At present, understanding the glass transition phenomenon is one of the most intriguing puzzles in the physics of condensed matter. It may ultimately influence different fields, in particular biophysics and biochemistry (8). Biological macromolecules like proteins and DNA show many similarities with glasses in the mesoscopic frequency range (9): There are harmonic low-frequency vibrations, similar to the boson peak in glasses, and there is a fast anharmonic motion. Also, some crossover temperatures were identified for biological macromolecules (8–10). It could be that the stabilization of biological objects below some T_c, which may be achieved not only by cooling but also by changes in the chemical composition of the solution (for example, by drying), is very important for their preservation, suppression of their degradation with time, and so on. Thus, the understanding of the glass transition phenomenon in relatively simple systems can bring new ideas in other fields of science and technology.

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Visualizing the Logic Behind RNA Self-Assembly

François Michel and Eric Westhof

Spliceosomes and ribosomes are the complex molecular machines that our cells use to assemble genetic messages and translate them into proteins. RNA, not protein, is the central player in both of these multicomponent complexes. Thus, the three-dimensional structure of RNA is key to our understanding of the chemistry at the heart of two essential processes catalyzed by living organisms: RNA splicing and protein synthesis. It may well also be the key to how the ancestors of life on Earth made a living, because large RNA molecules can carry out many of the catalytic functions previously believed to be specific to proteins. Although we know the three-dimensional structures of thousands of proteins, RNA crystallography has been slow to come of age. But we are now at a turning point; with two papers in this issue (*1*, *2*), it will be the third consecutive year during which the crystal structure of a large RNA molecule has been published. And as is fitting for an Olympics year, the 160-nucleotide RNA, the structure of which is reported by Cate *et al.* (*1*, *2*), shatters a 22-year-old record: transfer RNA, with a mere 76-odd nucleotide monomers, is no longer the largest RNA structure solved at atomic resolution.

This success can be attributed in part to the many theoretical and technical advances in macromolecular crystallography since the days of transfer RNA [for details on the resolution of the structure, see (*3*)]. As is often the case with crystallography, this breakthrough also required considerable preparatory biochemical work. Cate *et al.* have solved the structure of a fragment of the celebrated *Tetrahymena* intron, which 14 years ago was the first RNA molecule found to have catalytic activity. The key step to success was the identification of this fragment as an autonomously folding domain (*4*). In fact, both the hairpinlike overall fold of this molecular domain and the two clamps that maintain its bent shape had been anticipated from the biochemical work. However, a blurred image has now been replaced by a sharp 2.8 Å resolution picture teeming with exciting detail.

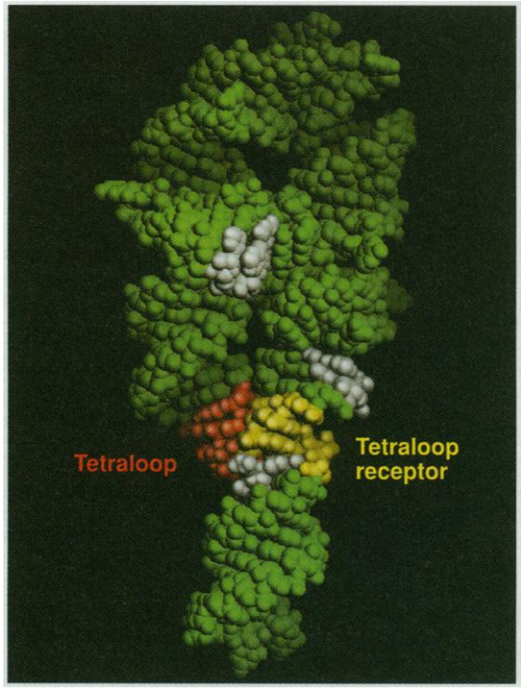

Image of a catalytic RNA. The 160-nucleotide domain of the *Tetrahymena* intron. The compactness of the structure is achieved through side-by-side helix packing and specific tertiary contacts in the shallow grooves of the RNA helices. The newly discovered A-A platform (white) occurs three times. One of the A-A platforms forms part of the 11-nucleotide receptor (yellow and white) for an apical GAAA tetraloop (red). This picture was made with DRAWNA (*10*) with the use of coordinates provided by Cate *et al.* (*1*).

It should come as no surprise that large catalytic RNA molecules, with only four nucleotide building blocks at hand, achieve the compact architectures that seem essential to their function by making intensive use of a small number of preferred motifs and their combinations. One example of these recurrent motifs is constituted by the so-called GNRA loops and their receptors. Four-nucleotide terminal loops with a GNRA sequence (R stands for A or G, and N can be any base) are frequent in large RNA molecules such as the ribosomal RNAs. A few years ago, it was proposed from sequence comparisons and model building (*5*) that the evolutionary success of GNRA loops reflects in part their ability to interact with specific sequence motifs in the shallow (minor) groove of RNA double helices. Since then, the existence of several varieties of GNRA loop–receptor pairs has been demonstrated. In one of these pairs, which was recently visualized as an intermolecular contact in crystals of the "hammerhead" RNA (*6*), the receptor consists essentially of two consecutive base pairs in a helix. But some receptors are larger; the one for GAAA loops, which is of special interest because of its particularly high affinity and remarkable abundance in large catalytic RNAs (*7*), comprises 11 nucleotides in its complete form. Because this particu-

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lar loop-receptor pair constitutes one of the two clamps that maintain the self-folding intron domain in its sharply bent form (see figure), we can now visualize it and understand the basis for the specificity of its receptor half toward its GAAA partner.

