

Welcome to the 19<sup>th</sup> edition of the BioSolveIT newsletter!

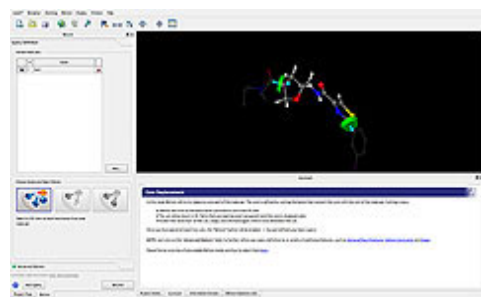
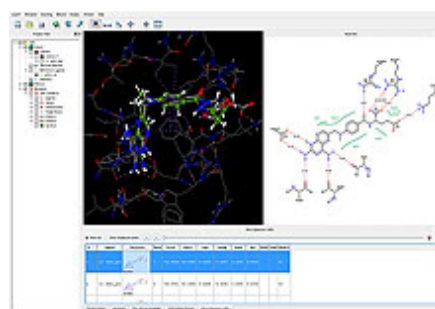
In our newsletter we publish information about new developments, events, milestones, and scientific facts on a quarterly basis.

### **LeadIT 1.2 – share thoughts, elucidate together to innovate further!**

**LeadIT** 1.2 is now out; this version of **LeadIT** contains many new features which make life simpler and allow research scientists to share their thoughts and analyses much easier with other scientists. Productively sharing and linking each other's thoughts in relation to different projects commonly proposes issues. Keeping track of active projects, data integration and which information belongs where is a significant problem. Transferring and exchanging data can be difficult enough with the vast amounts being produced. Disparate information relating to virtual screening results hidden in an email client or in a word document can prove to be tremendously cumbersome and extremely difficult to handle and find.

Questions relating to which information/email belongs to which project, which specific solutions have particular importance and further more complex analyses of screening results at deeper levels of detail for active molecules are important. Thus detailed notes can now be saved within a **LeadIT** Project File to consolidate all information in one place to stimulate joint conclusions and knowledge generation. Comments can also be appended to virtual screening solutions to permit the sharing of thoughts between researchers based on a specific **LeadIT** solution which may in the future be proposed as a candidate active molecule for testing. Additionally, viewing a particular solution in a specific 3D orientation may also be vitally important for understanding and interpreting others findings. Therefore a screen capture facility is a simple click away to allow each researcher to portray the exact same specific 3D angle and perspective used previously for analysis. Such features provide a platform for a much more rapid insight into proposed conclusions of researchers working within a team. Sharing ideas and discussing hypotheses about noteworthy screening solutions permits teams of researchers to affirm and together establish significant findings.

**PoseView** incorporated in **LeadIT**, is another piece of added value. It allows users to visualize protein-ligand complexes in 2D on the atomistic level. **PoseView** automatically generates high-quality 2D structure-diagrams of protein-ligand complexes provided as 3D-input. The atomistic 2D depiction of a complex shows hydrogen bonds as dashed lines between the interaction partners on either side. Hydrophobic interactions are illustrated as smooth contour lines between the respective amino acids and the ligand. The ligand itself is drawn utilizing the **2Ddraw** engine according to chemical drawing conventions. Within the context of **LeadIT** now docking solutions from **FlexX** can be visualized in 2D using **PoseView** and exported to a variety of graphics formats for automatic generation of publication-quality graphics. The 2D depictions permit researchers to swiftly scrutinize, identify and share how a ligand is interacting with a protein.



Another novel feature in **LeadIT** 1.2 is the 'Assistant' help which intuitively provides a resource for users to be guided through the correct procedure for performing their desired flavor of virtual screening. The 'Assistant' describes what must be 'done/clicked' to progress through the procedural steps required for successful screening. It may be thought of as an on-the-fly tutorial!

If any of this strikes you as interesting and in case of any questions or comments please do [email us](#).

