three to four molecular layers and report that at certain film thicknesses the density distribution is bimodal.

The authors argue that their results indicate the existence of unexpectedly large density variations, manifested by long-lived solid-liquid-gas phase transitions within the confined film and a highly statistical force distance profile. The study highlights the difficulty of distinguishing between a thermodynamic phase and fluctuations about the equilibrium state in small systems. Indeed, the concept of a thermodynamic phase or state, where the time-averaged properties of all the molecules should be the same everywhere, does not apply to molecularly thin films, whose molecules interact with the confining surfaces in an anisotropic manner, and, consequently, neither does the concept of a phase transition.

Heuberger *et al.* do not compare their results with any quantitative theory or model. It would be interesting to compare the results for the forces and structure with theoretical predictions based on grand canonical Monte Carlo or molecular dynamics simulations of cyclohexane between two molecularly smooth mica surfaces. Experimental results at different lateral locations of the film would provide information about in-plane correlations and fluctuations. Meanwhile, the results support some current thinking on the effects of confinement on the properties of matter (whether liquid or solid) but also raise new and unexpected questions.

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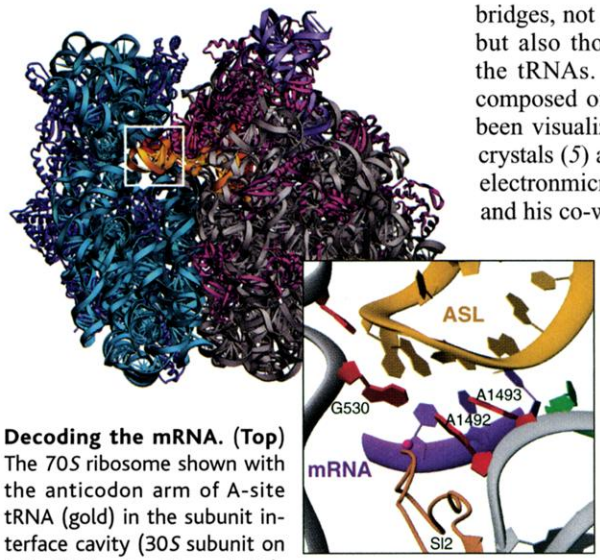
PERSPECTIVES: RIBOSOME STRUCTURE

The Ribosome in Action

Albert E. Dahlberg

Proteins, one of the basic building blocks of cells, are synthesized by linking amino acids together in macromolecular factories called ribosomes. The 20,000 ribosomes in a bacterial cell translate messenger RNA (mRNA) with remarkable speed and accuracy, and two articles in this issue provide fascinating new insights into how this is achieved. These publications come at a time of rapid progress in structural studies of the ribosome. Within the past year both the 30*S* and 50*S* subunit structures have been determined at atomic resolution (*1–3*); the large subunit (50*S*) and the small subunit (30*S*) comprise the whole ribosome (70*S*). Unlike previous reports, however, Noller, Ramakrishnan, and their co-workers have now more closely approximated the functional state of the ribosome by including transfer RNA (tRNA) and mRNA in their crystals, thus providing views of the ribosome in action.



Decoding the mRNA. (Top) The 70*S* ribosome shown with the anticodon arm of A-site tRNA (gold) in the subunit interface cavity (30*S* subunit on left, 50*S* subunit on right). **(Bottom)** The mRNA codon (purple) and cognate tRNA (gold) shown in the A site of the 30*S* subunit with A1492 and A1493 (red) sensing Watson-Crick pairing in the first two base pairs of the codon-anticodon double helix. G530 (red) and S12 (brown) both contact A1492.

