Physics-based Visual Characterization of Molecular Interaction Forces

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3 – Visual Computing Group (Ulm)

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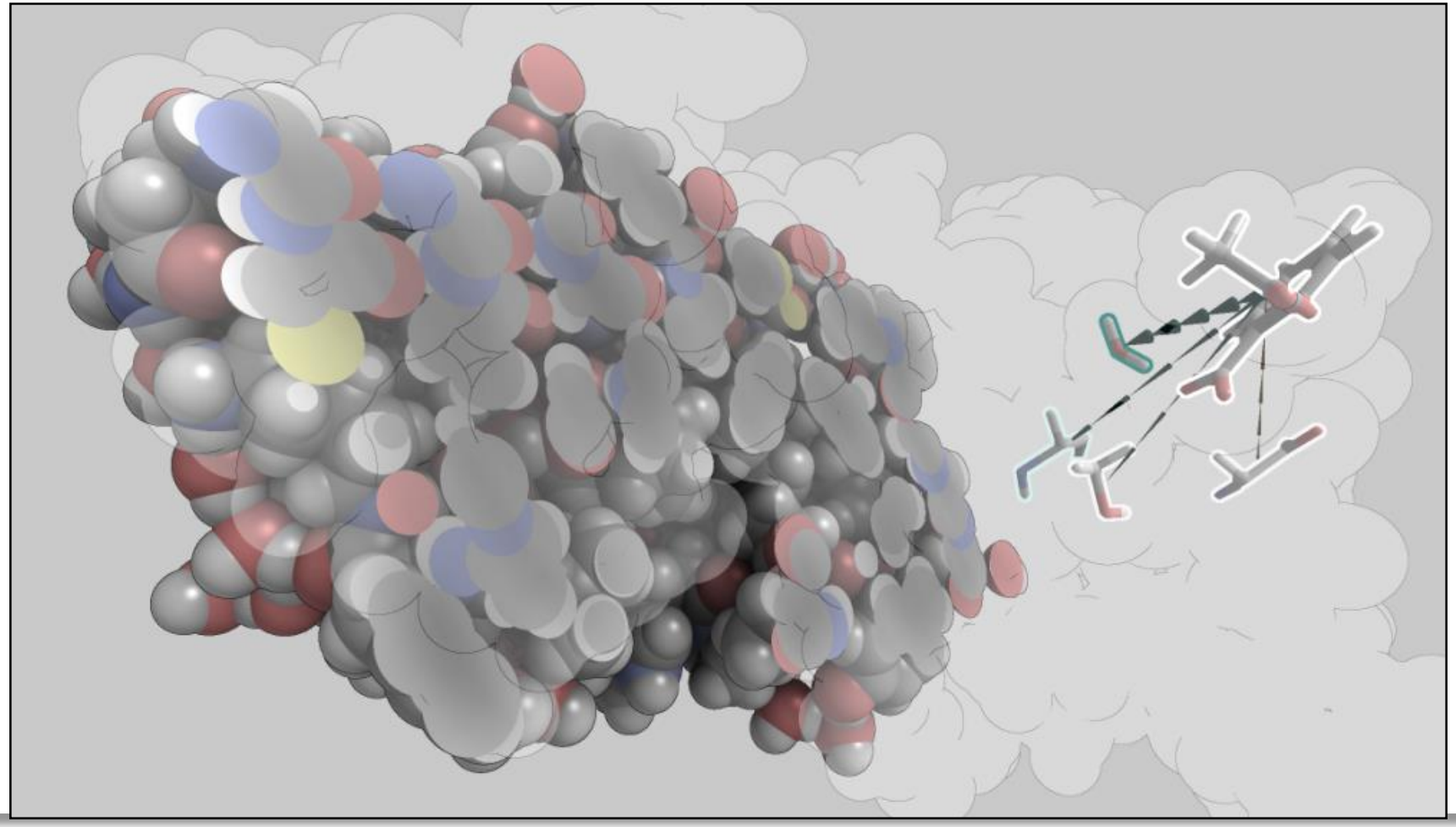
ViRVIG

UPC

Motivation

- **Why?**



Motivation

- Molecular dynamics simulations
  - Generate data to predict drug behavior
    - Previous to real experimentation
  - Helps understanding molecular interactions

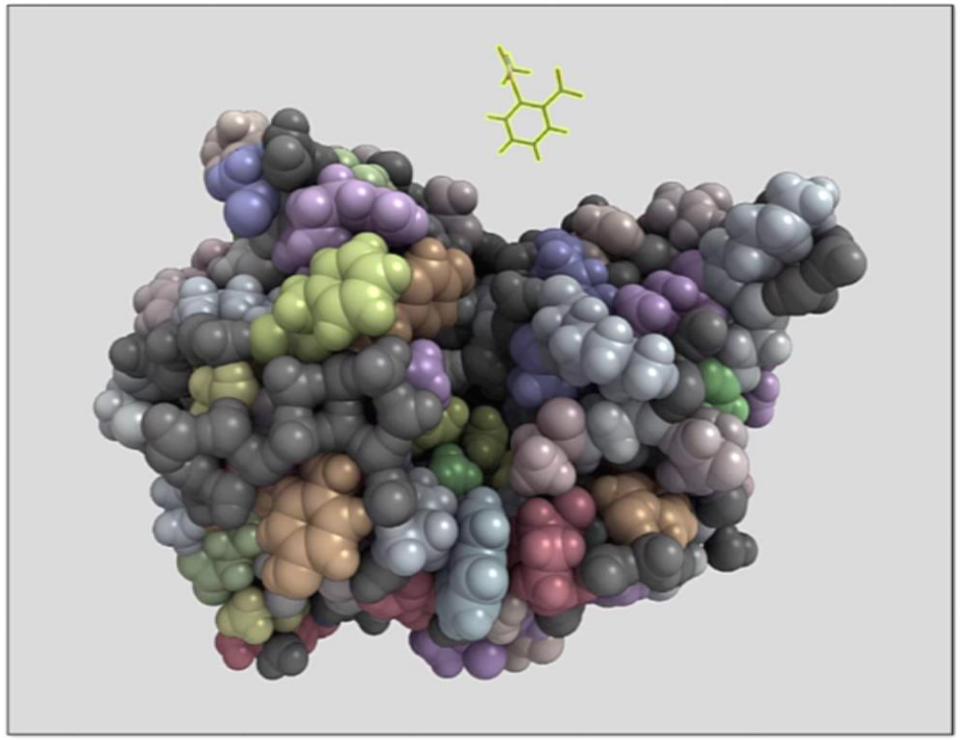
- Limited
  - Time, visualized features…

Motivation

- Commonly analyzed scenarios
  - Static frames
  - Only atom-atom interaction
- Desired scenarios
  - Residue-based analysis
  - Visual communication
  - Fast interaction & inspection
- We have you covered!

Motivation

Physics-based Visual Characterization of Molecular Interaction Forces



ViRVIG
Visualització, Realitat Virtual i Interacció Gràfica

UPC

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Goals & requirements

- Realtime visual analysis of interaction energies
  - Full pathway simulation
  - Explorative analysis
  - Individual energies
  - Distance & energy filtering

Goals & requirements

- Example questions to be answered
  - Q1: Which are the most active groups in the interactions between molecules?
  - Q2: Which are the most powerful binding energy components at a certain simulation configuration?
  - Q3: Is the proximity of the drug causing instability in any residue of the protein?
  - Q4: Is the ligand solvation force favoring or rejecting binding?
  - Q5: Which residues (if any) prevent drug delivery?

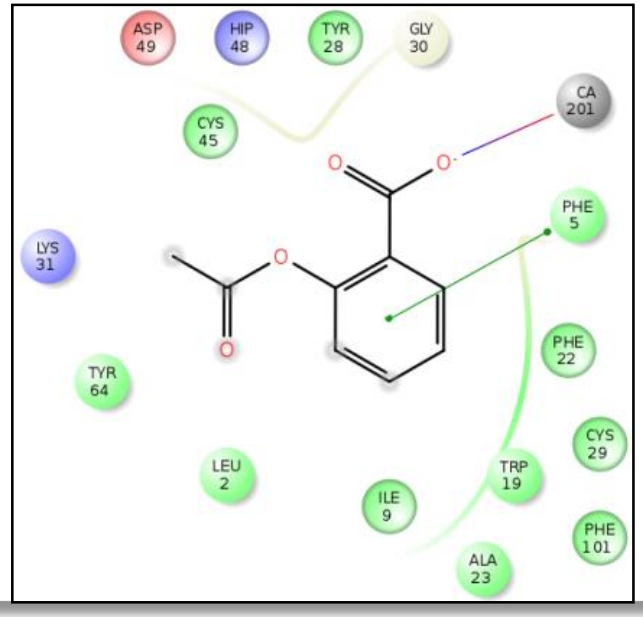
Outline

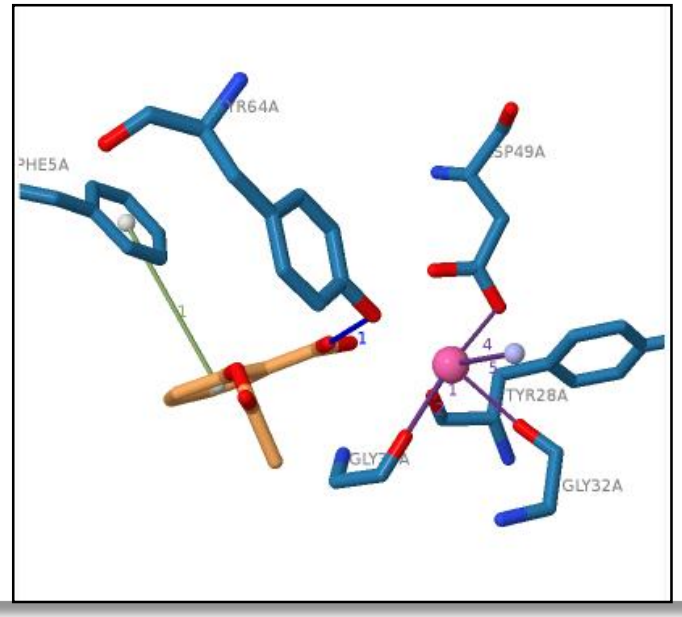
- Previous work
- Overview of the application
- Features
- Implementation
- Results & Conclusions

