

India Takes an Open Source Approach to Drug Discovery

Open source software may have been around for 17 years, but using an open source model to speed up drug discovery is a relatively new idea. This month, India is launching a new open source initiative for developing drugs to treat diseases such as tuberculosis, malaria, and HIV.

Biophysicist Samir Brahmachari, Director General of India's Council of Scientific and Industrial Research (CSIR), announced the launch this month of an open source drug discovery (OSDD) initiative to accelerate development of new drugs to treat infectious diseases that plague the developing world. "When it comes to health, India is in a state of war. There's a war between health as a right and health as business," said Brahmachari.

Just as the original open source software was propelled by software developers motivated to contribute to large collaborative projects, proponents of OSDD believe that the global need for new low-cost drugs, particularly for treating neglected tropical diseases, will make this model effective. Because drug research is so complex, different OSDD initiatives are applying different strategies. For example, CSIR aims to have a web-enabled interactive open source platform that will list the current design challenges for developing drugs to treat drug-resistant tuberculosis, malaria, and HIV. Research teams from CSIR labs across India and from other government institutions as well as individuals from universities and industry can volunteer to contribute solutions to the posted drug design challenges. Contributions could include, for example, posting a new algorithm or information about a new drug target. As it will be open source, any scientist can contribute. Brahmachari says that as an added incentive, software will be written enabling problem solvers and contributors to receive microcredits; once a certain number of microcredits has been accrued, the person will receive a monetary reward. The first step in CSIR's OSDD initiative is the launch of an open source website hosting information about *Mycobacterium tuberculosis*, the bacterial pathogen

that causes tuberculosis. This information includes gene sequences, expression, function, activity, and the response to drugs of all *M. tuberculosis* proteins as well as host-pathogen interactions (<http://mtbsysborg.igib.res.in>). Challenges for designing new drugs to combat tuberculosis will be posted shortly.

India's federal government has committed \$38 million for this initiative, and Brahmachari hopes to raise a third of the overall project cost from donations and charity. Sun Microsystems, a Californian technology company, has come on board as a long-term partner to "program manage" the IT part of the initiative, which like all modern drug discovery efforts involves significant computational infrastructure. "Sun will define the high level application and systems architecture for this initiative, and will provide help in identifying the appropriate software integrator for the IT part of the project," says Jaijit Bhattacharya, Director of public policy and corporate strategy at Sun Microsystems India. Sun will provide its open source software and will help in obtaining other software for the program, he says.

From Linux to Open Source Drug Discovery

OSDD is only a few years old but has its roots in the open source software movement started 17 years ago by Linus Torvalds, who developed the Linux operating system. Borrowing from the Linux concept, biologists started developing open source bioinformatics tools such as BioJava, BioSpice, BioRuby, BioPython, BioPerl, and others for data mining, visualization, simulation, statistics, data integration, and analysis. For example, Upinder S. Bhalla, associate professor at the National Center for Biological Sciences (NCBS) in Ban-

galore, spearheads two open source NCBS programs: a simulator software called MOOSE (Multi-scale Object Oriented Simulation Environment) and a database of signaling models called DOQCS (Database of Quantitative Cellular Signaling). "We use the simulator ourselves, and we use our database for our research. That seems to keep the development on a practical track and motivates development of real-world features," he says. MOOSE has four active developers and gets about 100 hits a day; DOQCS has one active developer and gets as many as 20,000 noncommercial queries a month.

