Science Highlight

Computational Study of Gleevec and G6G Reveals the Molecular Determinants of Kinase Inhibitor Selectivity

Yilin Meng, Yen-lin Lin, Lei Huang, Wei Jiang and Benoît Roux **Beagle Wiki**

Gleevec is a potent inhibitor of Abl tyrosine kinase but not of the highly homologous Src kinase. Because the ligand binds to an inactive form of the protein in which an Asp-Phe-Gly structural motif along the activation-loop adopts a so-called DFG-out conformation, it was suggested that binding specificity was controlled by a “conformational selection” mechanism. In this context, the binding affinity displayed by the kinase inhibitor G6G poses an intriguing challenge. Although it possesses a chemical core very similar to that of Gleevec, this compound is a potent inhibitor of both Abl and Src kinases. Both inhibitors bind to the DFG-out conformation of the kinases, which seems to be in contradiction with the conformational selection mechanism. To elucidate the molecular mechanism of Gleevec/G6G binding specificity and display the hidden thermodynamic contributions affecting the binding selectivity, large-scale molecular dynamics free energy simulations with explicit solvent molecules were carried out on Beagle.
Protein tyrosine kinases are crucial enzymes in cellular signaling pathways regulating cell growth, proliferation, metabolism, differentiation and migration. In their active state, protein tyrosine kinases catalyze the transfer of γ-phosphate of an adenosine triphosphate (ATP) molecule covalently onto a tyrosine residue in substrate proteins (phosphorylation of a tyrosine residue). Phosphorylation of a substrate protein usually results in a functional change of the substrate. To maintain normal regulation of cellular signal transductions, the activity of tyrosine kinases is tightly regulated by multiple mechanisms. Mutations of certain residues can disrupt normal inhibitory mechanisms and make tyrosine kinases constitutively active, leading to a number of diseases, such as cancers, diabetes, and inflammation. For this reason, protein tyrosine kinases represent attractive drug targets for certain types of cancers. In recent years, many small-molecule inhibitors of kinases have been developed as possible treatments of these diseases. Contrary to most standard chemotherapies which act on all rapidly dividing normal and cancerous cells, kinase inhibitors are deliberately designed to interact with specific target. They are a cornerstone of the precision medicine, a form of medicine that uses information about a person’s genes and proteins to prevent, diagnose, and treat disease. Although successes have been achieved, designing inhibitors that are targeting specific kinases in the active state is, however, difficult because they all present structurally similar catalytic pockets owing to the common enzymatic function requiring ATP binding. Inhibitors that are targeting inactive conformations of the kinases appear to be more selective. One notable example of inhibitors targeting an inactive state of tyrosine kinases is Gleevec (developed by Novartis). Gleevec is found to induce high remission rates in patients with chronic myeloid leukemia (CML), which is caused by the Bcr-Abl kinase (in this case, Bcr-Abl kinase is the target). Gleevec is also used in the treatment of gastrointestinal stromal tumors because it’s also a potent inhibitor of receptor tyrosine kinase c-Kit.

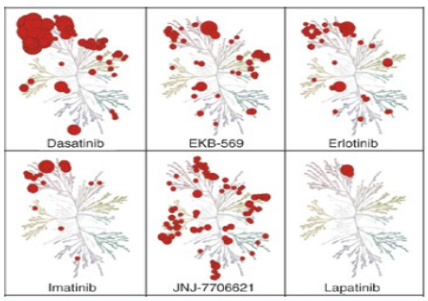


Figure 1. Graphical representation of the selectivity profile of kinase inhibitors based on the phylogenetic tree of human protein kinases. The size of the red circle represents the strength of binding. Anticancer drug Sprycel (dasatinib) binds to the active state and is a promiscuous inhibitor, whereas anticancer drug (lapatinib) binds to an inactive state and is a selective inhibitor. This figure was adapted from Nat. Biotechnol. 2008, 26, 127-132 with permission.

