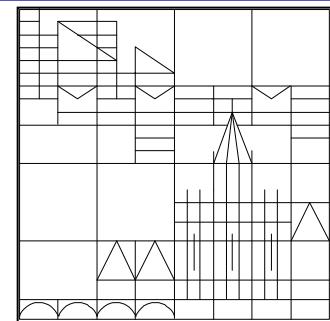




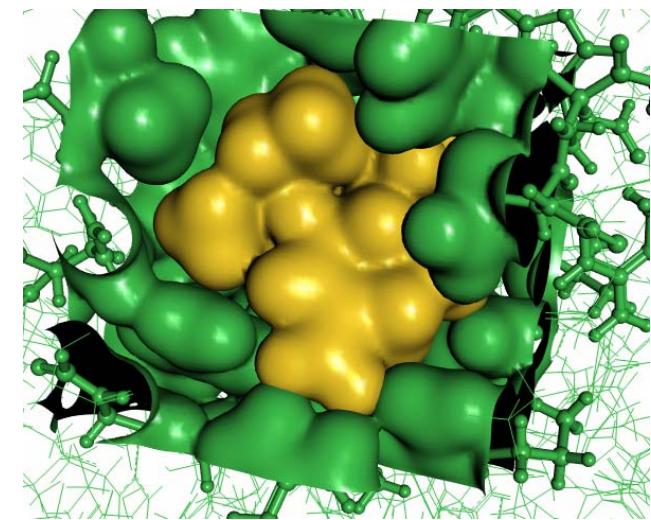
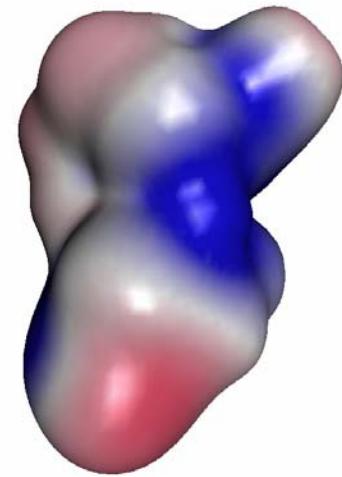
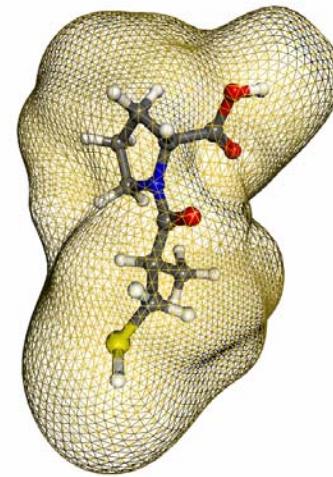
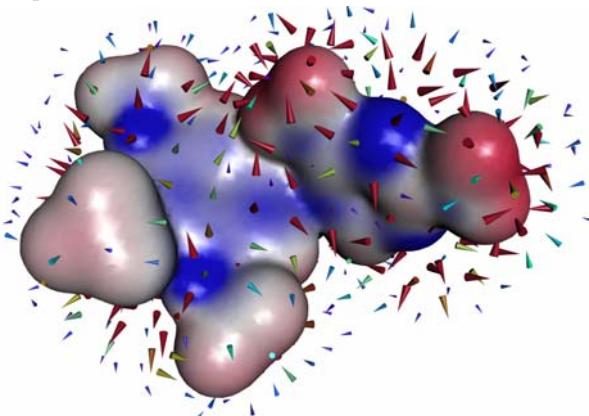
Visualization and Analysis of ParaSurf Output

Dr. Thomas E. Exner
MolCad GmbH and
Fachbereich Chemie
Universität Konstanz



Outline

- Introduction
- Visualization of ParaSurf Data
- Lipophilicity
- Neuraminidase Inhibitors
- Neuraminidase-Oseltamivir Complex



<http://www.molcad.de>

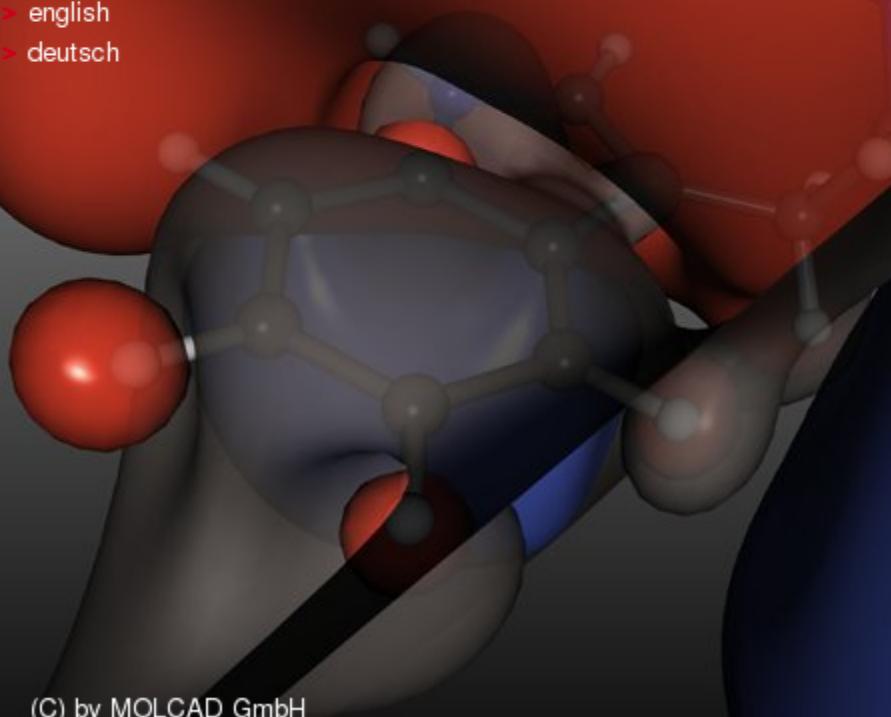


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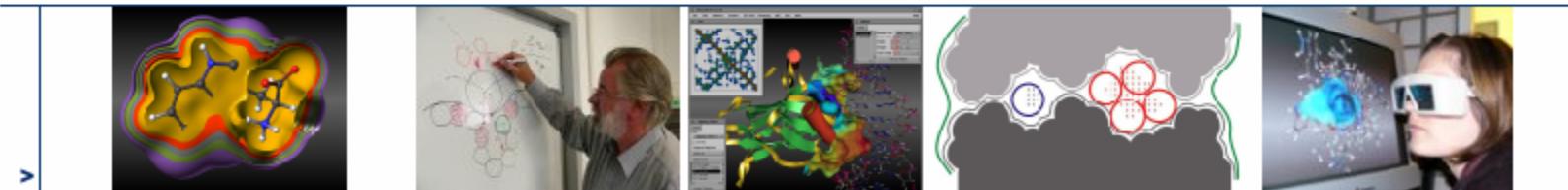
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- > training
- > publications

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- ◆ software development
- ◆ service | consulting | training
- ◆ design of molecular scenarios for publications | media
- ◆ mediating between universities and industry

