THE FRONT ROW
at Scripps Research

Predicting the chemistry of tomorrow for the medicines of the future

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ABOUT THE LECTURE

Small-molecule medicines have big effects on human health, but building up their complex networks of atoms forces chemists to choose among staggering numbers of possible chemical reactions. In his Front Row lecture, Scripps Research professor Ryan Shenvi explored how modern computation can narrow those choices and reduce trial and error. Drawing on examples from drug discovery and his own lab, Shenvi showed how computers help scientists anticipate how molecules might behave and find more efficient ways to make them.

TOP TAKEAWAY POINTS

- Molecules can be difficult to build, but control over their structures allows chemists to dictate their behavior. Precise edits, sometimes down to a single atom or even a subatomic particle like a neutron, can change their molecular properties and behavior dramatically. For instance, Shenvi highlighted work from Scripps Research's chemistry department that showed how changing a single atom in the antibiotic vancomycin increased its potency against a resistant bacterial strain by about 1,000-.

- Chemists are able to turn promising molecules into better medicines by redesigning their structures. New drug candidates can emerge from existing medicines, from collections of synthetic molecules, or from nature's molecules. Building a molecule atom-by-atom, a process called total synthesis, provides chemists with a wide variety of options for the structures they make.

- Creating a complex molecule is a lot like reverse engineering. Chemists begin this thought process with the molecule they want to make and work backward until they arrive at inexpensive starting materials. This process is called retrosynthetic analysis. As an example, Shenvi described an industrial pathway that converts beta-pinene [β-pinene] (a naturally occurring compound found in the solvent turpentine) into roughly 3,000 metric tons of menthol (the cooling compound in mint) each year. Shenvi compared choosing among the potential routes to playing chess: knowing which moves are possible is only part of the challenge; chemists also need to choose the best strategy.

- Machine-learning models are fed by huge amounts of data to make predictions. However, Shenvi's lab usually studies molecules that have never been made, so data isn't available. Physics-based simulations help researchers estimate how unfamiliar compounds might react before testing them in the lab. In one project, Shenvi's lab used these simulations to generate "virtual data" to feed a predictive model. The validity of this model was then demonstrated in the lab to create a collection of compounds of interest for their effects on neurons.

- The next step is to concurrently improve molecules and the routes used to build them. Shenvi calls this idea "dynamic retrosynthetic analysis," which would use computation to consider multiple related compounds rather than working backwards from a single target. Small structural changes could then be evaluated for both their biological effects and their impact on synthesis. Shenvi emphasized that fully automating this process is a distant goal, but one worth pursuing.

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