


Progress in understanding crystallisation: a personal perspective†

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After this Discussion meeting, most participants felt that we do not understand crystallisation. However, in the 1980s, I believe that most scientists would have considered that crystallisation was adequately understood. These concluding remarks give a personal impression of the progress that has been made towards appreciating the complexity of crystallisation over the past forty years.

Introduction

This meeting has discussed in depth 23 excellent papers, covering a wide range of systems using diverse techniques. The organisers have brought together many experts on crystallisation from around the world; many have been together in York, but there has also been active participation from those unable to travel because of distance or the Covid epidemic. Nonetheless, a show of hands at the end of the meeting showed, I think unanimously, that we do not understand crystallisation.

This was not a scientific survey, by today's standards, as the people in the room could see each other's responses. However, I think a more independent poll in the 1980s would have shown that the majority of scientists, particularly chemical engineers, felt that we understood crystallisation. It certainly was not a major academic research area. However, such a poll in the 1980s would have been conducted by face-to-face interviews, or possibly by telephone. Computer power was so limited that many scientists dismissed the emerging areas of electronic and atomistic simulations as irrelevant to specific systems. The experimental techniques were also limited in what could be determined at the atomic scale; crystal structures could only be determined from large, high quality crystals, not from powder X-ray data, the range of radiation sources was limited, and atomic force spectroscopy, let alone transmission electron spectroscopy, were a very long

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† This is a personal account from someone who has only done computational simulations of the organic solid state. It may inadvertently include some misinterpretations of the papers. Please check the references carefully.



way from being established techniques that could be applied to crystallisation studies.

Yet today, it would have been difficult for anyone who read the papers, let alone attended this *Faraday Discussion*, to conclude that we did understand crystallisation. The experimental evidence in many papers raised more questions, and a significant number mentioned the further work needed. New techniques were used (<https://doi.org/10.1039/d1fd00084e>; <https://doi.org/10.1039/d1fd00125f>; <https://doi.org/10.1039/d1fd00090j>), but it was clear that many experiments were studying systems that had been chosen or adapted to make the experiments viable. These adaptations, such as using D₂O rather than H₂O to ease the spectroscopy (<https://doi.org/10.1039/d1fd00078k>), using sugar solution to reduce mobility (<https://doi.org/10.1039/d1fd00115a>), or humidity control (<https://doi.org/10.1039/d1fd00090j>), could have affected the crystallisation. Perhaps a more significant development since the 1980s was that most papers were using multiple techniques. I estimate that 11 papers used only experimental techniques, 4 only computer simulations, and there were 8 that combined both experiment and computational modelling. In the 1980s, the emerging electronic structure and atomistic modelling work was done independently, and some cynics felt that the theoretical publications always lagged behind the published experimental results, with more accurate measurements leading to more expensive and, hence, more accurate calculations being performed. Now, there is far more complementary collaboration, with multi-author papers where multi-scale modelling with multi-technique crystallisation characterisation are used to provide a picture of what is going on during crystallisation (<https://doi.org/10.1039/d1fd00112d>).

We understand the crystallisation of what?

The most popular system for study at this Discussion meeting has been CaCO₃, but this has been investigated from many perspectives (<https://doi.org/10.1039/d1fd00084e>; <https://doi.org/10.1039/d1fd00095k>; <https://doi.org/10.1039/d1fd00082a>; <https://doi.org/10.1039/d1fd00111f>). The other ionic systems with polyatomic ions, NaBrO₃ (<https://doi.org/10.1039/d1fd00098e>) and SrSO₄ (<https://doi.org/10.1039/d1fd00092f>), are not similar in crystallisation behaviour: NaBrO₃ has a non-chiral solution but forms enantiomeric crystals (<https://doi.org/10.1039/d1fd00098e>) and SrSO₄ crystallisation can be modelled without considering polymorphism (<https://doi.org/10.1039/d1fd00092f>). We have discussed simpler systems, such as atomic Ni, but even here the study (<https://doi.org/10.1039/d1fd00099c>) showed deviations from the classical nucleation theory that held sway in the 1980s. The Ni melt simulations showed that dynamical heterogeneity in the supercooled liquid plays a key role in the mechanism of crystal nucleation. Sodium chloride is also popular as a system to study (<https://doi.org/10.1039/d1fd00090j>; <https://doi.org/10.1039/d1fd00098e>; <https://doi.org/10.1039/d1fd00089f>) because it is a simple system whose crystallisation from water has been utilised by humans from ancient times.

