



# The Schrödinger Quarterly Newsletter

February 2009

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In this issue of the newsletter:

**Ask the scripts expert:** Dr. Woody Sherman, Schrödinger's Vice President of Applications Science, describes how Schrödinger scripts allow users to detect disallowed torsions in homology models, view hydrophobic contacts, and perform spectral clustering

**New web interfaces for Glide and Phase** facilitate collaboration between modelers and medicinal chemists

Schrödinger announces **talks by applications scientists and modeling workshops** at the Spring 2009 ACS National Meeting in Salt Lake City

Schrödinger announces **web seminar topics for 2009** and welcomes your suggestions for additional talks

Schrödinger scientists and representatives will be at **Advances and Progress in Drug Design VIII**

**Recent publications** describe successful applications of Schrödinger software

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## **Ask the scripts expert**

### **Dr. Woody Sherman, Vice President of Applications Science**

*Dr. Sherman works closely with researchers using Schrödinger software for molecular modeling and drug design projects. In this newsletter, Dr. Sherman talks about displaying hydrophobic interactions, and more. All of the scripts discussed here may be downloaded free of charge from the Schrödinger Script Center, or by using 'Update...' from the Scripts menu in Maestro.*

*Q: I have just built a homology model and would like to automatically detect all disallowed phi/psi backbone or chi1/chi2 side chain torsional angles in my structure. Is there a way to do this?*

A: Yes, you can do so using the Disallowed Backbone/Sidechains script (select\_disallowed.py), which appears under the Workspace Tools category of the Scripts menu. This will detect disallowed phi/psi (backbone) or chi1/chi2 (side chain) angles in your Workspace structure. These residues will be selected in the Workspace so they can easily be corrected by running a Prime side chain prediction or loop refinement on the necessary residues. Additionally, the Ramachandran Plot under the Maestro Tools menu allows for interactive investigation of phi/psi values.

Q: I have tried to use the Contacts tab in the Measurements panel to display hydrophobic contact but it appears to show all contacts (not just hydrophobic). Is there a way to display only good hydrophobic contacts between a ligand and protein in the Workspace?

A: This can be done with the Display Hydrophobic Interactions script (display\_hydrophobic\_interactions.py), which is found in the Workspace Tools category of the Scripts menu. This script will automatically detect the hydrophobic contacts between the ligand and protein in the Workspace, and will display these contacts with green dotted lines.

Q: I read about Spectral Clustering as described in J. Chem. Inf. Model, 2007, 47, 1727-1733, and like many of the features of this method. Has Schrödinger implemented such a clustering technique?

A: Yes, we have implemented Spectral Clustering using our Canvas cheminformatics infrastructure (spectral\_cluster.py). It can be found under the Cheminformatics category of the Scripts menu. You can select from a range of fingerprint types and similarity metrics. The cluster membership, cluster eigenvalue, and normalized cluster eigenvector will be added to the Project Table for each entry. The eigenvalues represent the overall intermolecular similarity within each cluster. The eigenvectors show the relative contributions from each molecule within a cluster.

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## Schrödinger releases web interfaces for Glide and Phase

Maestro is a powerful, full-featured graphical molecular modeling interface that is widely used by modelers in pharmaceutical and biotechnology companies. However, researchers who only use modeling tools on an occasional basis may prefer a more streamlined

The screenshot shows a web interface for running a docking job. It contains the following elements:

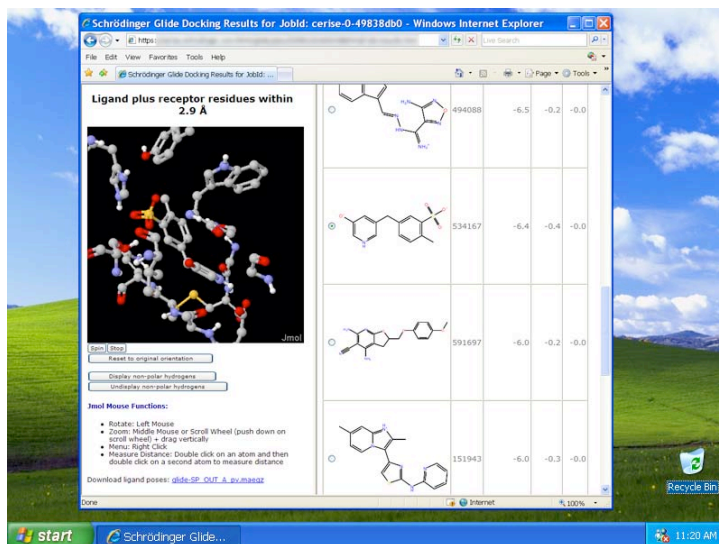
- Browse for a ligand file (?):** A text input field containing "ligand\_set1.smi" and a "Browse..." button.
- Enter a name for the job:** A text input field containing "glide".
- Select receptor "grid" file (?):** A dropdown menu showing "factorXa (tutorial)".
- Select a host/queue:** A dropdown menu showing "localhost (the web server)".
- Select Glide docking precision (?):** A dropdown menu showing "Standard Precision (SP)".
- Prepare ligand(s) with LigPrep (?):** A dropdown menu showing "Yes - with pKa prediction (Epik)".
- Submit Job** and **Reset** buttons at the bottom.

