

Role of Robot Scientists and Artificial Intelligence in Drug discovery

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Abstract

The paper gives an overview of the meaning of Artificial Intelligence, (AI) Advantages and disadvantages. There are several fields in AI-robotics, speech recognition and expert system-to name a few. Doing the laundry or the dishes may no longer seem a chore. Robots are programmed to perform these activities. The recent times saw the artificially developed robot “Eve” help in searching for new drugs. Eve uses a standardized form of assay to compute Boolean functions of compound properties. These assays can be quickly and cheaply engineered using synthetic biology, enabling more targets to be assayed for a given budget. Another discovery is the anti-cancer drugs which exhibited anti-malarial properties.

Keywords— Artificial Intelligence, robotics, medicine, robot scientist, QSAR

1. Introduction

Artificial Intelligence (abbreviated as AI) is the capability of a device to perform activities, which would otherwise only be expected of the human brain. John McCarthy coined the term Artificial Intelligence in 1956, and defines it as science of designing “intelligent” systems. These systems or agents perceives the environment and increases its chances of success.

Few of the “intelligent” tasks are pattern recognition, language learning, speech recognition and expert systems. Few advantages of AI are the increase in technological growth rate, uninterrupted work, aids for the elderly and children. Some of the disadvantages are there is no human touch to the work done.

Whether it is caring for elders or doing the laundry—it’s another robot doing the job. Technology can be misused or used unethically.

There is an urgent need to make drug discovery cheaper and faster. This will enable in the treatment of diseases which have been neglected for reasons. The robot-scientist, Eve is designed at the University Of Cambridge and Manchester. It makes the process of drug discovery economical. This laboratory automation system in conjunction with AI is used to obtain scientific knowledge.

One of the key, primary step is to develop an ‘assay’. This is a biological or computational experiment that determines whether a small compound is capable of treating the disease. This test should be relatively cheap and fast to execute as it will be run several times. Any compound that passes the trial is called a ‘hit’.

The next step is to run a drug screen, where a collection of compounds is tested against the assay. This consists of millions of compounds. Such mass screening is generally done using the brute-force approach, also called Proof by exhaustion. This is a method of mathematical proof in which the statement to be proved is split into a finite number of cases or sets of equivalent cases and each type of case is checked to see if the proposition in question holds good.

Since the probability of any compound being successful is low, designing an experiment that does not have a sizeable portion of false positive hits is important. This statistical term usually refers to the probability of falsely rejecting the null hypothesis for a particular test.

It is necessary to carry out the experiments in order to confirm the successes. These are relatively more expensive, slow to execute, and with a much lower false positive probability.

From this set of confirmed hits, a quantitative structure activity relationship (QSAR) is learnt. Quantitative structure–activity relationship models (QSAR models) are regression or classification models used in the chemical and biological sciences and engineering. QSARs, are mathematical models that attempt to relate the structure-derived features of a compound to its biological or physicochemical activity

The predictors consist of theoretical molecular descriptors of chemicals; the QSAR response-variable could be a biological activity of the chemicals. QSAR models first summarize a supposed relationship between chemical structures and biological activity in a data-set of chemicals.

Second, QSAR models predict the activities of new chemicals. As an example, biological activity can be expressed quantitatively as the concentration of a substance required to give a certain biological response. Additionally, when physicochemical properties or structures are expressed by numbers, one can find a mathematical relationship, or quantitative structure-activity relationship, between the two. The mathematical expression, if carefully validated can then be used to predict the modeled response of other chemical structures.

2. “Eve” –the artificially designed robot

2.1 Introduction

Meet Eve, the artificially-designed drug creating robot that could save your life.

To shorten development time and increase economy, scientists at the Universities of Cambridge and Manchester have built Eve, an artificially-intelligent robot-scientist.

It was designed specifically for drug development which could assist in faster and cheaper way of drug discovery. Eve has already identified a compound that could be used to fight malaria. These robots – scientists mark the extension and increased involvement of automation in the field of science.

