PERSPECTIVES: SINGLE MOLECULES

Molecular Entanglements

Michel Orrit

The relentless miniaturization of electronic circuits is driven by the increase at smaller sizes of both speed and efficiency of information-processing devices. Downsizing is, however, limited not only by molecular scales but also by the quantum behavior of atoms and electrons, which thwarts the operation principles of classical circuits. Quantum mechanics may thus seem detrimental, but it may also offer unexpected new routes for information processing, much as lasers opened a wealth of applications outside the reach of classical light sources.

A unique feature of quantum mechanics is entanglement—the possibility of preparing coherent mixtures of quantum states. Entangled states involve strong phase correlations between two subsystems. Although these systems can be physically separated, they can no longer be considered as independent, even when they are very far from one another.

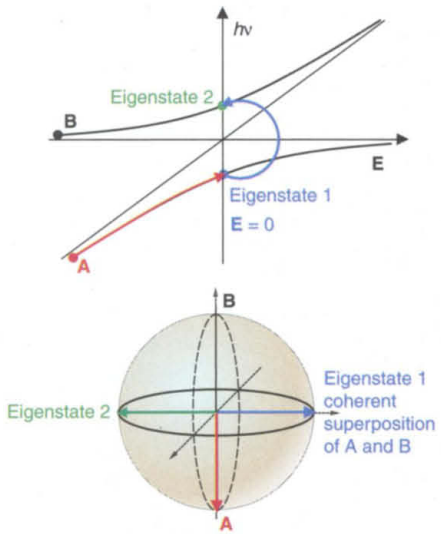
A simple example of an entangled state is the horizontally polarized state of a spin—representing the simplest quantum bit of information, or qubit—in a vertical magnetic field. The two vertically polarized states, parallel or antiparallel to the magnetic field, are unchanging "eigenstates." In contrast, the horizontally polarized states are coherent superpositions of the two eigenstates. They are thus entangled states that evolve with time.

When they exist in physically separated systems, such superpositions offer intriguing opportunities. Information encoded in quantum states may be transmitted with absolute safety against eavesdropping (*1*), processed in massively parallel ways by a quantum computer (*2*), or used for quantum teleportation—the reproduction of an object at a different place in space and time—albeit at the cost of the original's loss (*3*).

Because all systems obey quantum mechanics at the atomic level, quantum hardware could be made out of almost any type of particle, in the gas phase (for example, with isolated trapped ions/atoms or condensates) or in the condensed phase (exploiting, for example, nuclear spins in molecules or permanent currents in superconducting structures). The fascinating prospect opened by Hettich *et al.* on page 385 of this issue (*4*) is the use of single molecules as supports for qubits.

Since the early 1990s, single molecules have been investigated in condensed matter by purely optical means (*5*). If an exciting laser is focused into a dilute solution of absorbing molecules, and if there is, on average, less than one molecule in the focal spot, the fluorescence signal shows discrete spots in an image or in a spectrum, revealing single molecules. At low temperatures, the sharp line of a single molecule can be used in quantum optical experiments. For example, manipulation of its quantum state may cause a molecule to emit single photons on command (*6*), turning it into an appealing light source for quantum cryptography (*7*).

In ordinary single-molecule experiments, the probability of finding two single molecules close enough to interact is very low. But Hettich *et al.* have found such a pair. The main interaction mechanism between the molecules is the resonant dipole-dipole interaction, which is responsible for the delocalization of excitations in molecular crystals, aggregates, and complexes (*8*). This interaction would manifest itself via characteristic level shifts upon tuning one molecular excitation frequency with respect to the other. Instead, the authors have exploited a more exotic feature of the interaction: the simultaneous two-photon excitation of the two molecules in the pair. This nonlinear optical effect, predicted theoretically (*9*) but not clearly observed in earlier optical studies, can only arise in an interacting pair.