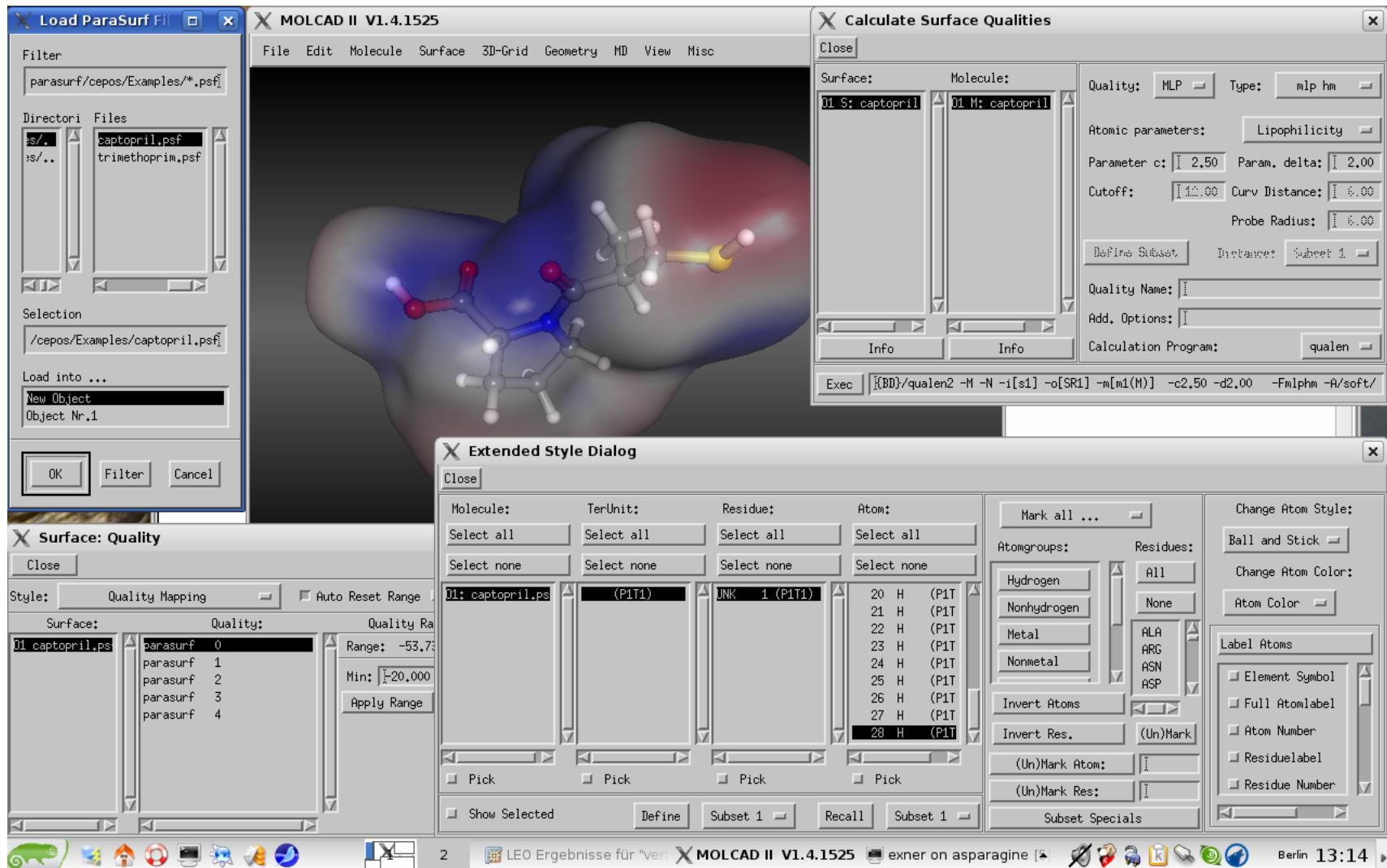


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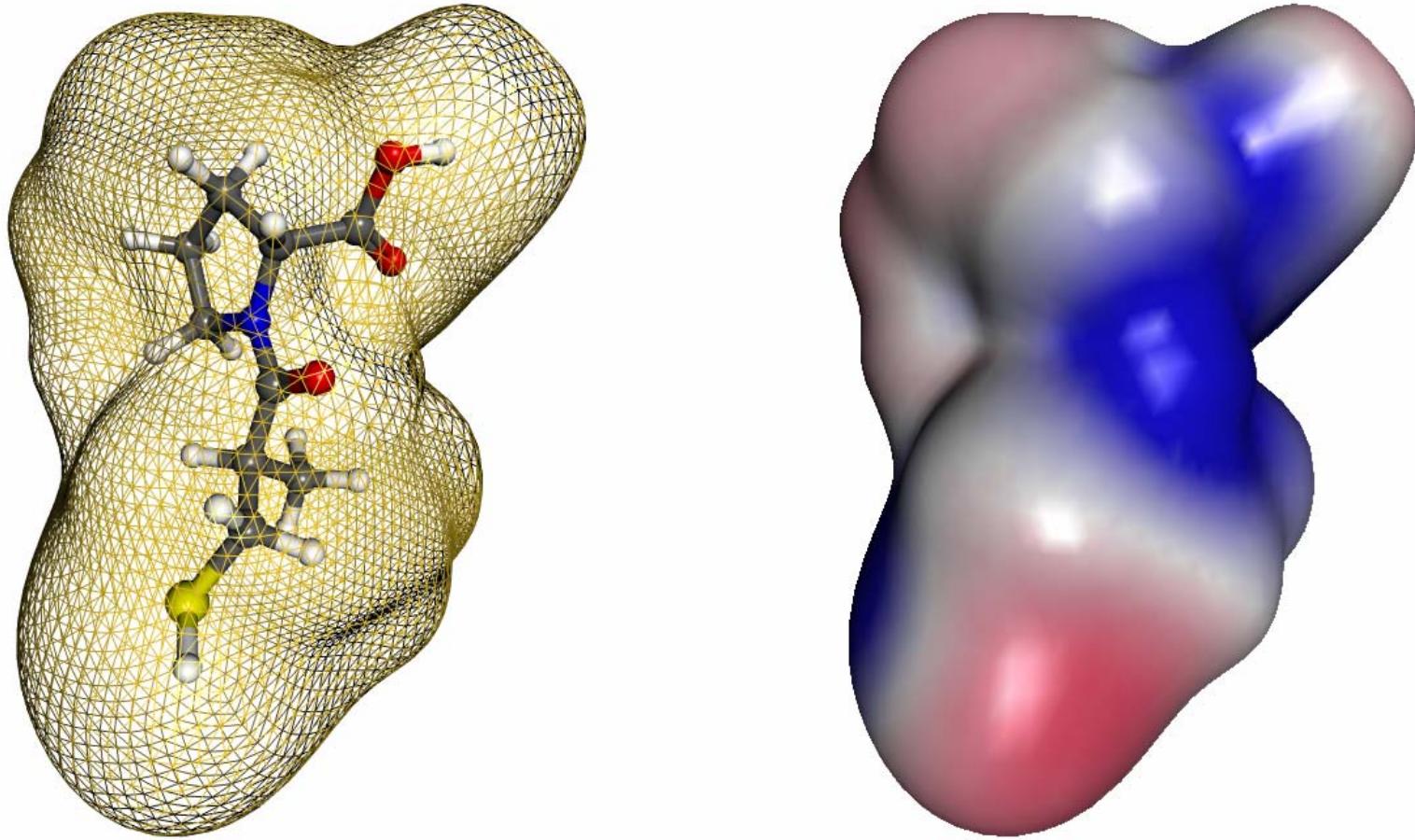
MolNet

- Prof. Jürgen Brickmann (Darmstadt)
- Dr. Thomas Exner (Konstanz)
- Prof. Stefan Kast (Dortmund)
- Prof. Dirk Zahn (Erlangen)
- Prof. Heiden Moeckel (Heidelberg)
- Prof. Wolfgang Heiden (Siegen)



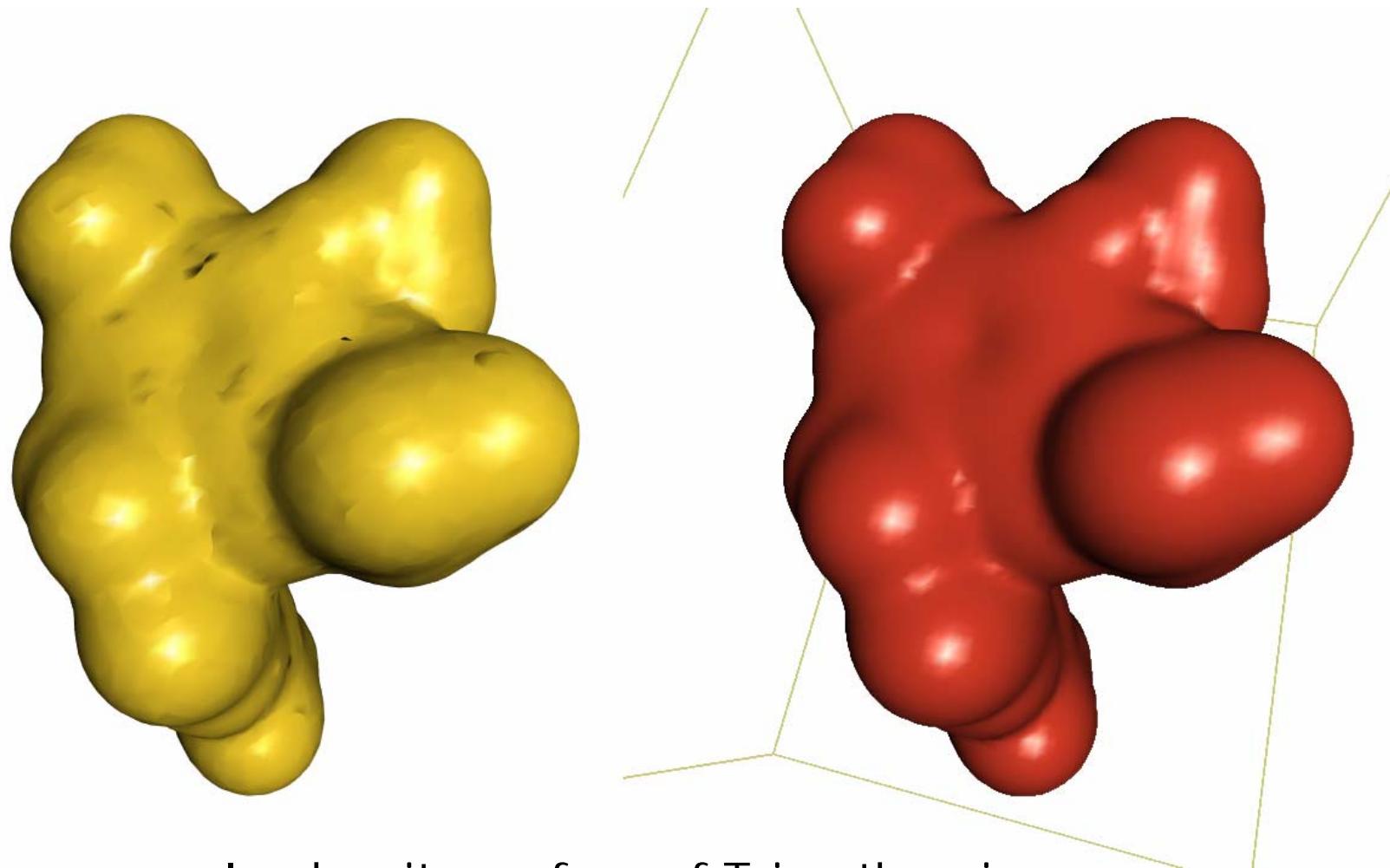
ParaSurf Output

ParaSurf Surfaces



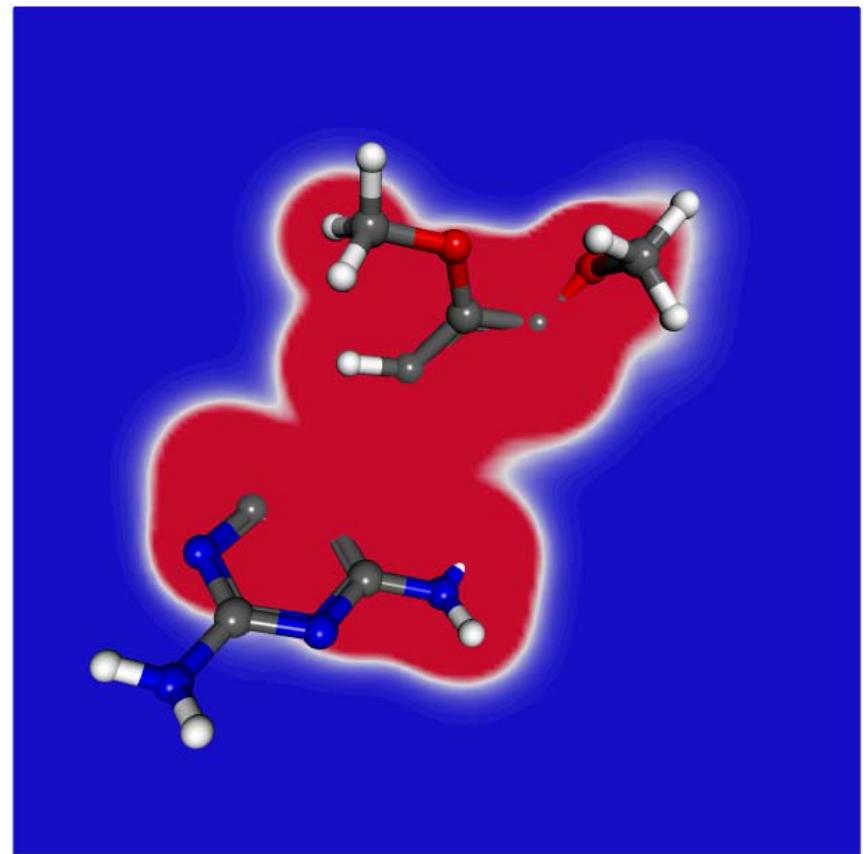
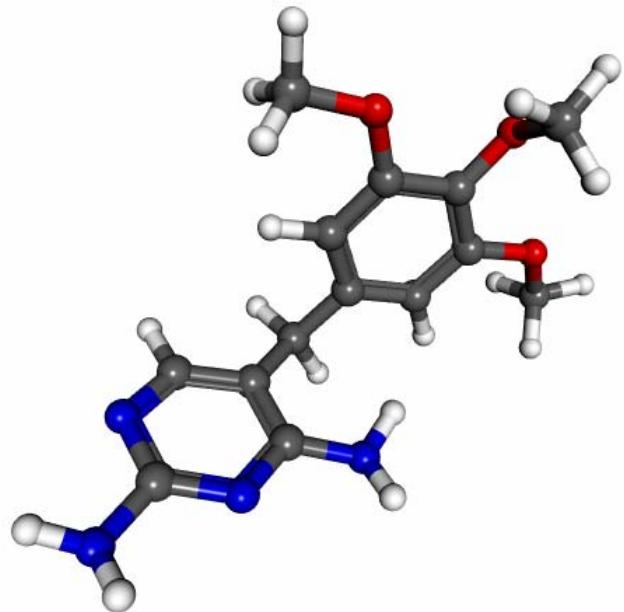
Spherical-harmonic approximation of a
shrink-wrap isodensity surface of Captopril