Resouces:

Beagle Wiki
Get detailed usage information from the Beagle team

Beagle Support
Contact the Beagle experts for help

Globus
Get started moving files to/from Beagle using this fast service

Other CI resources
Learn about other computing resources available at the Computation Institute

Training:

HPC Python
May 20th, 2PM
Room 240A, at the Computation Institute of the University of Chicago

Topics will include:

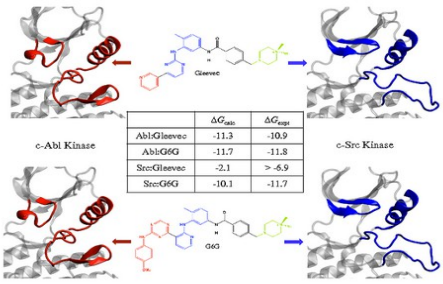
- Get a better grasp of Numpy, Cython, MPI for Python
- Learn how Python abstracts the underlying computer architecture
- Use profiling to find bottlenecks in CPU time and memory usage
- Write efficient programs by choosing appropriate data structures
- Speed up matrix and vector computations
- Use tools to compile Python down to machine code

Beagle2 Events To learn more about Beagle2 trainings.

Request for publications made using Beagle2

Please send us your most recent publications made possible by Beagle2. Make sure that your papers acknowledge Beagle and contain the grant number: 1S10OD018495-01

Computer modeling can provide a wealth of molecular details on the specificity of Gleevec. In this study, we aimed to quantify the thermodynamics of Gleevec and G6G binding to the homologous kinases, Abl and Src. We also intended to identify the physical/chemical determinants governing the differing selectivity of Gleevec and G6G. The importance of structural variations in the ligands as well as small differences in amino acid identity in the kinases on selective kinase inhibition was examined. To address those issues, large-scale molecular dynamics free energy calculations were performed on Beagle to study the binding of Gleevec and G6G to Abl and Src kinase domains, in which solute and solvent atoms are treated explicitly with atomic force fields. We took advantage of Beagle's supercomputing size and speed to allow for the rapid simultaneous simulations. The study demonstrates that detailed analyses can provide valuable information to explain the observed target preference. Information derived from this study will provide useful principles to guide lead optimization studies aimed at increasing potency and selectivity of drugs.



	ΔG_{calc}	ΔG_{expt}
Abl:Gleevec	-11.3	-10.9
Abl:G6G	-11.7	-11.8
Src:Gleevec	-2.1	> -6.9
Src:G6G	-10.1	-11.7

Figure 2. Free energy difference between the apo and the holo states upon Gleevec and G6G binding. The free energy difference consists of two parts: contribution from the conformational change (DFG-flip) and from protein (apo) – ligand interaction. The calculated binding free energy difference, which is the sum of the two contributions, agrees well with experiments.

To read full article go to: **Science on Beagle2**

Beagle2 Related Publications

Kazutaka Takahashi, Sanggyun Kim, Todd P. Coleman, Kevin A. Brown, Aaron J. Suminski5, Matthew D. Best & Nicholas G. Hatsopoulos
Large-scale spatiotemporal spike patterning consistent with wave propagation in motor cortex
Nature Communication

Aaron M. Fluitt and Juan J.de Pablo
An analysis of biomolecular force fields for simulations of polyglutamine
Biophysical Journal

Cockrell, Chase, Scott Christley Gary An
Investigation of inflammation and tissue patterning in the gut using a spatially explicit general-purpose model of enteric tissue (SEGMEnT)
PLoS computational biology 10, no. 3 (2014): e1003507

Cockrell, Robert Chase, Scott Christley, Eugene Chang, Gary An
Towards Anatomic Scale Agent-Based Modeling with a Massively Parallel Spatially Explicit General-Purpose Model of Enteric Tissue (SEGMEnT_HPC)
PloS one 10, no. 3 (2014): e0122192-e0122192

Searle Chemistry Laboratory
5735 South Ellis Avenue
Chicago, IL 60637

Help E-Mail:
beagle-support@ci.uchicago.edu
Beage2 CI Website:
beagle.ci.uchicago.edu