MUNI FI

Modern visualization of partial atomic charges in Mol*

Bachelor's thesis defense

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Partial atomic charges

- used to describe the distribution of electrons in a molecule
- applications:
  - molecular docking
  - pharmacophore modeling
  - molecular dynamics simulations
- calculation methods:
  - quantum mechanics - extremely slow
  - empirical methods - much faster with slight cost to accuracy

SB NCBR software tools

- developed at the Structural bioinformatics research group (SB NCBR) in Brno
- programs for calculating partial atomic charges:
  - Atomic Charge Calculator II (ACC II)
  - αCharges (AlphaCharges)

Motivation

- ACC II uses the LiteMol Viewer
  - no longer maintained $\rightarrow$ needs to be replaced
- the Mol* Viewer is the modern replacement for LiteMol
  - no support for partial atomic charges

Thesis objectives

1. study the minimum necessary theory on partial atomic charges
2. extend the Mol* Viewer to support charge visualization
3. integrate updated Mol* Viewer into:
   - ACC II
   - αCharges

Mol* extension

- created custom mmCIF categories for storing partial atomic charges
- extended the Mol* Viewer to support visualization of partial atomic charges
- integrated the extension into the Mol* repository

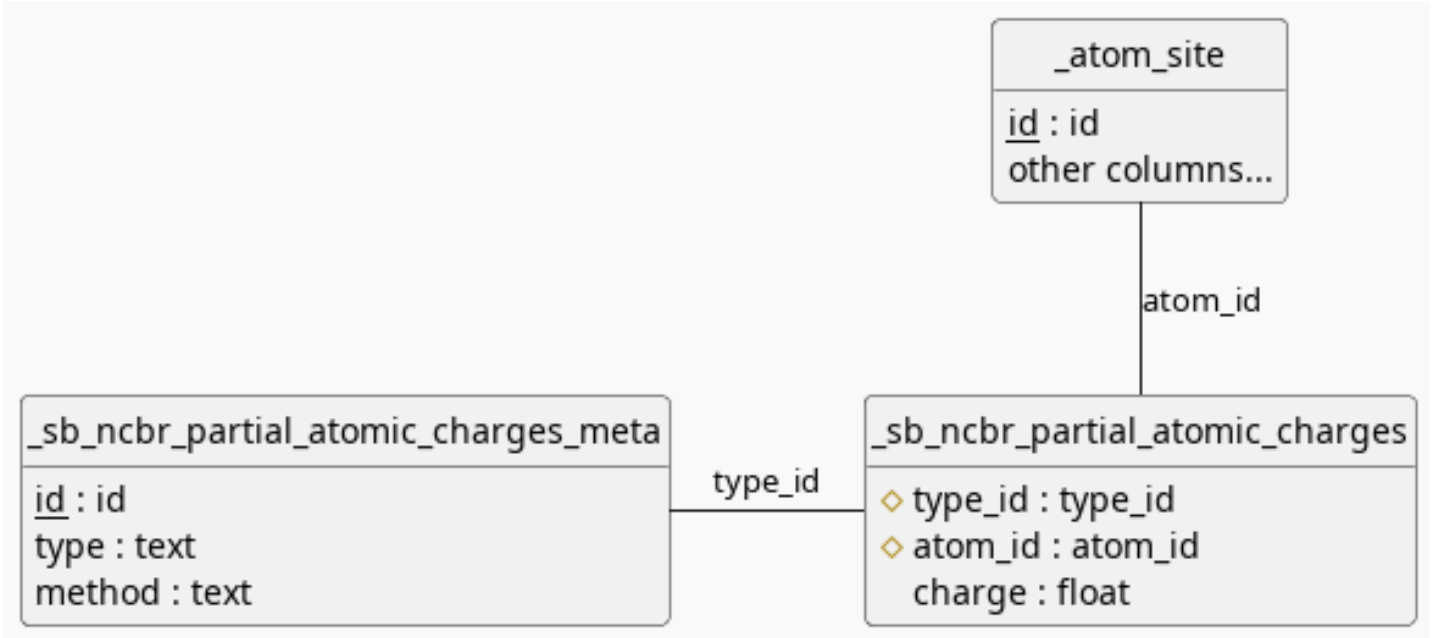
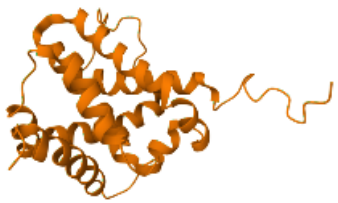


Figure: Diagram of the custom mmCIF categories

Mol* extension

mmCIF file

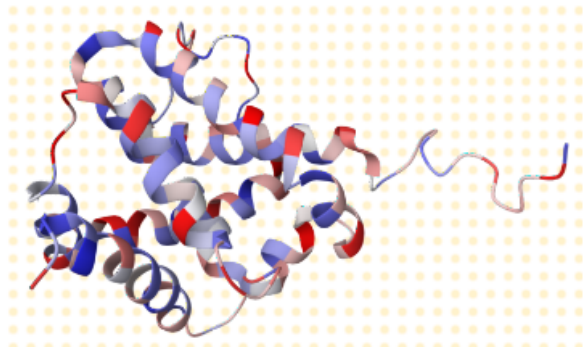
Structure

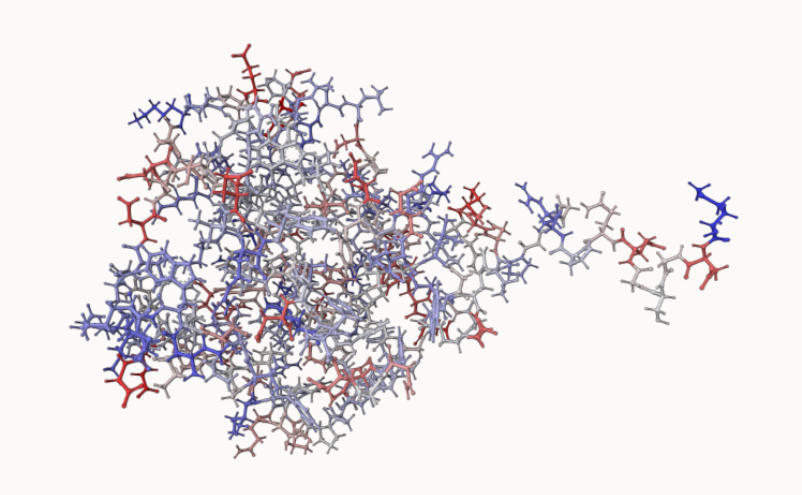


Charges

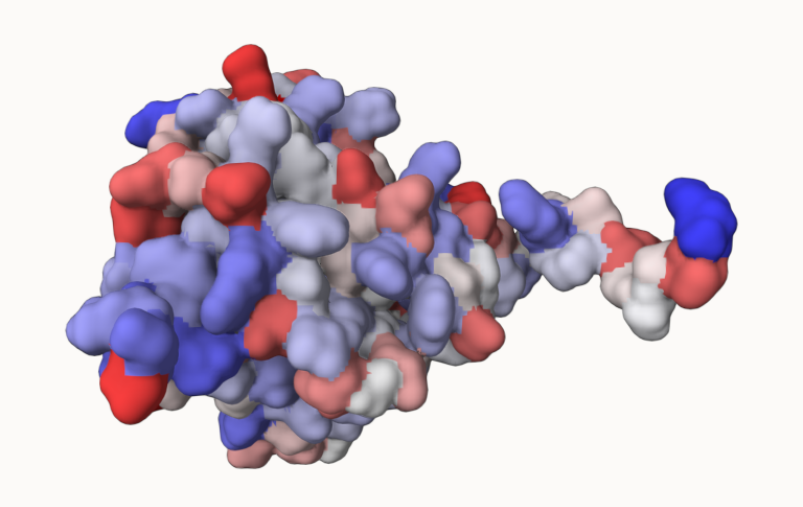
```
loop_
 _sb_ncbr_partial_atomic_charges_meta.id
_sb_ncbr_partial_atomic_charges_meta.type
_sb_ncbr_partial_atomic_charges_meta.method
1 'empirical' 'SQE+qp/Schindler 2021 (CCD_gen)'

loop_
 _sb_ncbr_partial_atomic_charges.type_id
_sb_ncbr_partial_atomic_charges.atom_id
_sb_ncbr_partial_atomic_charges.charge
1 1 -0.5288
1 2 -0.0717
1 3  0.6516
1 4 -0.6044
```

