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Picking out polymorphs: H-bond prediction and crystal structure stability

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A methodology has been developed to predict the propensity for hydrogen bonds to form in crystal structures, treating each potential H-bond as a binary response variable, and modelling its likelihood using a set of relevant chemical descriptors [1]. Modelling is tailored to a target using chemically similar known structures, from e.g. the Cambridge Structural Database [2], making it accessible to the complete spectrum of organic structures, including solvates, hydrates and cocrystals. Recent work has developed the approach to predicting inter- and intramolecular H-bonds when either type can occur.

By way of a comparison between possible and observed H-bonds, the method has been applied to assess structural stability, which shows much promise in the domain of polymorph screening in the pharmaceutical industry. We will introduce the methodology and illustrate its application using a selection of pharmaceutical compounds, one of which will be Abbott's well-publicised anti-HIV medication ritonavir (Norvir™). Owing to a hidden, more stable form II with much lower bioavailability, ritonavir was temporarily withdrawn from the market with significant financial impact [3]. Our method quickly suggests a real threat of polymorphism in this compound, and strongly supports the relative stability of form II over form I. For all examples, the high predictivity of the method is emphasised.

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References

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