Previous Work

- Limitations of existing software
  - Single visualization
  - Single frame analysis
  - Not interactive
  - Only limited to close-view visualizations/interactions

Maestro





PLIP

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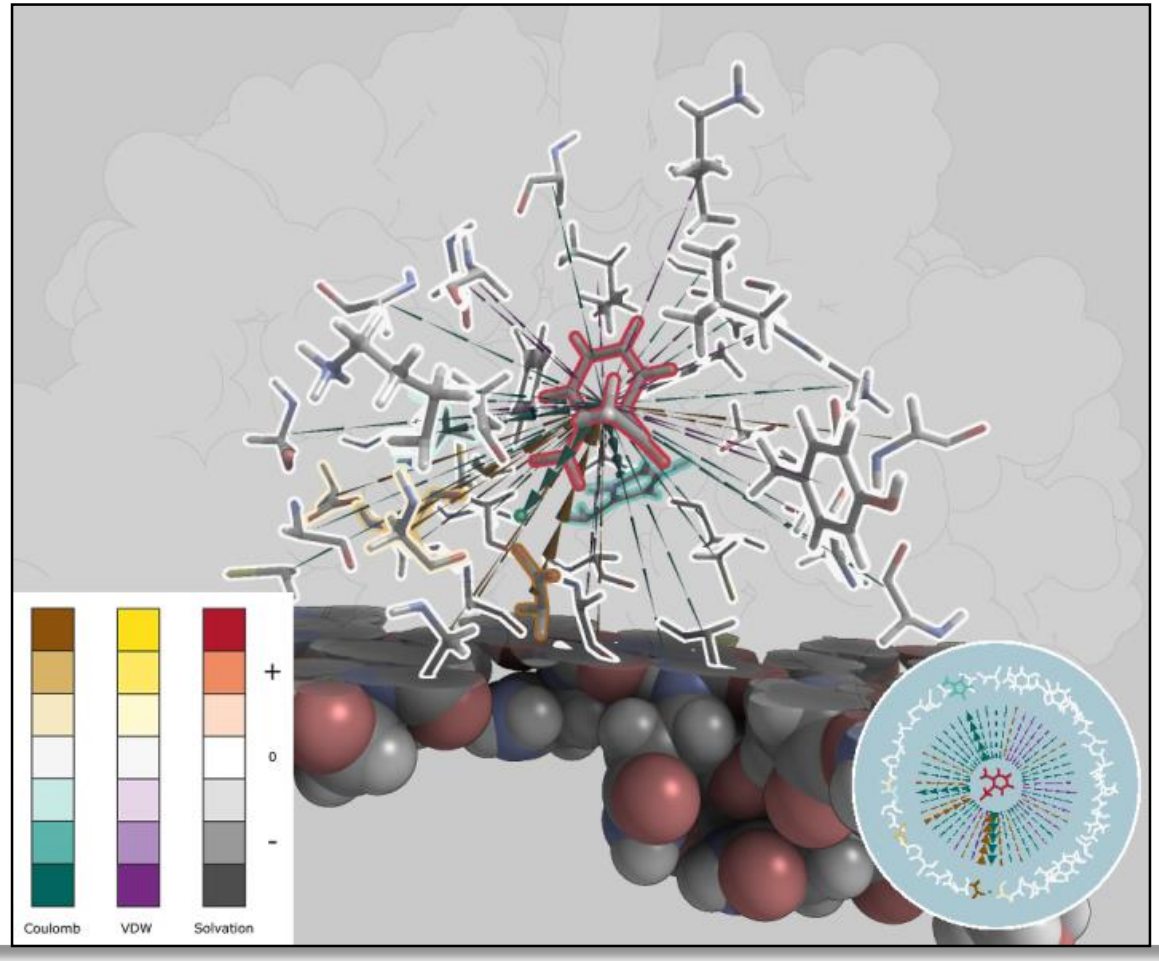
Application design

- Overview



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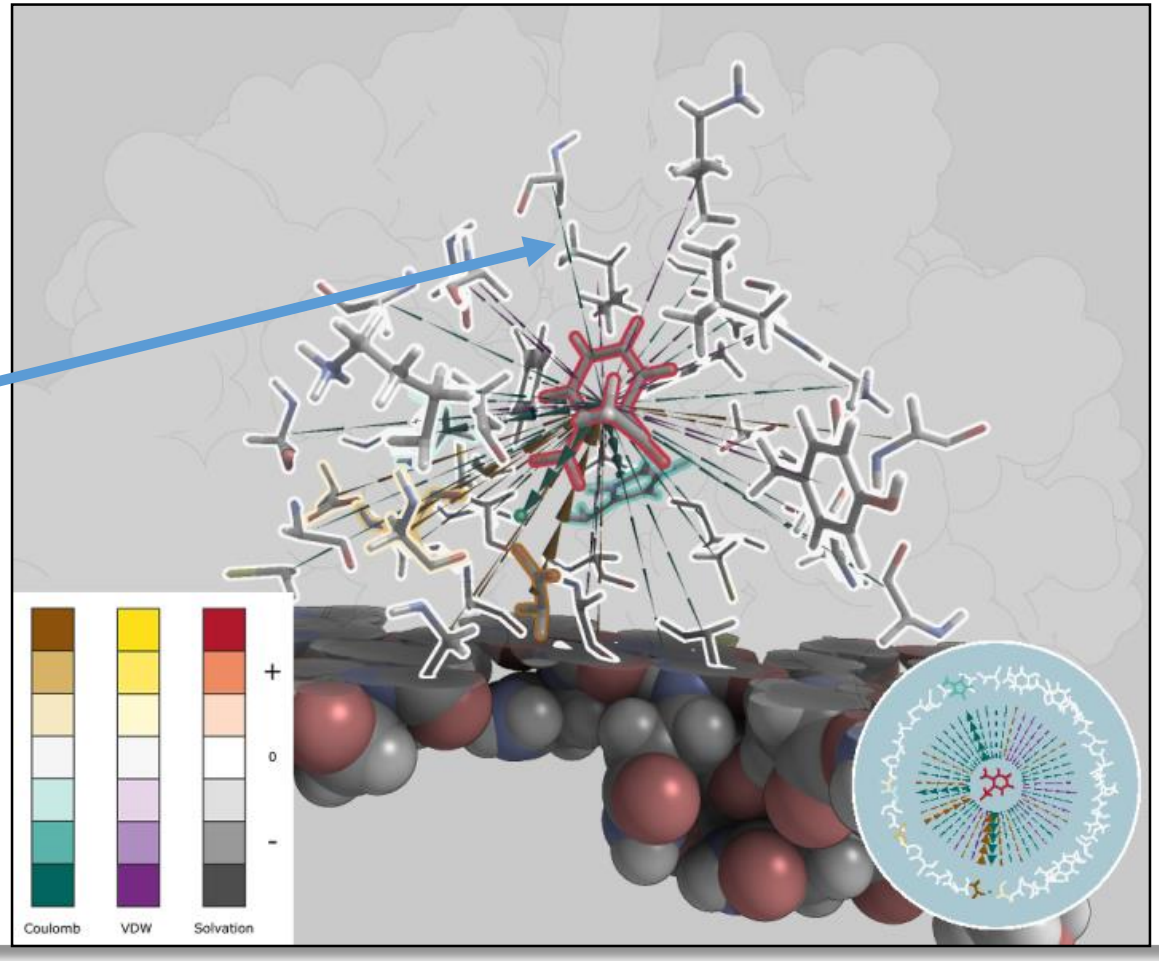
Application design

