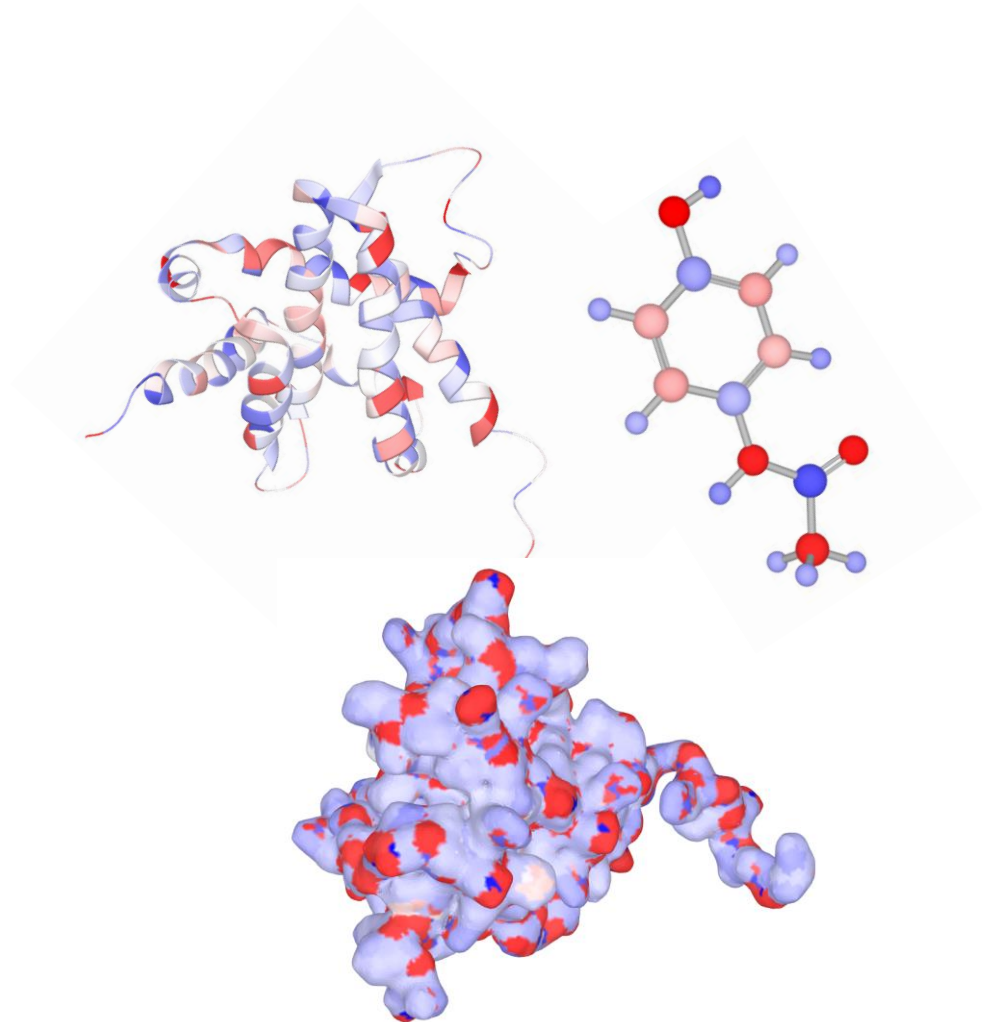# ACC II: Calculation of partial atomic charges
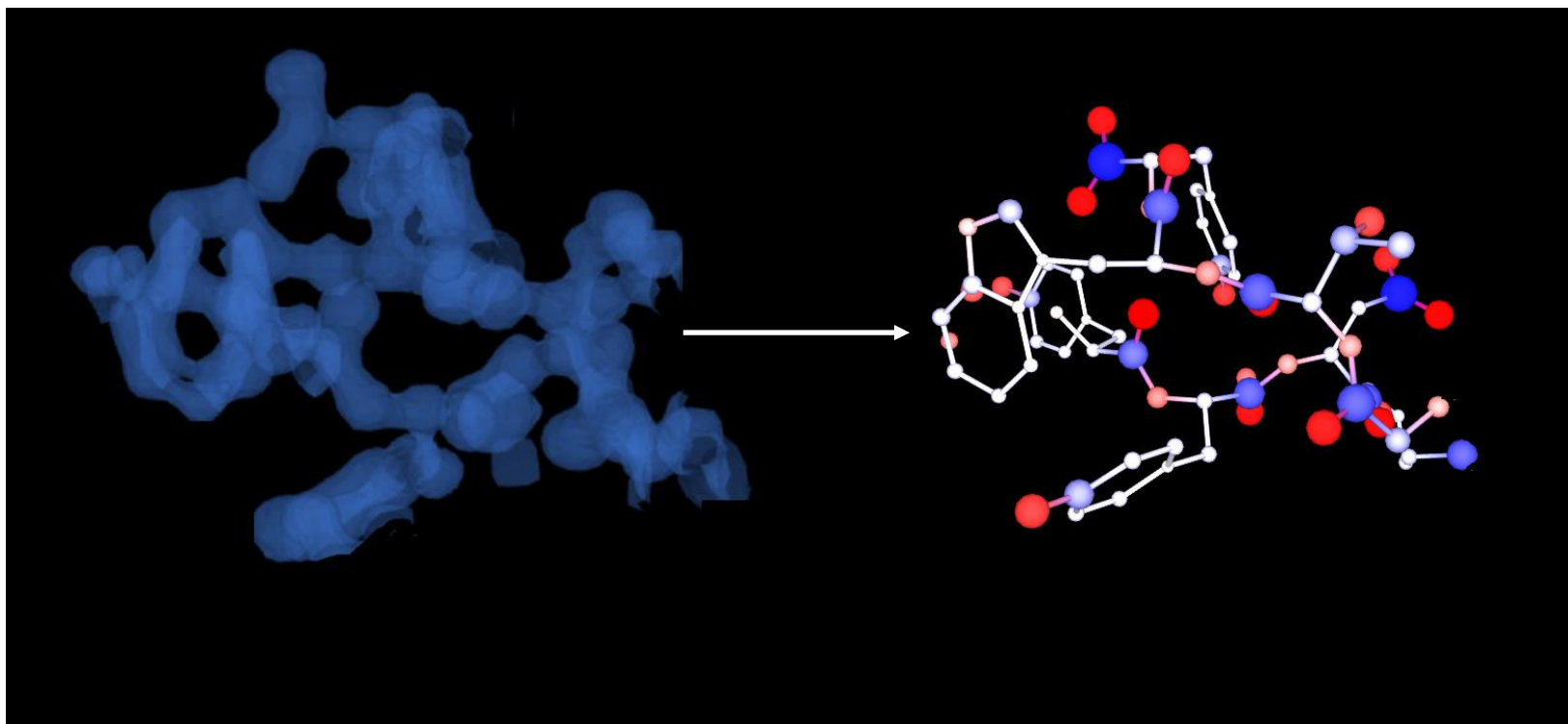
Radka Svobodová

