ACC II: Calculation of partial atomic charges

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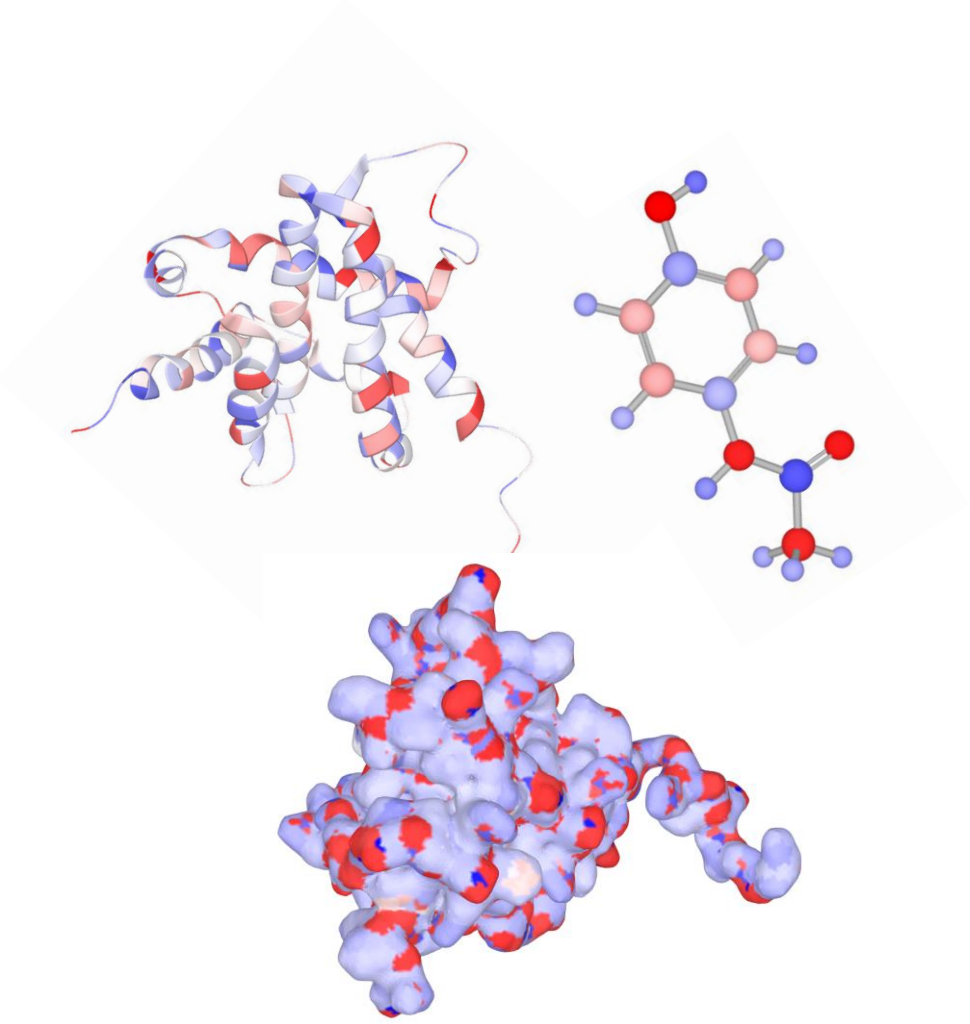
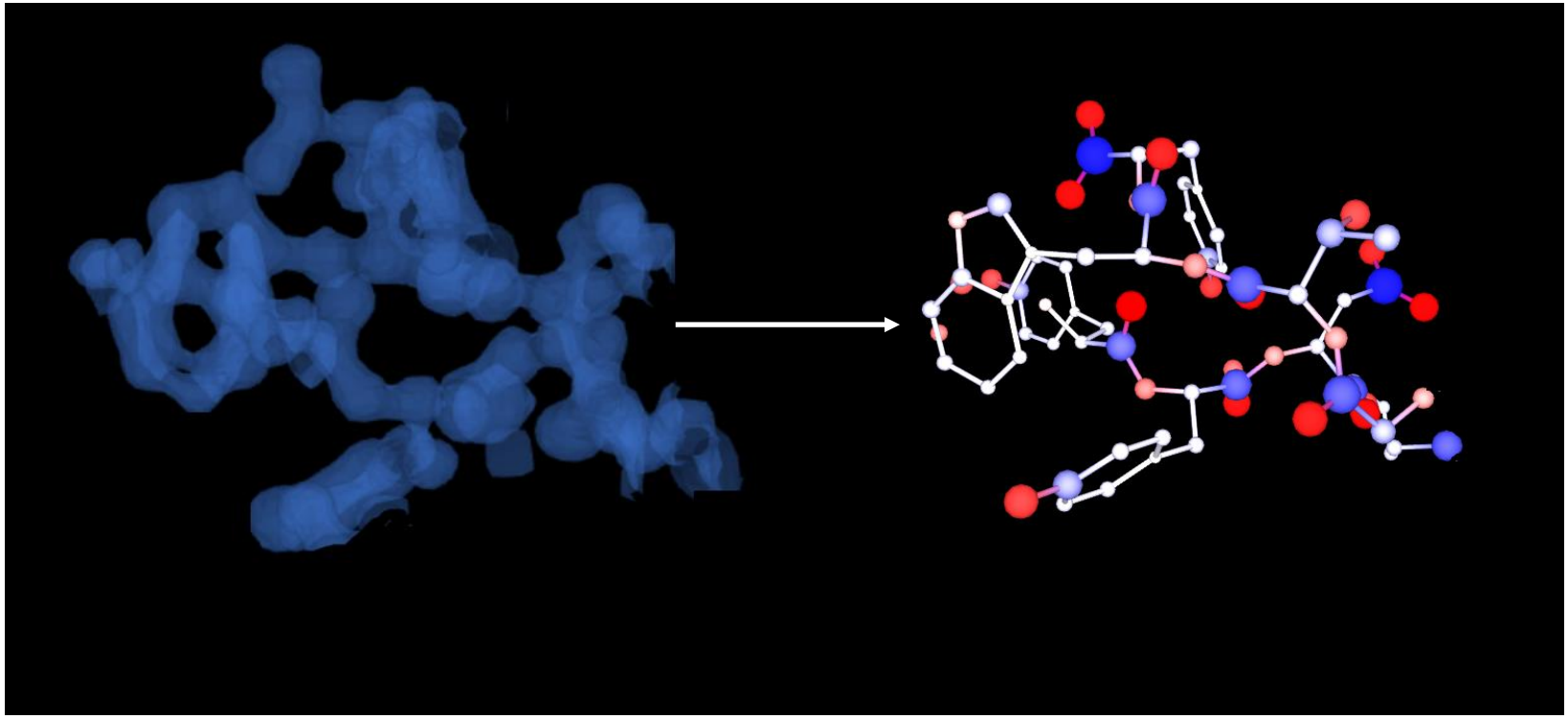


Partial atomic charges

Real numbers describing distribution of electron density among atoms.