Marching Cube

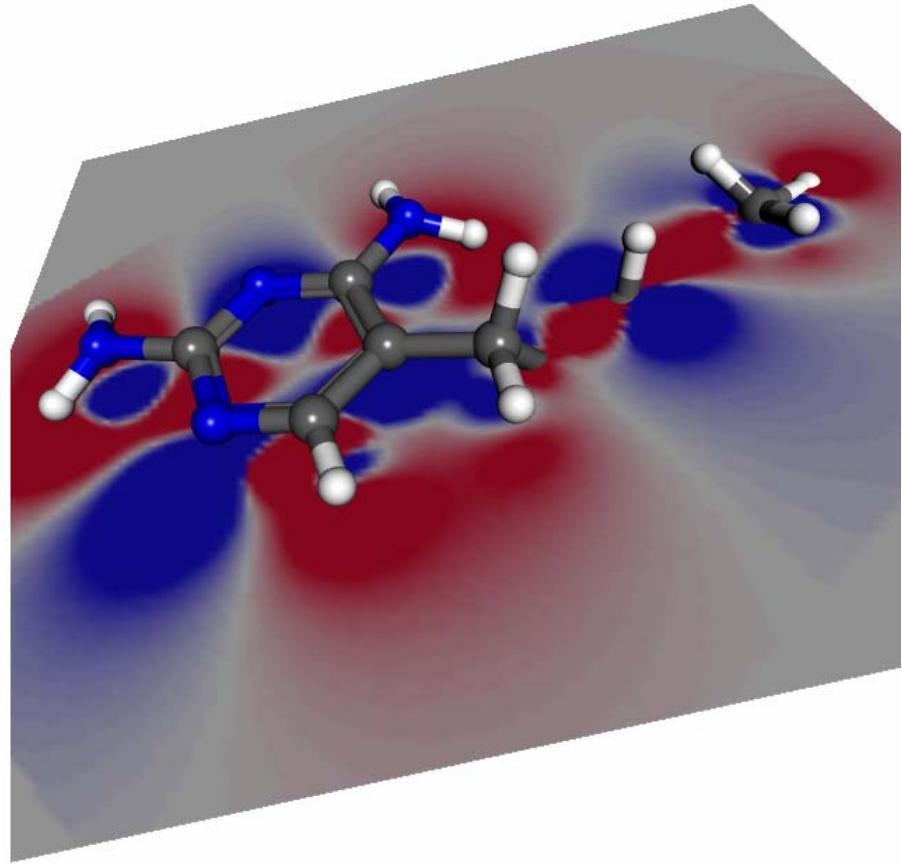
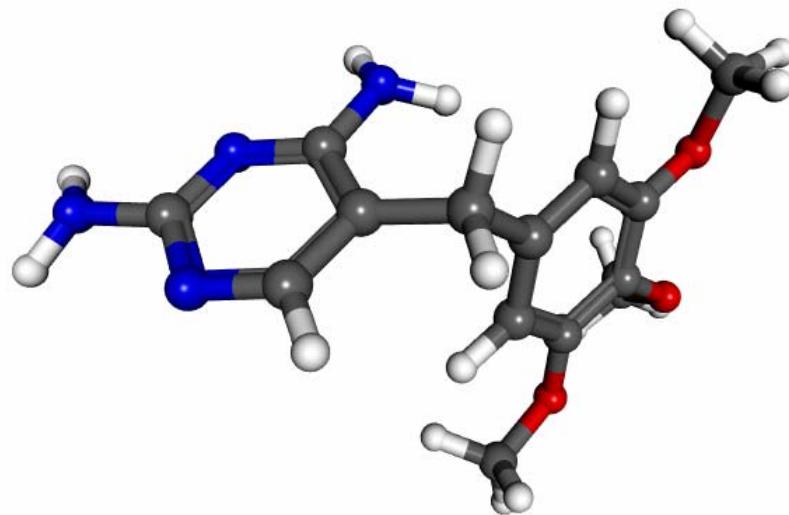


Isodensity surface of Trimethoprim

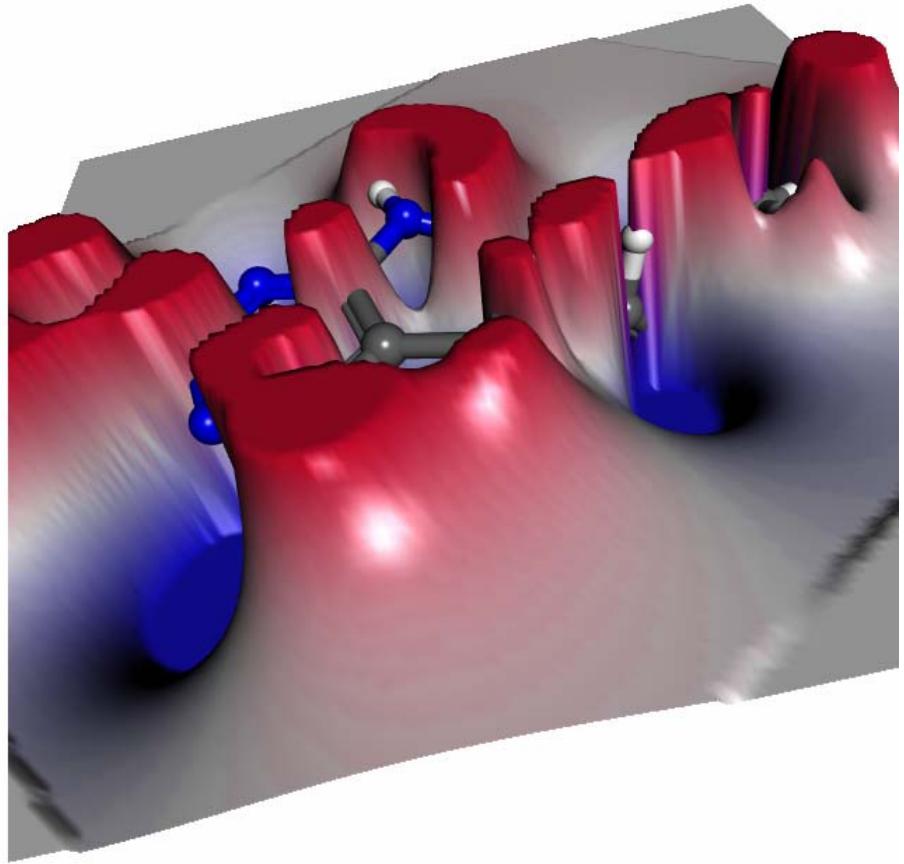
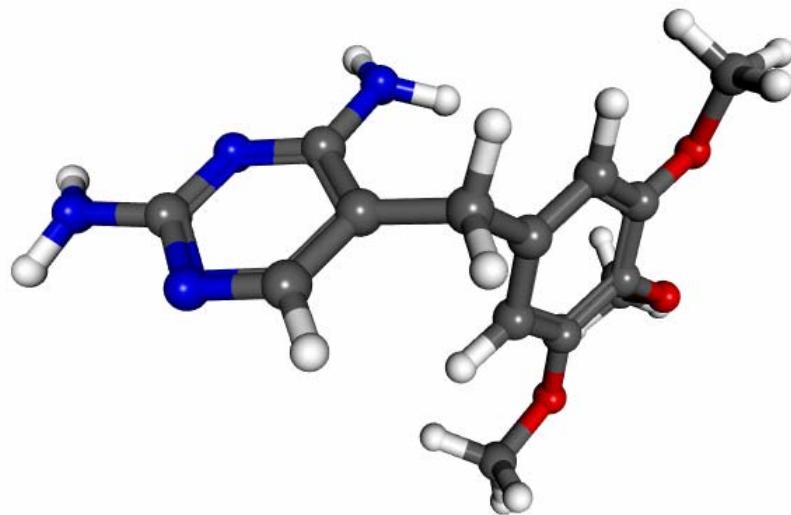
Slicing Plane



