ICCS
International Conference on Chemical Structures

11th ICCS, Noordwijkerhout, May 27 - 31, 2018

Generation of Structure-based Pharmacophore Models in Protein Binding Sites Obtained from Molecular Dynamics Simulations

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Thierry Langer

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The Pharmacophore Concept

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"A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supra-molecular interactions with a specific biological target and to trigger (or block) its biological response."

C.-G. Wermuth et al., *Pure Appl. Chem.* 1998, 70: 1129-1143

LigandScout Prototype 2003

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High Throughput Pharmacophore Model Generation from Ligand-Target Complexes as a Basis for Activity Profiling

euro QSAR 2004 istanbul turkey

Thierry Langer[1)] and Gerhard Wolbe

[1)] University of Innsbruck, Innsbruck, Aust
[2)] Inte:Ligand GmbH, Vienna, Aust

Gerhard Wolber
University of Innsbruck

LigandScout Prototype 2003

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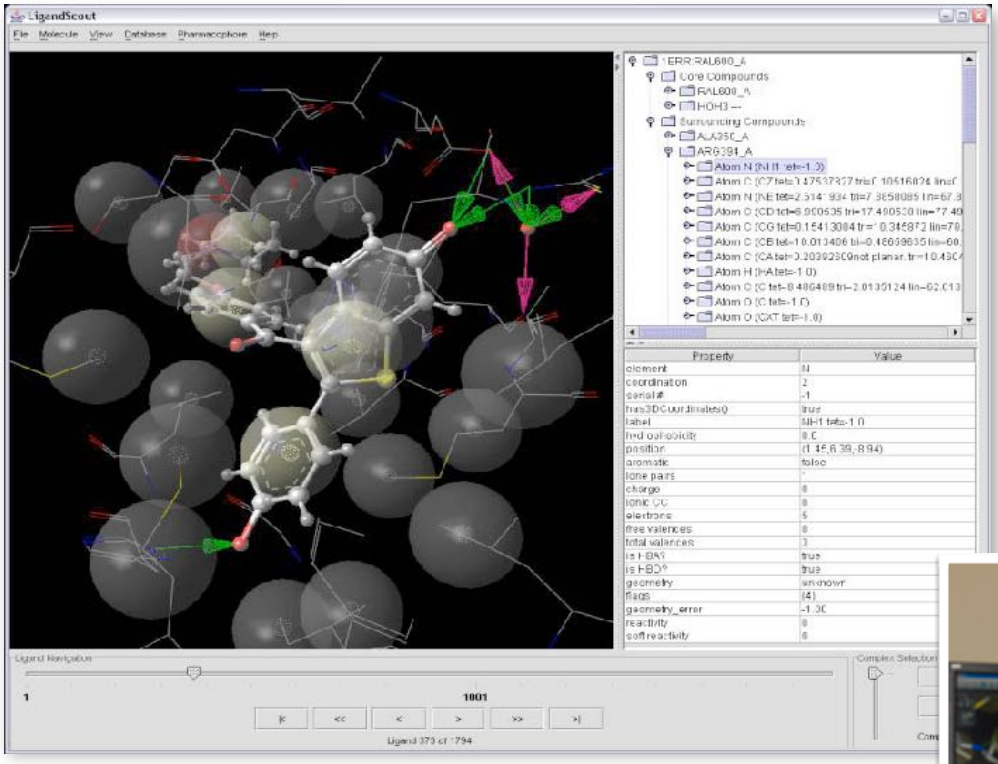

Gerhard Wolber
University of Innsbruck

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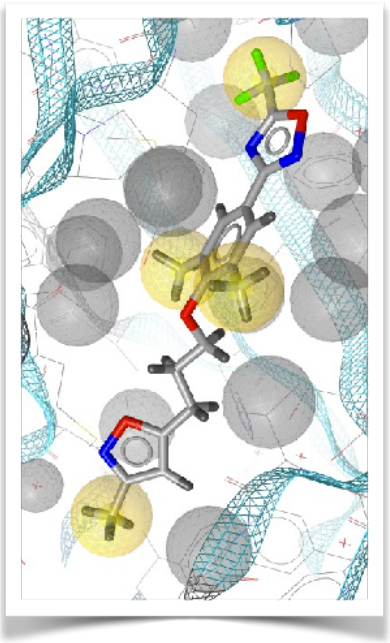
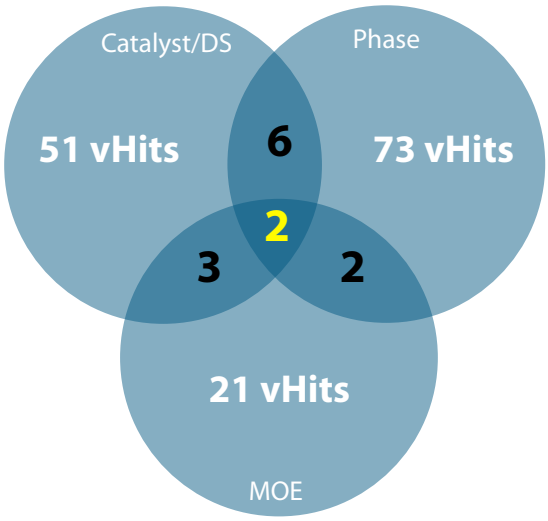
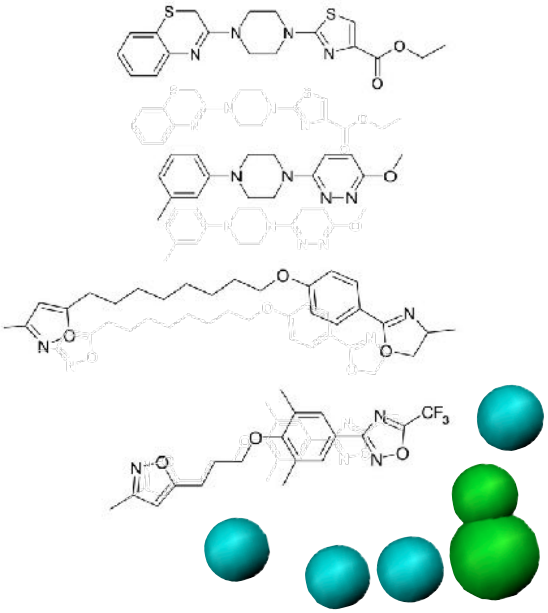
Pharmacophore Screening ...

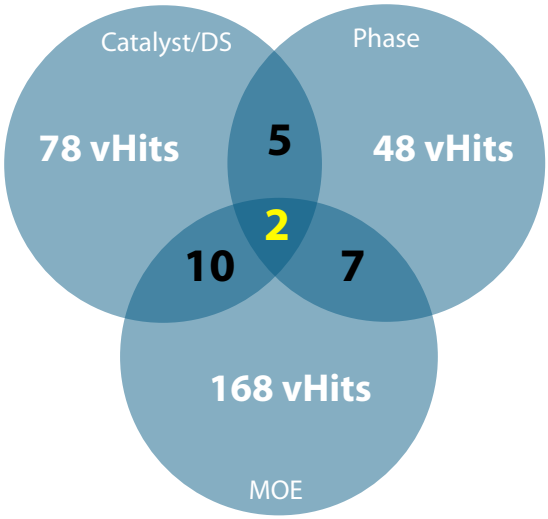




[Mangold 2006] Martina Mangold. *Human Rhinovirus Coat Protein Inhibitors - A Pharmacophore Modeling Approach.* Master's thesis at the University of Innsbruck (2006)

Pharmacophore Screening ...





[Mangold 2006] Martina Mangold. *Human Rhinovirus Coat Protein Inhibitors - A Pharmacophore Modeling Approach.* Master's thesis at the University of Innsbruck (2006)

There Is A Problem ...

- "Old" 3D pharmacophore methods suffer from severe limitations
  - different tools return inconsistent results
  - alignment by graph matching ----> slow
  - low number of features ----> inaccurate

What is the solution ?

