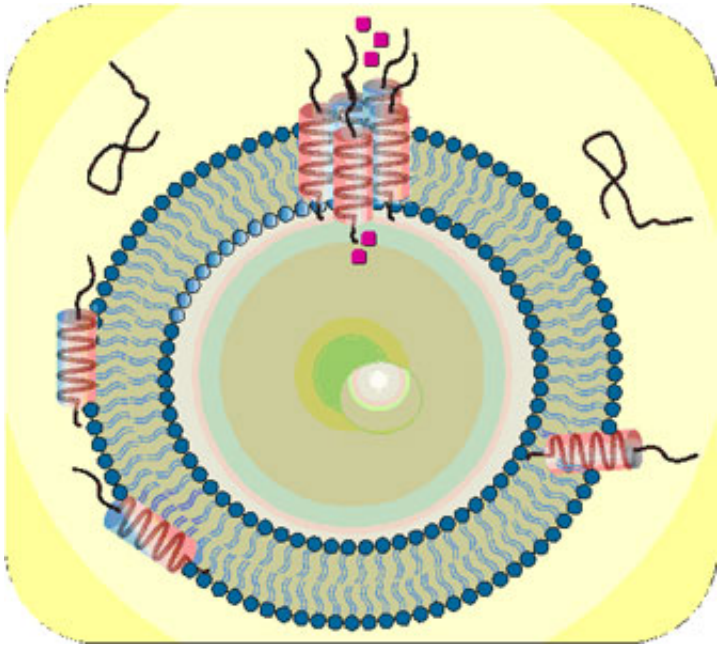


Permeation of drugs across biological membranes

- Absorption of a drug in the body is determined by its capacity to cross the lipid bilayer of cells.

- This phenomenon of diffusion is named permeation and permeability is the associated physical quantity.

Permeation of drugs across biological membranes



- Two types of processes characterise the transfer of molecules through the membrane:

passive diffusion

- Passive diffusion does not need energy supply and is due to concentration or electrical gradients through the membrane.
- Active diffusion requires the presence of a protein or an energy supply.
- Drugs mainly use the passive diffusion process to cross the membrane.
- Their absorption is influenced by their

Permeation of drugs across biological membranes

- A system of biopharmaceutical classification separates drugs into 4 different groups depending on their solubility and permeability:

Class I: High solubility and permeability

Class I: High solubility and permeability

Class II: Weak solubility and high permeability

- Compounds which belong to class I are the most searched for

- **High solubility** leads to a complete dissolution of the drug

- **High permeability** is the guarantee that the drug is fully absorbed during its passage in the intestine.

Permeation of drugs across biological membranes

Experimental and *in silico* methods

Permeation of drugs across biological membranes

3 approaches :

3 approaches :

- Partition coefficient octanol/water (log P)

- Partition coefficient octanol/water (log P)

- Diffusion through a layer of cells

Permeation of drugs across biological membranes

Experimental methods

Partition coefficient (log P)

- It is the most often used descriptor to characterise the lipophilic character of a drug.

- It is obtained using a two-phase solution octanol/water shaken with the solute and by measuring the concentration of solute in both phases.

- The correlation between the partition coefficient octanol/water and the permeability value is rather weak.

- It is however used together with an ensemble of other descriptors.

Permeation of drugs across biological membranes

Experimental method

Diffusion through a layer of cells

Diffusion through a layer of cells

- A layer of human colon adenocarcinoma cells (Caco-2) are used to model the transport of molecules through the intestine epithelium

• A layer of human colon adenocarcinoma cells (Caco-2) are used to model the transport of molecules through the intestine epithelium

- A good correlation was found between the permeability through this layer and the oral absorption in humans.

- However experimental procedures are not standard and it is difficult to compare permeability values from different labs.

Permeation of drugs across biological membranes

Experimental methods

- Good reproductibility of the results
- Rapidity of the tests and possibility to work on a large number of compounds
- Not too costly

- Several softwares have been designed to evaluate adsorption properties:

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Permeation of drugs across biological membranes

Lipinski's rule of five:

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1. Molecular weight of drug candidates < 500
2. Number of hydrogen bond donors < 5
3. Number of hydrogen bond acceptors < 10
4. Log P < 5

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Advantages : easy to implement

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Drawbacks : Problems of bioavailability can occur even for the molecules that passed the test.