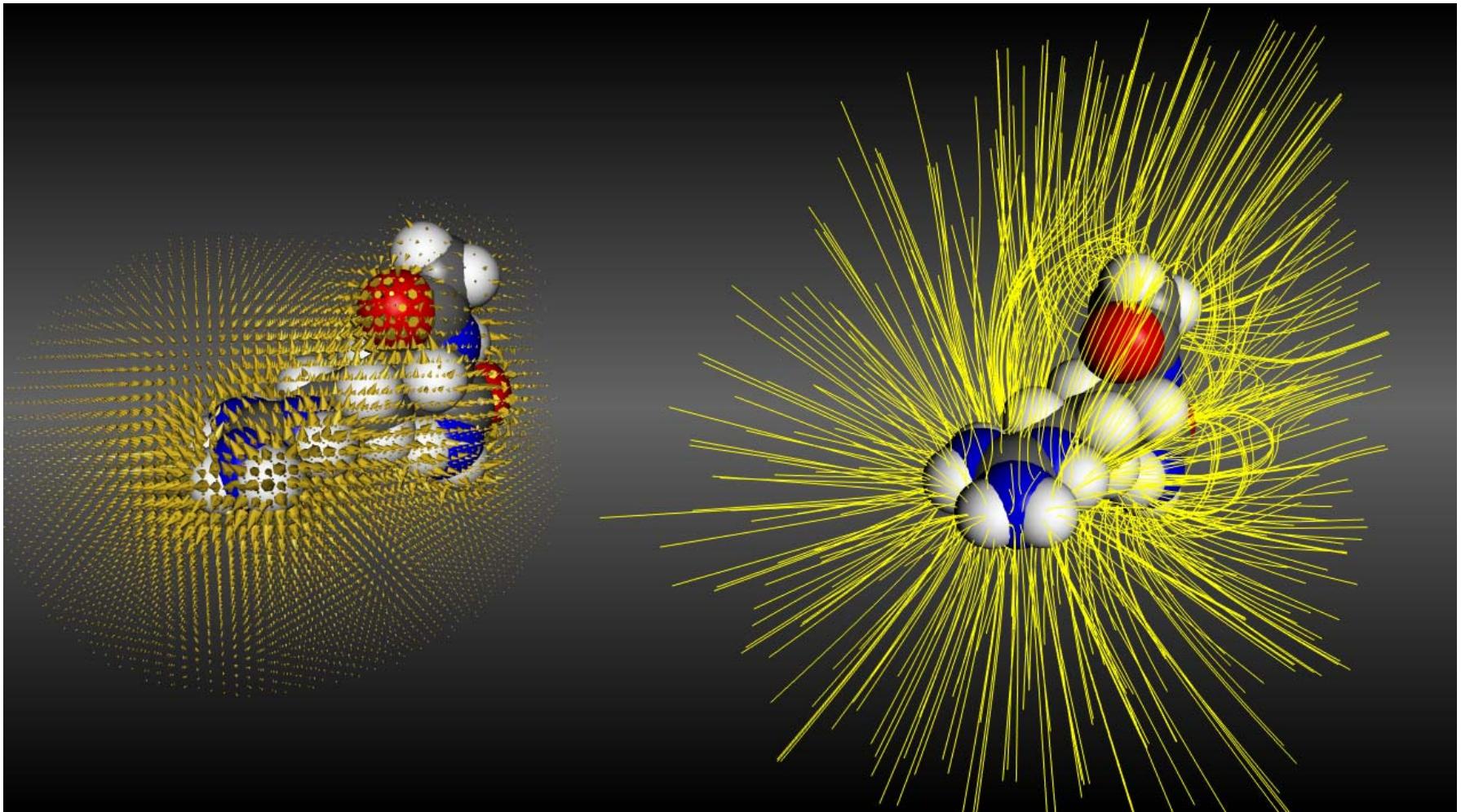
Slicing Plane – Electrostatic Potential



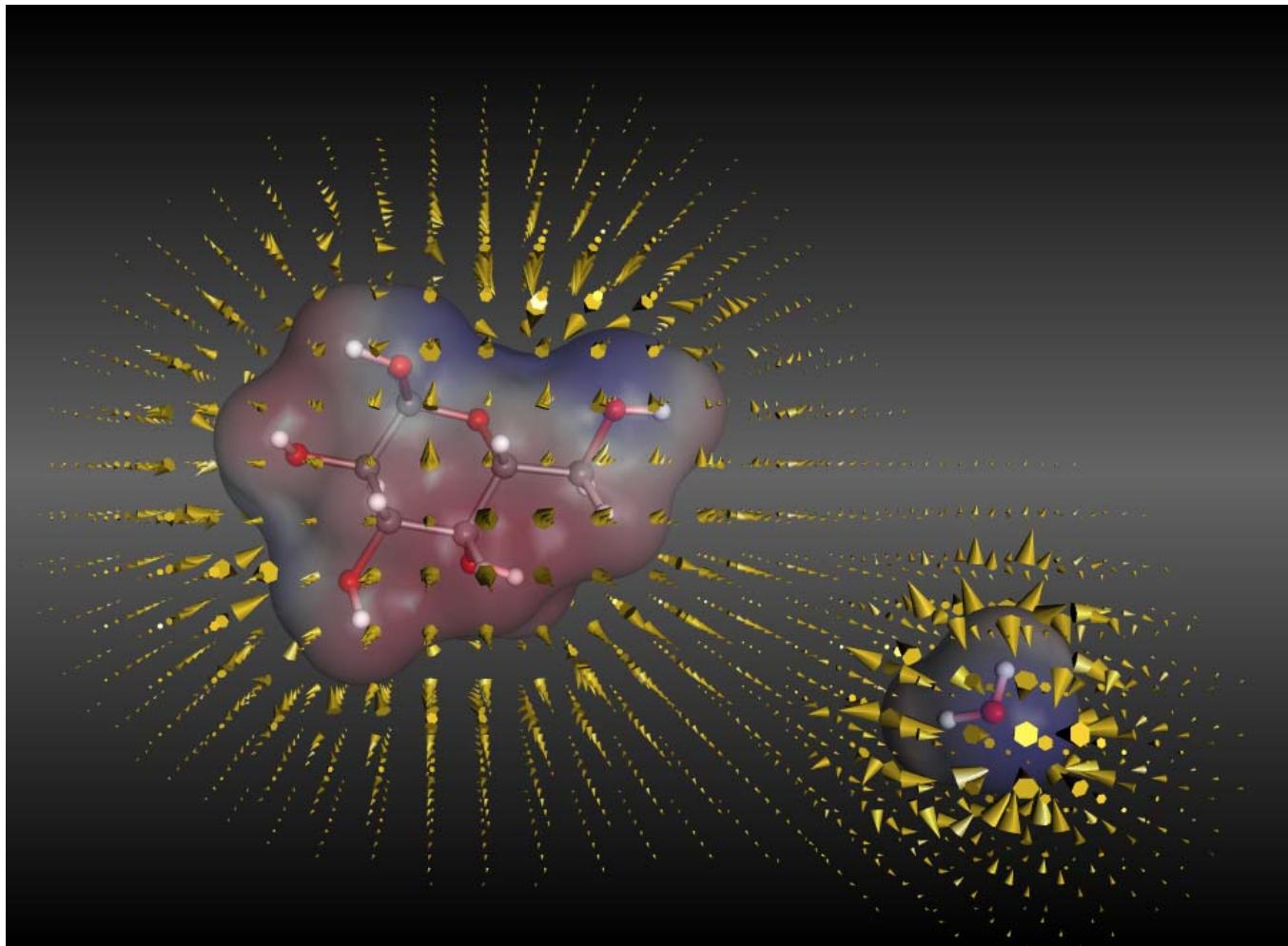
3D Slicing Plane



Electrostatic Field – Field Lines



Interactive Electrostatic Field



Lipophilicity

Lipophilicity – Atom Types

- $\log P$ is calculated as sum of atomic contributions

$$\log P = \sum_i f_i$$

- 120 atom types based on the definition of Ghose and Crippen
- Buried atoms contribute to the same degree as surface atoms

Ghose, A.K. and Crippen, G.M., J. Comput. Chem. 7 (1986) 565.

Heiden-Moeckel Function

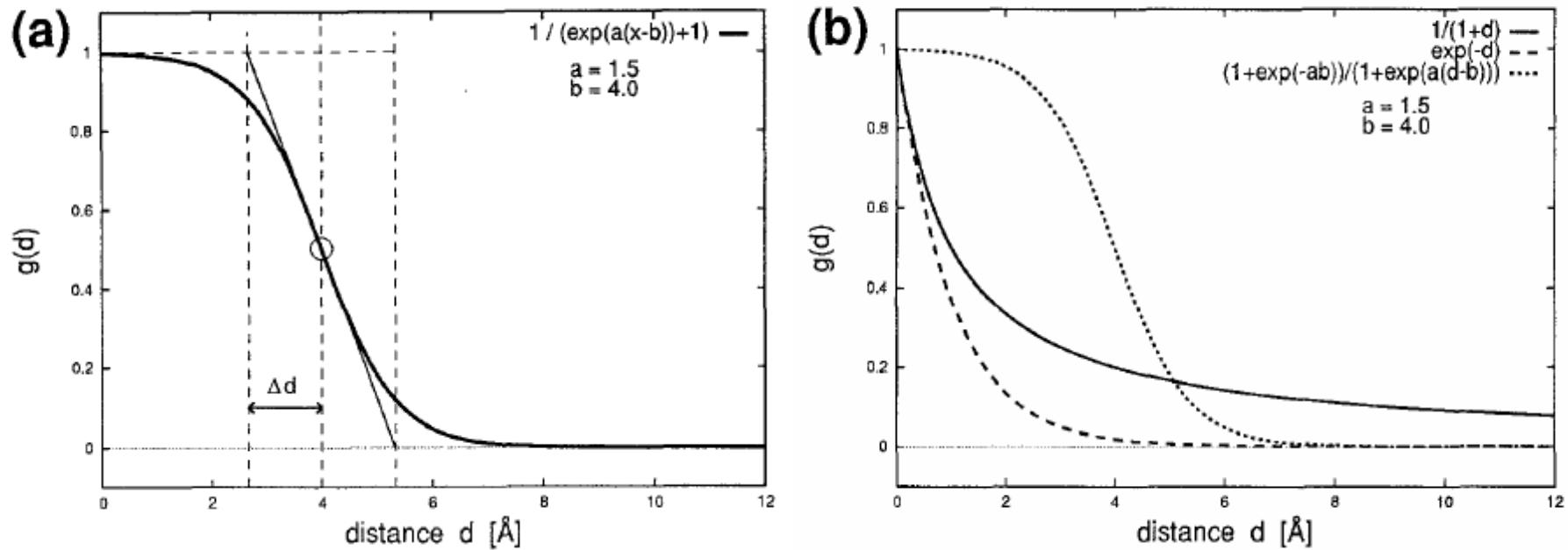


Fig. 3. (a) Fermi type distance function $g(d)$. The function decays from values $d \approx 1$ to $d \approx 0$ within a distance interval of $2\Delta d$. $\Delta d = 2/a \approx 1.33$ Å. (b) Three different distance functions $g(d)$ are used for MLP definitions.

Heiden, W.; Moeckel, G.; and Brickmann, J., J. Comput.-Aided Mol. Des. 7 (1993) 503

Lipophilicity – MolFESD

■ Molecular Free Energy Surface Density

$$\log P = -\frac{\Delta\Delta G_{solv}}{2.303RT} = \alpha \sum_{l=1}^{120} h_l \sum_{j=0}^1 a_{lj} c_j + \beta S + \gamma V$$

- Based on the same 120 atom types
- Contribution of each atom to molecular surface is calculated
- Summation of surface patches
- Parameterization with GRID's hydrophobic probe and experimental $\log P$ values

(1) Jäger, R.; Schmidt, F., Schilling, B., and Brickmann, J., J. Comput.-Aided Mol. Des. 14 (2000) 631. (2) Zerara, M., Brickmann, J., Kretschmer, R., and Exner, T.E., J. Comput.-Aided Mol. Des. 23 (2009) 105

Lipophilicity – ParaSurf

■ Surface integral

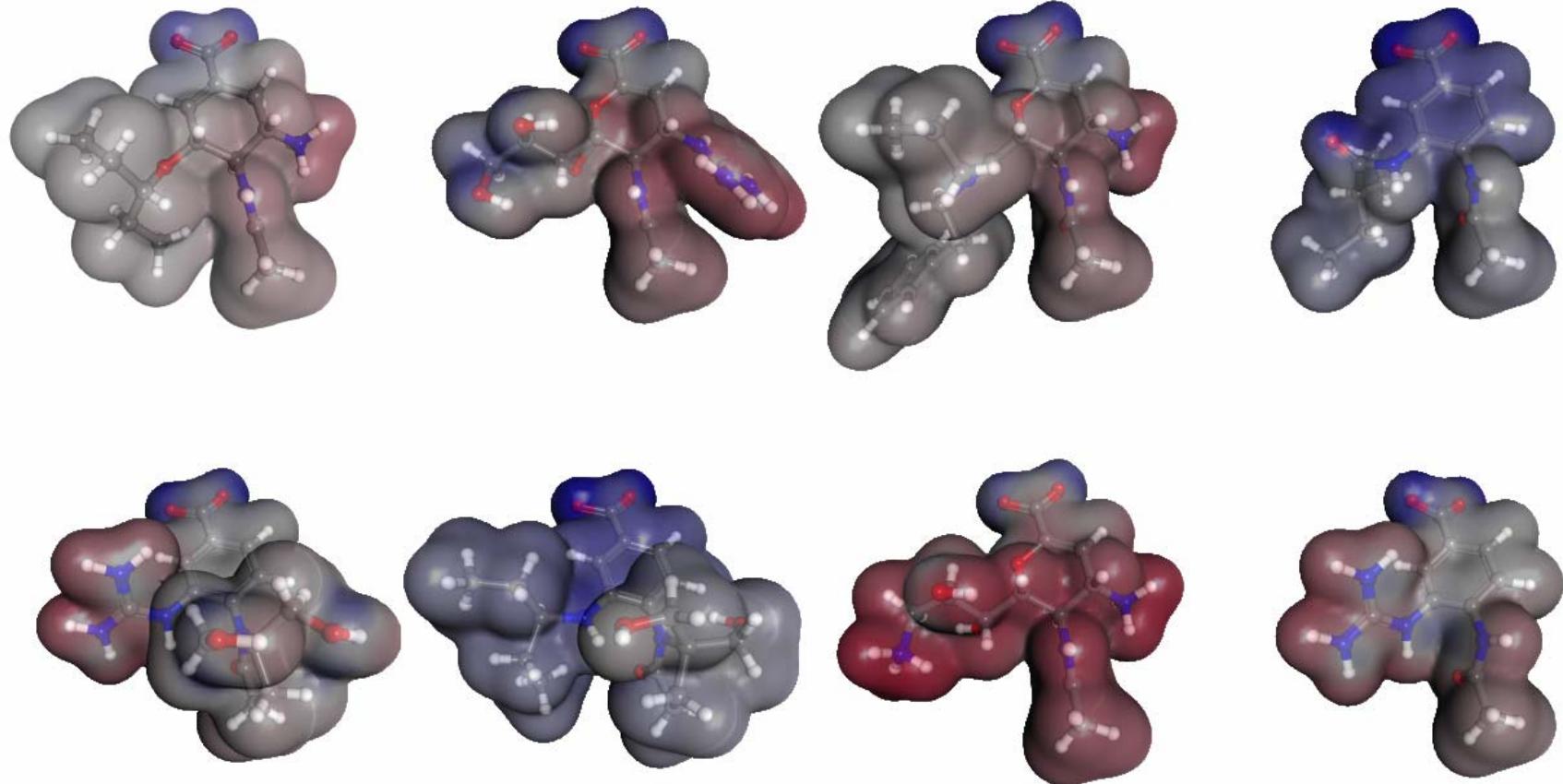
$$P = \int_O f(l_1, l_2, \dots, l_n) dO \approx \sum_{i=1}^{ntri} f(l_1^i, l_2^i, \dots, l_n^i) A^i$$

