Pharm Res (2014) 31:271–277
DOI 10.1007/s11095-013-1170-9

PERSPECTIVE

Computational Models for Neglected Diseases: Gaps and Opportunities

Elizabeth L. Ponder • Joel S. Freundlich • Malabika Sarker • Sean Ekins

Received: 2 May 2013 / Accepted: 28 July 2013 / Published online: 30 August 2013

ABSTRACT Neglected diseases, such as Chagas disease, African sleeping sickness, and intestinal worms, affect millions of the world's poor. They disproportionately affect marginalized populations, lack effective treatments or vaccines, or existing products are not accessible to the populations affected. Computational approaches have been used across many of these diseases for various aspects of research or development, and yet data produced by computational approaches are not integrated and widely accessible to others. Here, we identify gaps in which computational approaches have been used for some neglected diseases and not others. We also make recommendations for the broad-spectrum integration of these techniques into a neglected disease drug discovery and development workflow.

KEY WORDS African sleeping sickness · Chagas disease · computational models · leishmaniasis · malaria · schistosomiasis · tuberculosis

INTRODUCTION

Neglected diseases are a group of biologically unrelated diseases that are grouped together because they disproportionately affect marginalized populations, lack effective treatments or vaccines, or existing products are not accessible to the populations affected (1). While the definition of a neglected disease varies, the category generally includes: tuberculosis, malaria, Chagas disease, African sleeping sickness, schistosomiasis, leishmaniasis and others for which there is a lack of economic incentives or "market" to incentivize product development (2–4). Many of these pathogens, whether bacterial, parasitic, or viral, have complex life cycles and diverse approaches for evading the host immune system, rendering the development of new drugs and vaccines all the more challenging. Furthermore, these diseases receive a relatively small amount of research investment ($80 M to approximately $500 M) from governments and pharmaceutical companies in the developed world (Fig. 1), compared with the billions of dollars invested in other diseases, including cancer and heart disease. The scientific challenges and limited funding available for neglected disease drug discovery and development highlight the importance of exploring alternative, lower cost approaches to advance this process. Free, public databases that provide information on neglected disease drug

E. L. Ponder
Center for Emerging and Neglected Diseases, Berkeley
444A Li Ka Shing Center, Berkeley California 94720-3370, USA
e-mail: eponder@berkeley.edu

J. S. Freundlich
Department of Medicine
Center for Emerging and Reemerging Pathogens
Rutgers University-New Jersey Medical School, 185 South Orange Ave.
Newark, New Jersey 07103, USA

J. S. Freundlich
Department of Pharmacology and Physiology
Rutgers University-New Jersey Medical School
185 South Orange Ave., Newark, New Jersey 07103, USA

M. Sarker
SRI International, 333 Ravenswood Ave.
Menlo Park, California 94025, USA

S. Ekins (✉)
Collaborations in Chemistry, 5616 Hilltop Needmore Rd.
Fuquay Varina, North Carolina 27526, USA
e-mail: ekinssean@yahoo.com