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Permeation of drugs across biological membranes

In silico methods : qualitative methods derived from the analysis of data bases of drugs

Model used to evaluate the blood-brain barrier (Norinder and Haeberlein)
(The ability of a molecule to enter the nervous central system may also be desirable depending on the therapeutic target)

A high permeability for penetrating the brain is predicted if

1. The sum of the number of nitrogen (N) and oxygen (O) atoms in a molecule is ≤ 5
2. If log P - (N+O) is > 0 (N+O is the sum of the number of atoms of nitrogen and oxygen in a molecule)

Permeation of drugs across biological membranes

In silico methods: quantitative methods

- Computer predictions of permeability are based on quantitative structure-property relationships (QSPR).

- This method describes the chemical structure of a molecule into a series of descriptors of properties which can be related to the permeability of this molecule

- A mathematical relation is then elaborated to quantitatively associate the values of the descriptors with the value of the permeability.
  P = f(chemical descriptors)

- With this relation one can screen other chemical compounds to predict their permeability

Permeation of drugs across biological membranes

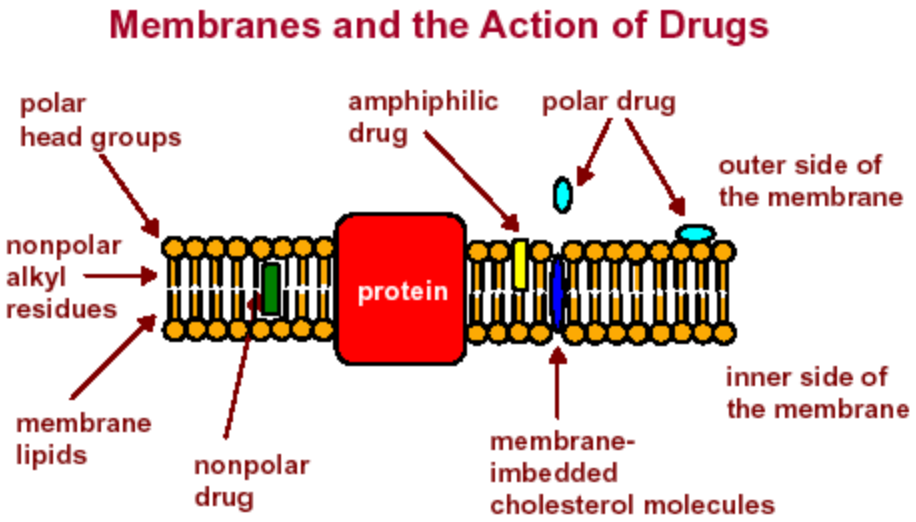
In silico methods : quantitative methods

These approaches have been designed to correlate the experimental measurements of permeability to one or more descriptors.

Descriptors used are :

- Lipophilic character of the molecules
- Properties related to the hydrogen bonds (number of donors and acceptors)
- Molecular weight

These descriptors can be obtained with the knowledge of the 2D structure of the compounds



Permeation of drugs across biological membranes

In silico methods: quantitative metho

Drawbacks :

