Poster Presentation

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Computational Pharmaceutical Materials Science: Beyond Static Structures.

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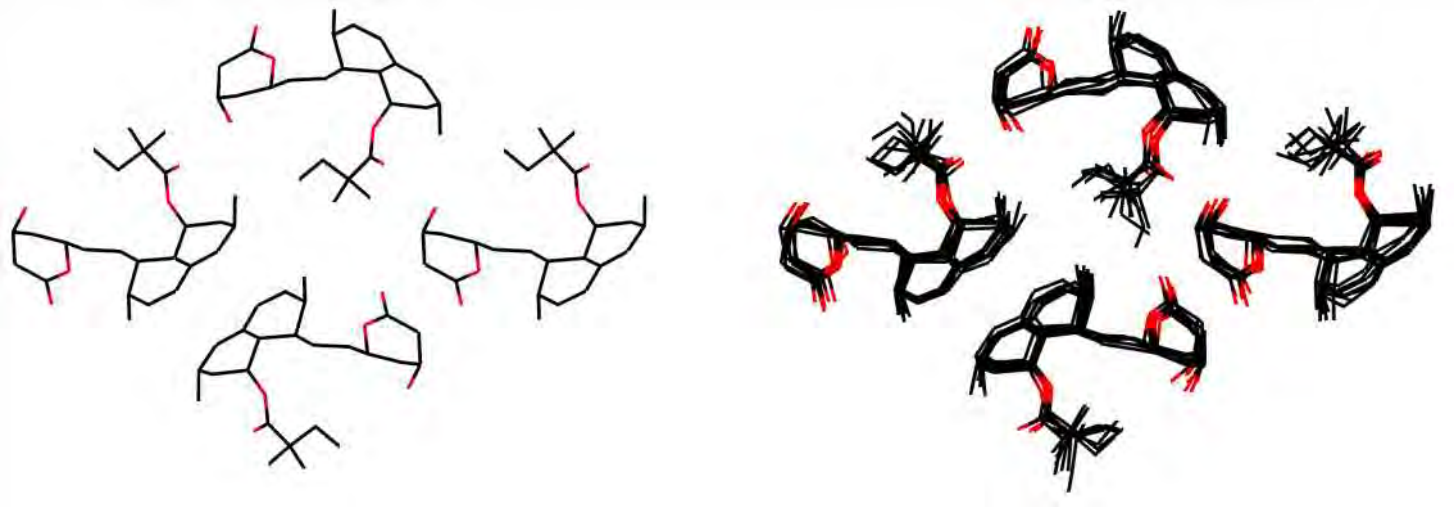
The five Crystal-Structure Prediction (CSP) Blind Tests have shown that molecular-mechanics force fields are not accurate enough for crystal structure prediction[1]. The first--and only--method to successfully predict all four target crystal structures of one of the CSP Blind Tests was dispersion-corrected Density Functional Theory (DFT-D), and this is what we use for our work. However, quantum-mechanical methods (such as DFT-D), are too slow to allow simulations that include the effects of time and temperature, certainly for the size of molecules that are common in pharmaceutical industry. Including the effects of time and temperature therefore still requires molecular dynamics (MD) with less accurate force fields. In order to combine the accuracy of the successful DFT-D method with the speed of a force field to enable molecular dynamics, our group uses Tailor-Made Force Fields (TMFFs) as described by Neumann[2]. In Neumann's TMFF approach, the force field for each chemical compound of interest is parameterised from scratch against reference data from DFT-D calculations; in other words, the TMFF is fitted to mimic the DFT-D energy potential. Parameterising a dedicated force field for each individual compound requires an investment of several weeks, but has the advantage that the resulting force field is more accurate than a transferable force field. Combining crystal-structure prediction with DFT-D followed by molecular dynamics with a tailor-made force field allows us to calculate e.g. the temperature-dependent unit-cell expansion of each predicted polymorph, as well as possible temperature-dependent disorder. This is relevant for example when comparing the calculated X-ray powder diffraction patterns of the predicted crystal structures against experimental data.

[1] *G. M. Day et al., Acta Cryst. B, 2009, 65, 107-125,* ***[2]*** *M. A. Neumann, J. Phys. Chem. B, 2008, 112, 9810-9829*



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