Crystals from first principles

SIR—Maddox[1] considers it a "continuing scandal" that "it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition". In response, Cohen[2] has claimed that, on the contrary, "structures of crystals can be predicted using information about their chemical composition as the only input". Without wishing to underestimate the significance of the results discussed by Cohen, I feel that he has greatly overstated the case.

The stated aim of first-principles calculations is to predict the structure and properties of a crystal given only its chemical composition. If calculations are started from a configuration close to the global energy minimum, this may be done very successfully for a variety of materials[1,2]. Given the correct bond connectivity (or approximate relative atomic positions), cell size (in number of atoms) and (in some cases) space-group symmetry, the metric properties of the structure can be calculated, together with various properties of its energy and energy derivatives[1-4], but clearly these calculations require as input much more than simply the chemical formula. Although both Maddox and Cohen gloss over this problem, it is far from a trivial one.

There are two ways in which the calculations may be approached. First, an assemblage of randomly arranged atoms may be allowed to move such that the total energy of the system is minimized. This process can proceed with no assumptions (concerning, for example, which atoms are bonded to which, or what coordination numbers occur). The global energy minimum will be reached only if the derivative of the energy with respect to every variable parameter allows a continuous downward path towards it. From a random starting position, it is likely that the process will converge instead to a local minimum that represents a (possibly unphysical) metastable state. The calculations for silica[3] discussed by Maddox show that several polymorphs are dynamically stable and will 'trap' any minimization that starts within their energy volume of influence. The actual occurrence of such metastable forms indicates that there is not a continuously decreasing energy path between the metastable and the stable forms. Simulated annealing techniques[5] can permit escape from local minima, but are viable only if the number of local minima is small; this number is, however, usually very large. In general, therefore, solution is possible only by imposing strong boundary constraints, usually in terms of symmetry and cell size. For the former, a calculation starting with triclinic symmetry should converge on the correct symmetry. Imposing constraints on cell size is more difficult. Calculations can be performed for all possible cell sizes up to some arbitrary cutoff (with periodic boundary conditions), or for some large number of atoms (without periodic boundary conditions), where the expectation is that minimization will converge to an arrangement with the correct cell size and periodicity. In the latter case, the minimum number of atoms must be quite large because the properties of the assemblage must be those of a bulk crystal; experiments[6] suggest that this requires something of the order of 100–1,000 atoms.

The alternative approach is to specify 'good' candidate structures to use as starting configurations, and this method is used most widely. It requires extensive assumptions about the material investigated, such as which types of atoms are bonded to which and what coordination numbers are present. Calculations have focused on materials that are quite well understood (silicon[2], silica[1,3], common minerals[7]) and the candidate structures used are the observed structures (under a variety of conditions) together with some other well-known arrangements of the correct stoichiometry. This selection of candidate structures can be considered neither rigorous nor exhaustive. Whether or not the minimization process incorporates directional chemical bonds, it is convenient to specify possible structural arrangements by their bond connectivity — the problem is then reduced to the study of periodic networks[8,9]. Major problems include an insufficient understanding of fundamental constraints on the maximum cell size, or on the minimum and maximum allowable densities. For example, the observed distribution of 4-connected three-dimensional zeolite nets falls within a fairly restricted density range[9]. Even incorporating such restrictions, together with additional stereochemical information, the number of stoichiometrically possible networks can be very large. For example, the approximately 500 nets described by Smith[8] could all be used as candidate structures for the silica polymorphs. In general, one needs realistic but more restrictive stereochemical constraints that reduce this number to more manageable proportions. Combinatorial studies of restricted structure types[10,11] show that many potential structures occur even for simple stoichiometries. All of these are likely to correspond to local energy minima, heralding significant problems for an *a priori* energy minimization approach.

Thus a rigorous general solution to the question of crystal-structure prediction may not be forthcoming in the near future. At least, for simple materials, it is possible to deduce accurate metric and physical properties from an approximate atomic arrangement, but much more work is needed in the area of predicting bond connectivities before the problem can even be considered as susceptible to solution.

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Gene candidate

SIR—The subregional localization of malignant hyperthermia susceptibility (MHS) to chromosome 19q12–13.2 recently reported in *Nature*[1] can be used to suggest or eliminate 'candidate' genes as the site for the primary defect in this disorder. Indeed, MacLennan *et al.* [2] suggest, on the basis of linkage data, that a mutation in the ryanodine-receptor gene probably causes MHS. While awaiting the description of the mutation in MHS individuals which would confirm which gene is responsible for MHS, we would like to suggest another candidate.

It is known that free fatty acid metabolism is abnormal in MHS skeletal muscle: muscle homogenates from humans[3] and isolated mitochondria from pigs[4] indicate that free fatty acid release is greater than two-and-a-half times that of normal controls. These free fatty acids seem to be derived from skeletal muscle triglycerides[5]. Elevated free fatty acid concentrations can increase the release and decrease the uptake of calcium in the sarcoplasmic reticulum[5]. The threshold for calcium-induced calcium release from sarcoplasmic reticulum is also reduced in MHS[6], and fatty acids enhance the release of calcium by lowering this threshold[7]. Free fatty acids are also well known to produce heat by uncoupling oxidative metabolism.

A hormone-sensitive lipase is crucial in mobilizing free fatty acids from stored triglycerides and is regulated by hormonal and neuronal factors[8]. This lipase is activated by catecholamines through cyclic AMP-mediated phosphorylation, and dephosphorylated (inactivated) by insulin[8]. If this insulin inactivation did not occur in MHS individuals, excess free