

## Structure prediction methods for molecular replacement and low-resolution crystallographic refinement

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Protein structure prediction tools, like the *Rosetta* structure prediction methodology, can be valuable when solving crystal structures. In this talk, I will describe the use of structure prediction methods to aid in crystallographic model building and refinement. First, I will give an overview of the Rosetta structure prediction methodology for *ab initio* structure prediction and homology modeling, as well as briefly introducing the Rosetta forcefield. Then, I will describe how sparse or noisy experimental data may be used to guide Rosetta's sampling, greatly reducing conformational space. I then will show the application of these methods to two different tasks that arise in X-ray crystallography. First, I will show how Rosetta homology modeling may be able to build models more suitable for molecular replacement than the template structure alone. More importantly, using poorly phased electron density data to constrain its search, Rosetta may rescue very weak molecular replacement solutions. This approach was recently used to solve eight protein structures, whose solution eluded a variety of current structure-determination methods. This approach is exceedingly valuable when solving structures from templates with less than 30% sequence identity to the target. Rosetta's forcefield may also be used when refining against low-resolution crystallographic data. Preliminary data show that in some cases, Rosetta can produce models with lower free R factors and better model geometry compared to standard crystallographic refinement tools. By coupling Rosetta's forcefield with sparse experimental data, we reduce the effective degrees of freedom of conformational space. In this way, Rosetta may be used to produce more accurate models from noisy or sparse experimental data.