from many phyla is now making the use of alignments of hundreds or even thousands of genes a standard procedure.

These studies have led to a widely accepted phylogeny of all animal phyla that has radically changed our views of animal evolution (3). Premolecular phylogenies generally envisaged a gradual increase in complexity from the earliest animals without a body cavity or coelom (acoelomate flatworms) via pseudocoelomate worms (such as nematodes and rotifers) to coelomate protostomes (annelids, arthropods, and mollusks) and deuterostomes (echinoderms and chordates) with a sophisticated mesoderm-lined coelomic body cavity.

In contrast, today’s tree divides bilaterally symmetrical animals into protostomes and deuterostomes (see the figure, panel B). Within the deuterostomes, the simple urochordates (sea squirts) are closer relatives of the vertebrates than the more fishlike chordates (sea squirts) are closer relatives of and more closely related to each other than to the flatworms, have rather controv-
singly been placed close to echinoderms to form a fourth phylum of deuterostome (J5). Pseudo-acoelomate phyla, including nematodes and rotifers, are scattered throughout the protostomes.

All these rearrangements suggest that many characters thought to be important—such as the coelomic body cavity—have in fact been gained and lost multiple times. Although much of the animal tree is now resolved, a number of problems remain. These problems tend to involve relationships either of taxa with extreme systematic biases or among groups that seem to have originated in a rapid radiation, resulting in a lack of signal supporting individual nodes. Future progress will depend on increasing useful signal with larger “phylogenomic” data sets from the widest possible taxonomic sample and on continued improvement in the correspondence between real data and the models used when reconstructing trees.

References and Notes

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Donald M. Crothers

On page 816 of this issue, Kim et al. (1) report that a DNA-bound protein can influence the properties of an adjacent protein if both are bound to the DNA strand within about 15 base pairs (bp) of each other. The authors attribute their observations to an allosteric effect, in which a distortion of the DNA strand by the first protein modulates the binding of the second protein. The observations have important implications for gene regulation.

The authors use single-molecule methods to detect the influence of the first protein (protein A) on the dissociation rate of the second protein (protein B), measured relative to the value without protein A. They show that the effect is strongly phase-dependent, with a periodicity of 10 bp and amplitude of ~4-fold change in the dissociation rate.

The natural first interpretation of these results would be that the effect is due to protein-protein contacts or through-space electrostatic effects. However, these explanations are rendered unlikely by control experiments, which show that a hairpin loop can replace protein A, the effect is nearly independent of salt concentration, and the rate constant oscillation is much attenuated in the absence of protein A. The observations indicate an allosteric coupling between two DNA-binding proteins A and B, both of which widen the major groove. Thus, binding of A energetically favors binding of B at positions where R is already widened (\(\delta R > 0\), top), but disfavors binding of B where R is narrowed (\(\delta R < 0\), bottom). [Adapted from (1)]

An allosteric effect in which distortion of the DNA duplex by one protein modulates the binding of another protein may be important in gene regulation.

BIOPHYSICS

Fine Tuning Gene Regulation

Donald M. Crothers

On page 816 of this issue, Kim et al. (1) report that a DNA-bound protein can influence the properties of an adjacent protein if both are bound to the DNA strand within about 15 base pairs (bp) of each other. The authors attribute their observations to an allosteric effect, in which a distortion of the DNA strand by the first protein modulates the binding of the second protein. The observations have important implications for gene regulation.

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The natural first interpretation of these results would be that the effect is due to protein-protein contacts or through-space electrostatic effects. However, these explanations are rendered unlikely by control experiments, which show that a hairpin loop can replace protein A, the effect is nearly independent of salt concentration, and the rate constant oscillation is much attenuated by a nick or unmatched base pair between the two proteins.

The authors studied various protein pairs, including the T7 RNA polymerase (T7 RNAP)–lac repressor (LacR) combination. In vitro single-molecule kinetic experiments showed that T7 RNAP stabilizes or destabilizes LacR, depending on the distance between them along the DNA strand. In transcription experiments in vivo, LacR was placed upstream of the T7 promoter used to transcribe the lac Z gene. It is a general thermodynamic principle that if one protein stabilizes/destabilizes the binding of another protein, the second must have the same stabilizing/destabilizing effect on the first. Lac Z expression levels, which
depend on the binding strength of the polymerase, were found to oscillate by a factor of three depending on how far upstream the lac repressor was bound. The results correspond to the effects of T7 RNAP on LacR stability, as required by thermodynamics.