Application of partial atomic charges

Application fields:

- Organic chemistry
- Physical chemistry
- **Computational chemistry**
- **Chemoinformatics**
- **Bioinformatics**
- Nanoscience

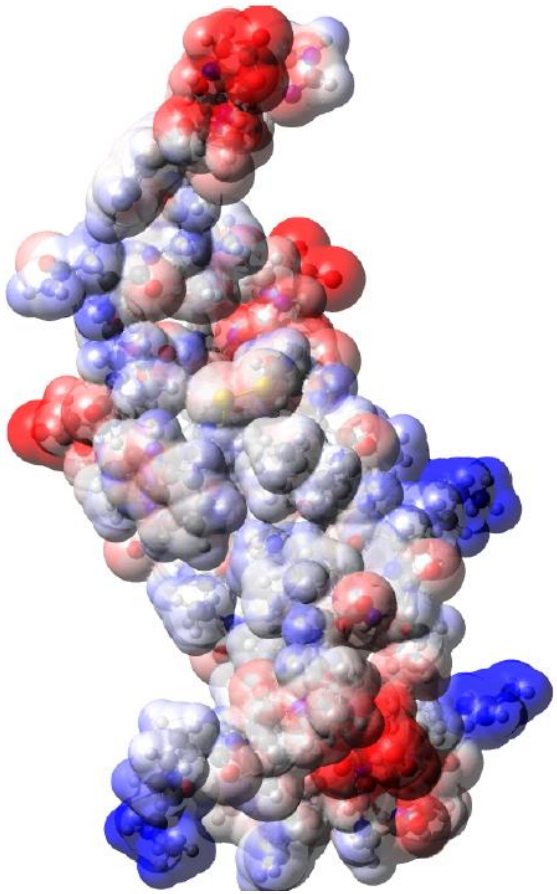
Applications:

- Prediction of electrostatic interactions
- Molecular mechanics and dynamics
- Docking
- Virtual screening
- QSAR/QSPR modeling
- Prediction of bonding sites
- Similarity search

How to obtain charges?

Partial atomic charges
= a theoretical concept

We cannot measure them!
We can only compute them.



Consequences:

- Many different charge calculation approaches were developed
- We cannot select the best approach

Validation:
We can calculate somethig mesurable from them.

Charge calculation approaches

Quantum mechanical methods

Advantages:

- Calculated ab-initio
- High quality charges

Disadvantages:

- Computationally expensive
- Complexity from O(E^3) to O(E^6), where E is a number of electrons
- Cannot be used for macromolecules

Charge calculation approaches

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- $O(E^3)$ to $O(E^6)$, where E is a number of electrons
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Empirical methods

Advantages:

- Fast calculation
- Complexity $O(N^3)$, where N is a number of atoms

Disadvantages:

- Fitted to QM charges
- Necessity of parameterization – not easy

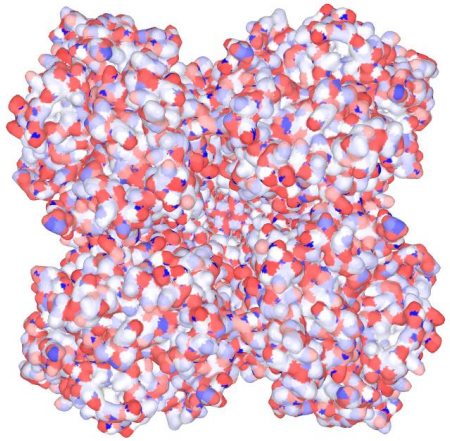
Empirical charge calculation approaches

Conformationally independent (2D):

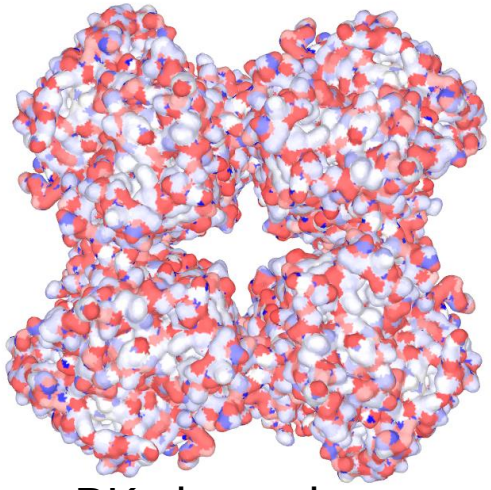
- Based on molecular 2D structure
- Does not reflect conformational changes

Conformationally dependent (3D):