- Based on local properties on the surface: MEP, IE_{loc}, AE_{loc}, Pol_{loc}, Ene_{loc}, HARD_{loc}, FN
- Binning of properties

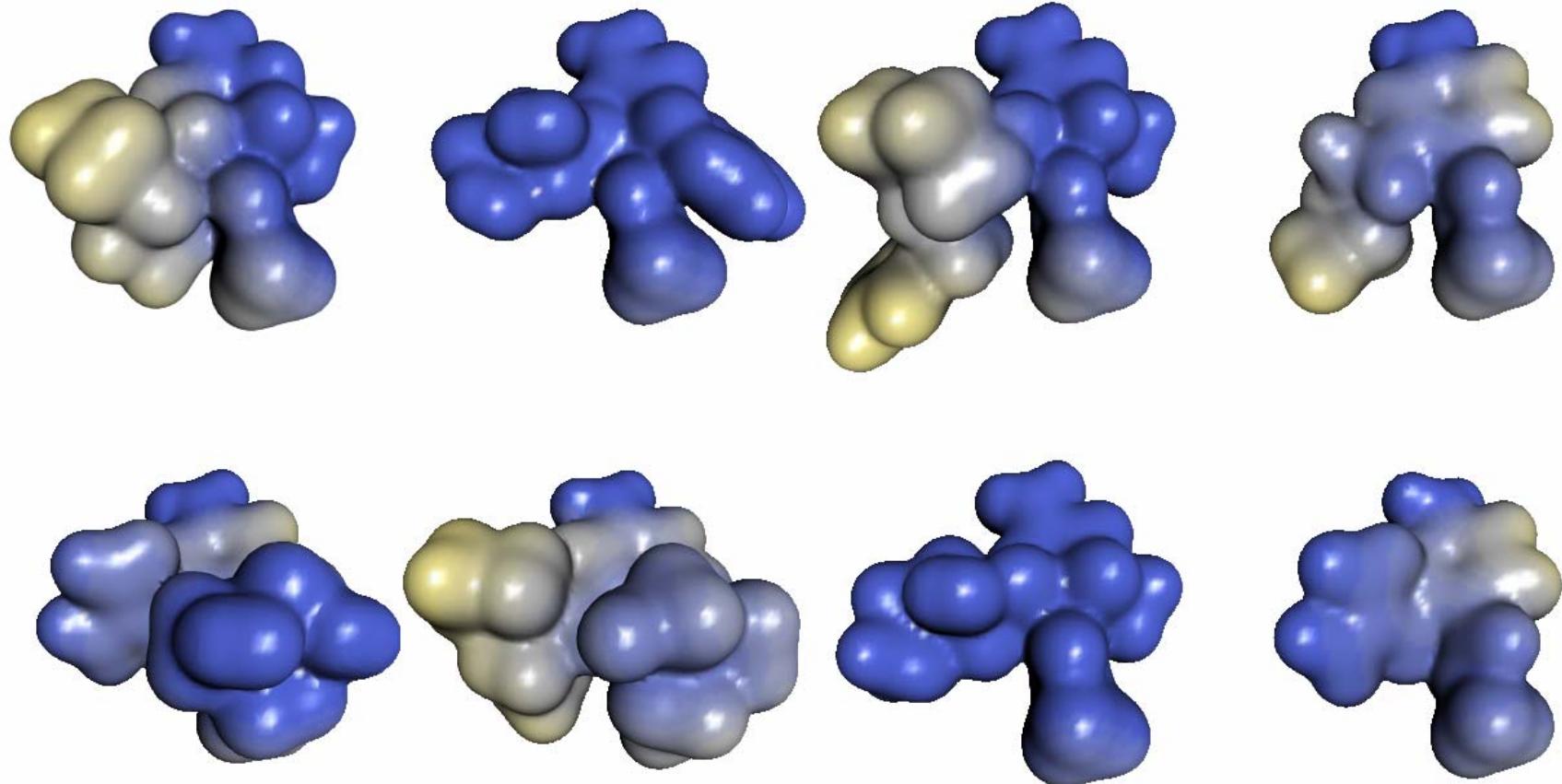
Christian Kramer, Ch., Beck, B., and Clark, T., J. Chem. Inf. Model. (2010)
10.1021/ci900431f

