Comparison of log P/D with bio-mimetic properties

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Bio-Mimetic Chromatography

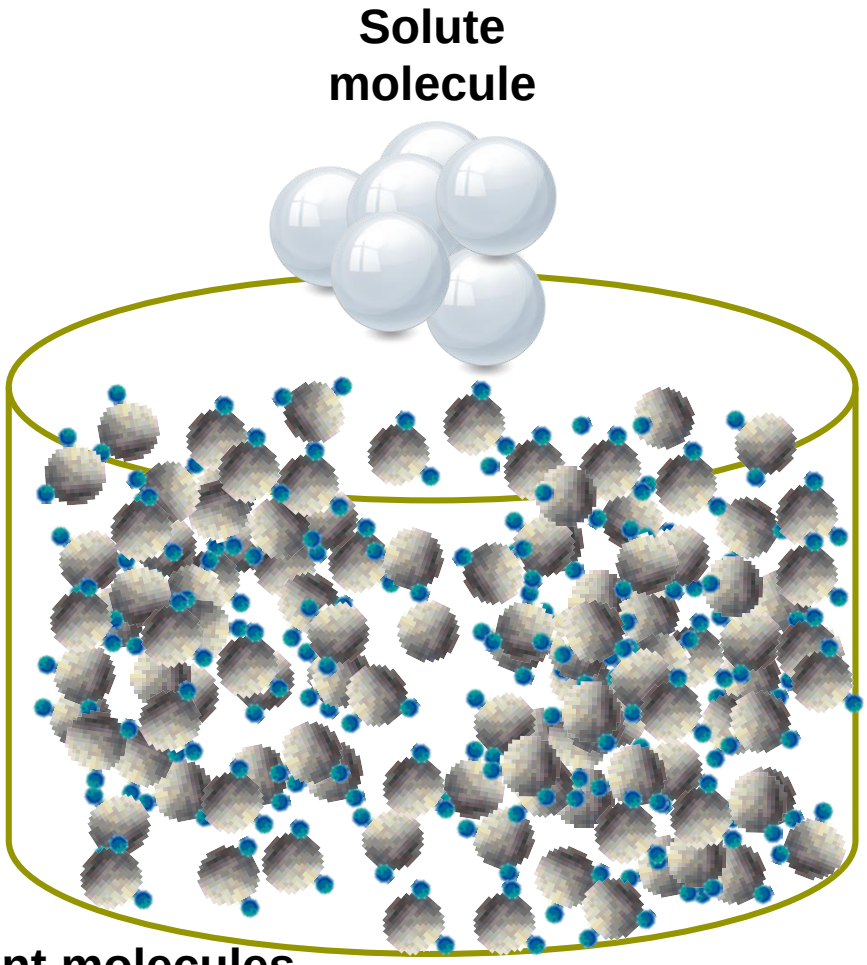
Consultancy for Successful Drug Discovery

Solvation process

First we need to create a cavity

Requires energy that depends on the size of the solute

Size descriptor: V

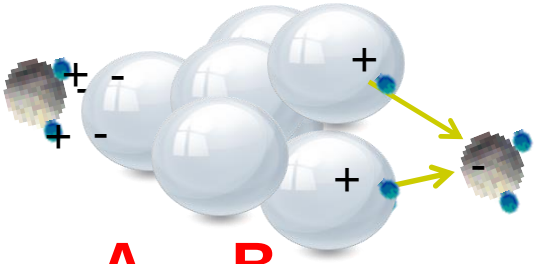


Solvation process

Second step to build new interactions between the solute and solvent molecules

We gain back energy.