- Overview

Interaction forces illustrated



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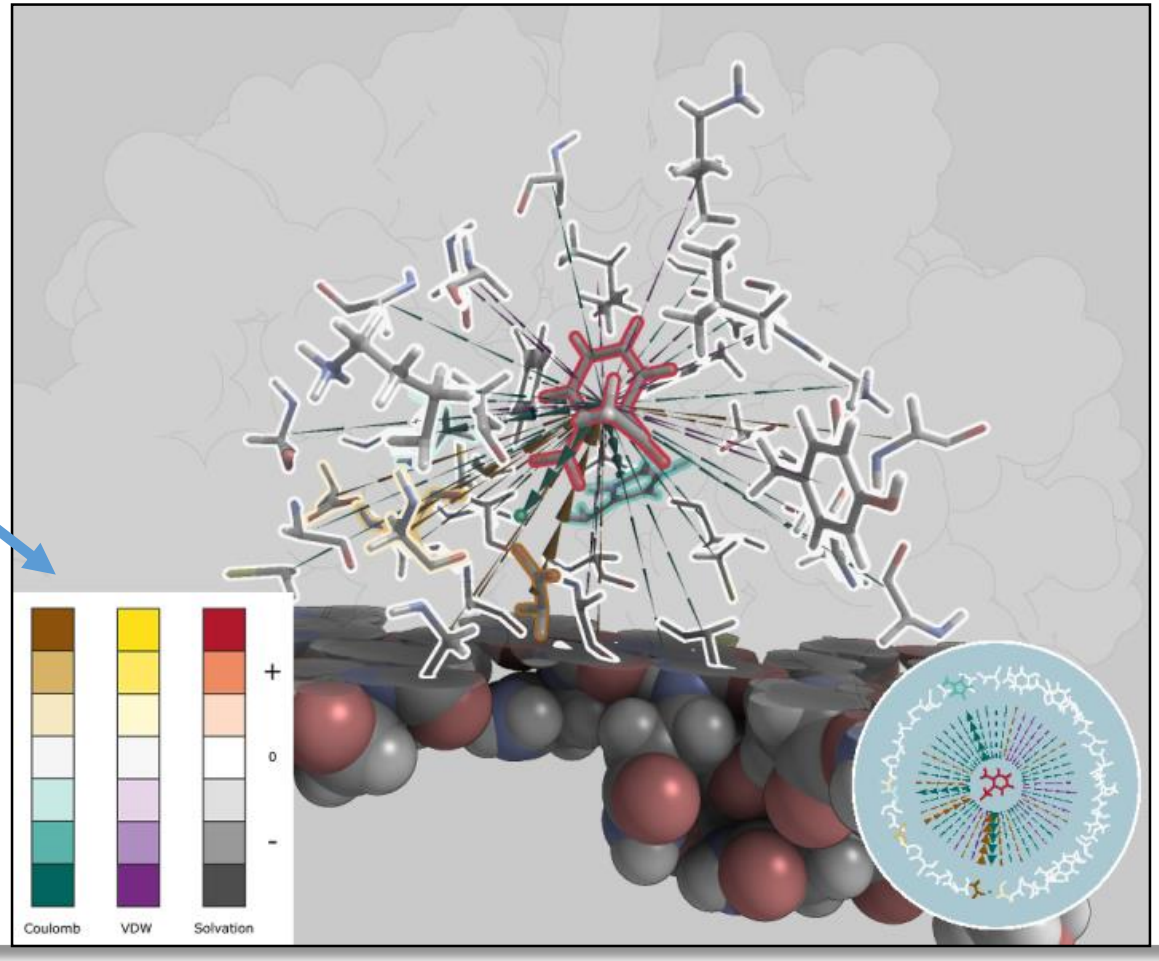
Application design

- Overview

Energy types



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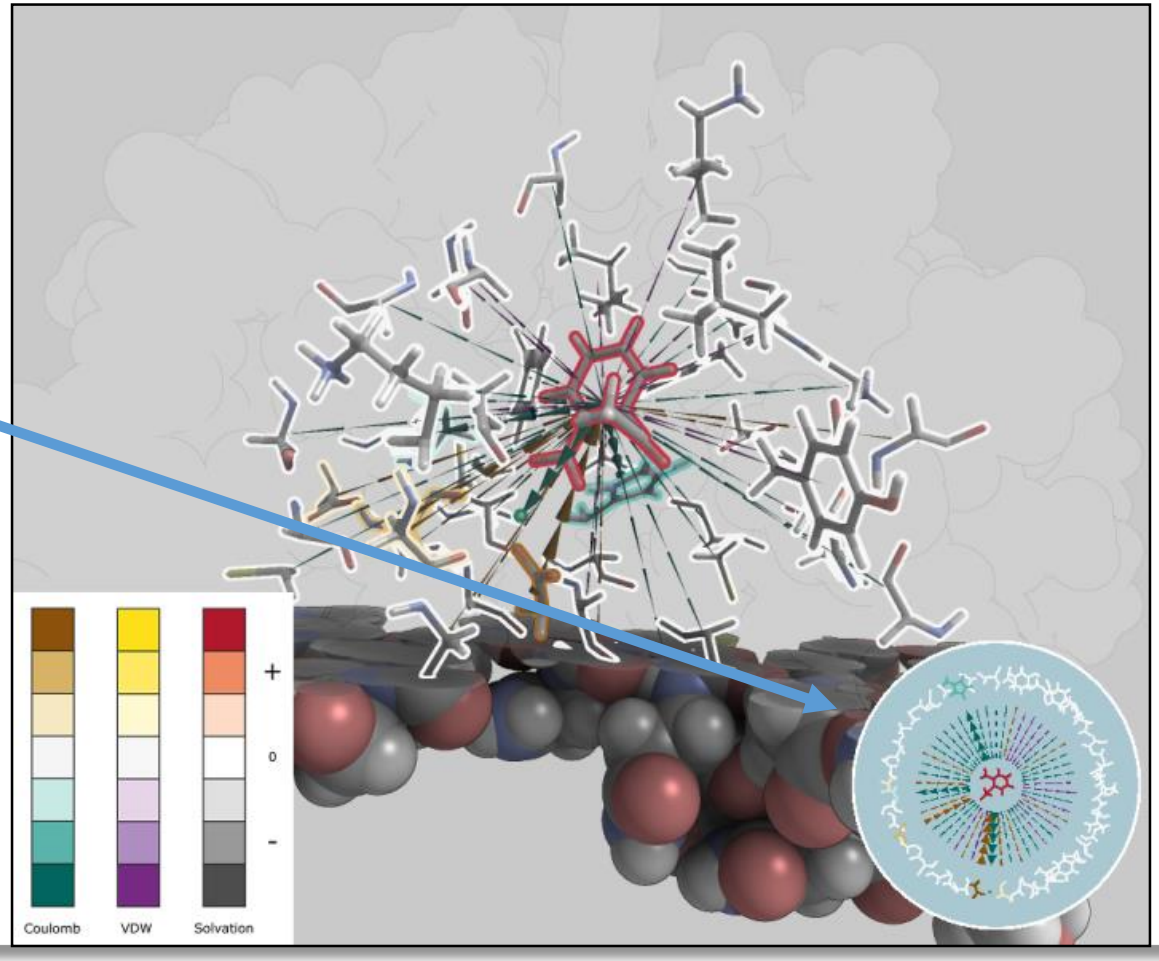
Application design

- Overview

2D abstract view



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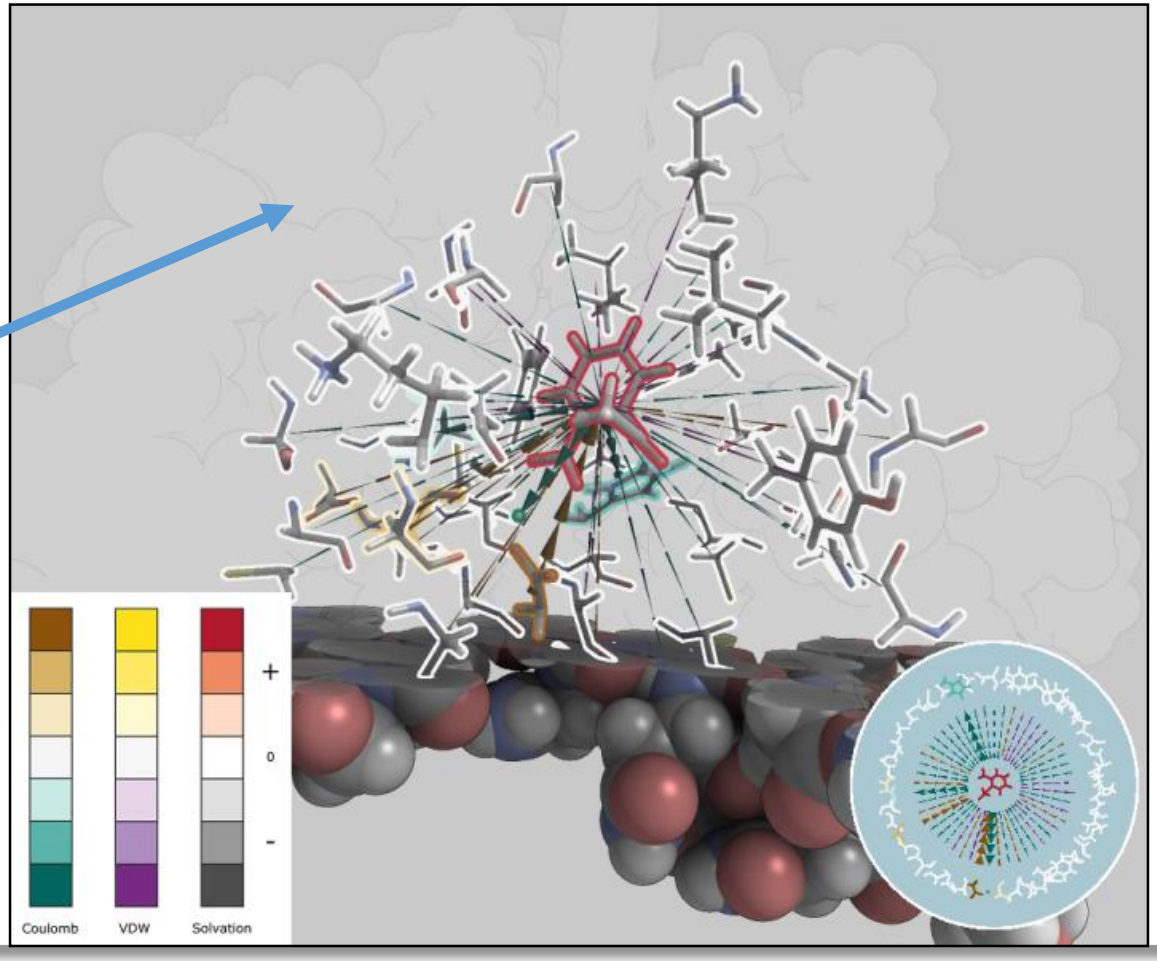
Application design