Getting entangled. (**Top**) Energy levels of a pair of uncoupled (straight lines) or coupled (curves) molecules, for only one excitation in the pair. The energies $h\nu$ are plotted as functions of an applied electric field **E**, which shifts one of the levels with respect to the other. Starting from an excitation on molecule A at high field (red arrow), one obtains the entangled eigenstate by adiabatically decreasing the electric field. By suddenly applying a short field pulse, one can obtain other superpositions, for example (blue arrow) the other eigenstate. (**Bottom**) The same processes can also be visualized on the Bloch sphere of a spin. The adiabatic sweeping of the field brings the state from the pure $|A\rangle$ state to an entangled state, which can then be modified by an electric field pulse.

Consider the following thought experiment with two interacting single molecules, A and B (see the figure). Assume that we can tune the difference in their resonance frequencies by means of a control parameter such as a quasi-static and inhomogeneous electric field **E**, and that the molecules are resonant for $\mathbf{E} = 0$. Starting with a high field, with only molecule A excited and molecule B in its ground state, we slowly decrease the field to zero. The state of the system adiabatically follows the field, ending up for $\mathbf{E} = 0$ in a coherent superposition of excitations on A and B—one of the eigenstates of the system.

If we now suddenly reapply the electric field, this state evolves, exploring all relative phases between the two eigenstates (see the figure). We have therefore "entangled" molecules A and B; that is, we have prepared a coherent superposition of their excitations. Further interactions with other molecules (that is, with other qubits) can lead to further entanglements, paving the way for quantum-state engineering, logic gates, and computing.

The attractive feature of such a scheme is that, although the qubits are physically carried by single molecules, the outcome of a quantum operation can be read optically. In comparison to gas-phase systems, the molecular environment is stable and the qubits can be easily manipulated with local probes, applied fields, or light.

Before applications of this idea can be envisioned, however, many obstacles must be overcome. The lifetime of coherent superpositions (the decoherence time) in the above thought experiment would be limited to a few nanoseconds by the lifetime of the molecular excited states. This is much too short to practically prepare and manipulate entangled states.

If the qubits were carried by single nuclear spins, whose optical detection was demonstrated several years ago (*10*), decoherence times could exceed milliseconds. This would be slow enough for manipulation, as recent experiments on large en-

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sembles of nuclear spins have demonstrated (*11*). The operations on qubits could be performed with applied magnetic fields while the measurement would be done optically. The structure of the interacting system would have to be carefully designed to control the interactions between qubits.

The molecules in the experiments of Hettich *et al.* (*4*) were distributed at random, but nanomanipulation has been progressing so quickly that such a control might very soon become real. Combining nanoscale structures with single molecules to process quantum information would then open a wide realm of fascinating opportunities.