... Breaking the Code

- Why Yuor Barin Can Raed Tihs

http://www.livescience.com/18392-reading-jumbled-words.html

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… Breaking the Code

- It deson't mttaer in waht oredr the ltteers in a wrod aepapr, the olny iprmoatnt tihng is taht the frist and lsat ltteer are in the rghit pcale. The rset can be a toatl mses and you can sitll raed it wouthit pobelrm.

http://www.livescience.com/18392-reading-jumbled-words.html

… Breaking the Code

- S1M1L4RLY, YoUR M1ND 15 R34D1NG 7H15 4U70M471C4LLY W17HoU7 3V3N 7H1NK1NG 4BoU7 17

http://www.livescience.com/18392-reading-jumbled-words.html

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Pattern Recognition Alignment

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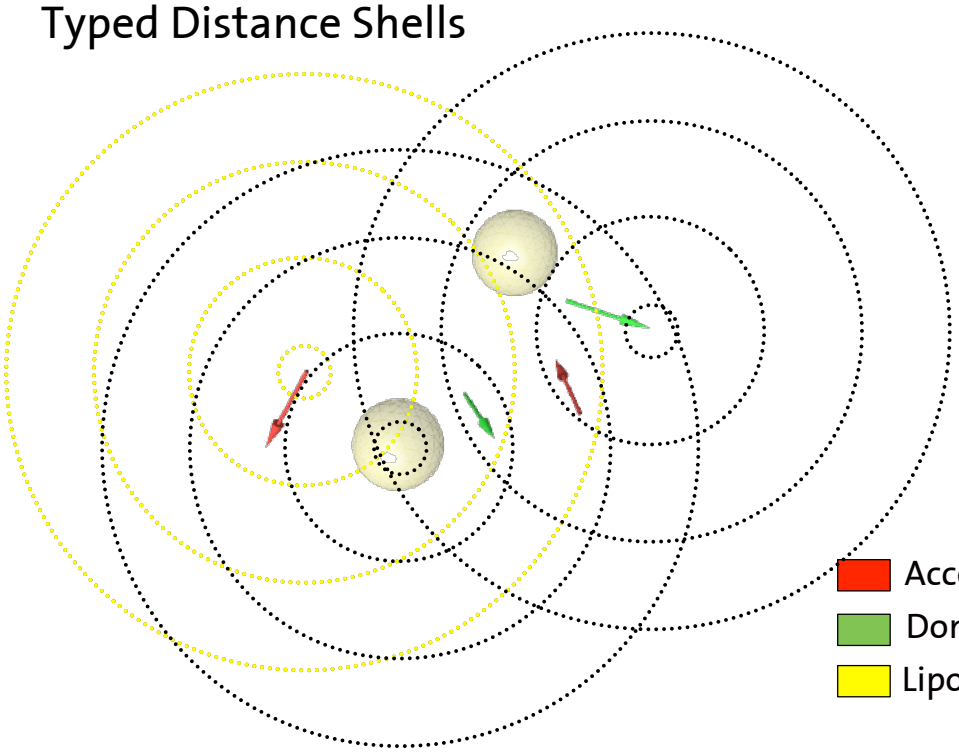
Typed Distance Shells



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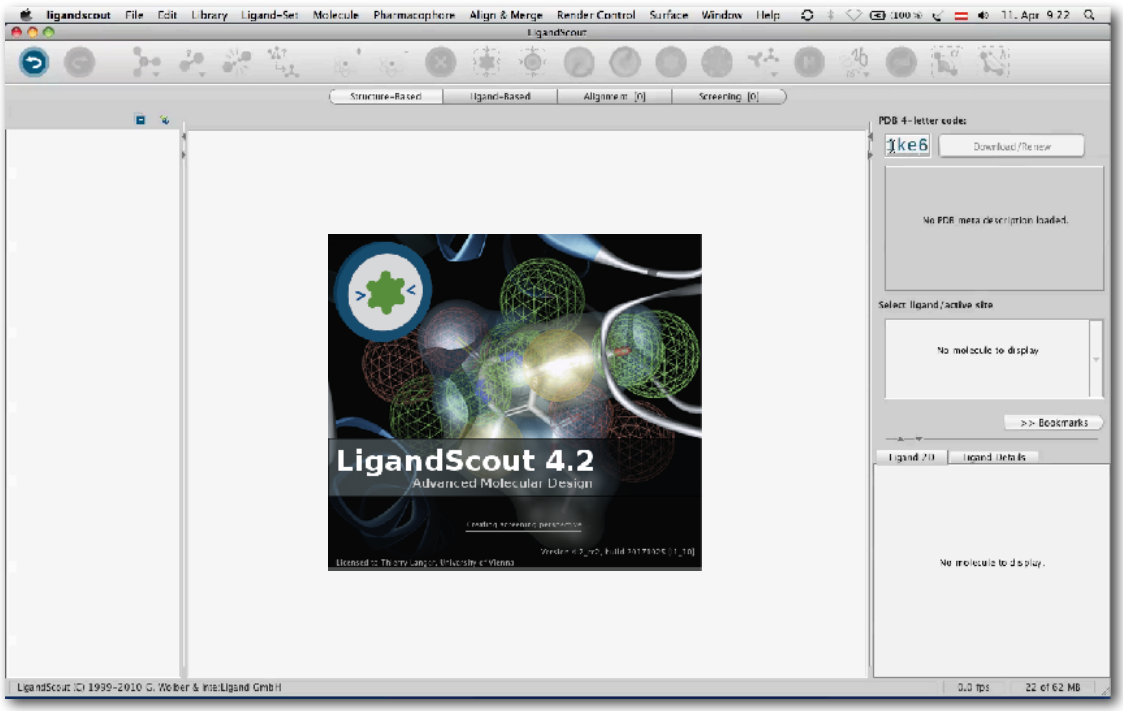

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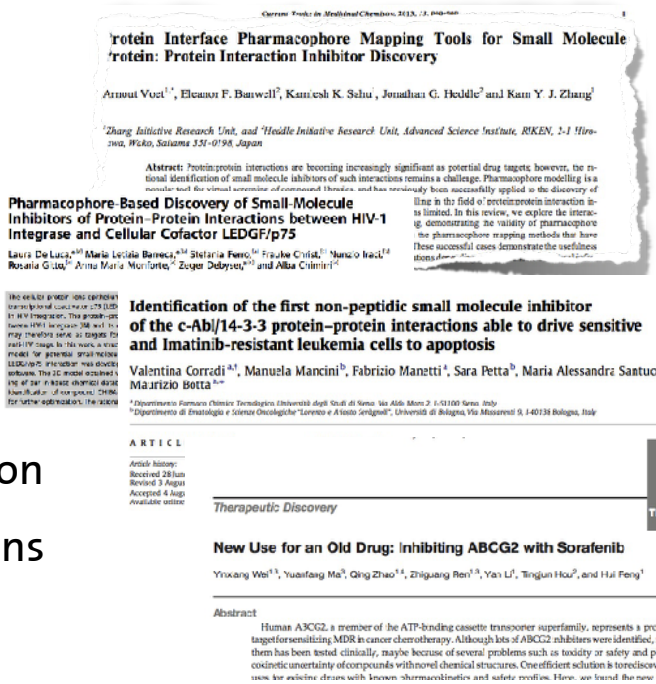
LigandScout Scientific Articles

- More than 1500 papers*
  - structure-based modeling
  - ligand-based modeling
  - virtual screening
- Hit identification
- Fragment-based design
- Lead structure optimization
- Protein-Protein Interactions
- Drug repurposing
- Profiling (side-effects)



rotein Interface Pharmacophore Mapping Tools for Small Molecule
rotein: Protein Interaction Inhibitor Discovery

Arnaut Voet[1,*], Eleanor F. Barwell[2], Kamlesh K. Sahu[1], Jonathan G. Heddle[3] and Kam Y. J. Zhang[1]

Abstract: Protein:protein interactions are becoming increasingly significant as potential drug targets; however, the ...