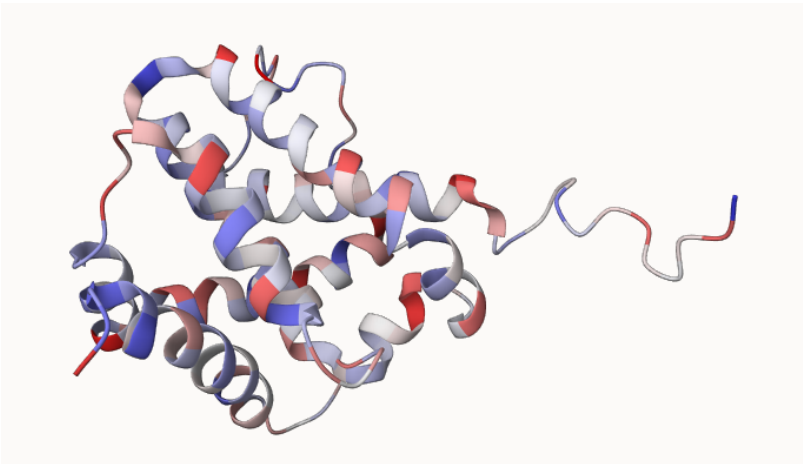




(a) Ball and stick



(b) Surface



(c) Cartoon

Integration of Mol* viewer into ACC II

- swapped the LiteMol Viewer for the Mol* Viewer
- added support for multiple calculations on one request
  - updated setup page to allow multiple calculations
  - added controls for switching between charge sets

Atomic Charge Calculator II

Computation results

Method: SQE+qp
Parameters: Schindler 2021 (CCD_gen)

Structure

1C0Q

Charge set

SQE+qp/Schindler 2021 (CCD_gen)

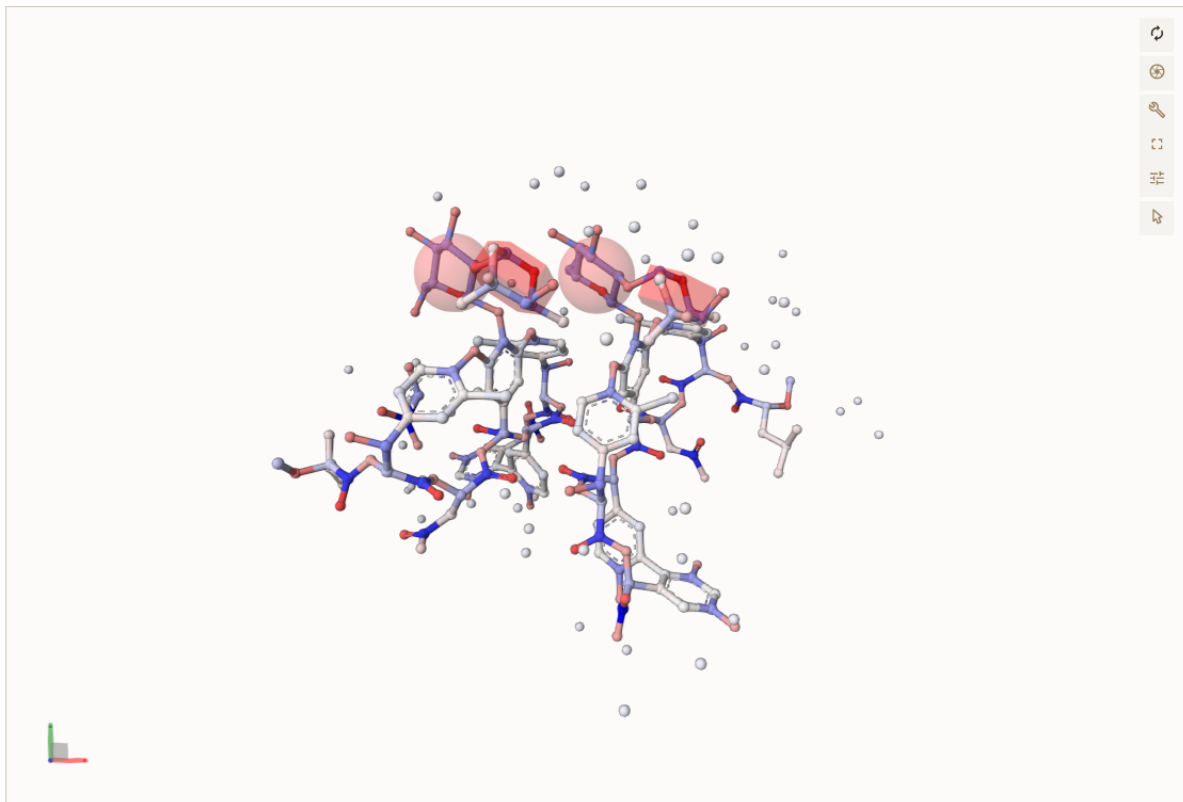
View

(•) Cartoon ( ) Balls and sticks ( ) Surface

Coloring

( ) Structure
(•) Charges (relative) ( ) Charges (absolute)

Max value: 1.410 Reset



Download charges Back to setup Back to main page

Method

SQE+qp

Full name

Split-charge equilibration with parametrized initial charges

Publication

Schindler, O., Raček, T., Maršavelski, A., Koča, J., Berka, K., & Svobodová, R. (2021). Optimized SQE atomic charges for peptides accessible via a web application. Journal of cheminformatics, 13(1), 1-11. doi:10.1186/s13321-021-00528-w

Parameters

The most suitable parameters are shown first.

Schindler 2021 (CCD_gen)

Publication

Schindler, O., Raček, T., Maršavelski, A., Koča, J., Berka, K., & Svobodová, R. (2021). Optimized SQE atomic charges for peptides accessible via a web application. Journal of cheminformatics, 13(1), 1-11. doi:10.1186/s13321-021-00528-w

Add to calculation

Will compute the following charges:

SQE+qp (Schindler 2021 (CCD_gen))	EEM (Racek 2016 (ccd2016_npa))
QEq (Rappe 1991)	EQeq (No parameters)

Compute

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Integration of Mol* viewer into αCharges

- Mol* Viewer is used for displaying the results
- new coloring by pLDDT confidence score
- added a page for describing problematic structures