The crystallisation of water in the atmosphere has been discussed (<https://doi.org/10.1039/d1fd00115a>), as it is vital for understanding environmental science. Water has been heavily studied from all aspects because of its importance to life. This has given rise to a vast literature on its diverse physical



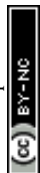
properties – which makes it clear that the force-fields for water used in atomistic simulations of aqueous crystallisation are not adequate for the spectroscopy of water clusters, lacking the accurate representation of the intermolecular, particularly many-body, forces.^{1,2} However, despite water's position as a uniquely important molecule, its crystallisation behavior and many known phases³ are unlikely to be uniquely complex, but reflect the extent to which water has been studied. The diversity of the intermolecular interactions and the molecular flexibility of the six organic molecules that have been discussed in this meeting are greater than those of water. Although we now know a lot about the crystallisation of glycine (<https://doi.org/10.1039/d1fd00098e>; <https://doi.org/10.1039/d1fd00101a>), diglycine, *p*-aminobenzoic acid (<https://doi.org/10.1039/d1fd00112d>), isonicotinamide (<https://doi.org/10.1039/d1fd00098e>), olanzapine and etioporphyrin (<https://doi.org/10.1039/d1fd00080b>), this hardly spans the types of molecular crystal that are of interest for pharmaceutical development, and *N,N'*-bis(*n*-hexyl)naphthalene-1,4,5,8-tetracarboxylicdiimide (NDI-C6) (<https://doi.org/10.1039/d1fd00100k>) is only one example of the huge range of organic molecules that are of interest as possible functional materials.

The gold nanorod study (<https://doi.org/10.1039/d1fd00087j>) was informative because it had a simple variation in shape with cylinders of varying aspect ratios, and so clearly showed that anisotropy was a major factor in heterogeneous crystallisation, with nucleation being faster if the rods were more spherical. Although there were significant differences in the nucleation of nanoparticle building units compared to the nucleation of atoms or molecules as building units (<https://doi.org/10.1039/d1fd00087j>), can we expect the crystallisation of organic molecules, with varying conformations and diverse interactions producing a complex anisotropy, to be simple?

Inorganic crystals can have additional complexities from the variability in composition, particularly if we seek to understand the crystallisation of minerals. The studies of zeolites (<https://doi.org/10.1039/d1fd00093d>; <https://doi.org/10.1039/d1fd00097g>; <https://doi.org/10.1039/d1fd00096a>) provide good examples of the need to consider the chemistry and energetics of the specific system in detail, for example, the morphology of the same zeolite framework being so sensitive to the ions within the channels (<https://doi.org/10.1039/d1fd00096a>).

This complexity reflects the fact that no two atoms are the same, and nuclear charge is integral. The charge and the number of associated electrons define the electron distribution according to the other atoms present, and cause the differences in the interatomic forces. We are used to recognising substantial changes in the atomic charge distribution with different oxidation or hybridisation states, and with the nature of the bonded atoms. However, the differences extend to the intermolecular interatomic forces, with the specific atomic charge density affecting all the intermolecular forces and, hence, all the properties relevant to crystallisation, such as size and mobility.

This has implications for crystal structures depending on the structural building blocks. In the 1980s, I was using the atomic radii of the cations to separate 172 chalconide spinels, AB₂X₄, into the normal or inverse spinel cation distribution.⁴ Only recently have I surveyed the crystal structures of a large group of closely related organic molecules, namely 232 chalcones with small substituents.⁵ The isostructural families are small because the most common 1D packing



motif is a close packed translation which can have a wide range of substituents sticking out, which pack differently in 3D.⁵ Strongly favoured 3D framework structures that can accommodate a wide range of ions or other small species are more prevalent in inorganic than organic systems.

The uniqueness of each atom's charge distribution affects crystallisation more than just determining the final product of the crystal structure. No atom will interact with a given solvent molecule in exactly the same way. We need to carefully distinguish between different ways of modelling solvent effects. Implicit solvation models, where the solvent is represented by a dielectric continuum, are great for modelling the differences between polar and non-polar solvents if the solvent can be assumed to be moving very quickly around the molecule. Explicit solvent modelling is needed if there are long-lived interactions between the solvent and solute, for example water forming a hydrogen bonded network around part of the molecule, which is in competition with hydrogen bonding between the solute molecules. For example, in *p*-aminobenzoic acid, the different hydrogen bonding and $\pi\cdots\pi$ bonding motifs that are found in the polymorphs and in solution (<https://doi.org/10.1039/d1fd00112d>) are detected by solution NMR.⁶ However, the dominant oligomers are remarkably solvent-dependent and also short-lived in molecular dynamics simulations,⁶ showing how difficult it can be to link the solution species to the polymorph formed *a priori*. We do tend to focus on hydrogen bonds, but the olanzapine dimer (<https://doi.org/10.1039/d1fd00080b>) that is found in virtually all its crystal structures (a notable exception is a polymorph that was crystallised within a polymer⁷) is held together with dispersion forces, with the hydrogen bonding between dimers or with other molecules (for the salts and solvates) determining the crystal structure.