Solute –solvent interactions

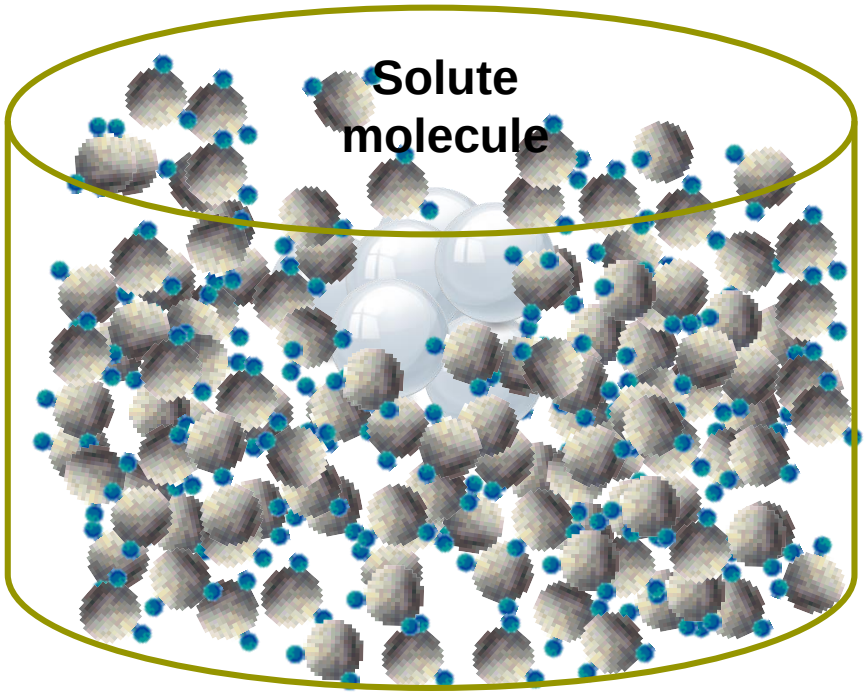


A B

-H --- O=C-

Dipole –dipole S

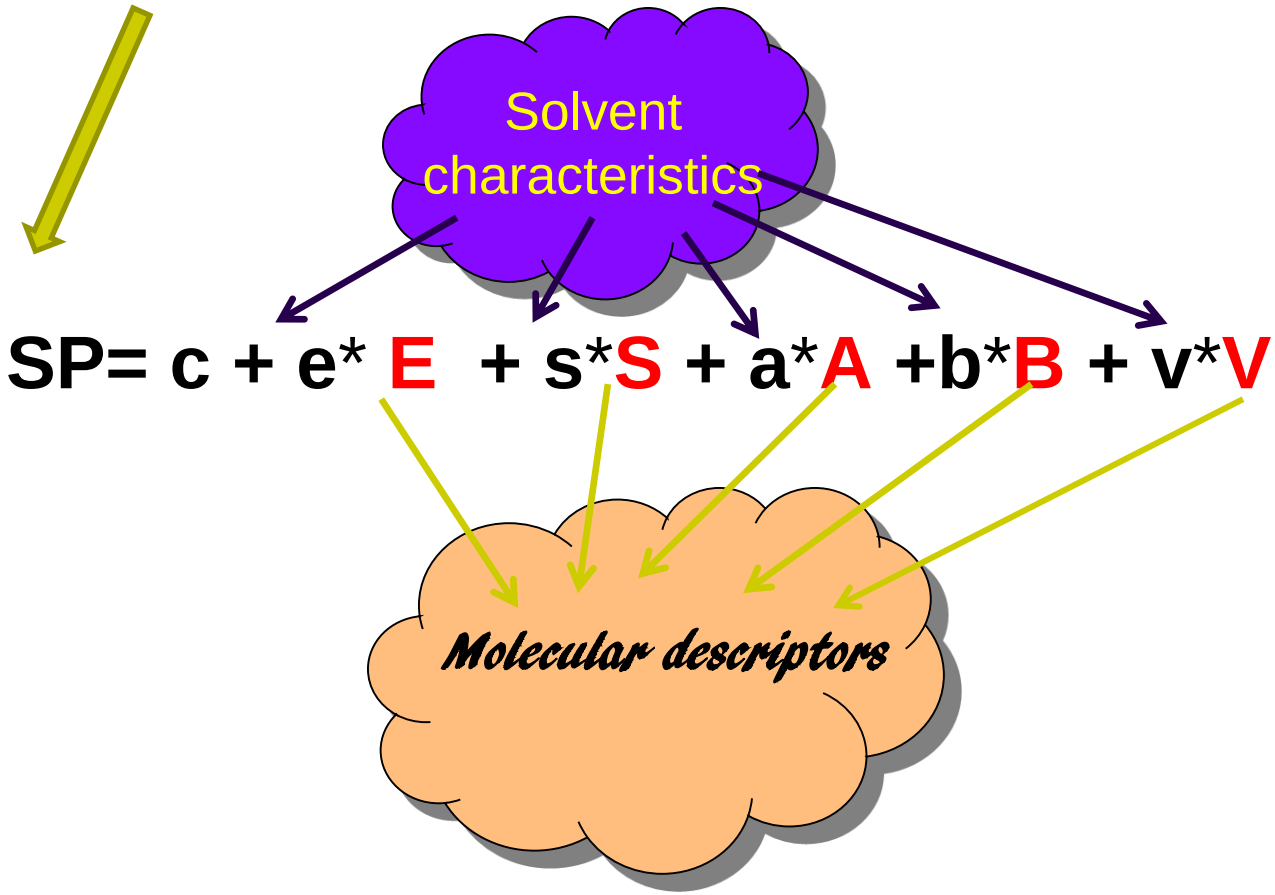
Excess molar refraction E



Solvent molecules (water)

Molecular descriptors describe various solvation and partition processes

SP is the solute property in a given system



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processes. Chem. Soc. Rev. 22 (1993) 78-83.