Eve starts the lead discovery process by mass-screening a subset of its collection to find ‘hit’ compounds for the experiment. This subset is currently chosen randomly. In its hit-confirmation mode Eve re-assays the hit compounds using several iterations to reduce any chance of false positives. Starting from the set of confirmed hits, Eve executes cycles of statistics/machine learning that speculates QSARs, and tests these QSARs on new compounds. As Eve currently does not have access to chemical synthesis automation, Eve is subjected to screen untested compounds from its library as a substitute for synthesizing compounds. Such intelligent library screening may be more economical than standard mass screening as it potentially saves on time and compound use.

In 2009, Adam, another robot scientist was developed by the same team, which carried out genetic experiments in yeast and provided scientific knowledge independently of its human creators. Occasional human assistance was required to top up reagents and remove waste.

Adam is able to perform independent experiments to test hypotheses and translate the findings without human guidance, removing some of the grind of laboratory experimentation. The robot-scientist is capable of:

- 1) Speculating in the observed values
- 2) Preparing experiments to test the thesis.
- 3) Physically running the experiments
- 4) Analysing the results
- 5) Repeating the cycle

2.2 Hardware

Eve’s robotic system is capable of moderately high-throughput compound screening. Depending on the length of time taken to assay compounds, it can screen more than 10000 compounds per day. Eve is designed to be sufficiently flexible that it can be rapidly redesigned to carry out a number of different biological experiments, using fluorescence, absorbance or cell morphology as read-outs.

Eve’s robotic system blends a range of off-the-shelf pieces of laboratory automation equipment into a single, comprehensive system that can perform library-screening, hit confirmation and cycles of QSAR hypothesis formation and testing using selected compounds from a compound library.

Eve can also be reconfigured to copy compound libraries. This is maintained in a dry-store, with the compounds dissolved in dimethyl sulphoxide (DMSO). The compounds which are later used for experiments are transferred from the storage plates

to the assay plates. This has the advantage of high accuracy. After assay compound is added, the target yeast strain is added.

The yeast pool is created externally and stored for Eve to use. Once the assay plates are formed, they are placed in a shaking incubator. Hourly, the plates are removed from the incubator and light emitted is measured. There are two micro plate readers which is capable of recording measurements and an automated microscope capable of taking images across a broad range of wavelengths. On completion of the experiment, the bar coded plates are removed automatically and movements recorded.

2.3 Low-level software

Software was written to accommodate Eve's AI software with the Robotics. Eve's early stage drug design functions were automated. It performed library-screening, hit-confirmation and QSAR cycles. The software to control the robotics, instrumentation and used to execute the experiments is written. An interface was written to a relational database that stores all experiment-related data and meta-data

. The software to parameterize growth curves for the different yeast strains in each well was taken from the Adam project-the first robot scientist.

. The main parameters are estimated maximum growth, doubling time and lag time. These growth parameters were then transferred to the AI QSAR software. Software was also written to coordinate library-screening, and to plan hit confirmation. This was also integrated with the AI software so that the active learning algorithm could select compounds to test.

2.4. Role of Eve in discovering drugs

According to the University of Cambridge, there is a huge bottle-neck in pharmaceutical research. An artificial intelligence system – or 'robot scientist' – capable of screening potential drugs almost completely independently could speed up drug development. This approach has been successful in discovering anti-cancer compounds which also showed anti-malarial properties.

It can take 10 years and US\$1 billion to create a new drug – time during which many people continue to suffer and that money needs to be recovered. It's due to this that drugs for fighting many diseases like malaria are lacking. The causes of the disease can be identified, and the parasites which cause them can be destroyed using small molecule drugs. The huge

cost and speed of this drug discovery makes them less attractive to the pharmaceutical industry.

One method where testing drugs can be automated is using the "brute force" method. This involves testing each and every compound until an effective compound is found. This is very time consuming. Another faster and cheaper method is robot scientists. They are capable of carrying routine drug tests, developing, testing and changing the hypotheses. The results are automatically selected.

The robot scientist 'Eve' – is actually a collection of machines including several computers hooked up to the kind of automated instruments already found in many labs. The idea is to automate scientific research. The system is "told" about the area of research interested in, and then the computer has an automated way of forming new hypotheses about that area of science. It can then design experiments to test these theories and the lab robots go ahead and actually perform the experiments.