Pathways to crystallisation

As pointed out in the opening lecture (<https://doi.org/10.1039/d2fd00061j>), classical nucleation theory was the theory in the 1980s and it was only in the past couple of decades that the range of mechanisms for crystallisation by particle attachment in synthetic, biogenic and geologic environments became clear. The range of mechanisms in the classic diagram⁸ has been illustrated throughout this *Discussion*, but the diversity and complexity has been amplified in the evidence for specific systems. For the simple system of NaCl, simulations suggest that there is a transition between predominantly one-step to two-step nucleation with concentration (<https://doi.org/10.1039/d1fd00089f>). The occurrence of different nucleation mechanisms for the same system can be explained using a toy model to describe the nucleation pathway, inspired by mesoscopic nucleation theory (<https://doi.org/10.1039/d1fd00092f>). This *Discussion* has also produced more detail within each mechanism, specific to variations in the local environment changing the nature and distribution of particles that are attaching. An example is the work on establishing causal relationships between amorphous precursor properties and their effects on the selection of mechanistic pathways of crystallisation and ultimately the properties of the crystalline product (<https://doi.org/10.1039/d1fd00096a>).

The diversity of crystallisation mechanisms is increased by heterogeneous nucleation with studies using mica, polystyrene sulfonate (PSS) functionalised substrates (<https://doi.org/10.1039/d1fd00087j>), alkanethiol self-assembled



monolayers (<https://doi.org/10.1039/d1fd00082a>), glass beads (<https://doi.org/10.1039/d1fd00101a>) and feldspars (<https://doi.org/10.1039/d1fd00115a>). The relevant surface for nucleation can be within defects (<https://doi.org/10.1039/d1fd00115a>). The effect may depend on specific intermolecular interactions such as hydrogen bonding (<https://doi.org/10.1039/d1fd00101a>). Certain “active” defects can affect the diffusion of ions in close proximity to the surface feature (<https://doi.org/10.1039/d1fd00082a>). In both cases, the molecular flexibility of the growth unit, heterogeneous substrate and how the process of crystallisation reduces the molecular flexibility could have a significant influence. The implication is that the crystallisation vessel surfaces, impurities, and other often unrecorded details, can affect the path of a crystallisation in a complex manner.

“In our opinion, virtually anything is possible” was said in rationalising the change in crystallisation of calcium carbonate on changing solvent from H₂O to D₂O (<https://doi.org/10.1039/d1fd00078k>), but may be typical of the complexity of the factors influencing crystallisation. “Who cares what you measure?” was said provocatively to emphasise the need for accuracy, reproducibility and careful definition of the experimental system. The papers in the meeting give food for thought – should the ideas emerging, albeit for other systems, be considered for interpreting your results? Examples that struck me as potentially important are:

“The dissolution process does not follow the same structural path as the growth process, or that the timescale for the dissolution process is much shorter than that of the growth process” (<https://doi.org/10.1039/d1fd00125f>)

“Relative stability is not the primary driving force for transformations between metastable phases” (<https://doi.org/10.1039/d1fd00086a>).

“... the lack of general rules to correlate the majority solute species and crystal structural blocks that carry the crystal symmetry” (<https://doi.org/10.1039/d1fd00080b>).

“Consequently, a separation between a specific class of pre-nucleation clusters and the eventual nucleation event becomes less and less evident as the supersaturation value increases. Eventually, the effective energy is so low that all possible pre-critical densities, *i.e.* from monomers and onward, are all likely to be observed, making it harder to differentiate any specific class of precursor clusters” (<https://doi.org/10.1039/d1fd00092f>).

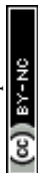
“This reveals that the highest cooling rates access a much wider range of supersaturations and nucleation cluster sizes when compared to lowest cooling rates” (<https://doi.org/10.1039/d1fd00112d>).

“...the necessity of generalizing the concept of a critical nucleus to that of a critical ensemble of nuclei” (<https://doi.org/10.1039/d1fd00089f>).

“Structural pre-ordering in the liquid without a decrease in mobility, therefore, does not promote the nucleation of the crystalline bulk phase” (<https://doi.org/10.1039/d1fd00099c>).

“Thus, it is possible to tune the pathway of crystallization by controlling the microstructural evolution of amorphous precursors” (<https://doi.org/10.1039/d1fd00096a>).

High-speed frequency modulation atomic force microscopy has shown that there is sometimes a transition layer of Ca(OH)₂ around calcite steps, with the steps sometimes being linear and sometimes complex (<https://doi.org/10.1039/>



[d1fd00084e](https://doi.org/10.1039/d1fd00084e)). I was also intrigued to hear that morphology could be affected by stacking faults (<https://doi.org/10.1039/d1fd00091h>) or synthesis temperature (<https://doi.org/10.1039/d1fd00093d>), and it was good to see the progress in modelling morphology (<https://doi.org/10.1039/d1fd00097g>).

These are just some of the many points raised in the Discussion and conclusion sections of the papers in this *Discussion*, which represent huge progress on the assumptions that were made in the 1980s. We are in a phase of observing the complexities of crystallisation and it will require more applications to different systems for a sense of what concepts are quite widely applicable, and which are very specific to a given experiment. However there are a few more questions that need consideration to define what we are aiming for as an understanding of crystallisation.

