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## Approaches to automated protein crystal harvesting

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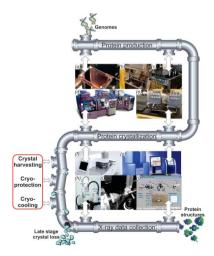
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Received 9 December 2013 Accepted 7 January 2014 The harvesting of protein crystals is almost always a necessary step in the determination of a protein structure using X-ray crystallographic techniques. However, protein crystals are usually fragile and susceptible to damage during the harvesting process. For this reason, protein crystal harvesting is the single step that remains entirely dependent on skilled human intervention. Automation has been implemented in the majority of other stages of the structure-determination pipeline, including cloning, expression, purification, crystallization and data collection. The gap in automation between crystallization and data collection results in a bottleneck in throughput and presents unfortunate opportunities for crystal damage. Several automated protein crystal harvesting systems have been developed, including systems utilizing microcapillaries, microtools, microgrippers, acoustic droplet ejection and optical traps. However, these systems have yet to be commonly deployed in the majority of crystallography laboratories owing to a variety of technical and cost-related issues. Automation of protein crystal harvesting remains essential for harnessing the full benefits of fourth-generation synchrotrons, free-electron lasers and microfocus beamlines. Furthermore, automation of protein crystal harvesting offers several benefits when compared with traditional manual approaches, including the ability to harvest microcrystals, improved flash-cooling procedures and increased throughput.

## 1. Introduction

Detailed knowledge of macromolecular three-dimensional structures is essential for understanding how cells work and how diseases progress at the molecular level. A common method used for determining three-dimensional structures is X-ray crystallography, which currently accounts for 88% of all macromolecular structures deposited in the Protein Data Bank (PDB; http://www.pdb.org; as of January 2014, 85 486 of 96 692 structures). Vital to X-ray crystallographic techniques is the growth of protein and other macromolecular crystals. Once grown, the protein crystals are exposed to an X-ray beam and diffraction data are collected. Key to this process is the harvesting of protein crystals, which in the broadest sense includes a series of manipulations that bring the protein crystal from its growth medium into the X-ray beam in a condition suitable for X-ray diffraction. Traditionally, much of this work is performed manually by skilled individuals. However, technological advances in robotics and automation, to a large extent spurred by structural genomics (SG), has fostered the development of high-throughput protein crystallography (HTPX; Terwilliger et al., 2009; Service, 2005). Automation is essential for an efficient HTPX/SG laboratory, playing a key role in all stages from cloning, protein expression and purification (Kim et al., 2004) to crystallization (Mueller-Dieckmann, 2006), data collection and processing (Adams et al., 2011) [reviews of automation include Cymborowski et al. (2010), Manjasetty et al. (2008) and Blow (2008); a simplified HTPX/SG pipeline is shown in Fig. 1]. Given the plethora of automation systems developed for HTPX/SG, it is somewhat surprising that only limited automation exists for the crystal-harvesting stage (highlighted in Fig. 1). Indeed, protein crystal manipulation represents a unique challenge for automated systems owing to the extremely fragile constitution of



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