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Electron Density Discrepancy Analysis of Energy Metabolism Coenzymes

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Abstract : Many macromolecular structure entries in the Protein Data Bank (PDB) have a range of regional (localized) quality issues, be it derived from x-ray crystallography, Nuclear Magnetic Resonance (NMR) spectroscopy, or other experimental approaches. However, most PDB entries are judged by global quality metrics like R-factor, R-free, and resolution for x-ray crystallography or backbone phi-psi distribution statistics and average restraint violations for NMR. Regional quality is often ignored when PDB entries are re-used for a variety of structurally based analyses. The binding of ligands, especially ligands involved in energy metabolism, is of particular interest in many structurally focused protein studies. Using a regional quality metric that provides chemically interpretable information from electron density maps, a significant number of outliers in regional structural quality was detected across x-ray crystallographic PDB entries for proteins bound to biochemically critical ligands. In this study, a series of analyses was performed to evaluate both specific and general potential factors that could promote these outliers. In particular, these potential factors were the minimum distance to a metal ion, the minimum distance to a crystal contact, and the isotropic atomic b-factor. To evaluate these potential factors, Fisher's exact tests were performed, using regional quality criteria of outlier (top 1%, 2.5%, 5%, or 10%) versus non-outlier compared to a potential factor metric above versus below a certain outlier cutoff. The results revealed a consistent general effect from region-specific normalized b-factors but no specific effect from metal ion contact distances and only a very weak effect from crystal contact distance as compared to the b-factor results. These findings indicate that no single specific potential factor explains a majority of the outlier ligand-bound regions, implying that human error is likely as important as these other factors. Thus, all factors, including human error, should be considered when regions of low structural quality are detected. Also, the downstream re-use of protein structures for studying ligand-bound conformations should screen the regional quality of the binding sites. Doing so prevents misinterpretation due to the presence of structural uncertainty or flaws in regions of interest.

Keywords : biomacromolecular structure, coenzyme, electron density discrepancy analysis, x-ray crystallography
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