The first article (on page 883 of this issue) represents an enormous achievement both in effort and content as Noller and his colleagues report on the complete structure of the *Thermus thermophilus* 70*S* ribosome at 5.5 Å resolution in the presence of mRNA and cognate tRNAs bound in the A (aminoacyl), P (peptidyl), and E (exit) sites (*4*). The 70*S* structure represents more than the sum of its parts. The careful analysis and interpretation of the numerous intersubunit bridges that mediate the functional interactions between the two subunits and the three tRNAs—built upon a wealth of biochemical, genetic, and structural data (much of it from Noller's own lab) accumulated over many decades—is intensely illuminating.

All three ribosome binding sites for tRNA (A, P, and E) are in universally conserved regions of the ribosome structure. The significant distance the tRNA must move (about 20 Å) during translocation from the A to the P site underscores the active nature of translation. Additionally, we can see precisely how these highly conserved nucleotides in ribosomal RNA (rRNA) and tRNA fit together in the peptidyl transferase and decoding sites.

Arguably, the observation with the greatest implication for understanding how the amino acid carriers (the tRNAs) are ratcheted through the center of the ribosome is the delineation of the numerous bridges, not only between the two subunits but also those between the subunits and the tRNAs. These bridging interactions, composed of both RNA and protein, have been visualized at lower resolution in 70*S* crystals (*5*) and, originally, by elegant cryoelectronmicroscopy studies (*6*), but Noller and his co-workers now define them at the molecular scale. That these bridges involve the translocating tRNAs marks these regions as dynamic, and thus it is no surprise that three bridges are located in regions of the large subunit that were disordered in the 50*S* crystal structure (*1*). In addition to orienting the subunits and facilitating movement, the bridges also may function in signaling between the subunits, coordinating the multiple steps in the cycle of peptide elongation. No doubt, many groups will now seize on this information to test their models.

An equally exciting report comes from the Ramakrishnan lab (on page 897 of this issue), describing in atomic detail the crystal structure of the *T. thermophilus* 30*S* subunit complexed with fragments of the cognate A-site tRNA and mRNA (*7*). Their structure shows how the ribosome checks for proper codon-anticodon interaction in order to achieve fidelity of translation. Viewing figure 4 of their manuscript (see the figure, lower panel) is like uncovering an ancient drawing, depicting in exquisite detail a universal mechanism

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for one of the original steps in the evolution of life. Earlier biochemical and genetic data provided clues about critical components of the active site, particularly the universally conserved rRNA residues A1492 and A1493 (*8*, *9*). However, it is the work of the Ramakrishnan group that identifies the precise contacts in decoding: Nucleotides A1492 and A1493 flip out to probe the minor groove of the codon-anticodon double helix, checking for Watson-Crick pairing of the first two base pairs. More flexibility is allowed the third codon-anticodon base pair, consistent with Crick's wobble hypothesis (*10*) that less stringent base pairing at this position accounts for how a single tRNA species can bind to more than one codon. Two additional participants include ribosomal protein S12, which contacts A1492, and G530, which flips from the *syn* to *anti* conformation to contact both the codon-anticodon double helix and A1492. Both S12 and the 530 loop have a long history in translational fidelity, and now we know why.

Once the crystal structure of the decoding region was resolved, the authors could address the question of how antibiotics such as paromomycin induce misreading of the genetic code. Residues A1492 and A1493 flip in a fashion similar to that occurring during decoding, although G530 is unmoved. Apparently, by paying part of the energetic cost of flipping the A residues, paromomycin facilitates binding of near-cognate tRNAs. This result must be particularly gratifying to pioneers such as Julian Davies and Walter Gilbert who, in 1964 along with the late Luigi Gorini (*11*), proposed that decoding occurred at an active site that distinguished between cognate and near-cognate tRNAs, and suggested that decoding could be perturbed by antibiotics such as paromomycin.

Both the Noller and Ramakrishnan manuscripts are landmark contributions to the understanding of ribosome structure and function. Francis Crick's Adaptor molecule (tRNA), first proposed by him to the RNA Tie Club in 1955 (*12*), has assumed its rightful place in the ribosome—bridges, wobble, and all. Our appetites have been whetted, and we now look forward to seeing crystal structures representative of different conformations of the dynamic ribosome.