S. Ekins
Collaborative Drug Discovery, 1633 Bayshore Highway
Suite 342, Burlingame, California 94010, USA

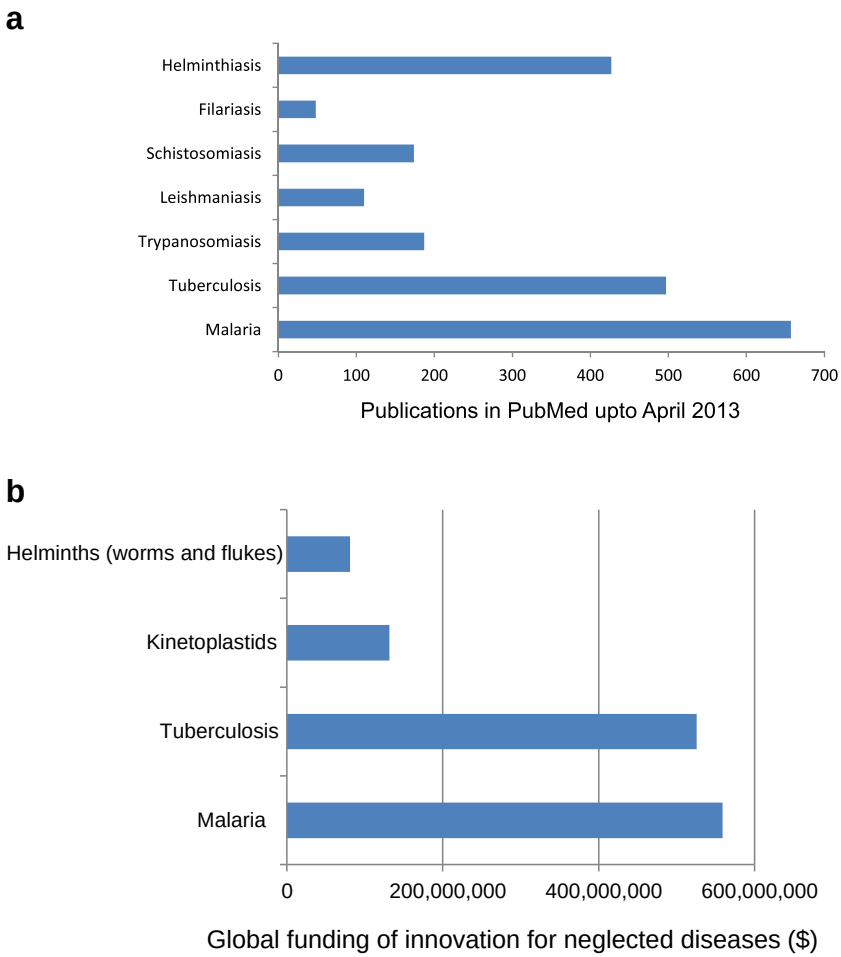

Fig. 1 Analysis of publications in PubMed (**a**) and global funding (**b**) for neglected diseases. The search query (for which "*Neglected disease*" is replaced by the name of the neglected disease) in PubMed was "*Neglected disease*"[Mesh] AND ("Computational Biology"[Mesh] OR "Databases, Factual"[Mesh] OR "Data Mining"[Mesh] OR "Bayes Theorem"[Mesh] OR "Models, Molecular"[Mesh]). The global funding data was obtained from G-FINDER (38). Trypanosomiasis includes Chagas disease, sleeping sickness, and leishmanisis.

discovery, funding, and the pertinent biology and chemistry are increasingly available (Table I). Predictive computational approaches have also been used to propose and test hypotheses before investing in costly and time intensive experiments for neglected diseases. While many databases and computational models exist in isolation within individual publications or websites, few have been extended to support analysis across neglected diseases (5,6) (Table II) to leverage similarities amongst advancing chemical tools/drug discovery compounds and/or targeted biological entities (proteins and/or pathways). Little or no connection between data sources and models exists, even for the most well-funded of the neglected diseases, such as tuberculosis (7) and malaria. Recent assessments of the use of computational methods (7–10), and advancing application of cheminformatics and bioinformatics in tuberculosis research begs the question, have these tools been effectively applied to other neglected diseases? Are there other computational approaches that should be additionally considered, and are there gaps that what would prevent their broader application and integration?

CHEMINFORMATICS: SAVING TIME AND MONEY

Cheminformatics, defined as the implementation of computational methodologies to learn from data describing the biological activity of molecules, exemplifies the important role that computational approaches can play in drug discovery (11). Applying computer algorithms to suggest new molecules that act on a specific targeted protein/pathway or disease/organism can narrow down the chemistry space to be explored by empirical high-throughput screening (12). Such approaches like docking have been successful in HIV drug discovery for the integrase inhibitor raltegravir (13) as well as many other important targets (14). The use of cheminformatics for tuberculosis drug discovery has been summarized (7,15,16) and can be readily implemented early in the process as a means to limit the number of compounds needing to be screened and therefore saving time and money (9,17). Such cheminformatics approaches have also been applied to other tropical diseases ((18–21), Table II). Additional computational methods are assumed to have similar relative cost savings by eliminating the need for some experiments or

Table I Useful Databases and Resources for Neglected Diseases

Data source	Website
TDR Targets	http://tdrtargets.org
WIPO Re:Search	http://www.wipo.int/research/en/search/
GNTD	http://www.gntd.org/login.html
SciDev.Net	http://www.scidev.net/en/health/neglected-diseases/
ChEMBL NTD and ChEMBL Malaria	https://www.ebi.ac.uk/chemblntd, https://www.ebi.ac.uk/chembl/malaria/
DrugEBIlity	https://www.ebi.ac.uk/chembl/drugebility
G-FINDER	https://g-finder.policycures.org/gfinder_report/ http://policycures.org/g-finder2012.html
Global Health Primer	http://www.globalhealthprimer.org/Diseases.aspx
WHO | Tropical diseases	http://www.who.int/topics/tropical_diseases/en/
NIAID on neglected tropical diseases	http://www.niaid.nih.gov/topics/tropicaldiseases/Pages/Default.aspx
CDC on neglected tropical diseases	http://www.cdc.gov/globalhealth/ntd/
DNDi	http://www.dndi.org/
CDD	www.collaborativedrug.com

testing many hypotheses which would not normally be possible without such models.

