posed to isopycnal, eddy mixing led to spurious upwelling from the abyss into the top kilometer of the ocean, inshore of the Gulf Stream, in virtually all North Atlantic models (8). As a consequence, the modeled southward flow of deep water near the western boundary was too weak. This problem appeared even when a numerical ocean model was fitted to observed temperature and salinity distributions with data assimilation (9), a statistically optimal way of combining a model and observations. In the Antarctic Circumpolar Current (a region dominated by eddy activity), circulation changes attributable to the new parameterization result in better placement of regions where surface waters sink into the deep ocean. Although one cannot expect a parameterization to fix all problems associated with large grid size—for instance, narrow currents like the Gulf Stream cannot be accurately represented—the list of improvements outlined by Danabasoglu *et al.* (2) is noteworthy for a single change to a model.

Parameterizations, sometimes disparaged as a necessary evil, are unavoidable for many climate processes. For instance, even a billionfold increase in computational power would not allow global atmospheric models to resolve cloud scales. However, in the case of mesoscale eddies in the ocean, small–grid-size models are becoming available (*10*) that resolve at least some portion of the mesoscale eddies explicitly. Why then is the Danabasoglu *et al.* work so exciting?

One answer is that smaller grids merely shift the problem to smaller scales and aspects of the new parameterization may also be useful for smaller eddies. A second answer is that a good parameterization is often more useful for understanding large-scale processes than is a simulation of small-scale details, as in the example of molecular diffusion. When diagnosing results in an eddy-resolving model, it can be helpful to contrast explicit eddy transports to parameterized estimates. But the most persuasive answer is that a good parameterization enables experimenters to work with models of various levels of complexity and computational requirements. Even when computational advances eventually make eddy-resolving models practical for routine multidecadal climate runs, models with parameterized eddies will remain very much in use. They will be used for examining still longer time scales, for the huge task of assimilating observations into the models, and for understanding the results of more costly models. The task of understanding phenomena once they have been simulated is a thought-intensive task that is facilitated by building a hierarchy of simpler models in which the phenomenon can be more easily examined. For example, McWilliams and Gent (*11*) examine the effect of their parameterization on the Gulf Stream in a model far simpler than the one considered here. The project that led to the results reported in this issue (*2*) thus epitomizes an approach to climate modeling that is complementary to brute force numerical simulation.

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Architectural Transcription Factors

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In textbooks, eukaryotic transcription factors bind to a specific DNA sequence and stimulate transcription by directly interacting with the basal transcriptional machinery. Different parts of the protein usually recognize DNA and activate transcription, such that removal of the activation domain prevents transcriptional stimulation. In spite of the strength of this paradigm, a growing number of DNA binding proteins are being characterized that stimulate transcription from specific genes, yet lack distinct transcriptional activation domains. A large family of these transcription factors function primarily through their control of DNA conformation. These proteins are architectural; they provide a correct framework for the rest of the transcriptional machinery to operate. A dramatic example of this phenomenon is described in this week's issue by Bazett-Jones *et al.* (*1*) in which a dimer of the transcription factor specific for the large ribosomal RNA genes, UBF, is shown to wrap more than 180 base pairs of promoter DNA into a distinct structural unit. UBF appears to position two dispersed regulatory elements into the optimal spatial arrangement for transcriptional enhancement.

UBF represents a family of transcription factors that contains a common DNA binding motif. Although this high mobility group (HMG) domain was originally described within the abundant nonhistone proteins HMG 1 and 2 (*2*), specific HMG domain proteins have now been defined that control lymphoid transcription, mating type switching, and sex determination (*3*). The HMG domain consists of an L-shaped arrangement of three α helices, with two independent DNA binding surfaces on the outside of the L at right angles to each other (*4*). A single HMG domain may cover 20 base pairs at a specific binding site and can potentially distort the DNA molelcule through as much as 130° (*3*). Proteins with a single HMG domain associate with specific DNA sites relatively weakly, probably because of the energy required to direct the distortion of inflexible DNA. However, other proteins often contain several HMG domains, which form more stable complexes with DNA.

The UBF protein contains five HMG domains flanked by an amino-terminal dimerization motif and an acidic carboxyl-terminal tail. Any adjacent pair of HMG domains will bind to DNA; however, the selectivity of binding is conferred by the three domains closest to the amino terminus (*5*, *6*). Each UBF dimer contains 10 HMG domains, a binding site that potentially includes up to 200 base pairs of DNA. This extended region contains a site of DNA distortion every two turns of the double helix as a consequence of the binding of an HMG domain. Because these sites occur on the same face of the helix, DNA is bent into a superhelical turn around the contiguous HMG domains. Deoxyribonuclease I digestion of UBF-DNA complexes reveals a 10– to 11–base pair periodicity of cleavage that is reminiscent of the restricted