If the mathematical relation is obtained with

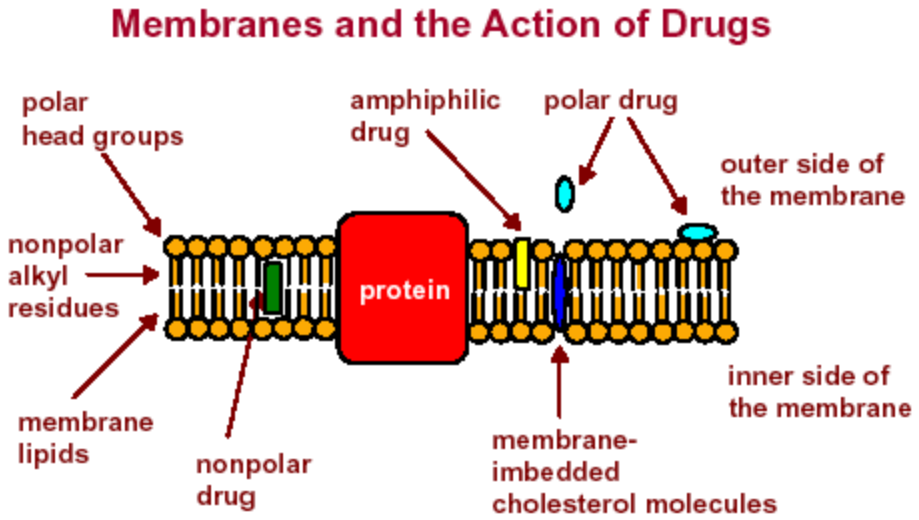
- A size of the data too small
- Data on compounds transported actively instead of passively

Permeation of drugs across biological membranes

In silico methods : quantitative methods

• Interactions between the drug and the biological membrane depend on the interactions between the 3D structures of the drug compound and the phospholipids of the membrane.

• Van der Waals, electrostatic, hydrogen bonds, hydrophobic interactions at the surface influence the passive permeability of the drugs across the biological membranes



Permeation of drugs across biological membranes

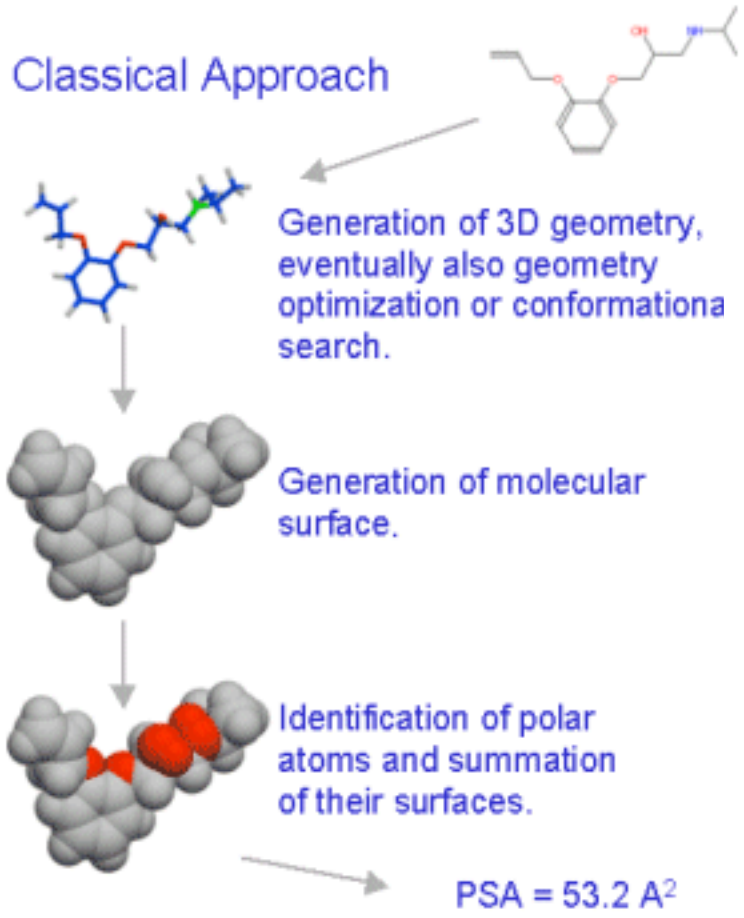
In silico methods : quantitative methods

- The surface properties of the drug candidates, in particular the Polar Surface Area (PSA), have been frequently used as a descriptor to predict the permeability of compounds across the membranes.

- PSA is defined as the sum of the partial surfaces associated with oxygen, nitrogen and polar hydrogen atoms which contribute to the total surface of the drug candidate.

Permeation of drugs across biological membranes

In silico methods : quantitative methods



- To compute the PSA one uses the van der Waals radius of each atom and the molecular 3D conformation of the molecules.