USING COMPUTATIONAL MODELS ACROSS NEGLECTED DISEASES

Taking a pragmatic approach, ligand-based computational models that are being widely applied for finding novel molecules for malaria (22) and tuberculosis (7–10) (using a diverse array of modeling or machine learning algorithms) are also readily extensible to other diseases, provided sufficient data are available. In addition, learning from targets in one disease and extending to another is also possible, albeit with caveats requiring the respective protein active sites to have some degree of similarity (homology or identity). Differences in target essentiality and vulnerability may exist across each disease in addition to unique permeability and metabolism issues pertinent to each organism. Besides these two groups of computational models, it is worth considering the status of the other computational models across an array of neglected diseases.

We have assessed the literature and thematically grouped computational approaches for neglected diseases to discern gaps (Table II). While some of the computational approaches require techniques that may be linked or are related (protein-protein interaction networks, host-protein interactions and metabolic modeling) others are not directly related to these and may form a second group (computational epidemiology, clinical deployment/diagnostic modeling and finding novel compounds). While we found computational modeling for host-pathogen interactions had been used in tuberculosis and malaria (Table II) they were generally absent in other kinetoplastid and helminth diseases. Protein-protein interaction network models were absent in helminth diseases, and there is a general paucity of biological data for these and kinetoplastids, which may limit computational models (23). While malaria biomarkers are known and used in rapid diagnostic tests, there is still a need for biomarkers that predict progression of malaria to severe disease. Chagas disease requires biomarkers to follow up

Table II Representative Examples of Computational Models Applied Across Neglected Tropical Diseases

Computational models	Tuberculosis	Malaria	Kinetoplastid diseases (Chagas, HAT, leishmaniasis)	Helminth infections (STH, filarial worms, schistosomiasis)
Metabolic modeling	Y (39–41)	Y (42–45)	Y[a] (46)	Y[b] (42)
Host-pathogen interactions	Y (47)	Y (43,48–50)	N	N
Protein-protein Interaction Networks	Y (51,52)	Y (23,50,53)	Y (54)	N
Computational epidemiology	Y (55)	Y (56)	Y (57)	Y(58,59)
Prioritizing drug targets	Y (39,40,51) 57	Y (43–45,60)	Y(60,61)	Y(60,61)
Predicting targets of active compounds	Y (62–65)	Y (66)	Y (67)	Y(68)
Finding novel compounds	Y(7,9,10,62,69–73)	Y (18,22,74,75)	Y (76,77)	Y(78)
Diagnostic biomarker discovery	Y(39)	N	Y (79,80)	N
Clinical deployment / diagnostic modeling	Y(81)	Y(82)	Y (83,84)	N
Model the disease process	Y(85,86)	N	N	N

[a] LeishCyc (Tier1), TrypCyc (Tier2)

[b] BioCyc Tier 2 database for schistosoma mansoni

HAT human African trypanosomiasis, *STH* soil transmitted helminthiases

treatments (e.g. those in clinical trials), diagnosing disease progression during the chronic stage, and in diagnosing congenital infections in newborns. A new diagnostic is a priority for schistosomiasis, so the observation of gaps can guide the next steps in performing further computational modeling. In addition, clinical deployment/diagnostic modeling was absent in helminths, while modeling the disease process appears to have been used with tuberculosis but not the other diseases (Table II).

Isolated computational models will likely have a diminished impact compared to efforts that combine approaches within a single disease, such as for malaria and tuberculosis, which have the greatest breadth of computational models available (Fig. 1b, (7,15)). For example, the integration of metabolic modeling, host pathogen interactions and protein-protein interaction network efforts could be advantageous. Similarly prioritizing drug targets, finding novel targets, diagnostic biomarker discovery, and predicting the targets of active compounds are inter-related and could be combined (Table II). Using computational models and data from one disease to make inferences for another disease (where there might be a lack of data for models) could be exploited if issues of model compatibility are overcome. This would be a hypothesis worth testing, although the types of models developed are frequently different.

LIMITATIONS AND RECOMMENDATIONS

What are the limitations of computational models? Very few of the studies, beyond those for tuberculosis, have performed validation of the predictions. While there are many examples of people assessing performance of computational models in general, there are few if any real examples of impact assessments for computational approaches as a whole and many of these relate to virtual screening efforts (14,24). The lack of validation of model predictions could be because the computational scientists have found it challenging to connect with experimental researchers interested in collaborating for testing their hypotheses. A solution needs to connect these different groups of scientists; efforts in social media (25) and collaborative consortia (26) may help facilitate this process for neglected tropical diseases.