Pharmacophore-Based Discovery of Small-Molecule Inhibitors of Protein–Protein Interactions between HIV-1 Integrase and Cellular Cofactor LEDGF/p75

Laura De Luca,[a,b] Maria Letizia Barreca,[a,b] Stefania Ferro,[a] Fraoke Christ,[c] Nunzio Iraci,[a] Rosalia Gitto,[a] Anna Maria Monforte,[a] Zeger Debyser,[c,d] and Alba Chimirri[a,d]

Identification of the first non-peptidic small molecule inhibitor of the c-Abl/14-3-3 protein–protein interactions able to drive sensitive and Imatinib-resistant leukemia cells to apoptosis

Valentina Corradi[a,1], Manuela Mancini[b], Fabrizio Manetti[a], Sara Petta[b], Maria Alessandra Santucci[b], Maurizio Botta[a,*]

ARTICLE

Therapeutic Discovery

Molecular Cancer Therapeutics

New Use for an Old Drug: Inhibiting ABCG2 with Sorafenib

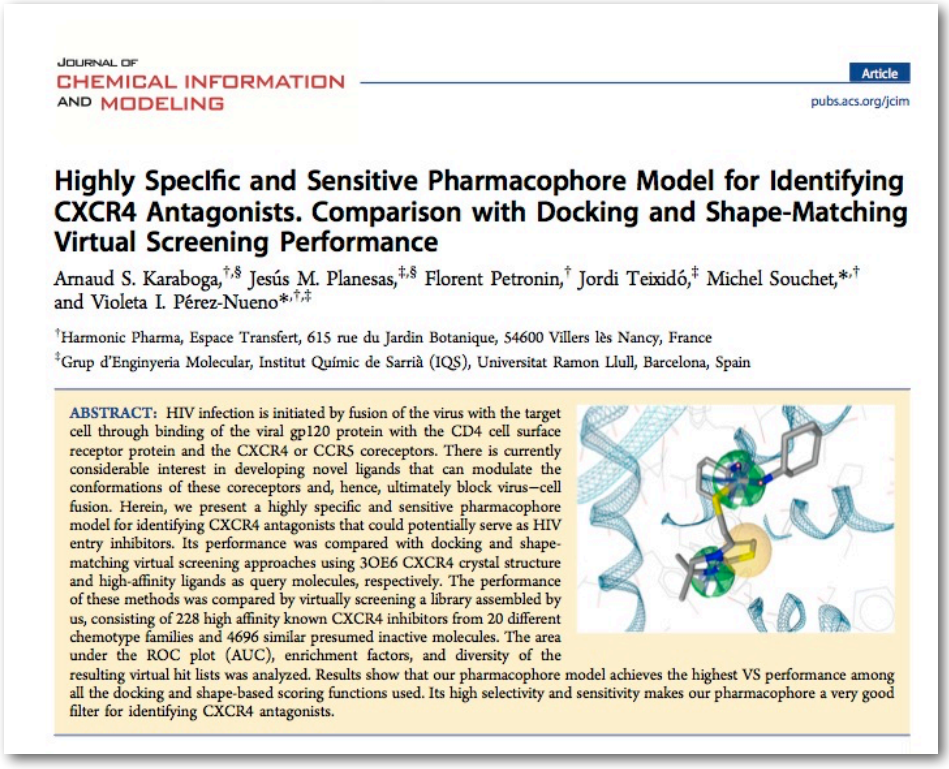
Yinxiang Wei[1,3], Yuanfang Ma[3], Qing Zhao[1,4], Zhiguang Ren[1,3], Yan Li[1], Tingjun Hou[2], and Hui Feng[1]

Abstract

Human ABCG2, a member of the ATP-binding cassette transporter superfamily, represents a promising target for sensitizing MDR in cancer chemotherapy. Although lots of ABCG2 inhibitors were identified, none of them has been tested clinically, maybe because of several problems such as toxicity or safety and pharmacokinetic uncertainty of compounds with novel chemical structures. One efficient solution is to rediscover new uses for existing drugs with known pharmacokinetics and safety profiles. Here, we found the new use for

* scholar.google.com, May 2018

An Interesting Article To Read ...



JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

pubs.acs.org/jcim

Highly Specific and Sensitive Pharmacophore Model for Identifying CXCR4 Antagonists. Comparison with Docking and Shape-Matching Virtual Screening Performance

Arnaud S. Karaboga,[†,§] Jesús M. Planesas,[‡,§] Florent Petronin,[†] Jordi Teixidó,[‡] Michel Souchet,*[,†] and Violeta I. Pérez-Nueno*[,†,‡]

[†]Harmonic Pharma, Espace Transfert, 615 rue du Jardin Botanique, 54600 Villers lès Nancy, France

[‡]Grup d'Enginyeria Molecular, Institut Químic de Sarrià (IQS), Universitat Ramon Llull, Barcelona, Spain

ABSTRACT: HIV infection is initiated by fusion of the virus with the target cell through binding of the viral gp120 protein with the CD4 cell surface receptor protein and the CXCR4 or CCR5 coreceptors. There is currently considerable interest in developing novel ligands that can modulate the conformations of these coreceptors and, hence, ultimately block virus−cell fusion. Herein, we present a highly specific and sensitive pharmacophore model for identifying CXCR4 antagonists that could potentially serve as HIV entry inhibitors. Its performance was compared with docking and shape-matching virtual screening approaches using 3OE6 CXCR4 crystal structure and high-affinity ligands as query molecules, respectively. The performance of these methods was compared by virtually screening a library assembled by us, consisting of 228 high affinity known CXCR4 inhibitors from 20 different chemotype families and 4696 similar presumed inactive molecules. The area under the ROC plot (AUC), enrichment factors, and diversity of the resulting virtual hit lists was analyzed. Results show that our pharmacophore model achieves the highest VS performance among all the docking and shape-based scoring functions used. Its high selectivity and sensitivity makes our pharmacophore a very good filter for identifying CXCR4 antagonists.

Karaboga et al.,
J. Chem. Inf. Model. 53
1043−1056 (2013)

LigandScout for VS

Pharmacophore from PDB entry 3OE6

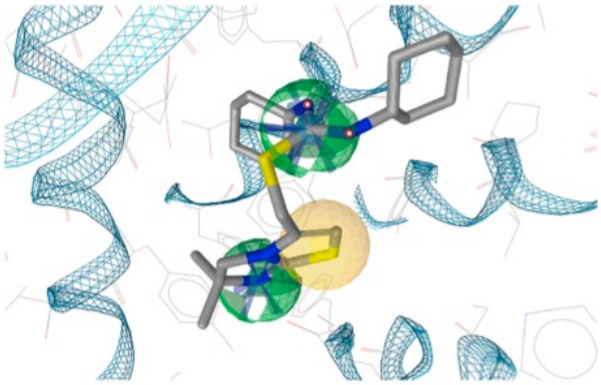


Figure 2. CXCR4 pharmacophore model with a high activity CXCR4 antagonist aligned. Five-featured manually refined final pharmacophore model. The pharmacophore hydrophobic features are shown in yellow. Positively charged features are shown in blue, and hydrogen bond donor features are shown in green.

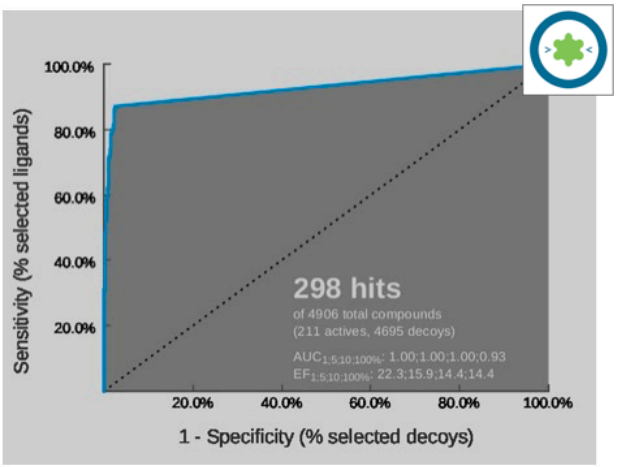


Figure 3. ROC plot validation of the pharmacophore model applied to CXCR4 antagonists. Values of area under the curve (AUC) and enrichment factor (EF) are displayed at 1, 5, 10, and 100% of screened database, respectively. These values highlight the high sensitivity and specificity of the designed pharmacophore model.

Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043−1056

The Conclusions

- Overall, the total area under de curve of the ROC plot and the early recovery results of the present pharmacophore model show that it is a highly specific and sensitive screening filter, which makes it very appropriate for identifying CXCR4 antagonists.
- Moreover, the scaffold retrieval analysis shows that the pharmacophore model is able to retrieve a diverse scaffold pool.

Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043−1056

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REVIEWS Drug Discovery Today • Volume 20, Number 6 • June 2015

Teaser An overview on molecular dynamics (MD) studies illustrating the range of applications in the field of drug design.

The impact of molecular dynamics on drug design: applications for the characterization of ligand–macromolecule complexes

Jérémie Mortier[1], Christin Rakers[1], Marcel Bermudez[1], Manuela S. Murgueitio[1], Sereina Riniker[2] and Gerhard Wolber[1]

[1] Institute of Pharmacy, Freie Universität Berlin, Königin-Luise-Strasse 2+4, 14195 Berlin, Germany
[2] Laboratory of Physical Chemistry, ETH Zürich, Vladimir-Prelog-Weg 2, CH-8093 Zurich, Switzerland

Among all tools available to design new drugs, molecular dynamics (MD) simulations have become an essential technique. Initially developed to investigate molecular models with a limited number of atoms, computers now enable investigations of large macromolecular systems with a simulation time reaching the microsecond range. The reviewed articles cover four years of research to give an overview on the actual impact of MD on the current medicinal chemistry landscape with a particular emphasis on studies of ligand–protein interactions. With a special focus on studies combining computational approaches with data gained from other techniques, this review shows how deeply embedded MD simulations are in drug design strategies and articulates what the future of this technique could be.

