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***LAFIRE*: Automated refinement software for biomacromolecular crystallography**

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Biomacromolecular structure determination by X-ray crystallography involves many steps starting from data collection, data processing, phasing, model building, model completion, refinement and validation. Now most of these steps are highly automated because of recent advances in development of the methods and the softwares.

When incomplete model is obtained, refinement and structure completion process would be started. Currently, many refinement softwares are available such as *REFMAC*, *CNS*, *BUSTER-TNT*, *SHELXL* and *phenix.refine*. Each refinement software has advantage, users can choose the best one depending on the circumstance. However, manual process is still required to complete the refinement process because refinement softwares cannot build and even fit the model due to the convergence radius problem. In such cases, users are required to build and fit models into electron density using graphical software such as *Coot*.

LAFIRE has been developed to automate these manual steps. *LAFIRE* builds the missing residues and fits the ill-fitted residues into electron density map. Subsequently, *LAFIRE* starts refinement program such as *REFMAC* or *CNS*. These steps will be iterated to improve *R*-free factor.

Recently, some new features including (1)nucleic acid fitting, (2)ligand fitting and (3)*LAFIRE-FBDD*, have been added into *LAFIRE*. Graphical user interface (GUI) is also developed, so users can start the job, monitor the running status and check the result by using GUI.

(1)Nucleic acid is rather flexible compared to protein since nucleotide unit has six rotatable bonds in main chain. Therefore, fitting nucleic acid structure is more complicated than that of protein. Here, we made conformational restraints for nucleic acid structures based on deposited structures in PDB.

(2)Ligand fitting function finds all possible ligand positions (electron density blobs), and then fit the ligand model into the blobs.

(3)Fragment based drug design (FBDD) by crystallography is powerful method to find drug candidates, but requires many crystal structures to be analyzed. *LAFIRE-FBDD* has been developed to automate crystallographic investigation in FBDD. *LAFIRE-FBDD* gives refined structures with built ligand models for all collected datasets, based on apo structure of protein and possible ligand models. The resultant ligand structure in electron density map can also be viewed with GUI.

LAFIRE is distributed freely for academic use at our website: http://altair.sci.hokudai.ac.jp/g6/Research/Lafire_English.html

Keywords: refinement, biomacromolecule

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Hydrogen Bonds: the Toolkit

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The hydrogen bond is a hugely valuable intermolecular interaction, in which interest continues at a high level. This interest covers both the fundamentals of the interaction (and indeed recently a further refinement of our definition of this interaction was issued), but also the widespread use of the hydrogen bond in attempting to control the self-assembly of molecular systems, in both the crystalline (for example in Crystal Engineering) and in non-crystalline forms. A goal of "Directed Assembly" of molecular materials with designed architectures or tunable properties using this ubiquitous yet challenging interaction seems always so close yet tantalisingly far away.

This presentation will attempt briefly to cover both aspects of the hydrogen bond tool-kit:

A discussion of the methods employed in the study of this interaction will be given, with particular reference to the combined use of diffraction experiments and computation, stressing modern approaches that attempt to understand hydrogen bonding and its evolution in increasingly complex molecular systems.

The use of hydrogen bonding as the glue to hold together molecules in predictable ways will also be discussed, with emphasis on the choice of relatively simple, robust hydrogen bonded supramolecular synthons, and attempts to use these not only to control the assembly of molecules and molecular complexes into predicted architectures but also to design into these systems some degree of structural; (and hence functional) tunability.

In addition, recent developments in the control of crystallization of hydrogen bonded systems will be mentioned briefly, with reference to isolation of elusive polymorphs and in the use of continuous crystallisation techniques for the manufacturing of molecular materials.

Keywords: hydrogen bonding, control of self-assembly, diffraction and computational methods

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Strong Hydrogen bonds in crystals under high pressure

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Although the hydrogen bonding (HB) is the most investigated interaction in molecular crystals, not much is known of HB at high pressure. Some crystallographic works [1] reported the characterization of structural features of strong HB systems under pressure. Very little is known from theoretical calculations, instead.

We have recently reported on the behavior of oxalic acid dihydrate (**1**) at high pressure [2], showing that the α form rapidly undergoes a transformation into a charge transfer crystal $(C_2O_4^{2-})(H_3O^+)_2$, produced by the proton shift occurring in the range 2-4 GPa. The β form, instead, is less keen on transformation and it remains a neutral crystal up to 10 GPa (theoretical prediction).

We have carried out further investigations [3] on other crystal species containing oxalic acid or oxalate anions, for example KHC_2O_4, $K(HC_2O_4)(H_2C_2O_4)(H_2O)_2$, $(C_4N_2H_{12})(HC_2O_4)_2$. These studies show that structural motifs like that found in **1** α (COOH----OH_2) are more suited for pressure induced proton transfer, at variance from COOH-OCO systems (either charge assisted or neutral). This behavior is explained with theoretical considerations and supported by experimental work.

[1] For example, a) A. Katrusiak, R.J. Nelmes, *J. Phys C* **1986**, *19*, L765; b) A. Katrusiak *Acta Cryst*, **1990**, *B46*, 246; c) M. Walker, C.R. Pulham, C.A. Morrison, D.R. Allan, W.G. Marshall, *Phys. Rev. B* **2006**, *73*, 224110; d) E.V.