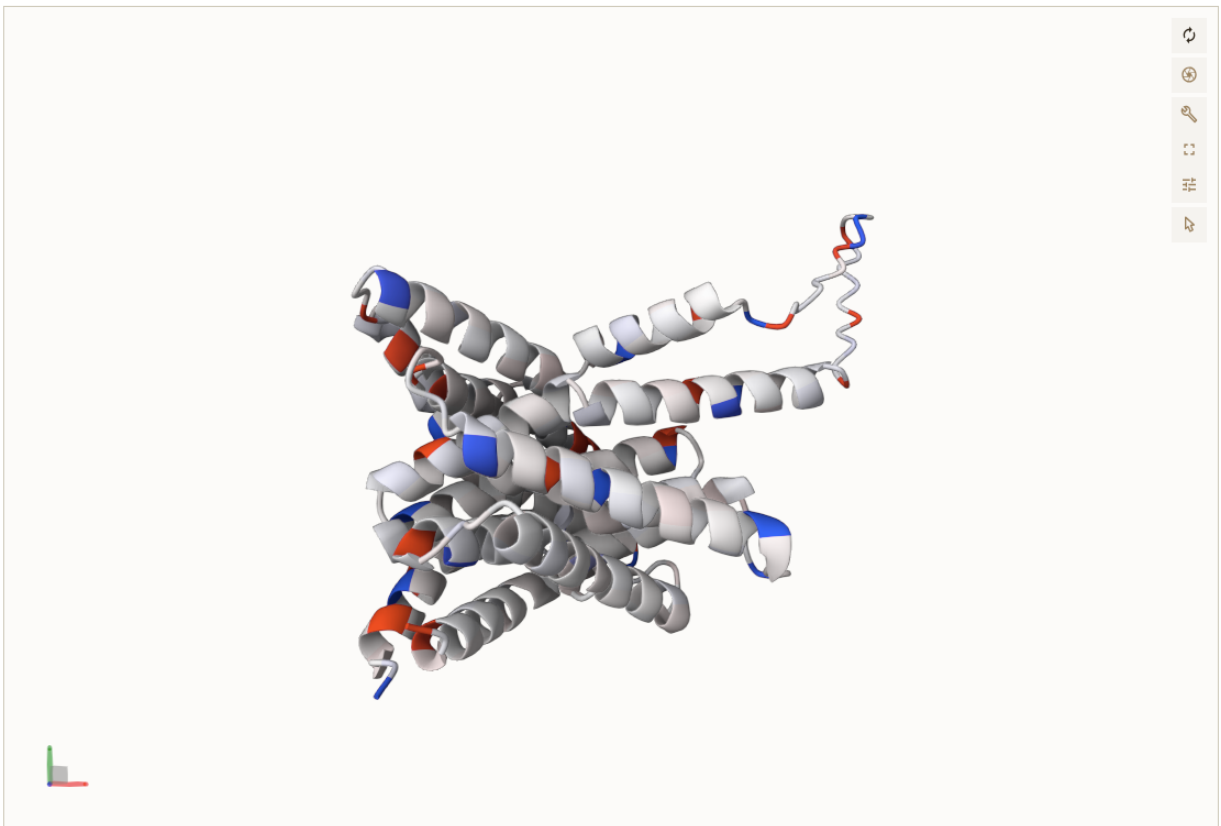
αCharges – Calculation results

UniProt code: Q9FFD0
AlphaFold2 prediction version: 4
pH: 7.2
Number of atoms: 5508

View
- (•) Cartoon
- ( ) Surface
- ( ) Ball & Stick

Coloring
- ( ) Structure
- ( ) Model confidence
- (•) Charges (relative) ( ) Charges (absolute)

Max value: 0.9703 Reset



Download charges and protonated structure

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αCharges – Wrong structure

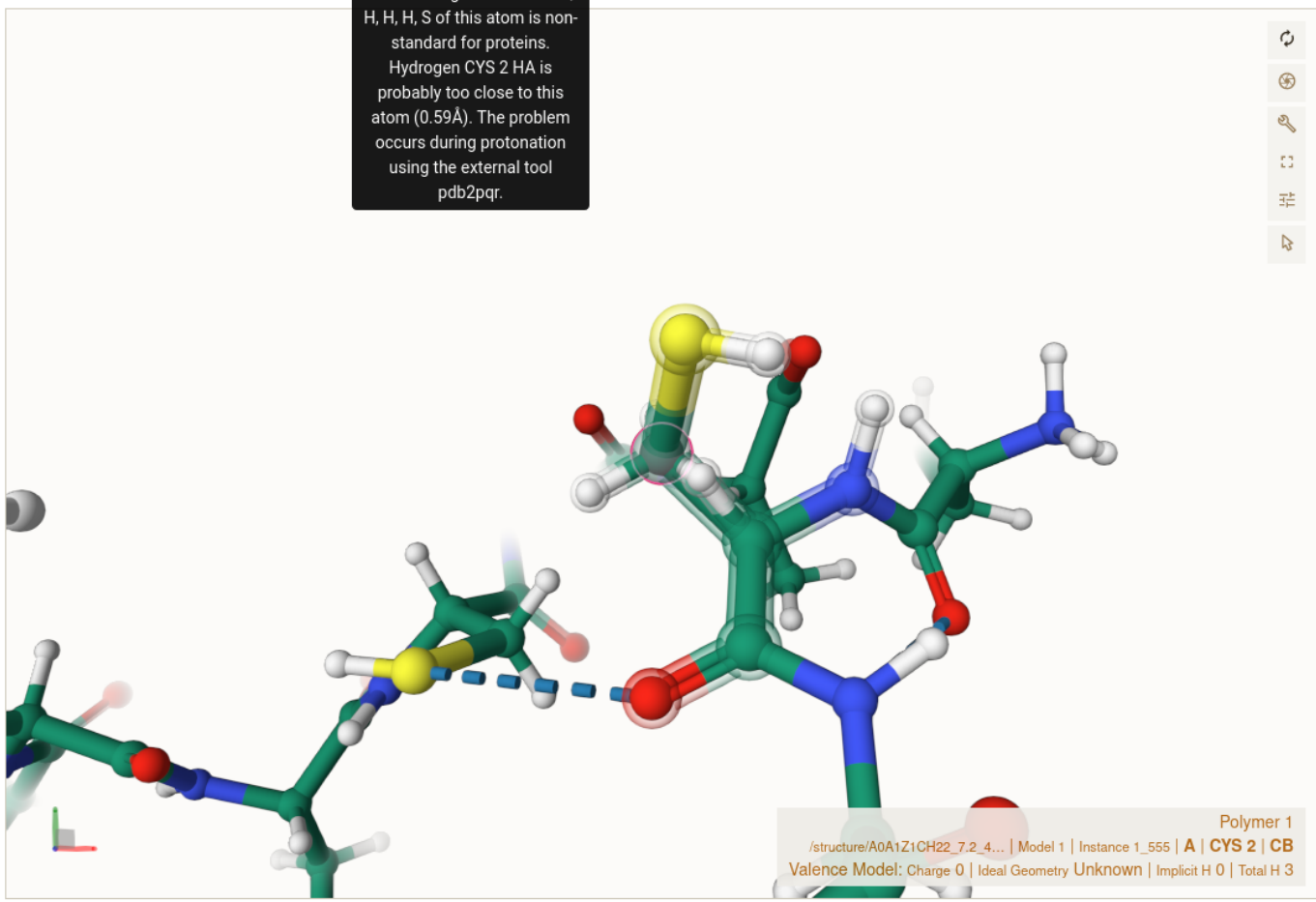
UniProt code: A0A1Z1CH22

AlphaFold2 prediction version: 4

pH: 7.2

⚠ There is a structural error with atoms CYS 2 CB ? ! Calculation of partial atomic charges is not possible. ×

The bonding environment C, H, H, H, S of this atom is non-standard for proteins. Hydrogen CYS 2 HA is probably too close to this atom (0.59Å). The problem occurs during protonation using the external tool pdb2pqr.



Download structure

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Nucleic Acids Research paper

JOURNAL ARTICLE

αCharges: partial atomic charges for AlphaFold structures in high quality

Ondřej Schindler, Karel Berka, Alessio Cantara, Aleš Křenek, Dominik Tichý, Tomáš Raček ✉, Radka Svobodová ✉

Nucleic Acids Research, gkad349, https://doi.org/10.1093/nar/gkad349

Published: 09 May 2023 **Article history** ▾

Figure: αCharges paper published in NAR [1]

Conclusion

- created an Mol* extension for visualizing partial atomic charges
- integrated the updated Mol* viewer into the ACC II and αCharges web applications
- extended the capabilities of ACC II to support multiple calculations on one request
- contributed with the work to the αCharges paper

Oponents' questions

1. Proč jste pro vývoj Mol* pluginu zvolil Vite build tool? Zvažoval jste i jiné alternativy?
2. V jakých formátech je možno načíst náboje do Mol*?
3. Jste schopen využít funkcionalitu pro vizualizaci nábojů v Mol* i pro více přiložených molekul? Pokud ano, mohl byste to ukázat na příkladu? Např. podle nábojů obarvit a přiložit PIN proteiny, které jsou využity jako use case na webu αCharges?
4. Bylo by možno do budoucna podle nábojů obarvit i jiné objekty než atomy, elementy sekundární struktury nebo povrchy atomů - např. póry a kanály v proteinech? A pokud ano, jak pracné by to bylo?