Jérémie Mortier is a postdoctoral fellow in Gerhard Wolber's computer-aided drug design group at the Free University of Berlin, Germany. His main field of research is at the interface of biological and medicinal chemistry, with a particular focus on the prediction and understanding of molecular systems, their structures and interactions. After a Master in Chemistry in 2006, he was first introduced to computational chemistry during his PhD in pharmaceutical and biomedical sciences at the University of Namur, Belgium, in 2010. His position is currently funded by a fellowship from the Deutsche Forschung Gemeinschaft.

Sereina Riniker received her PhD at ETH Zurich in the field of molecular dynamics simulations. In 2012, she moved on to take a postdoctoral position in cheminformatics at the Novartis Institutes for BioMedical Research in

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MD and Pharmacophores

- Using pharmacophore models as a new way to investigate ligand-protein interactions in MD trajectories
- Finding relevant interactions by pharmacophore frequency analysis
- Use pharmacophore vectors for calculating similarities
- Sampling and identification of rare (but important) events
- Potential applications:
  - Enhance VS efficiency
  - Better guidance for lead structure optimization

VS Screening Efficiency

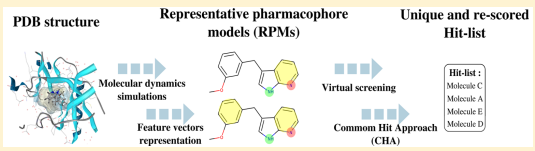
JOURNAL OF CHEMICAL INFORMATION AND MODELING
Article
pubs.acs.org/jcim

Common Hits Approach: Combining Pharmacophore Modeling and Molecular Dynamics Simulations

Marcus Wieder,*[†,‡] Arthur Garon,[†] Ugo Perricone,[†,¶] Stefan Boresch,[‡] Thomas Seidel,[†] Anna Maria Almerico,[¶] and Thierry Langer[†]

[†]Faculty of Life Sciences, Department of Pharmaceutical Chemistry, University of Vienna, Althanstraße 14, 1090 Vienna, Austria
[‡]Faculty of Chemistry, Department of Computational Biological Chemistry, University of Vienna, Währingerstraße 17, 1090 Vienna, Austria
[¶]Department of Biological, Chemical and Pharmaceutical Sciences and Technologies (STEBICEF), University of Palermo, Via Archirafi 32, Palermo, Italy

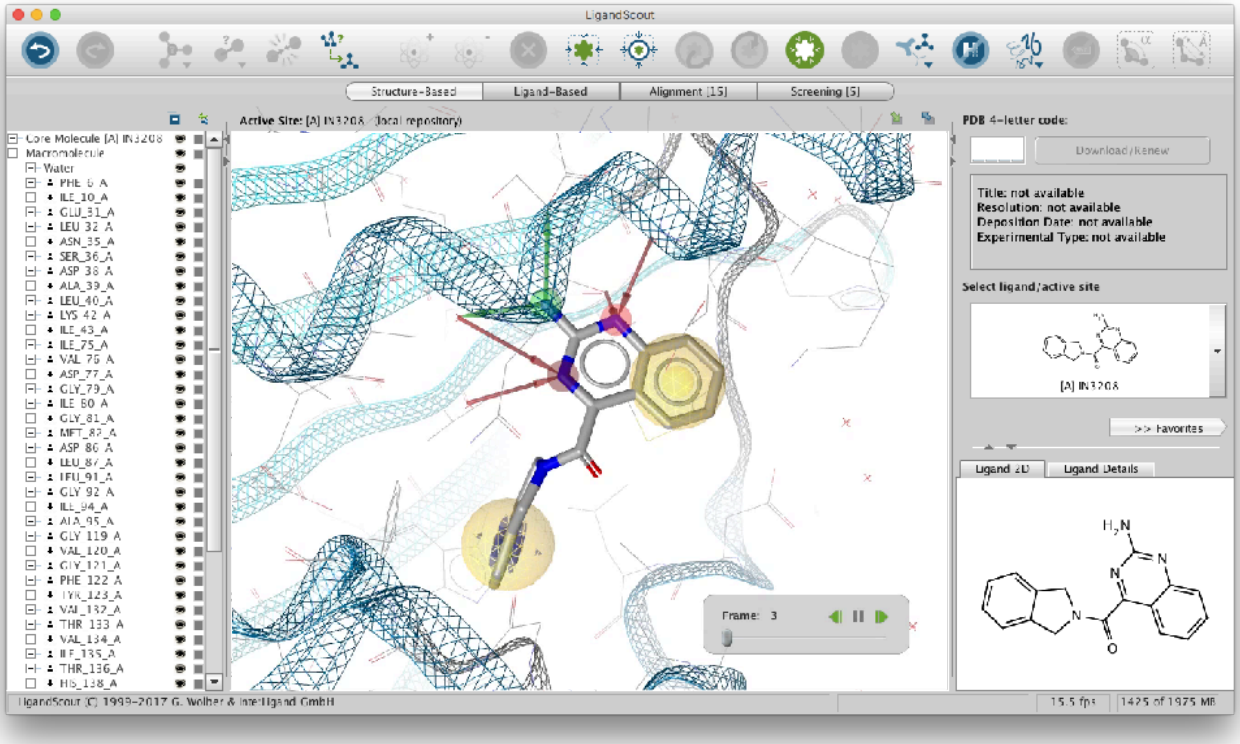
Supporting Information



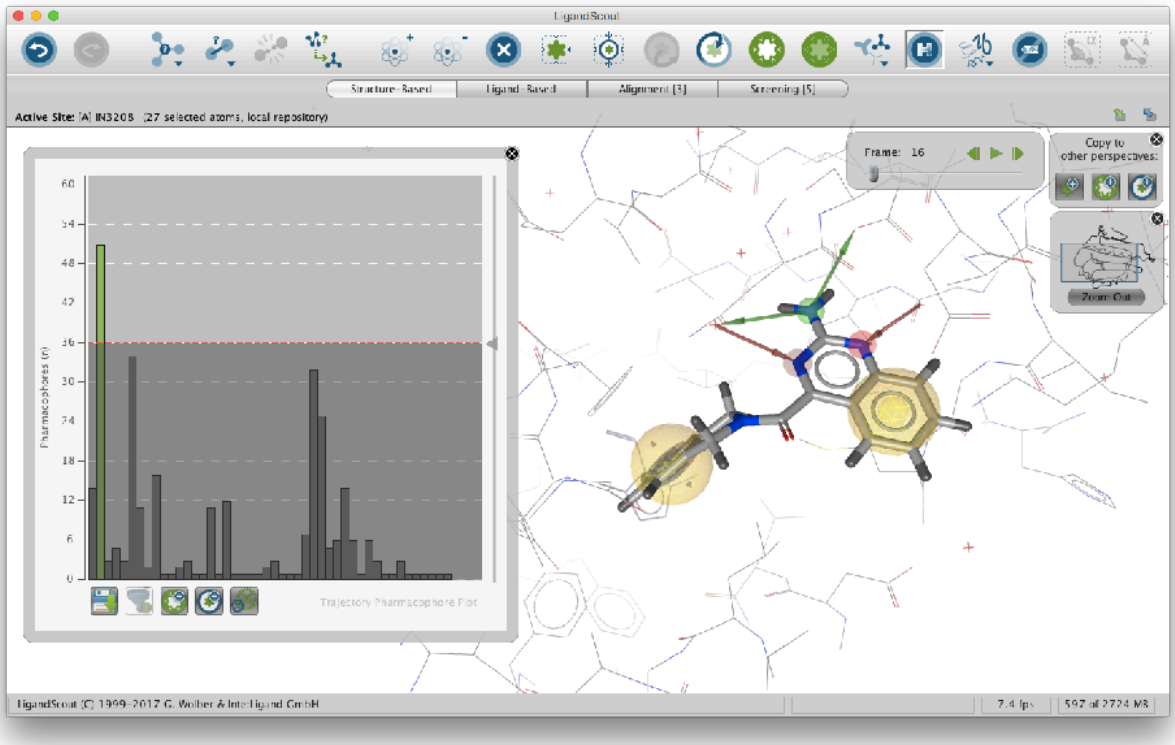
ABSTRACT: We present a new approach that incorporates flexibility based on extensive MD simulations of protein−ligand complexes into structure-based pharmacophore modeling and virtual screening. The approach uses the multiple coordinate sets saved during the MD simulations and generates for each frame a pharmacophore model. Pharmacophore models with the same pharmacophore features are pooled. In this way the high number of pharmacophore models that results from the MD simulation is reduced to only a few hundred *representative* pharmacophore models. Virtual screening runs are performed with every representative pharmacophore model; the screening results are combined and rescored to generate a single hit-list. The score for a particular molecule is calculated based on the number of representative pharmacophore models which classified it as active. Hence, the method is called common hits approach (CHA). The steps between the MD simulation and the final hit-list are performed automatically and without user interaction. We test the performance of CHA for virtual screening using screening databases with active and inactive compounds for 40 protein−ligand systems. The results of the CHA are compared to the (i) median screening performance of all representative pharmacophore models of protein−ligand systems, as well as to the virtual screening performance of (ii) a random classifier, (iii) the pharmacophore model derived from the experimental structure in the PDB, and (iv) the representative pharmacophore model appearing most frequently during the MD simulation. For the 34 (out of 40) protein−ligand complexes, for which at least one of the approaches was able to perform better than a random classifier, the highest enrichment was achieved using CHA in 68% of the cases, compared to 12% for the PDB pharmacophore model and 20% for the representative pharmacophore model appearing most frequently. The availabilithy of diverse sets of different pharmacophore models is utilized to analyze some additional questions of interest in 3D pharmacophore-based virtual screening.