**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?
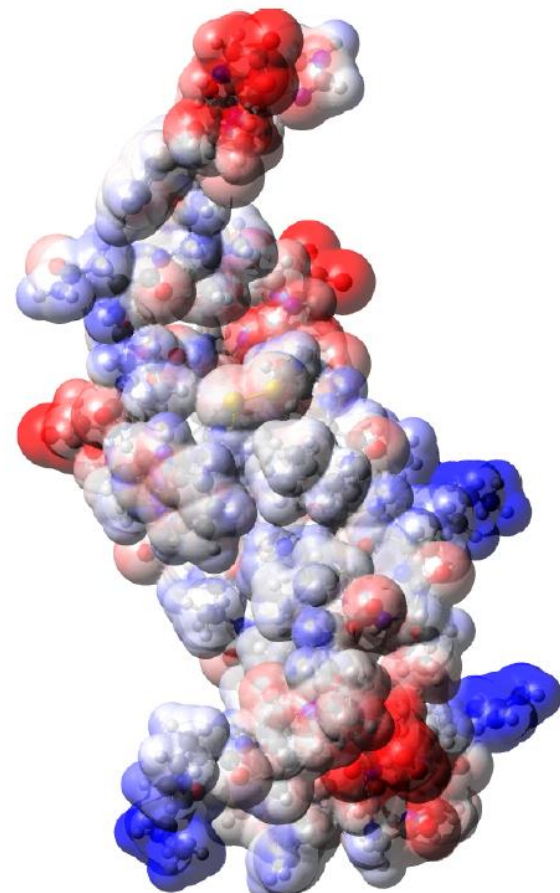
**Partial atomic charges
= a theoretical concept**

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 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

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
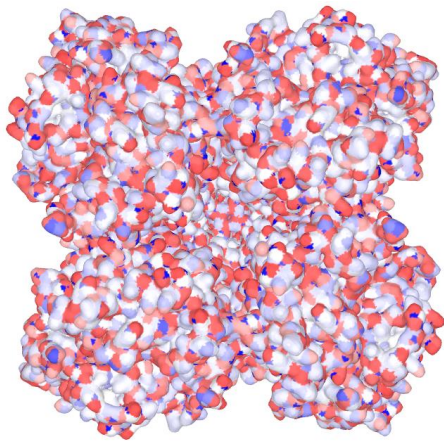- Necessity of parameterization – not easy

Empirical charge calculation approaches

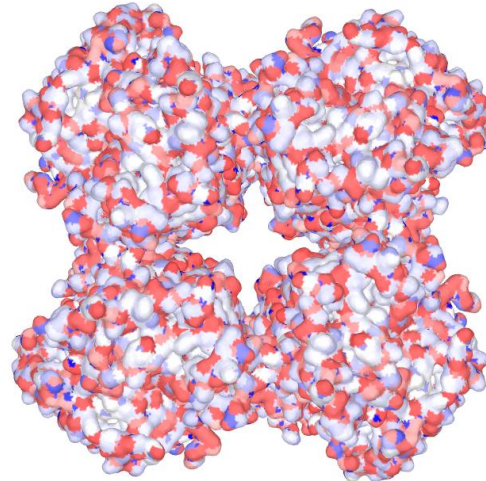Conformationally independent (2D):

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

Conformationally dependent (3D):

