characteristic X-ray emission energies.

I placed one of the remaining small crystals of aPP on a sample stub to air dry and to my surprise it did not disintegrate. After coating it with carbon, I examined the sample under vacuum in the microscope and it remained crystalline in appearance. I recorded EDAX spectra over a 400-s time period and observed a peak at 8.63-KeV characteristic of the K_α line for zinc. The addition of zinc acetate to the crystallization experiments resulted in much larger crystals, indicating that the original scavenged zinc must have been limiting[2]. The resulting high-resolution X-ray analysis indicated the key role this divalent ion played in forming the crystal lattice[2,3].

I have also applied this technique to porcine 2-zinc insulin crystals and to freezed-dried iron containing transferrin. The ability to detect and identify traces of heavy elements acting as essential cofactors in protein crystals may provide one escape route for the baffled crystallographer.

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Expanding family

SIR—We have recently described[1] a family of six fungal genes involved in mitosis and the regulation of RNA synthesis whose protein products have in common a repetitive sequence motif of 34 amino acids (tetratricopeptide repeat or TPR). Zhang *et al.* (manuscript in preparation) subsequently found 16 tandem TPR sequences in the *crooked neck* (*crn*) gene involved in neurogenesis in the fruitfly *Drosophila*. We have now identified two additional family members in the yeast *Saccharomyces cerevisiae*.

The product of one gene, first cloned in 1983 (refs 2, 3), is a protein of relative molecular mass (M_r) 70,000 and was used for studying the targeting of mitochondrial proteins encoded in the nucleus. The 41 amino acids at the amino terminus anchor the protein to the outer mitochondrial membrane and the rest lies in the cytoplasm. It is this portion that contains seven tandem TPR sequences; this arrangement of TPR repeats is remarkably similar to that of the cell-division cycle (CDC) subset of the TPR family[1]. It is known that a truncated version of the gene, whose product is shortened at the carboxy terminus by 203 residues, including almost all of the tandem TPR domain, is anchored normally but produces cells with the same mutant phenotype as that of cells that lack the protein. Could it be that the repeated sequence domain mediates the interaction of mitochondria with the cytoskeleton much as *nuc2*$^+$ is thought to interact with the nuclear 'scaffold'[4]?

The product of the second gene, *STI1*, is a protein of M_r 66,000 induced by stress but not similar to the HSP70 family of heat-shock proteins[5]. Again there are internal TPR sequences, but of variable length, in an arrangement resembling that of the product of SKI3 gene involved in RNA regulation.

The inferred amphipathic helical structure of the TPR unit[1,4] suggests several possible functions, including protein–lipid interaction and the mediation of protein dimerization. Our recent (unpublished) finding of intragenic complementation between temperature-sensitive alleles of *CDC23* by mutations in different TPRs suggests that protein-protein interactions are necessary for *CDC23* function.

In our original TPR dataset[1], we identified two more highly conserved subdomains, A and B, corresponding to the 'hole' and 'knob' in the repeat–repeat interaction model of *nuc2*$^+$ function[4]. In the new examples, the B submotif is maintained but there are different patterns of sequence conservation in A. We believe that TPR genes have evolved different functions based both on divergence of TPR sequences and also on the acquisition of separate, unrelated functional domains such as the targeting/anchoring sequence in the M_r 70,000 outer mitochondrial membrane protein and the *zeste*-like domain in *SSN6* (ref. 1). Consistent with this idea, we have now found that single amino-acid substitutions in *CDC23*, which cause a temperature-sensitive phenotype, cluster into two separate domains: the carboxy-terminal TPR sequence block and an amino-terminal domain of unique, unrelated sequence.

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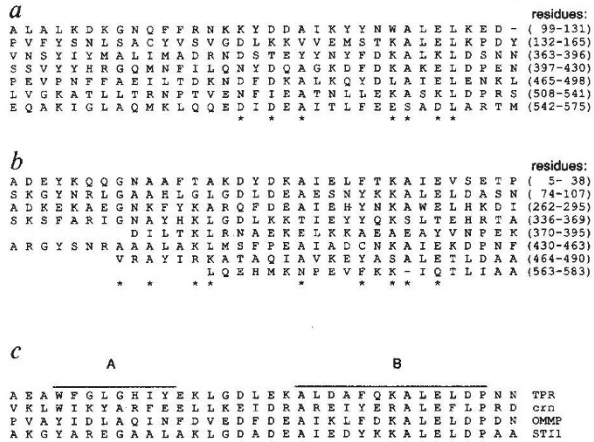

Internally repetitive sequences and their statistical significance were identified and characterized by standard methods as described in ref. 1. The M_r 70,000 protein and *STI1* have intra-sequence comparison scores of 7.09 and 12.37 s.d. units, respectively; inter-sequence comparisons with other members of the TPR family yielded scores ranging from 3.44 to 12.43 s.d. units. Only the repeats of highest significance are shown. Starred columns, the most highly-conserved positions in the aligned sequences. The original TPR motif was based on 47 repeats from five different proteins and showed two more highly conserved subdomains labelled A and B and represented by the sequences W..LG..Y and A...(Y/F)..A...P, respectively (ref. 1). The CDC subset of TPR proteins includes *CDC23*, *CDC16* (*S. cerevisiae*), *nuc2*$^+$ (*S. pombe*) and *bimA* (*A. nidulans*); the RNA regulation subset includes *SKI3* and *SSN6* (*S. cerevisiae*). To facilitate comparisons with new candidate TPR genes, a file containing all known TPR protein sequences, as well as suggestions for quantitative comparisons, is available from M.S.B.

Proportional time

SIR—If there is unease with the idea of a defined moment for the Big Bang, with no temporal predecessor, why not adopt E. A. Milne's logarithmic proposal, where $\tau = t \log(t/t_o) + t_o$, with τ as dynamical time and t as conventional time (*Proc. R. Soc.* **A158**, 324–348; 1937)? As Milne remarks, the epoch of creation t=0 on the kinematic scale is measured by $\tau = -\infty$ on the dynamical scale.

Indeed, more generally there is a case for thinking of time in proportionate rather than in arithmatically progressive terms. In sensory physiology, strength of sensation is usually proportional to log(stimulus); in pharmacology, drug effect is usually proportioned to log(dose); and on a wider canvas, wage negotiations, inflation, growth and what-not, are almost always expressed in proportionate terms. Why should the philosophy of time restrict itself to an unnatural arithmetical scale?

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