Modelling biological data with experimental restraints

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Macromolecular modelling problems often utilize experimental structures of biological macromolecules both as their basis and for validation of results. For over 50 years, X-ray crystallography has been the primary method to determine these structures. Recently, electron cryo microscopy (Cryo-EM) has also started to significantly contribute to the wealth of almost 150 000 experimentally determined structures.

However, these experimental methods have limitations: A model is strictly needed for the interpretation of experimental data [1], and has to be optimized to fit (potentially flawed) measured data. As a consequence, some biological questions - for example whether a ligand is bound - cannot be answered, some structures, such as large complexes or membrane proteins, cannot be solved at all and, worst of all, published and seemingly correct structure solutions can have flaws that might even lead to a retraction. In addition, the limitations of experimental structure solution directly affect computational modelling as a downstream method.

In this talk, I will describe these limitations and their implications in terms of both the data quantity [2] as well as the employed models. I will show how modelling can be improved (giving a previously unprecedented way to restrain the movement of bonded atoms as an example [3]) and describe how we ultimately realized that something might be fundamentally wrong with the atomic models which we employ to interpret experimental data.

[1] Holton, J.M., Classen, S., Frankel, K.A., Tainer, J.A., *FEBS*, **2014**, *281*, 4046–406
[2] Thorn, A., Parkhurst, J.M., Emsley, P., Nicholls, R., Vollmar, M., Evans, G. & Murshudov, G.N. (2017) *Acta Cryst. D,* **2017**, *73,* 729-737.
[3]Thorn, A., Dittrich, B., Sheldrick, G.M., *Acta Cryst. A*, **2012**, *68,* 448-451