Wieder M. et al., JCIM, 57, 365 (2017)

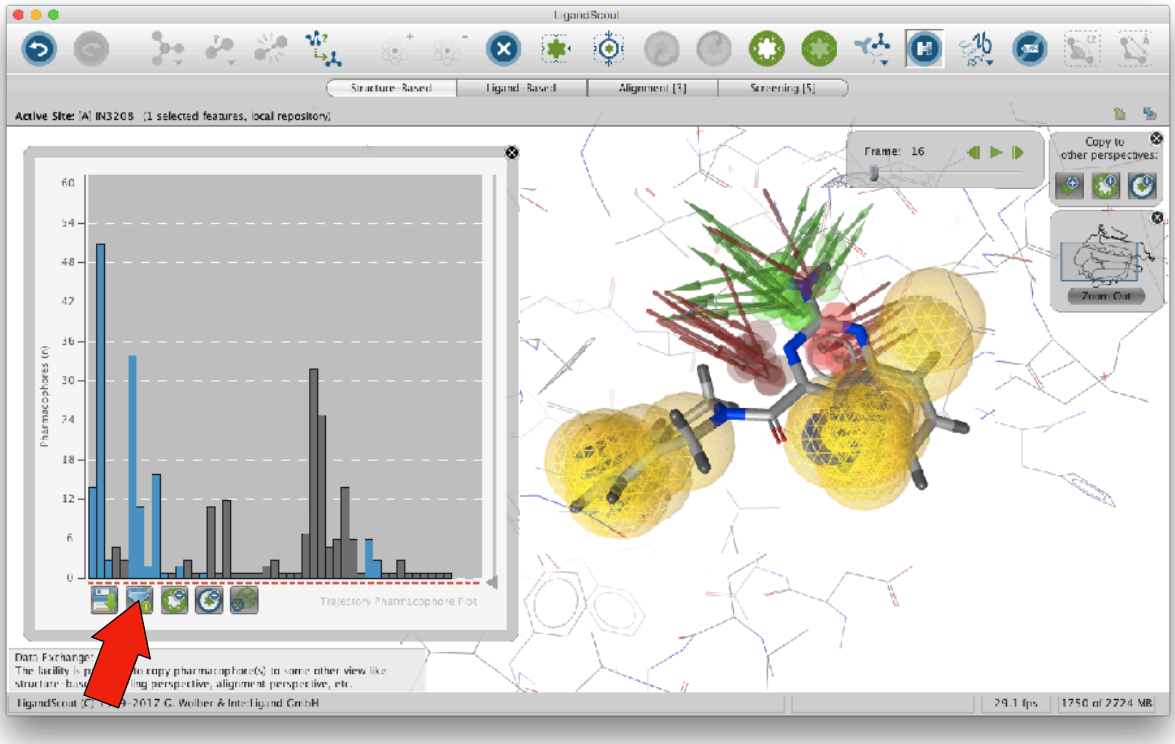
LigandScout Implementation



LigandScout Trajectory Analysis



Find Models With Specific Feature



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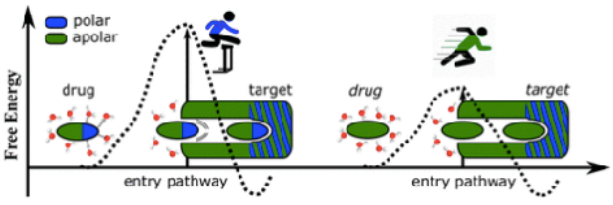
Further Analysis of MD Trajectories

- Identification of transient pockets
- Qualification of regions for additional interactions
- Analysis of the role of water molecules

Case study:

Ligand Desolvation Steers On-Rate and Impacts Drug Residence Time of Heat Shock Protein 90 (Hsp90) Inhibitors
Schütz D. et al., J. Med. Chem. Articles ASAP, April 27, 2018.
DOI: 10.1021/acs.jmedchem.8b00080



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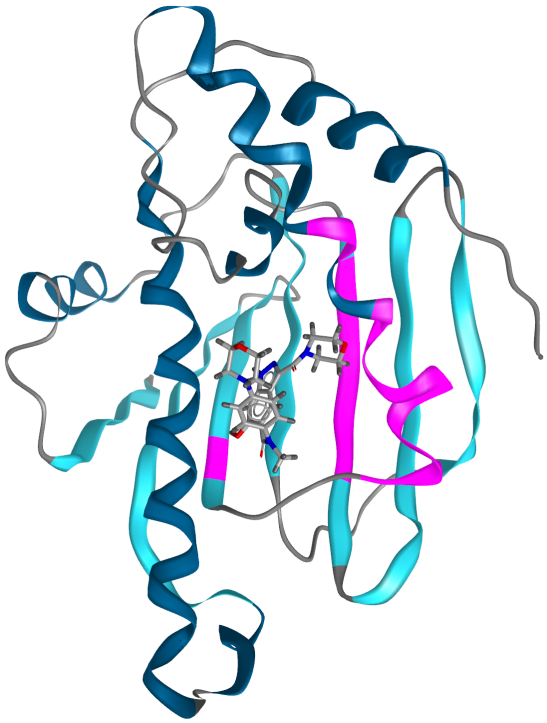
Feature Interaction Grids

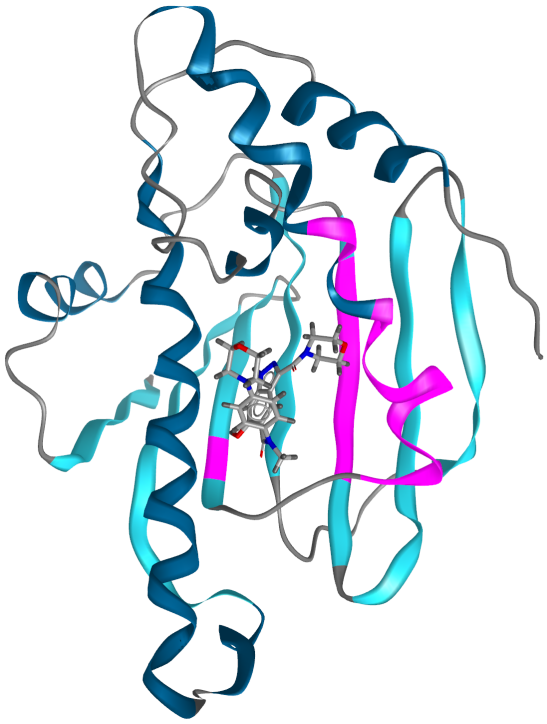
- Specify region of interest by defining key residues, which should be in the grid box
- Hsp90 example: Residues 76, 82-92, 95-96, 131-135



Schütz D., Seidel T. et al, JCTC, submitted

Feature Interaction Grids

- Specify region of interest by defining key residues, which should be in the grid box
- Hsp90 example: Residues 76, 82-92, 95-96, 131-135
- Alignment of frames done using a subset of 'static' residues: 131 - 135, 144, 152, 154, 167, 168



