Computational methods. The MARCH-INSIDE approach [1-3] is based on the calculation of the different physicochemical molecular properties as an average of atomic properties (ap). For instance, it is possible to derive average estimations of molecular descriptors or group indices [4, 5]: electron-negativities \( k_\chi(G) \), refractivities \( k_{MR}(G) \), polarizabilities \( k_\alpha(G) \), van der waals area \( k_{vdW}(G) \) and logarithms of water/n-octanol partition coefficients \( \log^3P \). In a compact notation we write \( kD_t(G) \) where \( D_t \) is the type of descriptor \( D_t = \chi, MR, \alpha, A_{vdW} \) and \( \log^3P \); \( G = \) total, Csat, Cinst, Hetero and Hx.

\[
k_\chi(G) = \sum_{j \in G} p_i(\chi_j) \chi_j \quad (1) \\
k_{MR}(G) = \sum_{j \in G} p_i(MR_j) \cdot MR_j \quad (2) \\
k_\alpha(G) = \sum_{j \in G} p_i(\alpha_j) \cdot \alpha_j \quad (3) \\
k_{vdW}(G) = \sum_{j \in G} p_i(A_{vdW_j}) \cdot A_{vdW_j} \quad (5)
\]

It is possible to consider isolated atoms (\( k = 0 \)) in the estimation of the molecular properties \( ^0_k \chi(G), ^0_kMR(G), ^0_k\alpha(G), \log^3P, ^0_kA_{vdW} \). In this case the probabilities \( ^0_kp(ap) \) are determined without considering the formation of chemical bonds (simple additive scheme). However, it is possible to consider the gradual effects of the neighboring atoms at different distances in the molecular backbone. In order to reach this goal the method uses a MM, which determines the absolute probabilities \( p_i(ap) \) with which the atoms placed at different distances \( k \) affect the contribution of the atom \( j \) to the molecular property in question.

For example, in the case of molecular polarizability:

\[
k_\alpha = \begin{bmatrix}
p_1 \cdot \alpha_1 & \ldots & p_n \cdot \alpha_n
\end{bmatrix} = \begin{bmatrix}
p_{1,2} & p_{2,1} & \ldots & p_{1,n}
p_{2,1} & p_{2,2} & \ldots & p_{2,n}
\vdots & \vdots & \ddots & \vdots 
p_{n,1} & \ldots & \ldots & p_{n,n}
\end{bmatrix} \begin{bmatrix}
\alpha_1 \\
\alpha_2 \\
\vdots \\
\alpha_n
\end{bmatrix} = \sum_{j=1}^n p_k(\alpha_j) \cdot \alpha_j 
\]

Where, from left to right, the first term is \( k_\alpha \), which is the average molecular polarizability of the molecule considering the effects of all the atoms placed at distance \( k \) over every atomic polarizability \( \alpha_j \).

The vector on the left-hand side of the equation contains the probabilities \( ^0_kp(a) \) for every atom in the molecule, without considering chemical bonds. The matrix in the center of the equation is the so-called stochastic matrix. The values of this matrix \( (p_k) \) are the probabilities with which every atom affects the polarizability of the atom bonded to it. Both kinds of probabilities \( ^0_kp(a) \) and \( ^1_kp(a) \) are easily calculated from atomic polarizabilities \( (\alpha) \) and the chemical bonding information:

\[
^0_kp_j = \frac{\alpha_j}{\sum_{k=1}^n \alpha_k} \quad (7) \\
^1_kp_j = \frac{\delta_{jk} \cdot \alpha_j}{\sum_{k=1}^n \delta_{jk} \cdot \alpha_k} \quad (8)
\]
The only difference is that in the probabilities \(^3p(\alpha_j)\) we consider isolated atoms by carrying out the sum in the denominator over all \(n\) atoms in the molecule. On the other hand, for \(^1p_{ij}\) chemical bonding is taken into consideration by means of the factor \(\delta_{ij}\). This factor has a value of 1 if atoms \(i\) and \(j\) are chemically bonded and is 0 otherwise.

Finally, it is interesting to note that one can sum only the atoms included in a specific group \((G)\) rather than all atoms. In this way we can approach specific classes of average properties such as average electronegativity for \(sp^3\) carbon atoms \((C_{sp^3})\) or average polarizability for heteroatoms \((Het)\). All calculations were performed using the program MARCH-INSIDE \([1-3]\), which was developed in-house, see recent reviews for details.