- Based on molecular 3D structure
- Different conformation ~ different charges

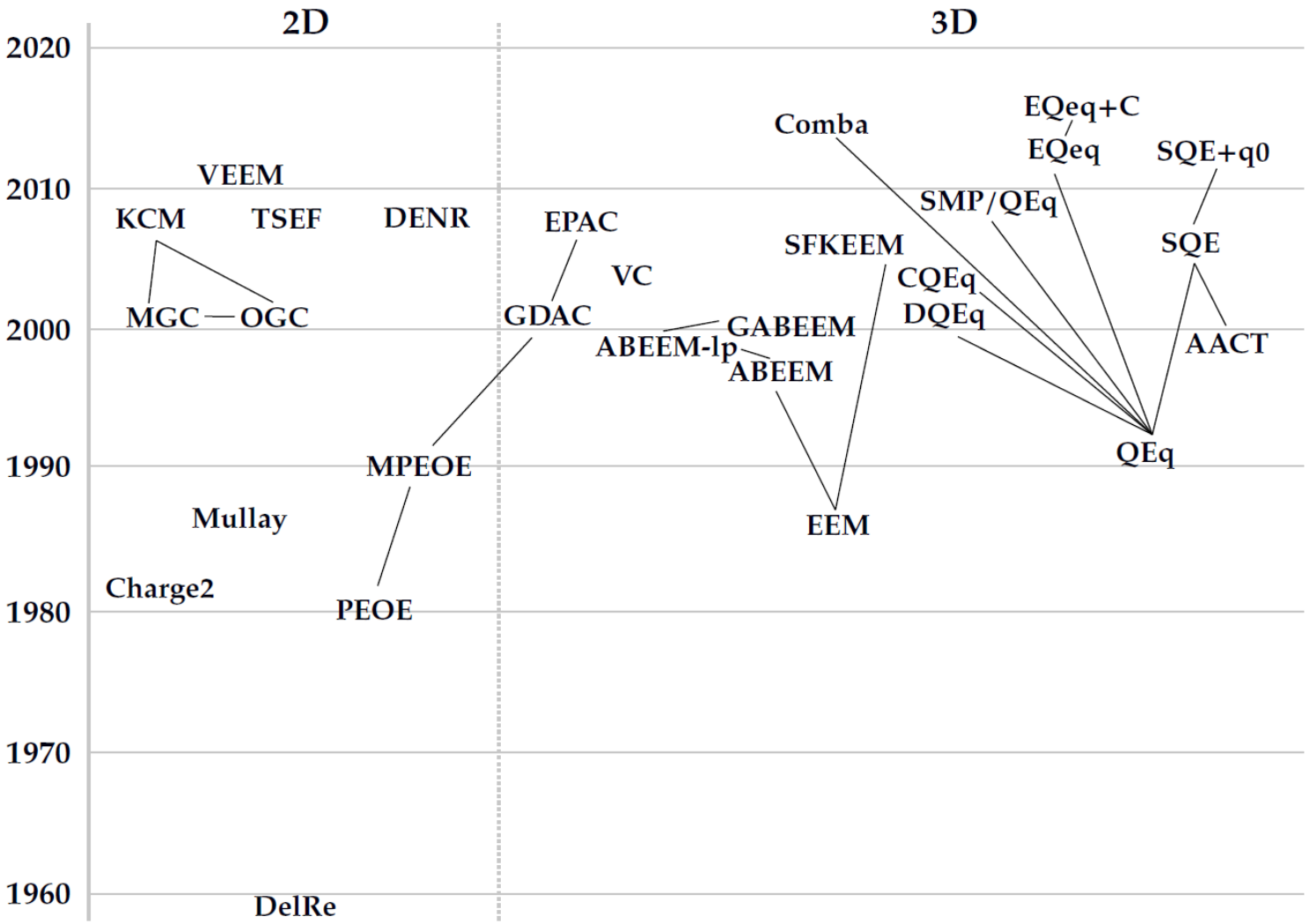


BK channel closed

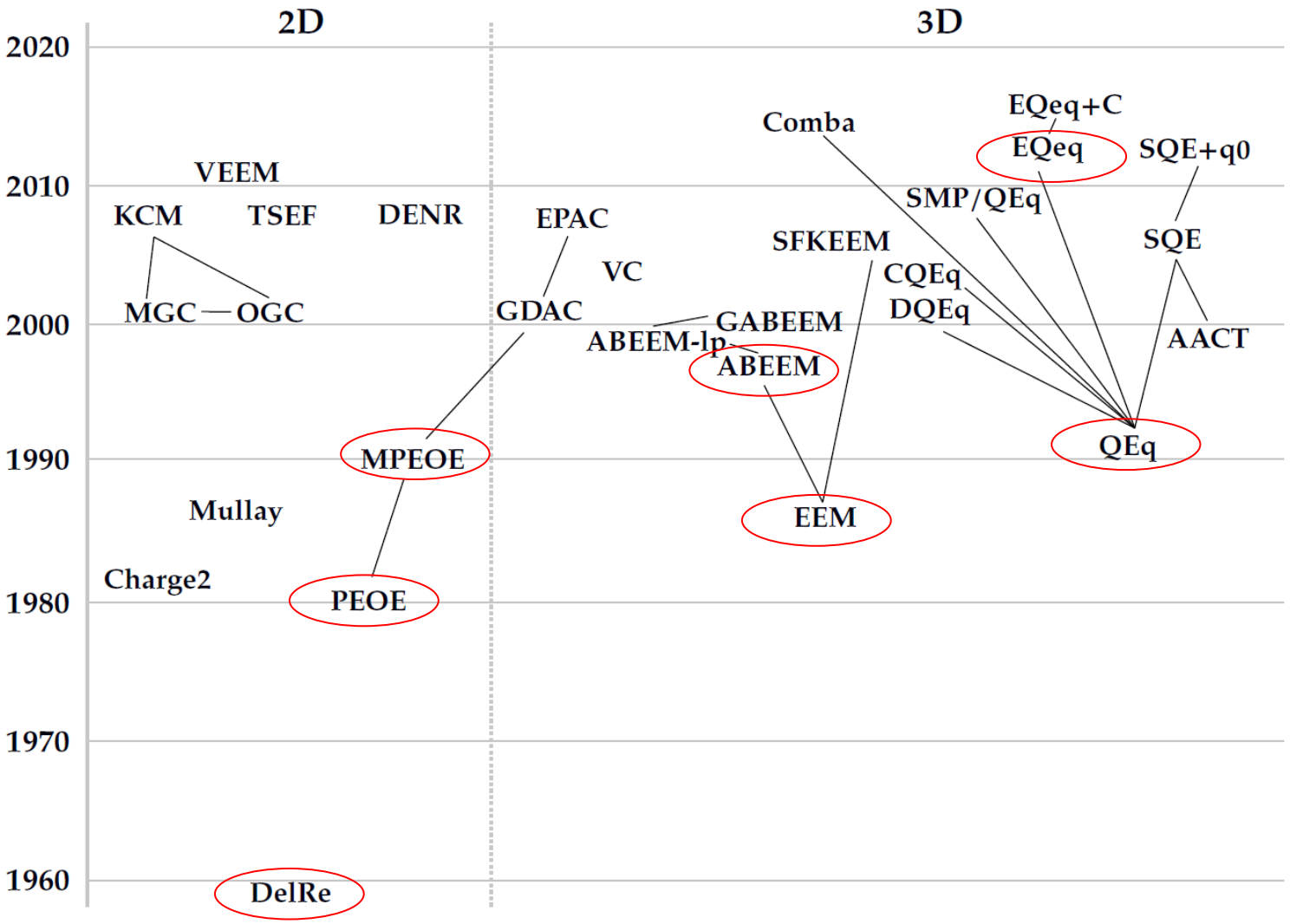


BK channel open

Empirical charge calculation approaches



Empirical charge calculation approaches



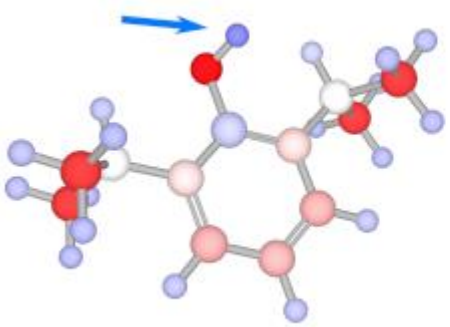
Electronegativity Equalization Method (EEM):

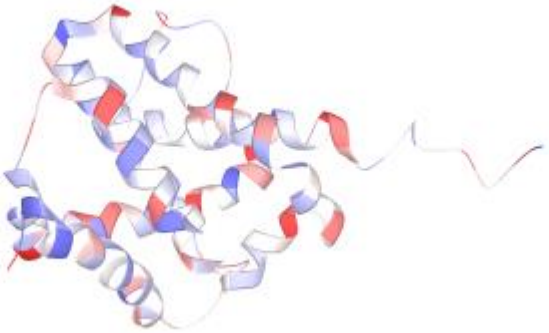
$$\begin{bmatrix} B_1 & R_{1,2}^{-1} & \cdots & R_{1,N}^{-1} & 1 \\ R_{2,1}^{-1} & B_2 & \cdots & R_{2,N}^{-1} & 1 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ R_{N,1}^{-1} & R_{N,2}^{-1} & \cdots & B_N & 1 \\ 1 & 1 & \cdots & 1 & 0 \end{bmatrix} \cdot \begin{bmatrix} q_1 \\ q_2 \\ \vdots \\ q_N \\ -\overline{\chi} \end{bmatrix} = \begin{bmatrix} -A_1 \\ -A_2 \\ \vdots \\ -A_N \\ Q \end{bmatrix}$$