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PERSPECTIVES: INTERSTELLAR CHEMISTRY

Tunneling Reactions in Interstellar Ices

Kenzo Hiraoka, Tetsuya Sato, Toshikazu Takayama

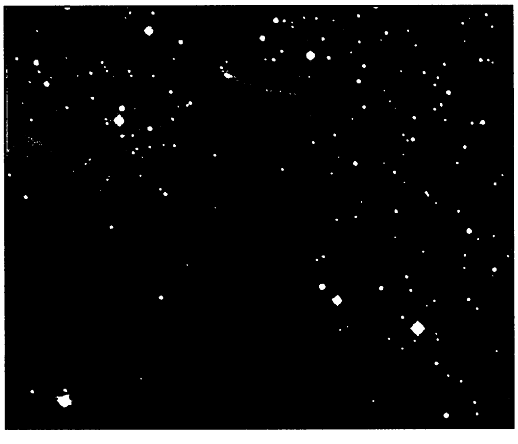
Light essentially cannot penetrate dense interstellar clouds, and temperature inside dark clouds is kept at about 10 K. About 120 interstellar molecules have been observed by millimeter and submillimeter spectroscopy in such dark clouds. It is becoming increasingly clear that gas-phase ion-molecule reactions—the dominant processes in diffuse interstellar clouds—are less important in dense clouds. Instead, chemical reactions on cosmic dust grains play an important role (*1*). Interstellar ices, which grow on solid dust particles in cold, dense clouds, also become the substrates for various chemical reactions. Recently, the Infrared Space Observatory (ISO) has provided much information about interstellar and cometary ices (*2*).

Unfortunately, direct observations of the solid-phase chemistry of dense clouds are difficult to come by. In the absence of direct evidence, we have to resort to laboratory studies. A wealth of data has been gathered on gas-phase ion-molecule reactions, but investigations on solid-phase reactions of various molecules remain scarce (*3*), although there have been experimental studies of molecular hydrogen formation on the surface of cosmic dust analogs (*4*).

Because of their high mobility in solids, hydrogen atoms are believed to play a particularly important role in the chemical evolution of dense clouds. Because of their wave nature (*5*) and their low atomic weight, hydrogen atoms can "tunnel" through seemingly insurmountable barriers. In a solid, a hydrogen atom can be visualized as a quantum liquid that creeps quickly from one site to another and participates in tunneling reactions wherever it encounters a suitable reactant.

Ammonia and formaldehyde are implicated in the origin of life. They are examples of molecules whose interstellar abundances are difficult to explain by gas-phase reactions alone (*6*). It has been suggested (*7*) that the substantial abundance of formaldehyde and methanol in the diffuse envelopes of dark clouds can be explained by consecutive hydrogenation reactions of CO molecules trapped on dust grains with hydrogen atoms:

$$CO \rightarrow HCO \rightarrow H_2CO \rightarrow H_2COH \rightarrow CH_3OH$$



The horsehead nebula. This well-known astronomical feature is part of a much larger dust cloud. It looks dark because of absorption of light by the dust. Starlight illuminates the nebula's background, causing hydrogen there to fluoresce. Thus, the "head" is silhouetted.

CREDIT: NASA

In a recent laboratory simulation of cosmic grain chemistry at cryogenic temperatures (*8*), formaldehyde was formed when a solid CO film was deposited on a cold silicon substrate and then reacted with hydrogen atoms at 10 K. The rather high energy barrier of 4.1 kcal/mol (*9*) for the reaction H + CO → HCO suggests that the reaction proceeds through a tunneling process. No CH_3OH could be detected, indicating that the addition reaction of H atoms with H_2CO to form CH_3OH is practically forbidden (*10*). These results suggest that interstellar ices may indeed play a role in the formation of interstellar saturated molecules.

The formation of saturated hydrocarbons in the interstellar medi-

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