Ferroelectricity in oxides

SIR — Cohen[1], using total energy calculations, ascribes the origin of ferroelectricity in $BaTiO_3$ and $PbTiO_3$ to transition metal–oxygen *p–d* hybridization effects. Here, we emphasize that this approach is, of course, not unique because dynamical properties, which are very important in ferroelectrics, are neglected by Cohen.

A unified interpretation of ferroelectricity that is not restricted to perovskite oxides has been offered by Migoni *et al.*[2], who argued that the O^{2-} ion may be crucial for the polar ferroelectric state to occur. These authors took into account the outstanding properties of O^{2-} by introducing a shell model description for the lattice dynamics of perovskite oxides. The temperature dependence of the oxygen-ion polarizability, which is assumed to drive the lattice instability, has been taken into account by introducing a fourth-order repulsive term in addition to a local attractive electron–ion coupling, thus inducing a local double-well potential in the core–shell interaction at the oxygen-ion lattice site. Within self-consistent phonon theory, quantitative agreement with experimental data has been achieved for phonon dispersion relations, second-order Raman spectra, temperature dependence of the soft-mode frequency and coupled branches as well as defect properties.

Extensions to systems other than perovskite oxides have been carried out within a simplified version[3] of the model of Migoni *et al.*, which quantitatively describes the temperature dependence of soft modes in various structurally different compounds[4]. The extremely transparent, physically understandable and analytically tractable model possesses, besides a wide range of applicability, highly interesting nonlinear solutions which exist on the lattice as well as in a continuum approach to the lattice[5]. From these studies on ferroelectric systems, we conclude that the origin of ferroelectricity in oxides is a consequence of the critical dynamics which are driven by crucial interplay of ionic and electronic interactions.

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Deviant TATA-box binding protein

SIR — In their paper reporting the crystal structure of one variant of the *Arabidopsis* TATA-box binding protein (TBP), Nikolov *et al.*[1] draw attention to the remarkable similarity of the C-terminal domains of all known TBP proteins, as does Greenblatt in the accompanying News and Views article[2]. Thus, in this 180-residue region, TBP molecules of fungal, plant, insect and mammalian origin are a minimum of 70% identical at the amino-acid level. On this basis, and the fact that variant residues map to positions unlikely to perturb the folding pattern, it is suggested that the reported structure of the TBP DNA-binding domain may be universal.

We have characterized the TBP homologue from the human malaria parasite *Plasmodium falciparum*[3], which we find to be strikingly divergent from these examples. In this case, the corresponding amino-acid identities range from 38 to 44%. In this organism, whose genome shows a highly biased base composition, putative promoter regions have an A+T content averaging close to 90% (ref. 4). Under these circumstances, the unambiguous recognition of conventional TATA-boxes will be difficult, and the observed divergence in protein composition may reflect an evolutionary response to this problem.

In any case, this dramatically altered sequence composition means that caution is needed in regarding the *Arabidopsis* TBP structure as being universal. In particular, the *P. falciparum* molecule may be subtly different from the structure presented. Any such differences between it and its equivalent from the human host might well be reflected in functional differences that in future could be exploited chemotherapeutically.

We would also point out that the residual sequence identities conserved between the *P. falciparum* TBP protein and those of other organisms (57, compared to the 126 seen in the data set of Nikolov *et al.*[1]) may help to define a much reduced number of residues likely to be critical to the interaction of TBP with other members of the transcription initiation complex. This information could aid the informed design of site-directed mutagenesis experiments to investigate further the nature of intermolecular interactions in other eukaryotic transcription systems.

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More on motor neurons

SIR — Vrbová *et al.*[1] raise questions with regard to our paper on the effect of ciliary neurotrophic factor (CNTF) on the mouse mutant progressive motor neuronopathy (*pmn*)[2]. They wonder whether the "relatively modest loss of facial motor neurons" (40%) can account for the death of untreated homozygotes. It certainly cannot.

However, the denervation of the diaphragm at the fourth postnatal week caused by the almost complete loss of motor axons in the phrenic nerve[3] would be sufficient to lead to the death of the animals 2 weeks later. The putative "sharp contrast" they note between the original observations[3] and our manuscript[2], that motor neurons of the spinal cord and cranial nuclei appear qualitatively normal at 5 weeks of age[3] whereas 40% of the facial motor neurons have degenerated at 6–7 weeks[2], simply reflects the rapid progression of the degeneration process in the *pmn* mutant. Moreover, cell numbers of spinal motor neurons were not determined in the original paper[3] so that loss of these neurons cannot be excluded. Similar observations (no loss of anterior horn cell somata) have also been reported for other animal models such as the Brittany spaniels with hereditary canine spinal muscular atrophy (HCSMA)[4]. If one should follow the criterion of Vrbová *et al.*, that any useful model for motor neuron disease should show an initial degeneration of the motor neuron cell body, then the HCSMA model should also be dismissed.

