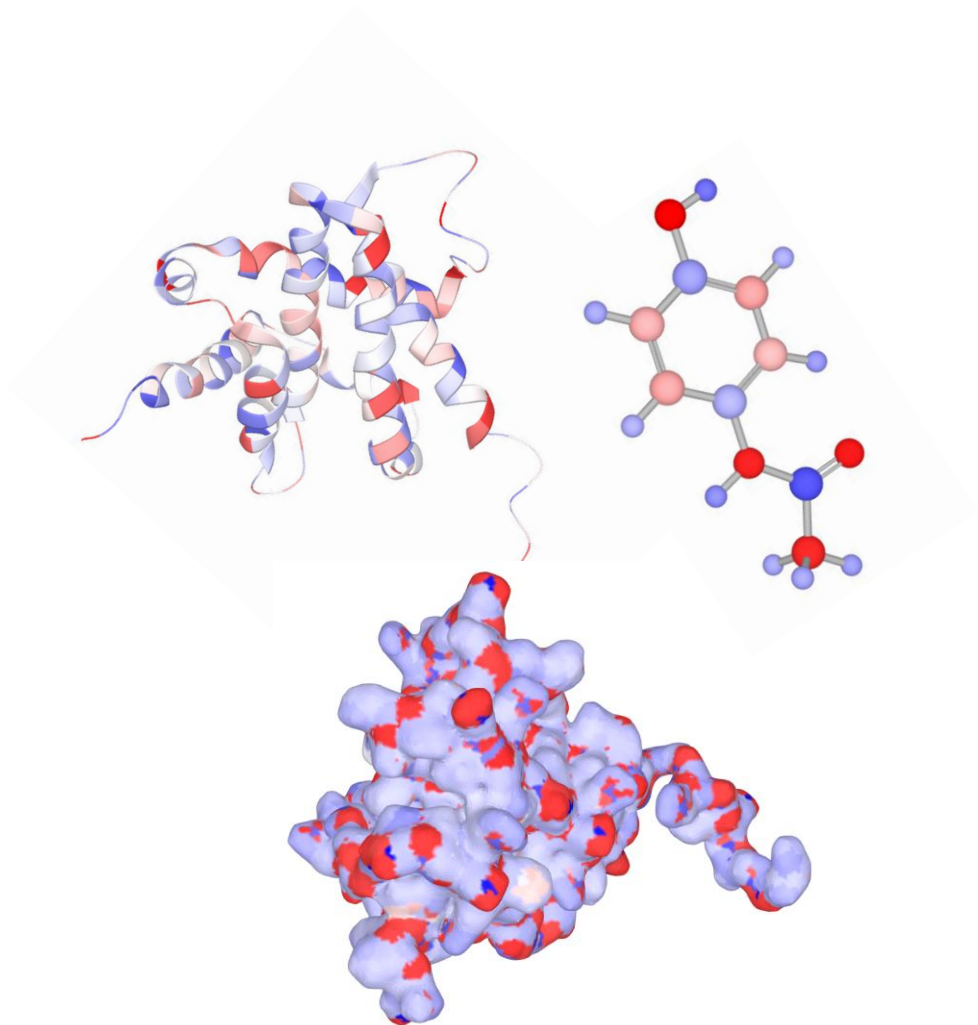


# ACC II: Calculation of partial atomic charges

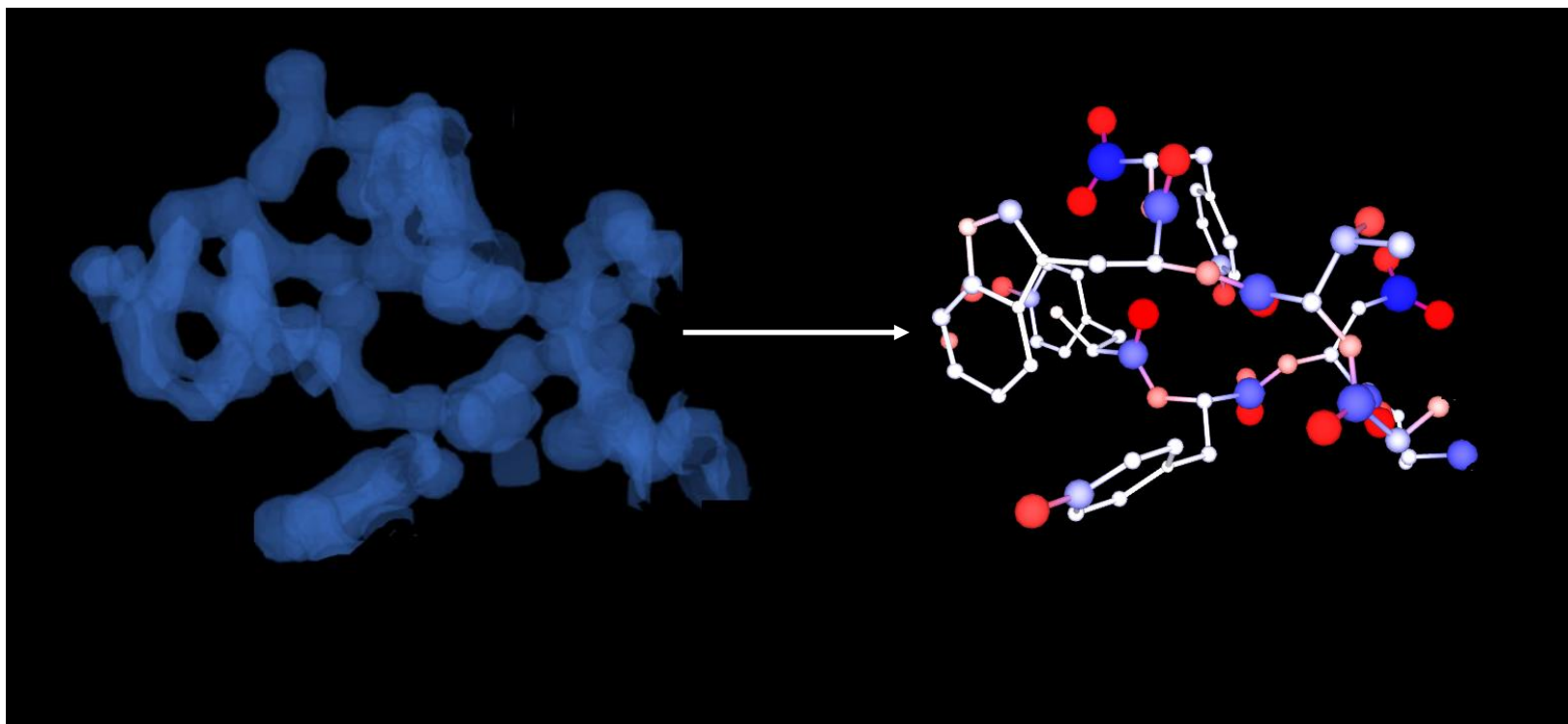
Radka Svobodová

**CEITEC  
MASARYK UNIVERSITY**



## 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**

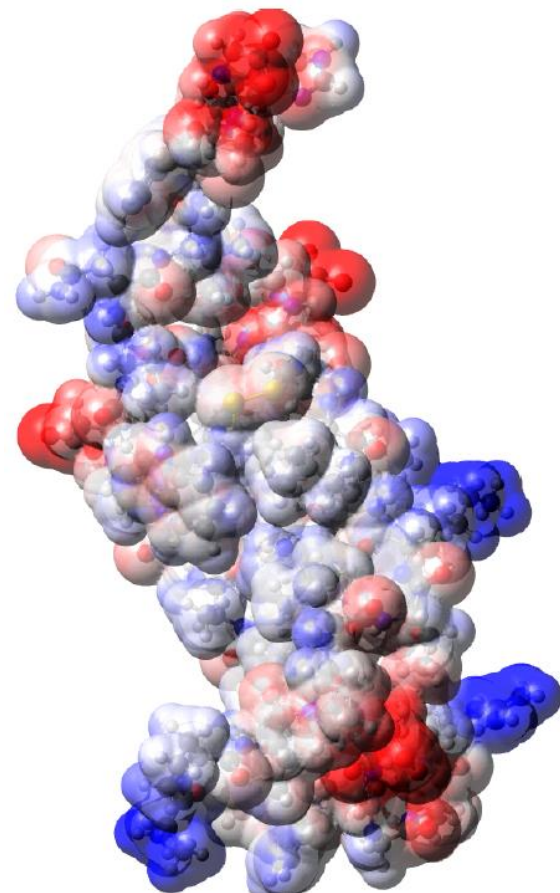
We cannot measure them!  
We can only compute them.

## **Consequences:**

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