A key limitation is the scarcity of data available to drive computational models for neglected diseases. While high-throughput screening has been performed on many millions of compounds for tuberculosis and malaria, data in the public domain is in the hundreds of thousands (27–31). For trypanosomal diseases, such as Chagas disease, public data is likely in the low thousands of compounds (32–36) screened, while for other diseases it may be far less. This clearly presents a problem for using machine learning models for virtual screening to find actives for each disease, for example. Similarly, the number of compounds with targets identified (or for which target-based large datasets have been created) is in the many hundreds for tuberculosis (10), and malaria. For other neglected diseases, the number of compounds with identified targets is far lower. This will hamper the generation of accurate target prediction algorithms that learn from prior data, thus requiring other approaches. Access to crystal structures for targets in each species would also assist in drug discovery and target prediction for new molecules. However, homology across species would be a limiting factor for using a model for a target in malaria to make predictions in kinetoplastid diseases.

Strategies to share computational models for neglected diseases more broadly may include using mobile devices and apps created for them. An example, like TB Mobile used to predict potential targets of molecules derived from phenotypic screening (37), could be applied to other diseases. Considering current existing neglected disease computational models may help us to imagine a future when they are integrated and

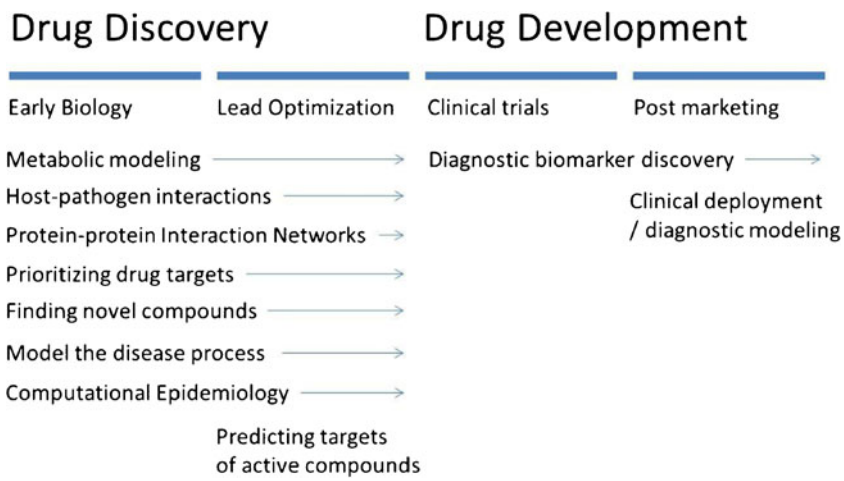

Fig. 2 Approximate positioning of computational models in the drug discovery and development workflow.

globally accessible to researchers on different hardware platforms. We suggest that first we need to fill the gaps we have identified by implementing the models in the appropriate positions in the drug discovery and development workflow (Fig. 2) for the respective neglected diseases and where necessary generate the appropriate data that is needed for their development.

ACKNOWLEDGMENTS AND DISCLOSURES

SE acknowledges discussions and collaborations with colleagues and collaborators at CDD and SRI.

ELP was a consultant for CDD.

SE Consults for Collaborative Drug Discovery on a Bill and Melinda Gates Foundation Grant#49852 "Collaborative drug discovery for TB through a novel database of SAR data optimized to promote data archiving and sharing".

