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The potential for serial crystallography in drug discovery

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Structure-based drug design has played a pivotal role in pharmaceutical discovery for over thirty years, leading to the development of numerous approved therapeutics. Protein crystallography, relying on data collection from large single crystals held at cryo temperature, provides a highly optimised and effective workflow for generating structures of complexes between compounds and their target protein. Still, this method requires manual manipulation of thousands of crystals per year for a company such as AstraZeneca.
Serial crystallography presents an attractive alternative, offering potential improvements in throughput and automation by circumventing labor-intensive crystal harvesting and facilitating streamlined sample preparation. Additionally, the feasibility of room-temperature data collection can reduce the risk of structural artefacts introduced by cryo-cooling. Nonetheless, the adoption of serial crystallography in early drug discovery remains challenging due to constraints in speed, protein and compound availability, and workflow optimization.
In this study, we demonstrate the development and implementation of an optimized serial crystallography workflow tailored for drug discovery applications. Our approach enables the high-throughput screening of 384 fragments, addressing some key limitations while paving the way for broader application of serial crystallography in pharmaceutical research.

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