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When good ligands go bad

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Tools for validating structural models of proteins are relatively mature and widely implemented. New protein crystallographers are introduced early on to the importance of monitoring conformance with expected ϕ/ψ values, favored rotamers, and local stereochemistry. The protein model is validated by the PDB at the time of deposition using criteria that are also available in the standard software packages used to refine the model being deposited. By contrast, crystallographers are typically much less familiar with procedures to validate key non-protein components of the model – cofactors, substrates, inhibitors, etc. It has been estimated that as many as a third of all ligands in the PDB exhibit preventable errors of some sort, ranging from minor deviations in expected bond angles to wholly implausible placement in the binding pocket. Following recommendations from the wwPDB Validation Task Force, the PDB recently began validating ligand geometry as an integral part of deposition processing. This means that many crystallographers will soon receive for the first time a "grade" on the quality of ligands in the structure they have just deposited. Some will be surprised, as I was following my first PDB deposition of 2014, at how easily bad ligand geometry can slip through the cracks in supposedly robust structure refinement protocols that their lab has used for many years. I will illustrate use of current tools for generating ligand restraints to guide model refinement. One is the jligand+coot+cprodrg pipeline integrated into the CCP4 suite. Another is the Grade web server provided as a community resource by Global Phasing Ltd. Furthermore I will show examples from recent in-house refinements of how things can still go wrong even if you do use these tools, and how we recovered. The new PDB deposition checks may expose errors in your ligand descriptions after the fact. This presentation may help you avoid introducing those errors in the first place.

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