A residue-focused protein crystal structure evaluation method based on electron density


1 Mitsubishi Tanabe Pharma Co., LTD., 1000, Kamoshida-cho, Aoba-ku, Yokohama, Japan, 2 Mitsui Knowledge Industry Co., LTD., 2-5-1, Atago, Minato-ku, Tokyo, Japan, 3 Graduate School of Medicine, Kyoto University, Kyoto, Japan, 4 Graduate School of Medical Life Science, Yokohama City University, 1-7-29, Suehiro-cho, Tsurumi-ku, Yokohama, Japan, 5 RIKEN Center for Computational Science, 1-7-22, Suehiro-cho

Keywords: electron density, machine learning, structure evaluation

In X-ray crystallography, the determination of coordinates using low-resolution electron density is a major challenge hindering the determination and use of protein structures. To overcome this, we propose a method using machine learning to evaluate the quality of the coordinate structure one residue at a time using electron density and coordinate structure as input data and report output using QAEmap [1].

QAEmap uses an entire box centered on the center coordinate of each amino acid of interest as a descriptor and predicts its correlation with a putative high-resolution electron density map using a 3D deep convolutional neural network. Since the amino acid of interest and its surrounding environment are both subject to evaluation by this method, it can be applied to evaluating docking poses by evaluating the structure of amino acids in contact with a compound. Thus, it has the potential to be used as a support tool when determining a docking pose using electron density that is unclear owing to low resolution, etc. A preliminary experiment using test data has yielded optimal results (Fig. 1).

In this presentation, we will discuss the applications of this method to bound-compound evaluation and prospects for its future use.

Figure 1. Preliminary experiment evaluating ligand docking pose using QAEmap.
(a) One correct and three incorrect poses and 2mFo-DFc electron density at 4.0Å resolution. Modified from PDB 3ARQ data.
(b) The poses and their corresponding electron densities calculated at various resolutions were input and evaluated with QAEmap. The correct structure yielded the highest score at all resolutions.