Oponents' question 1

Proč jste pro vývoj Mol* pluginu zvolil Vite build tool? Zvažoval jste i jiné alternativy?

- Mol* repository uses Webpack for bundling
- Vite provides a much faster development server
  - **Fast start**
    - prebundles dependencies using *esbuild*
    - serves source code with native ESM modules
  - **Fast updates**
    - HMR is performed over native ESM
    - leverages HTTP headers to speed up full page reloads
- Vite provides optimized production builds with Rollup

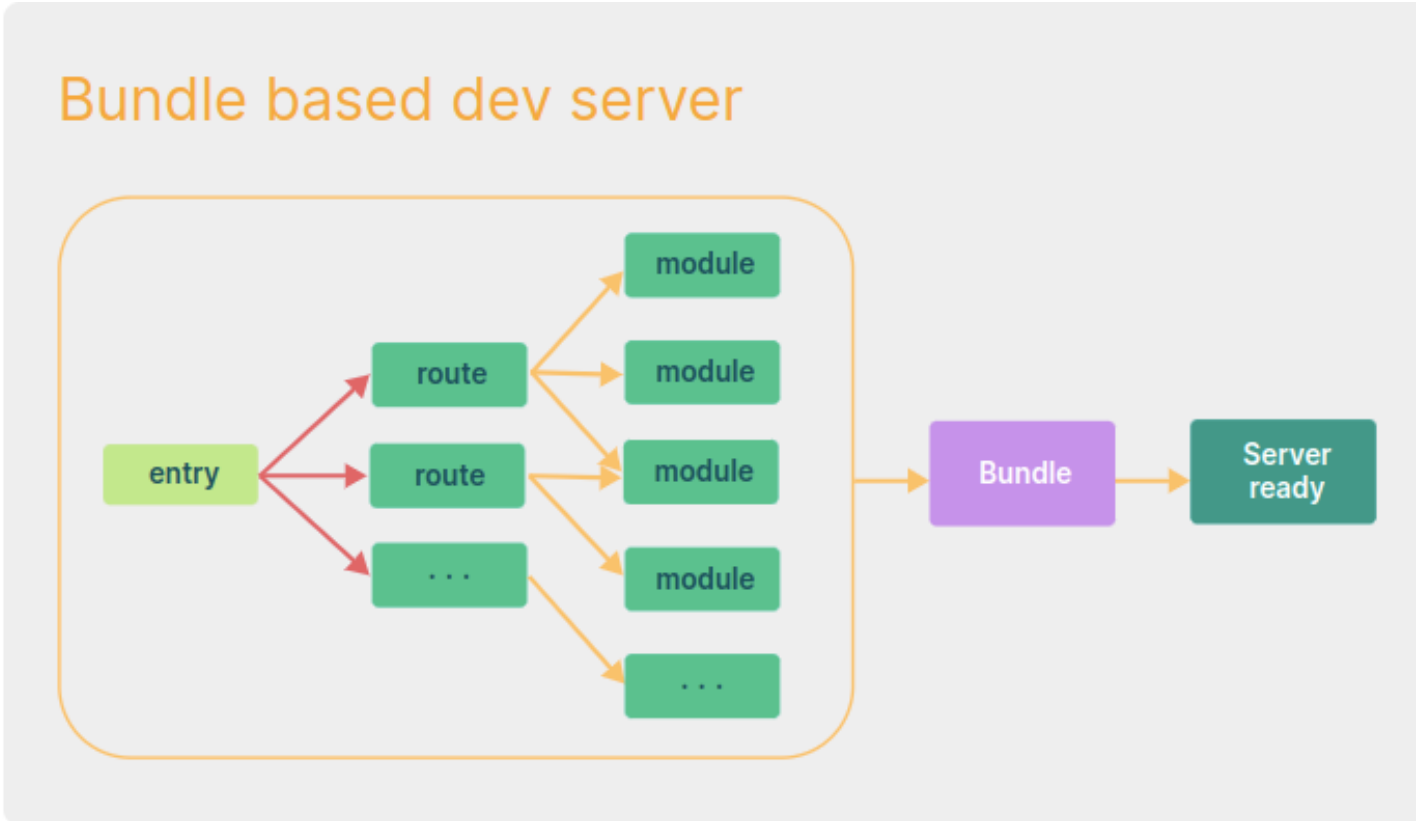


Figure: Bundle-based development server [1]

[1] https://vitejs.dev/guide/why.html

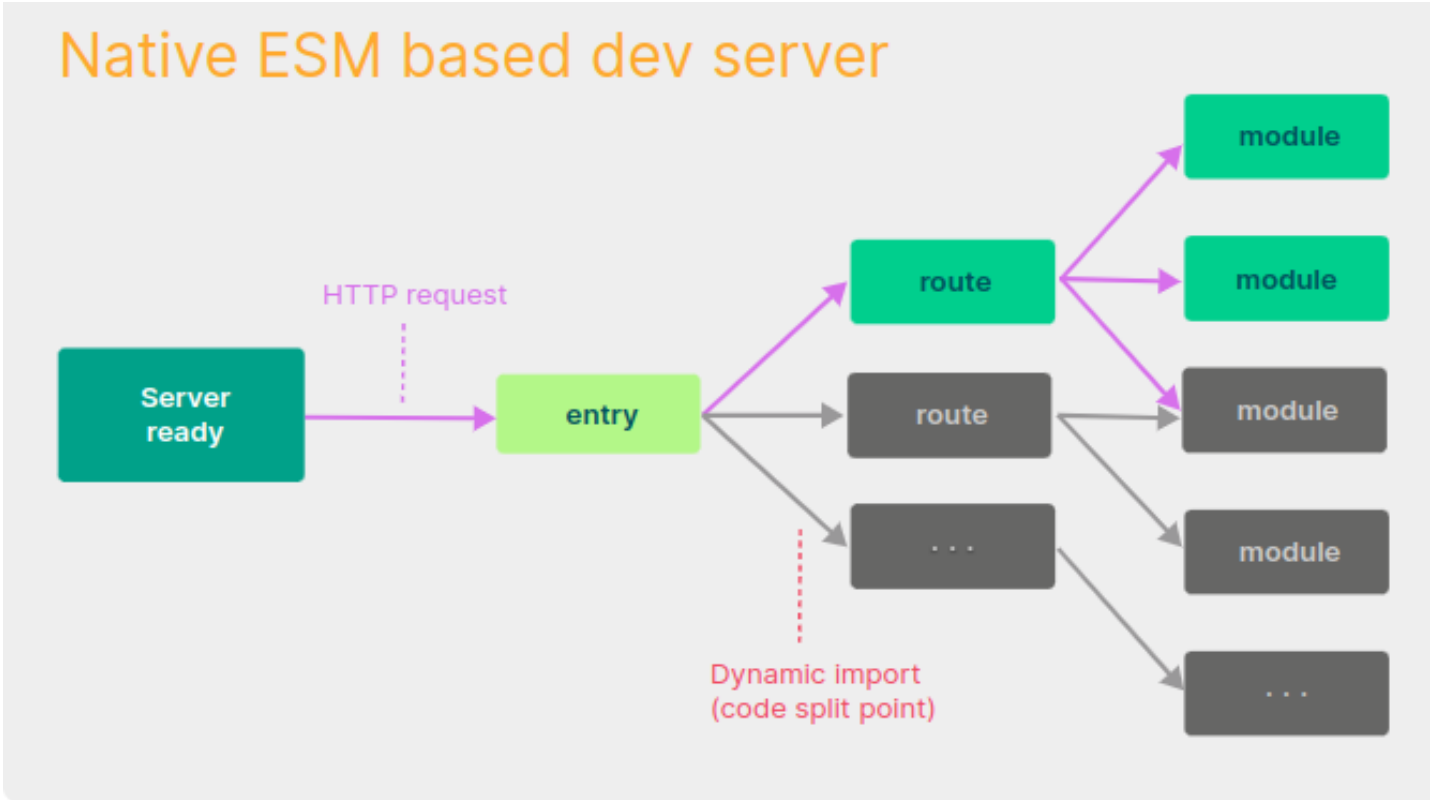


Figure: Native ESM module development server [2]

