Coronavirus motif

Sir — I report the presence of a leucine zipper motif at the carboxyl end of the spike (S) glycoprotein, a transmembrane protein of coronaviruses. All the coronavirus S proteins whose sequences are known — transmissible gastroenteritis virus (TGEV) FS77/20 (residues 1,342–1,377), feline infectious peritonitis virus (FIPV) 79–1146 (1345–1380), mouse hepatitis virus (MHV) A59 (1217–1252), MHV JHM (1128–1163), human coronavirus (HCV) 229E (1,067–1,102), bovine coronavirus (BCV) Mebus (1,266–1,294) and infectious bronchitis virus (IBV) Beaudette (1,058–1,079) — contain a leucine-zipper motif terminating 10 amino-acid residues upstream of the conserved KWP motif preceding the transmembrane domain.

The length of the leucine zippers range from three heptad repeats, as identified for the F glycoprotein of paramyxoviruses, to five heptad repeats. The observation that all coronaviruses S proteins sequenced so far contain the leucine-zipper motif 10 amino-acid residues from the transmembrane domain may imply some function of the motif in the dimerization of the S polytides.

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Biocontrol risks

Sir — Hochberg and Waage suggested in their News and Views article1 that some new genetically modified insect viruses will be acceptable as biological control agents because they have "highly restricted host ranges". There is widespread agreement that specific biological control agents are preferred, but the dangers of non-specific biocontrols are great, and much damage has resulted from their use2.

How specific are these genetically modified organisms? They are derived from the Autographa californica nuclear polyhedrosis virus (AcNPV), a baculovirus, which has a wide and sporadic host range in the lepidoptera. There are around 2,500 species of lepidoptera in Britain3, and of course many times more elsewhere. The records of host range of this virus4–6, based on a small fraction of the known species, show that, of twelve superfamilies tested, eight apparently contain 'permissive' species (species killed by fewer virus polyhedra than are produced by one dead caterpillar). With this and other baculoviruses' one species in a genus may be permisive, others resistant and the LD50s vary markedly between different permisive species, without apparent regard for taxonomy.

The superfamilies known to have permissive species are the Gelichioidae, Pyraloidea, Papilionoidea, Sphingoidae and Noctuaidae: the Bombycoidea, Geometroidea and Yponometroidea may have them, but this needs confirmation by DNA analysis. It seems that 5–10 per cent of British lepidoptera are permissive for AcNPV, a non-native virus, putting 125–250 species at risk, including some of great conservation value.

The two new genetically modified organisms7,8, like others derived from the same virus9, may have host ranges slightly different from that of the wild type. But unless they can be further engineered to be absolutely specific for a known set of (pest) species, it is difficult to see that they could be used safely in an uncontrolled way in the field. Would the risk assessment required under EC Directive 90/200, for instance, indicate that they are undesirable?

Hochberg and Waage1 also note that "disabling engineered viruses so that they do not persist has some appeal". Removing the polyhedrin gene to produce a non-occluded virus10 reduces both persistence and, to a small extent, the host range; neither of the two new genetically modified organisms has apparently been modified in this way.

Research into the molecular and other bases of host specificity is likely to be a sine qua non for the successful, much-desired, replacement of chemical control agents for insects by viral ones.

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Ionicity in silica

Sir — Kramer et al.1 suggest that a change in ionicity is responsible for the transition from the α to the β phase in silica. Their ab initio force-field method indicates that an increase by about 0.1 atomic units of the net charge on silicon stabilizes the β structure of quartz and cristobalite with respect to the α structures, implying that the former correspond to global minima of the Born–Oppenheimer potential-energy surface. Our recent Hartree–Fock calculations2 on the quartz structures of SiO2 and GeO2 came to opposite conclusions with respect to both the magnitude and the direction of the ionicity effect.

Our calculations were performed at a level of accuracy similar to that of the cluster calculations used to derive the force field of ref. 1. We used the P321 space group for both the α and the β structures. In α quartz there are two equivalent twinned configurations, α1 and α2, related by a rotation of the SiO4 tetrahedra around their C2 axes. The corresponding internal coordinate, the tilt angle δ (ref. 3), is negative in the α2 phase, positive in α1 and zero in β.