What is crystallisation?

Our knowledge of the inapplicability of the atomic level model of classical nucleation theory, and the extent to which we are beginning to replace it, is affected by the use of measures of crystallisation and structural purity that would not have been possible a few decades ago. No student has been mounting hundreds of crystals on a single crystal X-ray diffractometer for these papers. Only electronic structure work has considered infinite perfect static lattices to represent the crystal. Indeed, the molecular dynamics work illustrates the problem of a precise definition of crystallisation. How do you analyse the trajectories of hundreds or thousands of moving molecules (albeit in a periodically repeating simulation box) to have the possibility of identifying a clear transition state for crystallisation (<https://doi.org/10.1039/d1fd00089f>)?

The experimental definitions have been very careful, with three different probes to determine the time of nucleation (<https://doi.org/10.1039/d1fd00092f>) or testing to show that the experimental set up has eliminated heterogeneities and memory effects (<https://doi.org/10.1039/d1fd00090>). The need to control often unreported parameters, such as humidity, has been clearly demonstrated to be important (<https://doi.org/10.1039/d1fd00090>). A heterogeneous surface needs careful characterisation, given the evidence that certain atomic scale defects can affect the role of the surface in heterogeneous nucleation (<https://doi.org/10.1039/d1fd00082a>). The key nucleating surface can often be exposed on other surfaces through defects (<https://doi.org/10.1039/d1fd00115a>).

The role of absorbed species and stacking faults on crystallisation can be very significant, promoting growth in lateral directions and, hence, changing the morphology (<https://doi.org/10.1039/d1fd00091h>). The effect of defects on morphology has been modelled for zeolites (<https://doi.org/10.1039/d1fd00097g>). Stacking faults and polymorphic domains are also important in pharmaceuticals; there was considerable controversy over the finding of different polymorphic domains within single crystals of aspirin.⁹ The three racemic polymorphs of tazofelone are different stackings of the same sheet,¹⁰ but the different incidence of stacking faults, seen as diffuse streaks in the diffraction, gives rise to variations in melting temperatures and enthalpies between single crystals.



Finding useable definitions for the grey areas

There have been many discussions and findings which illustrate the problems of wanting black and white definitions:

The definition of whether a two component system is a salt or cocrystal can hinge on the location of a proton, but there is a salt–cocrystal continuum.¹¹ This distinction has been crucial in the emergence of cocrystals as a viable way of changing the crystalline properties of a pharmaceutical in the manufactured form.^{12,13} Hence, the refinement of the ΔpK_a rule for predicting whether two compounds will form a salt or cocrystal is important, with the new observation that water in the lattice shifts the range of ambiguity closer to the properties of water (<https://doi.org/10.1039/d1fd00081k>). For systems in the intermediate region of ΔpK_a , understanding this raises a chicken and egg type question. Does hydration occur because of proton transfer? Or does proton transfer occur because of hydration?

The conclusion that “long-range order structures form through continuous second order transformation from precursors with similar short-range order, but that interconversion between structures with distinct short-range order occurs *via* discontinuous first order transitions” (<https://doi.org/10.1039/d1fd00086a>) may well apply to systems other than barium calcium carbonates, but needs definitions of “short and long-range order”, as well as “similar”. How to differentiate between polymorphs and experimental variations of the same structure is not always trivial,¹⁴ as some polymorphs can be very similar.

Confinement is clearly linked to nucleation, but how closely do you have to define the size and shape of the confinement, as well as the nature of the exposed atoms and their charges within the inner surfaces, given that this can clearly determine polymorphic outcome (<https://doi.org/10.1039/d1fd00111f>)? If a specific surface has a strong influence on nucleation (<https://doi.org/10.1039/d1fd00115a>) and this is mainly exposed within defects, the convolution of confinement and templating effects will be hard to quantify in the laboratory, let alone model for natural samples. How much will this depend on the system?¹⁵

The discovery of a new surface polymorph, that is not observed in bulk (<https://doi.org/10.1039/d1fd00100k>), raises the question of how thin a crystal can be, and whether we can call a structure that diffracts a crystal if it cannot exist except on a specific substrate.

What do you understand by understand?

A pragmatist might say that all that we need is to understand crystallisation processes well enough to be able control industrial crystallisation processes. The observation that secondary nucleation is much more important than primary nucleation in the crystalliser (<https://doi.org/10.1039/d1fd00098e>) suggests that if this is the only goal, we have been looking in the wrong place.