Schütz D., Seidel T. et al, JCTC, submitted

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Pairwise Feature Interaction Scores

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- Calculated for every complementary probe/target feature pair *i* and *j* at every grid point, taking into account distance *D* and angle *A* dependent score contributions, together with a feature strength weighting factor *C*

$$FIS_{ij} = DS_{ij} \cdot AS_{ij} \cdot C_j$$

Schütz D., Seidel T. et al, JCTC, submitted

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Scoring Function

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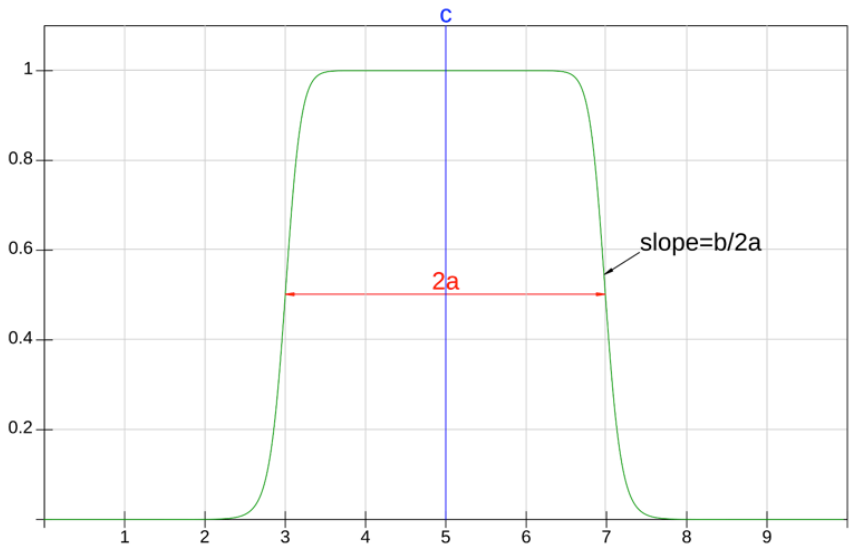
Generalized bell function:

$$GBF(x) = \frac{1}{1 + \left| \frac{x - c}{a} \right|^{2b}}$$

resulting in a vector of scores



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Schütz D., Seidel T. et al, JCTC, submitted

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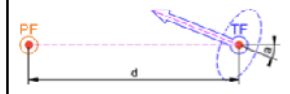
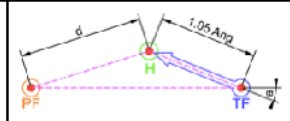
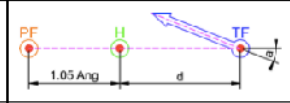
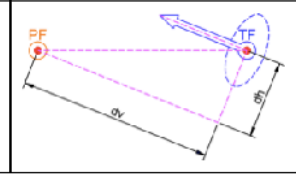
Scoring Function

For every interaction type: Optimum distances & angles defined

Complementary Feature Pair			Interaction Geometry	Distance Scoring Function/ Distance Range	Angle Scoring Function/ Angle Range
Probe Feature Type	Target Feature				
	Type	Geometry			
H	H	Point		*GBF(d)* d = 2.0 - 6.0	-
NI	PI	Point		*GBF(d)* d = 1.5 - 5.5	-
PI	NI	Point		*GBF(d)* d = 1.5 - 5.5	-
AR	PI	Point		*GBF(d)* d = 3.5 - 5.5	-

Schütz D., Seidel T. et al, JCTC, submitted

Scoring Function

Complementary Feature Pair			Interaction Geometry	Distance Scoring Function/ Distance Range	Angle Scoring Function/ Angle Range
Probe Feature Type	Target Feature				
	Type	Geometry			
PI	AR	Plane		*GBF(d)* d = 3.5 - 5.5	*GBF(a)* a = -60° - 60°
HBA	HBD	Vector		*GBF(d)* d = 1.2 - 2.8	*GBF(a)* a = -50° - 50°
HBD	HBA	Vector		*GBF(d)* d = 1.2 - 2.8	*GBF(a)* a = -85° - 85°
AR	AR	Plane		$GBF(d_v)*GBF(d_h)$ d_v = 3.5 - 6.0 d_h = 0.0 - 2.8	-

Schütz D., Seidel T. et al, JCTC, submitted

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Calculation of Atom Densities

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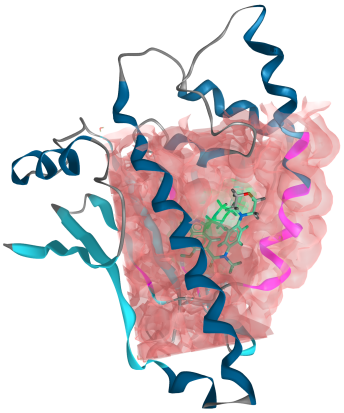
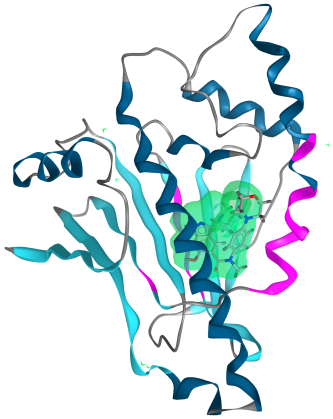
For protein and ligand atoms, and for water molecules:

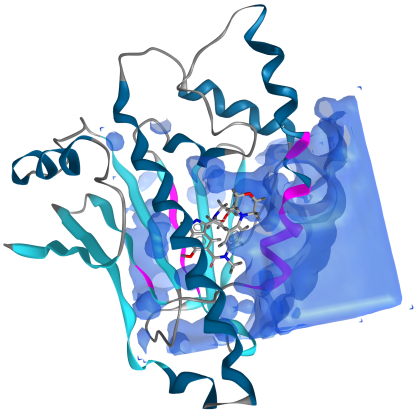
$$AD_i = max\left(GBF_j(d_{ij})\right) \qquad j = 1, \ldots, N_A$$



protein



ligand



water

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Final Feature Interaction Grid Score

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$$FIS_i = max\left(FIS_{ij}\right) \cdot \left(1 - AD_i\right) \qquad j = 1, \ldots, N_F$$

FIS_i: scalar feature interaction score at grid point i,

FIS_{ij}: pairwise feature interaction score (step 2) of the probe feature and a complementary target feature j,

AD_i: atom density (step 3) at grid point i

N_F: number of target features complementary to probe feature type

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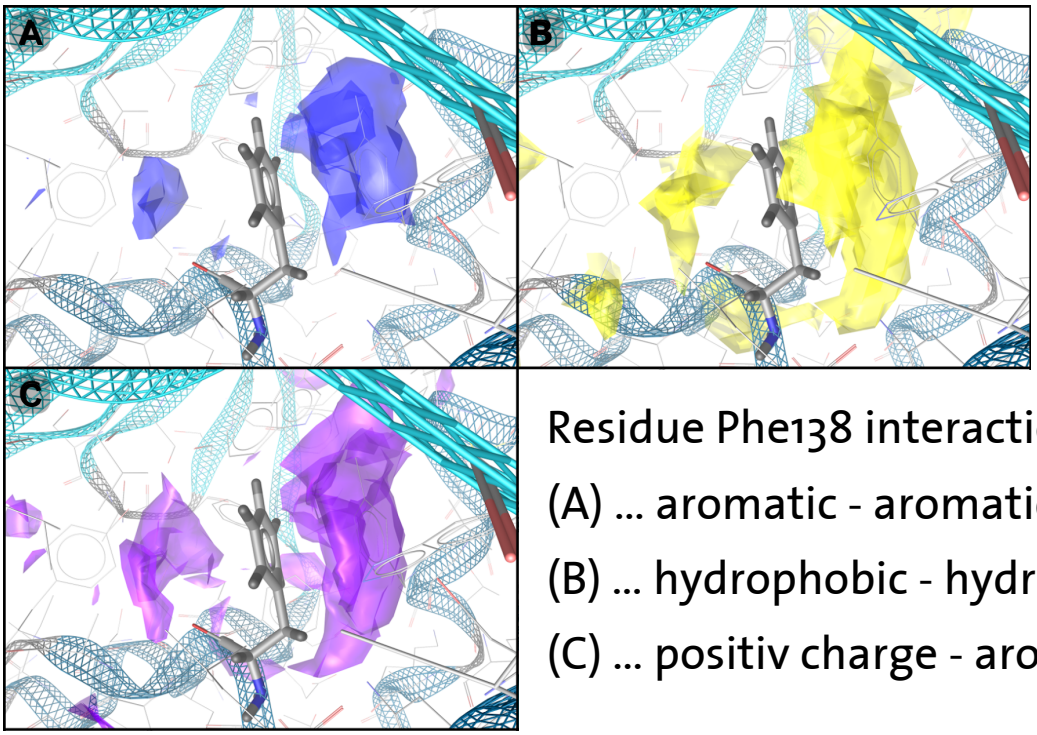
Vizualisation (1)