[2] https://vitejs.dev/guide/why.html

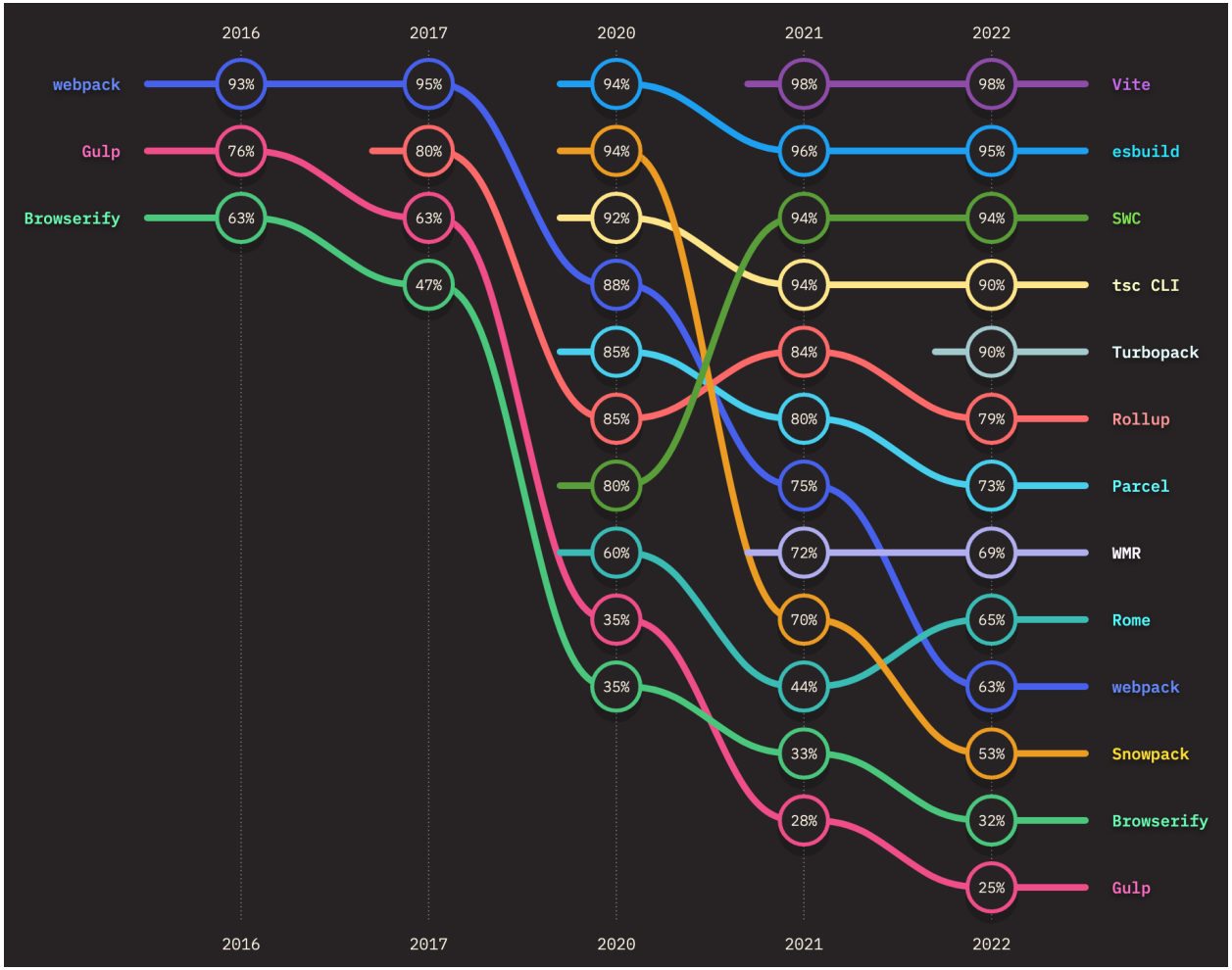


Figure: Build tools retention ranking [3]

[3] https://2022.stateofjs.com

Oponents' question 2

V jakých formátech je možno načíst náboje do Mol*?

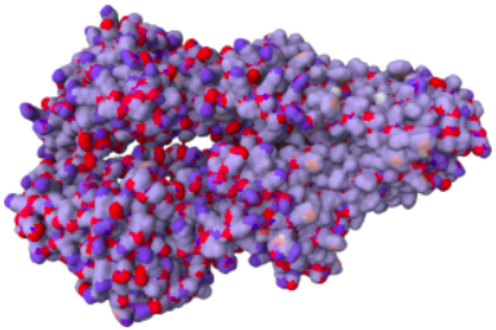
- the Mol* extension only supports the mmCIF format
- it is possible to add support for other formats which have data fields for charges
  - MOL2
  - PQR
- separate structure and charges files would require custom import controls
  - this approach was used in the LiteMol extension
  - would make the integration into Mol* more difficult

Oponents' question 3

Jste schopen využít funkcionalitu pro vizualizaci nábojů v Mol* i pro více přiložených molekul? Pokud ano, mohl byste to ukázat na příkladu? Např. podle nábojů obarvit a přiložit PIN proteiny, které jsou využity jako use case na webu αCharges?

Examples

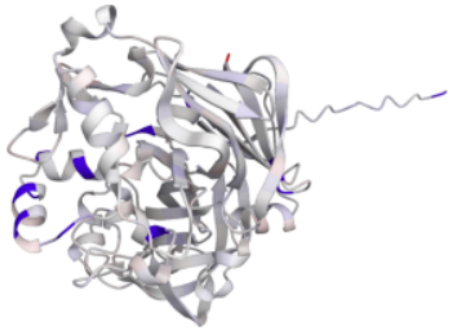
P-glycoprotein



P-glycoprotein is part of the ABC transporter proteins that decrease drug accumulation in cancer cells (Leslie2005). It is a 170-kDa protein which consists of a nucleotide-binding domain and a transmembrane domain (Ward2013). Partial atomic charges calculated by **αCharges** demonstrate the differences in charge distribution between transmembrane parts and the extracellular/intracellular one.

P-glycoprotein

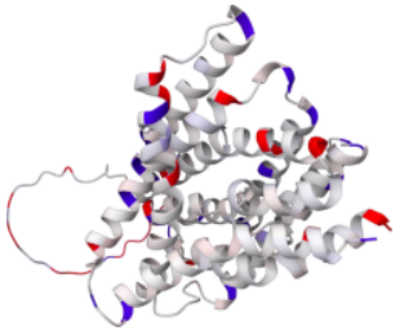
Pepsin pH: 1



Pepsin is the enzyme that is majorly involved in protein digestion in the stomach. It is secreted as a zymogen and activated by the acidic pH created by the stomach parietal cells. Pepsin is the most effective at a pH of approximately 1.5 to 2, and it becomes inactive when the pH rises above 6 (Heda2022). Pepsin remains structurally stable until at least a pH of 8. Differences in a charge distribution between its active form (pH 2) and inactive form (pH 8) can be seen in this use case. The alkaline environment causes an increase in negative charges, which contributes to the structural instability of the pepsin, causing the shift to an inactive form of the protein (Tanaka2001, Grahame2021).