## **Validation:**

We can calculate something measurable 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

## 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**

## 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

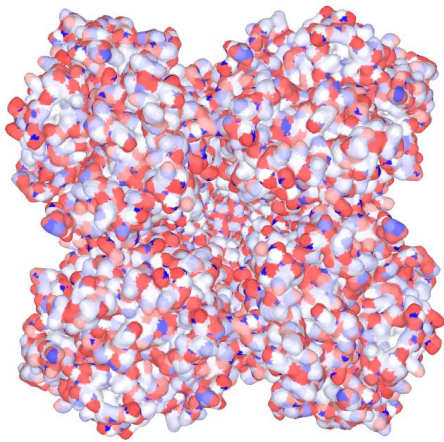
# Empirical charge calculation approaches

## Conformationally independent (2D):

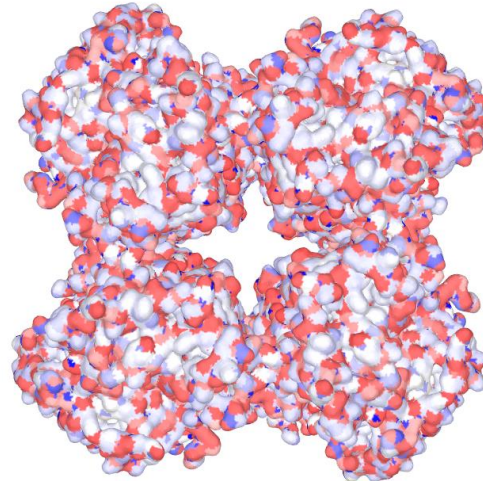
- Based on molecular 2D structure
- Does not reflect conformational changes