This sharing of bioinformatics know-how has paved the way for more ambitious projects such as CAMBIA, launched by molecular biologist Richard Jefferson in Australia as an international nonprofit institute for creating new technologies and tools to enable innovation in health, food security, and natural resource management for the developing world. CAMBIA has two spin-off projects: BIOS (Biological Innovation for Open Society; <http://www.bios.net/daisy/bios/about/3.html>) and most recently Patent Lens (<http://www.patentlens.net/daisy/patentlens/patentlens.html>). A big success for BIOS has been its licensing of a gene transfer technology called TransBacter that can be used instead of the costly *Agrobacterium* for genetically engineering plants. More recently, CAMBIA launched Patent Lens, an open source freely accessible database that searches the full-text of over 8 million patents and applications worldwide. "In biology we need new clarity in what's out there [in terms of patented research], what's coming down the turnpike, and the new legal and cultural instruments to get past them," says Jefferson. Patent Lens has a server that extracts DNA, RNA, and protein sequences from

US patents and links them to GenBank and BLAST searches. CAMBIA and the University of Melbourne are discussing ways to use Patent Lens to jointly launch an international open innovation platform (IOI) to assist in searching patents filed worldwide, as currently there is no universal system for doing this.

OSDD is an offshoot of these earlier ventures. One of the first OSDD initiatives, The Synaptic Leap (TSL) (<http://www.thesynapticleap.org/>), was launched by software engineer Ginger Taylor in November 2005. Her goal was to create an online research community that could connect and collaborate on research efforts for neglected tropical diseases such as the parasitic disease schistosomiasis. Currently, TSL has over 2000 unique site visits per month, most by active scientists from universities worldwide. Says chemist Matthew H. Todd at the University of Sydney, who leads the TSL's biochemistry group, "there's a huge pool of people out there wanting to do chemical synthesis and biological evaluation of compounds—you just have to find them and coordinate the effort efficiently." Todd is working on improving the chemical synthesis of praziquantel, a drug currently used to treat schistosomiasis. "The drug needed to be made enantiopure rather than racemic. We have received a suggestion for solving this problem and we are at least 75% of the way there," he says. A related initiative is UsefulChem (<http://usefulchem.wikispaces.com/>), set up by Drexel University chemist Jean-Claude Bradley. Bradley has pioneered Open Notebook Science in which lab notebooks and raw research data are posted on the web for anyone to see and respond to (<http://usefulchem.wikispaces.com/All+Reactions>). As for success, Bradley says, "Probably the best example of a positive outcome from UsefulChem is finding two compounds that are somewhat active against malaria [in vitro], blocking the activity of falcipain-2, a *Plasmodium falciparum* cysteine protease. "This demonstrates that a team of researchers can work together in the open—Rajarshi Guha from Indiana University did the docking calculations, my group at Drexel did the syntheses and Phil Rosenthal's group at UCSF did the testing."

A Global Quest for Collaborative Drug Discovery

Perhaps surprisingly, big pharma is becoming interested in OSDD. In 2000, the pharmaceutical giant Eli Lilly & Company in Indianapolis created a dedicated division, eLilly, to focus on using the Internet to improve the current drug R&D model. "Out of this came high profile ventures like InnoCentive and less visible ones such as Collaborative Drug Discovery (CDD), Scienteur and Chorus," says Bernard Munos, an advisor in corporate strategy to Lilly. In 2005, Lilly spun off InnoCentive and CDD as separate entities, retaining a small equity interest. InnoCentive, cofounded by organic chemist Alph Bingham, is an "open innovation marketplace" where users can select an R&D challenge posted by a company or a not-for-profit organization and attempt to solve it for a cash prize ranging from \$5000 to \$1 million (<http://www.innocentive.com/servlets/project/ProjectInfo.po?s=AW>). Bingham, who launched InnoCentive in 2001 with 21 drug discovery challenges, says about the launch "For all the reduction-to-practice postings of new chemical materials, we had requested that the solver submit a sample of the targeted chemical structures...The receipt of these samples later that year and postmarked from all around the world, was marked evidence that the model was working." Currently, InnoCentive lists a number of successes on its website such as new methods to synthesize fluorinated ethers and butanoic acid and the identification of new drug targets for treating Duchenne Muscular Dystrophy. Among the posted challenges is one to find a diagnostic biomarker for the neurodegenerative disease amyotrophic lateral sclerosis (ALS), posted by an ALS patient group called Prize4Life. The challenge was answered by a dermatologist who proposed looking for biomarkers in skin instead of blood and urine. The problem solver received a \$15,000 prize for his proposal and is working with the ALS Center at Columbia University to test the skin of about 50 ALS patients for suitable biomarkers.