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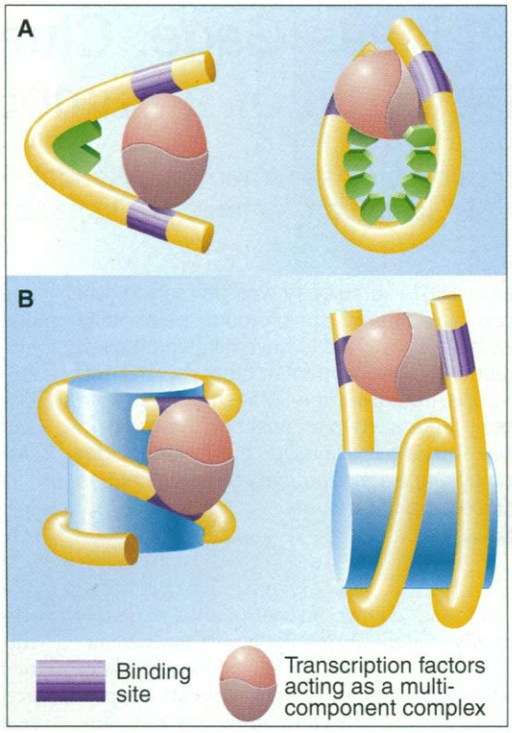
access that this enzyme has to DNA wrapped around the histones within the nucleosome (*7*). This wrapping of DNA around the surface of the UBF dimer is elegantly confirmed by the electron spectroscopic imaging analysis reported by Bazett-Jones *et al.* (*1*). Looping appears to be facilitated not only by DNA deformation directed by the HMG domains but also by protein-protein interactions between the acidic carboxyl-terminal tail and the HMG domains toward the amino terminus of the UBF molecule (*1*).

How might the wrapping of DNA by UBF facilitate the transcription process? Like other eukaryotic genes, transcription by RNA polymerase I requires TBP, which in this system is a component of a sequence-specific transcription factor, SL1. UBF and SL1 appear to bind cooperatively to the ribosomal promoter to form a stable complex that recruits RNA polymerase (*8*). Two binding sites for SL1 are separated by 120 base pairs within the DNA wound around UBF. These sites function cooperatively, are separated by an integral number of helical turns of DNA, and remain exposed to the solution within the UBF-ribosomal promoter complex. Bazett-Jones and colleagues speculate that UBF provides the correct scaffolding for productive interaction between individual SL1 molecules bound at the two recognition sites within each complex (*1*). This prediction remains to be directly tested; however, the architectural role proposed for the UBF transcription factor has been seen with other HMG domain proteins. Single HMG domains are found within the lymphoid enhancer binding factor LEF-1 and the HMG I/Y protein. Both proteins facilitate transcription by direct bending of the DNA helix and contact with other transcriptional regulators (*3*). In all of these cases, the association of the HMG domain with DNA directs the assembly of clusters of transcription factors bound to DNA into precise higher order nucleoprotein complexes.

The spatial arrangement of regulatory elements and transcription factors can also influence function. Experiments with histones reinforce this conclusion. Within each nucleosome, 160 base pairs of DNA are wrapped in two superhelical turns around a core of histones. Like the enhancesome, DNA is on the outside of the nucleosome and remains potentially accessible to transcription factors. Recognition of a particular set of structural features directs a nucleosome to a unique position with respect to DNA sequence, where individual histones have precise contacts with DNA sequences. A particular DNA sequence will face toward the histones or will face toward the solution.



Constraining DNA. The assembly of a multicomponent transcription factor complex depends on the distortion of DNA between dispersed binding sites. This is achieved by (**A**) architectural proteins or by (**B**) the histones.

Specific histone-DNA contacts are a common feature of the regulatory regions of genes (*9*). On the long terminal repeat of the mouse mammary tumor virus, a positioned nucleosome incorporates two binding sites for the glucocorticoid receptor separated by 80 base pairs. These sites are juxtaposed on the surface of the histones (*10*), just as the two SL1 binding sites appear to be placed in the optimal spatial arrangement on the surface of the enhancesome (*1*). This proximity most probably facilitates the disruption of local chromatin structure initiated by the glucocorticoid receptor (*9*). On the *Xenopus* vitellogenin gene, a positioned nucleosome constrains 180 base pairs between an enhancer and a promoter, facilitating communication between these elements and consequently potentiating the transcription process (*11*). Arrays of nucleosomes may also facilitate communication between regulatory elements spanning even greater distances (*12*, *13*). The clusters of regulatory elements at enhancers and promoters are commonly assembled into distinct higher order nucleoprotein complexes. The assembly of such extended structures comprising multiple independent protein-DNA interactions can impart extreme specificity to a biological process (*14*). Moreover, the dependence on architectural proteins to direct the assembly of these structures offers considerable regulatory opportunities.

For example, in phage λ integrative recombination, formation of a synaptic complex requires the precise assembly of large nucleoprotein complexes of both the sequence-specific integrase and three proteins that bend DNA—IHF, Xis, and Fis (*15*). Distortion of DNA is necessary for the tethering of widely separated DNA recognition sites by the integrase protein (*16*). IHF and Fis are encoded by the host bacterium, which regulates their expression. This creates a regulatory link between the recombination process and the physiology of the host. In a similar way, the activity of UBF changes depending on the cellular requirements for ribosomal RNA synthesis. This change depends on the reversible phosphorylation of the carboxyl-terminal tail (*17*), which may modify the folding of the ribosomal promoter and thereby modulate transcription. Precedent for such a mechanism exists in the nucleosome, in which reversible acetylation of the histones alters nucleosome structure (*18*) such that the accessibility of regulatory elements to transcription factors is modulated (*19*).

Transcription factors are not linearly arrayed along the DNA molecule like beads on a string. Rather, DNA is constrained into precise higher order structures directed by architectural proteins such as UBF or by association with the histones. This folding of DNA offers considerable advantage—increased specificity and regulatory flexibility of the transcription process. Presentation and packaging are important parameters to consider for any process, not least the regulation of eukaryotic genes.

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