The *pmn* mutant is certainly not identical with amyotrophic lateral sclerosis (ALS) (we never claimed that), but the pathological manifestations of ALS show striking similarities to those observed in

pmn mice. The traditional dogma that loss of motor neuron somata represents the primary lesion in ALS has never been supported by convincing data; on the contrary, it has been seriously questioned for both ALS[5–8] and spinal muscular atrophy[9]. Fewer myelinated nerve fibres are present in distal compared to proximal segments of the phrenic nerves of ALS patients[10], arguing in favour of a 'dying back' process as observed in *pmn* mice. Moreover, the pronounced axonal degeneration and regeneration in the ventral roots of ALS patients[11] is not compatible with the assumption of primary degeneration of motor neuron somata. Indeed, electron micrographs of degenerating motor endplates[7] strikingly resemble the initial changes detected in *pmn* mice.

We conclude from our data that CNTF not only prevents the loss of motor neuron somata, but also maintains axonal integrity and supports axonal regeneration. A recent report on the effects of CNTF on sprouting of motor neurons from endplates and nodes of Ranvier[12] is in agreement with this interpretation. The consequence of these effects is functional restoration of the motor innervation of the paralytic skeletal musculature. Thus, that CNTF interferes with pathological manifestations at both functional and morphological levels appears relevant to the potential usefulness of CNTF in the treatment of ALS patients.

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Per — no link to gap junctions

SIR — It has recently been determined that the results of certain experiments originally performed in the laboratory of one of the authors (D.C.S.), and described in our paper[1] entitled "The *Drosophila* clock gene *per* affects intercellular junctional communication", cannot be reproduced. This paper reported changes in gap-junction-mediated intercellular communication in salivary glands from *D. melanogaster period* (*per*) mutants. Three classes of coupling measurements were performed in the original study: (1) measurement of dye spread among cells in per^0, per^s and per^+ salivary glands; (2) determination of electrotonic coupling in intact salivary glands of these genotypes; and (3) determination of electrical coupling between isolated cell pairs from dissected salivary glands of these genotypes. For all three classes of experiments, measurements were performed by D.C.S. on material supplied by T.A.B. and M.K.B. This work led to a central conclusion put forth in the paper — that by all three criteria strong differences in intercellular coupling distinguished the *per* genotypes.

A reinvestigation of dye coupling[2] has concluded that no consistent differences in intercellular coupling in salivary glands can be attributed to *per* locus mutations. This new report[2] was initiated by K. Flint, M. Rosbash and J. C. Hall, who communicated their unpublished results to us. Similar data were then obtained by D.C.S. and K. Siwicki, and these two sets of data were pooled. The new paper, and the absence of any indication as to the cause of the discrepancy between the two studies, causes us to question the validity of the original measurements of dye and electrical coupling. We also wish to point out that these data were essential for support of a model proposed in our paper: that *per* might control circadian rhythms by modulating intercellular junctional communication in the nervous system.

In addition to the studies of intercellular communication described above, our paper included data supporting two other conclusions: (1) that antibodies against the *per* product can detect an antigen of unexpectedly high molecular mass, which is reduced in size by treatment with heparinase II; and (2) that *per* expression can be detected in developing *Drosophila* salivary glands. These experiments were carried out in the laboratory of M.W.Y. We note that our detection of antigen with proteoglycan properties was consistent with an earlier, related biochemical study of *per* antigens by others[3], and we know of no studies that further directly address this issue. We have no reason to question the data presented in support of this aspect of our study. Indirect evidence does suggest that such modification of *per* may not be required for expression of circadian rhythms[4]. As has been previously acknowledged[5], *per* expression in developing salivary glands has not been confirmed by studies from another laboratory[6,7], while, for example, work in M.W.Y.'s laboratory indicates consistent labelling of these glands with *per* antibodies and with strand-specific *per* RNA probes following *in situ* hybridization. More direct support for *per* expression in developing salivary glands has come from blot analysis of RNA from hand-dissected larval tissue[8]. The latter analysis also shows that hybridizing transcripts from the glands are indistinguishable in size from *per* RNA extracted from heads[8]. It may also be important that evidence for *per* expression in *adult* salivary glands has been presented by others[6].

In conclusion, we wish to retract those portions of our paper reporting evidence for the involvement of *per* in gap-junction-mediated intercellular communication. We acknowledge the shared responsibilities for that work as coauthors of a collaborative effort. We deeply regret any difficulties our original report may have caused other researchers working in this field.

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