MS02-P10

ISOLDE: Bringing macromolecular model building to life

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While model building in atomic-resolution maps is a straightforward and largely automated task these days, achieving high-quality results at resolutions below ~3Å is far more challenging. The scale of this challenge is reflected in the stereochemical quality of deposited models, with outlier rates often 1-2 orders of magnitude higher than expected. Beyond about 3.5Å, analysis of deposited models shows no correlation between stereochemical quality and Rfree.

Historically, tools for interactive model building have been severely limited by the modest computational power of the average workstation, and as such were limited to simple visualisation and (more importantly) relatively simple stereochemical restraints. In general, only direct bonded interactions (bond lengths, angles and torsions) were considered, relying heavily on the density map to provide the remaining information necessary to precisely position individual atoms. Today, however, even a modestly-priced "gaming" laptop is capable of high-framerate 3D rendering of complex scenes, while the advent of massively-parallel GPU computing has dramatically increased the speed at which many computational tasks can be performed.

ISOLDE is a new interactive model-building environment designed to make maximum use of this explosion in computational resources to ease the task of low-medium resolution model building. Almost all manipulations of the model take place as interactive molecular dynamics simulations (composed of any arbitrary subset of the modelled atoms) which explicitly include all non-bonded van der Waals and electrostatic interactions, such that every movement of an atom automatically leads to accommodating movement of its surroundings. Simulations may be guided by direct tugging on atoms or by interactive addition/removal of position, distance and/or dihedral restraints (or their combinations as rotamer or secondary structure restraints). This approach ensures that the model is always settling towards low-energy conformations, effectively helping to "fit itself" as the user manipulates it.

A key design philosophy behind ISOLDE is to reduce the time involved in the adjust-validate-adjust cycle by providing, wherever possible, real-time structure validation as markup directly on the model. This is currently implemented for Ramachandran, rotamer and peptide omega validations: these are re-calculated with every coordinate change, with clearly-identifiable indicators appearing directly on or adjacent to problematic residues.

In this talk I will demonstrate the key features of ISOLDE and show some real-world examples of its use, and discuss some new features currently in planning.

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MS02-P11

How can data collection affects the success of solving crystal structures using Single-wavelength Anomalous Dispersion?

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Nowadays, different techniques exist to study macromolecular structures, however, X-ray crystallography still being one of the more powerful technique to obtain atomic structural information. Crystallography has two main limitations - obtain crystals and solve the phase problem. Even the data collection and analysis methods have highly improved in the last decades, the phase problem can be critical if there is not a model with high similarity for molecular replacement. SAD/MAD are the second approach after MR to succeed solving the phase problem. These techniques require a tunable X-ray beam and the presence of an atom in the crystal that absorb X-ray radiation and produce anomalous signal, such as Se, S, Zn^{+2}... In this study, we analyze two different SAD data collection approaches to increase the success of direct methods for phase determination - continuous collection and inverse-beam geometry (where Friedel's pairs are collected close to each other avoiding radiation damage effect). This analysis has been done using crystals from the well study egg-hen lysozyme and the human protein survivin, which test the methods when the resolution and the diffraction are not optimal. In addition, a pairing reflections analysis using Bayesian inference has also been done. Our preliminary results show that inverse-beam geometry collection not only does not improve phasing but can also make it difficult to solve the structure when the collection is not optimal. Moreover, the use of bayesian inference for reflection pairing looks to improve the further data analysis.

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