Solvation equations for biomimetic distributions

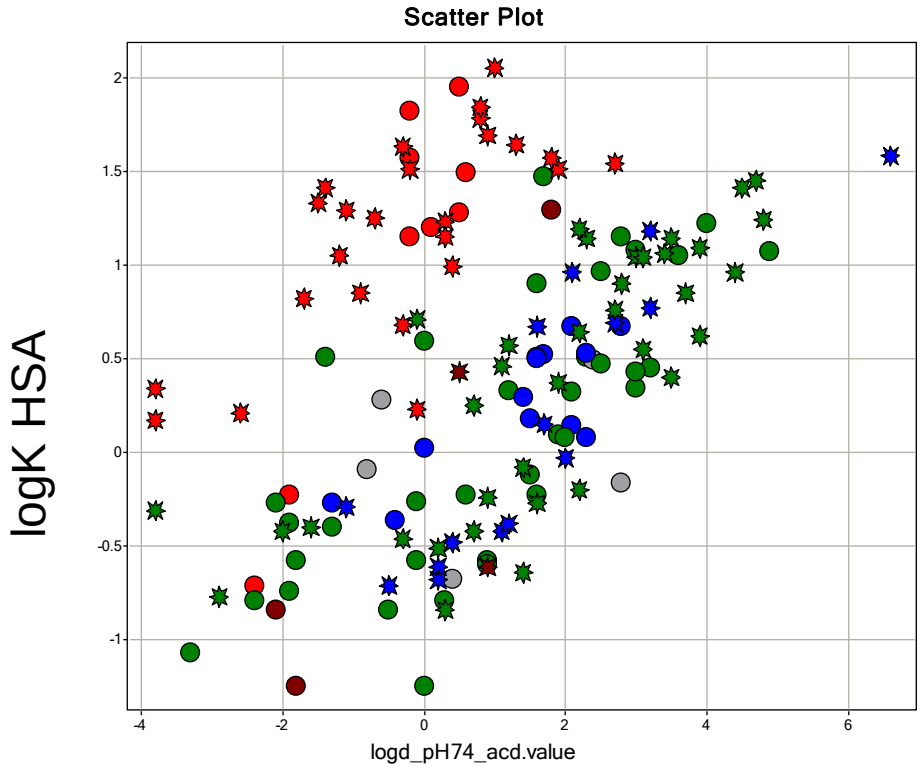
	e/v	s/v	a/v	b/v
• Log K (HSA)	0.02	-0.07	0.16	-1.21
• Log K (AGP)	0.46	-0.38	-0.33	-0.85
• $CHI_{RP,AcN}$	0.09	-0.24	-0.30	-0.98
• $logP_{octanol}$	0.15	-0.28	0.01	-0.91
• Log K (IAM)	0.11	-0.03	0.01	-1.05
• Blood/brain	0.59	-1.03	-0.84	-0.78
• water/skin	0.00	-0.33	-0.35	-1.95

•The octanol/water partition system is an excellent model for compounds binding to HSA and IAM.