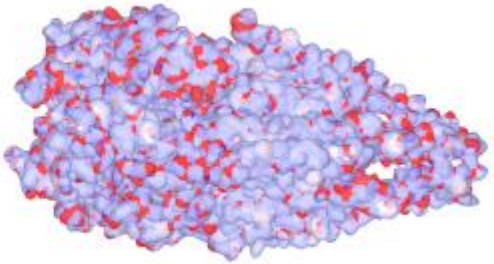
$$Q = \sum_{i}^{N} q_i$$

Atomic Charge Calculator II (ACC II)

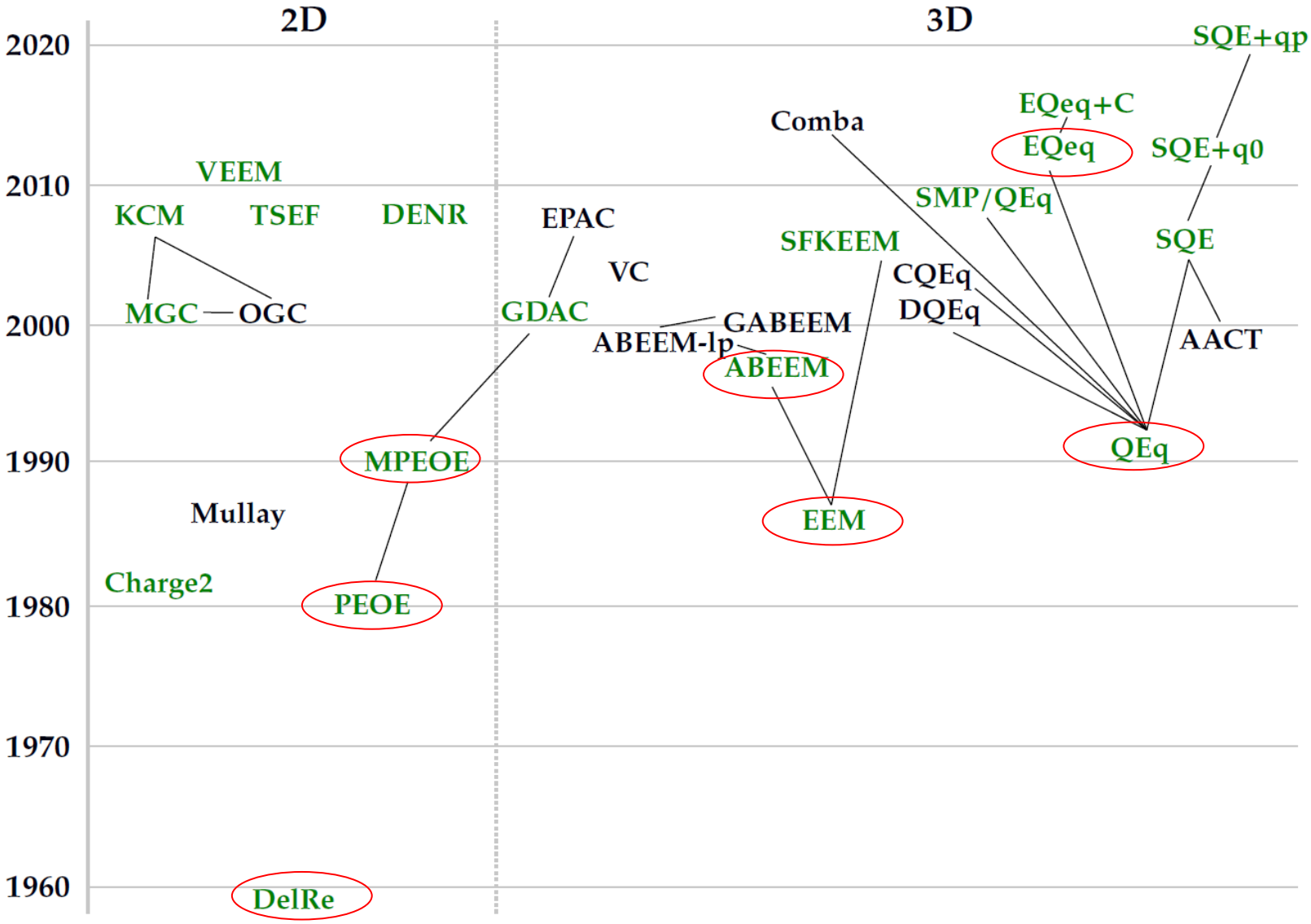
- **Includes 20 empirical charge calculation methods**
- **Inputs:** SDF, MOL2, PDB, mmcif
  or archive with these files
- **Outputs:** plain text, Mol2, PQR
- **Visualization:** LiteMol plugin
- **Web page:** https://acc2.ncbr.muni.cz
- **Command line application available**





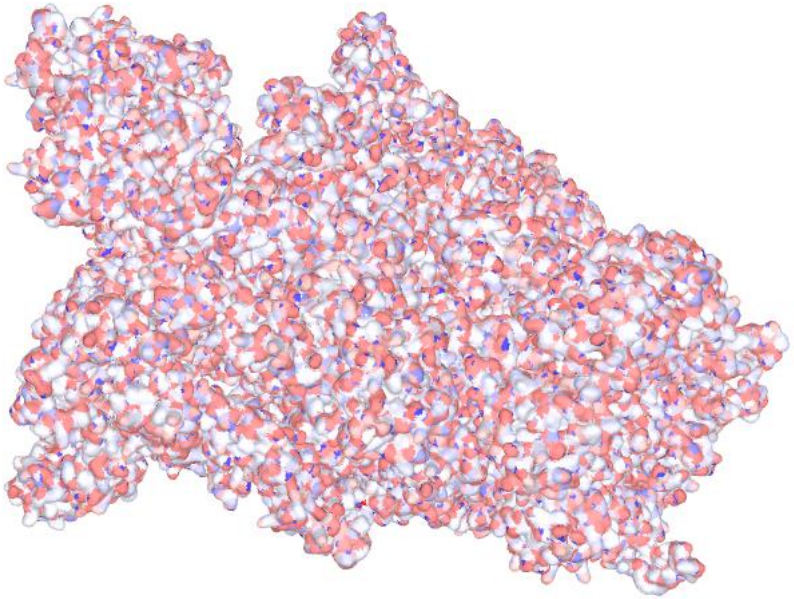


ACC II: empirical methods included



ACC II: workflow

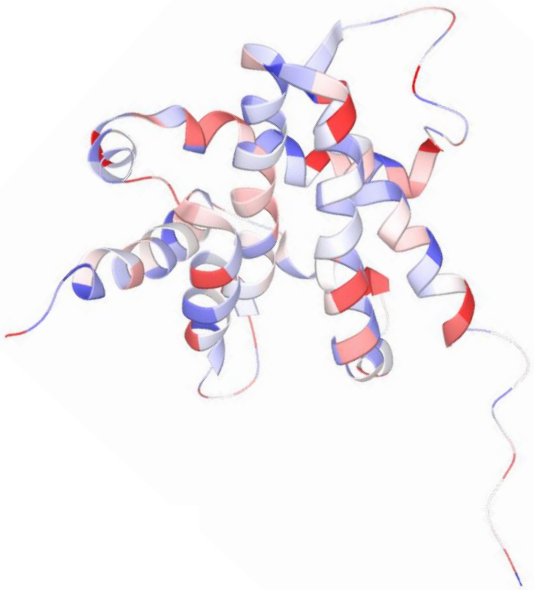
- Uploading the structure(s)
- Internal validation
- Selecting the empirical method and its parameter set
- Executing the selected method:
  - If large molecules, the Cutoff or Cover approaches are used
- Visualizing the computed charges



