

A BioSolveIT White Paper

Visually Informed LeadOpt

Intuitive Understanding
Fast Improving
Solid Validation

PREMIER SCIENTIFIC SOLUTIONS

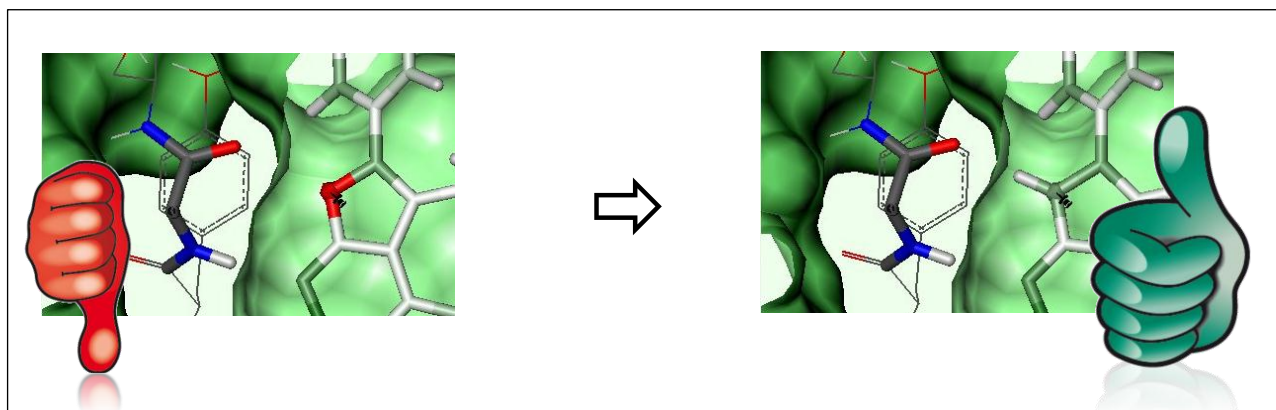


Have you ever thought about visually optimizing activity in a computer?

Now you can!

- Colors will guide you.
- Instant rescaffolding will open new doors.
- Rock-solid validation will assure you.

We suggest this to be used by your Medicinal Chemists and Modelers.



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Authors

Marcus Gastreich, Christian Lemmen
BioSolveIT GmbH
An der Ziegelei 79
53757 St. Augustin, Germany
<http://www.biosolveit.de>
[facebook.com/biosolveit](https://www.facebook.com/biosolveit)

For further information:

contact@biosolveit.de
+49-2241-2525-0

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Executive Summary

This Whitepaper reports on an entirely novel concept:

Visual Lead Optimization.

Three ingredients will boost your benefit:

1. Visual understanding of affinities. See where and why(!) to optimize your hit or lead (an unparalleled capability).
2. Instantaneous scaffold hops facilitate brainstorming new ideas (profit from the world record in accuracy and speed).
3. On-the-fly in silico validation ensures the most viable designs to come up first (using top-notch SBDD technology).

Visual LO: See where to improve



This is why especially your chemists will love this technology:

Novel actives based on appealing chemistry

- Integrated synthetic feasibility optimization, so the new actives will have appealing chemistry.
- Performance and success rate improvements.
- Super easy usage with virtually no learning curve.
- Reporting assistance in child's play style (essentially just drag&drop).
- Sound scientific footing.

However, most importantly, this is why taking a close look at it is worth your time:

Unleash MedChem know-how

This technology is applied successfully in real life by numerous pharma companies. Its speed is work-style changing and reinforces teams of Medicinal Chemists and Modelers. As a result, your LeadOpt stage will be faster and much denser in information and understanding. Altogether it is unleashing your most powerful resource: Your Medicinal Chemists' know-how.

Understanding Binding / Where to Improve?

Your lead compound is not perfectly binding yet... and you would like to know why. The core of this very task is “scoring”, i.e., the affinity assessment of a ligand in a pocket.

This is the hardest nut to crack in our field!

For more than 8 years now, BioSolveIT in a consortium of Bayer and the distinguished scientists at Hamburg University (Rarey Group) have come up and refined a globally unrivaled method.

