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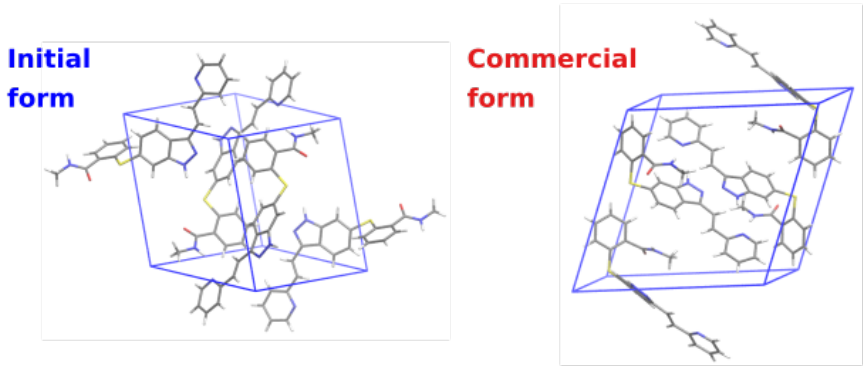
Next-Generation NMR Crystallography Through Ab Initio Structure Refinement

Anti-Cancer Drug Axitinib

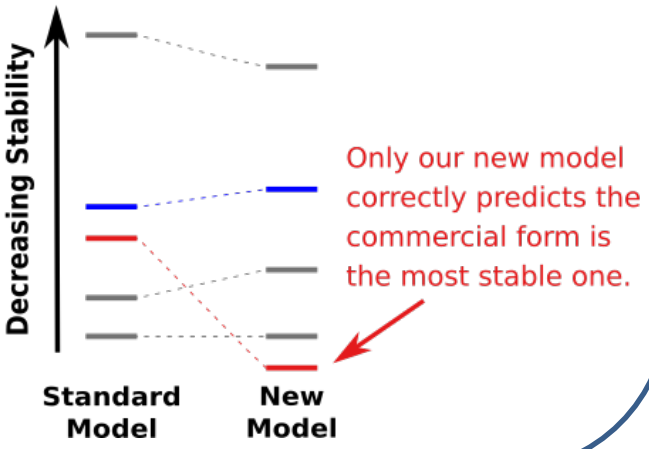
Pfizer initially targetted a crystal form of this drug that was not the most stable one, which might have proved problematic.

More stable crystal forms, including the eventual commercial one, were only later discovered by chance.



Crystal structure prediction can help prevent such problems by helping to ensure that all important, stable forms have been discovered experimentally. But only if the models are correct...

Standard models rank the Axitinib crystal forms incorrectly.



Project Outcome: Crystal structure prediction is increasingly used by the pharmaceutical industry to explore potential drug formulations. While mainstream modeling techniques often predict the most stable crystal structures successfully, we showed that these techniques fail badly for certain flexible molecules which are prevalent among pharmaceutical drug candidates. We developed new practical models which overcome this limitation and predict the relative stabilities of different crystal structures far more accurately, as exemplified by the drug Axitinib at left.

Impact & Benefits: Bringing a new pharmaceutical to market requires extensive screening of possible solid forms and their properties. The problems caused by the surprise appearance of a "missed" crystal form can force market recalls or allow others to circumvent intellectual property protections. Crystal structure prediction can help pharmaceutical companies ensure that they have discovered all important crystal forms, but only if the predictions are reliable. By identifying a serious flaw in existing models and developing a practical solution for it, our research has improved the reliability of these models considerably.

Background & Explanation: This research has been carried out by graduate students in the Beran group, some of who are first-generation college students and/or are members of traditionally underrepresented demographic groups. NSF funding has been essential for this research. Students trained by this project and prior NSF funding to our group on related themes have subsequently performed postdoctoral research at top-tier U.S. universities, founded a successful start-up company focused on pharmaceutical crystal structure prediction, and worked as highly skilled employees in information technology.

Image Credit: G. Beran