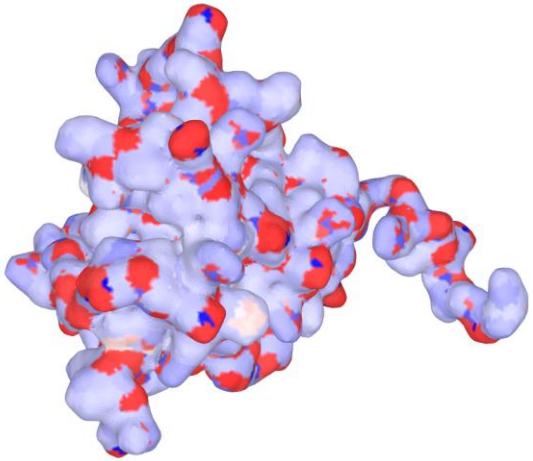
ACC II: visualization

balls and sticks

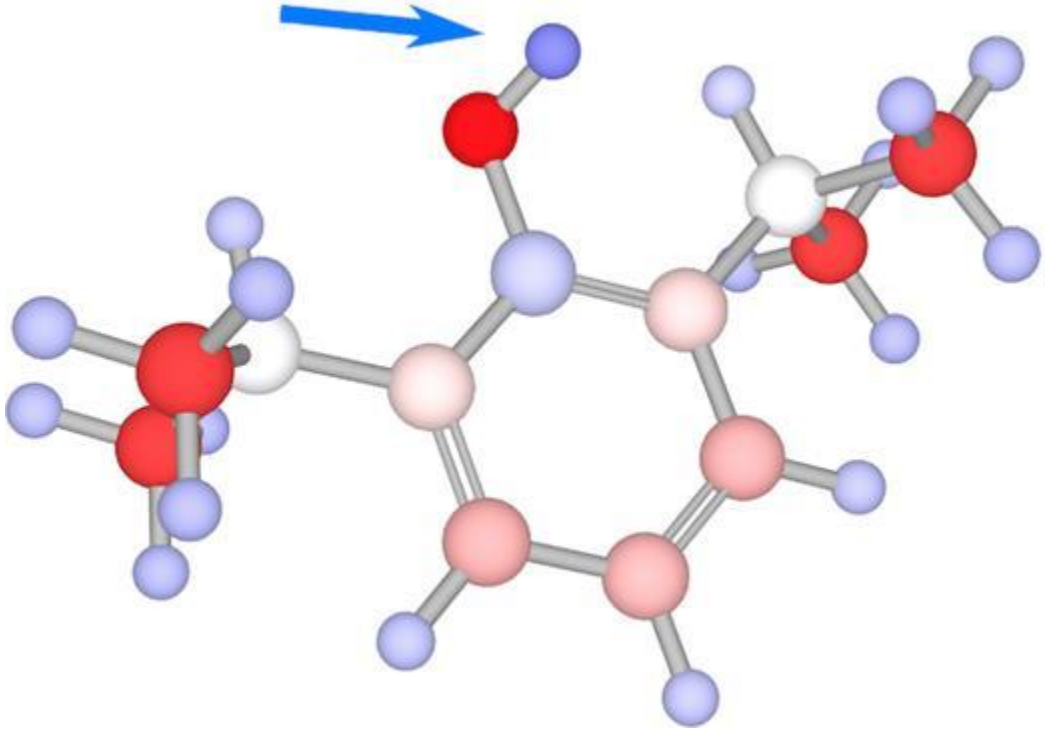
cartoon



surface



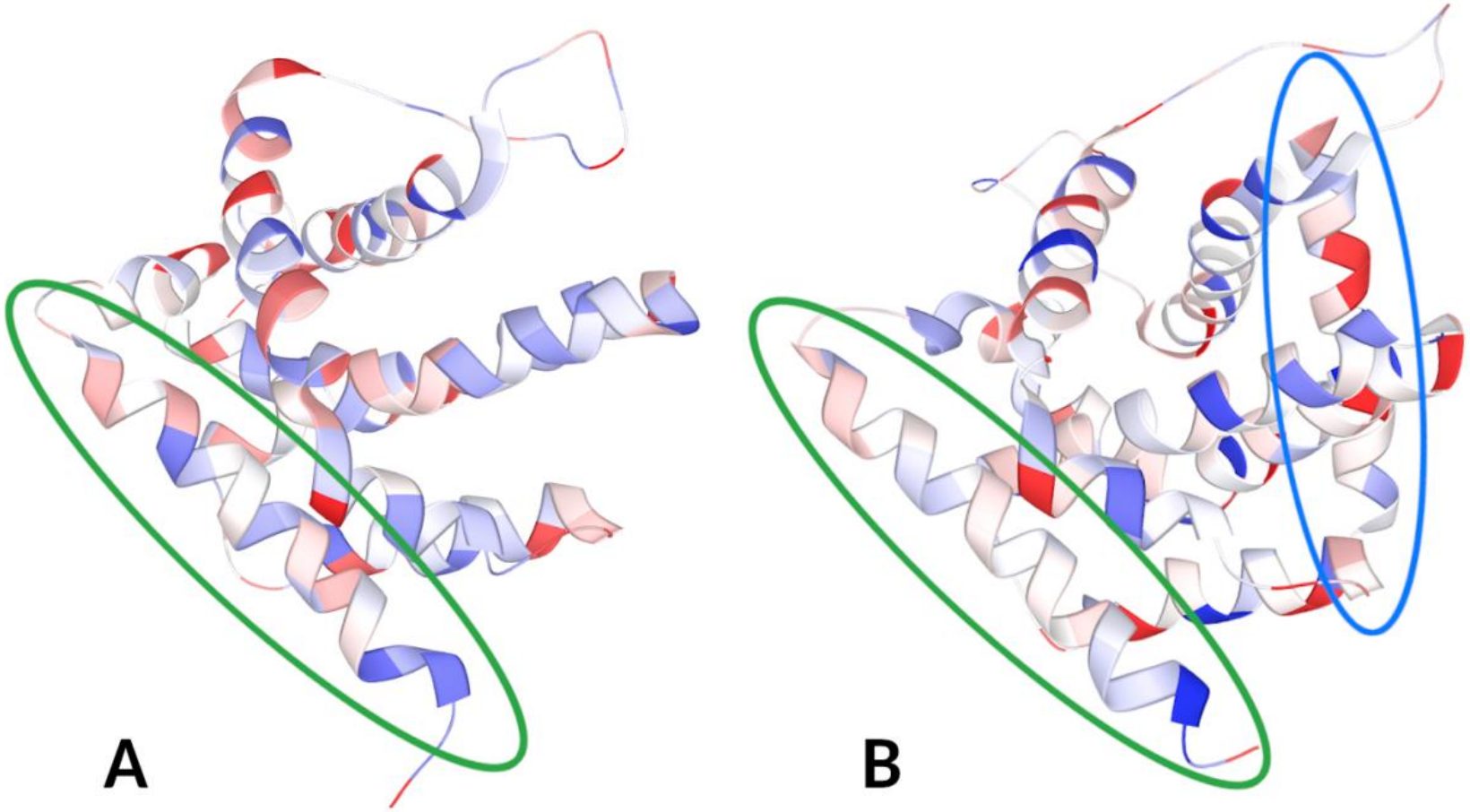
ACC II example 1: phenols



Partial atomic charges in propofol. The phenol hydrogen is marked with a blue arrow.