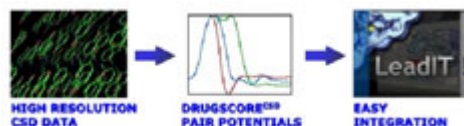
## DrugScore is back in *FlexX* oozing CSD quality

---

**DrugScore** is a widely recognized knowledge-based scoring function for protein-ligand complexes. It comprises a sum of pseudo-energies for interactions of each pair of non-bonded atoms. The pseudo energy-term calculated is dependent on the types of the two atoms as well as their distance and is taken from a statistically derived pair-potential. DrugScore was originally developed by Holger Gohlke in the group of Gerhard Klebe at the Philipps University of Marburg. The original pair potentials were derived from the PDB. However, DrugScore-CSD an extension of the concept was developed by Hans Velec using the CSD as a knowledge base. The CSD version has been shown to be superior compared to the PDB-based version and a recent assessment demonstrated it to be one of the best scoring functions available.

DrugScore-CSD may now be used for docking and scoring within *FlexX* (integrated in *LeadIT*, starting from Release 1.2). *LeadIT-FlexX* effortlessly and efficiently implements the use of pair potentials by means of a generic interface.

A settings file containing the CSD potentials includes all the necessary parameters for *FlexX*-Docking to utilize DrugScore-CSD potentials for scoring. As always a very generic approach to integrating such data was undertaken. In the case of DrugScore the so-called pair-potential interface (check out 'PPI' in the *FlexX* User Guide) provides a generic platform for integration. Generally speaking the PPI reads lengthy tables of pairs of atom-types with a distance-dependent pair potential. Aside of the two types of DrugScore, it handles all sorts of pair potential data. Users may even derive their own pair-potentials and use them, e.g., as a custom-made scoring function.



Thanks to our collaborators in the Klebe-lab of the University of Marburg as well as the Cambridge Crystallographic Data Centre we can make this terrific scoring function available. Particularly we would like to thank Gerd Neudert who implemented the final touches to this version of the DrugScore function and in making sure that our integrated version performs as consistently as his stand-alone version. To obtain your copy of **DrugScore-CSD** you will need a username and password – enter your 2010 CSD subscriber Site Number as your username, and Confirmation Code (without the leading 'CC') as the password in order to download the package. The README-file within the package will guide user, if you do experience any problems using DrugScore-CSD in *LeadIT*, or have any questions about DrugScore-CSD, *FlexX*, or *LeadIT*, please [contact our support](#).

## ReCore indexing – here, there, anywhere, value everywhere

---

The scaffold hopping and FBLD screening tool **ReCore** within *LeadIT* uses a set of fragments as a data source to perform calculations to propose novel fitting cores, ligands which have been grown or merged ligands. To suggest these molecules **ReCore** searches, within just a couple of seconds, huge sets of fragments in the form of an index. An index can be thought of as a telephone book, when searching a telephone book it would be nonsensical when searching for the name 'Lipinski' to start searching at the beginning from A to reach L. Plus the search time is pretty much independent of the size of the phone book. The search uses a descriptor to utilize information efficiently, the alphabet in the case of a telephone book. In **ReCore** the positions of vectors are used as a descriptor instead of the alphabet, the positions of bonds or pharmacophoric points in 3D space are used. This method provides a sound basis for an instant hit of diverse medicinal chemistry due to the indexing technology.

BioSolveIT ships *LeadIT* with a toy sandbox indexed fragment set based on the DUD subset of ZINC. This is primarily designed to allow users to 'play' with all the functionality within *LeadIT* rather than perform scientific analyses!!! This keeps the initial installation package of *LeadIT* to a minimal size and users can use the software within minutes of downloading. Additionally, a much more comprehensive indexed fragment set was created from 3.27 million molecules of the ZINC 'Lead Like' subset. All compounds from this 'Lead Like' subset only had their unique Bemis-Murcko scaffolds taken into account during index creation. This second indexed fragment set is the recommended dataset to work with when performing scientific studies therefore we highly recommend its [installation](#).

