Robust total X-ray scattering workflow to study correlated motion of proteins in crystals

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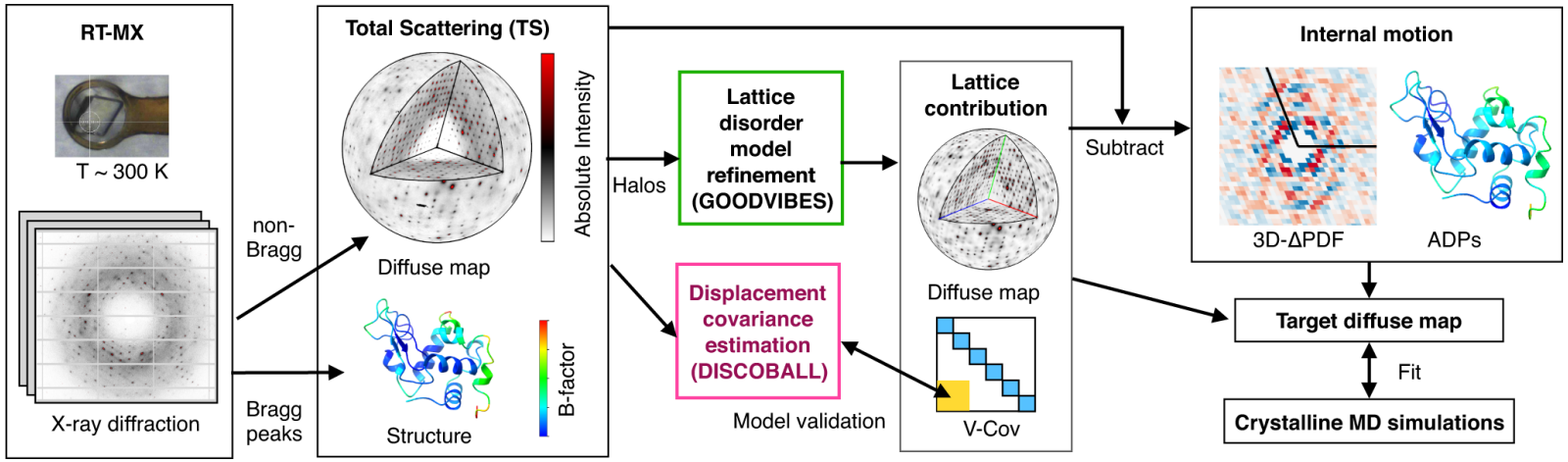

What is the discovery?

A new method for analyzing protein crystals promises new applications for drug discovery, bio-technology and bio-chemistry. The development, outlined in a paper published Nature Communications, provides researchers with the tools to interpret the once-discarded data from X-ray crystallography experiments – an essential method used to study the structures of proteins. This technique should yield better understanding of a protein's movement, structure and overall function. Protein crystallography studies at synchrotrons typically analyze bright spots in the diffraction patterns known as Bragg peaks, providing high-resolution information about the shape and structure of a protein. The experiment also captures blurry images – patterns and clouds related to the movement and vibrations of the proteins – hidden in the background of the Bragg peaks. These background images are typically discarded by protein crystallographers, with priority given to the bright features that are more easily analyzed. In the present study, researchers including MacCHESS and CHEXS staff scientist Steve Meisburger and Cornell Chemistry professor Nozomi Ando have developed and released a robust computational workflow to decode the weak diffuse scattering signals from crystallography experiments. This allows researchers to analyze the total scattering from crystals, which depends on both the protein's structure and the subtle blur of its movements. Their two-part method – which the team dubbed GOODVIBES and DISCOBALL – simultaneously provides a high-resolution structure of the protein and information on its correlated atomic movements. GOODVIBES analyzes the X-ray data by separating the movements – subtle vibrations – of the protein from other proteins that might be moving around it. DISCOBALL independently validates these movements for certain proteins directly from the data, allowing researchers to trust the results from GOODVIBES and understand what the protein might be doing. These tools will enable new kinds of data-driven discoveries and can be retroactively applied to previously collected data, reanalyzing existing measurements to mine new insights.

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Why is this important?

The potential for using diffuse scattering in structural biology been long recognized, however the act of accurately measuring the subtle signal while processing the data for something useful has been very difficult to do. It is much more computationally intensive to analyze total scattering when compared to Bragg intensity alone, and no generally available tools have existed for people to try. The key contribution of the present work is not just the demonstration of the method, but also the dissemination of the tools to the broader community. These tools are now freely available on github. The overarching goal is to turn GOODVIBES and DISCOBALL into a widely-adopted structural technique that can be used by researchers at synchrotrons all over the world. Understanding how proteins move and interact with other molecules has wide applications in biochemistry and drug design.

Why did this research need CHEXS?

The CHEXS and MacCHESS facilities are a hub for cutting-edge, fundamental research in molecular biology. They also share a mission to harness the data revolution and deliver new computational tools for users, enabling more complete information to be acquired from all performed experiments. Diffuse scattering studies of functional and quantum materials have long been a core mission of the QM2 beamline, and now CHESS scientists are applying similar methods to protein crystal studies at the HPBio/FlexX beamline. The re-analysis of historical data enabled by GOODVIBES and DISCOBALL can also be applied to the extensive data archives maintained by CHEXS and MacCHESS.

How was the work funded?

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Reference

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