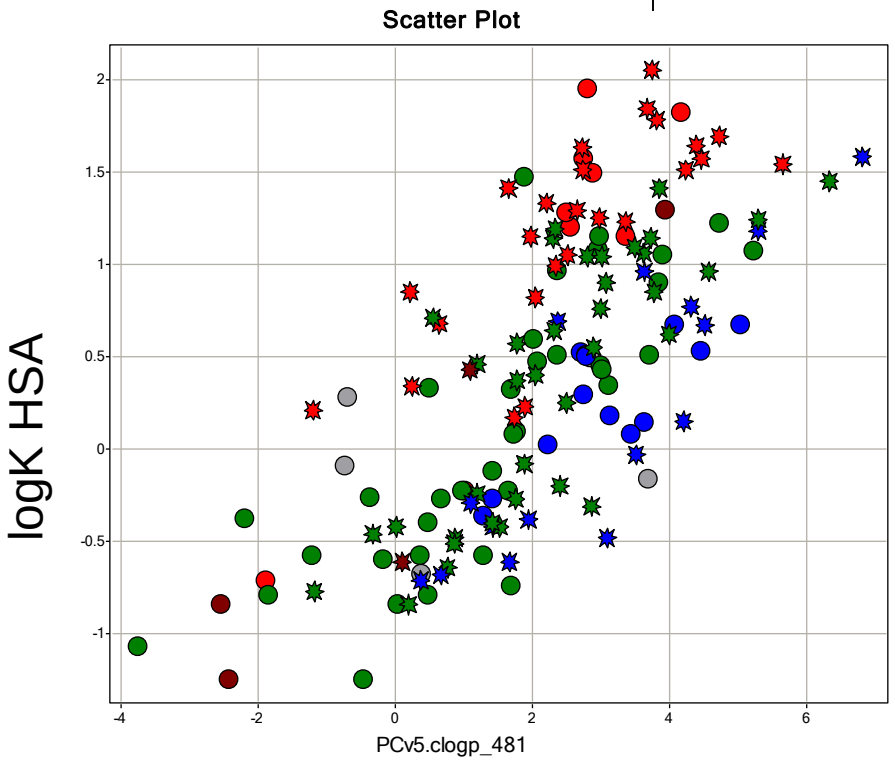
•AGP binding , CHI (reversed phase with acetonitrile) and blood/brain barrier partition are different from octanol/water.

•Equations are derived from the data of non-ionized compounds.

Are we just measuring another lipophilicity by HSA binding?

