FINDING CURES FOR TROPICAL DISEASES: IS OPEN SOURCE AN ANSWER?

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Abstract

Computation plays an increasing role in biology. The convergence between computing and biology suggests that open source methods can be used to organize early phase drug discovery. We argue that a new approach, which we call "open source drug discovery," would significantly reduce the cost of discovering, developing and manufacturing cures for tropical diseases. First, it would give hundreds of scientists a practical way to donate urgently needed manpower. Second, open source discoveries would not be patented, permitting sponsors to award development contracts to the company that offered the lowest bid. Finally, competition from generic drug makers would keep manufacturing prices at or near the cost of production, significantly accelerating drug development for the 500 million people who currently suffer from tropical diseases.

Introduction

More than 500 million people – one tenth of the world's population – suffer from tropical diseases at any one time. Malaria alone causes between 1.5 to 2.7 million deaths per year, almost all of them in developing countries. Additional high mortality rates result from African sleeping sickness, dengue fever, river blindness, elephantiasis, leishmaniasis, Chagas disease, and schistosomiasis.[1] Why do so many die? The reasons are more economic than scientific. Traditional pharmaceutical companies cover their R&D costs by selling patented products. This strategy fails in the developing world, where would-be consumers are often penniless. Most reform proposals try to save the patent system by asking governments and charities to subsidize developing country purchases at a guaranteed price.[2] However, economists have shown that no innovation institution – including patents – is ideal for every R&D problem.[3] During the 1990s, sponsors decided that existing institutions could not meet the challenges posed by tropical diseases. They therefore invented an entirely new institution, called "Virtual Pharmaceutical Companies," or "Virtual Pharma," to accelerate drug development for tropical diseases. Unlike conventional pharmaceutical houses, Virtual Pharma does little or no development in-house. Instead, they develop a portfolio of promising drug candidates through a web of agreements with commercial and academic partners. Today, Virtual Pharma manages most of the world's R&D effort for tropical diseases.[4]

But Virtual Pharma is not enough. First, its development pipeline will run dry without more upstream research. Early-stage R&D has been particularly weak in exploiting genomic insights.[5] Second, tropical disease research is badly underfunded.[6] For this reason, further progress will require rigid cost containment. We argue that a new community-wide consortium called the Tropical Disease Initiative, or "TDI," can attack both problems. Success would help keep Virtual Pharma's pipeline full. Furthermore, TDI would publish its results. This would put discoveries in the "public domain" and prevent anyone else from patenting them. We explain below how public domain status can help Virtual Pharma contain costs.

Like Virtual Pharma, TDI would not resemble any previous institution. Instead, it would exploit the ongoing convergence between computation and biology. LINUX-style "open source" methods provide a powerful model for organizing early-phase drug discovery. We envision a de-centralized, community-wide effort where scientists from laboratories, universities, institutes, and corporations can work together in a common cause.

Open Source Drug Delivery

Computational drug discovery is much like de-bugging software. Both activities require workers to find and fix tiny problems hidden in an ocean of source code. The main difference is that biologists call their source code "the genome" and look for "targets" – genes whose activation or inactivation produce desired effects – rather than bugs. Instead of writing patches, they then select chemicals ("drug candidates") to turn the targets on and off. Like programmers, computational biologists also check to see whether the proposed fixes are likely to cause inadvertent problems elsewhere.

These are scientific matters. Big computational drug discovery projects also have a social dimension. Somehow, workers must find institutions that let them coordinate work, make choices, build on each other's results, and stay focused on a common goal. The classic solution relies on top-down, hierarchical institutions like corporations. Recently, computer scientists have shown that a second institution works equally well. Open source software collaborations are loose, atomistic, and only minimally hierarchical. Nevertheless, the random and undirected process of using software is a good way to find bugs and write patches.[7] We argue that these same methods can be used to organize large computational biology projects. Admittedly, nothing like this has ever been done. Current references to "open source biology" invariably mean software development (e.g., Bioperl) or depositing un-patented data in a community repository (e.g., the SNP Consortium, the Alliance for Cell Signaling).[8] By contrast, TDI would discover drug candidates in much the same way that LINUX builds operating systems. We see TDI as a decentralized, community-wide effort that (a) searches parasite genomes for new targets, (b) finds chemicals that bind to known targets, (c) evaluates each candidate drug's chances for success, and (d) selects the most promising candidates for further development. Unlike traditional biotech or pharmaceutical companies, TDI would lack formal bosses and hierarchies. [See Box].

