

Beyond Engh and Huber: Towards Development of More Accurate Methodology in Macromolecular Crystal Structure Refinement. T.R. Transue, J.M. Krahn, & T.A. Darden, Nat'l Inst. of Env. Health Sci., NIH, RTP, NC 27709, USA.

For over a decade the results of Engh and Huber¹ have been widely used in refining protein crystal structures. Bonds and angles are restrained toward mean values from small molecule distributions using forces proportional to $1/\sigma^2$. Upon analysis of the entire PDB, however, we show how implementations of this method have lead to systematic distortions of protein crystal structures even at very high resolution. We offer three explanations for these distortions: (1) typographical errors (panel A) in parameter sets, (2) arbitrarily chosen or poorly adjusted parameter values, (3) statistics assuming independent functions do not account for correlated parameters. While the first two suggest that adjusting parameter values might improve refinement accuracy, the third explanation indicates that the current methodology is limited in its ability to accurately handle certain situations. For example in proline (panel B), multiple forces combine to produce complex correlated distributions not captured by independent parameter sets.

We provide resolution and software dependencies, examples, and implications to data mining. We also propose future methodology based on interdependent forces and maximum likelihood target functions.

1. Engh & Huber, *Acta Cryst.* A47:392