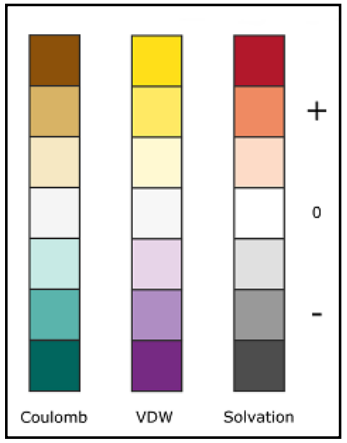
- Overview

Cut-away & context

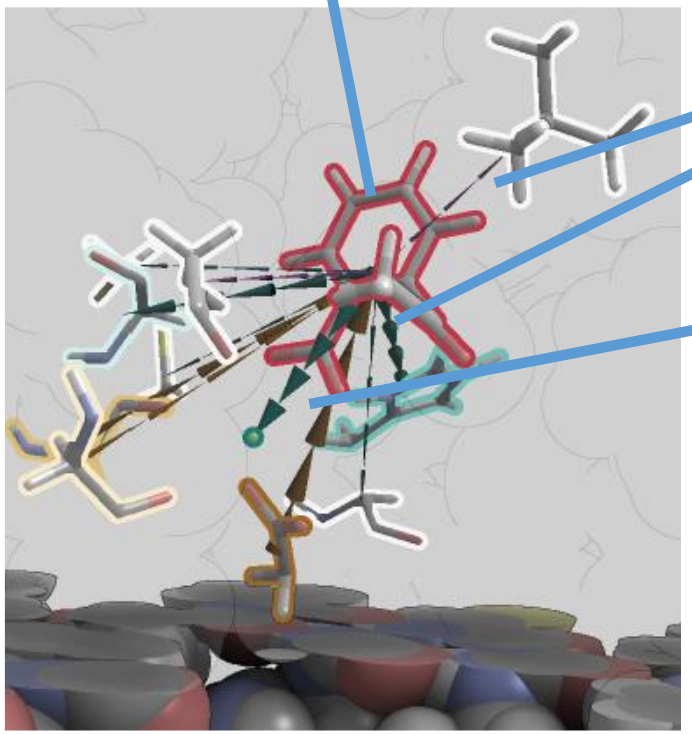


Zoom & Filter

- Visual illustration of energies
- Visual illustration of energies
  - Type, strength & direction
    - Color
    - Cone size
    - Cone orientation



Energy codings



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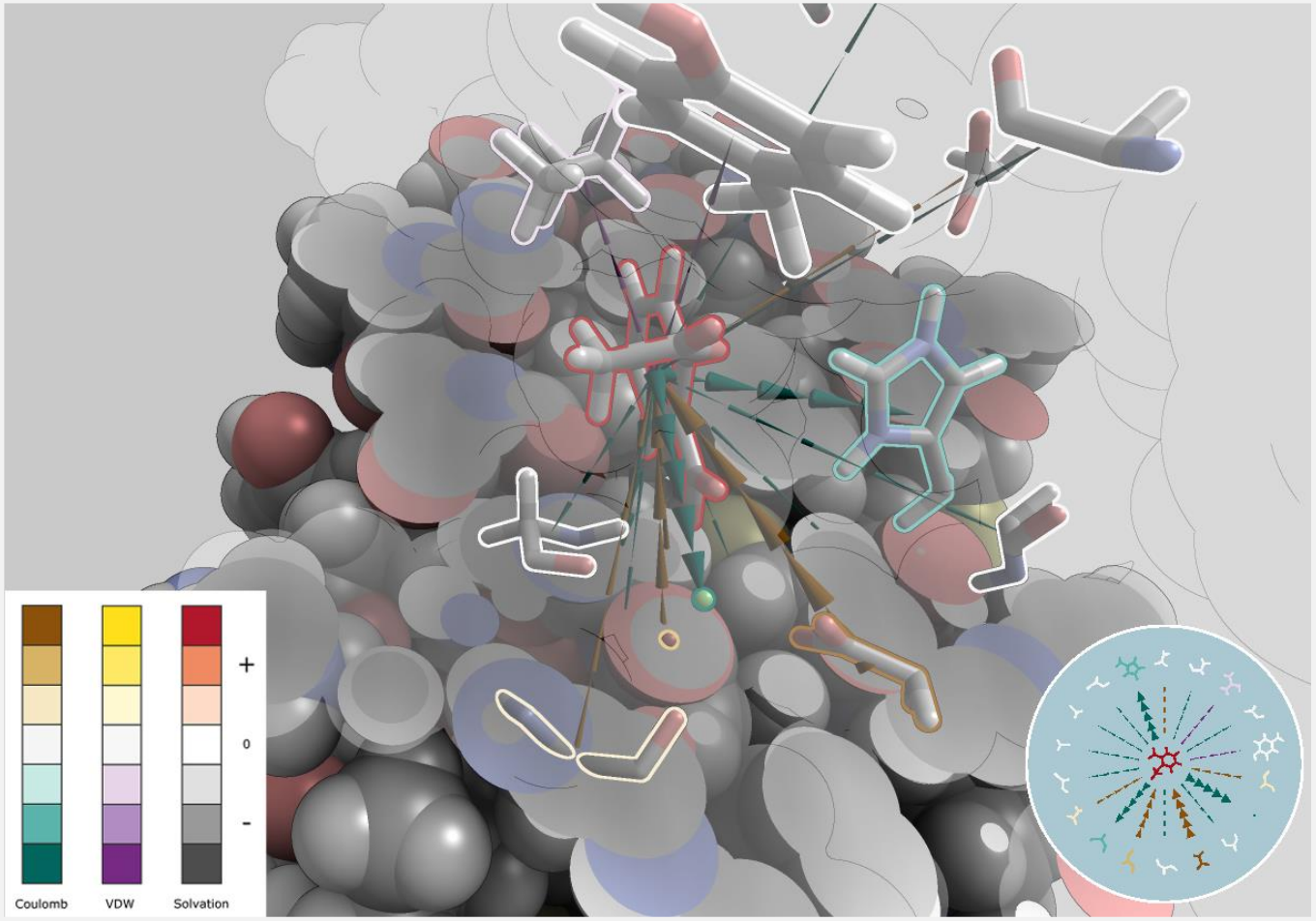
Zoom & Filter

- Visual illustration of energies
  - Type, strength & direction
    - Both in the 3D & 2D views
  - Individually toggle on/off
  - Different rendering modes
    - Provide room for energy coding



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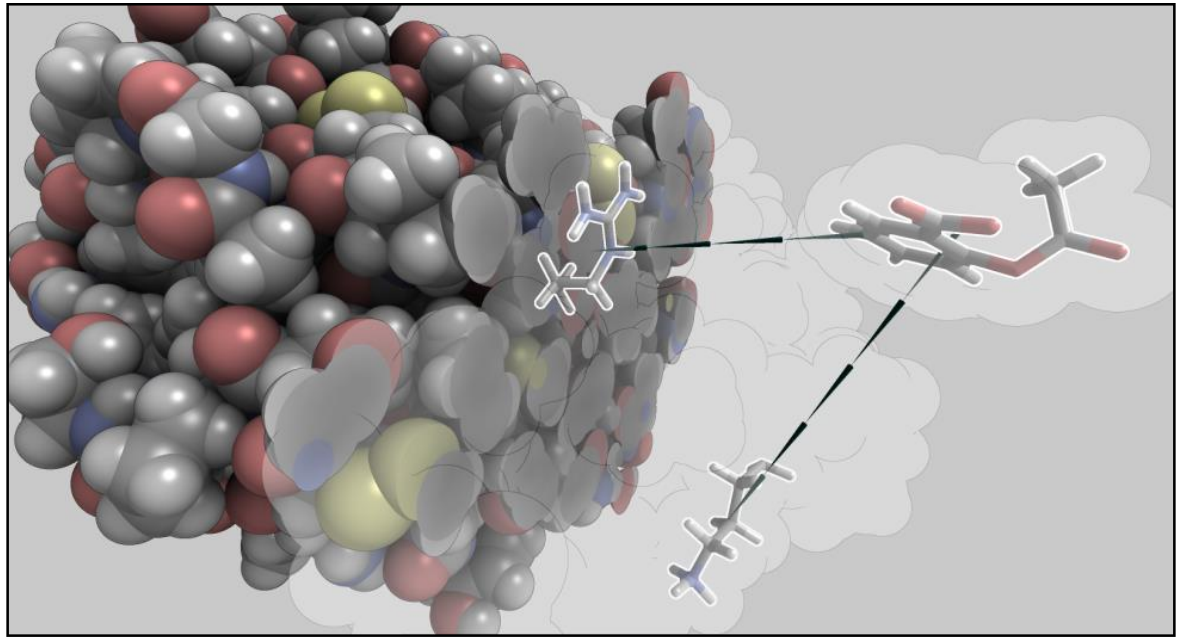
Zoom & Filter

- Context
  - Clipping plane
  - Semi-transparent visualization of the molecule
  - Different rendering types (space-filling, ball & sticks, licorice…)
- Selection
  - Residues