## Conformationally dependent (3D):

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

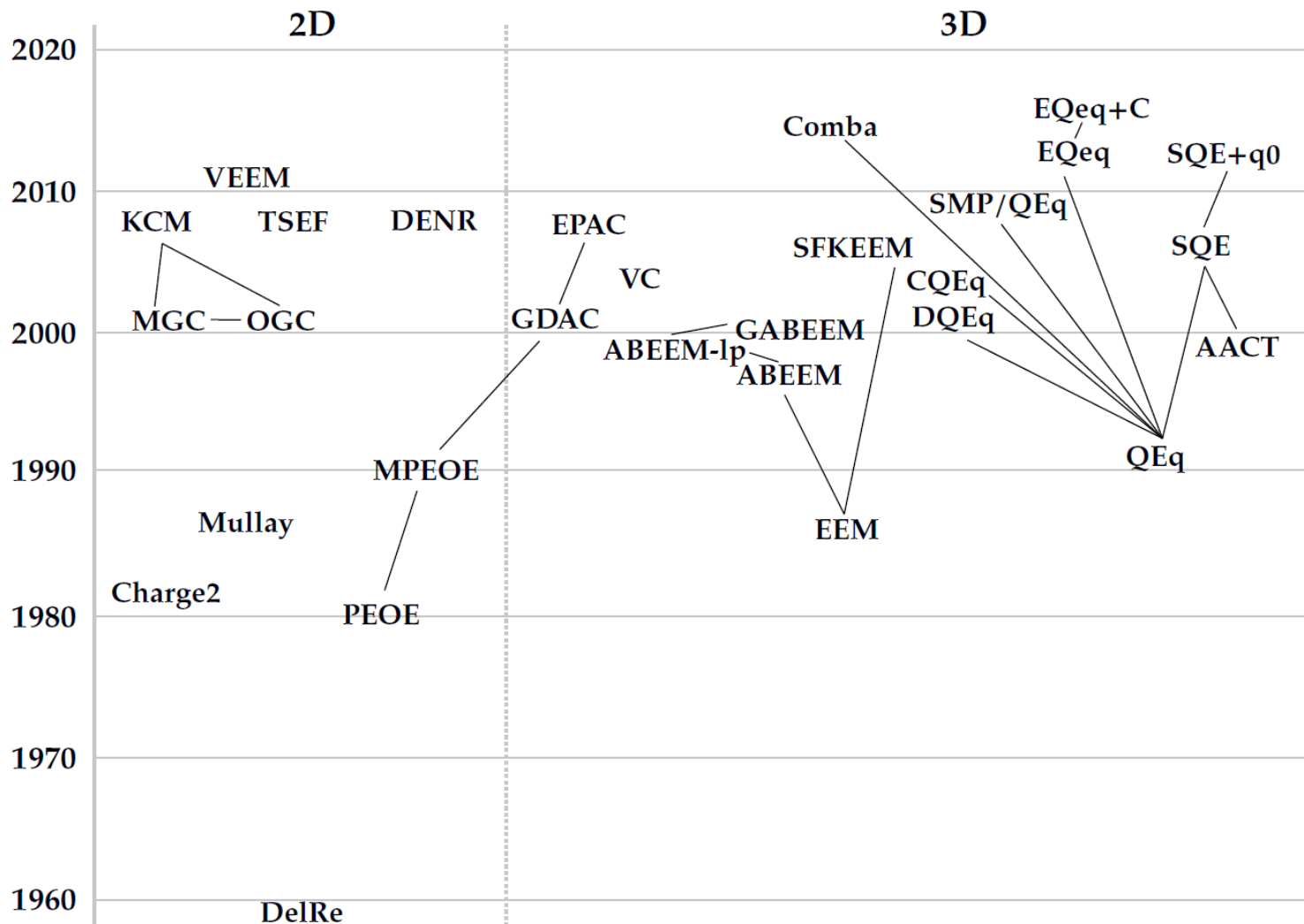


BK channel closed



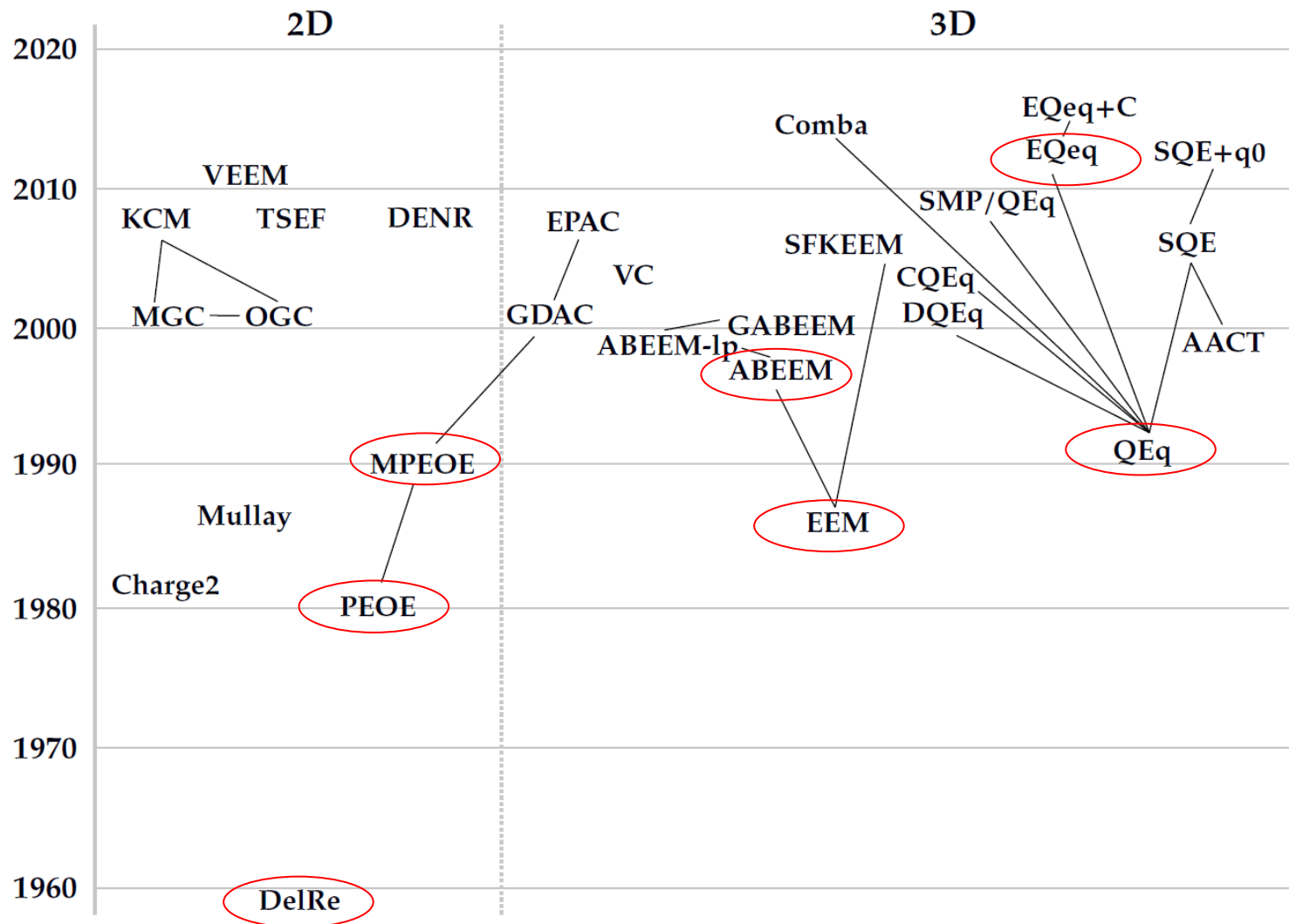
BK channel open

# Empirical charge calculation approaches





# Empirical charge calculation approaches



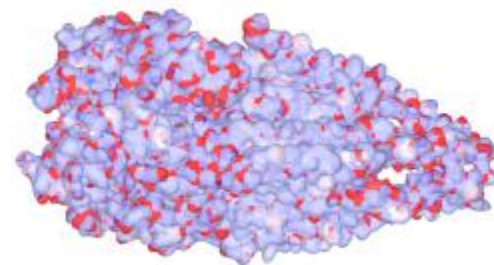
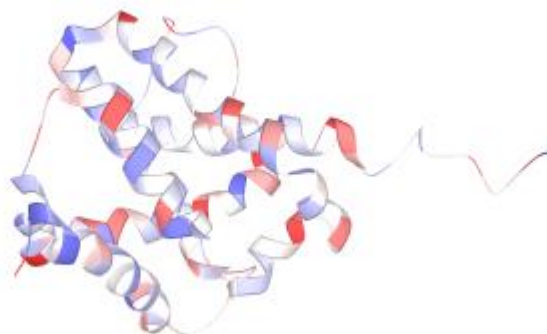
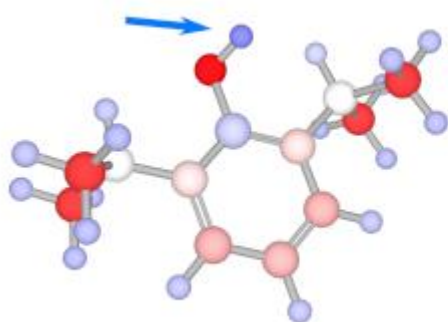
# Electronegativity Equalization Method (EEM):