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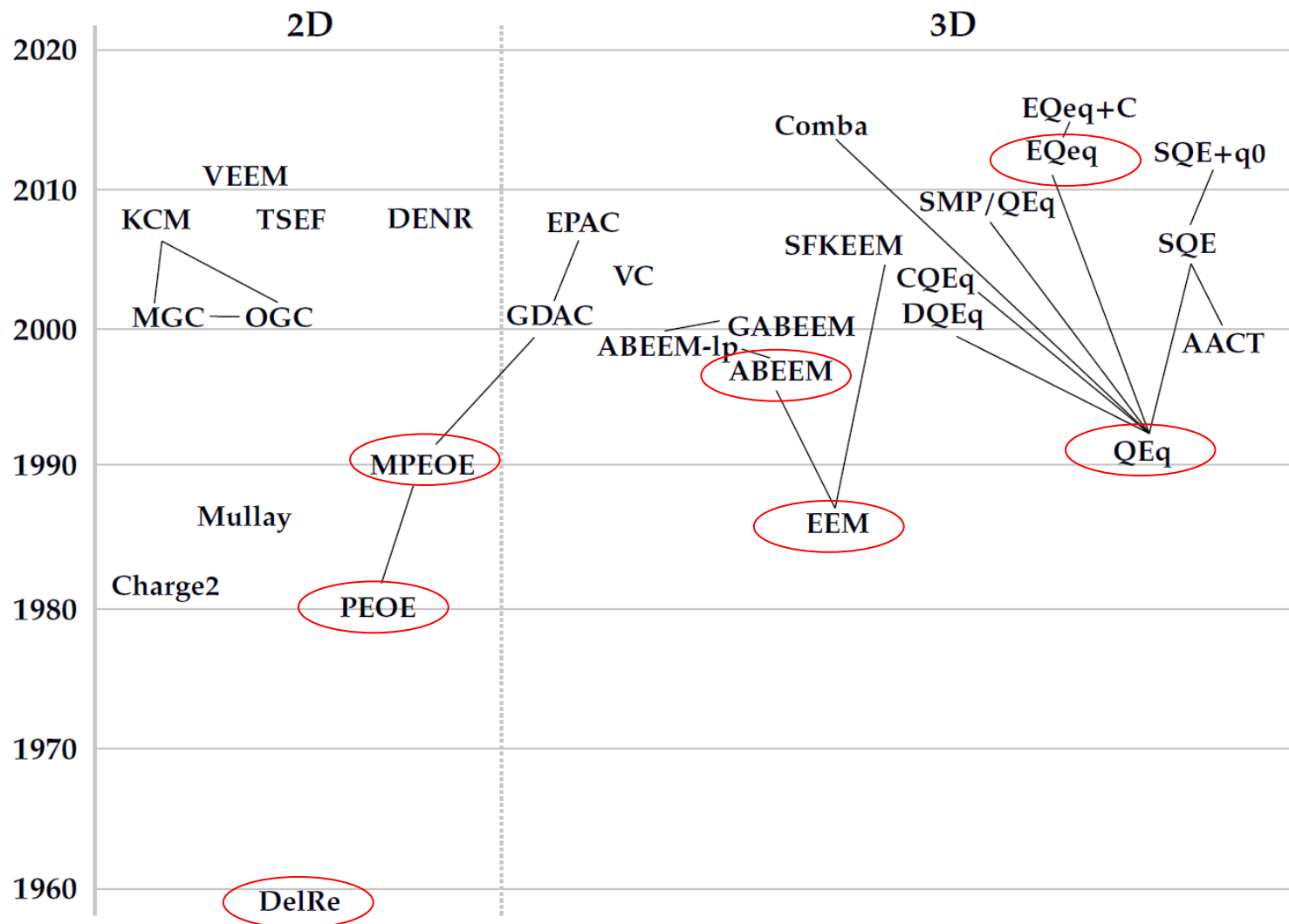- Different conformation ~ different charges

BK channel closed

BK channel open

Empirical charge calculation approaches

# Empirical charge calculation approaches

Electronegativity Equalization Method (EEM):

