tures of complex networks. Moreover, biological networks can be broken down into groups of interacting molecules or modules, each responsible for different cellular functions[7,8]. This is evident in the protein-protein interaction network of the yeast, *Saccharomyces cerevisiae*, obtained from two-hybrid experiments, which has a clear hierarchical and modular architecture.

In their new study, Wuchty *et al.*[1] obtain quantitative evidence that proteins belonging to specific topological motifs in the protein interaction networks seem to be highly conserved across species during evolution. Interacting proteins can be assigned to defined motifs, such as triangles, squares and pentagons, which describe potential functional modules. By identifying the list of conserved proteins across five eukaryotes, the authors find that proteins belonging to topological motifs in the protein interaction networks of *S. cerevisiae* are conserved with higher probability than those not present in such motifs. Furthermore, the more internal connections in the motif, the more highly conserved it is. These results suggest that conserved proteins are more likely to be parts of topological motifs and that these motifs could identify the functional modules used as building blocks in the evolutionary process. This conclusion is further supported by the authors' observation that specific motifs are more likely to be associated with certain cellular functions.

The results of Wuchty *et al.*[1] should be confirmed by investigating conservation of motifs in higher organisms. Such experiments would require new high-throughput techniques capable of reconstructing the protein interaction networks of higher organisms. Although this issue and the concerns regarding the reliability of two-hybrid experiments require further consideration, the work of Wuchty *et al.*[1] represents the first step in connecting the topological architecture of biological networks with its evolution and function. This work should have an immediate impact on evolutionary models aimed at identifying the structure of the protein interaction network based on gene duplication-divergence mechanisms[9,10]. Furthermore, the relevance of specific motifs and local configuration analysis in identifying cellular function modules may enrich local and global algorithms for protein function assignment based on the protein interaction network[11,12].

With this paper, network analysis seems to have entered a new stage in which the general theoretical framework developed so far is beginning to provide answers to specific and detailed questions about complex biological processes.

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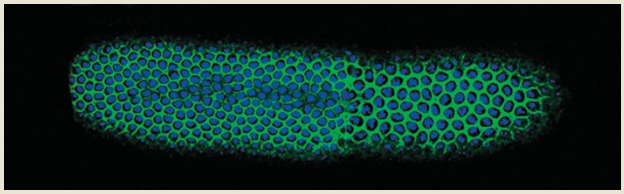
Frühstart at the midblastula transition

In 1982, Newport and Kirschner defined the midblastula transition (MBT), a key developmental event in *Xenopus laevis* and other animal embryos. The *X. laevis* embryo undergoes 12 rapid divisions after fertilization, with the thirteenth division initiating a new developmental program characterized by zygotic gene transcription and blastomere motility. Only fitful progress has been made in defining the molecules that regulate the MBT, but Jörg Grosshans and colleagues have now identified a protein that may have an important role (*Dev. Cell* **5**, 285–294; 2003).

Previous work showed that although the pre-MBT *X. laevis* embryo is fully competent to initiate zygotic transcription, the rapid cell cycles of the first 12 cleavages don't allow enough time for such transcription to occur. Several groups have contributed to a model proposing that the increasing nucleocytoplasmic ratio in the blastomeres of the early embryo depletes factors that are required for DNA replication or cell cycle progression, thus lengthening interphase and allowing time for zygotic transcription. Such a model has also been suggested for the equivalent of the MBT in the *Drosophila melanogaster* embryo, in which zygotic transcription accompanies a checkpoint-dependent elongation of cell cycles 11–13. The fly embryo, which consists of shared cytoplasm up to this point, then pauses at cleavage cell cycle 14 and cellularizes. A central question that remains is the nature of the additional factors that link nucleocytoplasmic ratio with control of the cell cycle.

Grosshans *et al.* show that the cytoplasmic protein frühstart (meaning 'false start') has all the expected properties of a linchpin



of the MBT in the fly embryo. Frühstart (frs) was originally identified as a mitotic inhibitor that delays division in cells of the ventral furrow during gastrulation. Noting that *frs* is first expressed coincident with the pause in the mitosis at cycle 14, the authors asked whether it might also delay mitosis at the MBT. As pictured here, injection of *frs* mRNA into the posterior end of the embryo (at right) during cycles 10–12 results in large patches where there are fewer cell divisions. Taking a closer look at *frs*-null embryos, they observed that a small fraction of them have patches of higher nuclear density, which the authors suggest is due to an extra cleavage before cellularization.

Is expression of *frs* regulated by the nucleocytoplasmic ratio? Expression of the gene, which peaks shortly after cycle 13, is delayed in haploid embryos. This and other lines of evidence lead the authors to argue that *frs* transcription is probably a direct readout of this ratio. Future work will focus on the identification of *cis*-acting regulatory elements that control expression of *frs* in response to the amount of DNA in the embryo as a whole.

Alan Packer