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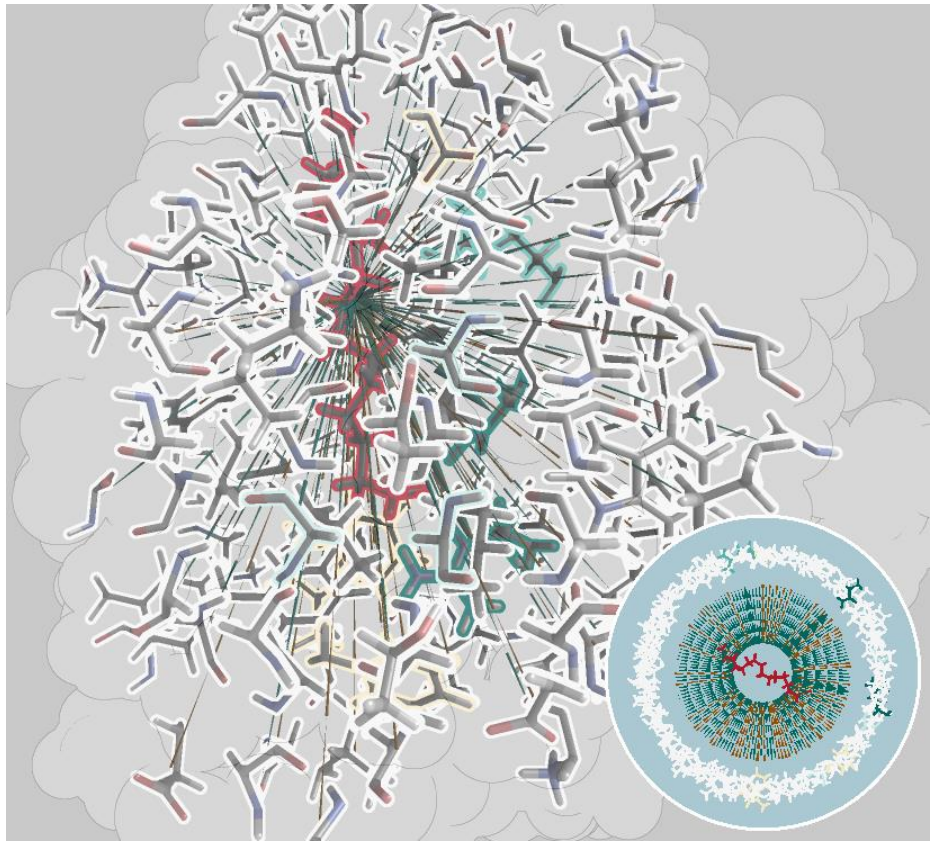
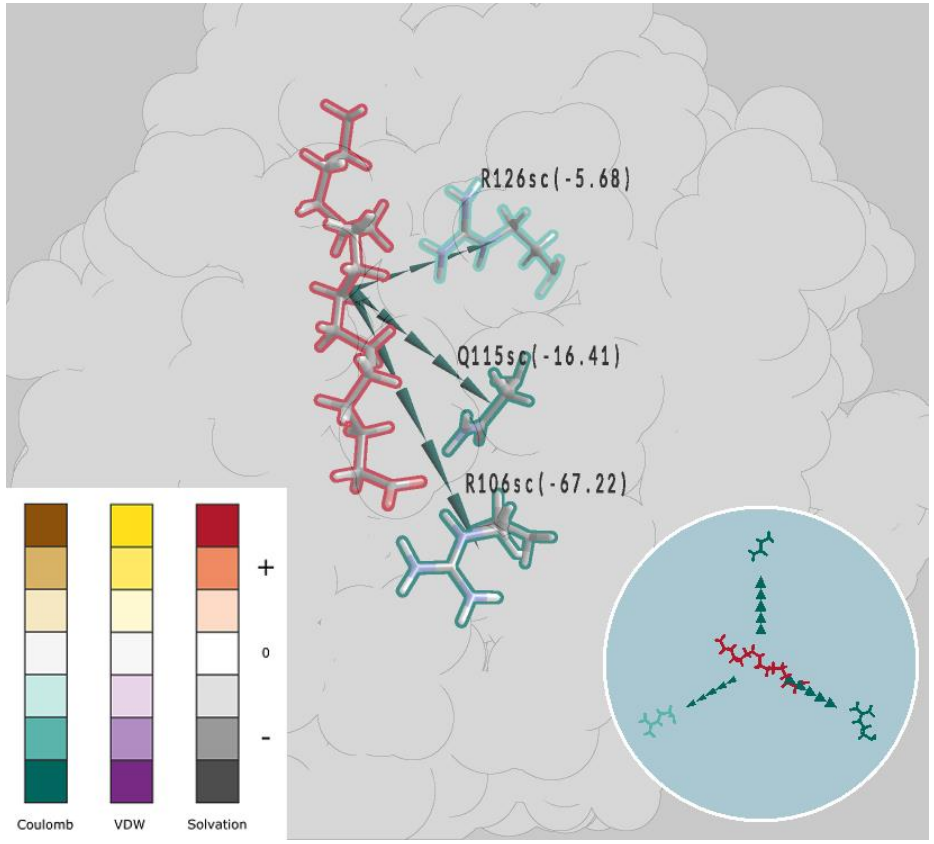
Zoom & Filter

- Initial exploration → Energy filtering to under -5kcal/mol
  - [Solves Q1]





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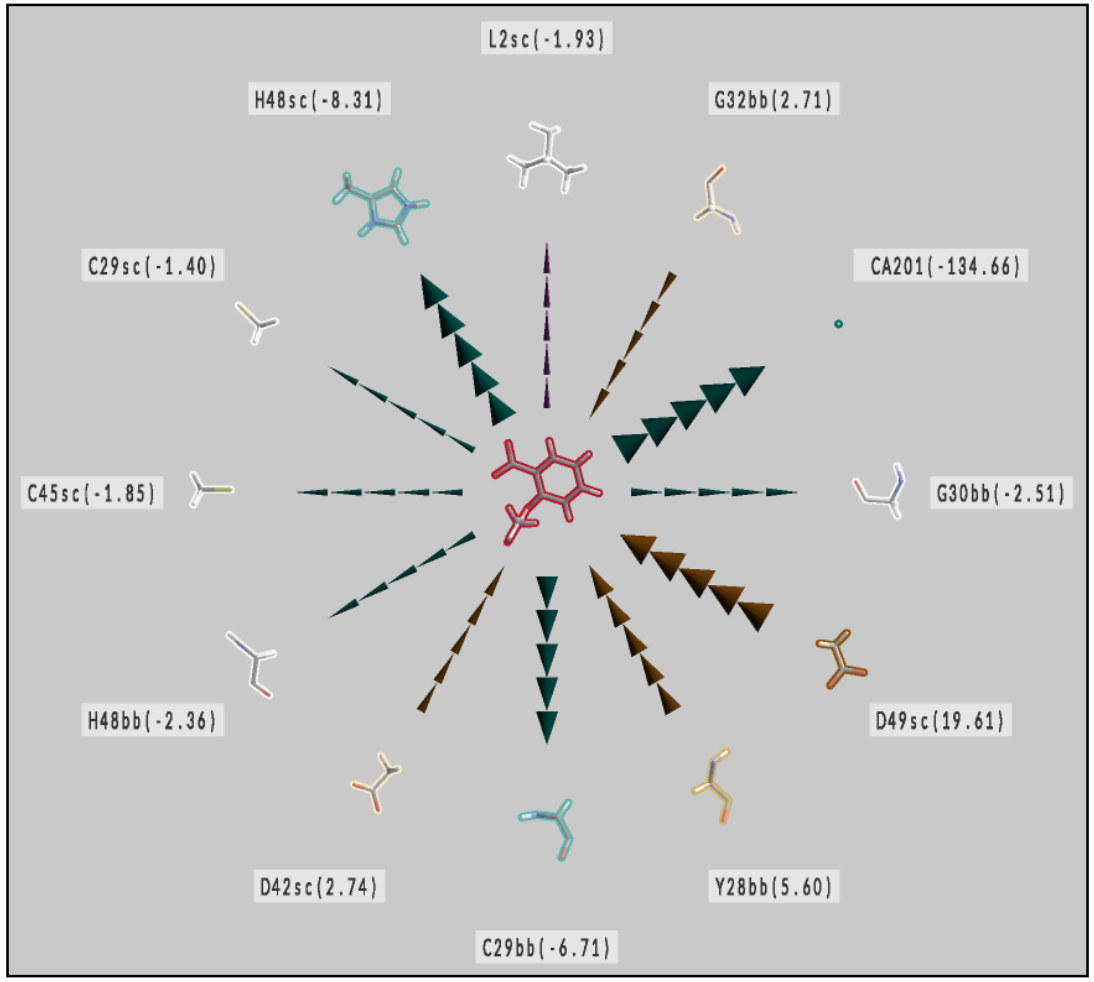
Details on demand

- Abstract view
  - Provides details on residues
  - Linked view
  - Coordinated with frame step