REFERENCES

1. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD, *et al.* Control of neglected tropical diseases. N Engl J Med. 2007;357:1018–27.
2. Guiguemde WA, Shelat AA, Bouck D, Duffy S, Crowther GJ, Davis PH, *et al.* Chemical genetics of Plasmodium falciparum. Nature. 2010;465:311–5.
3. Ribeiro I, Sevcsik AM, Alves F, Diap G, Don R, Harhay MO, *et al.* New, improved treatments for Chagas disease: from the R&D pipeline to the patients. PLoS Negl Trop Dis. 2009;3:e484.
4. Bettiol E, Samanovic M, Murkin AS, Raper J, Buckner F, Rodriguez A. Identification of three classes of heteroaromatic compounds with activity against intracellular Trypanosoma cruzi by chemical library screening. PLoS Negl Trop Dis. 2009;3:e384.
5. Magarinos MP, Carmona SJ, Crowther GJ, Ralph SA, Roos DS, Shanmugam D, *et al.* TDR Targets: a chemogenomics resource for neglected diseases. Nucleic Acids Res. 2012;40:D1118–1127.
6. Gaulton A, Bellis LJ, Bento AP, Chambers J, Davies M, Hersey A, *et al.* ChEMBL: a large-scale bioactivity database for drug discovery. Nucleic Acids Res. 2012;40:D1100–1107.
7. Ekins S, Freundlich JS, Choi I, Sarker M, Talcott C. Computational databases, pathway and cheminformatics tools for tuberculosis drug discovery. Trends Microbiol. 2011;19:65–74.
8. Miller K. Where tuberculosis meets computation: 10 points of intersection. Biomed Comput Rev. 2012;20–28.
9. Ekins S, Reynolds R, Kim H, Koo M-S, Ekonomidis M, Talaue M, *et al.* Bayesian models leveraging bioactivity and cytotoxicity information for drug discovery. Chem Biol. 2013;20:370–8.
10. Sarker M, Talcott C, Madrid P, Chopra S, Bunin BA, Lamichhane G, *et al.* Combining cheminformatics methods and pathway analysis to identify molecules with whole-cell activity against Mycobacterium tuberculosis. Pharm Res. 2012;29:2115–27.
11. Duffy BC, Zhu L, Decornez H, Kitchen DB. Early phase drug discovery: cheminformatics and computational techniques in identifying lead series. Bioorg Med Chem. 2012;20:5324–42.
12. Krueger BA, Weil T, Schneider G. Comparative virtual screening and novelty detection for NMDA-GlycineB antagonists. J Comput Aided Mol Des. 2009;23:869–81.
13. Schames JR, Henchman RH, Siegel JS, Sotriffer CA, Ni H, McCammon JA. Discovery of a novel binding trench in HIV integrase. J Med Chem. 2004;47:1879–81.
14. Kubinyi H. Success stories of computer-aided design. In: Ekins S, editor. Computer applications in pharmaceutical research and development. Hoboken: John Wiley and Sons; 2006. p. 377–424.
15. Sundaramurthi JC, Brindha S, Reddy TB, Hanna LE. Informatics resources for tuberculosis–towards drug discovery. Tuberculosis (Edinburgh, Scotland). 2012;92:133–8.
16. Ekins S, Freundlich JS. Computational models for tuberculosis drug discovery. Methods Mol Biol (Clifton, NJ). 2013;993:245–62.
17. Ekins S, Reynolds RC, Franzblau SG, Wan B, Freundlich JS, Bunin BA. Enhancing hit identification in mycobacterium tuberculosis drug discovery using validated dual-event Bayesian models. PLoS ONE. 2013 (in press).
18. Anderson JW, Sarantakis D, Terpinski J, Kumar TR, Tsai HC, Kuo M, *et al.* Novel diaryl ureas with efficacy in a mouse model of malaria. Bioorg Med Chem Lett. 2012;23:1022–5.
19. Alvarez G, Martinez J, Aguirre-Lopez B, Cabrera N, Perez-Diaz L, Gomez-Puyou MT, *et al.* New chemotypes as Trypanosoma cruzi triosephosphate isomerase inhibitors: a deeper insight into the mechanism of inhibition. J Enzym Inhib Med Chem. 2012. doi:10.3109/14756366.2013.765415.
20. Pires DE, de Melo-Minardi RC, da Silveira CH, Campos FF, Meira Jr W. aCSM: noise-free graph-based signatures to large-scale receptor-based ligand prediction. Bioinformatics (Oxford, England). 2013;29:855–61.
21. Gunatilleke SS, Calvet CM, Johnston JB, Chen CK, Erenburg G, Gut J, *et al.* Diverse inhibitor chemotypes targeting Trypanosoma cruzi CYP51. PLoS Negl Trop Dis. 2012;6:e1736.
22. Zhang L, Fourches D, Sedykh A, Zhu H, Golbraikh A, Ekins S, *et al.* Discovery of novel antimalarial compounds enabled by QSAR-based virtual screening. J Chem Inf Model. 2013;53:475–92.
23. Suthram S, Sittler T, Ideker T. The Plasmodium protein network diverges from those of other eukaryotes. Nature. 2005;438:108–12.
24. Schneider G. Virtual screening: an endless staircase? Nat Rev. 2010;9:273–6.
25. Ekins S, Clark AM, Williams AJ. Open drug discovery teams: a chemistry mobile app for collaboration. Mol Inform. 2012;31:585–97.
26. Bunin BA, Ekins S. Alternative business models for drug discovery. Drug Discov Today. 2011;16:643–5.
27. Gamo F-J, Sanz LM, Vidal J, de Cozar C, Alvarez E, Lavandera J-L, *et al.* Thousands of chemical starting points for antimalarial lead identification. Nature. 2010;465:305–10.
28. Ballell L, Bates RH, Young RJ, Alvarez-Gomez D, Alvarez-Ruiz E, Barroso V, *et al.* Fueling open-source drug discovery: 177 small-molecule leads against tuberculosis. ChemMedChem. 2013;8:313–21.
29. Reynolds RC, Ananthan S, Faaleolea E, Hobrath JV, Kwong CD, Maddox C, *et al.* High throughput screening of a library based on kinase inhibitor scaffolds against Mycobacterium tuberculosis H37Rv. Tuberculosis (Edinburgh, Scotland). 2012;92:72–83.
30. Maddry JA, Ananthan S, Goldman RC, Hobrath JV, Kwong CD, Maddox C, *et al.* Antituberculosis activity of the molecular libraries screening center network library. Tuberculosis (Edinburgh, Scotland). 2009;89:354–63.
31. Ananthan S, Faaleolea ER, Goldman RC, Hobrath JV, Kwong CD, Laughon BE, *et al.* High-throughput screening for inhibitors of Mycobacterium tuberculosis H37Rv. Tuberculosis (Edinburgh, Scotland). 2009;89:334–53.
32. Mackey ZB, Baca AM, Mallari JP, Apsel B, Shelat A, Hansell EJ, *et al.* Discovery of trypanocidal compounds by whole cell HTS of Trypanosoma brucei. Chem Biol Drug Des. 2006;67:355–63.
33. Engel JC, Ang KK, Chen S, Arkin MR, McKerrow JH, Doyle PS. Image-based high-throughput drug screening