So far, we have assumed that TDI would use purely computational methods. This approach is likely to create useful leads to be followed up by experimentalists, but it would not create drugs by itself. Therefore, in practice, it makes more sense to balance computation with at least modest chemistry and biology experiments. TDI should include these disciplines from the outset.

People, Data, Equipment

Apart from human capital, open source software development does not require much in the way of resources. Many projects survive on whatever volunteers can scrounge. By comparison, TDI needs access to various scarce assets. Can TDI acquire the people, data, software, reagents, and equipment it needs? Perhaps the most basic question is whether universities and corporations will let their scientists join the project. This looks feasible. Unpublished survey research by one of us (A.R.) shows that university licensing offices hardly ever interfere with open source projects that lack commercial value. Tropical disease research fits this description to a "T." Life sciences companies are likely to adopt a similar stance.[9]

TDI also needs access to information. This includes gene sequences, chemical databases, and software tools. Although much of this information is public, some of it is proprietary. In principle, TDI volunteers could create work-arounds. In practice, they won't have to. Life sciences companies have obvious moral and political reasons to help. Furthermore, drug companies already share proprietary data with non-profit rice and malaria collaborations[10] and Virtual Pharma[11]. The key is to assure sponsors that donated information will not leak back into commercial (i.e., non-tropical disease) drug discovery. This challenge is substantial for a large, loosely-knit collaboration like TDI. However, today's life sciences companies are already adept at controlling redistribution. The simultaneous existence of high corporate subscription rates and deep academic discounts suggests that leakage is manageable.[12] Corporations could also accelerate progress by promising to warn TDI if it started to investigate known dry holes.[13]

Finally, TDI needs reagents and equipment, including computers and laboratories. TDI's academic members are likely to have significant discretionary resources. Beyond this, many biologists already ask the public to donate time on home computers by installing special screensavers.[14] Corporate tax write-

offs could produce similar donations of laboratory time. TDI's openness can also generate resources. Experimental scientists have an obvious incentive to scan TDI's web pages for new ideas, take the best ones, and write grant proposals. For this reason, even an unsponsored collaboration will likely receive substantial support from public science budgets.

The foregoing discussion suggests that TDI can make do without sponsors. However, sponsors invest where their dollars go furthest. If TDI attracts and organizes enough volunteers, sponsors will want to put tools in their hands. The most natural investment would be to fund costly activities like chemistry and biology experiments. This would extend the open source model to activities where the scrounging model is limited. Discretion over which experiments to fund could be delegated to TDI and/or individual experimentalists. In either case, the need to prioritize experiments would provide a fascinating exercise in on-line democracy.

Cost Containment

"Open source drug discovery" is not an end in itself. To be useful, TDI must offer distinct advantages over existing, patent-based institutions. Some of these are scientific: A community-wide collaboration can tap and combine more information than individual groups. However, most advantages involve cost. We argue that TDI constrains the life cycle cost of discovering, developing and manufacturing drugs in three different ways. First, and most obviously, the open source model relies on unpaid volunteers. Economists often criticize open source software projects for ignoring consumer demand. In the case of tropical disease research, this is a virtue. Open source volunteers do not care whether consumers can afford to pay. Instead, volunteers respond to such "supply side" incentives as idealism, learning new skills, gaining reputations, and impressing potential employers.[15] These incentives should work equally well in biology.[16] LINUX-style collaborations already attract large numbers of volunteers. TDI can do a great deal of good if it attracts a similar fraction of biologists. This manpower would be particularly significant in tropical disease research, where funds are scarce.