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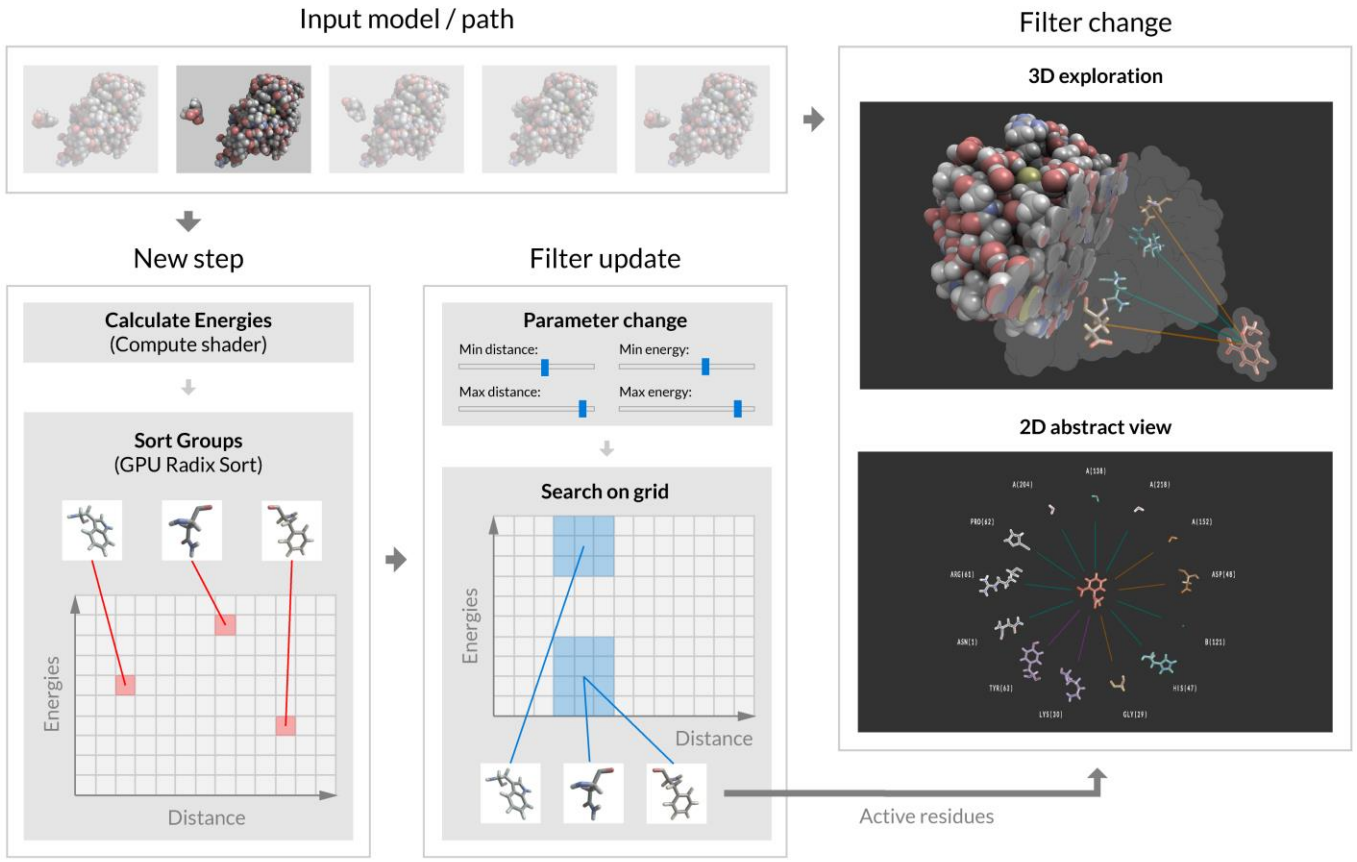
Implementation details

- Application workflow



Implementation details

- Energy model: $\Delta G_{bind} = E_{VDW} + E_{ele} + \Delta G_{sol}$
  - $E_{VDW} \rightarrow O(n)$
  - $E_{ele} \rightarrow O(n)$
  - $\Delta_{Gsol} \rightarrow O(n^2)$

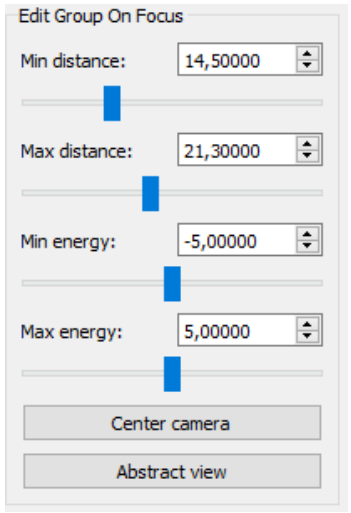
Implementation details

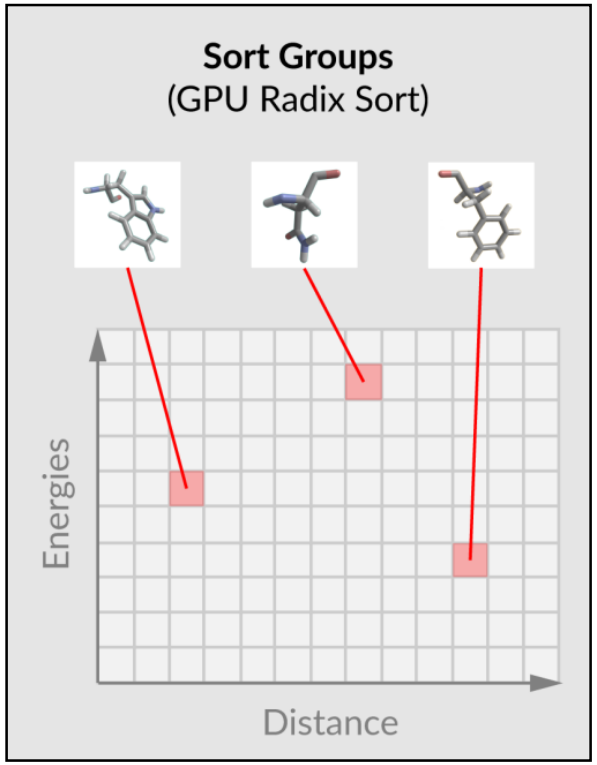
- Calculation
  - Δ_{Gsol} → Compute shader
    - Each thread computes 16 interactions
  - E_{VDW} and E_{ele} → Compute shader
    - Each thread computes the interaction between ligand and atom group

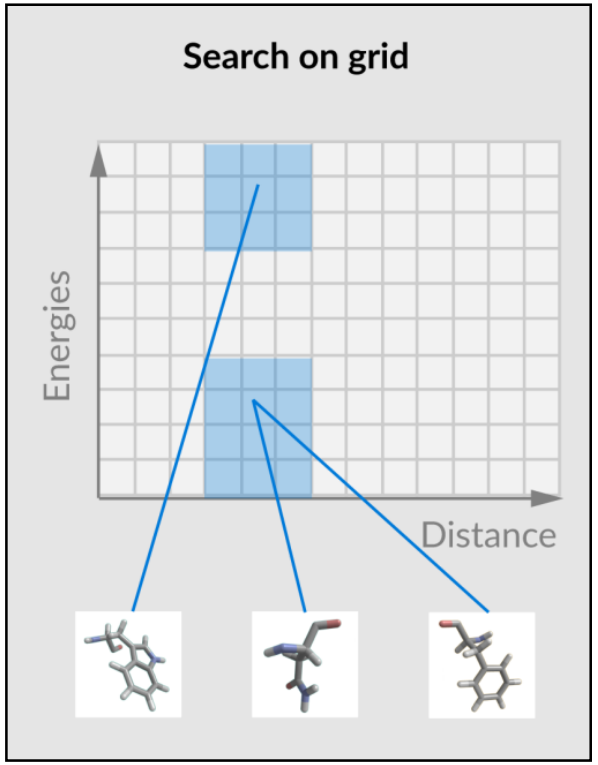
- More than 20 times per second for molecules up to 18k atoms (GTX 980)

Implementation details

- Filtering:
  - Energy types
  - Distance range [d_{min}, d_{Max}]
  - Energy range [-∞, emin-] [eMin+, + ∞]