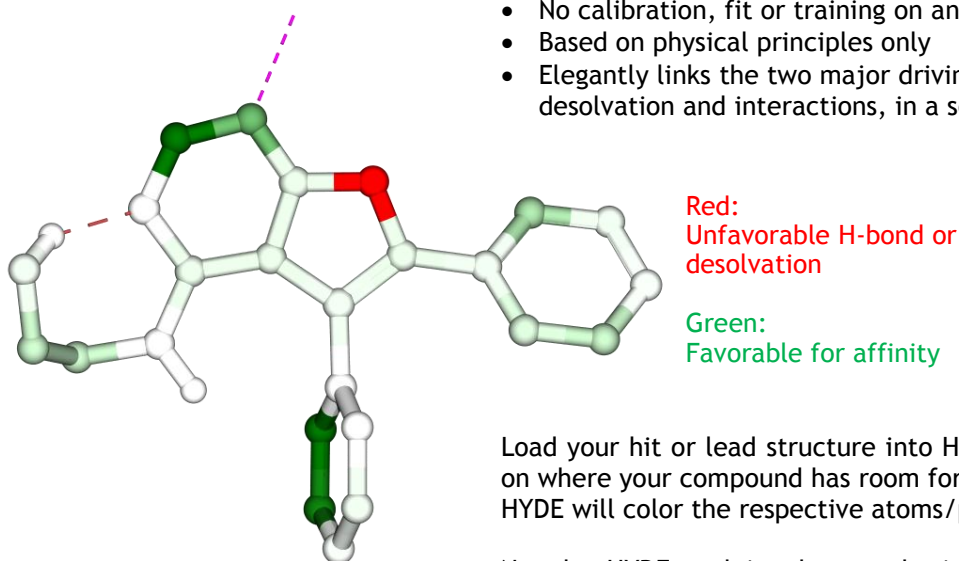
Within just seconds, this tool...

- predicts realistic Free Energies of binding
- pinpoints affinity problems of a bound ligand
- allows interactive hypothesis generation and validation to reason about the best possible next step.

“HYDE”:
Visual and intuitive
binding affinities

The magic method behind this is called HYDE. It is worldwide unique and patent protected [1,2]. Affinity predictions are generally possible for protein-ligand complexes, protein-protein interactions, as well as DNA & RNA binders etc. This is because HYDE has the following outstanding characteristics:

- No calibration, fit or training on any particular data
- Based on physical principles only
- Elegantly links the two major driving forces, desolvation and interactions, in a sound scientific manner.



Load your hit or lead structure into HYDE, and get visual feedback on where your compound has room for improvement; HYDE will color the respective atoms/parts red.

Now let HYDE explain what can be improved here; some of these scenarios could be:

- Desolvation penalties for buried hydrophilic atoms
- Weak/questionable H-bonds
- “Indifferent” scaffold or linker, not contributing to ΔG .

The beauty is: The moment you see it, it becomes obvious. HYDE is an eye-opener. It will present you the data in an unbiased way. Now leverage from your expertise; you know best what and how to make of it.

HYDE is an eye-opener

Interactively probing your complex is now possible: Exchange an unfavorable donor by a hydrophobic function or even an acceptor. Smaller the compound to improve the ligand efficiency. Find the best possible substitution pattern... - all fast and under full visual control.

Improve! On Exploring New Chemical Spaces

Now let us talk about dead-ends and the need for innovation:

Unfortunately besides binding there are a myriad of other considerations, ADMET properties, freedom to operate, or ease of chemical access, to name just a few.

In any case, if you are facing a dead end, you will need to break out of your 'current chemistry space'. In this scenario what you do *not* want is to start from scratch, but instead the best of both worlds, i.e., a new scaffold in the old binding mode.

Here, our module ReCore selects and positions the new scaffold such as to leave the remaining parts exactly in place [3]. It does that...

- Google-like at unprecedented speed: Snip, snap, click ⇒ done.
- proposing scaffolds from within your IP space
- ensuring high likelihood of synthetic access.

ReCore is widely and successfully used throughout the industry (Roche, Sanofi, Merck, Novartis, Genentech, Elan, and many more). The fact that none of the successes have been published yet just underscores the point - they are all still being worked on!

Other important Fragment-Based Ligand Design (FBLD) scenarios are addressed as well: Link or merge weak binders to form more potent leads, or grow from a known binder to explore new binding sites by fragment evolution.

“ReCore”:
Fragment-based LeadOpt,
industry-proven

Snip, snap, click!
A new scaffold proposal
from your IP space

Fragment evolution or linking?
No problem!



Validate at 96% Accuracy: Just Dock It!

When you enter the lead optimization phase, you usually have a lead. At least you will have an 'idea' - a starting point - maybe just as a sketch on a piece of paper. Obviously this idea must fit your target cavity.

Quality molecular docking is the key to master this challenge. Docking must be fast and accurate. It must yield a reliably scored pose for further analysis of the binding hypothesis.

Successes cited 6.000+ times

BioSolveIT has long-standing expertise in virtual screening tools. Our fast and reliable docker grounded on FlexX technology, has been cited more than 6.000 times by today [4]. Starting from being one of the very first industry-standard flexible ligand molecular dockers, it has evolved during 15+ years of experience to a situation in which the problem in essence can be considered solved!

ACS 2011 Competition:
Better than others in both
accuracy & virtual screenings

FlexX flexibly builds up a ligand in a cavity within seconds. In March 2011, an independently organized docking & scoring contest showed that in 96% of the cases, FlexX delivered 3D structures, which mimic the experimentally determined structure.