Furthermore, an indexed fragment set has also been created from the Cambridge Structural Database (CSD) using precise crystal structure data which forms the highest quality input fragment data for scaffold hopping and FBLD with *LeadIT*. This fragment set can also easily be [downloaded](#) with CSD subscription data (please see above, final paragraph of the DrugScore section). However, there

are no limitations with **LeadIT**, creation of your own individual indexed fragment dataset is easily possible with **ReCore's** built-in shredding functionality. The procedure is very simple and may be followed in this month's [tips and tricks section](#). Many companies have already created manipulated and conformationally enumerated fragments to successfully create unique and personalized indices to search their in-house data. If you have any questions please do [contact us](#), or if you fancy picking up a copy of our super playful tool **LeadIT** just [grab a copy](#).

## summer school kicks off **LeadIT** worldwide workshop series

---

BioSolveIT are happy to inform you that a summer of fun and learning with their ongoing variety of workshops around the world has kicked off. The great line-up of events provides occasions for users or potential new users to play with and learn about our software in a hands-on workshop environment.

BioSolveIT will be holding a variety of different workshops in the future tailored to the specific events they are linked to. The first two workshops which kicked off the series of BioSolveIT workshops were the Chemoinformatics Summer School in Obernai, France 20-24<sup>th</sup> June and an FBDD workshop held in conjunction with the 5<sup>th</sup> Sheffield Chemoinformatics Conference in Sheffield, UK on 13<sup>th</sup> July. These workshops were a great success with around 140 and 35 attendees, respectively.



The third workshop of the summer will be also held in the UK, at Oxford University. This event is within the context of a week long training event provided by eCheminfo, which brings many different people from industrial and academic organizations together to be taught how to perform drug discovery on real practical drug design problems. The event incorporates a session from BioSolveIT where our FBLD methods will be applied on various case studies for many popular drug design targets.

The fourth event is a specialist workshop tailored to medicinal chemists that may have no prior experience in using software for computer-aided drug design. The workshop is being hosted at the [21<sup>st</sup> International Symposium on Medicinal Chemistry IFMC-ISMC conference](#) in Brussels, Belgium on the 7<sup>th</sup> September.

The fifth and probably not the last workshop is being held at FBLD 2010 in Philadelphia, USA on the 10<sup>th</sup> October. This workshop will be split into two separate parts, the first in conjunction with the Chemical Computing Group highlighting the synergies between BioSolveIT software and CCG's Molecular Operating Environment (**MOE**<sup>®</sup>) modeling suite. The second component will be solely focusing on BioSolveIT software relating specifically to our individual FBLD approaches. If you have any interest in any of these workshops please do [contact us](#).

## tips & tricks: **ReCore** in **LeadIT** – indexing

---

The section today focuses on the indexing aspects of **ReCore** within **LeadIT**, we will see how easy it is to create and index your own fragments for use in **LeadIT**. In this issue we present a step wise guide of indexing for our tips'n'tricks which will help you learn how to work more effectively with **LeadIT** by working on your own data! [Read more!](#)

You can view previous topics of tips'n'tricks [here](#). If you have any questions or know of any tip-s'n'tricks yourself that you would like to share with the BioSolveIT user community, we would appreciate your input at [support@BioSolveIT.de](mailto:support@BioSolveIT.de).

## BioSolveIT news in brief

---

- A paper published by our academic partners, The Center for Bioinformatics (ZBH) of the University of Hamburg, based on [focused library design](#) is in the JCI's top-10 most accessed articles in the first quarter of 2010.
- Recently released BioSolveIT Software: [FTrees 2.2.0](#) and [CoLibri 1.3.0](#).

