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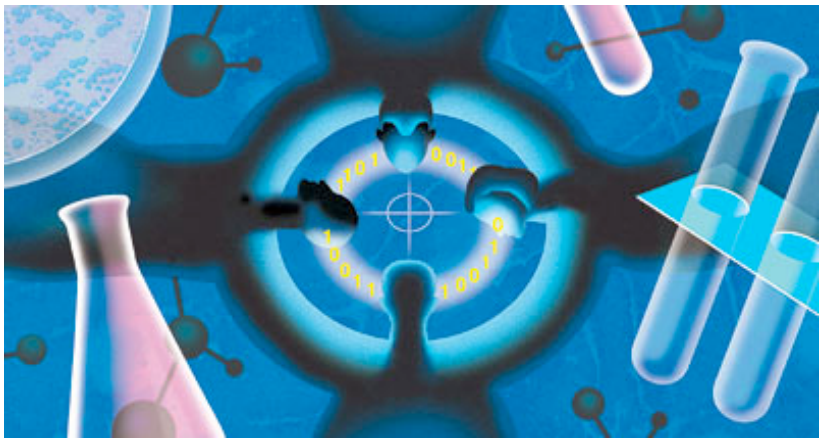
An open-source shot in the arm?

Jun 10th 2004
From The Economist print edition



Medicine: The open-source model is a good way to produce software, as the example of Linux shows. Could the same collaborative approach now revitalise medical research too?

CAN goodwill, aggregated over the internet, produce good medicine? The current approach to drug discovery works up to a point, but it is far from perfect. It is costly to develop medicines and get regulatory approval. The patent system can foreclose new uses or enhancements by outside researchers. And there has to be a consumer willing (or able) to pay for the resulting drugs, in order to justify the cost of drug development. Pharmaceutical companies have little incentive to develop treatments for diseases that particularly afflict the poor, for example, since the people who need such treatments most may not be able to afford them.

It is in this environment that a number of medical biologists, lawyers, entrepreneurs and health-care activists have sought improvements. They have suggested borrowing the "open-source" approach that has proven so successful in another area of technology, namely software development. This is a decentralised form of production in which the underlying programming instructions, or "source code", for a given piece of software are made freely available. Anyone can look at it, modify it, or improve it, provided they agree to share their modifications under the same terms. Volunteers collaborating in this way over the internet have produced some impressive software: the best-known example is the Linux operating system. So why not apply the open-source model to drug development too?

Source for the goose

In fact, open-source approaches have emerged in biotechnology already. The international effort to sequence the human genome, for instance, resembled an open-source initiative. It placed all the resulting data into the public domain rather than allow any participant to patent any of the results. Open source is also flourishing in bioinformatics, the field in which biology meets information technology. This involves performing biological research using supercomputers rather than test-tubes. Within the bioinformatics community, software code and databases are often swapped on "you share, I share" terms, for the greater good of all. Evidently the open-source approach works in biological-research tools and pre-competitive platform technologies. The question now is whether it will work further downstream, closer to the patient, where the development costs are greater and the potential benefits more direct.

Open-source research could indeed, it seems, open up two areas in particular. The first is that of non-patentable compounds and drugs whose patents have expired. These receive very little attention from researchers, because there would be no way to protect (and so profit from) any discovery that was made about their effectiveness. To give an oft-quoted example, if aspirin cured cancer, no company would bother to do the trials to prove it, or go through the rigmarole of regulatory approval, since it could not patent the discovery. (In fact, it might be possible to apply for a process patent that covers a new method of treatment, but the broader point still stands.) Lots of potentially useful drugs could be sitting under researchers' noses.

The second area where open source might be able to help would be in developing treatments for diseases that afflict small numbers of people, such as Parkinson's disease, or are found mainly in poor countries, such as malaria. In such cases, there simply is not a large enough market of paying customers to justify the enormous expense of developing a new drug. America's Orphan Drug Act, which provides financial incentives to develop drugs for small numbers of

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Stephen Maurer, Arti Rai and Andrej Sali just published an article on the application of open-source to medicine. Other researchers in the field include Eric Von Hippel, Peter Lansbury (founder of the Laboratory for Drug Discovery in Neurodegeneration) and Janet Hope.

patients, is one approach. But there is still plenty of room for improvement—which is where the open-source approach might have a valuable role to play.