Second, open source resolves a longstanding problem with drug development costs. Most proposals to reform tropical disease research assume that patents are unavoidable. This forces them to save the patent system by asking governments and charities to subsidize production if and when new drugs are developed. That would be a fine solution if money were no object. The rub, from the sponsor's perspective, is figuring out how small the subsidy can be and still elicit development. In principle, thrifty sponsors should offer a subsidy that barely covers expected R&D costs. In practice, per-drug R&D costs are very poorly known, with published estimates ranging from $100 to $500 million.[17] Given this uncertainty, sponsors must guess the right amount. Provided that the subsidy works at all, the sponsor almost always overpays. Open source escapes this trap by depositing drug candidates in the public domain where anyone can develop them. This dramatically changes the problem. Now sponsors can award development contracts to which ever company offers the lowest bid. Unlike subsidies, competitive bidding guarantees the lowest price automatically.

Finally, public domain status constrains the prices that companies can charge once new drugs are approved and go into production. Competition among generic drug makers is a powerful mechanism for keeping prices at or near the cost of manufacturing.

Implementation

Virtual Pharma is ready to develop scientifically promising candidates whether or not they are patented.[18] Can it also exploit public domain status to hold down costs? Virtual Pharma clearly has the expertise to write and negotiate cost-plus contracts. Furthermore, significant numbers of companies are likely to submit bids. Examples include Western companies that specialize in generic (i.e. unpatented) drugs, pharmaceutical houses in the developing world, contract research organizations, and biotech firms that already do drug development in developing countries.[19] Finally, Virtual Pharma would have to make sure that companies do not try to earn additional fees by prolonging research that ought to be abandoned. Fortunately, FDA regulations make it hard to hide test results. Virtual Pharma has extensive experience monitoring and administering outside research.
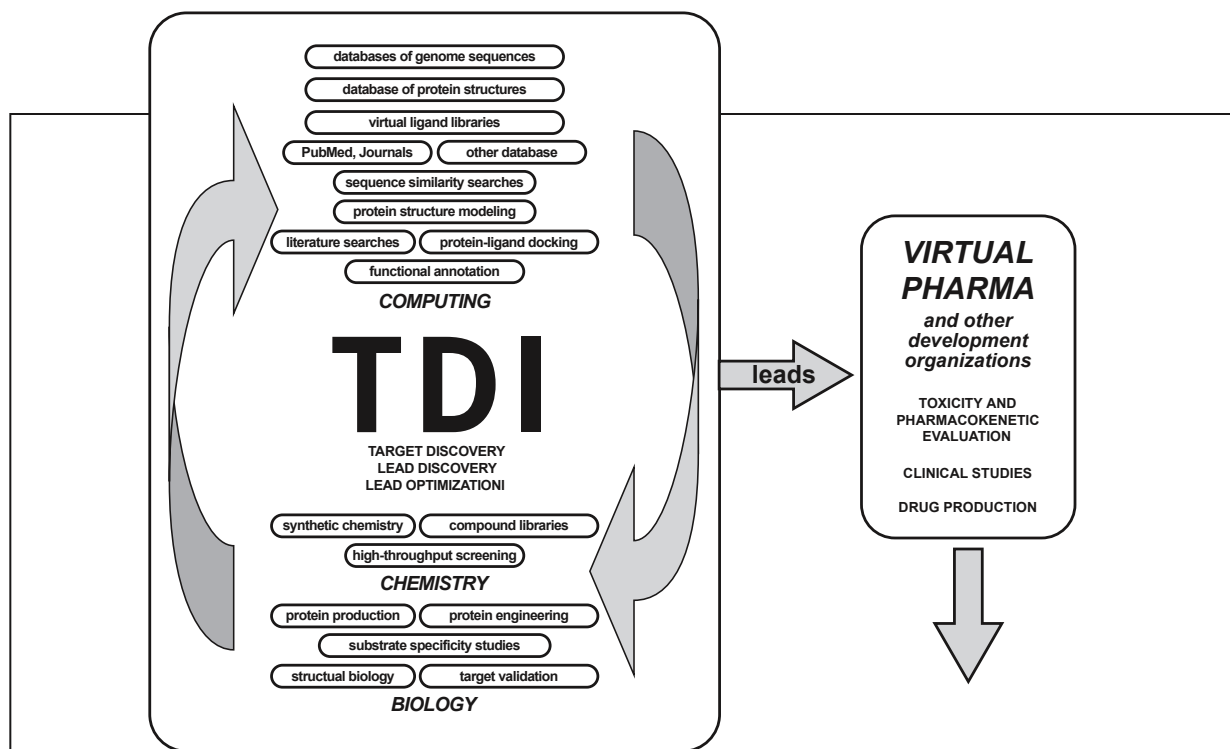
Conclusion