targeting the intracellular stage of Trypanosoma cruzi, the agent of Chagas' disease. Antimicrob Agents Chemother. 2010;54:3326–34.
34. Abdulla MH, Ruelas DS, Wolff B, Snedecor J, Lim KC, Xu F, *et al.* Drug discovery for schistosomiasis: hit and lead compounds identified in a library of known drugs by medium-throughput phenotypic screening. PLoS Negl Trop Dis. 2009;3:e478.
35. Andriani G, Chessler AD, Courtemanche G, Burleigh BA, Rodriguez A. Activity in vivo of anti-Trypanosoma cruzi compounds selected from a high throughput screening. PLoS Negl Trop Dis. 2011;5:e1298.
36. Ferreira RS, Simeonov A, Jadhav A, Eidam O, Mott BT, Keiser MJ, *et al.* Complementarity between a docking and a high-throughput screen in discovering new cruzain inhibitors. J Med Chem. 2010;53:4891–905.
37. Ekins S, Clark AM, Sarker M. TB Mobile: a mobile app for anti-tuberculosis molecules with known targets. J Cheminform. 2013;5:13.
38. G-FINDER. https://g-finder.policycures.org/gfinder_report/.
39. Galagan JE, Sisk P, Stolte C, Weiner B, Koehrsen M, Wymore F, *et al.* TB database 2010: overview and update. Tuberculosis (Edinburgh, Scotland). 2010;90:225–35.
40. Anishetty S, Pulimi M, Pennathur G. Potential drug targets in Mycobacterium tuberculosis through metabolic pathway analysis. Comput Biol Chem. 2005;29:368–78.
41. Raman K, Vashisht R, Chandra N. Strategies for efficient disruption of metabolism in Mycobacterium tuberculosis from network analysis. Mol Biosyst. 2009;5:1740–51.
42. Caspi R, Foerster H, Fulcher CA, Kaipa P, Krummenacker M, Latendresse M, *et al.* The MetaCyc database of metabolic pathways and enzymes and the BioCyc collection of pathway/genome databases. Nucleic Acids Res. 2008;36:D623–631.
43. Huthmacher C, Hoppe A, Bulik S, Holzhutter HG. Antimalarial drug targets in Plasmodium falciparum predicted by stage-specific metabolic network analysis. BMC Syst Biol. 2010;4:120.
44. Plata G, Hsiao TL, Olszewski KL, Llinas M, Vitkup D. Reconstruction and flux-balance analysis of the Plasmodium falciparum metabolic network. Mol Syst Biol. 2010;6:408.
45. Fatumo S, Plaimas K, Mallm JP, Schramm G, Adebiyi E, Oswald M, *et al.* Estimating novel potential drug targets of Plasmodium falciparum by analysing the metabolic network of knock-out strains in silico. Infect Genet Evol. 2009;9:351–8.
46. Anon. PathCase for metabolic analysis. http://nashua.case.edu/PathwaysMAW_Trypanosoma/web/. Accessed 3 Aug 2013.
47. Raman K, Bhat AG, Chandra N. A systems perspective of host-pathogen interactions: predicting disease outcome in tuberculosis. Mol Biosyst. 2010;6:516–30.
48. Wuchty S. Computational prediction of host-parasite protein interactions between P. falciparum and H. sapiens. PLoS ONE. 2011;6:e26960.
49. Davis FP, Barkan DT, Eswar N, McKerrow JH, Sali A. Host pathogen protein interactions predicted by comparative modeling. Protein Sci. 2007;16:2585–96.
50. Dyer MD, Murali TM, Sobral BW. Computational prediction of host-pathogen protein-protein interactions. Bioinformatics (Oxford, England). 2007;23:i159–166.
51. Kushwaha SK, Shakya M. Protein interaction network analysis–approach for potential drug target identification in Mycobacterium tuberculosis. J Theor Biol. 2010;262:284–94.
52. Cui T, Zhang L, Wang X, He ZG. Uncovering new signaling proteins and potential drug targets through the interactome analysis of Mycobacterium tuberculosis. BMC Genomics. 2009;10:118.
53. Ramaprasad A, Pain A, Ravasi T. Defining the protein interaction network of human malaria parasite Plasmodium falciparum. Genomics. 2012;99:69–75.