Last year, Novartis Institutes for Biomedical Research in Cambridge, MA, together with the Broad Institute of Harvard and MIT and Sweden's Lund University, collaborated to make all infor-

mation about genes implicated in type 2 diabetes obtained from genome-wide association studies freely available on the web in an effort to speed up elucidation of the mechanisms underlying this complex disease (<http://www.broad.mit.edu/diabetes/>). "This complexity is one of the reasons why we took the open approach to this collaboration. Clearly it will require many laboratories to clarify how and when these genes and loci may exert their influence on the development and/or progression of diabetes," says Thomas E. Hughes, head of diabetes research at Novartis. "We are committed to having interactive and open collaborations with innovative partners from academia and biotech," he says. "It is not often that we have the injection of new information of this type in our field." If the right opportunity presents itself in the future "we would consider using this collaboration model again," says Hughes.

Taking industry involvement to a different level is the European Union's new Innovative Medicines Initiative (IMI), a unique partnership between the European Community and the European Federation of Pharmaceutical Industries and Associations (EFPIA) (<http://www.imi-europe.org/>). The goal of IMI is to help resolve key bottlenecks in European R&D with the goal of accelerating drug development in areas such as cancer, inflammation, and infectious diseases. With 2 billion Euros in funding from the EU 7th Framework Program and EFPIA members, and a call for proposals to be issued at the end of this month, all researchers working in Europe are eligible to apply. IMI adviser and intellectual property expert Bo Heiden of Sweden's Chalmers University says, "IMI facilitates an open innovation platform for pre-drug development to facilitate the creation of safer drugs faster, not necessarily the open distribution of the drugs themselves developed through the help of the IMI platform."

Negotiating the IP Maze

As the software open source model is translated into drug discovery efforts, issues of intellectual property (IP) and assigning credit need to be addressed. Says InnoCentive cofounder Bingham, "we are constantly learning and experimenting with new approaches for both

the legal and the intellectual recognition of widespread contributions.” Meanwhile, Lilly’s Munos believes that IP protection is “an enabler of open-source drug R&D, not a threat.” The surest way to create a vibrant innovation network, he says, is to protect the IP it generates. “In each organization, there will be a debate, especially early on, between how much to disclose versus how much to protect,” he says. However, as organizations gain more experience in this field and as IP issues get streamlined, confidence and sharing will increase. “I do not expect free-riding to be a significant problem because members will

want to influence the direction of the network of researchers, and they will have to share in order to do so,” says Munos. As for India’s new OSDD initiative, CSIR’s Brahmachari says, “I am not a socialist reformer and I am not anti intellectual property regime.” He predicts that CSIR’s new initiative will follow a hybrid IP model by using a “click-wrap” license that requires the users to agree that they will not file product patent applications in cases where they rely on open source data.

India’s OSDD initiative is still in its infancy and it is impossible to know how successful it will be. InnoCentive’s Bing-

ham truly applauds “the CSIR objective of mainstreaming this mode of research and its widespread applicability to drug development” but suggests that CSIR could use the InnoCentive platform. Matthew Todd thinks CSIR could adopt the existing TSL network to jumpstart the OSDD project. For his part, Brahmachari is open to collaboration with these programs but still thinks India needs to go ahead with its own OSDD initiative. As Maharaj K. Bhan, head of the Indian Federal Department of Biotechnology, points out, “It is good for the country. I don’t know if it will work, but champions don’t look for outcomes.”

Seema Singh

Bangalore, India

DOI 10.1016/j.cell.2008.04.003