Follow the ant trail for drug design

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New drugs often fail because they cause undesirable side effects. ETH researchers have developed simulation software that predicts the properties of active agents and virtually builds new ones. The software's search process is modeled after the behavior of ants.

The path to developing new drugs is a long one. If a target is identified for a new active agent – for instance a particular protein that plays a key role in a disease – an active molecule that binds to the target must then be developed. Pharmaceutical companies trawl through their collections of chemicals for substances that act on the target protein in the desired fashion. However, these compounds are often just the starting point for a long process of adjustment and testing. Chemists use computer simulations to design new molecules to yield innovative compounds with the desired properties; however, undesirable effects often come to light only after the active agent has been synthesised and tested, and in the worst-case scenario only during the clinical trials.

To date, the prediction of side-effects using a computer has been limited. "Our aim is to detect problems as early as possible and synthesise only the most promising active agents," explains Gisbert Schneider, Professor of Computer-Assisted Drug Design at the Institute of Pharmaceutical Sciences, ETH Zurich. Many potential candidates that prove to have undesirable effects can thus be eliminated quickly.

Effective predictive module

Schneider's research team has developed a simulation module that can

predict possible target activities of drug-like molecules more quickly and precisely than previous programmes. The algorithm checks the interaction of a molecule with up to 640 human proteins in just a few minutes. "This is currently the most effective predictive module in existence," says Schneider. A trial run with a cholesterol lowering agent, fenofibrate, which has a range of side-effects, showed all known interactions with unintended targets as well as some previously unknown. Some of the unexplained side-effects of the drug could be attributed to the latter.

However, the computer module is capable of even more: it combines molecular building blocks from a virtual building set to suggest new chemical entities. It also checks the interactions of these with the 640 human proteins and suggests the best module combination.

Following the scent mark

In order to allow the software to search for new composite agents, the research team uses an ant algorithm. Like an ant colony on the search for food, the algorithm screens through the molecular building blocks for components with the desired properties. Depending on the strength of the desirable and undesirable effects of the virtual products, the building blocks receive a 'grade'. In the ant world, this would equate to marking the trail to food with pheromones. In the next step, the components are recombined and the properties reassessed. In the process, a building block that received a high grade at the start can drop out of the short list, because it might has too many predicted adverse effects in combination with another building block. The 'scent mark' of the ant algorithm fades in this case, while the 'scent mark' for a better block combination is increased with every virtual combination step. In the end, the algorithm – like the ants – finds the quickest or best way to the goal by adaptive trial and error.

"Ant algorithms are used in robotics, for example for optimising manufacturing processes, but we have now transferred the trick to drug discovery," says Schneider. As not only one ant but an entire colony of ants looks for the path – in this case, numerous parallel and intercommunicating search processes – the simulation module designs new active agents within minutes and suggests the necessary chemical synthesis steps. "What previously took up to two weeks can now be done in a day, thanks to the new software." In a next step, Schneider's team wants to connect the computer module to a synthesis robot to fully automate the design and subsequent synthesis.

According to Schneider, in the future it may be possible to not only find the best active agent for a particular disease, but to develop medication for the individual patient. "If we could give the algorithm extra information, such as what the patient's protein world looks like, it could calculate the interactions to be expected for that particular patient." A suitable active substance could be selected and the patient treated with as few side-effects as possible.

More information: Reker, R., Rodrigues, T., Schneider, P. and Schneider, G. Identifying the macromolecular targets of de novo designed chemical entities through self-organizing map consensus. *Proc. Natl. Acad. Sci.* USA, March 3, 2014, DOI: 10.1073/pnas.1320001111

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