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

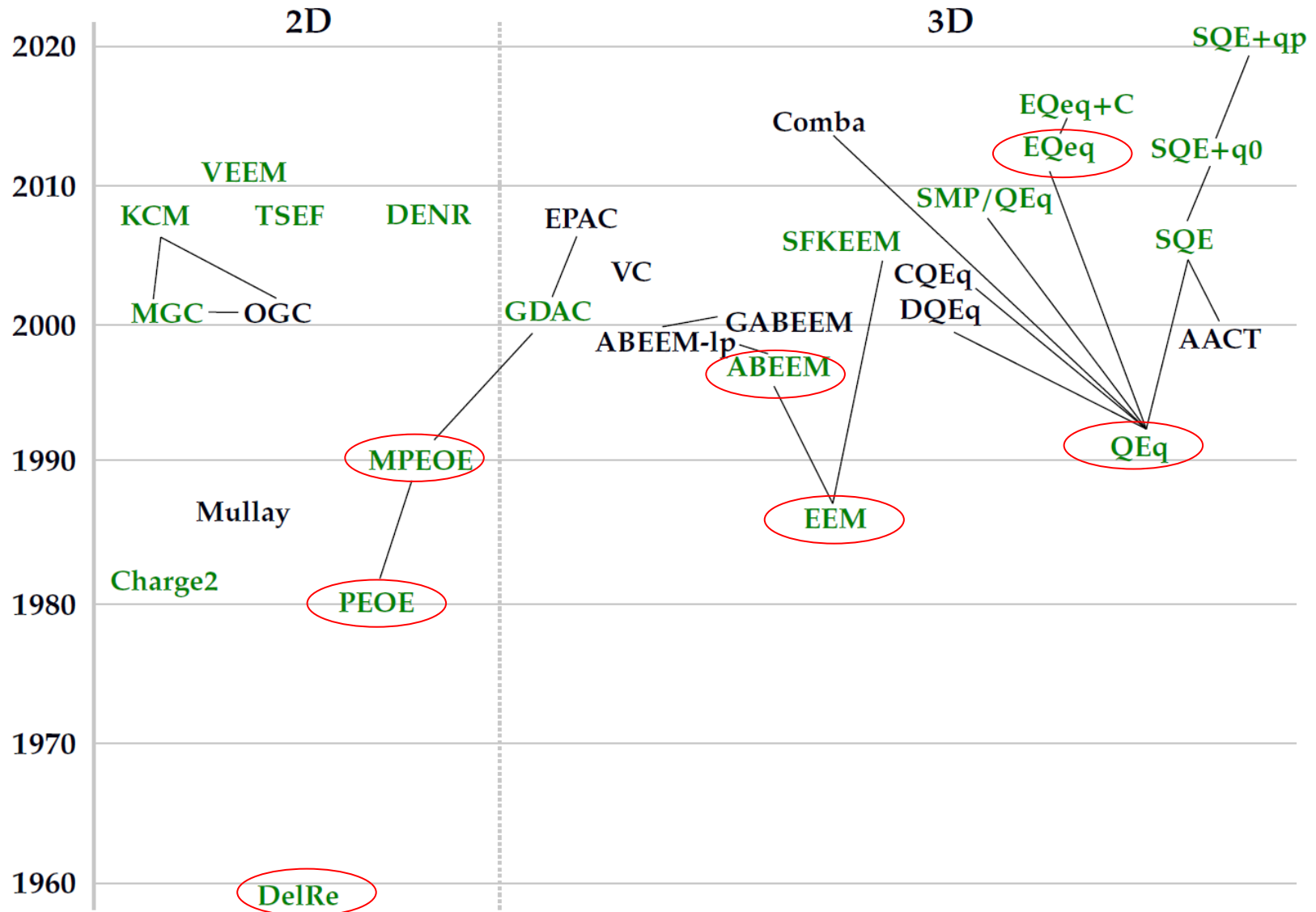
$$Q = \sum_i^N q_i$$

# 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**

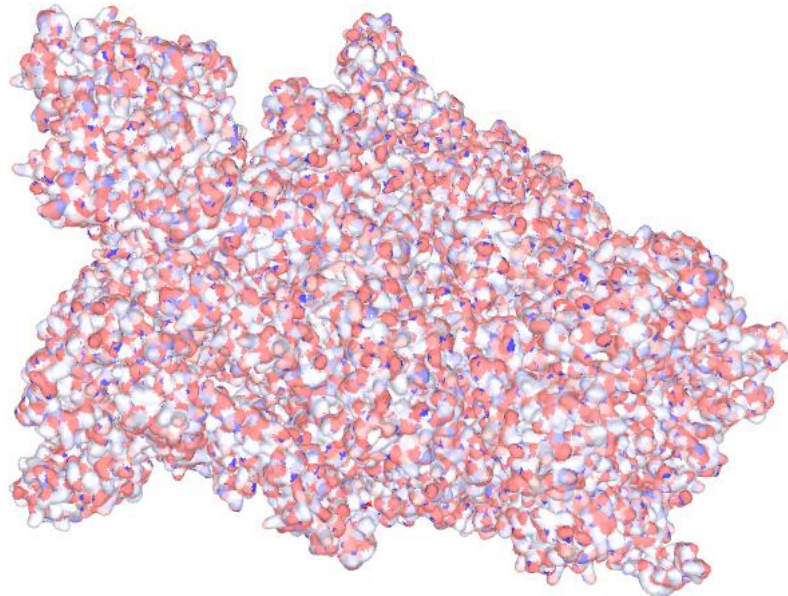


# ACC II: empirical methods included



## 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

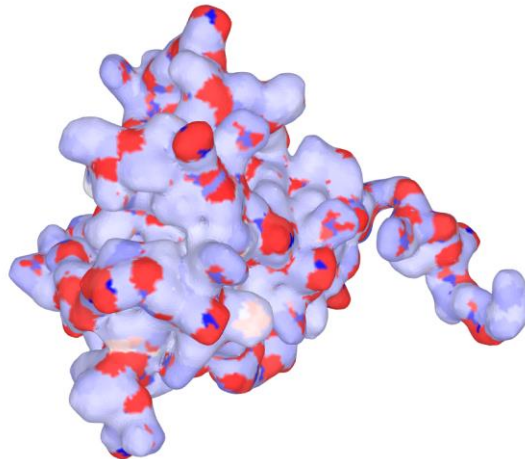