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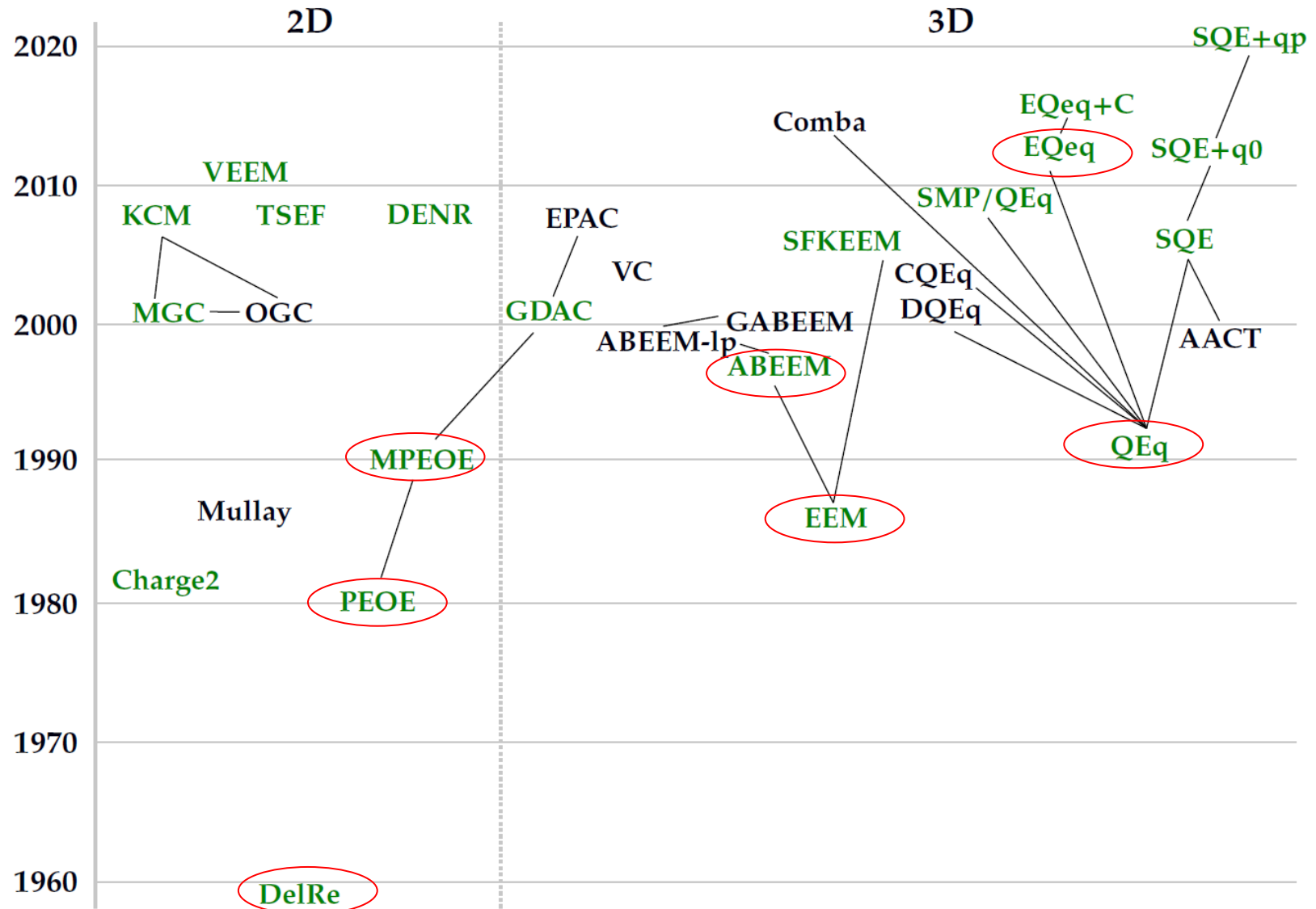
$$Q = \sum_i^N q_i$$

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
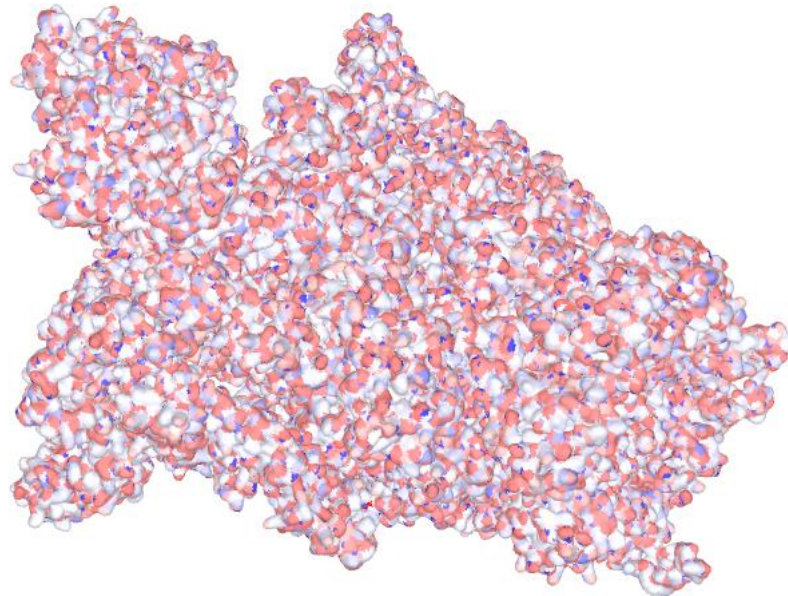- **Command line application available**
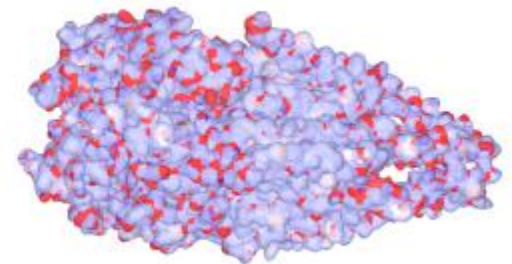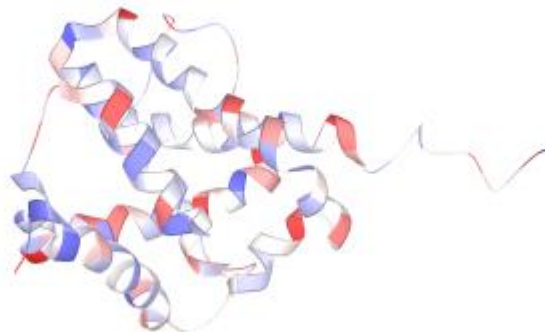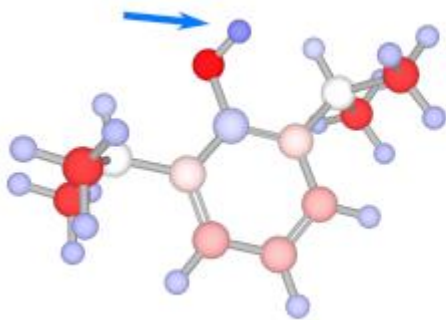
ACC II: empirical methods included