Docking involves:

- Loading the protein and small molecule:
Just drag and drop standard input into the GUI.
2D gets automatically converted to 3D!
- The preparation of a binding site:
Traditionally, this used to be a core task for computational chemistry experts. Today an automatically prepared binding pocket can be generated by any scientist with a few mouse clicks - yet under full chemical and visual control.
- Kicking off the docking with or without constraints:
Essentially: Select ⇒ Click ⇒ Go ⇒ Done.
- Analyzing the results:
A table view allows you to browse through results. Side by side you see poses in 3D (stereo if you like) and atomic resolution sketches using our revolutionary PoseView technology to plot 2D images of the complex [6].

FlexX coupled to HYDE exhibited an outstanding performance in the 2011 ACS Docking & Scoring Competition [5]. Not only came the duo out top but showed its strength also in detecting & visualizing issues in crystal data, regarding protonation/tautomers etc.

In the triangle based on docking and HYDE Visual Affinities, new scaffold proposals from ReCore can instantaneously be checked: The docking will validate the fit of the new scaffold; HYDE shows if and how to gain affinity - surely indicating more ways forward.

A Word on Speed. Real Speed That Is.

When speed really takes influence, it entirely changes the way we work. We are not talking fractions (20%, 30%, ...) or even factors (times 2 or 3 faster). We mean orders of magnitude. Remember the Internet before Google? Very similarly, the algorithms behind LeadIT facilitate this Big Leap. Consider these comparisons:

Google vs. **Searching the entire Internet page by page:**

= **Seconds** vs. **undoable**

Synthesis check doable
by humans on-the-fly

ReCore Fragment Replacement vs. **anything else:**

= **Seconds** vs. **minutes or even hours**

New:
“In-situ collaboration” of
Medicinal Chemists and
Modelers

HYDE Visual Affinities vs. **MM-GBSA etc.:**

= **Seconds** vs. **hours to days**

The Big Leap here is that now Computational Chemistry and Medicinal Chemistry can go hand in hand, in real time.

Previously, these processes were largely separate, i.e., the Modeler came up with ‘designs’ from which the Medicinal Chemist ‘picked’ what he or she liked. Besides re-iterated frustration on both sides, such cycle times were lengthy, inhibiting innovation.

Real speed makes your
Medicinal Chemistry staff
spend less time in front of a
computer

Now the two parties can create & validate novel compounds on-the-fly, INCORPORATING Medicinal Chemistry input while the Modeler prepares a session to ensure the best possible use of resources. No need to say, that this can also be done with the entire chemistry team in a brainstorming session, or by any chemist alone if he or she has fun using computers.



Summary & Advantages

For the first time, visually controlled lead optimization is possible.

You are enabled to UNDERSTAND binding affinities, and to SEE how to improve your leads using a radically different scoring system and the most advanced fragment-based technology.

Synthetically working chemists can use the software - either independently or in teams with modelers.

All synthetic feasibility is under control of a novel concept involving both user and computer instantaneously; this "*in situ*" checking is powered by algorithms which work at unparalleled speed.

Pharma industry participated in developing this software; it is used globally, producing euphorically commented successes.

Related Publications

- Hyde Visual Affinities:

[1] Lange G, Klein R, Albrecht J, Rarey M, Reulecke I (2010), Patent Nr. EP2084520

[2] Schneider, N, Lange, G, Hindle, S, Klein, R, Rarey, M (2012), A Consistent Description of HYdrogen Bond and DEhydration Energies in Protein-Ligand Complexes: Methods Behind the HYDE Scoring Function, Journal of Chemical Information and Modeling, submitted.

- ReCore Instant Rescaffolding

[3] Maaß, P, Schulz-Gasch, T, Stahl, M, Rarey, M (2007), Recore: A fast and Versatile Method for Scaffold Hopping Based on Small Molecule Crystal Structure Conformations, Journal of Chemical Information and Modeling, 47:390-399.

- FlexX/SIS Docking

[4] Rarey M, Kramer B, Lengauer T, Klebe G (1996), A fast flexible docking method using an incremental construction algorithm, Journal of Molecular Biology 261(3):470-89.

[5] Schneider, N, Hindle, S, Lange, G, Klein, R, Albrecht, J, Briem, H, Beyer, K, Claußen, H, Gastreich, M, Lemmen, C, Rarey, M (2012), Substantial improvements in large-scale redocking and screening using the novel HYDE scoring function, Journal of Computer-Aided Design, 26(6):701-23
<http://dx.doi.org/10.1007/s10822-011-9531-0>

- 2D Visualization of Complexes

[6] Stierand, K, Maaß, P, Rarey, M (2006), Molecular Complexes at a Glance: Automated Generation of two-dimensional Complex Diagrams, Bioinformatics, 22, 1710-1716,
<http://www.poseview.de>

“Hyde proposed to remove a carbonyl.
The newly designed compound is 10 times more active.”

“We never had such rapid impact
as when using ReCore.”

“Our chemists use it regularly.”

“Oh no, this is too simple!”

“Hit rates of 70% in a virtual screening
during an ongoing project.”

“Including an F in a ring, the compound Hyde favored
now turned out to be the most active one.”