Many parts of the process, such as high throughput library screening, are already highly automated, and Eve is built with all the necessary equipment to screen tens of thousands of compounds a day and identify leads. But the system can also intelligently respond to results and create standardised assays using synthetic biology. Once it has identified a lead compound, Eve can engineer specific strains of yeast needed to screen for activity against a particular disease. This makes it both quicker and cheaper than standard drug screening methods, even those that already use automated equipment.

Eve automates early-stage drug testing and design. A series of tests are subjected to machine screening at a low cost. Rather than testing all the available compounds, the robot scientist takes a random subset of compounds. They are tested several times to eliminate any false results. These results are further analysed using statistical methods and machine learning. This detects new and small molecules that yields better results. Compounds that have a high chance of being active against the particular drug target are chosen. A smart screening system which is based on genetically engineered yeast is used. These modified microorganisms will locally deliver antigens in order to stimulate an immune response and ensure protection against bacteria, viral and parasitic disease.

Eve excludes compounds that are toxic in nature and selects the compounds that block the action of the dependent protein. It leaves any equivalent human

protein untouched. As a result, this reduces the costs, and time involved in drug screening, while improving the lives of people.

The molecules are tested for parasites that spread contagious diseases like malaria. The molecules are compared with 1500 compounds to check if any of them were effective molecule.

The system already has proven to be successful, highlighting several drug candidates that could be reused. For example, it showed the anti-cancer compound can also attack the malarial parasite *Plasmodium vivax* by inhibiting an essential enzyme. This compound is now being looked at in Brazil, where this form of malaria is prevalent. Researchers observed that though treatments against the molecule already existed, alternatives were being discovered in case the parasites developed an immunity to traditional treatments.

No new antimalarial drug had been discovered, and this discovery by Eve shows a new approach to drug discovery. Though Eve is not capable of synthesizing compounds that it can design based on tests. This robotic system can screen nearly 10,000 compounds in a day.

In future, robot scientists like Eve could be used by pharmaceutical companies to streamline the drug development process, or explore potential new functions for existing drugs.

The diagram below shows Eve in action



Fig. Eve in action

3. Future of Robot Scientists

Technological advancements in medicine are happening daily. Companies and universities alike are advancing the pace at which the quality of health care for many people are being provided.

However, the importance of robotics seems to be incredibly undersold in its importance to medicine. Instead, robotic medicine should be at the forefront of science.

A surgical robot in London called the Da Vinci XI conducted its first surgery on a patient with colon cancer. The procedure with a surgeon is a challenging one, requiring incredibly intrusive procedures. The robot acted as an extension of the surgeon's hands and assisted in carrying out complex surgeries.

The advantage of the non-invasiveness of these procedures cannot be exaggerated. . These procedures in renal and kidney surgeries can result in an increase in mortality and increased risk of renal failure. A recent study concluded that there were potential risks involved in surgeries related to renal system.

The accuracy that is offered by robotic tools can help to increase the range of procedures that doctors could perform on patients. But surgical robots aren't the only area of research where the future of robotics thrives. Soft robots could be used in drug delivery and in performing biopsy. Equipped with "micro grippers," they have the capacity to hold on to specific tissues in the body. These robotic arms have six degrees of freedom, thus enabling them to carry out any complex procedure.

A recent article by the New York Times explained that the treatment of Ebola was getting incredibly difficult. Doctors were being forced to use full-body suits to prevent contamination and running the risk of an infection. The use of a stethoscope proved to be incredibly risky. This explores an area where there is potential for robotics. Doctors wouldn't need to actually touch a patient to incur a risk of infection from any disease. Research has been driving robots to develop a sense of touch by sensing pressure applied to objects surrounding it.

However, medical robots cannot be seen as companions that would solve all of our problems. Robotics are the future of innovation and hold endless possibilities in the world of health research.

On the flip side are high development and maintenance costs of these robots. A robot in the household or even outdoors may not be a familiar sight in India, which despite its vast size is faced with enough challenges in accommodating its increasing human population. In several parts of Asia, robot workers including vacuum cleaners have grown in popularity in recent years. Automation has been criticised for loss of jobs for human beings. Yet

robotics is set to come in handy in diverse fields including medicine, agriculture and military.