This meeting has been about fundamental science, using our developing techniques, rather than targeted on improving an industrial crystallisation process. In recent decades, the impetus for scientific understanding, or at least for funding fundamental science, is wanting an ability to design new industrial processes. This meeting has demonstrated potential for novel industrial processes. The role of iodide in controlling the growth of copper, allowing the



crystallisation of Cu microplates, has been modelled and realised experimentally (<https://doi.org/10.1039/d1fd00091h>). We have seen how CaCO₃ can be made to crystallise with diverse inclusions of μm size <https://doi.org/10.1039/d1fd00095k>, which is really impressive when decades ago crystallisation was used for its ability to exclude impurities. This approach for occluding μm hollow calcite spheres within calcite single crystals could be used to create a delivery system for active compounds. In zeolites, the interaction strength of the cation with the pre-nucleation cluster and crystal surface determines crystal morphology and size, a rationalisation of observations that suggests a route for quality control (<https://doi.org/10.1039/d1fd00093d>). Knowing that alkali infusion significantly reduces the crystallisation times of certain zeolites, and that polymer addition markedly enhances the rates of crystallisation, suggests that these paths can improve the efficiency of hydrothermal syntheses in commercial zeolite production (<https://doi.org/10.1039/d1fd00096a>).

Increasingly, scientific understanding is defined by having an atomistic model in agreement with experiment. This is going way beyond the expectations in the days before computer simulations could tackle real systems realistically. Indeed, the surprise that a proposed model, despite extensive simplification, adequately describes the kinetics of the observed zeolite crystallisation (<https://doi.org/10.1039/d1fd00093d>) gives a sense of how much our expectations of scientific modelling have changed. Nonetheless, most of the papers are careful to use terms like “consistent with” or “suggest”.

Computer aided design as a measure of understanding

What we aspire to is the quantitative agreement of simulation results with experiments for the observables that experiments can measure, so that we can have enough trust in the underlying atomistic understanding to be able to use it to design new processes. The concept of the digital design of crystals and processes has been emerging over the last decade or so.¹⁶ At a Directed Assembly meeting hosted at Pfizer in 2011, Robert Docherty envisioned that we should aim for the design of a drug product and its manufacturing processes to be like aircraft design – all done computationally before the first piece of steel is cut. This reflects the intimate and inter-dependent relationship among the structure, properties, performance, and processing of a drug.¹⁷ The processing includes crystallisation and the filtering and drying that will depend on the morphology and hydroscopicity of the crystals and the spectra used for monitoring, all properties which will depend on the specific crystal structure. The crystal particles that are within the pharmaceutical product will have the required stability and dissolution rate only if any phase transformations are under control, which will depend on the particle sizes, surfaces and defects.¹⁷

My own research area is organic crystal structure prediction, and in the opening talk of the 2018 *Faraday Discussion* on this topic, I developed a 2D schematic for progress towards what most experimentalists want from an ideal organic crystal structure prediction (CSP) code.¹⁸ The current form is CSP_0, based on the relative lattice energies of the many computer generated structures containing the same molecule. One axis is the complexity of the system, going



from small rigid organic molecules through to more flexible pharmaceuticals with a variety of competing functional groups and range of conformations, to multi-component crystals such as pharmaceutical salt solvates. However, CSP_thd is based on the assumption that the most thermodynamically stable structure will crystallise, and the lattice energy does not include the effects of temperature. It is impossible to crystallise a molecule at 0 K, and many polymorphs are enantiotropically related, *i.e.* the stability order changes below the crystallisation temperature, as seen in NDI-C6 (<https://doi.org/10.1039/d1fd00100k>) (CSP is mainly useful because some polymorphic phase transitions are not observed experimentally, at least on a time-scale of pharmaceutical development). However, getting the relative thermodynamics right at ambient temperatures is demanding of the calculations as many organic molecules are relatively close to their melting points and may have a large amplitude of motion of parts of the molecule. Pressure and shearing can also affect the bulk relative thermodynamic stability. However, the relative thermodynamic stability of polymorphs can also depend on particle size when the particles are small enough that the surfaces affect the relative thermodynamics (<https://doi.org/10.1039/d1fd00111f>).¹⁹ The relative thermodynamic stability, particularly of other phases such as hydrates, may also be affected by other variables like the solvent and relative humidity.²⁰ However, even if we were accurately ranking the thermodynamic stability of the computer-generated structures, there would be a major problem of over-prediction for most molecular systems:²¹ far more crystal structures appear to be thermodynamically plausible than there are observed polymorphs.²² The CSP over-prediction problem is consistent with our discussions, as the suggestion that each pre-nucleation crystal might consist of a different polymorph (<https://doi.org/10.1039/d1fd00125f>) implies that many low energy structures may be ephemeral phases that are involved in crystallisation. It is clear from this meeting that there is no simple computational model for crystallisation kinetics that could provide an experimental recipe to crystallise a predicted polymorph for the first time. We also do not have sufficient understanding of crystallisation to say that the most thermodynamically stable computer-generated crystal structure could never be found, or at least, is unlikely to affect the crystallisation of a readily crystallised metastable form.²³

Over-prediction and synthesisability is also a major issue in inorganic crystal structure prediction, though the emphasis is on the composition as well as the structure for targeting novel materials.²⁴ Organic CSP is also used to help target new functional materials,²⁴ but there is the additional commercial interest as a complement to pharmaceutical development, where the molecule is chosen for its medicinal effects.