54. Rodriguez-Soca Y, Munteanu CR, Dorado J, Pazos A, Prado-Prado FJ, Gonzalez-Diaz H. Trypano-PPI: a web server for prediction of unique targets in trypanosome proteome by using electrostatic parameters of protein-protein interactions. J Proteome Res. 2010;9:1182–90.
55. Ioerger TR, Koo S, No EG, Chen X, Larsen MH, Jacobs Jr WR, *et al.* Genome analysis of multi- and extensively-drug-resistant tuberculosis from KwaZulu-Natal, South Africa. PLoS ONE. 2009;4:e7778.
56. Gething PW, Patil AP, Smith DL, Guerra CA, Elyazar IR, Johnston GL, *et al.* A new world malaria map: Plasmodium falciparum endemicity in 2010. Malar J. 2011;10:378.
57. Computational epidemiologic models developed. http://compepid.tuskegee.edu/CCEBRA/compmod.htm.
58. Gurarie D, King CH, Wang X. A new approach to modelling schistosomiasis transmission based on stratified worm burden. Parasitology. 2010;137:1951–65.
59. Raso G, Vounatsou P, McManus DP, Utzinger J. Bayesian risk maps for Schistosoma mansoni and hookworm mono-infections in a setting where both parasites co-exist. Geospat Health. 2007;2:85–96.
60. Crowther GJ, Shanmugam D, Carmona SJ, Doyle MA, Hertz-Fowler C, Berriman M, *et al.* Identification of attractive drug targets in neglected-disease pathogens using an in silico approach. PLoS Negl Trop Dis. 2010;4:e804.
61. Capriles PV, Guimaraes AC, Otto TD, Miranda AB, Dardenne LE, Degrave WM. Structural modelling and comparative analysis of homologous, analogous and specific proteins from Trypanosoma cruzi versus Homo sapiens: putative drug targets for chagas' disease treatment. BMC Genomics. 2010;11:610.
62. Kinnings SL, Liu N, Buchmeier N, Tonge PJ, Xie L, Bourne PE. Drug discovery using chemical systems biology: repositioning the safe medicine Comtan to treat multi-drug and extensively drug resistant tuberculosis. PLoS Comput Biol. 2009;5:e1000423.
63. Kinnings SL, Xie L, Fung KH, Jackson RM, Xie L, Bourne PE. The Mycobacterium tuberculosis drugome and its polypharmacological implications. PLoS Comput Biol. 2010;6:e1000976.
64. Prathipati P, Ma NL, Manjunatha UH, Bender A. Fishing the target of antitubercular compounds: in silico target deconvolution model development and validation. J Proteome Res. 2009;8:2788–98.
65. Raman K, Yeturu K, Chandra N. targetTB: a target identification pipeline for Mycobacterium tuberculosis through an interactome, reactome and genome-scale structural analysis. BMC Syst Biol. 2008;2:109.
66. Jensen K, Plichta D, Panagiotou G, Kouskoumvekaki I. Mapping the genome of Plasmodium falciparum on the drug-like chemical space reveals novel anti-malarial targets and potential drug leads. Mol Biosyst. 2012;8:1678–85.
67. Durrant JD, Amaro RE, Xie L, Urbaniak MD, Ferguson MA, Haapalainen A, *et al.* A multidimensional strategy to detect polypharmacological targets in the absence of structural and sequence homology. PLoS Comput Biol. 2010;6:e1000648.
68. Krasky A, Rohwer A, Schroeder J, Selzer PM. A combined bioinformatics and chemoinformatics approach for the development of new antiparasitic drugs. Genomics. 2007;89:36–43.
69. Ballester PJ, Mangold M, Howard NI, Robinson RL, Abell C, Blumberger J, *et al.* Hierarchical virtual screening for the discovery of new molecular scaffolds in antibacterial hit identification. J R Soc Interface. 2012;9:3196–207.
70. Ekins S, Bradford J, Dole K, Spektor A, Gregory K, Blondeau D, *et al.* A collaborative database and computational models for tuberculosis drug discovery. Mol BioSyst. 2010;6:840–51.
71. Periwal V, Rajappan JK, Jaleel AU, Scaria V. Predictive models for anti-tubercular molecules using machine learning on high-throughput biological screening datasets. BMC Res Notes. 2011;4:504.