Open source is not magic. In the end, nothing will happen unless Western governments and charities foot the bill. But that is true of all serious proposals for delivering new drugs to fight tropical diseases. What open source can do is guarantee the lowest possible cost. Success would also show that open source methods can create products beyond software – and give biologists an exciting new model for community-wide collaborations.■

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databases of genome sequences

database of protein structures

virtual ligand libraries

PubMed, Journals   other database

sequence similarity searches

protein structure modeling

literature searches   protein-ligand docking

functional annotation

COMPUTING

TDI

**TARGET DISCOVERY
LEAD DISCOVERY
LEAD OPTIMIZATIONI**

leads →

VIRTUAL PHARMA
and other development organizations

TOXICITY AND PHARMACOKENETIC EVALUATION

CLINICAL STUDIES

DRUG PRODUCTION

synthetic chemistry   compound libraries

high-throughput screening

CHEMISTRY

protein production   protein engineering

substrate specificity studies

structual biology   target validation

BIOLOGY

What Would It Look Like?

TDI would almost certainly be built around a Web site where volunteers could examine and annotate shared databases. Individual pages would focus on particular computational drug discovery tasks like searching for new targets, finding new chemicals to attack existing targets, or checking the feasibility of known drug candidates. Volunteers would annotate the genome each time they made a discovery and discuss discoveries in chat rooms. Chemistry and biology experiments would have their own pages. TDI leaders would also get together by more traditional means, including Internet conferencing and face-to-face meetings at scientific conferences. In analogy to software, the most dedicated and proficient volunteers would eventually become leaders, exercising their influence through posted suggestions on which research avenues looked promising or needed workers. While most volunteers would look to these comments when deciding what to do, some individuals would prefer to follow their own hunches. Unlike traditional hierarchical organizations, such indiscipline is inevitable in projects that depend on volunteers. In the long run, we think that it will provide useful insurance against pathological "group think." One widely-recognized strength of software open source projects is that they encourage people with varying perspectives to tackle the same problem.

Ten years ago, TDI would not have been feasible. The difference today is the vastly greater size and variety of chemical, biological and medical databases; new computer software; and powerful web servers. Increases in computing power and improved computational tools will continue making databases more useful. As a result, researchers are often able to identify promising protein targets and small sets of chemicals including good lead compounds using computation alone. For example, scanning of the proteins encoded by the SARS genome against proteins of known structure revealed a SARS protein with similarity to mRNA cap-1 methyltransferases, a class of proteins with available inhibitors, therefore providing a good starting point for experimental validation and iterative lead optimization. [20] Likewise, known protein targets can have their structures predicted computationally by comparative protein structure modeling, followed by in silico screening of virtual ligand libraries, often resulting in useful leads for subsequent experiments [21]. Such efforts can already explore multiple protein targets and millions, even billions of compounds, as demonstrated by the in silico screening for anti-cancer drugs at the Center for Computational Drug Discovery at Oxford University [14]. Existing academic projects, such as the Tropical Disease Research Unit at UCSF, show that even relatively modest computing, chemistry and biology resources can deliver compounds suitable for clinical trials [22].

Economic and social considerations would also shape the design. In the software world, many volunteers join open source collaborations to build reputation and attract employers. TDI would enhance these benefits by providing full attribution and credit, awarding honorifics to outstanding volunteers, and providing links to contributor home pages. The organization could attract volunteers by demonstrating its commitment to exploiting and developing discoveries. But these are only ideas. Open source initiatives depend on volunteers and ignore them at their peril. In the end, the collaboration would have the last word.