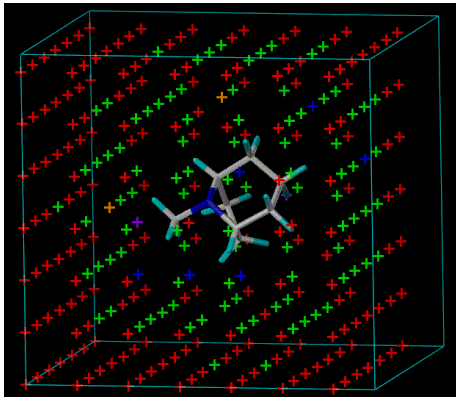
- This polar area or PSA accounts for the capability of a molecule to form hydrogen bonds.

- The PSA descriptor does not of course discriminate between molecules having a similar PSA value but with different sizes and lipophilic character.

Permeation of drugs across biological membranes

In silico methods : quantitative methods

Another method (VolSurf) proposes another approach relating the physicochemical properties essential for the permeation and the 3D structure of the drug candidates.



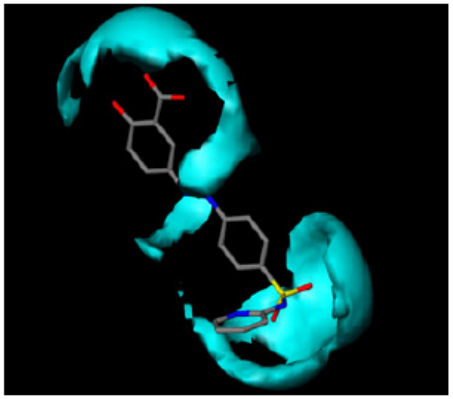
VolSurf is a computational procedure to produce 2D molecular descriptors from 3D molecular interaction energy grid maps.

The basic idea of VolSurf is to compress the information present in 3D maps into a few 2D numerical descriptors which are very simple to understand and to interpret.

The most important descriptors are

The properties of hydrogen bonds (number of hydrogen bond acceptors and donors)

The lipophilic character

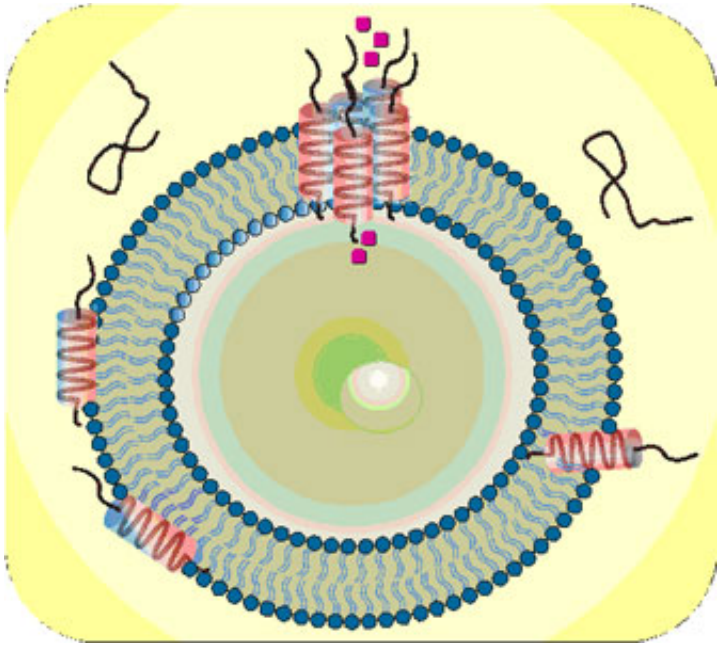


The hydrophilic surface area of an anti-inflammatory drug as determined by VolSurf.