Conclusion

This is a personal perspective on how the understanding of crystallisation has changed during my scientific career. I trained as a theoretical chemist interested in developing models for intermolecular forces from the molecular charge distribution. This was justified by the belief that an accurate model for intermolecular forces between (rigid) molecules would be capable of predicting the behavior of molecules in all phases, gas, liquid and solid.² My assertion that in the



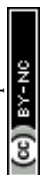
1980s most scientists thought that crystallisation was understood is based on having my career path changed by a sudden spectacular increase in interest in polymorphism and CSP. This was mainly due to Abbot Laboratories losing control of the manufacture of ritonavir.²⁶ The idea that crystallisation was not reliably reproducible was completely anathema to scientists (indeed, “disappearing” polymorphs was the one example from the physical sciences in the book by Rupert Sheldrake, “A New Science of Life: The Hypothesis of Morphic Resonance”, whose publication in 1981 led to a *Nature* editorial entitled “A book for burning?”²⁷). Abbott Laboratories quickly reformulated ritonavir to get around the problems of manufacturing the drug product after the appearance of the more stable form II,²⁸ but it required heroic efforts by their scientists and cost the company dearly. Joel Bernstein, who was one of the very small number of academic experts in polymorphism at the time,²⁹ did a considerable amount of legal and scientific work on “disappearing” polymorphs.³⁰ It can require extraordinary precautions, such as work being done in new labs by scientists who have not entered labs where the more stable form has been produced, to crystallise the metastable form again.³⁰ Our understanding of crystallisation now reflects why polymorphs may appear to “disappear”.³¹

There has been a huge amount of work on trying to develop experimental³² and computational methods to mitigate the risk of the late appearance of a more stable form during drug development, as exemplified by ritonavir.^{32,33} This provided a new motivation for developing crystal structure prediction methods, which were initially being developed as a test of the hypothesis that a molecule would crystallise in the most stable structure and as an aid to the discovery of functional organic materials, such as energetics and non-linear optical materials. Arguably, crystal structure prediction is now changing from basic science to an applied technology³⁴ as it could have prevented the late appearance of a more stable form affecting the treatment of patients suffering from Parkinson's disease.³⁵ Thus, as understanding crystallisation involves controlling polymorphism, as well as particle size and morphology, there has been considerable progress during my scientific career.

Consider the infamous quote from Donald Rumsfeld in 2011. “There are known knowns, things we know that we know; and there are known unknowns, things that we know we don't know. But there are also unknown unknowns, things we do not know we don't know”. There are aspects to crystallisation that very few people knew about in the 1980s that are now well established. The experimental work in this discussion has helped move some “unknowns” to “knowns”. The feeling that we currently don't understand crystallisation is a result of how much more we now know, through the application of new techniques and through scientific discussion. We now know a lot more about the complexity of the factors that determine the path of crystallisation. However, if you feel that the more you learn about crystallisation, the more you realize how much you don't know, then you are in good company.

Author contributions

SLP is the sole author, and this is a merely a quickly written version of her concluding remarks at the *Faraday Discussion*.



Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 A. Albaugh, H. A. Boateng, R. T. Bradshaw, O. N. Demerdash, J. Dziejczak, Y. Z. Mao, D. T. Margul, J. Swails, Q. Zeng, D. A. Case, *et al.*, Advanced Potential Energy Surfaces for Molecular Simulation, *J. Phys. Chem. B*, 2016, **120**(37), 9811–9832, DOI: [10.1021/acs.jpcc.6b06414](https://doi.org/10.1021/acs.jpcc.6b06414).
- 2 A. J. Stone *The Theory of Intermolecular Forces*; Oxford University Press, 2013.
- 3 C. G. Salzmann, P. G. Radaelli, B. Slater and J. L. Finney, The polymorphism of ice: five unresolved questions, *Phys. Chem. Chem. Phys.*, 2011, **13**(41), 18468–18480.
- 4 G. D. Price, S. L. Price and J. K. Burdett, The Factors Influencing Cation Site-Preferences in Spinel - a New Mendelyevian Approach, *Phys. Chem. Miner.*, 1982, **8**(2), 69–76.
- 5 L. S. Price and S. L. Price, Packing Preferences of Chalcones: A Model Conjugated Pharmaceutical Scaffold, *Cryst. Growth Des.*, 2022, **22**(3), 1801–1806, DOI: [10.1021/acs.cgd.1c01381](https://doi.org/10.1021/acs.cgd.1c01381).
- 6 R. Bobrovs, L. Drunka, A. Auzins, K. Jaudzems and M. Salvalaglio, Polymorph-Selective Role of Hydrogen Bonding and pi-pi Stacking in *p*-aminobenzoic Acid Solutions, *Cryst. Growth Des.*, 2021, **21**(1), 436–448, DOI: [10.1021/acs.cgd.0c01257](https://doi.org/10.1021/acs.cgd.0c01257).
- 7 S. Askin, J. K. Cockcroft, L. S. Price, A. D. Goncalves, M. Zhao, D. A. Tocher, G. R. Williams, S. Gaisford and D. Q. M. Craig, Olanzapine Form IV: Discovery of a New Polymorphic Form Enabled by Computed Crystal Energy Landscapes, *Cryst. Growth Des.*, 2019, **19**(5), 2751–2757, DOI: [10.1021/acs.cgd.8b01881](https://doi.org/10.1021/acs.cgd.8b01881).
- 8 J. J. De Yoreo, P. U. P. A. Gilbert, N. A. J. M. Sommerdijk, R. L. Penn, S. Whitelam, D. Joester, H. Z. Zhang, J. D. Rimer, A. Navrotsky, J. F. Banfield, *et al.*, Crystallization by particle attachment in synthetic, biogenic, and geologic environments, *Science*, 2015, **349**(6247), aaa6760, DOI: [10.1126/science.aaa6760](https://doi.org/10.1126/science.aaa6760).
- 9 A. D. Bond, R. Boese and G. R. Desiraju, On the polymorphism of aspirin: Crystalline aspirin as intergrowths of two “polymorphic” domains, *Angew. Chem., Int. Ed.*, 2007, **46**(4), 618–622.
- 10 L. S. Price, J. A. McMahon, S. R. Lingireddy, S. F. Lau, B. A. Diseroad, S. L. Price and S. M. Reutzler-Edens, A molecular picture of the problems in ensuring structural purity of tazofelone, *J. Mol. Struct.*, 2014, **1078**, 26–42, DOI: [10.1016/j.molstruc.2014.01.014](https://doi.org/10.1016/j.molstruc.2014.01.014).
- 11 S. L. Childs, G. P. Stahly and A. Park, The salt-cocrystal continuum: The influence of crystal structure on ionization state, *Mol. Pharmaceutics*, 2007, **4**(3), 323–338.



- 12 S. L. Childs and M. J. Zaworotko, The Reemergence Of Cocrystals: The Crystal Clear Writing Is On The Wall (Introduction to Virtual Special Issue on Pharmaceutical Cocrystals), *Cryst. Growth Des.*, 2009, **9**(10), 4208–4211.
- 13 C. B. Aakeroy, M. E. Fasulo and J. Desper, Cocrystal or salt: Does it really matter?, *Mol. Pharmaceutics*, 2007, **4**(3), 317–322, DOI: [10.1021/mp060126o](https://doi.org/10.1021/mp060126o).
- 14 J. van de Streek, Searching the Cambridge Structural Database for the 'best' representative of each unique polymorph, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2006, **62**, 567–579.
- 15 U. V. Shah, C. Amberg, Y. Diao, Z. Q. Yang and J. Y. Y. Heng, Heterogeneous nucleants for crystallogenes and bioseparation, *Curr. Opin. Chem. Eng.*, 2015, **8**, 69–75, DOI: [10.1016/j.coche.2015.03.002](https://doi.org/10.1016/j.coche.2015.03.002).
- 16 M. Bryant, I. Rosbottom, I. Bruno, R. Docherty, C. Edge, R. Hammond, R. Peeling, J. Pickering, K. Roberts and A. Maloney, "Particle Informatics": Advancing Our Understanding of Particle Properties through Digital Design, *Cryst. Growth Des.*, 2019, **19**(9), 5258–5266, DOI: [10.1021/acs.cgd.9b00654](https://doi.org/10.1021/acs.cgd.9b00654).
- 17 C. C. Sun, Material Science Tetrahedron-A Useful Tool for Pharmaceutical Research and Development, *J. Pharm. Sci.*, 2009, **98**, 1671–1687.
- 18 S. L. Price, Is zeroth order crystal structure prediction (CSP_0) coming to maturity? What should we aim for in an ideal crystal structure prediction code?, *Faraday Discuss.*, 2018, **211**, 9–30, DOI: [10.1039/c8fd00121a](https://doi.org/10.1039/c8fd00121a).
- 19 A. M. Belenguer, G. I. Lampronti, A. J. Cruz-Cabeza, C. A. Hunter and J. K. M. Sanders, Solvation and surface effects on polymorph stabilities at the nanoscale, *Chem. Sci.*, 2016, **7**(11), 6617–6627, DOI: [10.1039/c6sc03457h](https://doi.org/10.1039/c6sc03457h).
- 20 D. E. Braun, L. H. Koztecki, J. A. McMahon, S. L. Price and S. M. Reutzel-Edens, Navigating the Waters of Unconventional Crystalline Hydrates, *Mol. Pharmaceutics*, 2015, **12**(8), 3069–3088, DOI: [10.1021/acs.molpharmaceut.5b00357](https://doi.org/10.1021/acs.molpharmaceut.5b00357).
- 21 R. M. Bhardwaj, J. A. McMahon, J. Nyman, L. S. Price, S. Konar, I. D. H. Oswald, C. R. Pulham, S. L. Price and S. M. Reutzel-Edens, A Prolific Solvate Former, Galunisertib, under the Pressure of Crystal Structure Prediction, Produces Ten Diverse Polymorphs, *J. Am. Chem. Soc.*, 2019, **141**(35), 13887–13897, DOI: [10.1021/jacs.9b06634](https://doi.org/10.1021/jacs.9b06634).
- 22 D. E. Braun, J. A. McMahon, R. M. Bhardwaj, J. Nyman, M. A. Neumann, J. van de Streek and S. M. Reutzel-Edens, Inconvenient Truths about Solid Form Landscapes Revealed in the Polymorphs and Hydrates of Gandotinib, *Cryst. Growth Des.*, 2019, **19**(5), 2947–2962, DOI: [10.1021/acs.cgd.9b00162](https://doi.org/10.1021/acs.cgd.9b00162).
- 23 D. E. Braun, H. Oberacher, K. Arnhard, M. Orlova and U. J. Griesser, 4-Aminoquinoline monohydrate polymorphism: Prediction and impurity aided discovery of a difficult to access stable form, *CrystEngComm*, 2016, **18**, 4053–4067, DOI: [10.1039/C5CE01758K](https://doi.org/10.1039/C5CE01758K).
- 24 W. Sun, S. Dacek, S. Ong, G. Hautier, A. Jain, W. Richards, A. Gamst, K. Persson and G. Ceder, The thermodynamic scale of inorganic crystalline metastability, *Sci. Adv.*, 2016, **2**(11), e1600225, DOI: [10.1126/sciadv.1600225](https://doi.org/10.1126/sciadv.1600225).
- 25 G. M. Day and A. I. Cooper, Energy-Structure-Function Maps: Cartography for Materials Discovery, *Adv. Mater.*, 2018, **30**(37), 1704944, DOI: [10.1002/adma.201704944](https://doi.org/10.1002/adma.201704944).
- 26 S. R. Chemburkar, J. Bauer, K. Deming, H. Spiwek, K. Patel, J. Morris, R. Henry, S. Spanton, W. Dziki, W. Porter, *et al.*, Dealing with the impact of ritonavir



