**Docket #:** S14-108

# Compact grid device for fast, automated crystallography

This invention is a simple, versatile, high density grid designed to enable rapid X-ray crystallography by greatly reducing the time spent exchanging and positioning samples. In addition, these grids can be used as scaffolds for growing crystals, eliminating the crystal harvesting step and protecting crystals from human handling. This technology couples highly automated instrumentation (mounting systems and positioning stages) with the specialized grid and customized software for efficient data collection with minimal sample consumption.

In practice, 75 holes embedded in the grid serve as mounting ports for either conventionally-sized crystals or microcrystals samples. These samples can then be stored cryogenically or at room temperature in an SSRL cassette or an uni-puck storage container. The grids enable consistent production of diffraction patterns to collect high redundancy data from either synchrotron or X-ray free-electron laser (XFEL) sources. They can derive high-resolution structures, particularly for very small and delicate crystals that are sensitive to radiation exposure.

**Stage of Research**
The inventors have used the grid for automated goniometer-based analysis and performed femtosecond crystallography (FX) on a variety of sample types. Their results included a 1.6-A resolution electron density map of rod-shaped Cpl hydrogenase from 125 still diffraction patterns using only 5 crystals and about 30 minutes of beam time. The inventors have also demonstrated their specialized tools and software for the grids for applications including room temperature and cryogenic crystallization experiments that employ commercial liquid-handling robots and incubation chambers which support vapor-diffusion and lipidic cubic phase (LCP) crystallization.

# Applications

- **X-ray crystallography** - high-throughput structural biology studies of microcrystals, suspensions of crystals, amorphous material and sample fluids, with end-user applications such as:
    - determining protein and macromolecular structure
    - characterizing drug leads
    - identifying drug binding sites

# Advantages

- **Fast data collection**
    - mounting multiple samples simultaneously circumvents most of the time spent in sample exchange and positioning (less than 1 hour of beam time for 1000 conventionally-sized crystals using the grid vs. ~12 hours without the grid)
    - automated sample alignment and data collection from each grid port
    - crystal harvesting may be avoided entirely if grids used as scaffold for growing crystals
- **Versatile and compatible** with:
    - either synchrotron or X-ray free-electron laser (XFEL) sources
    - commercial liquid handling robots and storage containers (e.g. SSRL cassette or uni-puck)
    - hanging or sitting drop experiments and LCP (lipid cubic phase) crystallization experiments
    - cryogenic or room temperature experiments
- **Compact:**
    - small grid to efficiently store and transport samples
    - using grids with SSRL cassettes increases capacity from 96 samples to 7200 samples
- **Simple, inexpensive** design
- **Safeguards sample:**
    - protects sample from human handling if grid used for crystal growth
    - enables experiments in near darkness (e.g., for light-senstive samples)

## Publications

- Baxter, E. L., Aguila, L., Alonso-Mori, R., Barnes, C. O., Bonagura, C. A., Brehmer, W., ... & Degrado, W. F. (2016). High-density grids for efficient data collection from multiple crystals. *Acta Crystallographica Section D: Structural Biology*, 72(1).
- Cohen, A. E., Soltis, S. M., González, A., Aguila, L., Alonso-Mori, R., Barnes, C. O., ... & Calero, G. (2014). Goniometer-based femtosecond crystallography with X-ray free electron lasers. *Proceedings of the National Academy of Sciences*, 111(48), 17122-17127.
- High Density Grids (U.S. Patent Application, Publication No. US 2016/0019994)

## Patents

- Issued: 9,869,648 (USA)

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