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Innovating AI today for better drug discovery tomorrow:
Machine Learning at Merck KGaA, Darmstadt, Germany, helps researchers find potential drugs faster and more easily

Artificial intelligence, or AI, has crept into our daily lives in many ways: via Siri who recognizes our voices, Alexa who tells jokes, and that helpful, unnamed woman who instructs us to turn left just as our cars approach an intersection. In the area of drug discovery, Merck KGaA, Darmstadt, Germany, is pushing AI to the next level to save lives, by using it to help find new and better treatments for disease—which it may be able to do more quickly and efficiently than is possible with traditional methods.

The type of AI we most frequently encounter—also known as Narrow AI—uses voice- or face-recognition programs (algorithms) that are trained using millions or billions of examples of voices or faces. In contrast, Merck KGaA, Darmstadt, Germany, is looking to use AI to solve problems in niche areas, such as drug discovery or materials science, where the data points for training the algorithms exist only in the tens of thousands.

“That makes it more challenging for us to build the AI models,” says Helmut Linde, global head of Data Science & Analytics at Merck KGaA, Darmstadt, Germany. “While the most common machine-learning approaches rely on pattern detection in large data sets, we need to find new ways to combine this statistical approach with domain knowledge that we feed into the models explicitly.”

In drug discovery, for example, Merck KGaA, Darmstadt, Germany, is already leading the way by using AI models and software to predict which chemical structures would make the best drug candidates to pursue, screen in the laboratory, and then test in preclinical and clinical trials. Only 10% of new drugs that enter into the first phase of clinical trials eventually get approved for use (1). AI experts and chemists at Merck KGaA, Darmstadt, Germany think that deploying machine-learning AI at the earliest stages of drug discovery—to identify the most promising molecular structures for drug candidates—will help improve that efficiency.

Machine learning uses neural networks modeled somewhat on the neural networks found in our brains. In machine learning, a computer model is first trained on a large set of data points or images that have first been sorted by humans. From this data set, the computer program “learns” all the characteristics that make up, for instance, an image of a panda. Once the training is over, the model should be able to then sift through new images on its own and correctly identify images of pandas, without any guidance from a human operator.

Machines learn to design drugs
Advanced machine learning, including deep learning, a special architecture of neural networks, can now be applied to drug discovery challenges. For example, the recent explosion in molecular knowledge about what causes disease has given us thousands of known drug targets—the molecules in the human body that are responsible for disease, which are mostly proteins. And we have billions of possible drug candidates—usually small, chemically synthesized molecules that could be discovered or designed and used to block, enhance, or modify these targets.

Identifying potential small-molecule drugs typically involves researchers either screening huge libraries of compounds to find those with a desired activity or designing novel compounds based on structures likely to produce that activity. Importantly, both approaches represent bottlenecks in drug discovery, because even with automated processes, it still takes 1-3 years and often the synthesis of a few thousand molecules to come up with a small molecule that modifies a target activity in the desired way and is selective for the desired target (to ensure there will be no side effects)—this represents a lot of money and person-hours.

AI systems offer very high data processing speed and efficiency that could accelerate the designing and screening process for drug candidates, resulting in the delivery of better treatments to patients more quickly. One study predicted that using AI in the drug discovery process could save USD 70 billion by 2028 (2).

“Predictive models are central to our work,” says Friedrich Rippmann, director, Global Computational Chemistry & Biology at Merck KGaA, Darmstadt, Germany. “These are statistical models that predict whether a compound idea—a not-yet-synthesized molecule—will produce a desired activity.”

These deep neural networks can identify novel compounds and the chemical groups responsible for wanted or unwanted activities. As Rippmann explains, the predictive models go further than simply informing scientists that “this compound will or will not work.” The models can also tell chemists why something won’t work and can
even highlight the areas of a molecule that are responsible for an activity. "This immediately indicates to chemists how to remove a certain unwanted activity from a candidate drug molecule," says Rippmann.

Rippman's team, working alongside company collaborators and partners, has developed about 300 new models to predict compound properties. The company’s chemists use these models to decide which invented compounds have higher odds of success and should therefore be synthesized first for further testing.

**SYNTIA™ helps chemists walk backward**

Organic chemists are the sophisticated experts who will synthesize the molecules suggested by Rippmann's group, based on the drug target protein as a starting point, and design them to inactivate it or modify it. In a practice called retrosynthesis, those chemists then work from the desired molecule backward to small starting materials to figure out the most feasible pathway to synthesize it.

MilliporeSigma, one of the three businesses of Merck KGaA, Darmstadt, Germany, is continuing to develop an AI-enabled software program called SYNTIA™ to help chemists navigate retrosynthesis more efficiently. Coded by expert organic chemists and computer scientists over the course of more than 15 years, SYNTIA™’s algorithms are driven by more than 100,000 expert-coded chemical reaction rules that describe known synthetic steps and allow the algorithms to stitch together several viable routes from commercial or known starting materials to the desired drug-like molecule.

At each retrosynthesis step, SYNTIA™ considers local chemical interactions or potential conflicts between chemical groups within a molecule. SYNTIA™ also explores both novel and known solutions at each step, eliminates unworkable options, and presents the synthesis pathways with the highest potential for success in the lab. To further refine the returned pathways, chemists can add filters—such as limiting the results to the fewest number of steps or the lowest cost for starting materials—making SYNTIA™ a highly customized tool to fit the needs of the chemist.

However, there are limitations to current AI efforts. For computers, it is still a significant challenge to transfer knowledge from one domain to a new context, or even to make the knowledge it has "learned" understandable. An artificial neural network may be able to recognize cat breeds in images, but that does not mean that it can "explain" what a cat is or that it can use this knowledge (without human intervention) to get a head start in learning to identify dog breeds. These limitations have a particularly strong effect on the life sciences, where training data is often rare and expensive to obtain, while a huge corpus of domain knowledge is just waiting to be included in AI models.

Linde believes it will take more interdisciplinary work between neuroscientists, computer scientists, mathematicians, and theoretical physicists to find a new generation of machine-learning algorithms—algorithms that are inspired by a deeper understanding of the human brain. "The AI of the future must be much better at grasping the essence of things and deriving meaningful levels of abstraction on its own—rather than relying on a kind of interpolation between huge numbers of annotated data points," Linde says. If this hope is realized, researchers in the life sciences will find their digital helpers even more useful than today. And, who knows, maybe someday Alex will even understand the jokes she tells us.

**References**


**For more info:**


The company’s AI-enabled software program, SYNTIA™, now helps chemists more efficiently conduct retrosynthesis, the backwards creation of molecules to an already-known drug target protein.
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