Automated design for drug discovery

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A system of 'automated design' for new drugs could help develop the complex therapies needed for many medical conditions while also improving drug safety and efficiency, new research from the University of Dundee has shown.

The 'Moneyball' approach taken by the research team utilises the principles of advanced statistical and data analysis which have seen to be increasingly influential in areas as varied as sport, finance and in forecasting the recent US Presidential election.

As more complex drugs are needed to treat more complicated problems - particularly in areas such as neuroscience, infectious diseases and cancer - the task facing biologists and chemists is daunting. However, researchers at the College of Life Sciences at Dundee, in collaboration with partners in North America, have shown that an automated computational process analysing huge amounts of existing data could provide a valuable new tool in drug discovery.

The innovative approach taken by the research team mimics the creative process of human chemists, where drug molecules are steadily improved through successive cycles of design and selection.

"One of the things that makes drug discovery so hard is that you're trying to improve several different properties at the same time," said Professor Andrew Hopkins, Chair of Medicinal Informatics at Dundee. "Evolution is a mechanism than can be applied to solving these kinds of optimisation problems, and the iterative process of adaption and

selection of hundreds of thousand of possible solutions can be simulated in a computer.

"We have effectively proved the concept of automated design of new compounds, showing that by using algorithms to process massive amounts of data we can tackle problems of huge complexity. The system solves the design problem by using computational evolution to mimic the design process of human chemists but running it on a very large scale."

The research is published in the journal *Nature*.

Drugs have to be able to deliver their primary effects and not present adverse side effects or toxicity that render them unsafe. But for complex conditions drugs also have to be designed to hit multiple targets. Designing drugs to this kind of multi-target profile is a complex and exceedingly difficult task for medicinal chemistry.

Professor Hopkins and colleagues developed an automated adaptive design approach that can mimic the creative, iterative process of medicinal chemists by using computational evolution of large numbers of compounds. They initially used it to look at an existing drug, Donepezil, which is used in treating Alzheimer's Disease.

"Professor Sir James Black, the Nobel Laureate and former Chancellor of the University, proposed that 'the most fruitful basis for the discovery of a new drug is to start with an old drug' and we followed that advice," said Professor Hopkins.

"We took the structure of Donepezil as a starting point and from there the system evolved its structure, computationally, over many generations to a variety of different profiles across a range of drug targets. The predicted profiles were then tested experimentally and we found that 75% of them were confirmed to be correct.

"This proof of concept shows that we could make significant advances in discovering and designing complex drugs, which could lead to improvements in safety and efficacy, while also potentially reducing the cost of drug discovery, which is a high-risk and expensive process."

Professor Hopkins said improvements in data capture and management were key to developing the research.

"Just a few years ago this would not have been possible because we need the existing drug data to build on and it was not held in a way that it could be analysed like this. But there have been significant developments, aided by groups like ChEMBL in Cambridge, who are funded by The Wellcome Trust, in making drug design data available in a format computers can process. What we have found particularly exciting is the way the algorithm has been able to learn from the human experience of drug design and mimic it on a massive scale to solve complex design problems."

This phenomenon is reflected in the name of a new spin out company which has been formed to commercialise the technology – ex scientia – which is the Latin for "from knowledge".

Provided by University of Dundee