balls and sticks



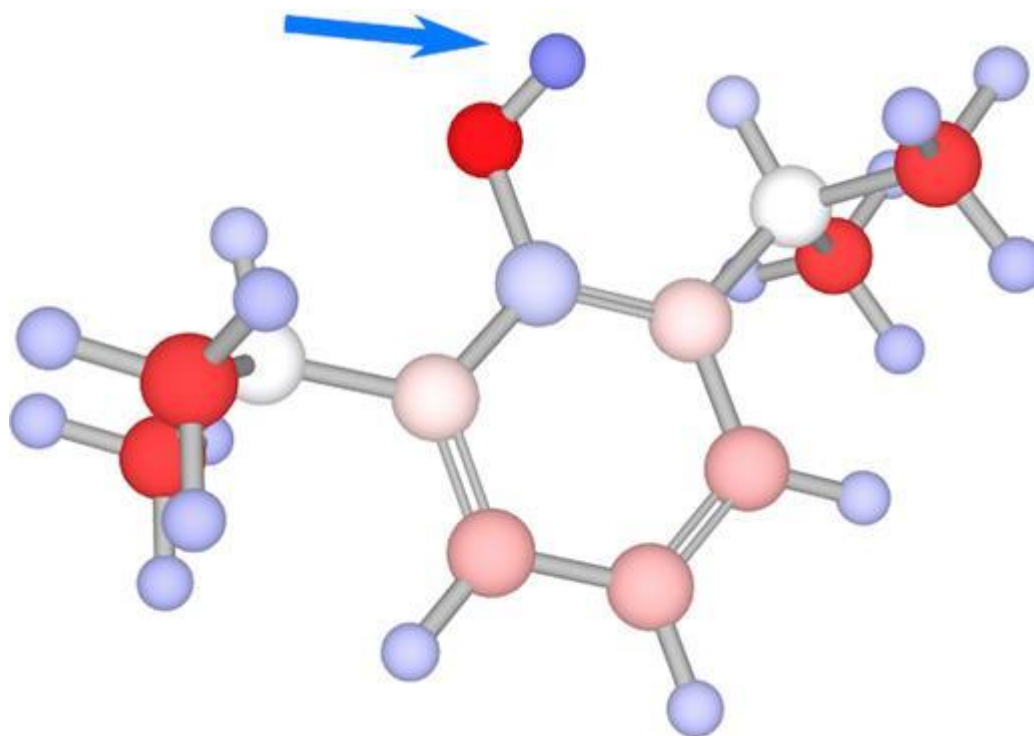
cartoon



surface



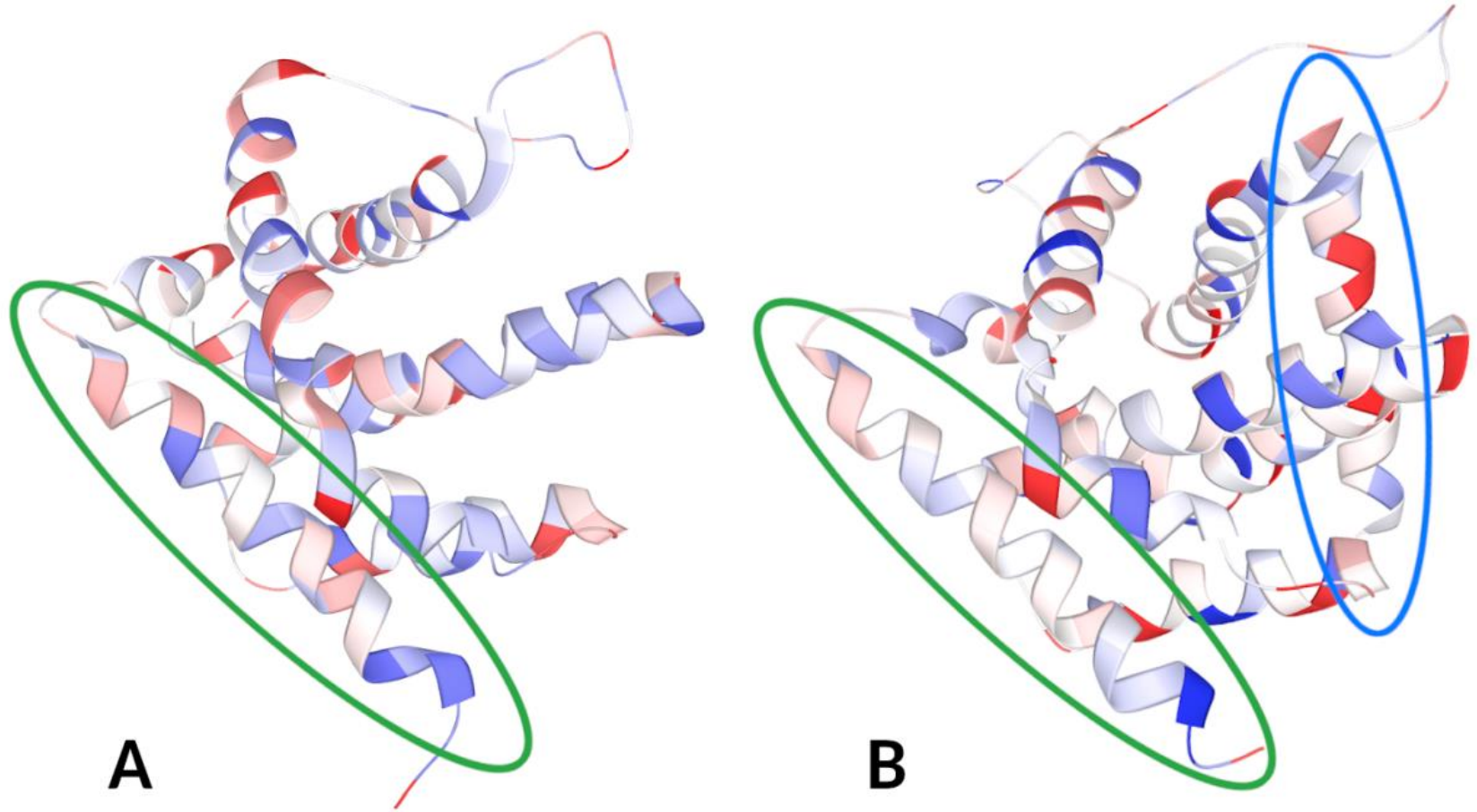
# ACC II example 1: phenols



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.

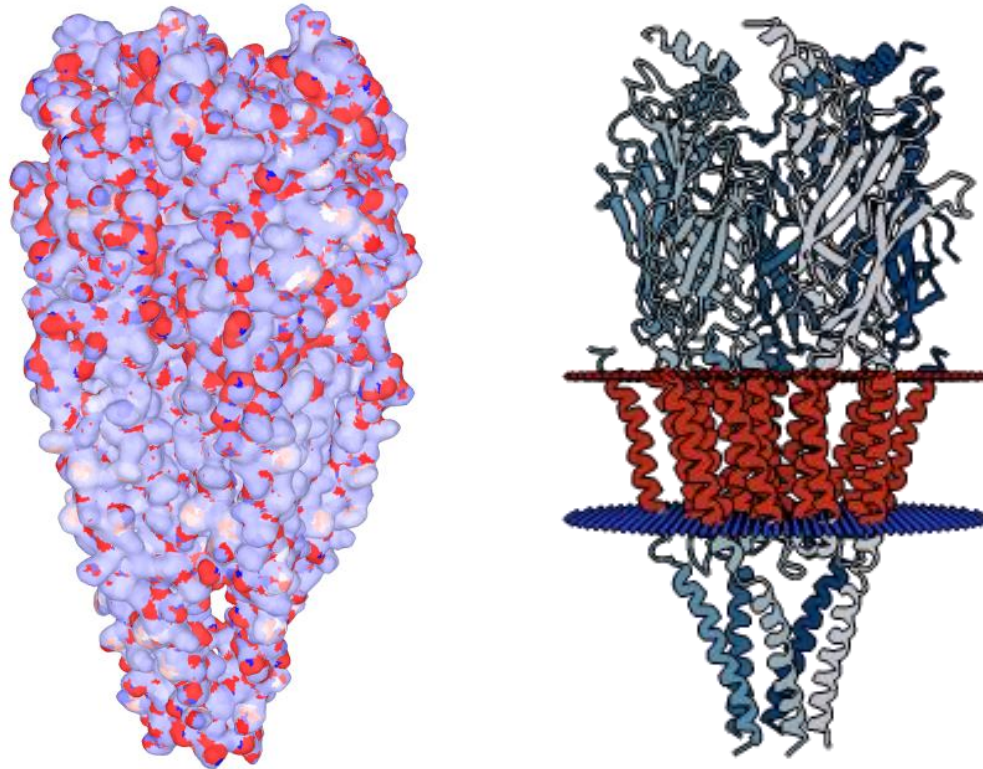
## ACC II example 2: apoptotic protein BAX



(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**

## Atomic Charge Calculator II

**Atomic Charge Calculator II** (ACC II) is an application for fast calculation of partial atomic charges. It features [20 empirical methods](#) along with parameters from literature. [Short introduction](#) covers the basic usage of ACC II. All methods and parameters are also available in a command-line [application](#) that can be used in user workflows.