Conclusion

Eve's standardized assays could easily be engineered for other targets classes or target species (e.g. bacteria), drug import, or to screen for drugs. In addition to this, the experiments could be blended with several parasitic targets within the same yeast cell. This creates several cells that mimic or imitate parasitic or human behaviour.

Preventing drug failures in its late-stage-development is a hard problem. On the contrary, a fundamental decrease in the cost and or this. Increase in the discovery of drugs could be achieved. Automating and standardizing the procedures are necessary for this. A robotic system when given a target could independently come up with a standard test for the target, screen a collection of compounds using this test. All the successful compounds are confirmed and the lead compounds identified.

Synthetic biological assay deals with the redesign and fabrication of existing biological systems. They can be automated using the existing technology. There a machines which execute several chemical reactions in order to obtain a product. This machine could be integrated with Eve, which would achieve the purpose of a robotic system. Successes of targets could be automatically generated. Costs of drug discovery can be decrease d with a proportional increase in the speed.

References

1. Inset JR, Chang S. 2011 Drugs for neglected diseases initiative model of drug development for neglected diseases: current status and future challenges. *Future Med.*
2. Leslie M. 2011 Drug developers finally take aim at a neglected disease. *Science* 333, 933–935. (doi:10.1126/science.333.6045.933)
3. Pammolli F, Magazzini L, Riccaboni M. 2011 The productivity crisis in pharmaceutical R&D. *Nat. Rev Drug Disc.* 10, 428–437. (doi:10.1038/nrd3405)
4. Schneider G. 2010 Virtual screening: an endless staircase? *Nat. Rev. Drug Disc.* 9, 273–276. (doi:10.1038/nrd3139)
5. Deutsch D. 1985 Quantum theory, the Church Turing principle and the universal quantum computer. *Proc. R. Soc. Lond. A* 400, 97–117 (doi:10.1098/rspa.1985.0070)
6. Benenson Y, Gil B, Ben-Dor U, Adar R, Shapiro E. 2004 An autonomous molecular computer for logical control of gene expression. *Nature* 429, 423–429. (doi:10.1038/nature02551)
7. Smith AM, Ammar R, Nislow C, Giaeever G. 2010 A
8. Bizer C, Heath T, Berners-Lee T. 2009 Linked data—the story so far. *Intl. Semantic Web Info Syst.* 5, 1–22.
9. Zhang P, Nicholson DE, Bujnicki JM, Su X, Brendle JJ, Ferdig M, Kyle DE, Milhous WK, Chiang PK. 2002 Angiogenesis inhibitors specific for methionine aminopeptidase 2 as drugs for malaria and leishmaniasis. *J. Biomed. Sci.* 9, 34–40. (doi:10.1007/ BF02256576)
10. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. 2011 Open Babel: an open chemical toolbox. *J. Cheminform.* 3, 33. (doi:10.1186/1758-2946-3-33)
11. Besnard J et al. 2012 Automated design of ligands to polypharmacological profiles. *Nature* 492, 215–219. (doi:10.1038/nature11691)
12. Bilsland E, Pir P, Gutteridge A, Johns A, King RD, Oliver SG. 2011 Functional expression of parasite drug targets and their human orthologs in yeast. *PLoS Negl. Trop. Dis.*
13. Rasmussen CE, Williams CKI. 2006 Gaussian processes for machine learning. Cambridge, MA: The MIT Press.

14. Arico-Muendel C et al. 2009 Antiparasitic activities of novel, orally available fumagillin analogs. *Bioorg. Med. Chem. Lett.* 19, 5128–5131. (doi:10.1016/j. bmcl.2009.07.029)

Website source:

1. <http://blog.adlegant.com/artificially-intelligent-robot-eve-helps-in-drug-discovery-could-find-malaria-cure/>

2. <http://www.gizmag.com/eve-robot-scientist-drugs/35935/>

3. <http://rsif.royalsocietypublishing.org/content/royint/12/104/20141289.full.pdf>

4. <http://www.cam.ac.uk/research/news/artificially-intelligent-robot-scientist-eve-could-boost-search-for-new-drugs>

5. <http://www.rsc.org/chemistryworld/2015/02/robot-scientist-eve-speeds-drug-discovery>