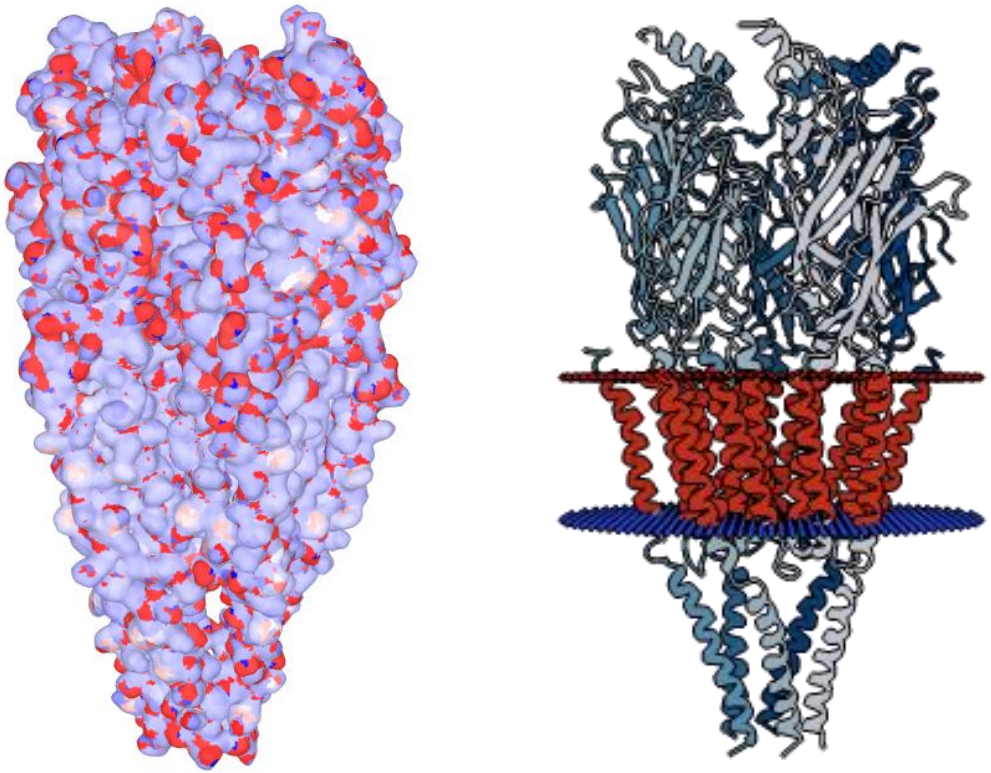
Svobodová, R., Geidl, S., Ionescu, C.M., Skřehota, O., Bouchal, T., Sehnal, D., Abagyan, R. and Koča, J., 2013. Predicting p K a values from EEM atomic charges. *Journal of cheminformatics*, *5*(1), pp.1-15.

ACC II example 2: apoptotic protein BAX



(A) Inactive BAX (PDB ID 1f16). (B) Activated BAX (PDB ID 2k7w). An activator is marked with a blue oval, the C domain is marked with a green oval. The C domain of activated BAX is depolarized – it is mainly white or whitish in colour. This depolarization causes the C domain to be released and penetrate the mitochondrial membrane and initiate apoptosis.