### Upload structure

#### Input file

Conformer3D\_CID\_145996610.sdf

Single sdf, mol2, pdb or mmCIF file or archive (zip, tar.gz) of those files. Maximum file size: 10 MB

# ACC II: How to use ACC II?

## Molnupiravir

### Structure

145996610

### View

Cartoon  Balls and sticks  Surface

### Coloring

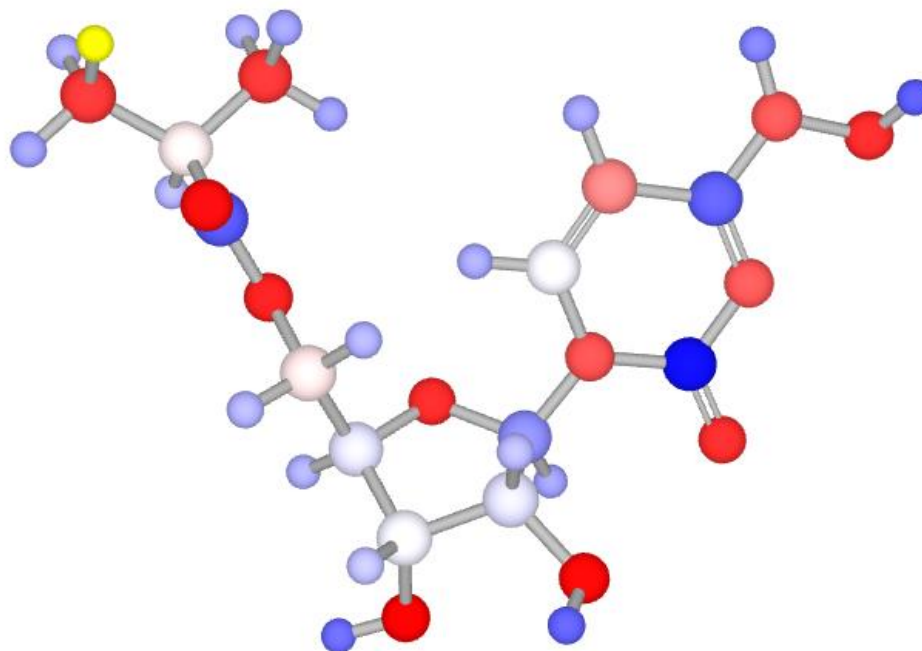
Structure

Charges (relative)  Charges (absolute)

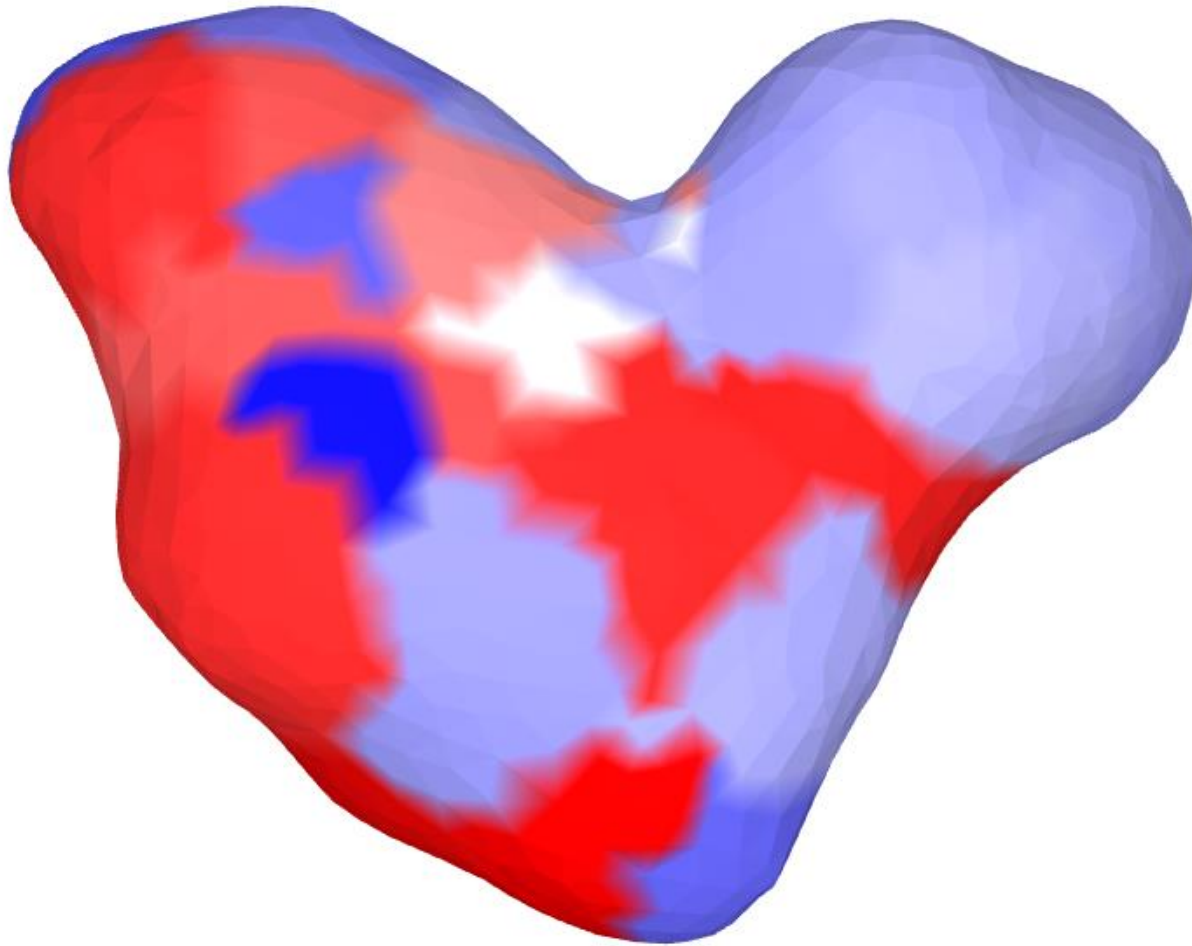
Min value: -0.66272

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?