Similarity - Ligand Based

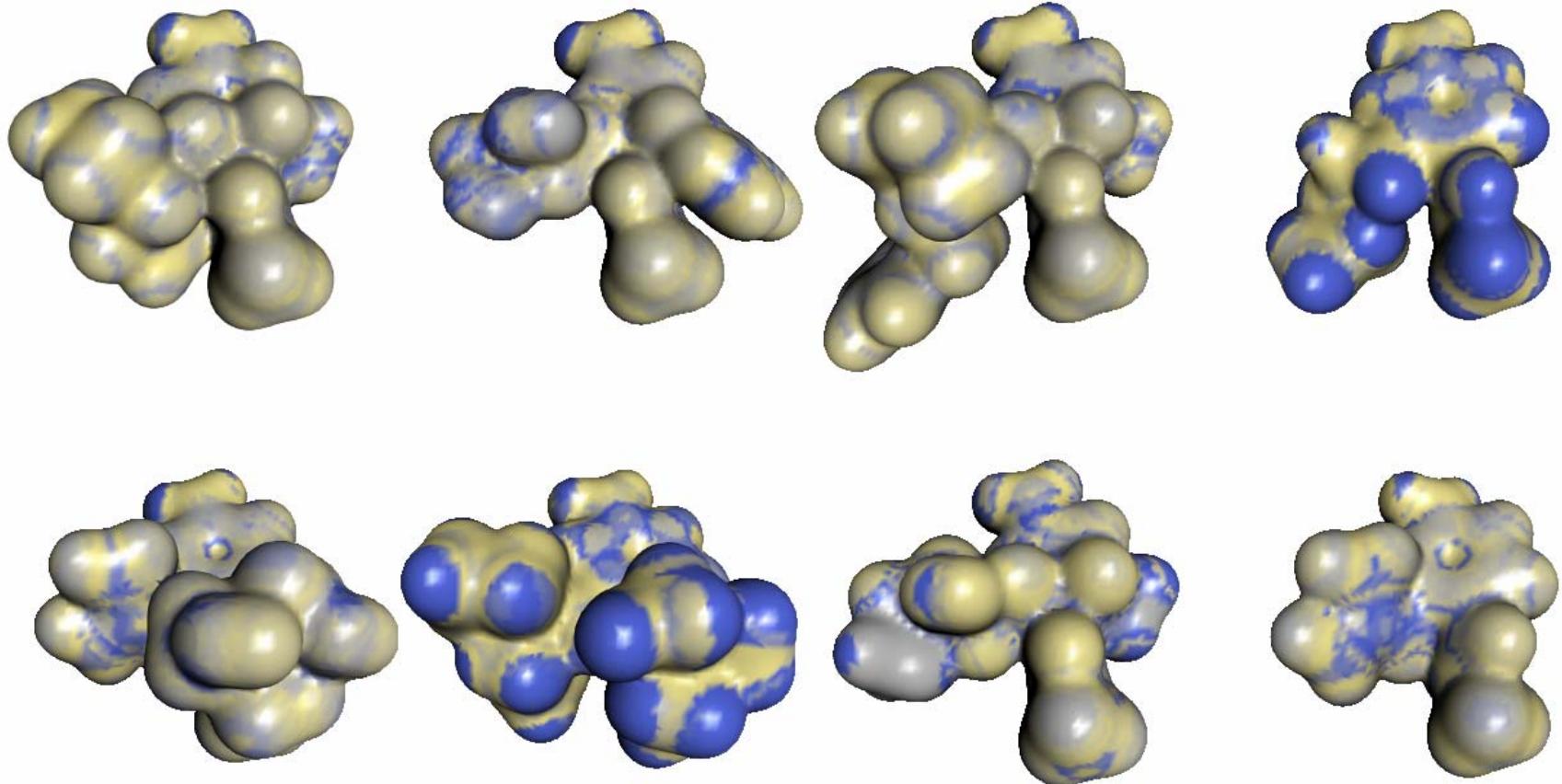
Neuraminidase Inhibitors



Lipophilicity – MolCad

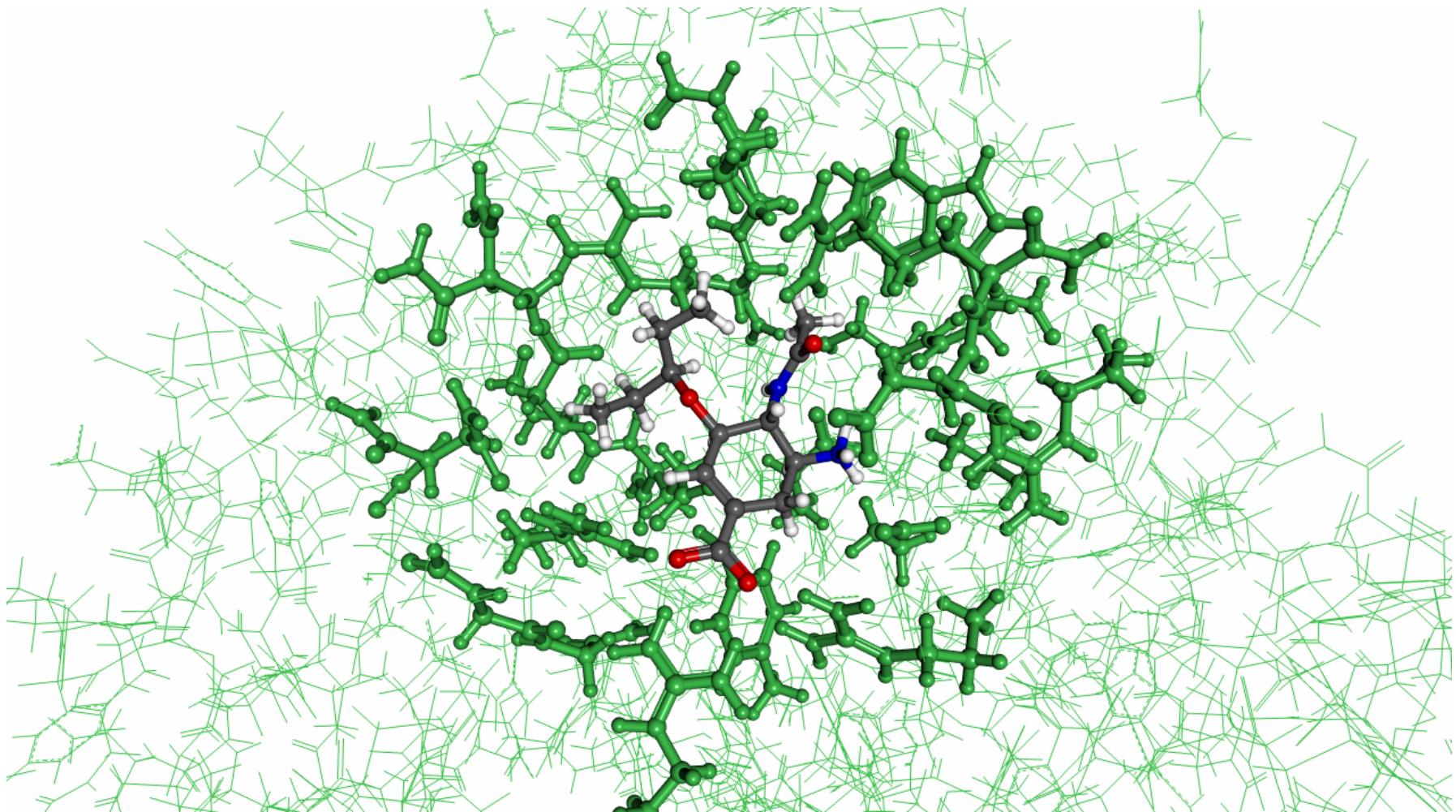


Lipophilicity – ParaSurf

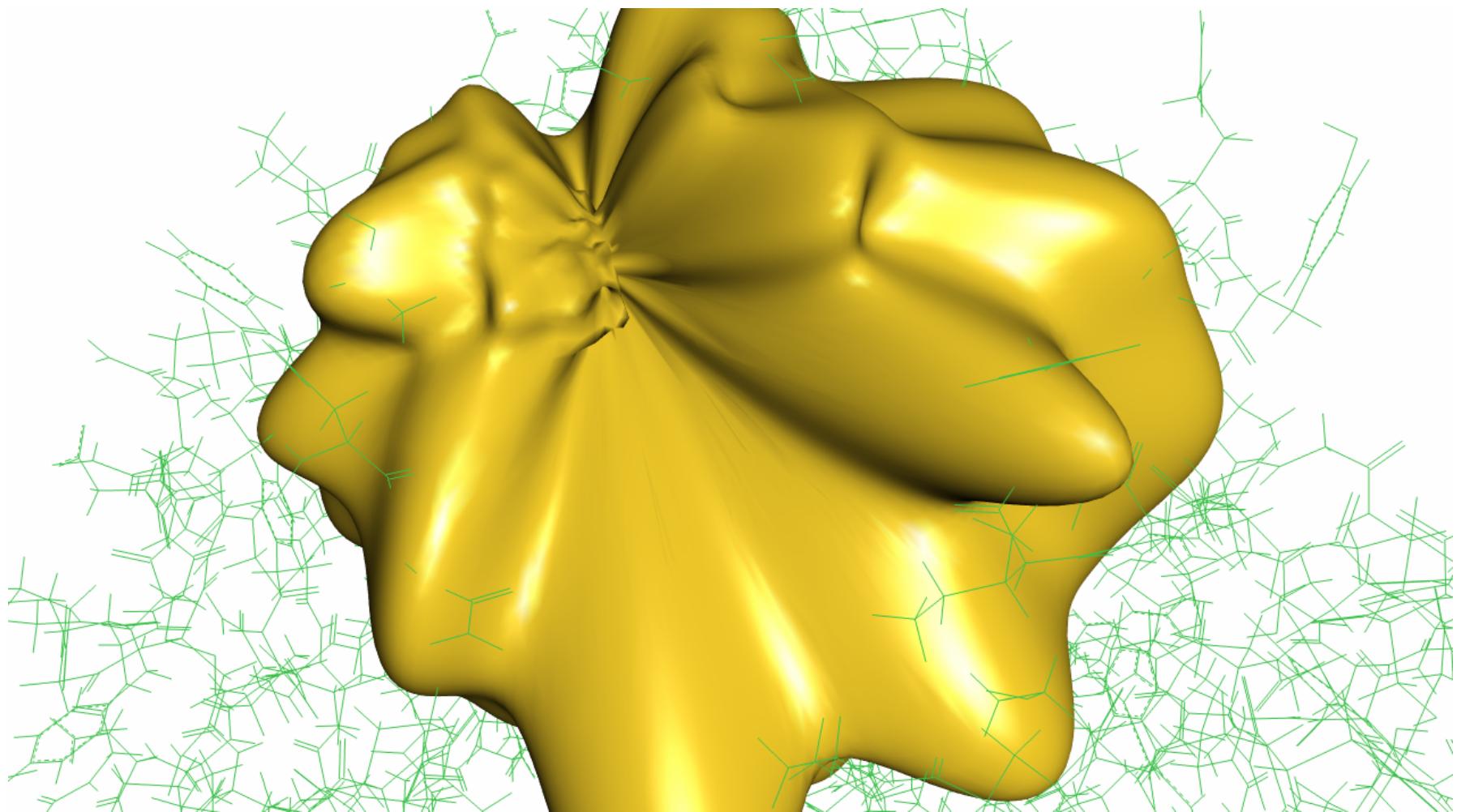


Complementarity - Structure Based

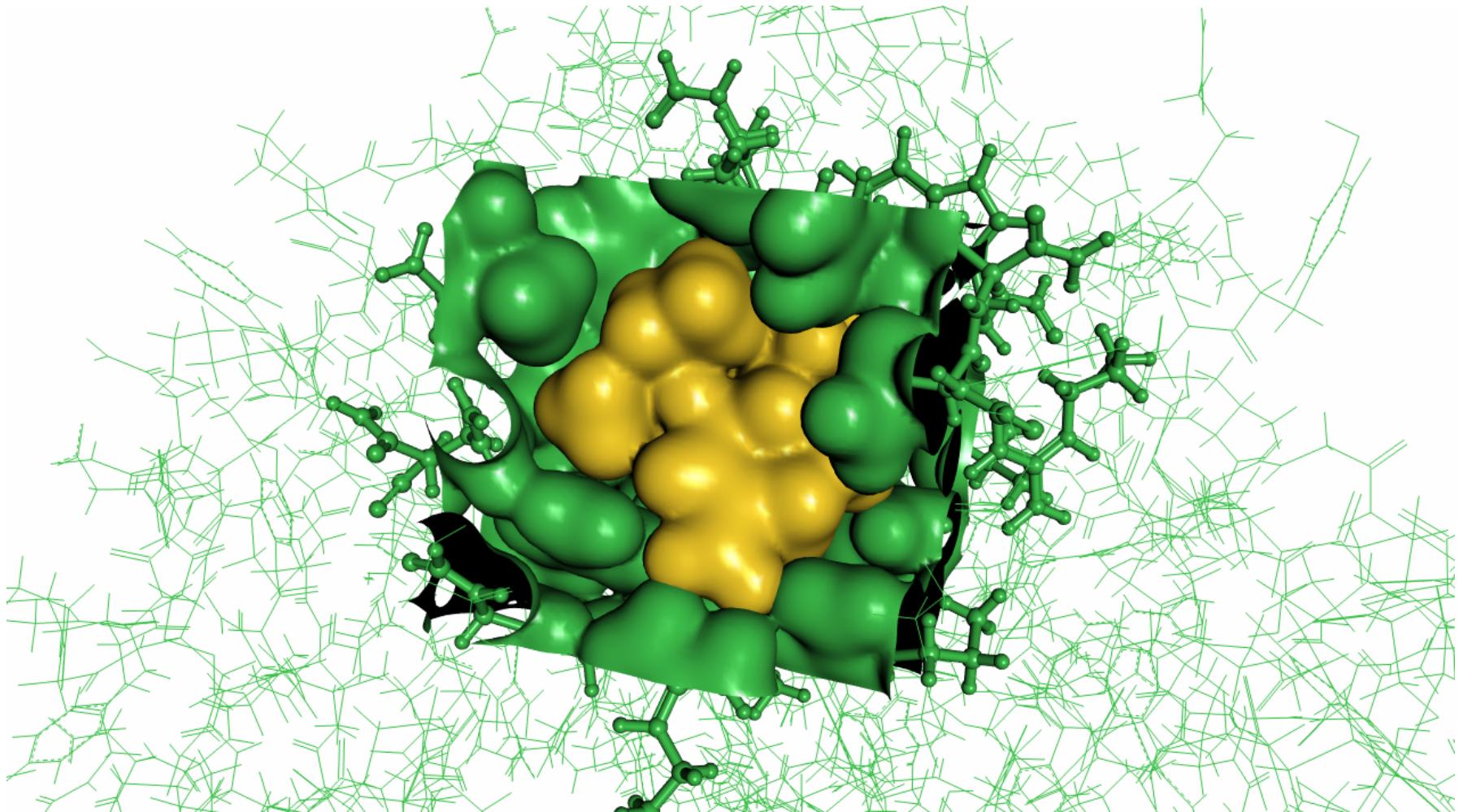
Neuraminidase-Oseltamivir Complex



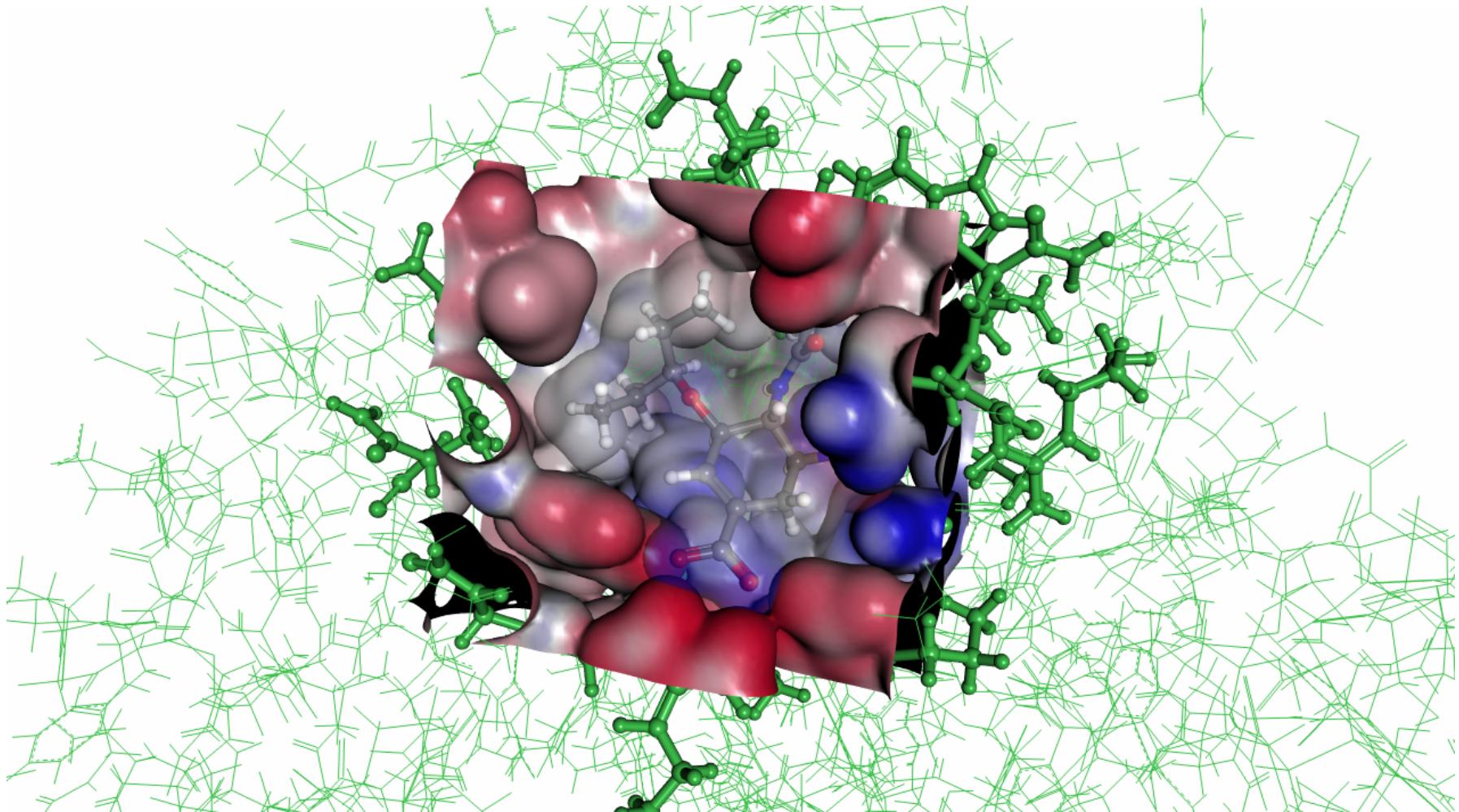
Shrink-wrap Surface



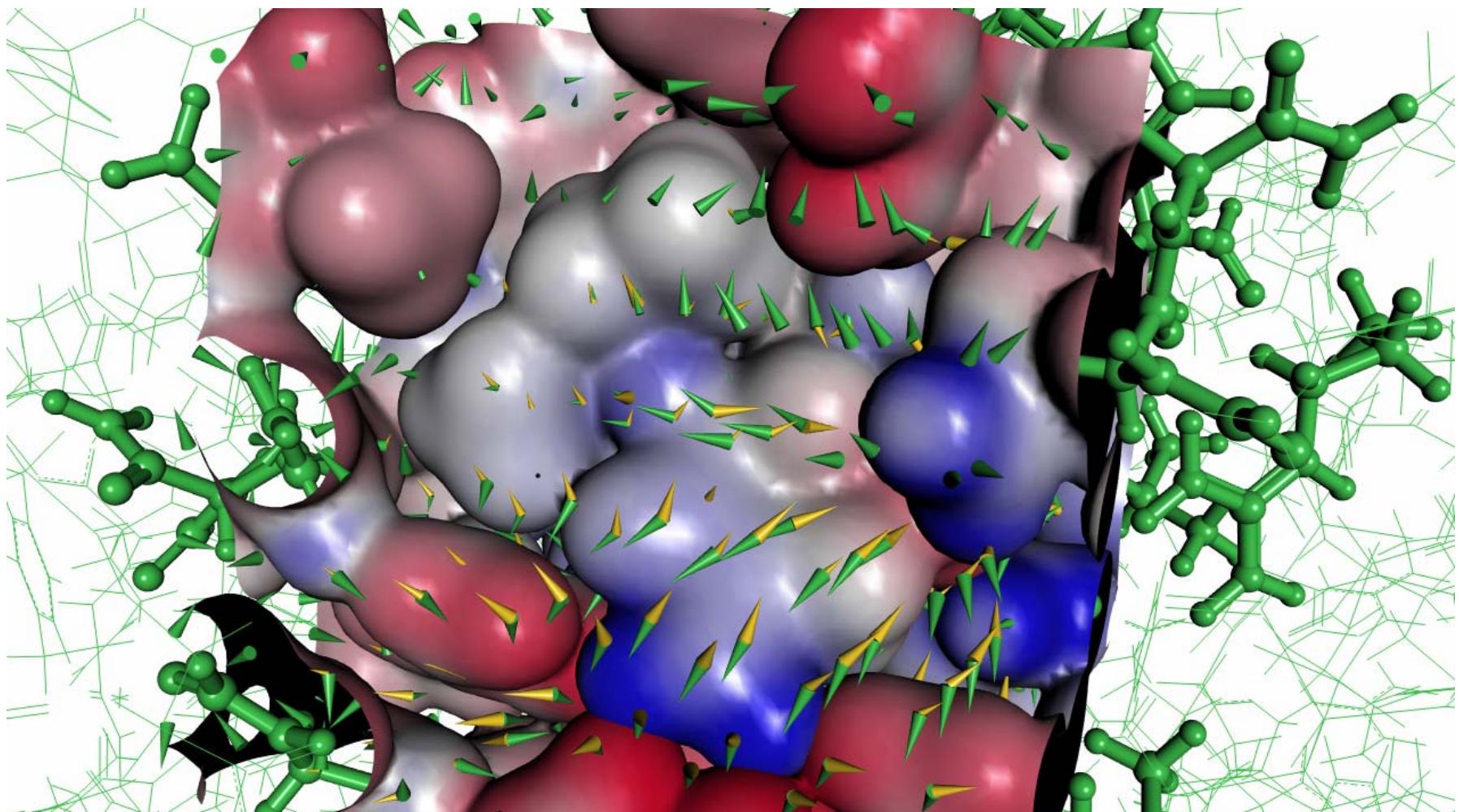