- The tools [PoseView](#) and [FTrees](#) are both accessible to play with online, a resource provided by our academic partners at The Center for Bioinformatics (ZBH) of the University of Hamburg.
- Our Indian customers and potential users can now learn more about our tools on a weekly basis as our Indian distributors Apsara Innovations are starting to provide a [weekly webinar series](#).
- Dates for your diary:** BioSolveIT will be present at the following events:

July 26 - 30	<a href="#">eCheminformatics Drug Discovery Workshop</a> , Oxford, UK
August 22 - 26	<b><a href="#">240<sup>th</sup> ACS National Meeting &amp; Exposition</a></b> , Boston, MA, USA – August 23, 2010 10:00 am, Room 157A COMP: Challenges in Industrial Computational Methods <i>Lightning-fast 3D-shape and feature-based virtual screening</i> (C. Lemmen) – August 25, 2010 8:30 am, Room 157B COMP: Docking & Scoring: What Have We Learned and Where Are We Now? <i>Recent advances in computational fragment-based lead discovery</i> (C. Detering) – August 25, 2010 1:35 pm, Room 157B COMP: Docking & Scoring: What Have We Learned and Where Are We Now? <i>Importance of pharmaceutically relevant benchmark data</i> (C. Lemmen)
September 05 - 09	<b><a href="#">XXI<sup>st</sup> International Symposium on Medicinal Chemistry</a></b> , Brussels, Belgium – <i>A New Fragment Based Ligand Design Tool to Boost Communication Between MedChems and CompChems</i> (poster by M. Gastreich)
September 19 - 24	<b><a href="#">18<sup>th</sup> European Symposium on Quantitative Structure-Activity Relationships</a></b> , Rhodes, Greece Presentations by our project partners: – September 20, 2010, 9:30 <i>Qsearch: A new method for de novo ligand design</i> (T. Schulz-Gasch, Hoffmann-La Roche, Basel, Switzerland) – September 23, 2010, 9:55 <i>From activity cliffs to target-specific scoring models and pharmacophoric hypothesis</i> (B. Seebeck, University of Hamburg, Germany) – September 23, 2010, 15:05 <i>HYDE scoring of protein ligand complexes</i> (G. Lange, Bayercropscience, Frankfurt, Germany)
October 04 - 06	<b><a href="#">Dutch Medicines Days 2010</a></b> , Lunteren, The Netherlands There will be a tutorial workshop given.

If you would like to meet one of our representatives to discuss any questions or have any kind of feedback please email us at [Contact@BioSolveIT.de](mailto:Contact@BioSolveIT.de).

## literature corner

- Ligand-protein docking studies of potential HIV-1 drug compounds using the algorithm FlexX***  
 George Patargias, Gary Ewart, Carolyn Luscombe and Wolfgang B. Fischer  
 Anal Bioanal Chem. 396(7):2559-63, (2010)  
[details here](#)
- Identification of the First Low-Molecular-Weight Inhibitors of Matriptase-2***  
 Mihiret Tekeste Sisay, Torsten Steinmetzer, Marit Stirnberg, Eva Maurer, Maya Hammami, Jürgen Bajorath and Michael Gütschow  
 J.Med.Chem. Publication Date (Web): July 14, 2010  
[details here](#)
- In Pursuit of Fully Flexible Protein-Ligand Docking: Modeling the Bilateral Mechanism of Binding***  
 Angela M. Henzler and Matthias Rarey  
 Molecular Informatics, 29:164-173, (2010)  
[details here](#)

## upcoming articles

---

- HYDE protein-ligand complex scoring
- KNIME*<sup>®</sup> nodes

## contact

---

For further information please contact:

**BioSolveIT GmbH**  
An der Ziegelei 79  
53757 Sankt Augustin  
Germany  
email: [newsletter@BioSolveIT.de](mailto:newsletter@BioSolveIT.de)  
www: [www.BioSolveIT.de](http://www.BioSolveIT.de)  
phone: +49 2241 2525-0  
fax: +49 2241 2525-525