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Interaction frequencies as a means to design multicomponent forms

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The relationships between crystal structure and physical properties of molecular organic materials are of extreme importance across multiple industrial arenas (Bianchi *et al.*, 2021; Bacchi & Mazzeo, 2021; Mazzeo *et al.*, 2019; Birolo *et al.*, 2022; Schultheiss *et al.*, 2010; Karimi-Jafari *et al.*, 2018; Trask, 2007; Shan & Zaworotko, 2008; Javoor *et al.*, 2017; Jagadeesh Babu & Nangia, 2011; Almarsson *et al.*, 2012). Key physical attributes, including melting point, solubility or hygroscopicity are intrinsically linked to the arrangement of molecules in the crystal structure and to the intermolecular interactions between them. These structure–property relationships are particularly important in the pharmaceutical industry, as the physical properties of drug compounds are central factors in how effective they are. These properties also influence the physical and chemical stability of pharmaceutical products, their mechanical behaviour, manufacturability, bioavailability and ultimately dosage requirements.

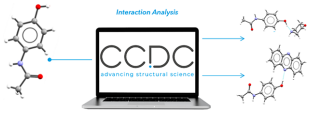
Although active pharmaceutical ingredients (APIs) often exhibit excellent therapeutic efficacy, the physical properties associated with the solid form in which the API exists may not always be ideal. Consequently, strategies for tailoring solid-state properties are of considerable interest. One such method that has attracted considerable interest in recent years is cocrystallization. Cocrystals are multicomponent single-phase crystalline materials made of different chemical entities (*i.e.* coformers) that crystallize in a stoichiometric ratio within the same crystal structure, held together by non-covalent intermolecular interactions (Karimi-Jafari *et al.*, 2018; Bolla & Nangia, 2016; Berry & Steed, 2017; Mazzeo *et al.*, 2022).

As the new intermolecular network drives the final physical properties of the molecular compound in its solid form, by appropriately selecting the molecular partner it is possible to tailor the API properties while mitigating undesirable behaviour (Guo *et al.*, 2021; Montisci *et al.*, 2022; Bacchi & Mazzeo, 2021; Montisci *et al.*, 2024; Mazzeo *et al.*, 2019; Parisi *et al.*, 2025; Capucci *et al.*, 2017).

The existence of a stable cocrystal depends on the ability of the two molecular components to assemble into a crystal structure with lower free energy than the pure individuals. The concept of crystal engineering (Desiraju, 2007), where 'supramolecular synthons' (reliable interactions such as hydrogen and halogen bonds between particular functional groups) (Daolio *et al.*, 2025; Mazzeo *et al.*, 2020, 2021; Bacchi & Mazzeo, 2021; Desiraju, 1995; Feliciano *et al.*, 2026; Braga *et al.*, 2010) are used to design new solid forms, has long been used to rationalize cocrystal design and synthesis for several decades. Computational and informatics-based methods of identifying these synthons (Corpinot *et al.*, 2016; Fornari *et al.*, 2022; Musumeci *et al.*, 2011; Etter & Frankenbach, 1989; Fukte *et al.*, 2014; Grecu *et al.*, 2014; Prandini *et al.*, 2024; Prencipe *et al.*, 2025; Issa *et al.*, 2009) are particularly useful to reduce the number of experiments needed to ensure a successful outcome, and Stevens *et al.* (2026) demonstrate a new approach that makes use of the Cambridge Structural Database (CSD) (Groom *et al.*, 2016) in order to identify likely functional group interactions.

The method proposed by Stevens *et al.* makes use of a knowledge base of hydrogen-bonding interactions derived from the CSD to identify particular functional groups that demonstrate an increased likelihood of interaction with the functional groups of a target molecule. The method can also provide suggestions for molecules that contain these functional groups and thereby increasing the likelihood of successful cocrystal formation.

For pairs of functional groups that are capable of hydrogen bonding with each other, all structures containing those moieties are identified, and then the number of structures



that containing hydrogen bonds between the two groups are counted and used to calculate a frequency of occurrence. In their approach, Stevens *et al.* interpret this frequency of occurrence as an assessment of the strength of a particular interaction, given that stronger interactions are more likely to occur more frequently and can therefore be considered as *structure directing*. This approach therefore provides a statistical means to identify synthons for crystal engineering strategies.

The analysis of the dataset also highlights several observations that support established chemical intuition. Stevens *et al.* demonstrate the application of their method on literature data available for cocrystal screening of Paracetamol, Praziquantel, and Loratadine. The speed of the method and the resulting prioritization of functional groups and coformers based on experimental crystal structure data makes it a useful tool for cocrystal design. While the method is demonstrated for the identification of coformers, as the authors point out, it is extensible across a wide range of molecules. For example, using a library of common solvent molecules rather than potential coformers could similarly be used to assess the propensity for solvate formation.

The work by Stevens *et al.* highlights the benefit of large datasets of crystallographic data and how these can be used to design new solid forms. New crystal structures generated through these approaches further enrich those databases, providing an increasingly powerful foundation for future crystal engineering efforts. This creates a virtuous cycle in which experimental discoveries enrich structural databases, enabling better predictive tools that in turn accelerate further discoveries.

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