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
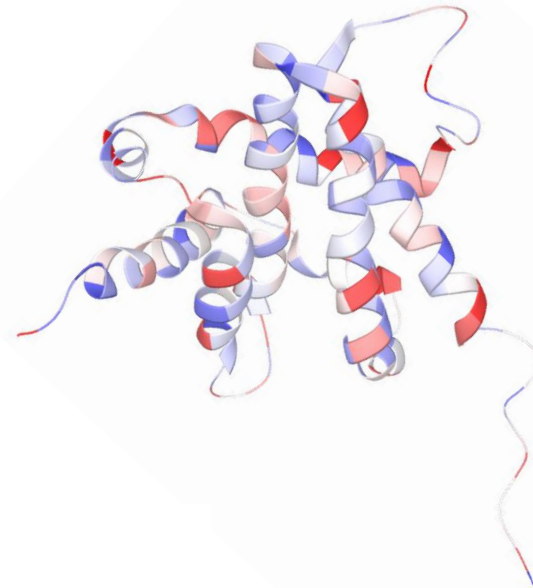- Visualizing the computed charges
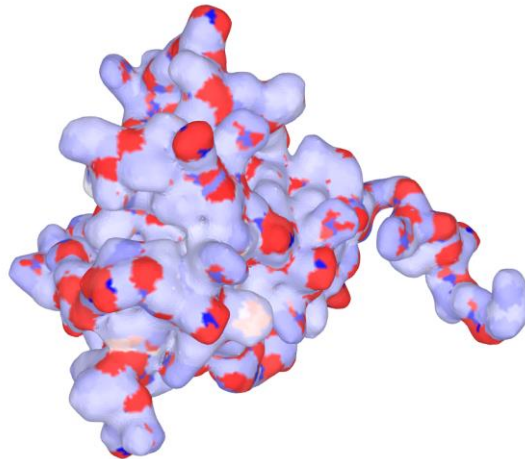
ACC II: visualization
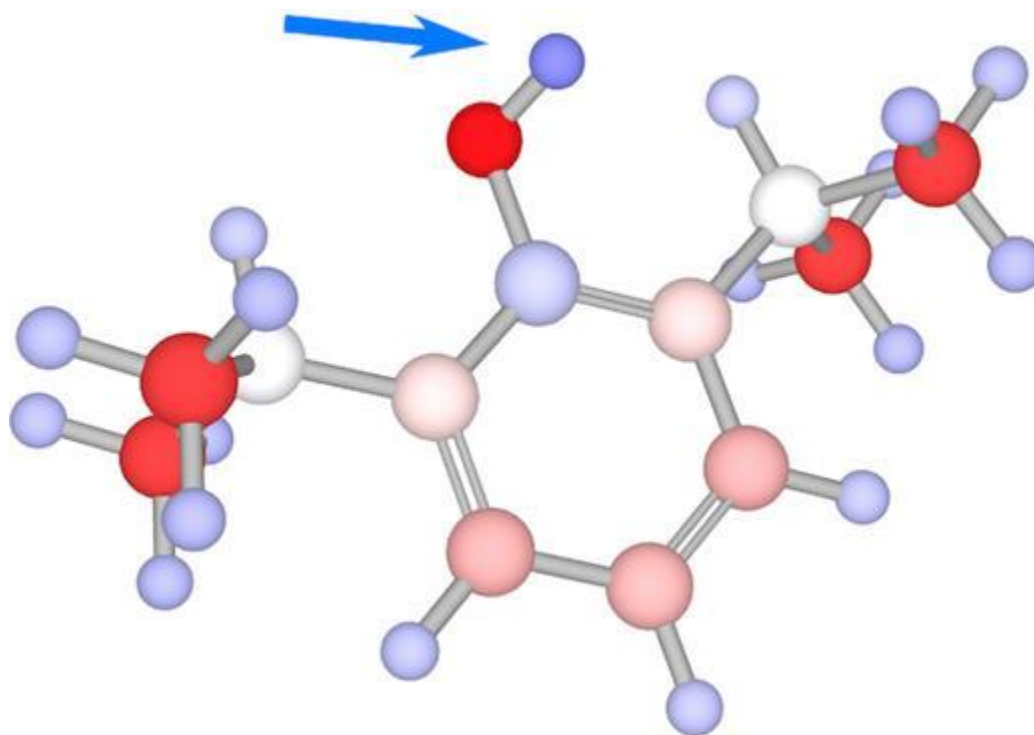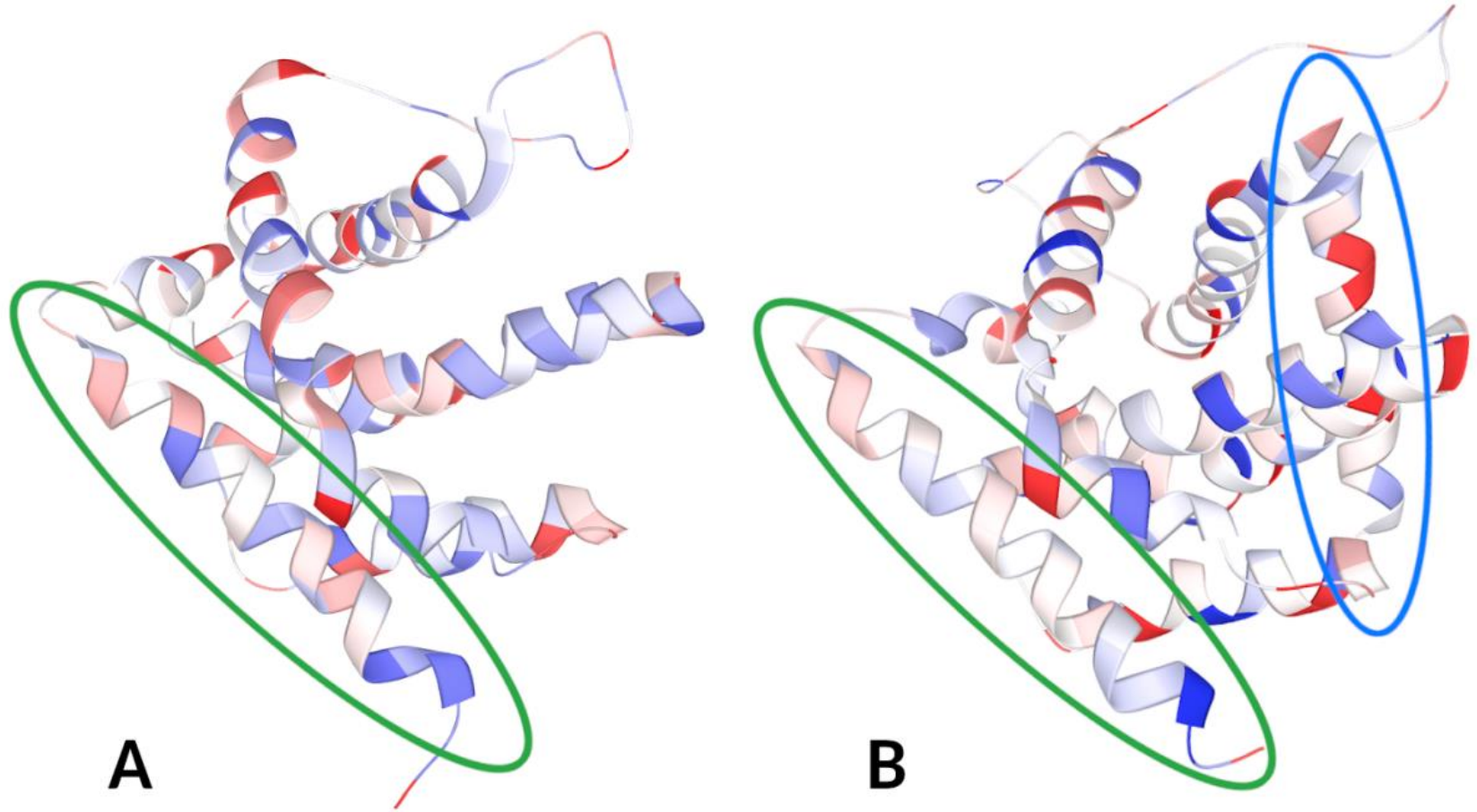
balls and sticks