In a paper presented this week in San Francisco at BIO 2004, the Biotechnology Industry Organisation's annual conference, Stephen Maurer, Arti Rai and Andrej Sali—two lawyers and a computational biologist, respectively—called for an open-source approach to invent drugs to fight tropical diseases. It would work like this: a website they call the Tropical Disease Initiative would allow biologists and chemists to volunteer their expertise on certain areas of a specific disease. They would examine and annotate shared databases, and perform experiments. The results would be fully transparent and discussed in chat rooms. The authors expect that the research, at least initially, would be mainly computational, not carried out in "wet" laboratories.

The difference between this proposal and earlier open-source approaches in biomedical research is that where before scientists swapped software, here they would collaborate on the data. And where projects such as the mapping of the human genome relied on massive top-down government involvement, this proposal would, like an open-source software project, be the result of bottom-up self-organisation among researchers themselves. That said, the authors acknowledge that a government or grant-giving charity would probably have to provide the initial funds.

"We are so used to patents that we forgot ways to discover drugs in the public domain, and we need to rediscover them"

Moreover, the results of the research would not be made available under an open-source licence of the kind that governs software projects. Instead, the final development of drug candidates would be awarded to a laboratory based on competitive bids. The drug itself would go in the public domain, for generic manufacturers to produce. This, the authors state, would achieve the goal of getting new medicines to those who need them, at the lowest possible price. "We are so used to patents that we forgot ways to discover drugs in the public domain, and we need to rediscover them," says Mr Maurer, of the Goldman School of Public Policy at the University of California in Berkeley.

This is just one of many attempts to extend elements of the open-source software-development model to drug research. Yochai Benkler, a law professor at Yale, imagines test-tube and animal studies organised in this manner, exploiting the "excess capacity" of graduate students and university labs, much as students and academics also contribute to open-source software development.

Trial and error

Eric von Hippel, a professor at the Massachusetts Institute of Technology's Sloan School of Management, is investigating how secondary uses for drugs are discovered, with a view to harnessing doctors and patients to record data. Many medications are approved for one purpose, but are regularly prescribed for another, "off-label" use. In many instances, new uses for a drug are discovered only after it is on the market, when a sort of natural experimentation takes place. For instance, Botox was approved in America for treating eye-muscle disorders, and only later found to remove wrinkles. In Europe and America, as many as half of all drug prescriptions for certain diseases fall into this category. The drugs often do not go through the formal process for other uses because the cost of regulatory approval is so high.

This is a problem for a number of reasons. First, it means that drug companies are

prohibited from advertising the medications based on these additional uses, so some patients may not get the treatment that would benefit them. Next, insurance companies in America usually only cover on-label use. And the effectiveness of the treatment is not formally evaluated. Dr von Hippel's idea is to decentralise the process of obtaining data on the off-label use, by collaborating with volunteer doctors and patients. By defraying costs in this way, it might then be possible to obtain regulatory approval. It is, in effect, an open-source clinical trial. Because the drug has already been approved, it has passed first-phase tests for safety. These do not have to be repeated. Second and third-phase drug-approvals test for efficacy and side-effects—and these are the very areas where getting formal approval for off-label use is sensible.

Meanwhile, not far from Dr von Hippel at MIT, thousands of fruit flies are being decapitated. Peter Lansbury, the head of a research lab at Harvard Medical School, avows that they are treated with chloroform, so "they don't feel a thing". The fruit flies have Parkinson's disease, and Dr Lansbury's research is examining the therapeutic effect of a thousand approved drugs, on which the patent has expired in most cases. Might one of them turn out to be an effective treatment?

This sort of research is unusual because there is no working hypothesis to prove and no way to profit if the project is successful. It has simply never been studied before, and should be, says Dr Lansbury, who is the co-founder of the Laboratory for Drug Discovery in Neurodegeneration. The laboratory has around 25 researchers and an annual budget of $2.5m to work on neurodegenerative diseases, such as Parkinson's or Huntington's, to which the major commercial drug companies devote few resources because their potential market is small.