Residue Phe138 interactions:

(A) ... aromatic - aromatic

(B) ... hydrophobic - hydrophobic

(C) ... positiv charge - aromatic

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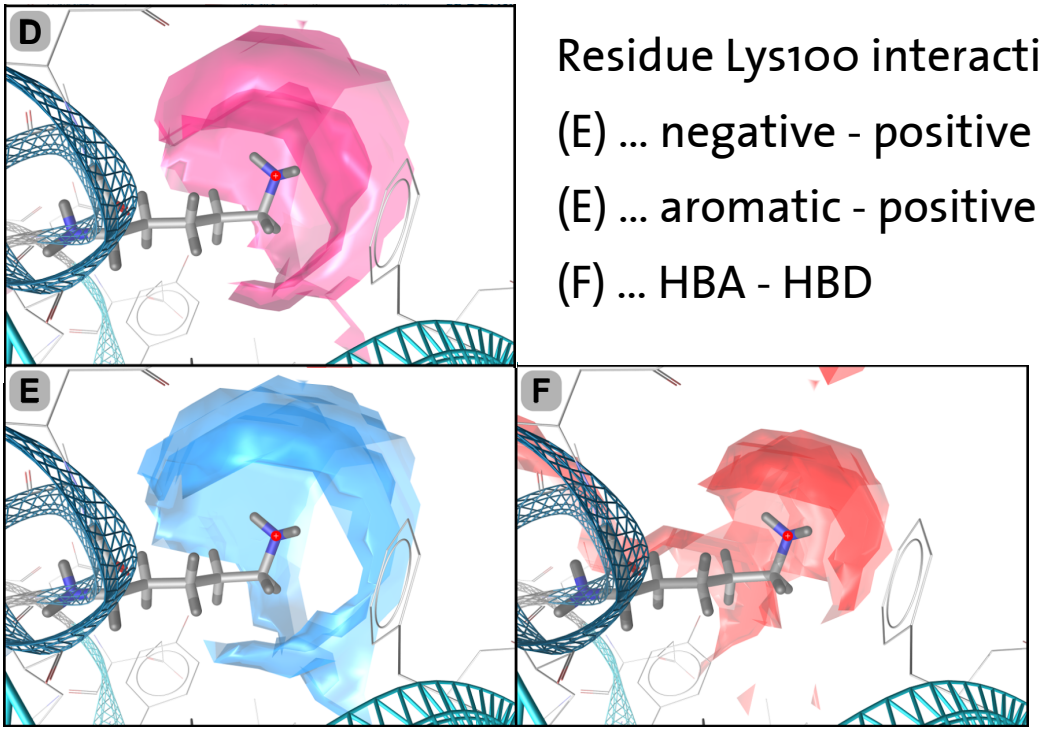
Vizualisation (2)



Residue Lys100 interactions:

(E) ... negative - positive charge

(E) ... aromatic - positive charge

(F) ... HBA - HBD

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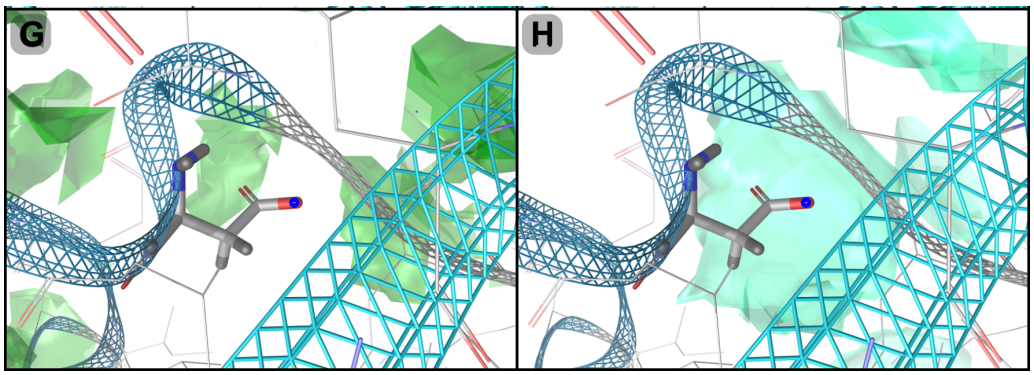
Vizualisation (3)



Residue Asp85 interactions:

(G) ... HBD -> HBA

(H) ... hydrophobic - hydrophobic

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Further Steps in the Procedure

- Create grid covering the binding site for each frame of the MD
- Perform calculations at grid points:
  - Buriedness and drugability threshold
  - Interaction probabilities for each feature at each point
- Align the grids
- Visualize and analyze
  - Look for emerging binding pockets
  - Find hot spots for interactions
  - Evaluate water molecules

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Vizualisation (4)

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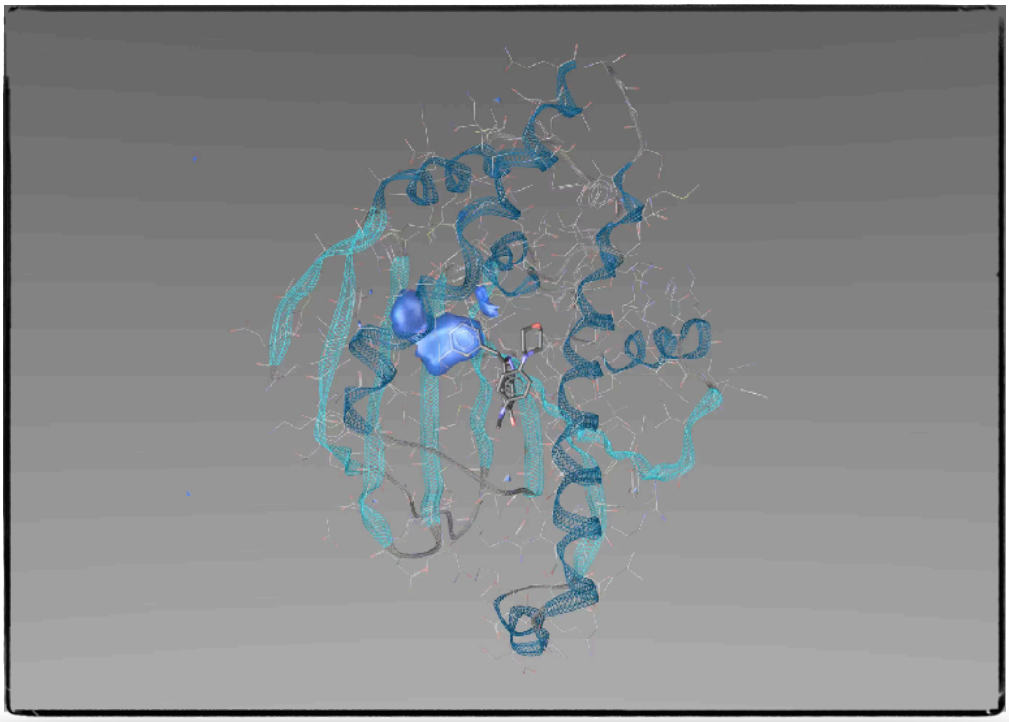