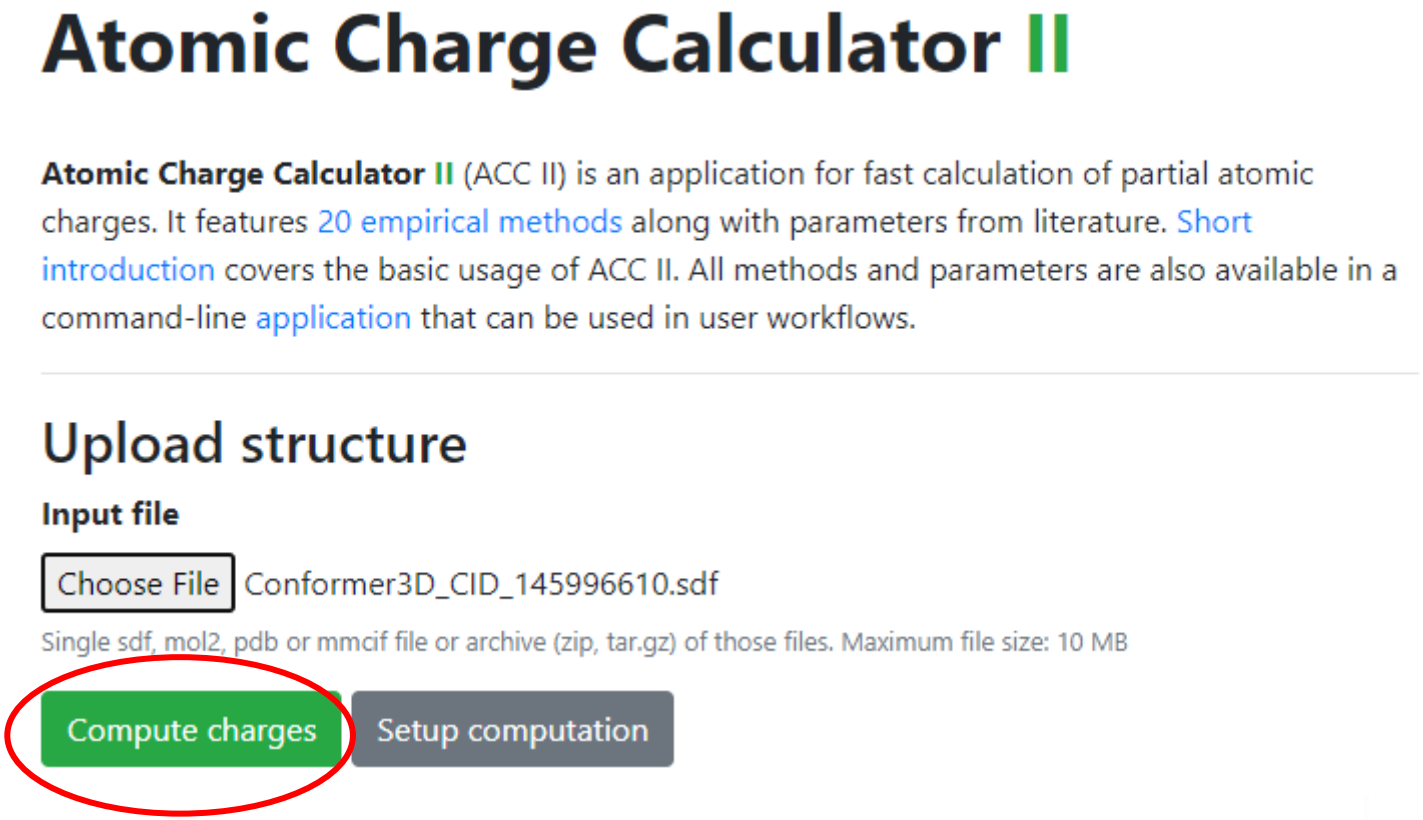
ACC II example 3: membrane protein



Structure of nicotinic acetylcholine receptor (PDB ID 2bg9). Nonpolar transmembrane part and polar surface of extracellular and cytoplasmic parts

ACC II: How to use ACC II?
Molnupiravir

- Download 3D structure from PubChem
- Upload to ACC II
- Press **Compute charges**



ACC II: How to use ACC II?
Molnupiravir

Structure

145996610

View

○ Cartoon ◉ Balls and sticks ○ Surface

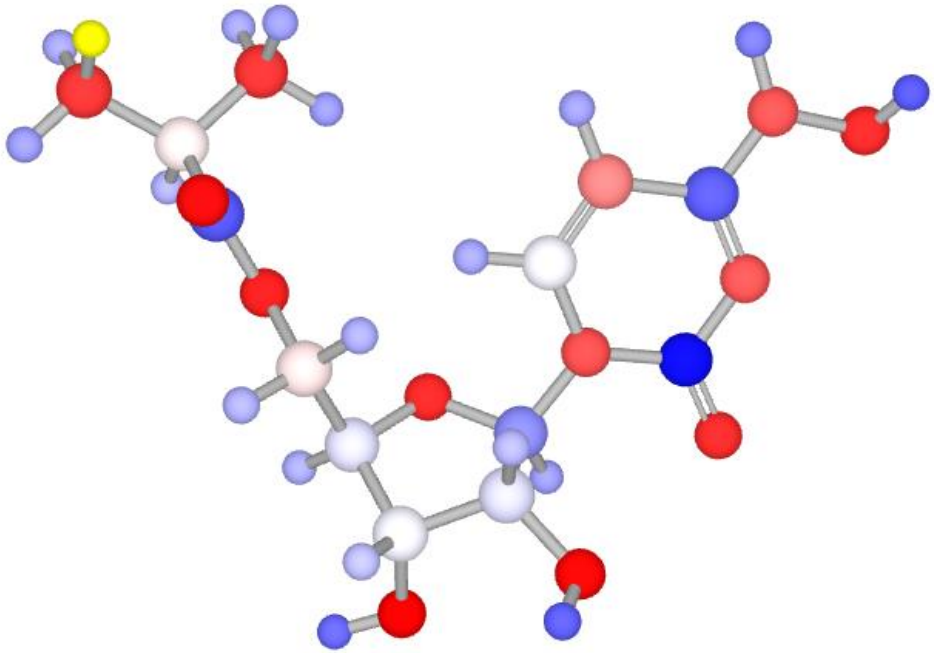
Coloring

○ Structure

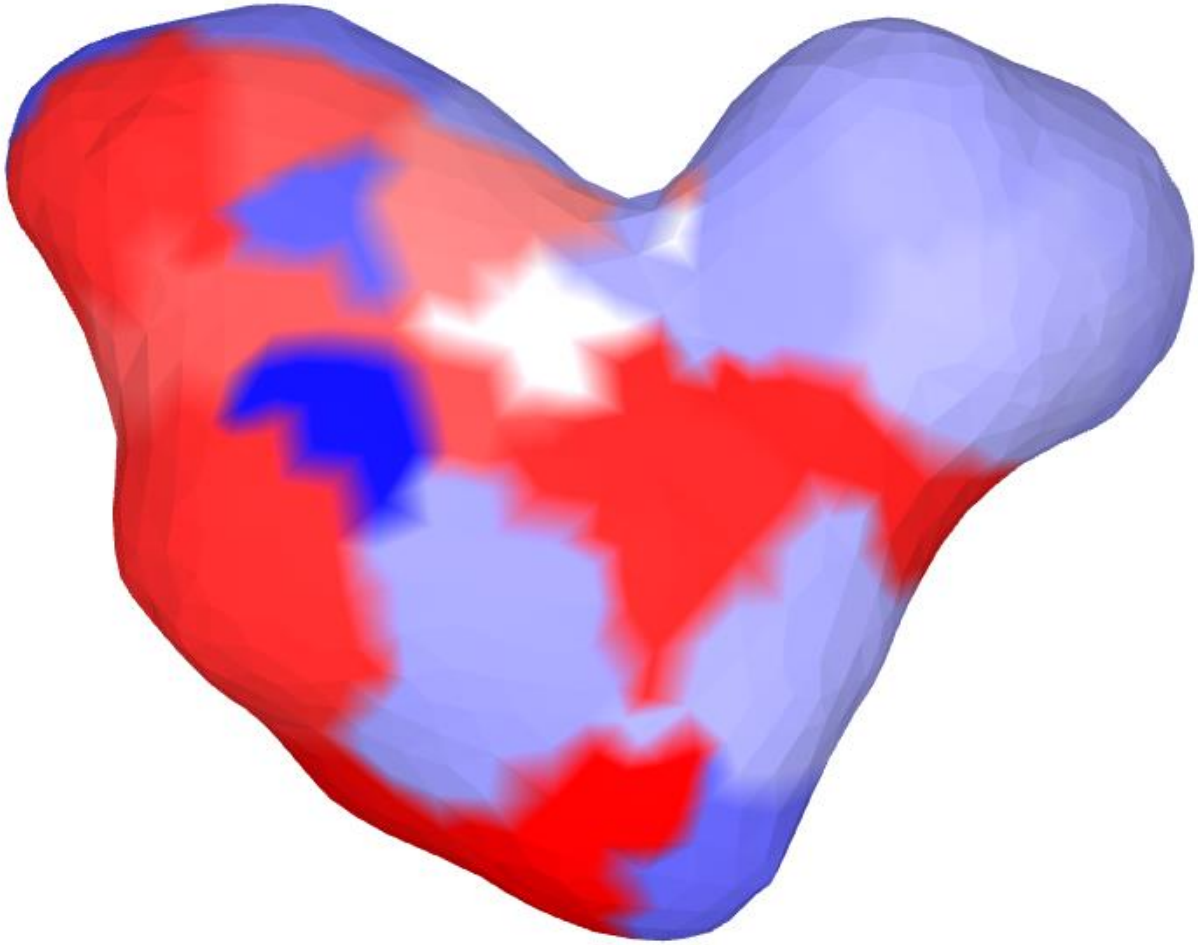
◉ Charges (relative) ○ Charges (absolute)

