

proteins and drug molecules in several days. This is not only to save the time and the cost used in drug development, but also for us able to understand the structural implications used for further design. However, it is still currently difficult to formularize efficient software to carry out the docking simulations as a standard procedure leading to definite results with high accuracy. Therefore, we are in attempt to propose a new category of programming, for which the standard effectiveness for docking procedure can be anticipated in the near future. To initiate such computer simulations, many factors have to be taken into consideration. The first is to decide which algorithms should be applied to perform the job. The next concern is the determination of scoring function. As being the best commercially available scoring function with high accuracy and flexibility, X-score is used to satisfy this purpose. Target protein is at first regarded as a rigid body, whereas the drug molecule is allowed to be entirely flexible. According to our results, GA and GP indeed improve the search of docking sites between the target protein and the drug molecules in both accuracy and efficiency. Partially flexible protein regions were then added into the docking system. Three complex systems of tubulin and tubulin inhibitors (taxol, colchicine and vinblastine) were used to demonstrate our software in application.

Keywords: docking,, genetic programming, genetic algorithm

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An investigation into protonation prediction implications for protein crystallography

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Biology rests on chemical reactions, many of which involve hydrogens or protons. The determination of hydrogens, as is well known, is particularly challenging for protein crystallography. These limitations are being steadily improved upon via complementary neutron and X-ray developments [eg see Blakeley et al 2004] including perdeuteration biological expression for the neutron approach. In parallel we have investigated the effectiveness of the protein protonation prediction computational tools H++, pKa and MCCE by comparing their agreement against a database of neutron and ultra-high resolution X-ray protein crystal structures, and that are growing in number. These test results indicate that predictions of the protonation states of Asp, Glu and His can be correct but not confidently so. This work may help fine-tune their predictive capabilities and thus benefit cases which are out of range of neutron or X-ray protein crystallography. One such is that of beta-crustacyanin, whose bathochromic shift colouration properties include, as one theory, two critical His residues in the structure [Cianci et al 2002] proposed to be protonated by Durbeej and Eriksson [2006] thereby causing an electronic polarisation of the carotenoid astaxanthin.

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M Cianci, P J Rizkallah, A Olczak, J Raftery, N E Chayen, P F Zagalsky and J R Helliwell (2002) *PNAS USA* 99, 9795-9800.

Durbeej, B. & Eriksson, L. A. (2006). *PCCP*, 8, 4053 – 4071.

Keywords: protonation states in proteins prediction, complementarity of X-rays and neutrons, beta-crustacyanin

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Advanced strategy for *ab initio* structure determination of pharmaceutical compounds by powder data

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The pharmaceutical compounds are still difficult targets for *ab initio* structure determination by X-ray powder experiments. For such molecules to be determined by X-ray powder experiments there would be no argument to admit synchrotron radiation (SR) source is necessary. Even SR source is used, *ab initio* structure determination of pharmaceutical compounds is challenging theme. It is, therefore, useful to find out what would be better strategy for that purpose. In this study, an advanced strategy which utilizes the variations of Maximum Entropy Method (MEM) will be described. The important points of the strategy are mainly comprised by the following three points. First point is that it is extremely important to collect very high counting statistics data not only low angle region (say, $d > 2.0 \text{ \AA}$) but also high angle region (typically $d > 1.0 \text{ \AA}$). Because information concerning atomic coordinates is included intensity data in high angle region, there is no way to determine the accurate crystal structure of the specimen. The most difficult and important part of *ab initio* structure determination is refinement process. The main concern must be how to eliminate model bias. For this purpose, it is very powerful to obtain omit MEM charge density distribution, which are successfully employed in the analysis of a protein crystal. At the final stage of the refinement, small adjustments of the atomic coordinate are very often required without deforming molecular shape. This could not be done by simply employing restrain refinements. It is helpful to obtain difference MEM density distribution, which often gives clue how to make the small adjustment of the atomic coordinates. A few examples based on the present strategy will be shown.

Keywords: structure determination from powder diffraction, maximum entropy method, pharmaceutical compounds

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Validation of molecular crystal structures using dispersion-corrected DFT

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The information content of an XRPD pattern is too low to determine all atomic coordinates of a molecular crystal structure independently: on top of the lack of phase information, powder patterns suffer from peak overlap and preferred orientation (PO), introducing uncertainties in the intensity data. This is generally solved by relying on the user to supply the correct chemical contents of the asymmetric unit, including most of the molecular geometry. That, however, is a source of errors and bias in itself. It is therefore justified to ask how we can be certain whether a structure determined from XRPD data is correct. Rietveld refinement and its figures of merit can only provide partial reassurance (see e.g. [1]), especially if a PO correction was necessary or if the data is of limited quality. If the powder pattern can be indexed, the unit cell can usually be determined very reliably from powder data, and a good validation method should therefore be aimed