Hybrid Programming in Crystallography: Phenix.refine and Phenix.hyss

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The *Phenix* project [1] is an international collaboration aimed at the development of a comprehensive, highly automated software system for the solution and refinement of macromolecular crystal structures. At Lawrence Berkeley Laboratory we have developed algorithms for the determination of substructures (*phenix.hyss*), the refinement of macromolecular structures (*phenix.refine*), and the underlying "hybrid" open-source software framework, *cctbx*.

The *Phenix* Hybrid Substructure Solution (*phenix.hyss*) combines Patterson methods and dual-space direct methods, automatic substructure comparisons and simple substructure refinement into a highly integrated algorithm. The *Phenix* refinement tools include Cartesian dynamics simulated annealing, a novel robust bulk-solvent correction procedure including overall anisotropic scaling, maximum likelihood refinement with and without experimental phases, and isotropic and anisotropic refinement of displacement parameters.

Both *phenix.hyss* and *phenix.refine* are designed to minimize the need for tedious and error-prone manual intervention. Development of the required tools is made practical by the tight integration of a scripting language (Python) with a compiled language (C++), and maximization of source code reuse through a library-based approach.

[1] Adams P.D., Gopal K., Grosse-Kunstleve R.W., Hung L.-W., Ioerger T.R., McCoy A.J., Moriarty N.W., Pai R.K., Read R.J., Romo T.D., Sacchettini J.C., Sauter N.K., Storoni L.C., Terwilliger T.C., *J. Synchrotron Rad.,* 2004, **11**, 53-55.

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