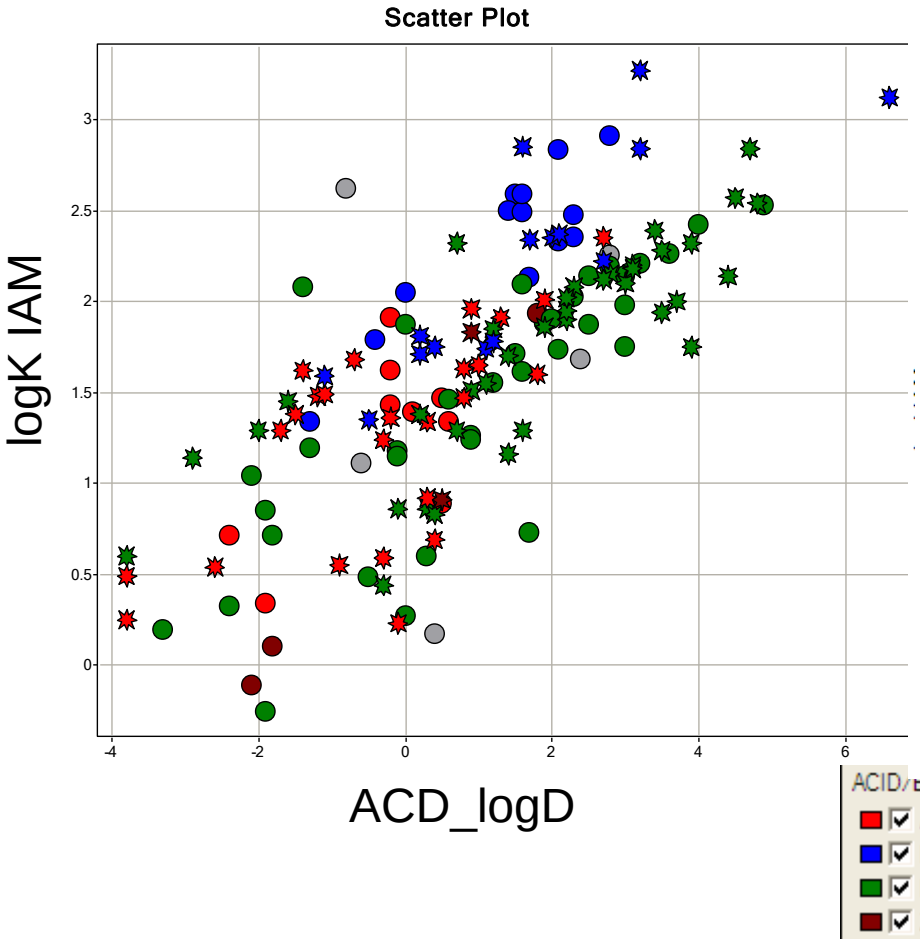


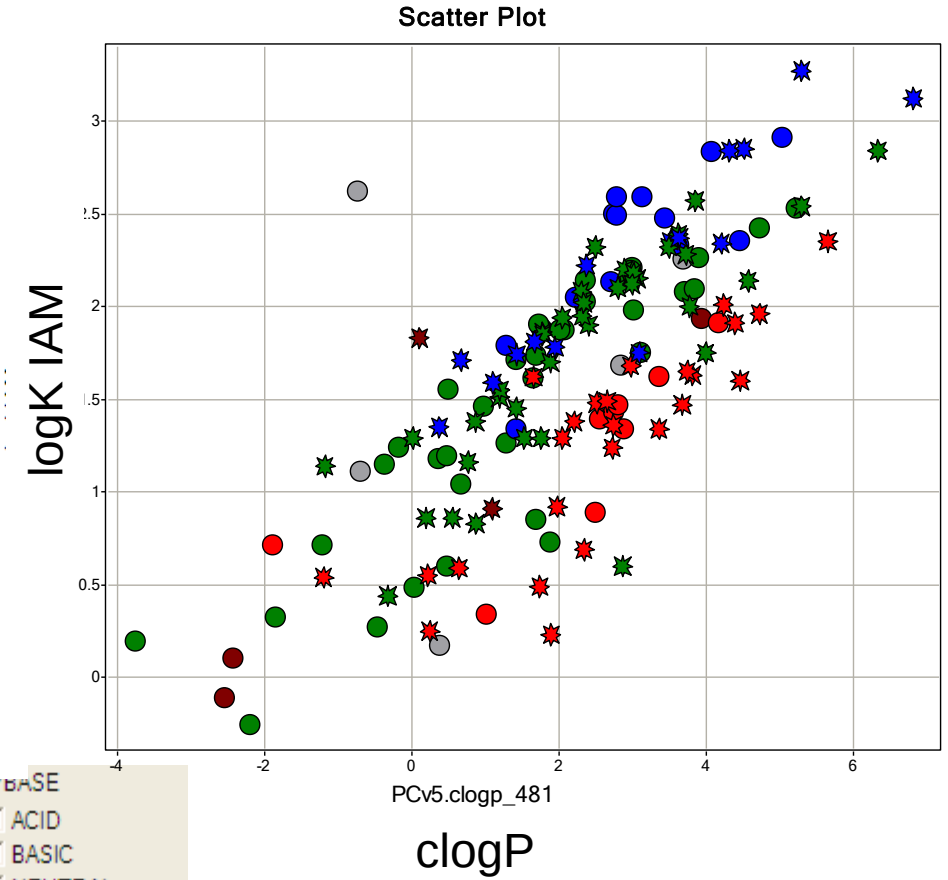
ACD_logD