Although the existence of the GAAA receptor had previously been recognized, its structure had a nice surprise in store: there is another, smaller recurrent motif embedded within the larger one. This unanticipated constituent of RNA structure, to which Cate *et al.* devote their second paper (*2*), has been named the A-A platform (see figure). It consists of two contiguous unpaired A's that are followed by a strand of bases that form part of a double helix. One of the adenines stacks on the base following it—at the 5′ end of the helix, just as it should—but unexpectedly, the other adenine stacks on the base opposite the first one, at the 3′ end of the other helical strand. Thus, the two A's end up forming a sort of platform that extends the double helical stack by one unit. At the same time, the shallow groove is enlarged, which should facilitate interactions with other molecules. Judging from the fact that there are no less than three A-A platforms in the 160-nucleotide intron domain, this motif must indeed be a remarkably common building block of RNA three-dimensional structure.

In order to reach its compact folded form, the intron domain must also bring different parts of its uniformly charged backbone into close proximity. As is well known from studies of transfer RNA, this problem is solved in part by the use of magnesium ions that coordinate to the oxygens of two or more phosphate groups. As for the rest of the necessary binding energy, it is now seen to be provided by a network of hydrogen bonds between the 2′-OH groups of riboses (which can act both as acceptor and donor) and the acceptor groups of bases in the shallow groove of helices. This extended network, which Cate *et al.* call a ribose zipper, brings the shallow grooves of two neighboring helices next to one another while rejecting the phosphates on the outside [ribose zippers also ensure packing of helices in crystals (*8*)].

Formation of GNRA loops and their receptors, A-A platforms, and ribose zippers does not require rearrangement of the double-stranded helices and classical base pairs that constitute RNA secondary structure. Rather, these tertiary motifs serve to organize in three-dimensional space those helices which, for the most part, are local elements of structure that forms early in the folding process (*9*). This neatly hierarchical view of RNA self-assembly should be particularly appealing. Now that the structural database for RNA is rapidly expanding, the prospects look brighter for eventually predicting RNA three-dimensional structure from its sequence. In the meantime, we will await answers as to how group I introns, the family of molecules to which the *Tetrahymena* intron belongs, perform their catalytic tricks. The crystallographic resolution of an entire group I intron might well constitute the next structural achievement in this field.

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A K^+ Channel Worthy of Attention

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Two new families of K^+ channels have now been cloned (*1*, *2*), one of which is reported in this week's issue. This success continues neurobiology's reductionist approach to formerly philosophical questions: What are learning and perception? How does experience change the brain? In this heady paradigm, all molecules and their regulation must be known. Because ion channels pattern the electrical messages that are the currency of rapid neural signaling, they are high on the list. Almost yearly, members of new families of channels are cloned and catapulted to prominence.

The K^+ channels are structurally the simplest in their superfamily of ion channels. They can be recognized by a short "signature sequence" known to lie in the pore region and to establish K^+-ion selectivity (*3*). Full-length sequences corresponding to about 40 mammalian K^+-channel genes are now known. In the related families of voltage-gated Na^+ and Ca^{2+} channels and the cyclic nucleotide–gated channels, we can include another 30 genes. After the cloning of several families of outwardly (K_v, K_vCa) and inwardly (K_{ir}) rectifying K^+ channels and additional unsuspected relatives (*eag*, *twik*), one might have thought that the action in this field was about over. There have remained, however, at least three types of K^+ channels and a (presumably) related nonselective cation channel. These are the small-conductance Ca^{2+}-activated K^+ channels (SK), the Na^+-activated K^+ channels K(Na), muscarinically regulated K^+ channels (I_M), and hyperpolarization-activated cation channels (I_h). Köhler *et al.* (*1*) now report the cloning of three members of the SK Ca^{2+}-activated K^+ channel family, and elsewhere Stansfeld *et al.* (*2*) report a good candidate (within the *eag* family) for I_M channels, a bumper crop for 1996.

Although SK channels are found in endocrine cells such as chromaffin cells and gonadotropes, they are principally known for their role in central neurons (*4*). In hippocampal pyramidal cells, for example, they respond to the Ca^{2+} ions brought into the cell interior by bursts of action potential firing. Being K^+ channels, they then cause the cell to hyperpolarize, which dramatically slows the action potential firing rate. Such "spike-frequency adaptation" caused by SK channel opening makes these neurons respond primarily to the beginning of an incoming stimulus and then adapt. But SK channels and spike-frequency adaptation can be shut down by a variety of classical neurotransmitters (*5*). Thus, spurts of norepinephrine, delivered when the brain commands arousal and attention, increase the cytoplasmic cyclic adenosine monophosphate and cause phosphorylation of some component of the SK channel. When its SK channels are phosphorylated, the neuron can follow inputs more faithfully without adaptation (*5*, *6*)—a molecular correlate of paying attention. Köhler *et al.* show that there are several SK channels that differ in their sensitivity to the bee venom peptide apamin. Although they have the K^+-channel signature sequence and a typical K_v-channel hydropathy plot, the transmembrane segment controlling voltage sensitivity has a low number of charges, and the overall sequence puts them in a family of their own. As hoped for in a channel that regulates attention, there are numerous potential sites of phosphorylation. This finding is a significant step in the reductionist approach to cerebration.

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