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PERSPECTIVES: RNA EVENTS

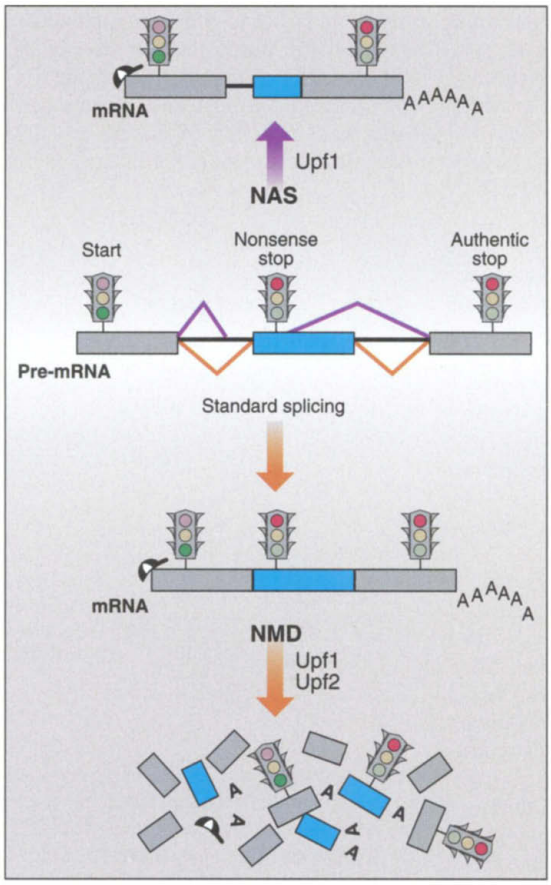
No End to Nonsense

Melissa J. Moore

Two of the hottest topics in eukaryotic gene expression research involve absolute nonsense: nonsense-mediated mRNA decay (NMD) and nonsense-associated altered splicing (NAS). "Nonsense" in this case refers to a type of mutation in mRNA transcripts that causes the protein synthesis machinery to terminate prematurely their translation into proteins. Nonsense mutations were originally thought to affect only the length, and therefore the function, of the encoded protein. However, it is now apparent that they can dramatically decrease the half-lives of mutant mRNAs as well as alter the pattern of precursor mRNA (pre-mRNA) splicing (see the figure). The molecular basis of the latter phenomenon (NAS) is particularly mysterious, because it is generally accepted that nonsense mutations cannot be recognized as nonsense until after the splicing process is complete. Two papers, one by Mendell *et al.* on page 419 of this issue (*1*) and another by Wilkinson and co-workers in a recent issue of *Molecular Cell* (*2*), now begin to unravel this mystery by showing that NMD and one type of NAS (reading frame–dependent NAS) are functionally distinct processes that rely on different, but overlapping, sets of proteins.

NMD is the quality control system by which mRNAs containing premature stop (nonsense) codons are selectively eliminated by eukaryotic cells. It is thought that by removing these defective mRNAs, NMD protects cells from potential damage due to inappropriately truncated proteins. To date, a number of proteins required for NMD have been identified in a variety of organisms, and analysis of how they regulate this process is well under way (*3*, *4*). NAS, on the other hand, has proven much more controversial (*5*–*7*). Although numerous examples of NAS have been described, most of these can be readily explained by conventional mechanisms involving chance disruption of RNA sequences called exonic splicing enhancers (ESEs). ESEs are target sites for proteins that help to define pre-mRNA splice sites; their disruption by almost any type of mutation can cause altered splicing. Therefore, the promotion of alternate splicing by most nonsense mutations is simply due to the destruction of a key recognition element for the splicing machinery and has nothing to do with the ability of nonsense mutations to be recognized subsequently as stop signals during protein synthesis. Recently, however, Wilkinson and co-workers convincingly demonstrated that NAS of certain T cell receptor gene transcripts does require that the mutations act as protein synthesis stop signals (*2*, *8*). They showed that certain nonsense mutations only mediated alternate splicing if they were "in frame" with a start signal, meaning that they had to be detected by the protein translation machinery. In addition to the T cell receptor case, available evidence suggests that nonsense mutations can alter splicing in a reading frame–dependent manner in other systems as well (*9*–*12*).

One aspect of T cell receptor NAS that is particularly difficult to reconcile with our current understanding of eukaryotic gene expression is that this type of NAS depends on the mRNA reading frame, something that is not established until after splicing is complete. A pressing challenge, therefore, is to understand how the apparent downstream process of reading-frame recognition can feed back to alter the apparent upstream process of pre-mRNA splicing. Given that reading frame–dependent NAS is triggered by the same signals that trigger NMD, one possibility is that NAS is an indirect consequence of NMD. If so, then both phenomena should be dependent on the same subcellular machinery. What both groups now show is that this is not what actual-



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Circumventing stop signals. Alternate fates of mRNA transcripts containing nonsense mutations. **(Top)** Shown is a pre-mRNA harboring a nonsense stop signal within an internal exon (colored box). In the majority of such molecules, introns (lines) are removed at the usual sites, resulting in retention of the nonsense mutation in the mature mRNA. Such aberrant mRNAs are then subject to degradation by NMD. **(Bottom)** In some cases, however, a nonsense mutation can activate an alternate splicing pathway (NAS), yielding a stable mRNA lacking the mutation. These two effects of nonsense mutations are dependent on different protein factors. Whereas NMD requires both Upf1 and Upf2, reading frame–dependent NAS is Upf2-independent.

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