The net charges calculated by this method should provide reliable trends of ionicity in connected structures when identical basis sets are used. We find that the net charge on silicon decreases

1. Kramer, G. J., van Beest, B. W. H. & van Santen, R. A. C. Nature 351, 638–639 (1991).
2. Silvi, B., D'Arco, B. & Catena, M. J. chem. Phys. 93, 7225–7229 (1990).
3. Goren, H. & Domer, B. J. Phys. Chem. Solids 44, 407–413 (1975).
4. Tsuneyuki, S., Aoki, H., Tsukada, M. & Matsu, Y. Phys. Rev. Lett. 64, 2356–2359 (1991).
The position of the mutation Arg for this interpretation. Starting from the of the atomic coordinates with respect to temperature is raised, and at 850 K the rather in terms of the expectation values predicted by our ab initio calculations on infinite crystals.

The Born-Oppenheimer energy curve suggests that Arg 239 in the analogous of the EGF-like domain calcium SIR - Dietz factor IX which is known to bind repeats of the filbrillin gene found in two patients with Marfan syndrome. These mutations in one of the 34 Arg 239 of factor IX containing EGF-like repeats described an (1) D D E N (11) D D E D (III) D D E D (II) D D E N (I) D D E N

Calcium binding to fibrillin?

SIR — Dietz et al.1 described an Arg 239→Pro mutation in one of the 34 epidermal growth factor (EGF)-like repeats of the filibrillin gene2 found in two patients with Marfan syndrome. These repeats contain a consensus sequence (see diagram) analogous to that found in the first EGF-like domain of coagulation factor IX which is known to bind calcium3. It therefore seems likely that fibrillin will also bind calcium. Moreover, the two-dimensional NMR structure of the EGF-like domain4 of factor IX suggests that Arg 239 in the analogous fibrillin EGF-like domain is located on the second strand of an antiparallel β-sheet adjacent to the inferred calcium binding site. We propose that local disruption of this calcium-binding site could be responsible for the defect in fibrillin function, although long-range effects of the proline substitution on protein structure cannot be excluded. Supporting the concept of local disruption is the identification of two mutations in the factor IX EGF-like domain, Asp 47→Glu and Asp 64→Asn, present in patients with haemophilia B. These mutations reduce calcium binding appreciably but do not grossly affect the protein’s structure5. Several groups have proposed that EGF-like domains are involved in protein–protein interactions; we would like to draw attention to a recent paper6 where notch and delta, two Drosophila proteins containing EGF-like repeats with the calcium-binding consensus, interact in a calcium-dependent manner. Could calcium interaction with EGF-like repeats in fibrillin be intimately linked with its function in connective tissue?

Bell’s inequality

SIR — Maddox’s article1 on non-locality in quantum mechanics reminded me that Bell’s inequality has a long history which may be of some interest. A few years ago, I attempted to trace the origins of the probability metric. (The distance between two events is the probability that one of them occurs but not both. Strictly speaking, this is a pseudo-metric from which a metric can be constructed by standard techniques.) My colleague, D. A. Edwards, pointed out that the treatise by Dunford and Schwartz2 contains both a discussion of a more general metric on measure spaces and a survey of its history. There it is traced back to work of Aronszajn and Nikodym3 in the late 1920s. Moreover, that metric is actually just a special case of the $L^1$ metric on integrable functions discussed 10 years earlier by Fréchet4. (One restricts the $L^1$ metric to indicator functions of events.)

The fact that the basic inequality was known for so long makes it all the more surprising that, until Bell’s independent rediscovery of it in the 1960s, no one seems to have observed that the triangle inequality fails in quantum mechanics and can therefore provide a test of large classes of hidden variable theories. The new paper by Fivel5, which Maddox discusses, provides an interesting new insight by comparing the probability metric with the quantum-mechanical Hilbert space metric and thereby isolating the mechanism which gives rise to Bell’s inequality in one case but not in the other.

### Calcium binding to fibrillin?

**SCIENTIFIC CORRESPONDENCE**

**Bell’s inequality**

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