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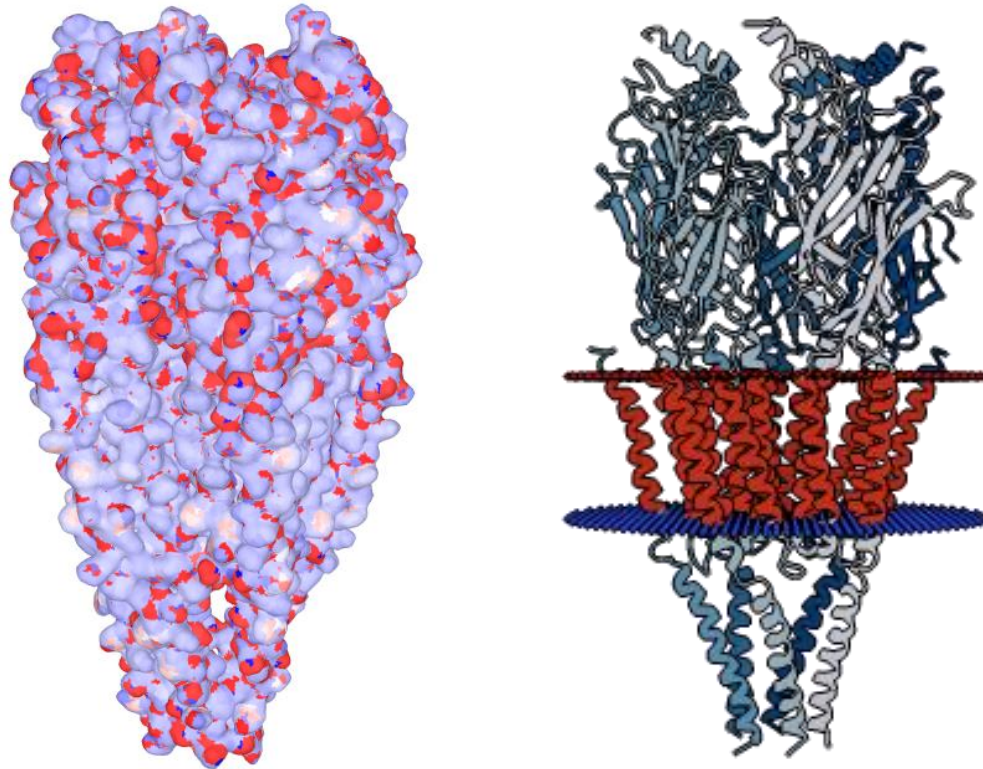
Structure of nicotinic acetylcholine receptor (PDB ID 2bg9). Nonpolar transmembrane part and polar surface of extracellular and cytoplasmic parts