Min value: -0.66272 Max value: 0.66272

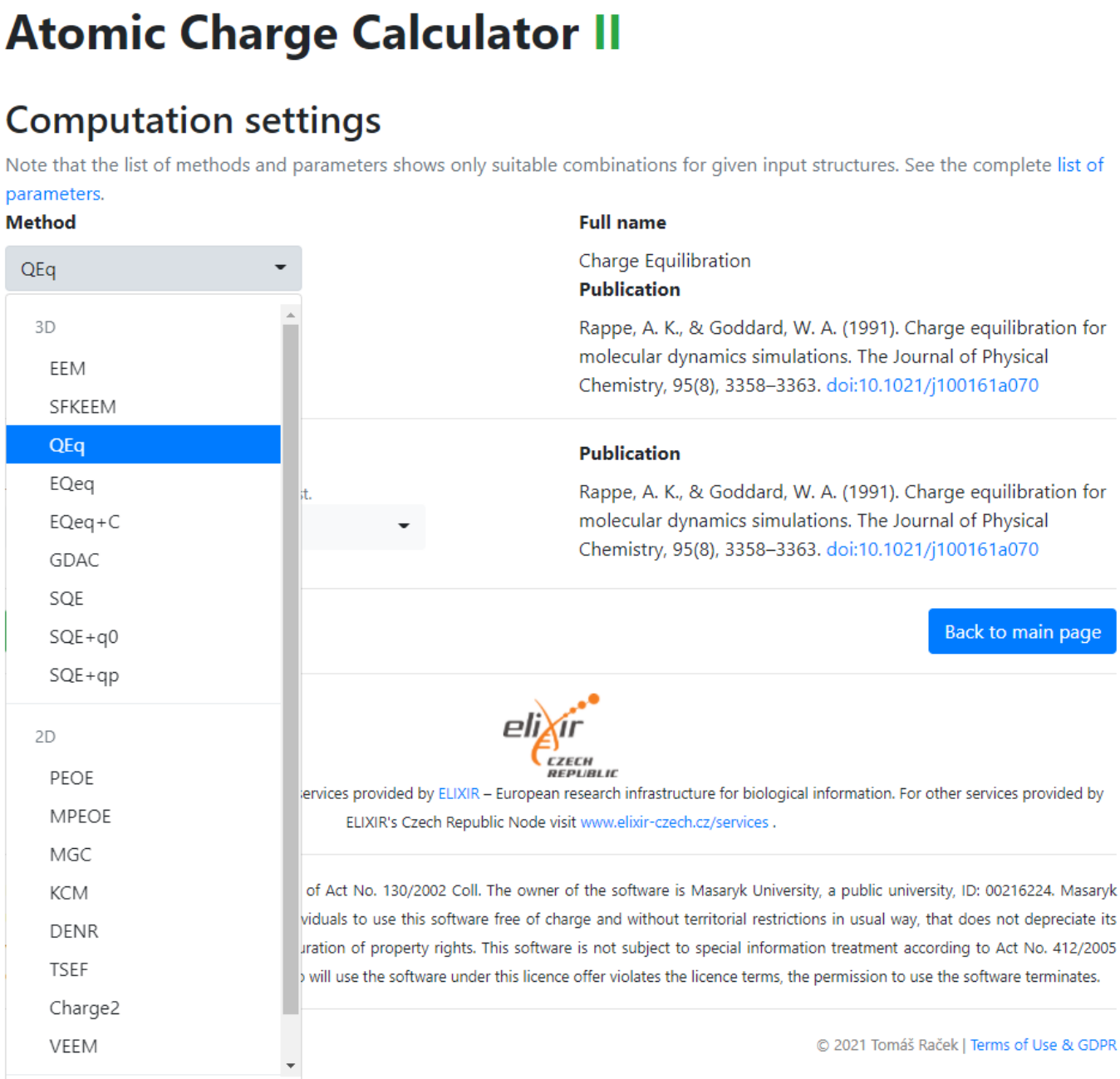
H H 34 at (-5.6, -2.8, -0.8) on UNK X 0 [145996610], **Charge:** 0.2624

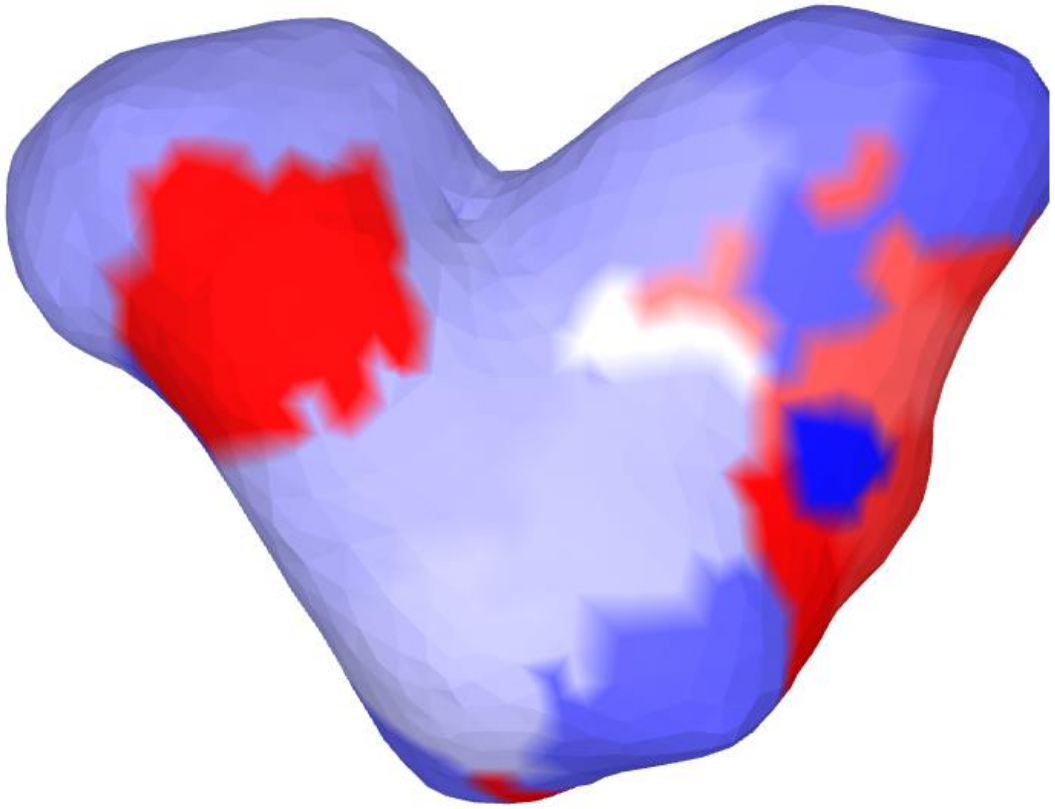


ACC II: How to use ACC II?
Molnupiravir



ACC II: How to use ACC II?





Thank you for your attention