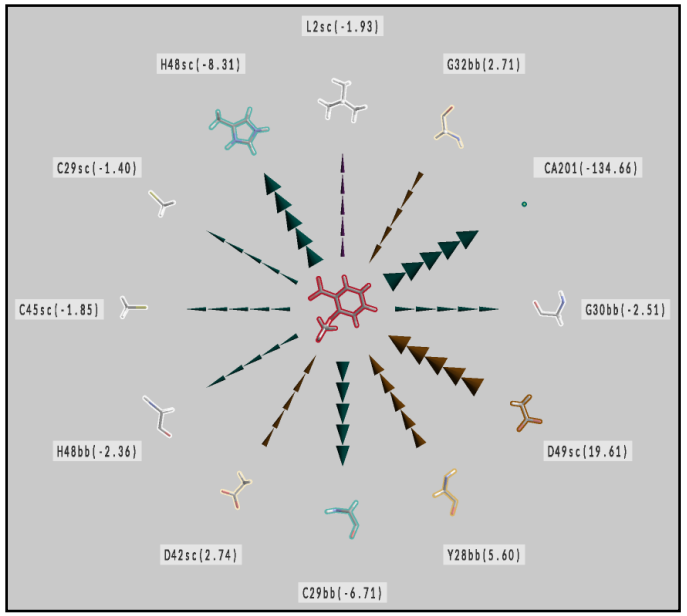






Implementation details

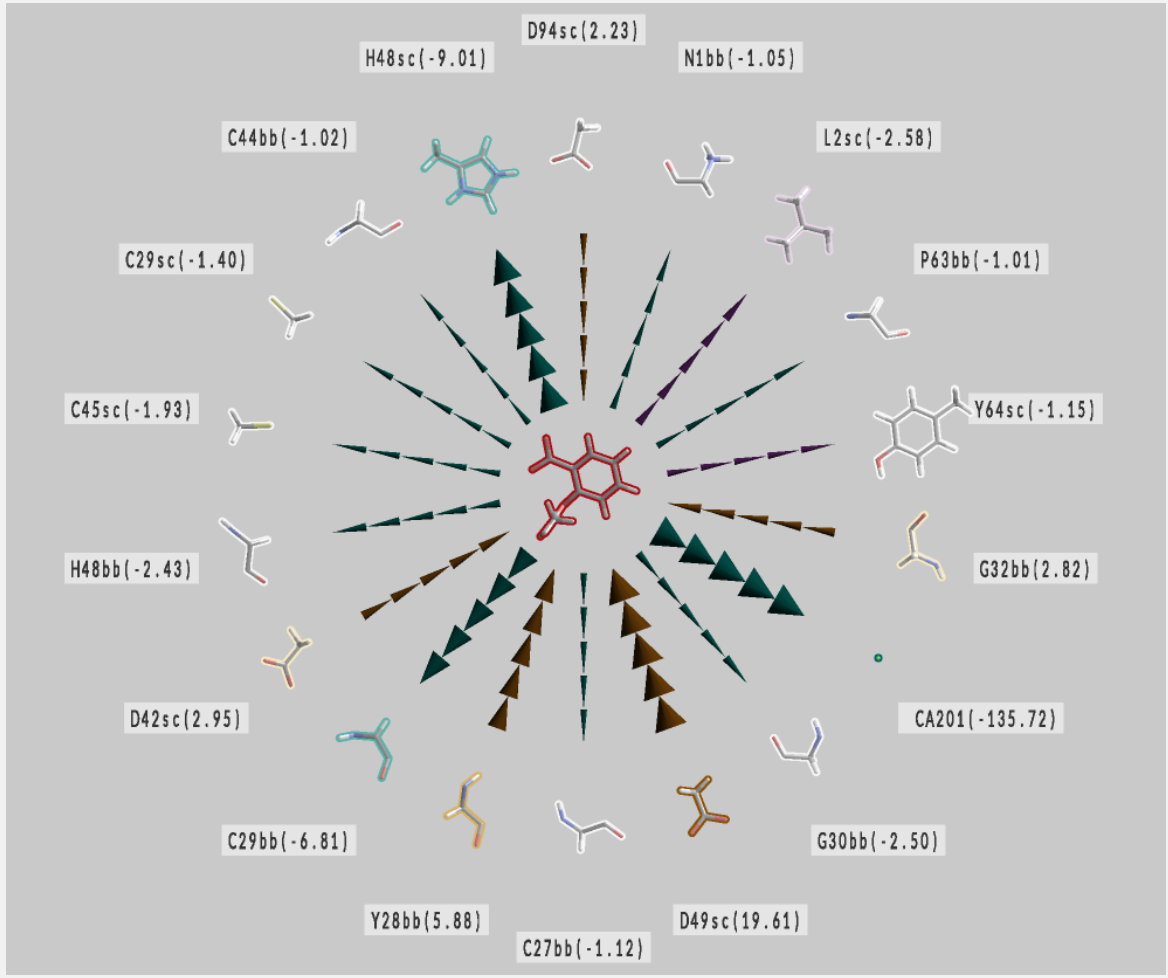
- Abstract view. Algorithm:
  - Calculate projection plane
  - Determine number of active groups
  - Divide plane around ligand in sectors
  - Project atom groups onto the plane and sort them clockwise
  - Render the groups in the sectors



- All groups are rendered maximizing their projected area (PCA)

Results

- Single conformation analysis
  - Binding energy analysis
    - [Solves Q2]



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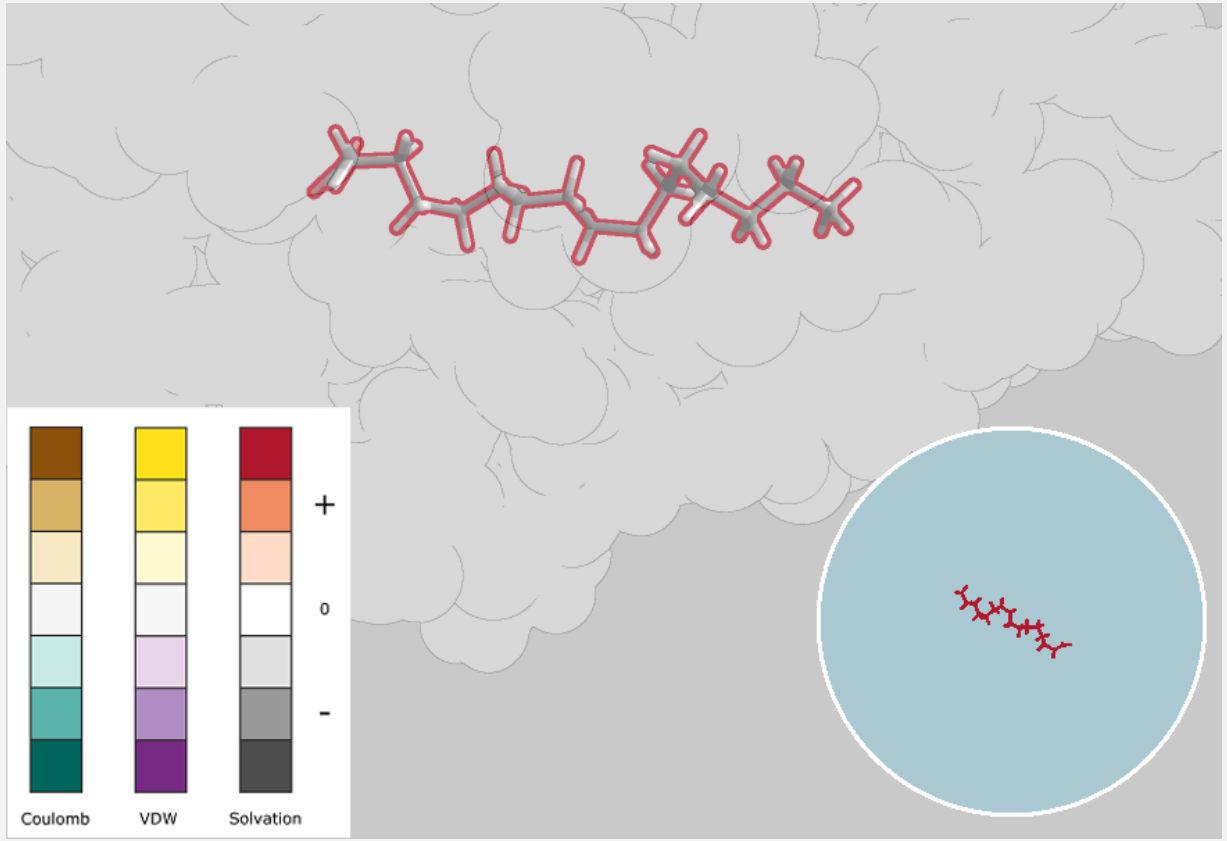
Results

- Single conformation analysis
  - Hypothesis testing: Palmitate's solvation term, when inside the protein, indicates that, contrary to the hypothesis, it does not favor binding.
    - Note the high energy value color coded in its silhouette
    - Being a fatty molecule, the expected value would be low (grey)



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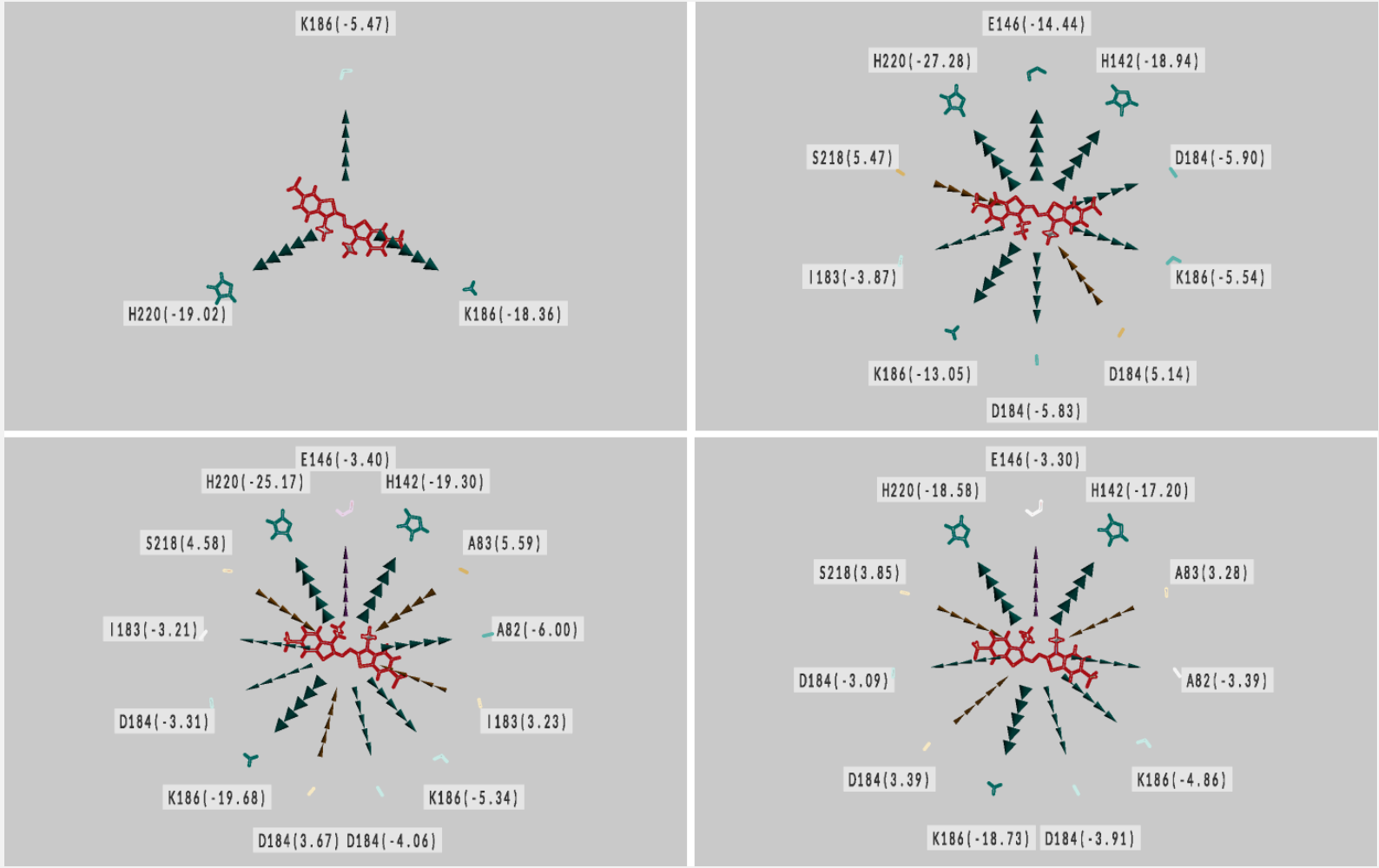
Results