interface tailored solely to the task of interest. In response to these needs, we recently released web interfaces to two of our most popular programs, Glide and Phase, and there are plans to develop web interfaces for additional programs. The web interfaces provide a highly intuitive way to run these programs from a web browser on either your local web server or from dedicated machines.

The Schrödinger web interfaces place an emphasis on ease of job submission and subsequent visual interpretation of results. The Glide web interface allows users to simply select a ligand file and a receptor model, while users of the Phase interface need only to select a pharmacophore model and a Phase database. For both interfaces, a small selection of additional job options is provided directly on the submission page. Once the job is submitted, a progress page is displayed that allows users to monitor the status of the job. When the job completes, a results page is automatically displayed. The results page for both interfaces provides an embedded 3D graphics window as well as a results table with 2D images of the ligands. In the Phase interface, the 3D graphics window also displays the pharmacophore model.

These web interfaces were designed to facilitate collaboration between modelers and medicinal chemists. We expect that modelers will first prepare the initial receptor structures (for Glide) or develop pharmacophore models (for Phase). Then, using the simple mechanism we supply, modelers can make these receptor structures and pharmacophore models available for docking or screening experiments that can be performed by anybody who has access to the web interface, such as colleagues in medicinal chemistry.

We encourage you to email us at [help@schrodinger.com](mailto:help@schrodinger.com) with your suggestions for additional web interfaces that you would like to see us develop.



Above, the Glide web interface as it appears while visualizing results.

The Glide and Phase web interfaces can be downloaded using the respective links:  
<https://www.schrodinger.com/Documentation.php?mID=6&sID=6&cID=5000&pdID=2372>  
<https://www.schrodinger.com/Documentation.php?mID=6&sID=16&cID=5000&pdID=2537>

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## Schrödinger talks and events at the 237th ACS National Meeting & Exposition, Salt Lake City, Utah, March 22-26

### **Talks by Schrödinger scientists at the ACS National Meeting**

Schrödinger application scientists and members of the company's Scientific Advisory Board will be presenting talks on a variety of topics in Salt Lake City. A short list of selected talks is given below. A complete list of talks is available on our website.

#### **Selected talks by Schrödinger scientists at the spring 2009 ACS National Meeting**

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<b>PHYS 33</b> Sunday, 3/22, 11:00 am Convention center room 251 C	<i>Richard A. Friesner</i> : Polarizable modeling of proteins: Force fields and empirical corrections
<b>CINF 64</b> Wednesday, 3/25, 10:35 am Convention center room 254 A	<i>Richard A. Friesner</i> : Development of scoring functions for computing protein-ligand binding affinities
<b>COMP 195</b> Wednesday, 3/25, 1:30 pm Convention center room 258	<i>Thijs Beuming</i> : Accurate calculation of explicit water molecule free energies: Applications to PDZ binding domains
<b>COMP 190</b> Wednesday, 3/25, 2:00 pm Convention center room 257	<i>Noeris K. Salam</i> : A novel method for generating structure-based pharmacophores using energetic analysis
<b>COMP 217</b> Thursday, 3/26, 2:40 pm Convention center room 257	<i>Mee Shelley</i> : Prediction of cytochrome P450 mediated oxidation using induced fit docking

### **One-on-one consultations with Schrödinger applications scientists**

We invite you to visit the Schrödinger booth (#601) in the exhibition hall, where you can make an appointment to meet with one of Schrödinger's applications scientists attending the Meeting. Whether you're looking to bounce ideas on a research project or have a technical question, you're welcome to schedule a one-on-one session. Attending scientists and the subjects of their recent projects include:

Thijs Beuming - Free energy calculation and molecular dynamics

Noeris Salam - Ligand-based drug design, pharmacophore modeling, and structure-based pharmacophore models

Mee Shelley - Structure-based drug design, induced fit docking, and prediction of cytochrome p450-mediated oxidation

### **Introductory Workshops on general modeling and computer-aided drug design**

Schrödinger is hosting two introductory workshops during the ACS. There is no cost to participate, but we kindly ask that you register in advance at our booth (#601 in the exhibition hall), as space is limited.