Dr Lansbury refers to the work as "not-for-profit drug discovery", but he sees direct parallels with the open-source approach. For one thing, his group places much of its data in the public domain. Secondly, though the research is mainly happening among different research labs within the confines of Harvard at the moment, the goal is to involve other scientists around the world. Only through this sort of collaborative, distributed approach will treatments be found for these diseases, he says. As for the intellectual property that may be created, the goal is to use patents only to license treatments cheaply to pharmaceutical companies to ensure a supply of drugs at low cost. But the most important thing is to discover the drugs in the first place—something commercial drug-development seems unable to do.

There are a number of other similarities between biomedical research and open-source software development. First, both fields attract the same sort of people. Biology, like software, relies on teams of volunteers, notably graduate students and young professionals, who have an incentive to get involved because it will enhance their professional reputations or establish expertise. Both medical biologists and computer scientists aim to improve people's lives and make the world a better place. And as the human-genome project showed, both cultures respond strongly to grand projects, not just financial incentives—possibly because they are generally highly paid to begin with.

"What does it mean to apply the term 'open source' in fields outside software development, which do not use 'source code' as a term of art?"

That said, the dissimilarities are profound. The financial needs and time to complete projects are wildly different. A new piece of software can be thrown together in days or weeks, and rarely more than a few months. The barriers to entry are low: many pieces of software begin life in an enthusiast's bedroom or garage. Pharmaceutical research, in contrast, is measured in years, fails more often than it succeeds, and requires hard-core credentials and in many cases expensive equipment, not just hard work.

Moreover, the computational portion of the drug-discovery process—typified as upstream, far from the patient, at the early-stage level, where profits are thinner—is not the costly bit. Rather, it is the less computer-intensive things such as toiling in wet laboratories, performing clinical trials and navigating the regulatory-approval process where one finds the bulk of the cost of bringing a drug to market. The closer to the patient one goes, the tougher it is to imagine open-source processes making a significant impact.

The application of the open-source approach to drug development may prove to be more useful as an analogy than an application, notes Janet Hope, a lawyer completing a doctorate on "open-source biotechnology" at the Australian National University, in Canberra. One reason is that different intellectual property rights apply, and are protected differently. Software usually falls under copyright, which arises automatically and without cost to the author. Biomedical discoveries are generally protected by an entirely different legal regime, patents, which are costly to obtain.

This helps explain why the drug-discovery and development projects place their work in the public domain, rather than trying to enforce some form of reciprocal openness through an open-source licensing agreement, as software does. Those involved in the human-genome project investigated the possibility in 2000 of applying an open-source licensing agreement to the results, but decided that simply throwing the results into the public domain—without any restriction on their use—was better. Its successor project, the International HapMap Project, which is mapping the common patterns of variation within the genome, imposes an open-source licence for research in progress. But it places the completed data in the public domain and allows patents on subsequent discoveries.

This suggests that continued reciprocal sharing, a key part of open-source software development, may not have a meaningful equivalent on the biological side of the fence. With open-source drug discovery in the public domain, where there is no legal obligation to share one's inventions, there is no guarantee that philanthropic sentiments will override self-interest. Participants can always choose to send their results to the patent office rather than the communal web site. While the open-source approach shows much promise in drug discovery, it is certainly no panacea.

Back to the source

More broadly, two big questions remain unanswered as the open-source approach starts to colonise disciplines beyond its home ground of software development. The first is whether open-source methods can genuinely foster innovation. In software, all that has been developed are functional equivalents of proprietary software—operating systems, databases, and so on—that are sometimes slightly better and sometimes glaringly worse than their proprietary counterparts. Their main distinction, from users' point of view, is simply that they are available free of charge. Curiously, this matches the complaint levelled against pharmaceutical companies for developing "me-too" drugs to compete with other firms' most successful product lines—witness the current crop of Viagra imitators—rather than spending their research money in an entirely new area.

The second question is semantic. What does it mean to apply the term "open source" in fields outside software development, which do not use "source code" as a term of art? Depending on the field in question, the analogy with source code may not always be appropriate. It seems the time has come to devise a new, broader term than "open source", to refer to distributed, internet-based collaboration. Mr Benkler calls it non-proprietary peer-production of information-embedding goods. Surely someone,

somewhere can propose something snappier.