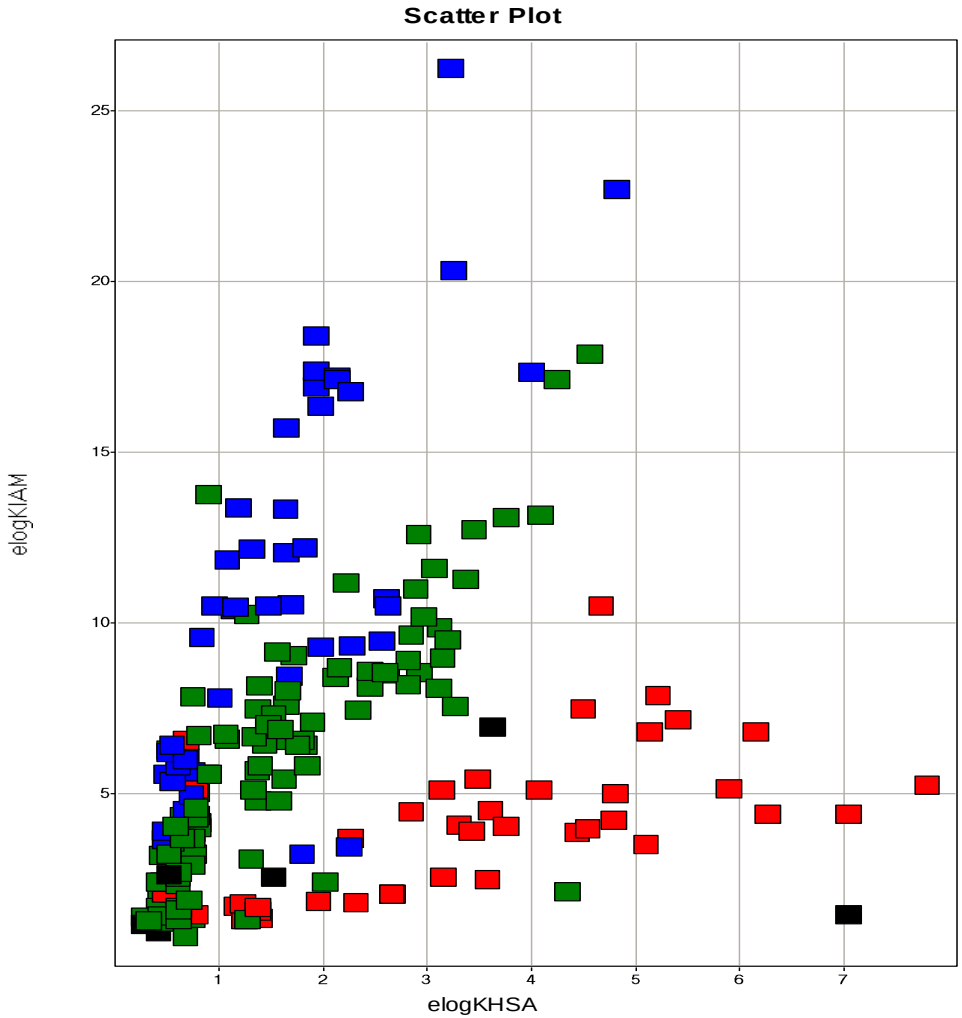
clogP

Are we just measuring another lipophilicity by IAM binding?





