Computer Aided Drug Design Methods

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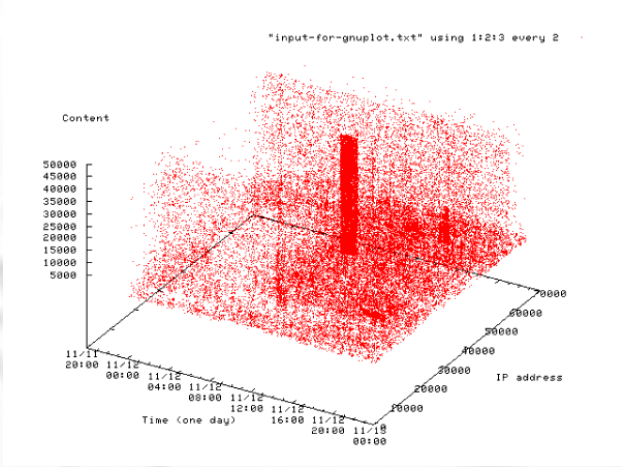
QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS (QSAR)

- QSAR methods are various forms of mathematical or statistical models that seek to predict the biological effects of chemicals based on their structure.

- Being able to predict biological activities of chemical structures by QSAR analysis dates back to the nineteenth century.



The aim of the QSAR is:

- to design a new compound that can shows better activity using the QSAR equation developed from a series of compounds,
- to reduce the toxicity of an existing compound,
- to optimize the hit compound (lead) with the optimum lipophilic property to pass a selected barrier (e.g. blood-brain barrier)

Biological Responses Used in QSAR Studies

- **Affinity data:** substrate or receptor binding
- **Rate constants:** association, dissociation
- **Inhibition constants:** IC50, enzyme inhibition values
- **Pharmacokinetic parameters:** absorption, distribution, metabolism, excretion
- ***In vitro* and *in vivo* biological activity data**
- **Pharmacodynamic data of drugs** (drug-receptor interaction)
- **Toxic effect parameters**

Physicochemical Parameters Used in QSAR Studies

PHYSICOCHEMICAL PARAMETERS	SYMBOL
LIPOPHILIC (HYDROPHOBIC) PARAMETERS	
Partition Coefficient	Log P, $(\log P)^2$
π-Substituent Constant	π, $(\pi)^2$
Chromatography Distribution Coefficient (Liquid-liquid)	R_M
Hydrophobic Fragmental Constant	f
ELECTRONIC PARAMETERS	
Ionization Constant	pK_a
Sigma Aromatic Substituent Constant	σ_m , σ_m
Modification σ Aromatic Substituent Constants	σ^+ , σ^- , σ_1 , σ_R , σ^o
Sigma Aliphatic Substituent Constant	σ^*
Substituent Resonance Effect	*R*
Substituent Inductive Effect	*F*
QUANTUM MECHANICAL PARAMETERS	
Atomic σ Elektron Charge	q^σ , Q^σ
Atomic π Elektron Charge	q^π , Q^π
Nucleophilic Delocalization State	S_r^N
Electrophilic Delocalization State	S_r^E
Energy of Lowest Unoccupied Molecular Orbital, "electrophilicity"	E_{LUMO}
Energy of Highest Occupied Molecular Orbital, "nucleophilicity"	E_{HOMO}
STERIC PARAMETERS	
Steric Substituent Constant	E_S
Molar Volume	MV
Molar Refractivity Substituent Constant	MR
Molecular Weight	MW
Van der Waals Radii	R
Sterimol Width and Length Parameters	L, B_1-B_4

Lipophilic Property

- is the most used physicochemical property in QSAR studies.
- Lipophilicity can be defined as the dispersion between water and oil phase.

Log P = Partition Coefficient

- It is a parameter that expresses the concentration of the chemical compound distributed between the lipid-water layers. For this purpose, it was found that the most suitable solvent system is 1-octanol / water.
- As the water, the buffer solution is prepared to mimic the physiological pH (pH = 7.4).

Structure-Activity Relationships (QSAR) Analysis

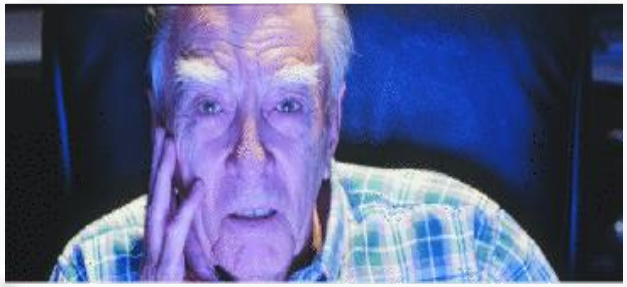
In the 1960s, two different QSAR analysis methods were developed. They were developed by

- Hansch and Fujita,
- Free and Wilson.

Quantitative structure-activity relationships (QSAR) are the mathematical methods for describing the relationships between molecular properties of chemical compounds **(structural / physicochemical properties)** and biological activities.

Hansch Analysis Method

In the analysis method, Hansch expressed that the observed biological effects of the compounds in a homologous series are a function of the physicochemical properties of these compounds and developed the following formula;


Hansch

biological effect = f (hydrophobic) + f (electronic) + f (steric) + c (constant)

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Log 1 / C = Logarithmic biological effect

Independent variables of physicochemical parameters

$$Y \text{ (biological activity)} = k_o + k_1X_1 + k_2X_2 + ... + k_nX_n$$

correlation constant indicating the contribution of the unexplained residue to the biological activity

The constants (regression coefficients) that define (+) or (-) contribution of physicochemical properties to biological activity

Hansch equations

$$\log 1/C = 1.22\ \pi - 1.59\ \sigma + 7.89$$

$$(n=22;\ s=0.238;\ r= 0.918$$

$$\log 1/C = 0.398\ \pi + 1.089\ \sigma + 1.03\ Es + 4.541$$

$$(n=9;\ r= 0.955)$$


250
200
150
100
50
25