- Trajectory analysis
  - Using the abstract view
    - Evaluates stability
    - [Solves Q2]



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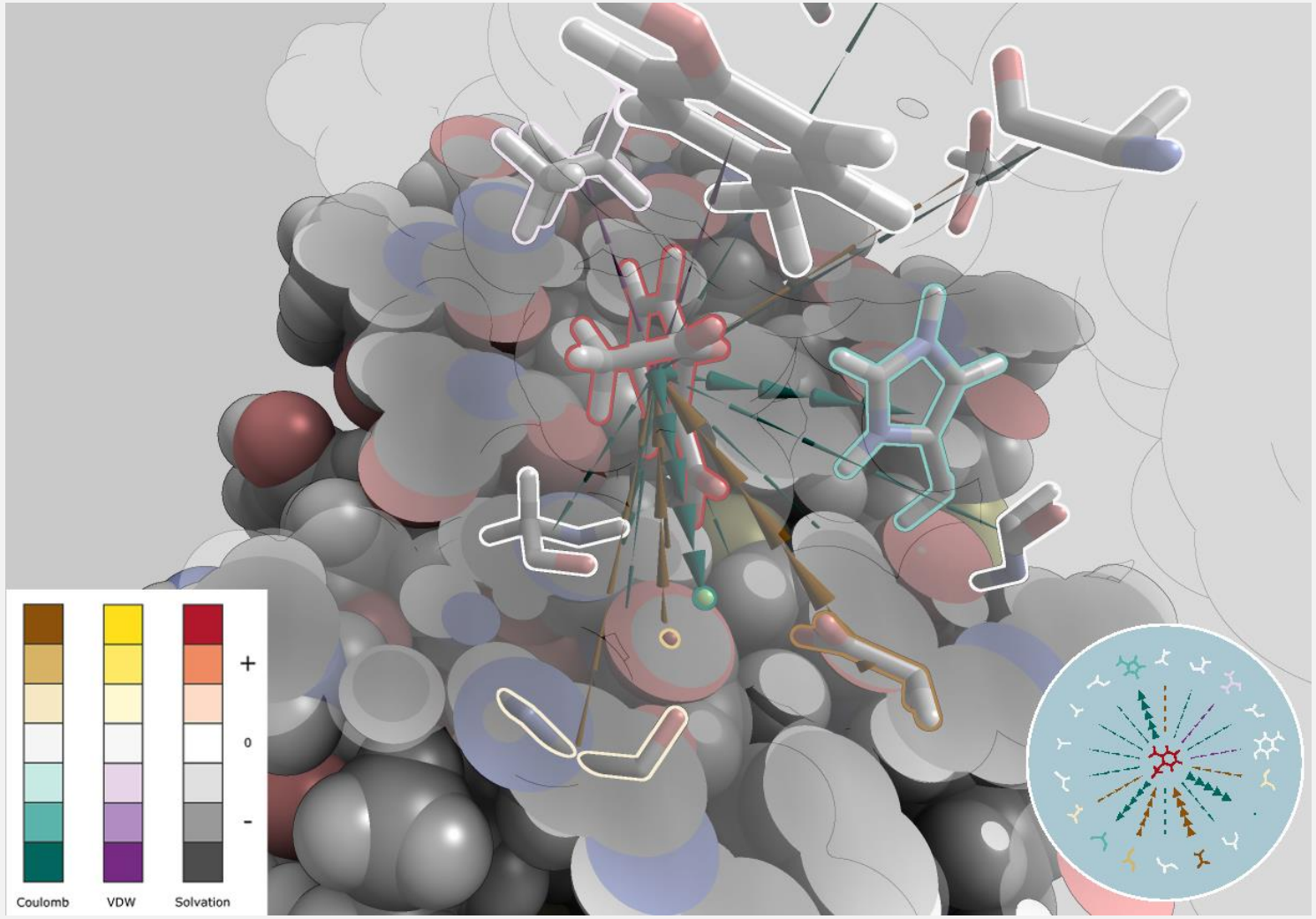
Results

- Trajectory analysis
  - Close-view binding energy analysis
    - Identifies strong interactions
    - [Solves Q2]



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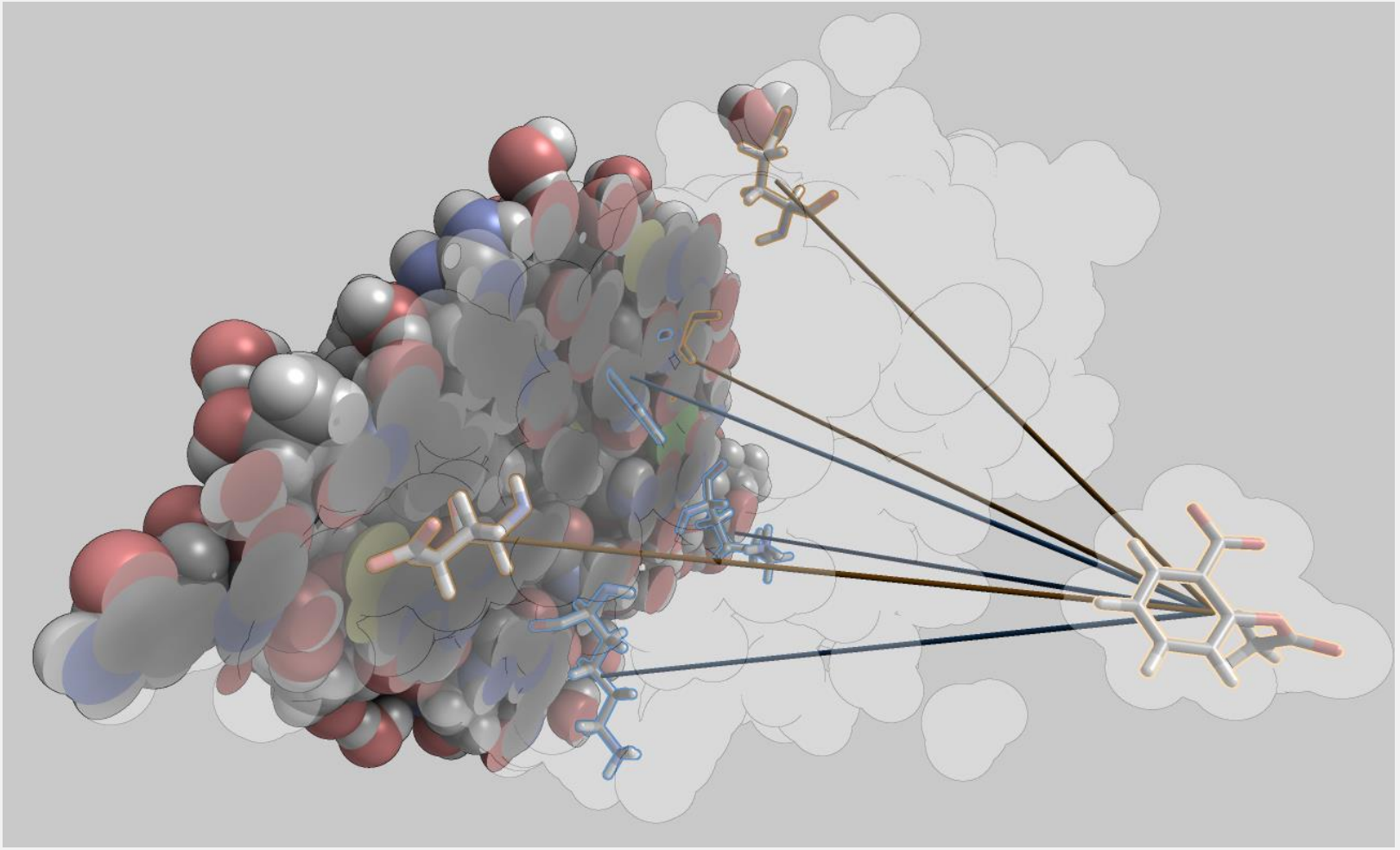
Results

- Trajectory analysis
  - Filter by distances
  - Distant interactions identification



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Evaluation

- Shown to two different experts (protein engineering and computer aided drug design)
  - Very useful
  - Suitable for protein engineering tasks
  - Could be used for enzyme engineering
  - Data presentation
  - “Very intuitive”
  - Semi-transparent context “very interesting”
  - Cones permit easy identification of interaction forces and direction

Conclusions & Future Work

- New visualization application for binding forces analysis
  - Residue-level
- Facilitates gaining understanding on docking simulations
  - Explanations on the interacting residues
- Identifies strong actors
- Identifies distant binding energies

Conclusions & Future Work

- Support full interactive analysis
  - In contrast to Maestro or PLIP
- Show full path
  - Other tools only single steps
- Linked views provides 2D and 3D visualizations at the same time

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