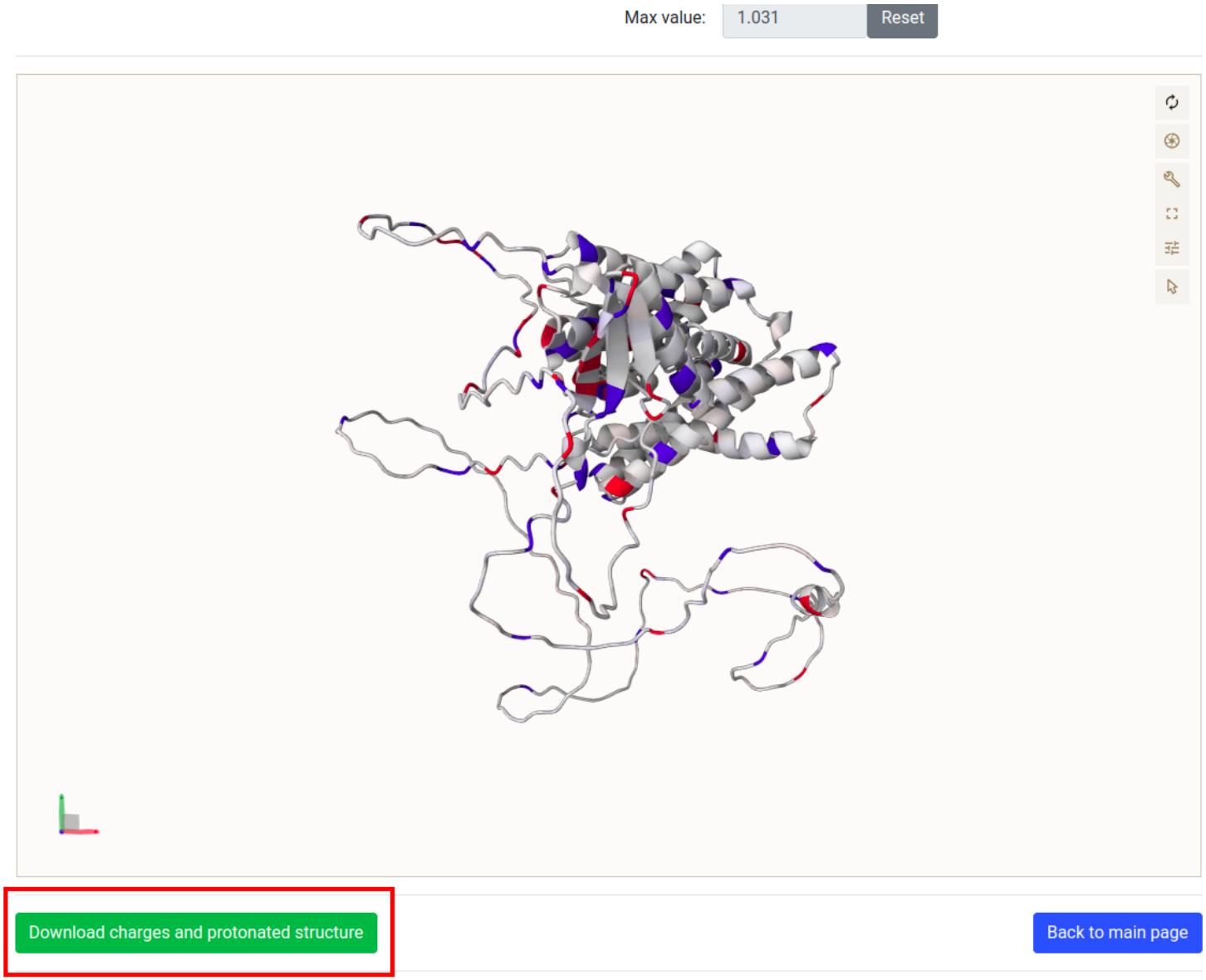
Active Inactive

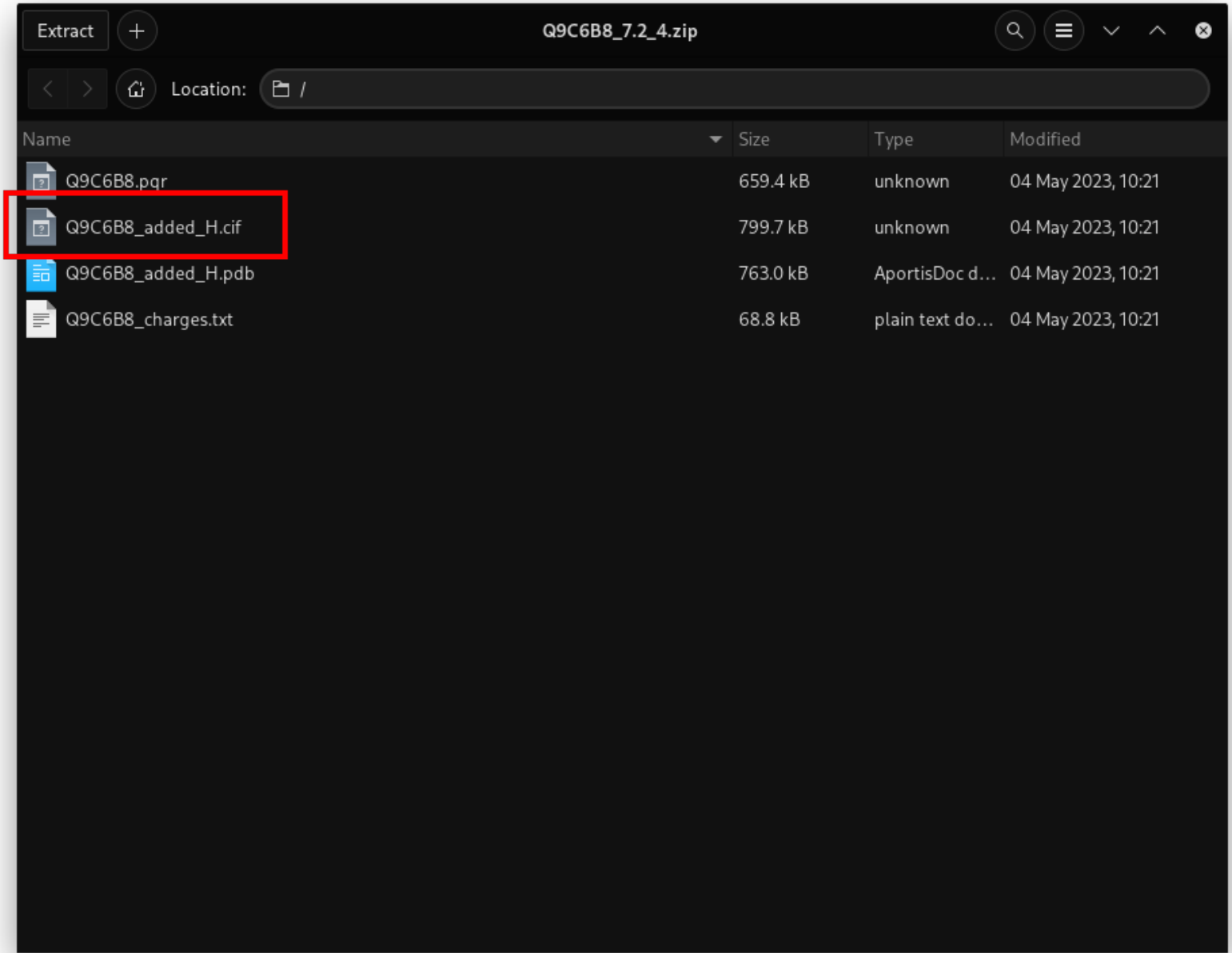
PIN proteins

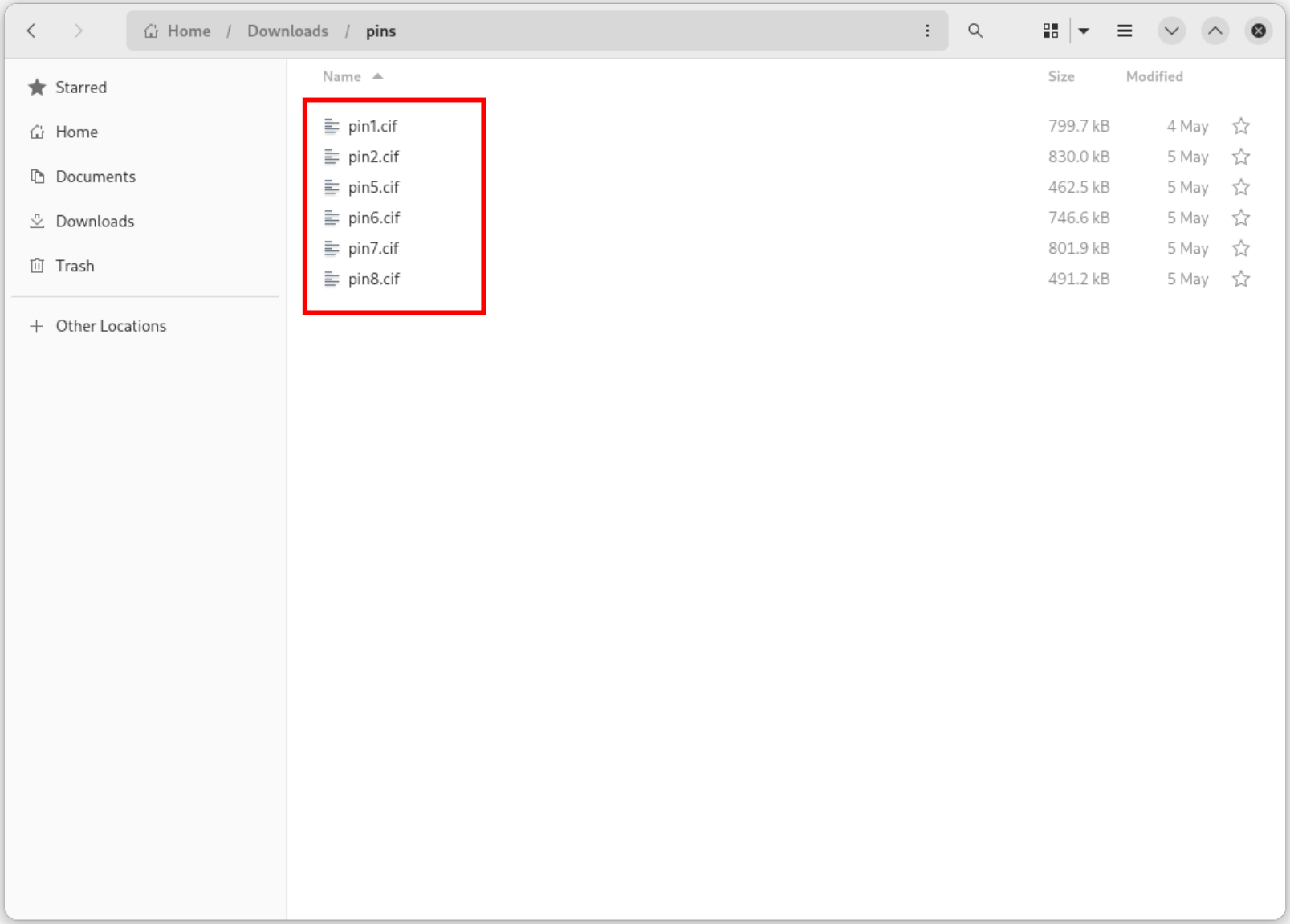


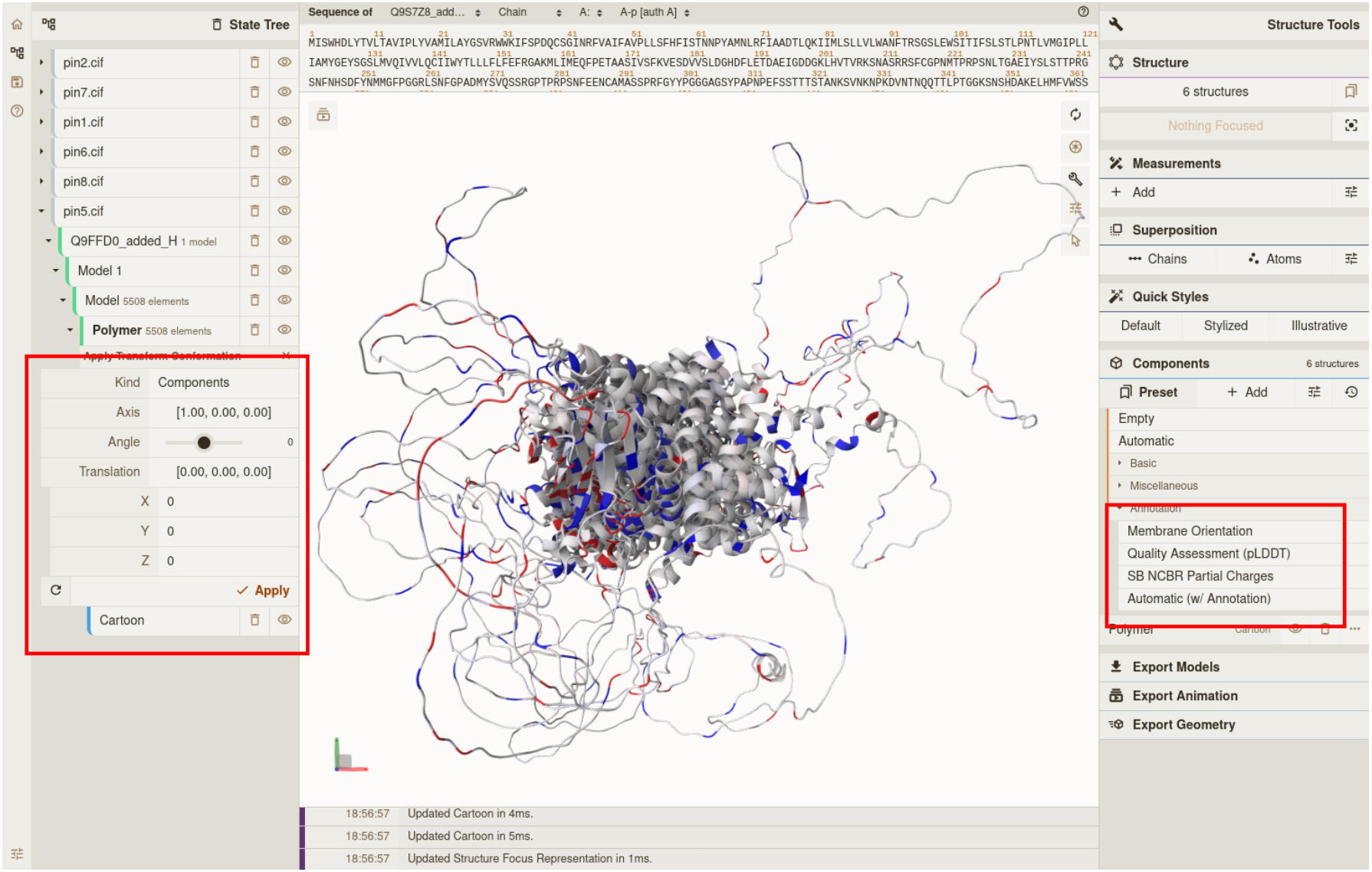
The PIN family proteins control plant growth by regulating auxin export from the cytosol to the extracellular space. Eight types of PIN proteins are known (PIN1-PIN8), and last year, structures of three of them were discovered and published in Nature (i.e., articles about PIN1, PIN3, PIN8). Partial atomic charges play an important role in PINs functionality. The PIN protein part inside the cytosol (containing the cytosolic loop) is charged more than the part outside the cytosol. Questionable is the charge distribution of PIN5, which structure differs from other PINs (Ung2022) and was not experimentally determined yet. In the use case, you can compare the charge distribution of AlphaFold2 predicted PINs from *A. thaliana*.