Marching Cube



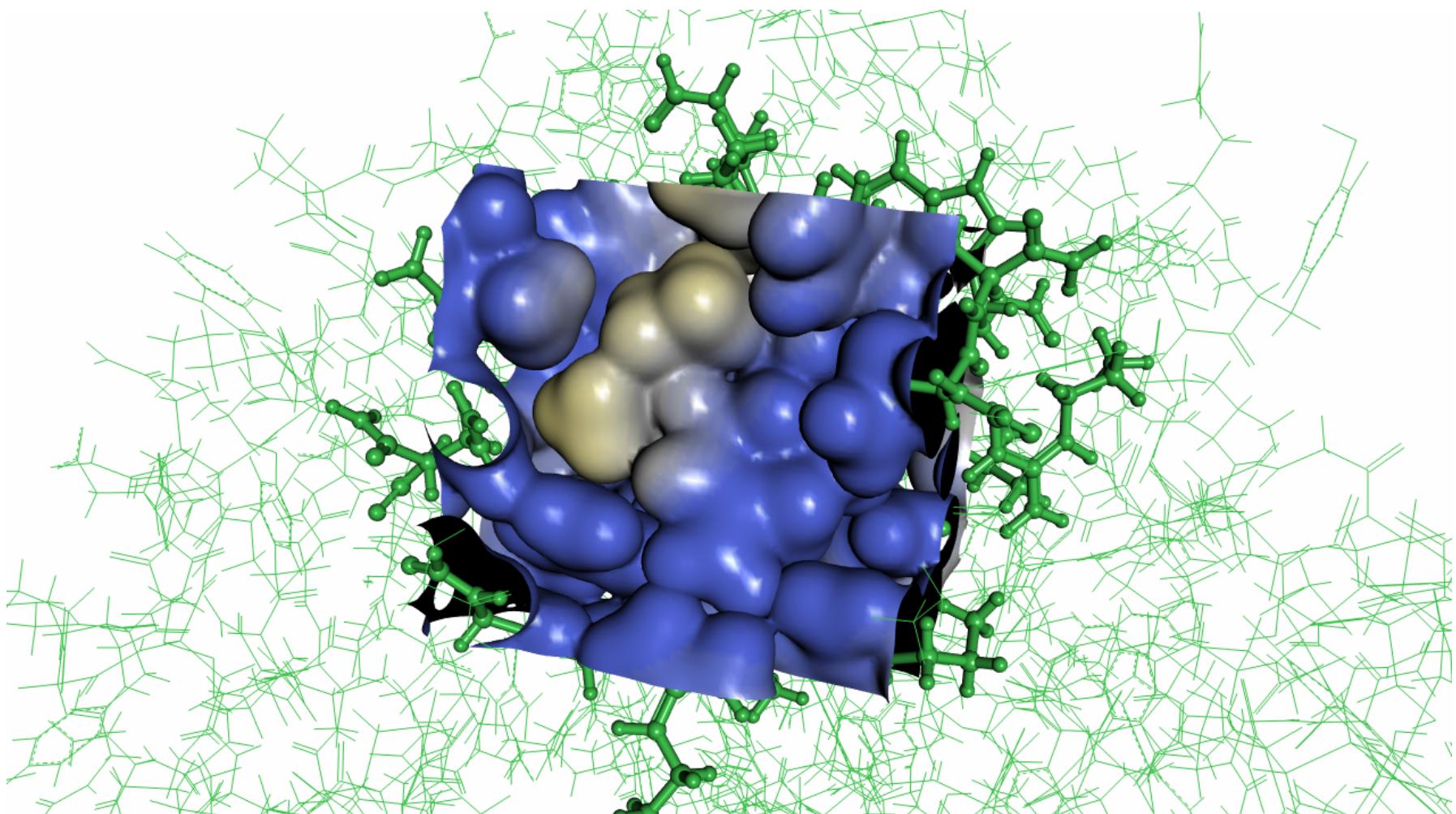
Electrostatic Potential



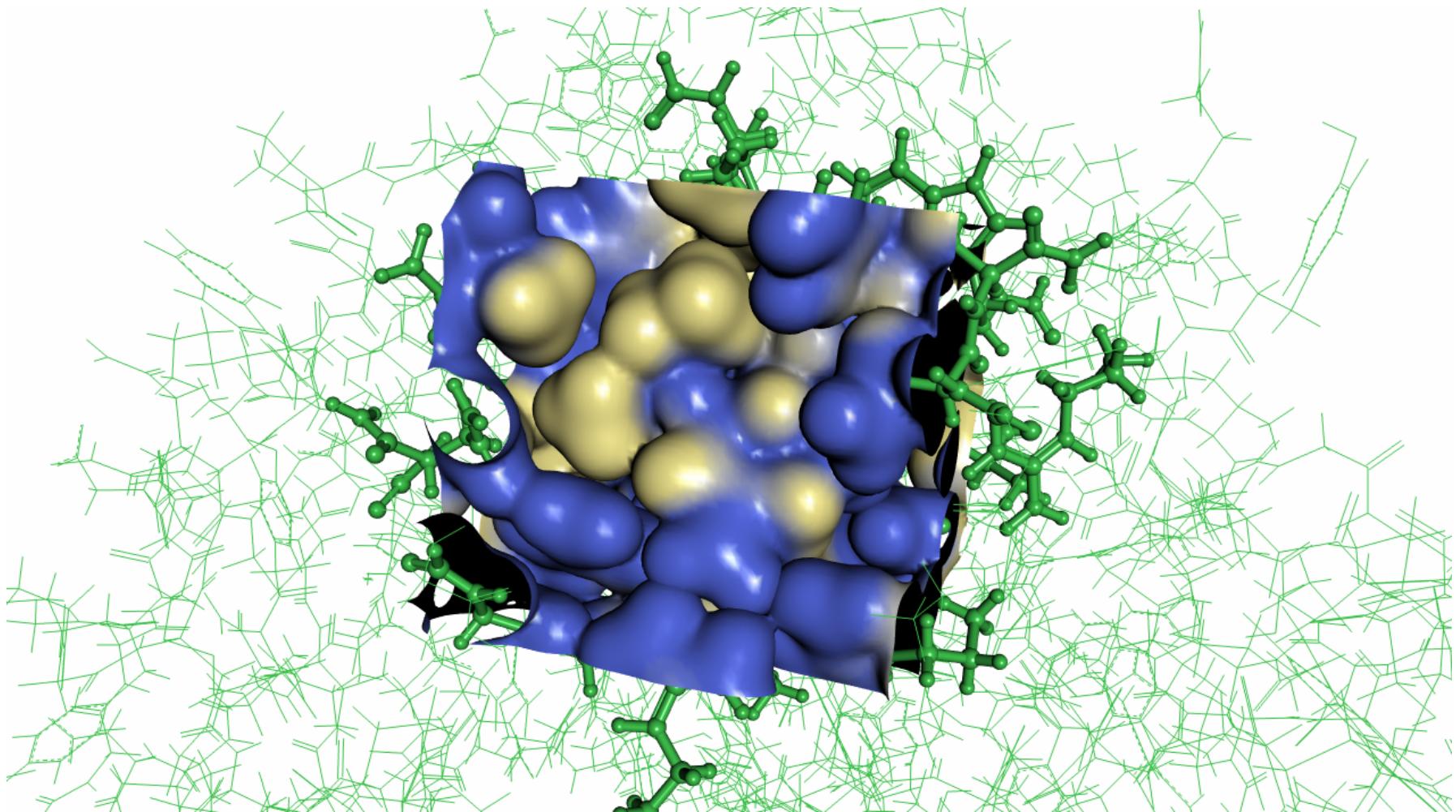
Electrostatic Potential



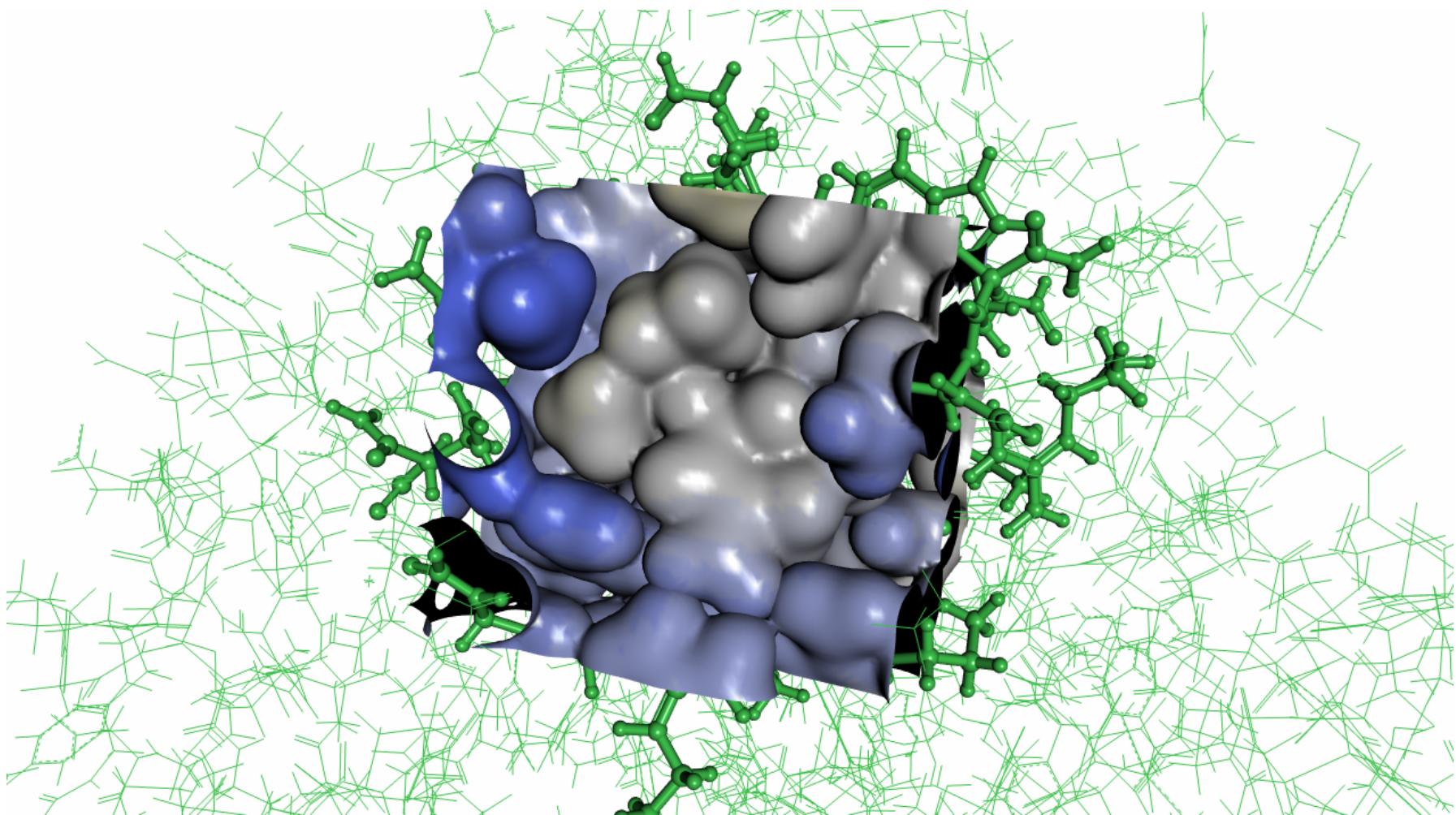
Lipophilicity – MolCad



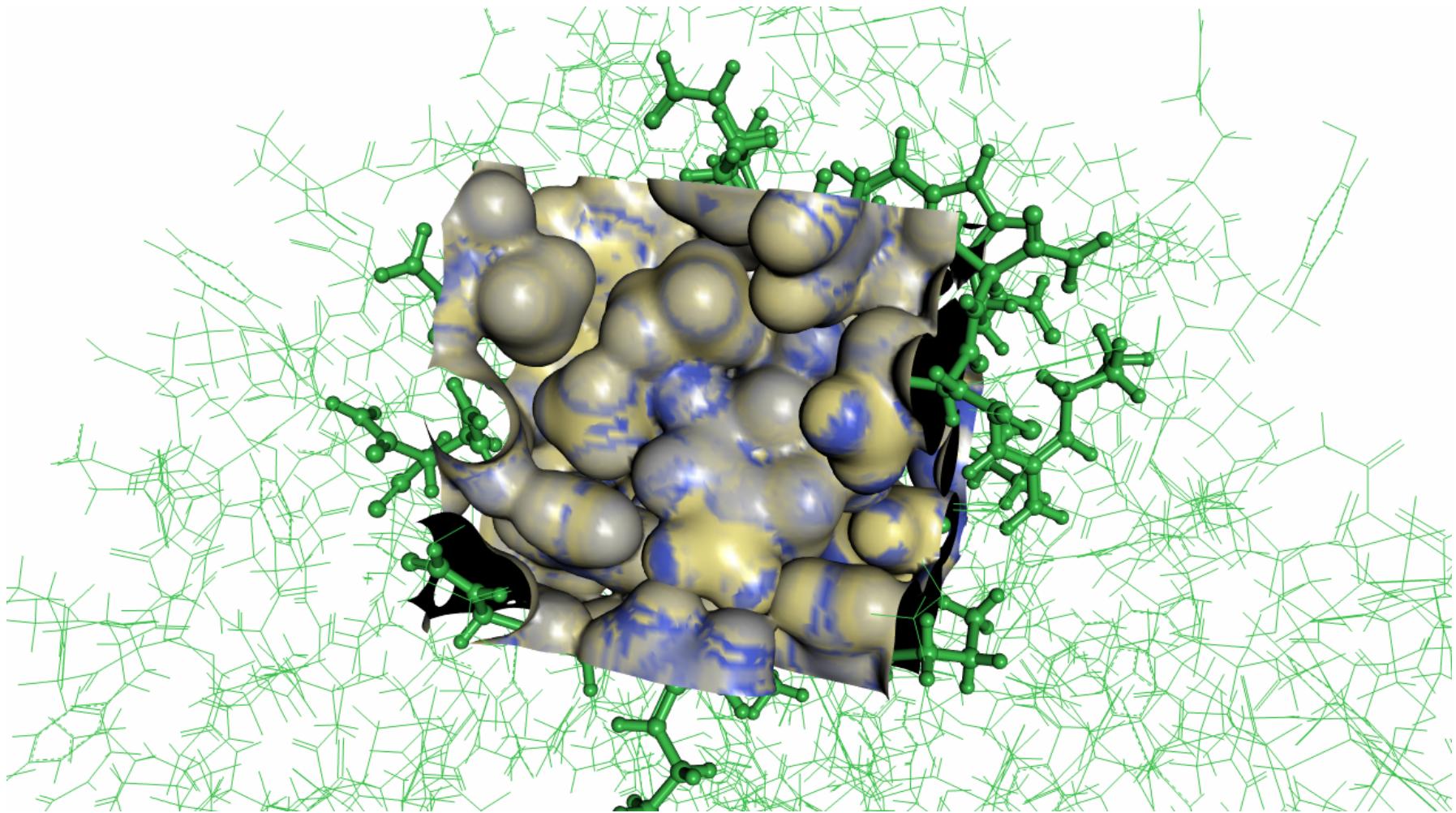
Lipophilicity – Localized



Lipophilicity – MolFESD

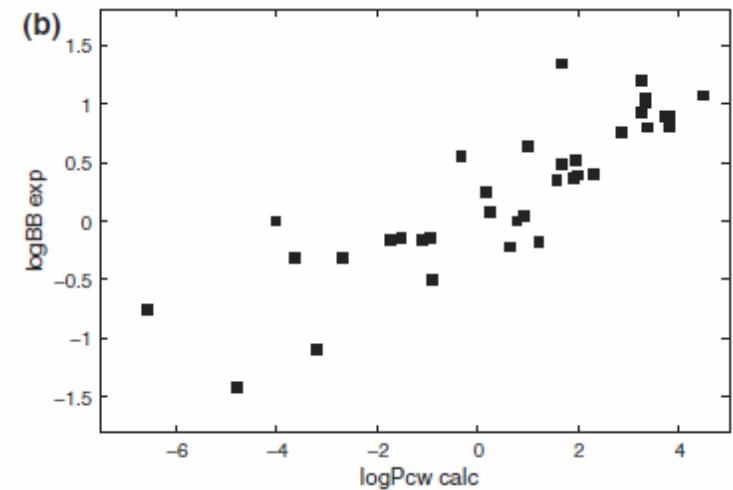


Lipophilicity – ParaSurf



Future Work

- Implementation of marching cubes algorithm in ParaSurf
- Combination of multiple shrink-wrap surfaces for concave regions
- Combination of advantages of lipophilicity model – compromise between prediction of $\log P$ and interpretability
- Other solvents models: water-cyclohexane
- Improvement of the compatibility ParaSurf \leftrightarrow MolCad
- MolCad as GUI for ParaFit



Acknowledgement

- Prof. Dr. Jürgen Brickmann
- Dr. Matthias Keil



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