ACC II: How to use ACC II? Molnupiravir

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

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

Choose 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

Compute charges   Setup computation

ACC II: How to use ACC II? Molnupiravir

Structure

145996610

View

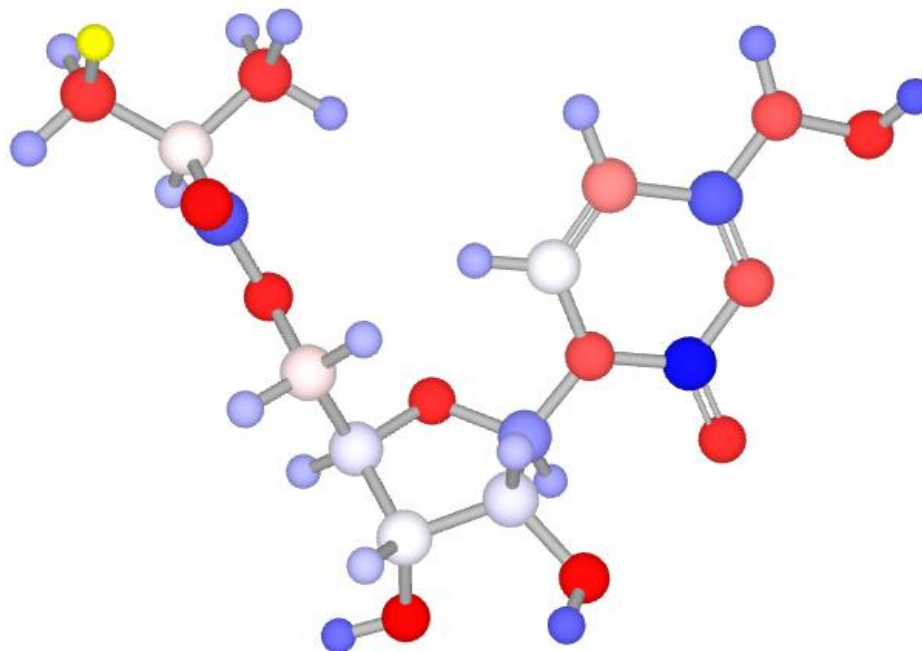○ Cartoon ● Balls and sticks ○ Surface

Coloring

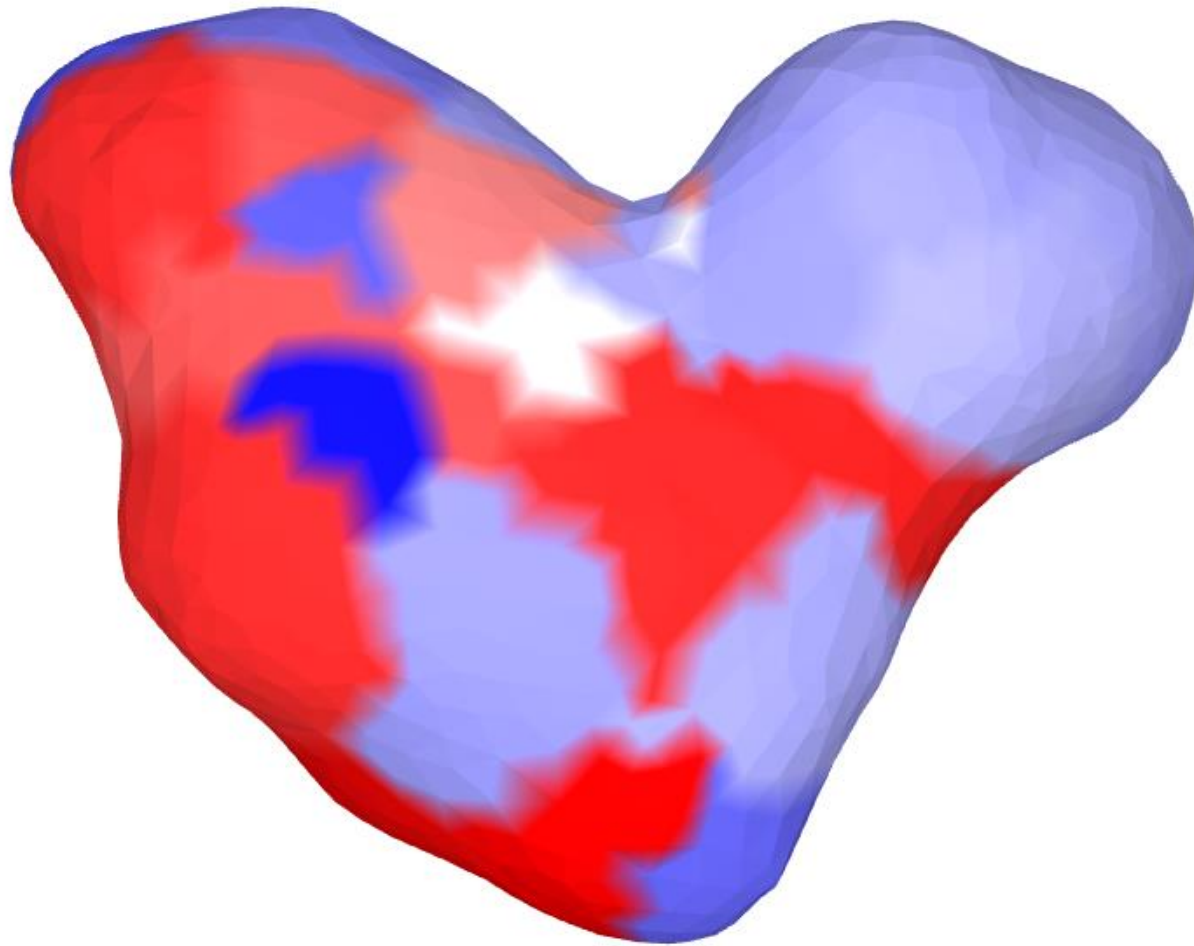○ Structure

● 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?

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

QEq ▾

3D
EEM