Permeation of drugs across biological membranes

In silico methods : quantitative methods

Models of membranes are essential
for a better understanding of the general principles controlling the membrane organisation
and to better apprehend the interaction between biological membranes and other chemical entities such as drugs

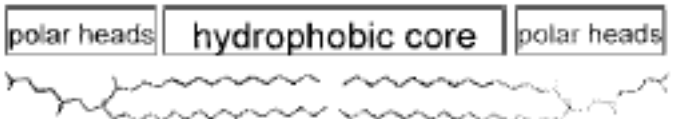


Permeation of drugs across biological membranes

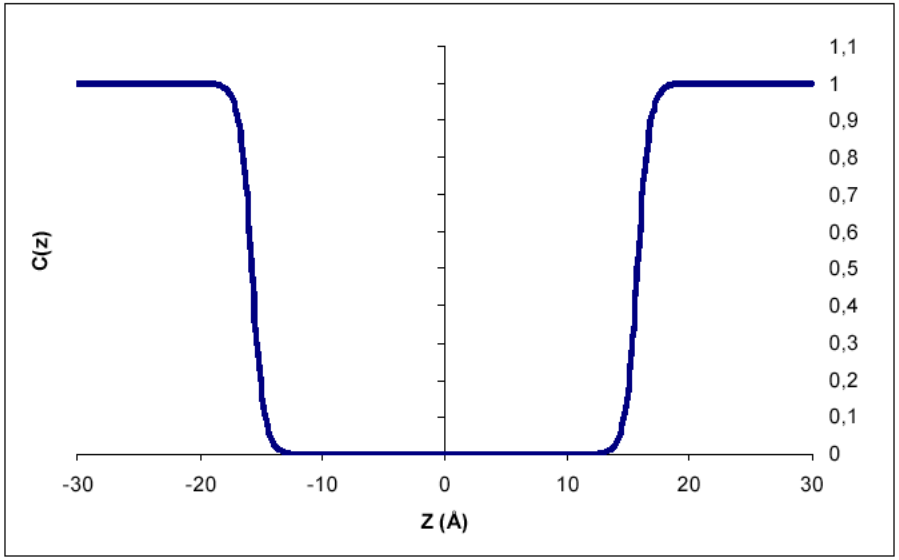
In silico methods : quantitative methods

- Membrane can be considered as a continuum medium characterised by macroscopic properties.

- In IMPALA (Brasseur et al.) lipid/water interfaces are described by a function which varies along a Z axis perpendicular to the membrane.



$$C_{(z)} = 1 - \frac{1}{1 + e^{\alpha(|Z| - Z_0)}}$$



Permeation of drugs across biological membranes

In silico methods : quantitative methods

Two different types of interactions are considered

One simulates the hydrophobic interaction which depends on the accessible surface S(i) of the different atoms i, of the transfer energy $E_{tr}(i)$ of the corresponding atom

The values of $E_{tr}(i)$ are calculated from experimental free energies of transfer of amino acids

$$E_{\text{int}} = \sum_{i=1}^{N} S_{(i)} E_{tr(i)} \, (1 - C_{(z_i)})$$

The general behaviour is that E is unfavourable when hydrophilic atoms penetrate the membrane (E_{tr} >0) and favourable (<0) when hydrophobic atoms do

Permeation of drugs across biological membranes

In silico methods : quantitative methods

The perturbation in the organisation of the phospholipids caused by the penetration of the molecule into the membrane.

This function minimises the interaction of the molecule with lipids relative to that between the phospholipids themselves.

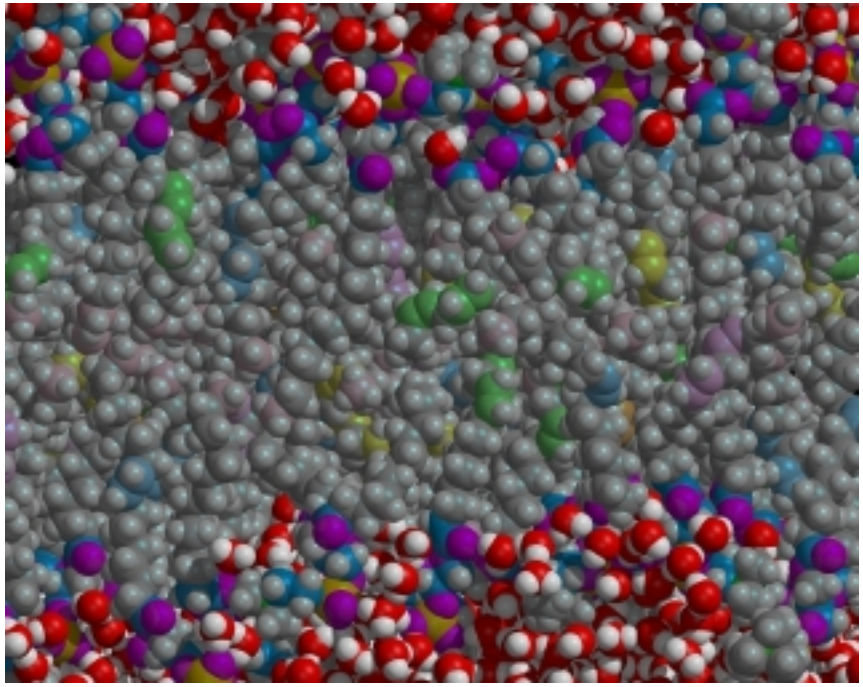
$$E_{lip} = a_{lip} \sum_{i=1}^{N} S_{(i)} (1 - C_{(z_i)})$$