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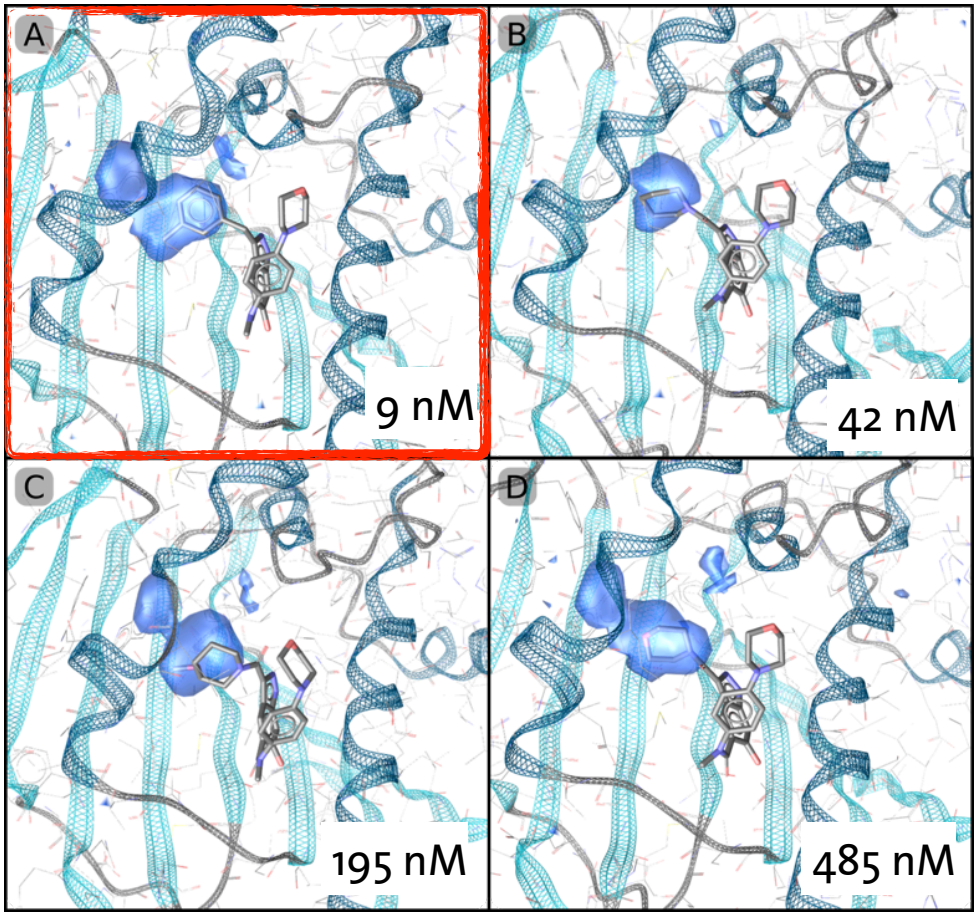

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Visual Analysis

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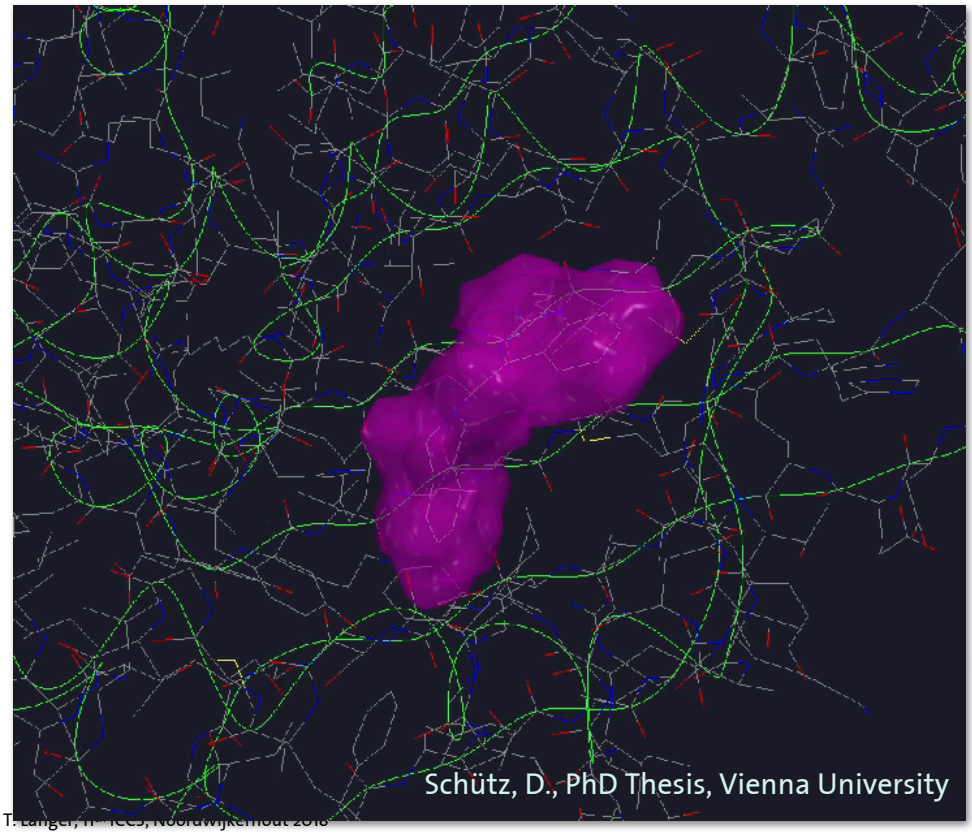

'unhappy' water molecules

'happy' water molecules

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Atom Density Grids

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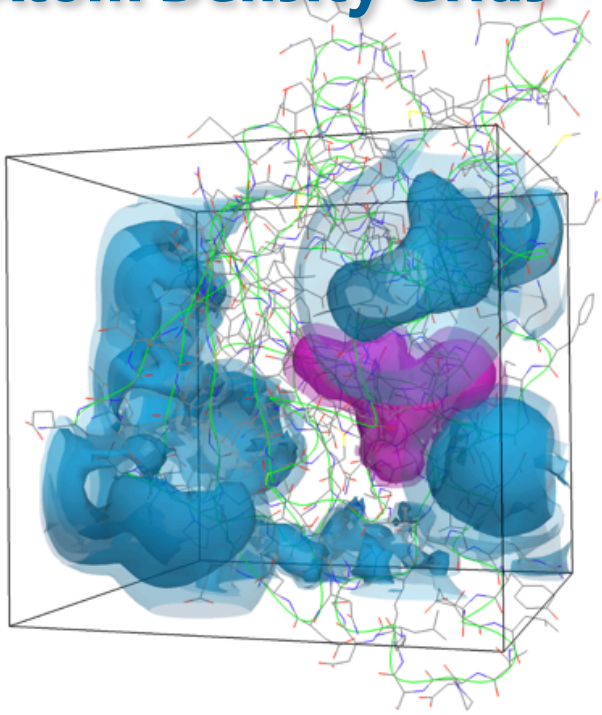
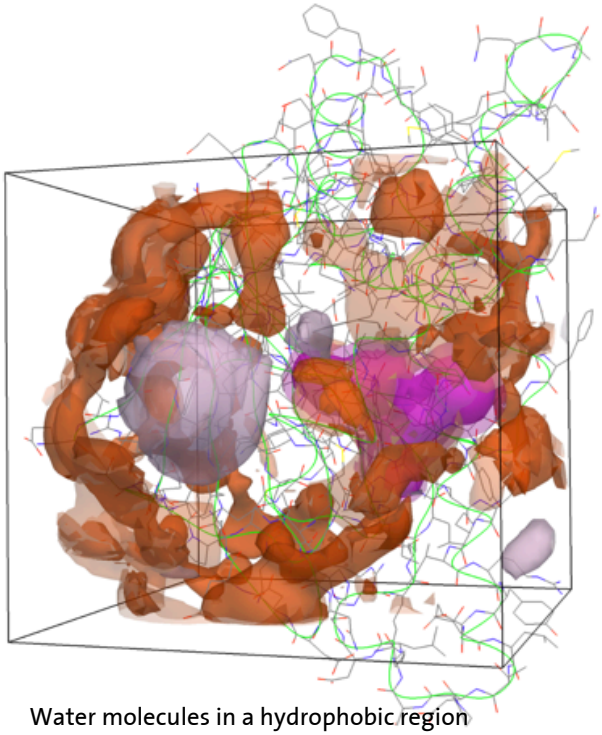


AR-PI grids are depicted in light blue



Water molecules in a hydrophobic region without potential H-bond interactions calculated grids are represented in light pink

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Use in Lead Optimization

- Easy understandable design guidance provided
- Focus on specific regions
  - e.g. replacing 'unhappy' water molecules with small hydrophobic substituent ("magic methyl positioning")
- Pharmacophore hotspot feature frequency analysis
  - for prioritizing replacement/modifications of molecular substructures
  - providing interaction preference guidance
  - easily adaptable for automatization for de novo design

Conclusions

- The pharmacophore interaction analysis concept is no more limited to static observation but is available in a convenient dynamic approach
- The novel pharmacophore-feature based grid calculations allow in-depth analysis of protein regions for optimized ligand design

➡ **Highly useful for lead structure optimization**

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Thank you for your attention

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