- polymorphs on the late stages of bulk drug process development, *Org. Process Res. Dev.*, 2000, **4**(5), 413–417.
- 27 https://en.wikipedia.org/wiki/Rupert_Sheldrake.
- 28 J. Bauer, S. Spanton, R. Henry, J. Quick, W. Dziki, W. Porter and J. R. Morris, An extraordinary example of conformational polymorphism, *Pharm. Res.*, 2001, **18**(6), 859–866.
- 29 J. Bernstein. *Polymorphism in Molecular Crystals*; Clarendon Press, 2020.
- 30 J. D. Dunitz and J. Bernstein, Disappearing Polymorphs, *Acc. Chem. Res.*, 1995, **28**(4), 193–200.
- 31 D. K. Bucar, R. W. Lancaster and J. Bernstein, Disappearing Polymorphs Revisited, *Angew. Chem., Int. Ed.*, 2015, **54**(24), 6972–6993, DOI: [10.1002/anie.201410356](https://doi.org/10.1002/anie.201410356).
- 32 S. L. Morissette, S. Soukasene, D. Levinson, M. J. Cima and O. Almarsson, Elucidation of crystal form diversity of the HIV protease inhibitor ritonavir by high-throughput crystallisation, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**(5), 2180–2184.
- 33 C. Wang, I. Rosbottom, T. Turner, S. Laing, A. Maloney, A. Sheikh, R. Docherty, Q. Yin and K. Roberts, Molecular, Solid-State and Surface Structures of the Conformational Polymorphic Forms of Ritonavir in Relation to their Physicochemical Properties, *Pharm. Res.*, 2021, **38**(6), 971–990, DOI: [10.1007/s11095-021-03048-2](https://doi.org/10.1007/s11095-021-03048-2).
- 34 J. Nyman and S. M. Reutzel-Edens, Crystal structure prediction is changing from basic science to applied technology, *Faraday Discuss.*, 2018, **211**, 459–476, DOI: [10.1039/c8fd00033f](https://doi.org/10.1039/c8fd00033f).
- 35 M. Mortazavi, J. Hoja, L. Aerts, L. Quere, J. van de Streek, M. A. Neumann and A. Tkatchenko, Computational polymorph screening reveals late-appearing and poorly-soluble form of rotigotine, *Commun. Chem.*, 2019, **2**, 70, DOI: [10.1038/s42004-019-0171-y](https://doi.org/10.1038/s42004-019-0171-y).