A_{lip} is an empirical factor

Permeation of drugs across biological membranes

In silico methods : quantitative methods

• Statistical simulations (Molecular dynamics or Monte Carlo) to the estimation of transfer free energies of pharmacologically relevant organic molecules are used.

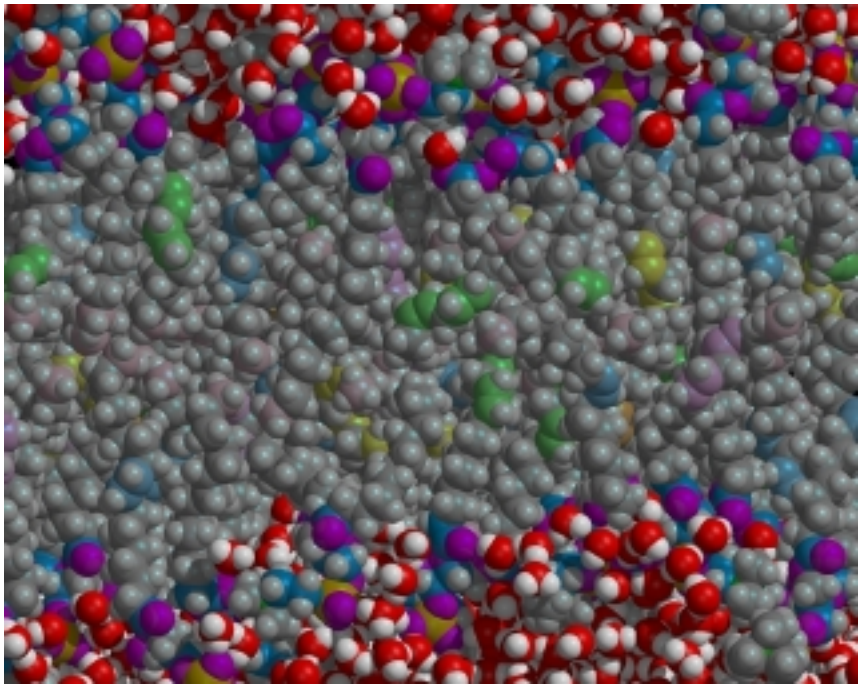


Permeation of drugs across biological membranes

In silico methods : quantitative methods

• Large-scale molecular dynamics simulations were carried out on a series of four solutes, viz. antipyrine, caffeine, ganciclovir, and alpha-D-glucose, at the water-dodecane interface as a model of a biological water-membrane interfacial system.

• Agreement with experimentally determined partition coefficients is remarkable, demonstrating that free energy calculations, when executed with appropriate protocols, have reached the maturity to predict thermodynamic quantities of interest to the pharmaceutical world.



Permeation of drugs across biological membranes

In silico methods : quantitative methods

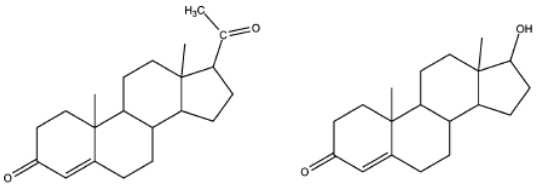


Fig. 2 Steroid hormone structures.