Fundamentals of computational chemistry using Jaguar and MacroModel  
Wednesday, March 25<sup>th</sup>, 8:30 - 11:00 am  
ACS National Meeting

Join us for a hands-on introduction to molecular modeling that uses the programs MacroModel and Jaguar for classical and quantum mechanical calculations respectively. Following a discussion on common uses of these programs in research and in education, attendees will get an opportunity to carry out various modeling experiments including energy minimization, conformation search, and transition state identification, all within Schrödinger's unified graphical interface - Maestro. Attendees will receive a step-by-step tutorial with corresponding example files that can be used for future training.

Introduction to Schrödinger's Drug Design Software Suite  
Thursday, March 26<sup>th</sup>, 10 AM to 12:30 PM  
INSCC Auditorium room 110, University of Utah campus

This workshop will introduce attendees to Schrödinger's full line of drug design software for both structure- and ligand-based research. A presentation of real-life applications will be followed by hands-on introduction to Schrödinger's unified graphical user interface, Maestro. Attendees will get an opportunity to learn how to set up calculations and analyze results using Maestro.

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**Schrödinger welcomes your suggestions for 2009 web seminar topics**

We are now putting together the lineup for Schrödinger's 2009 web seminar series, and we would love to hear from you. We welcome suggestions from modelers, medicinal chemists, and all prior seminar attendees. Are there any previous seminar topics that you'd like to see us revisit with either a repeat or a follow-up talk? Would you like to see new seminars developed around particular subjects or programs?

In addition to planned talks on the forthcoming Schrödinger Suite 2009, our new cheminformatics program Canvas, and applications studies aimed at predicting p450 metabolites, the Spring seminar series will include a presentation on Maestro that guides users through the process of performing various modeling tasks. We'd like to invite all Maestro users, from novices to experts, to submit suggestions for tasks that they'd like to see demonstrated in this presentation.

Please email [newsletter@schrodinger.com](mailto:newsletter@schrodinger.com) to send us all your great ideas.

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## **Schrödinger scientists and representatives at Advances and Progress in Drug Design VIII, London, UK, February 23-24**

Schrödinger will be at the Advances and Progress in Drug Design VIII conference, taking place February 23-24, 2009, in London, UK.

Dr. Jörg Weiser, Senior Vice President of International Operations, will give a talk titled "Mapping Water Molecules: The Role of Water in Binding Affinities of Protein-Ligand Complexes." Schrödinger is a sponsor of the event and will be exhibiting at the conference.

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### **Recent publications**

Below are recent publications highlighting the successful use of Schrödinger software:

Cournia Z, Leng L, Gandavadi S, Du X, Bucala R, Jorgensen WL. "Discovery of Human Macrophage Migration Inhibitory Factor (MIF)-CD74 Antagonists via Virtual Screening." *J. Med. Chem.* **2009**, 52, 416-424.

Dasgupta T, Chitnumsub P, Kamchonwongpaisan S, Maneeruttanarungroj C, Nichols SE, Lyons TM, Tirado-Rives J, Jorgensen WL, Yuthavong Y, Anderson KS. "Exploiting Structural Analysis, in Silico Screening, and Serendipity To Identify Novel Inhibitors of Drug-Resistant Falciparum Malaria." *ACS Chem. Biol.* **2009**, 4, 29-40.

Jiang J, Ghoreschi K, Deflorian F, Chen Z, Perreira M, Pesu M, Smith J, Nguyen D, Liu E, Leister W, Costanzi S, O'Shea J, Thomas C. "Examining the chirality, conformation and selective kinase inhibition of 3-((3R,4R)-4-methyl-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile (CP-690,550)." *J. Med. Chem.* **2008**, 51, 8012-8018.

Jorgensen A, Topiol S. "Driving forces for ligand migration in the leucine transporter." *Chem. Biol. Drug Des.* **2008**, 72, 265-272.

Poulsen A, William A, Lee A, Blanchard S, Teo E, Deng W, Tu N, Tan E, Sun E, Goh K, Ong W, Ng C, Goh K, Bonday Z. "Structure-based design of Aurora A & B inhibitors." *J. Comp.-Aided Mol. Des.* **2008**, 22, 897-906.

Rao S, Sanschagrin P, Greenwood J, Repasky M, Sherman W, Farid R. "Improving database enrichment through ensemble docking." *J. Comp.-Aided Mol. Des.* **2008**, 22, 621-627.