72. Scheich C, Szabadka Z, Vertessy B, Putter V, Grolmusz V, Schade M. Discovery of novel MDR-Mycobacterium tuberculosis inhibitor by new FRIGATE computational screen. PLoS ONE. 2011;6:e28428.
73. Lamichhane G, Freundlich JS, Ekins S, Wickramaratne N, Nolan S, Bishai WR. Essential metabolites of M. tuberculosis and their mimics. Ambio. 2011;2:e00301–00310.
74. Marrero-Ponce Y, Iyarreta-Veitia M, Montero-Torres A, Romero-Zaldivar C, Brandt CA, Avila PE, *et al.* Ligand-based virtual screening and in silico design of new antimalarial compounds using nonstochastic and stochastic total and atom-type quadratic maps. J Chem Inf Model. 2005;45:1082–100.
75. Go Fight Against Malaria. http://gofightagainstmalaria.scripps.edu/.
76. Freymann DM, Wenck MA, Engel JC, Feng J, Focia PJ, Eakin AE, *et al.* Efficient identification of inhibitors targeting the closed active site conformation of the HPRT from Trypanosoma cruzi. Chem Biol. 2000;7:957–68.
77. Castillo-Garit JA, Vega MC, Rolon M, Marrero-Ponce Y, Gomez-Barrio A, Escario JA, *et al.* Ligand-based discovery of novel trypanosomicidal drug-like compounds: in silico identification and experimental support. Eur J Med Chem. 2011;46:3324–30.
78. Khanna V, Ranganathan S. In silico approach to screen compounds active against parasitic nematodes of major socio-economic importance. BMC Bioinforma. 2011;12 Suppl 13:S25.
79. Carmona SJ, Sartor P, Leguizamon MS, Campetella O, Aguero F. A computational pipeline for diagnostic biomarker discovery in the human pathogen Trypanosoma cruzi. BMC Bioinforma. 2010;11 Suppl 10:O11.
80. Carmona SJ, Sartor PA, Leguizamon MS, Campetella OE, Aguero F. Diagnostic peptide discovery: prioritization of pathogen diagnostic markers using multiple features. PLoS ONE. 2012;7:e50748.
81. Lin HH, Langley I, Mwenda R, Doulla B, Egwaga S, Millington KA, *et al.* A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools. Int J Tuberc Lung Dis. 2011;15:996–1004.
82. Smith T, Ross A, Maire N, Chitnis N, Studer A, Hardy D, *et al.* Ensemble modeling of the likely public health impact of a pre-erythrocytic malaria vaccine. PLoS Med. 2012;9:e1001157.
83. Lee BY, Bacon KM, Shah M, Kitchen SB, Connor DL, Slayton RB. The economic value of a visceral leishmaniasis vaccine in Bihar state, India. Am J Trop Med Hyg. 2012;86:417–25.
84. de Araujo Pereira G, Louzada F, de Fatima Barbosa V, Ferreira-Silva MM, Moraes-Souza H. A general latent class model for performance evaluation of diagnostic tests in the absence of a gold standard: an application to Chagas disease. Computational Math methods Med. 2012;2012:487502.
85. Abu-Raddad LJ, Sabatelli L, Achterberg JT, Sugimoto JD, Longini Jr IM, Dye C, *et al.* Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. Proc Natl Acad Sci U S A. 2009;106:13980–5.
86. Aandahl RZ, Reyes JF, Sisson SA, Tanaka MM. A model-based Bayesian estimation of the rate of evolution of VNTR loci in Mycobacterium tuberculosis. PLoS Comput Biol. 2012;8:e1002573.