IAM binds positively charged compounds and HSA binds negatively charged compounds



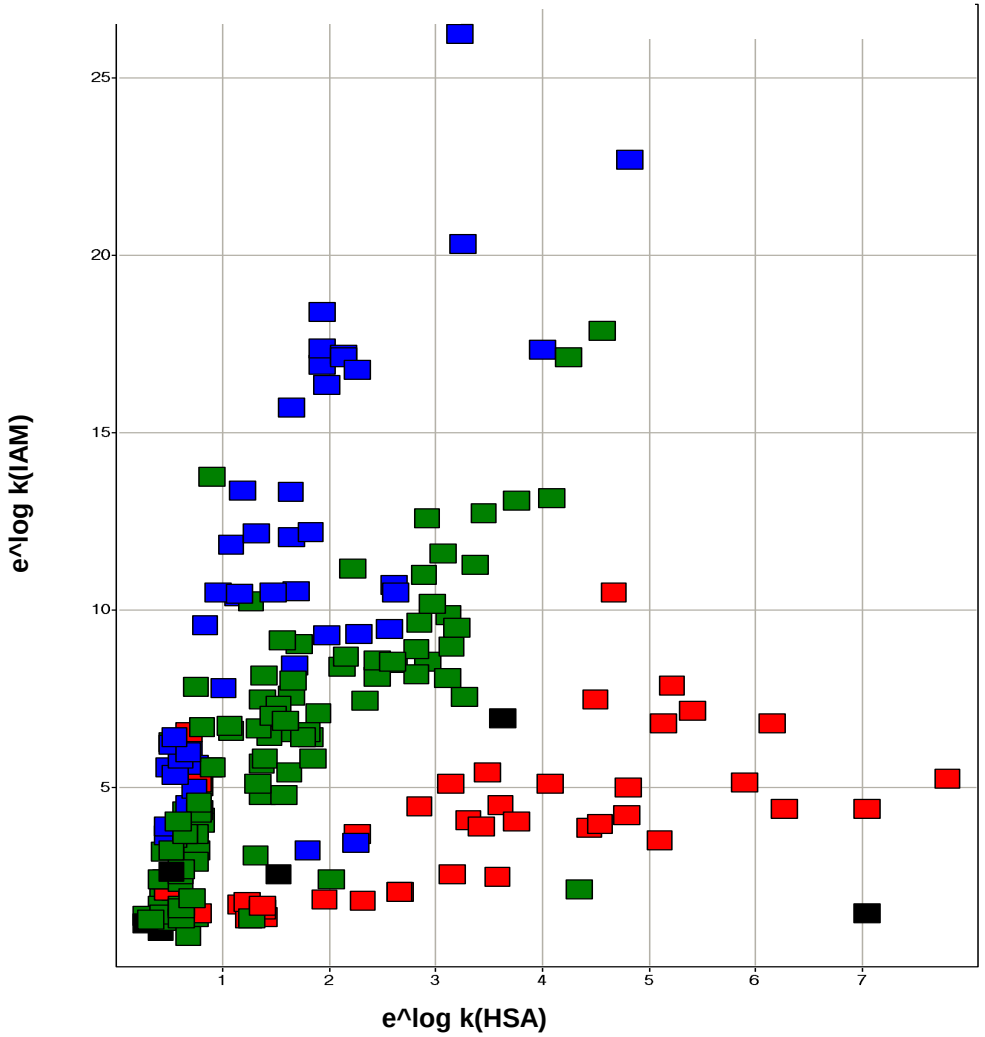
Our mechanistic model shows the importance of HSA and IAM binding in modelling volume of distribution.

Both HSA binding and membrane partition can be related to lipophilicity of the compounds.

However the presence of positive or negative charge makes a significant difference between the two types of binding.

