New computational method reduces risk of drug formulation

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One major factor that determines the efficacy of a drug is the structure that its molecules form in a solid state. Changed structures can entail that pills stop functioning properly and are therefore rendered useless.

An international cooperation

A team led by researchers from the University of Luxembourg in collaboration with Princeton University, Cornell University, and Avant-garde Materials Simulation GmbH, has developed a new method to calculate and predict how drug molecules in molecular crystals arrange themselves under changing energetic conditions. For pharmaceutical companies, this approach could be used to avoid expensive development failures, production errors, and potential litigation.

Minor changes in production conditions may affect drug effectiveness

As the majority of drugs is marketed in a solid state, for example as pills, manufacturers have to make sure that they function properly and release the pharmaceutical agents in the required dose. "In the past, there have been several scandals in the pharmaceutical industry, when companies had identified a molecule that works, marketed it, and then, sometimes years later, due to minor changes in production conditions, the drug formulation stopped being effective," explains Prof. Alexandre Tkatchenko from the Physics and Materials Science Research Unit at the

University of Luxembourg, the leading author of the resulting paper that was published in *Science Advances*. Consequently, some drugs needed to be reformulated and taken off the market for a long period of time.

In most cases, the reason for these changed properties lies in the interactions between the molecules. In a solid state, molecules organise in crystalline structures stabilised by a variety of intermolecular interactions. As molecules are very flexible, they can form many different arrangements with differing physical and chemical properties. "In order to predict this, pharma companies usually rely on 'trial and error' in crystallisation experiments. However, realistically you can't study all possible forms experimentally, because you never know what will change in experimental conditions. The possibilities are exponential," explains Prof. Robert DiStasio, a co-author of the study from Cornell University.

Predictive calculations to replace empirical studies

In order to be able to replace these experiments with predictive calculations, the researchers teamed up with the company Avantgarde Materials Simulation that provides services for pharma companies to predict crystal structures of organic solids. Together, they developed a method that enables them to calculate how the energy of different solids changes depending on their structure. "The new approach improves the energy ranking accuracy at acceptable computational cost. It will change the way how crystal structure prediction is used throughout the pharmaceutical industry," comments Dr. Marcus Neumann, founder and CEO of Avant-garde Materials Simulation GmbH.

For the future, the authors plan to further develop the method and combine it with machine learning in order to increase the computational efficiency.

More information: Johannes Hoja et al. Reliable and practical computational description of molecular crystal polymorphs, *Science Advances* (2019). DOI: 10.1126/sciadv.aau3338