The authors propose that the helical phase-dependence of DNA-bound protein stability is due to transmission of allosteric effects through DNA. The concept of allostery was initially proposed to explain how the properties of the active site of an enzyme can be affected by binding an effector at a distant site, but it is useful in a wider context. Monod et al. (2) have defined allosteric effects broadly as indirect interactions between distinct specific binding sites. In accordance with this definition, Pohl et al. (3) described the cooperative binding of ethidium to a left-handed Z-DNA sample in terms of an allosteric conversion of the structure to B-form, to which ethidium binds tightly. Because B-Z junctions have a large unfavorable free energy, there are not many of them. As a consequence, large blocks of DNA are converted simultaneously. Only a small increase in ethidium concentration is needed to tip the balance, and hence the conversion is cooperative.

More recent studies of allostery in DNA have invoked subtle transmission of structural influence, rather than a switch between canonical structural models. Proposed effects include influence of the detailed sequence of a protein binding site (4) and strain induced by DNA bending (5, 6).

Probably the most relevant study to that of Kim et al. is the characterization by Wang et al. (7) of the net repressor binding to a DNA strand containing 256 tandem repeats of the lac operator. In DNA molecules attached to fused silica surfaces or constrained in nanochannels, they found that only about 2.5% of the lac operator sites are occupied, at protein concentrations well above the solution-phase dissociation constant. The results imply strong anticooperative effects in repressor binding with a range of ~150 bp (8), ascribed to strain induced in the DNA. It would be of interest to see the tandem lac operator system analyzed by the kinetic method of Kim et al.

The model proposed by Kim et al. to explain the allosteric effects invokes correlation and anticorrelation between DNA groove widths, depending on distance between sites. The authors show in a molecular dynamics simulation that such correlations exist. Thermal fluctuations lead to variation in major groove width at position zero; when the groove is wider/narrower at position zero, it is likely to be wider/narrower at a position ~10 bp away. When the sites are half a helical turn apart, the correlation is reversed to narrower/wider (see the figure). These correlated motions reflect low-frequency vibrational modes of DNA. In simple terms, widening the groove by binding a protein at position zero widens the groove at +10 bp, enhancing binding of a protein that favors a wider major groove. This can also be viewed as quenching one or more long-range vibrational modes by binding protein A, an entropic cost that does not have to be paid by binding protein B.

It is now clear that the quantitative aspects of gene regulation are influenced quite substantially by the relative placement of regulatory elements. Distance changes of half a helical turn can alter stability and rates by a factor of three or more. This effect provides evolution with fine-tuning capability for adjusting relative kinetics in regulatory networks and makes our comparative interpretation of genome sequences even more challenging.

References

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PHYSICS

Beating Classical Computing Without a Quantum Computer

James D. Franson

Q uantum computers are expected to be able to solve mathematical problems that are not feasible on a classical computer. Although considerable progress has already been made, building a full-scale quantum computer would require controlled interactions between the quantum bits, or qubits, in order to implement the logic operations required for addition, subtraction, and multiplication. On pages 798 and 794 of this issue, Spring et al. (1) and Broome et al. (2), as well as Tillmann et al. (3), have shown that quantum systems—in this case, photons interacting along waveguides—could outperform a classical computer for certain kinds of matrix calculations without the need for logic operations.

This new method for performing calculations is based on the random walk process, as illustrated in the figure. In a classical random walk, one or more particles travel along a channel or path. At each moment in time, there is a probability $P_\text{L}$ that a particle will hop over to the channel to its left and a probability $P_\text{R}$ that it will hop over to the channel to its right. These probabilities may vary as a function of channel number and time. It is assumed that the particles do not interact with each other, so that the total probability of finding a particle in a given output channel is just a sum of the independent probabilities for the individual particles.

A quantum random walk (4) differs from a classical random walk because the particles also have wavelike properties in quantum mechanics. The wavelike properties of a particle are described by its wave function $\Psi(x)$, which depends on its position $x$. Although a particle propagates as a wave, it will only be detected at a single location. The probability of detection at location $x$ is equal to the square of the magnitude of $\Psi(x)$. As illustrated in panel A of the figure, a particle will spread out as a wave while it propagates through the random walk process, but it will only be detected in a single output channel.