Positively charged compound Negatively charged compound Neutral compound

IAM binds positively charged compounds
HSA binds negatively charged compounds

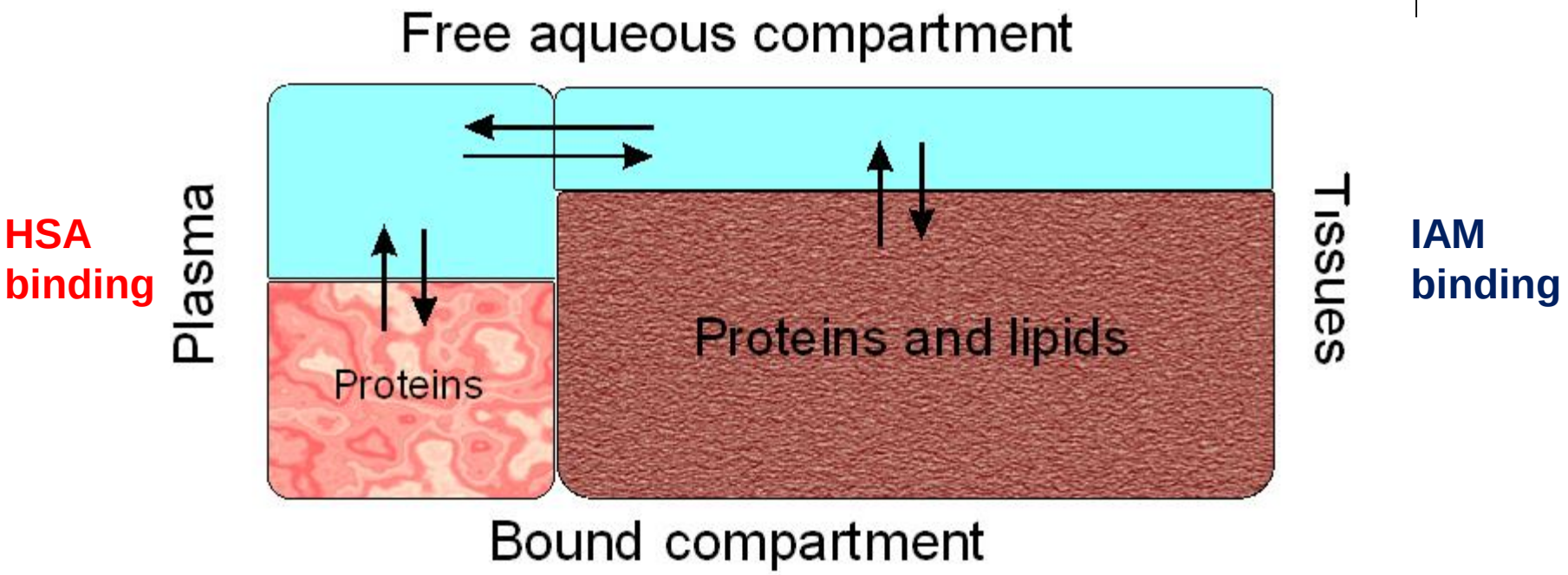


Positively charged compound

Negatively charged compound

Neutral compound

In vivo distribution of drugs



Human Clinical Volume of distribution showed good correlation to the binding difference of compounds between phospholipids (IAM) and albumin (HSA)

Drug efficiency showed good correlation with the sum of the two types of binding (IAM + HSA) which is the reciprocal value of the unbound volume of distribution Vdu

Conclusion

- The biomimetic protein and phospholipid binding data obtained by HPLC can be used to model compounds *in vivo* distribution.

- Both protein and phospholipid bindings are governed by lipophilicity.
- There are major differences in the effect of charge on the octanol/water lipophilicity, protein binding and phospholipid binding.

- Positively charged compounds bind strongly to phospholipids and AGP, while negatively charged compounds bind strongly to albumin.

- The *in vivo* volume of distribution can be modelled by the difference of compounds binding to phospholipids (IAM) and albumin (HSA).

- The overall non-specific binding of the compounds in vivo, the drug efficiency and the unbound volume of distribution can be modelled by the sum of IAM and HSA binding.

- Measurement of the physico-chemical binding behaviour of compounds using biomimetic HPLC are helpful in drug design and discovery and can predict *in vivo* distribution of compounds.

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