SFKEEM
QEq
EQeq
EQeq+C
GDAC
SQE
SQE+q0
SQE+qp
2D
PEOE
MPEOE
MGC
KCM
DENR
TSEF
Charge2
VEEM

Full name

Charge Equilibration

Publication

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

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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

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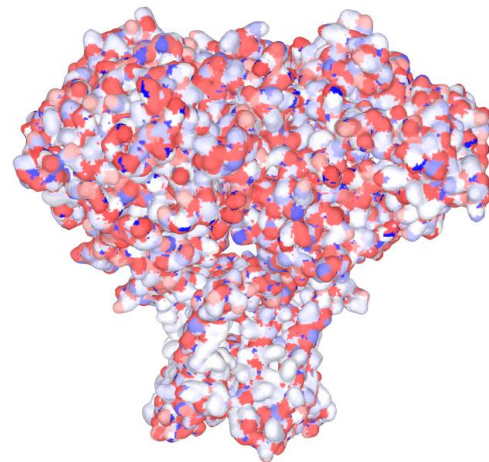
Atomic Charge Calculator II Impact

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
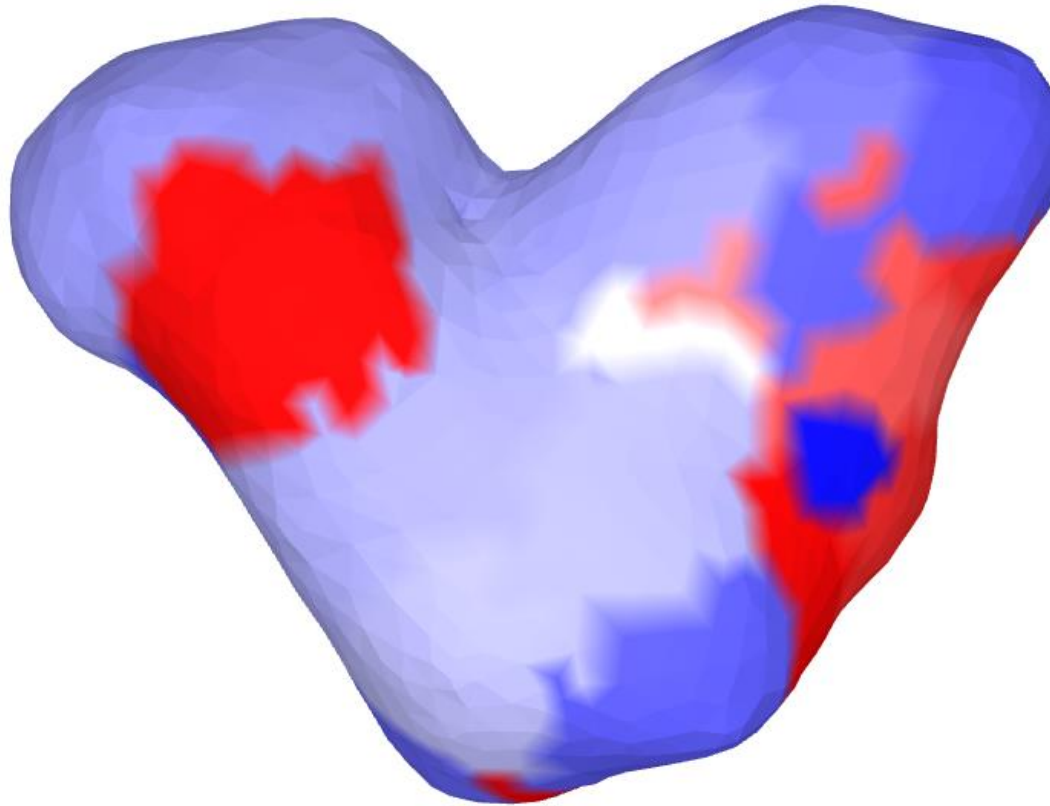Aleksandra Maršavelski
Karel Berka

Thank you for your attention