## Atomic Charge Calculator II

### Computation settings

Note that the list of methods and parameters shows only suitable combinations for given input structures. See the complete [list of parameters](#).

Method	Full name
QEq	Charge Equilibration
	<b>Publication</b> Rappe, A. K., & Goddard, W. A. (1991). Charge equilibration for molecular dynamics simulations. The Journal of Physical Chemistry, 95(8), 3358–3363. doi:10.1021/j100161a070
3D	
EEM	
SFKEEM	
QEq	<b>Publication</b> Rappe, A. K., & Goddard, W. A. (1991). Charge equilibration for molecular dynamics simulations. The Journal of Physical Chemistry, 95(8), 3358–3363. doi:10.1021/j100161a070
EQeq	
EQeq+C	
GDAC	
SQE	
SQE+q0	
SQE+qp	
2D	
PEOE	
MPEOE	
MGC	
KCM	
DENR	
TSEF	
Charge2	
VEEM	

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# Atomic Charge Calculator II

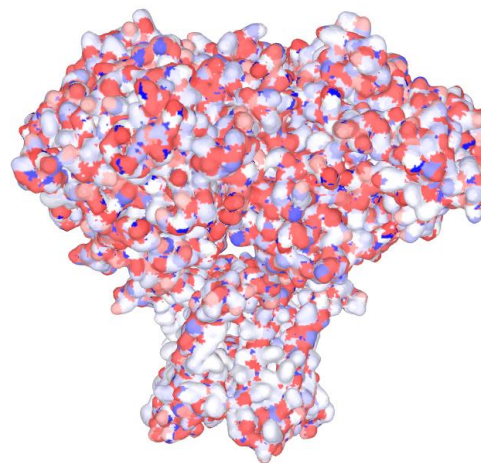
## Impact

### Publications:

- Ionescu, C.M., Sehnal, D., Falginella, F.L., Pant, P., Pravda, L., Bouchal, T., Svobodová, R., Geidl, S. and Koča, J., 2015. *AtomicChargeCalculator: interactive web-based calculation of atomic charges in large biomolecular complexes and drug-like molecules*. **Journal of cheminformatics**, 7(1), pp.1-13.
- Raček, T., Schindler, O., Toušek, D., Horský, V., Berka, K., Koča, J. and Svobodová, R., 2020. *Atomic Charge Calculator II: web-based tool for the calculation of partial atomic charges*. **Nucleic acids research**, 48(W1), pp.W591-W596.

### Users:

300 unique users / year  
5000 computations



# Atomic Charge Calculator II

## Future plans

- **Develop methodology, covering whole PDB**
  - Automatic adding of hydrogens
  - Prediction of total charge based on pH
- **Integrate into PDBe-KB and PDBe**



# Acknowledgement

**Jaroslav Koča**

**Tomáš Raček, Ondřej Schindler, Vladimír Horský**

David Sehnal, Stanislav Geidl, Crina-Maria Ionescu

Aleksandra Maršavelski

Karel Berka

ELIXIR and ELIXIR CZ



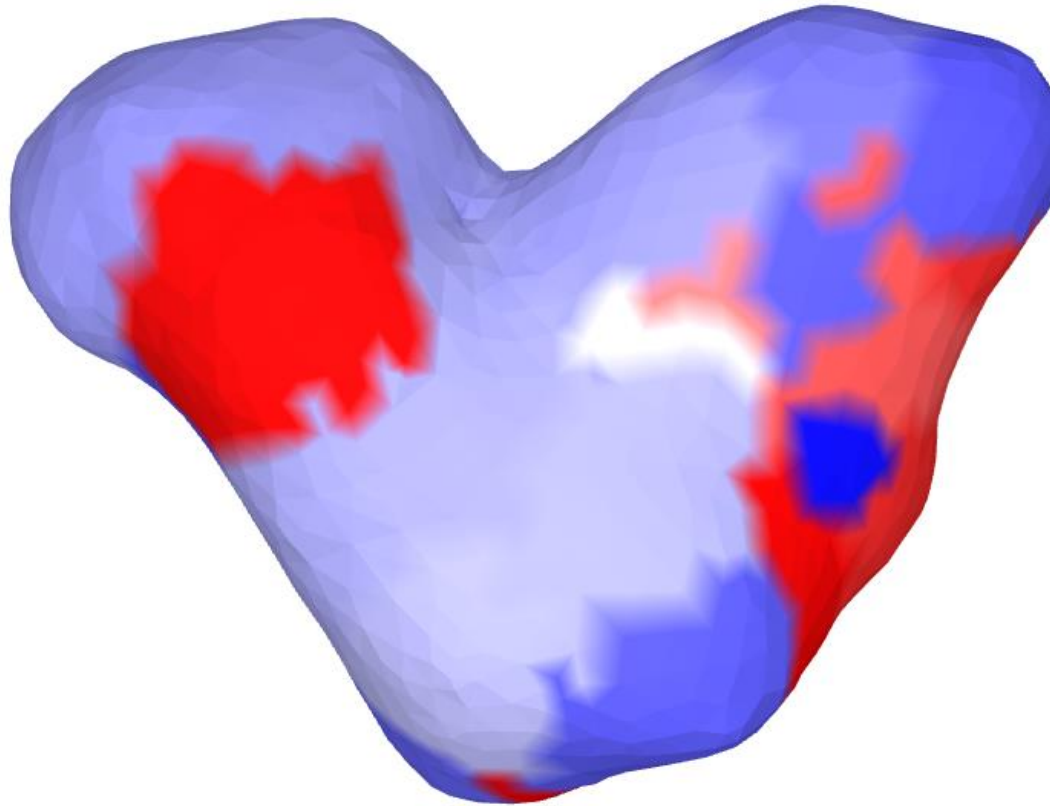
MetaCenter



EMBL-EBI, PDBe: Dr. Sameer Velankar







Thank you for your attention