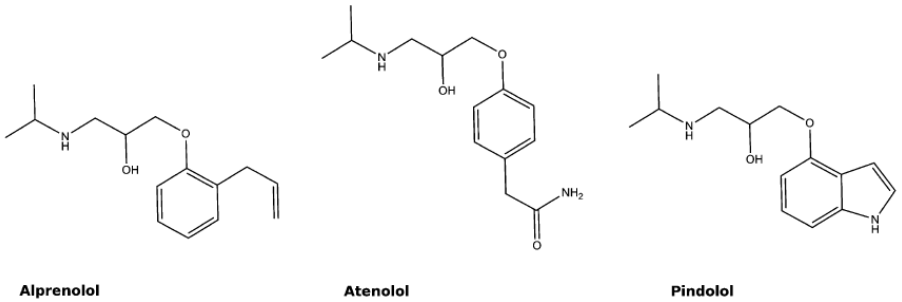


Fig. 1 β-blocker structures.

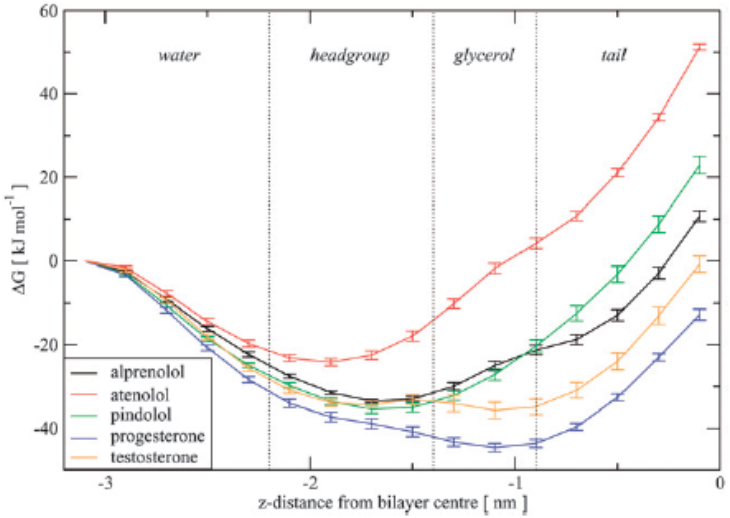


Fig. 3 Free energies of transfer from water to selected z-distances along the bilayer normal. To facilitate interpretation, different regions across the system are marked in italics, namely, the bulk *water* region, the lipid *headgroup* region, the lipid *glycerol* region and the hydrocarbon *tail* core. Approximate boundaries between these regions are defined by the vertical dotted lines.

Orsi and Essex, Soft Matter, 2010

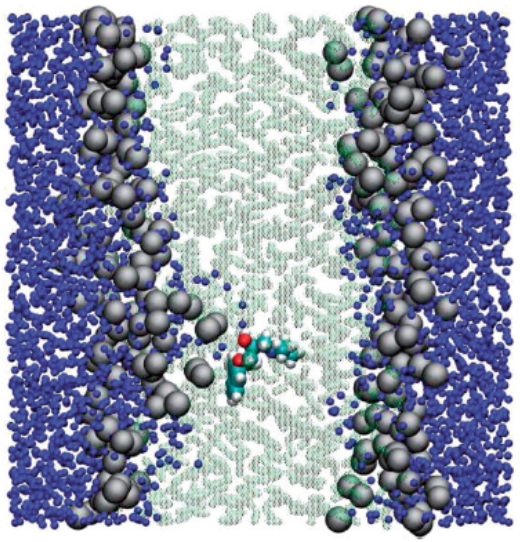


Fig. 6 Simulation snapshot from a dual-resolution z-constraint simulation. The permeant alprenolol is located at a distance of 0.1 nm from the bilayer centre towards the left monolayer. CG colour code: water molecules are blue, lipid headgroups are grey, lipid tails are transparent green. AL permeant colour code: carbon atoms are cyan, hydrogen atoms are white, oxygen atoms are red, nitrogen atoms are blue.