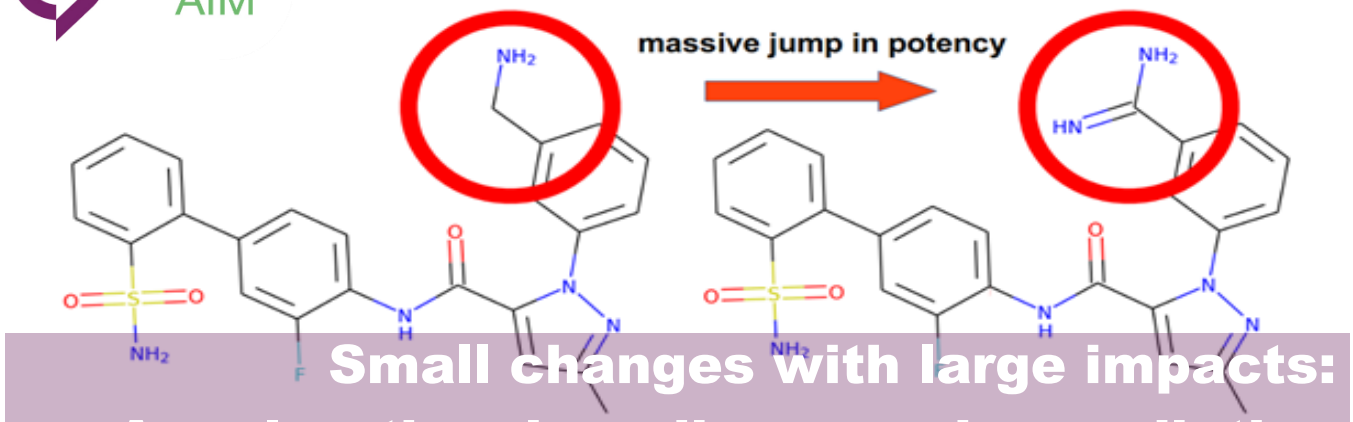

Small changes with large impacts: Accelerating drug discovery by predicting activity cliffs in chemical space

TakeAIM 2021 – 2nd Place

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The Smith Institute, enabled by the generous sponsorship of our leading corporate partners, ran the TakeAIM competition in 2021 to make visible the crucial role that mathematics will increasingly play in all aspects of our lives. The competition, also celebrating its 11th anniversary this year, was open to undergraduate and postgraduate students working in the mathematical sciences. The first-place prize was £1000, the two second-place prizes were £500, and the two third-place prizes were £250.

What makes the difference between a life-saving drug and an ineffective or even toxic molecule? Remarkably, sometimes all it takes to turn one into the other is a tiny structural modification such as the exchange of a single atom.

Pairs of molecular compounds that share an almost identical chemical structure but exhibit a large activity difference against a given pharmacological target are known as activity cliffs. Activity cliffs are often puzzling since they run counter to the intuitive idea that molecules with similar structures should have similar activity levels. At the same time, activity cliffs offer precious insights into the complex link between molecular structure and biological activity because they explicitly reveal small chemical transformations that abruptly switch on a biological effect. This makes activity cliffs powerful tools in fields such as structure-activity-relationship research and compound optimisation, both of which form core parts of modern drug discovery.

Unfortunately, activity cliffs are very hard to find. They represent rare gems in the vastness of chemical space and are usually stumbled upon experimentally. In our research, we are developing novel mathematical and computational techniques to address this challenge. In particular, we are exploring the potential of state-of-the-art deep learning models such as graph neural networks and Siamese neural networks to classify whether a given pair of similar molecules forms an activity cliff. What drives us is the hope that our research can help to accelerate and rationalise modern drug discovery, thus leading to life-saving medicines in the future.