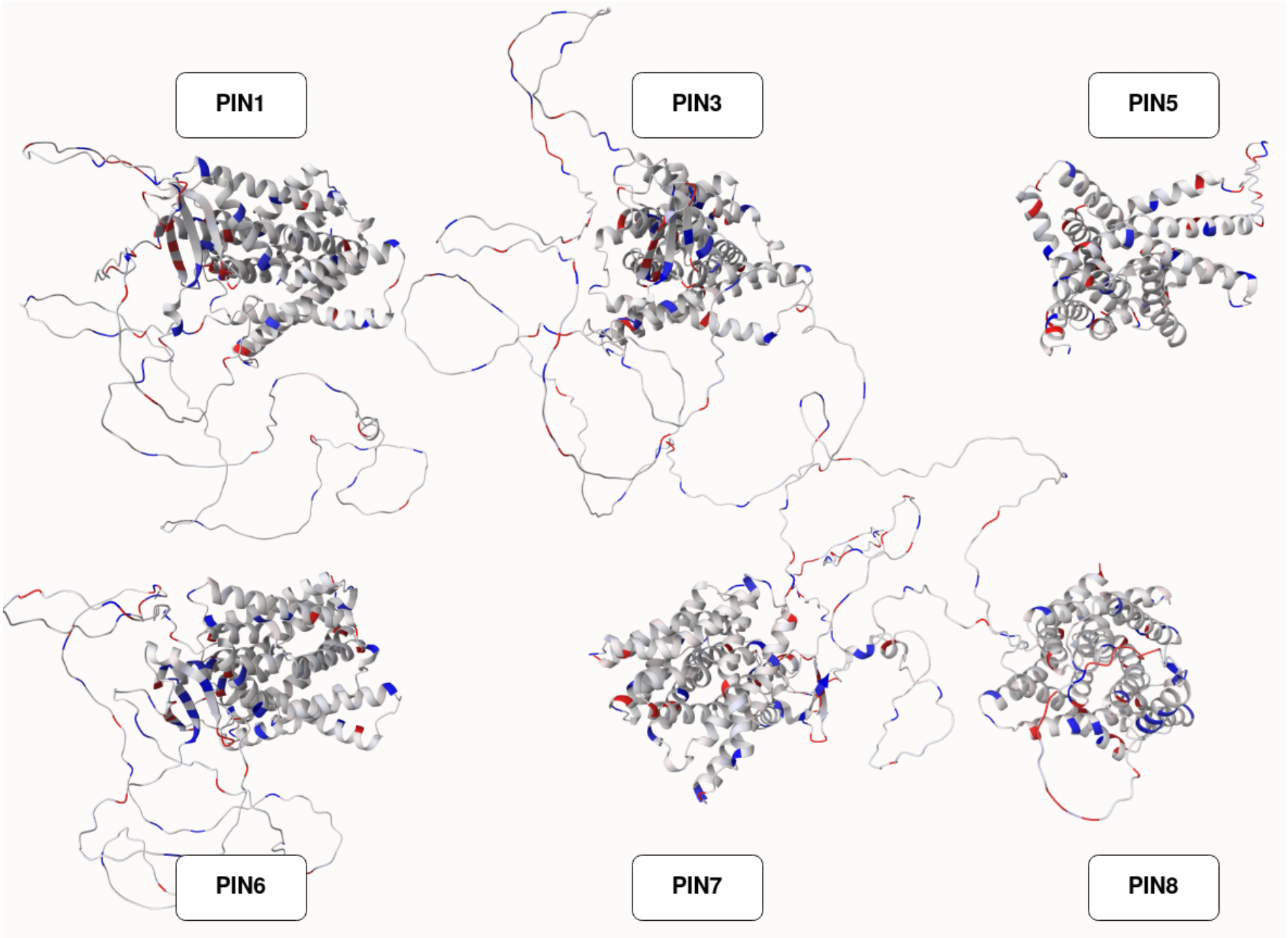
PIN1 PIN3 PIN5
PIN6 PIN7 PIN8


Max value:
1.031
Reset
Download charges and protonated structure
Back to main page


Extract
Q9C6B8_7.2_4.zip
Location: /
Name
Size
Type
Modified
Q9C6B8.pqr
659.4 kB
unknown
04 May 2023, 10:21
Q9C6B8_added_H.cif
799.7 kB
unknown
04 May 2023, 10:21
Q9C6B8_added_H.pdb
763.0 kB
AportisDoc d...
04 May 2023, 10:21
Q9C6B8_charges.txt
68.8 kB
plain text do...
04 May 2023, 10:21


Home / Downloads / pins
Starred
Home
Documents
Downloads
Trash
Other Locations
Name
Size
Modified
pin1.cif 799.7 kB 4 May
pin2.cif 830.0 kB 5 May
pin5.cif 462.5 kB 5 May
pin6.cif 746.6 kB 5 May
pin7.cif 801.9 kB 5 May
pin8.cif 491.2 kB 5 May


State Tree
pin2.cif
pin7.cif
pin1.cif
pin6.cif
pin8.cif
pin5.cif
Q9FFD0_added_H 1 model
Model 1
Model 5508 elements
Polymer 5508 elements
Kind Components
Axis [1.00, 0.00, 0.00]
Angle 0
Translation [0.00, 0.00, 0.00]
X 0
Y 0
Z 0
Apply
Cartoon
Sequence of Q9S7Z8_add... Chain A: A-p [auth A]
MISWHDLYTVLTAVIPLYVAMILAYGSVRWWKIFSPDQCSGINRFVAIFAVPLLSFHFISTNNPYAMNLRFIAADTLQKIIMLSLLVLWANFTRSGSLEWSITIFSLSTLPNTLVMGIPLL
IAMYGEYSGSLMVQIVVLQCIIWYTLLLFLFEFRGAKMLIMEQFPETAASIVSFKVESDVVSLDGHDFLETDAEIGDDGKLHVTVRKSNASRRSFCGPNMTPRPSNLTGAEIYSLSTTPRG
SNFNHSDFYNMMGFPGGRLSNFGPADMYSVQSSRGPTPRPSNFEENCAMASSPRFGYYPGGGAGSYPAPNPEFSSTTTSTANKSVNKNPKDVNTNQQTTLPTGGKSNSHDAKELHMFVWSS
18:56:57 Updated Cartoon in 4ms.
18:56:57 Updated Cartoon in 5ms.
18:56:57 Updated Structure Focus Representation in 1ms.
Structure Tools
Structure
6 structures
Nothing Focused
Measurements
Add
Superposition
Chains Atoms
Quick Styles
Default Stylized Illustrative
Components 6 structures
Preset Add
Empty
Automatic
Basic
Miscellaneous
Membrane Orientation
Quality Assessment (pLDDT)
SB NCBR Partial Charges
Automatic (w/ Annotation)
Export Models
Export Animation
Export Geometry


PIN1
PIN3
PIN5
PIN6
PIN7
PIN8

Oponents' question 4

Bylo by možno do budoucna podle nábojů obarvit i jiné objekty než atomy, elementy sekundární struktury nebo povrchy atomů - např. póry a kanály v proteinech? A pokud ano, jak pracné by to bylo?

- the coloring uses a Location object to determine which color to assign to the given representation element (e.g. atom, residue, surface)
- it would be necessary to create a custom representation (e.g. for pores, channels)
  - the represenation would need to provide a Location object for each of its elements

Bibliography I

[1] Ondřej Schindler et al. “αCharges: partial atomic charges for AlphaFold structures in high quality”. In: *Nucleic Acids Research* (May 2023). gkad349. ISSN: 0305-1048. DOI: 10.1093/nar/gkad349. eprint: https://academic.oup.com/nar/advance-article-pdf/doi/10.1093/nar/gkad349/50252244/gkad349.pdf. URL: https://doi.org/10.1093/nar/gkad349.

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