

considered. For example, when a highly purified population of stem cells responds in vitro to cytokines, the resultant single-cell derived clones differ in size, configuration, and cell type (11). Such studies remind us of both the multipotentiality and the heterogeneity of the source cells. Thus, population studies may be more important than single (clonal) cell studies in defining the plasticity of stem cells.

Cell fusion has been the biggest red herring of all. Reports showed that embryonic stem cells could fuse with neural stem cells or whole marrow cells, at a low rate. Lagasse *et al.* (1) demonstrated replacement of up to 50% of liver cells due to fusion of donor bone marrow cells with host hepatocytes. In this case, fusion was the mechanism underlying therapeutically effective replacement of diseased liver cells. Fusion, then, can be a good thing, under some circumstances.

As with “robustness,” the phenomenon of fusion is model dependent. Some reports

of bone marrow cell plasticity show fusion and others indicate plasticity without fusion. Purified umbilical cord blood cells convert to fetal liver cells in sheep, without fusion (12). Studies by Harris *et al.* (13) with a Cre-lox transgenic approach showed that lung and skin conversions were not due to fusion. Thus, fusion may occur in some but not all models and can produce therapeutically beneficial results.

Should our ignorance of the mechanism of incorporation stop clinical trials from going forward? We think not. Many thousands of individuals have been cured by allogeneic transplantation for acute leukemia; yet our views on the underlying mechanisms continue to change. Recently, bone marrow cells have been used to treat acute myocardial infarction in nine clinical trials (involving more than 100 patients) (14). Approaches differed in each study, but various aspects of cardiac function were improved and there was little acute toxicity.

In these studies, the mechanisms are unknown and long-term results are pending.

Despite the controversy, our knowledge of stem cells continues to advance. Studies on both basic mechanisms of plasticity and clinical utility should proceed in parallel. Let the good work go forward.

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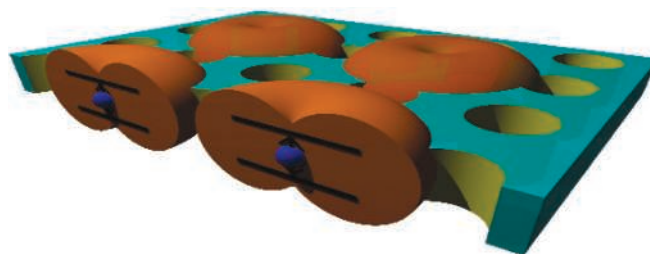
PHYSICS

Control at the Quantum Level

Thomas F. Krauss

The ability to control interactions between light and matter has led to many exciting technological developments, most notably the laser, which has enabled the information technology revolution as we know it. On page 1158 of this issue, Badolato *et al.* (1) demonstrate such control at the quantum level between a quantum dot (a nanometer-scale emitter of electromagnetic radiation) and a nanometer-scale optical resonator (nanocavity) in a photonic crystal. The approach allows multiple quantum interactions (see the figure) to be combined. The work is an important step toward the realization of solid-state quantum computers.

There have been several recent demonstrations of strong light-matter interactions between quantum dots and optical nanocavities (2, 3), but these studies relied on chance: Researchers fabricated large numbers of cavities and then searched for those that happened to incorporate quantum dots that emitted light at the right wavelength. Badolato *et al.* (1) add an unprecedented element of design and control that is essential for taking these concepts further toward the fabrication



A multiple coupled quantum system. To realize a coupled quantum system—which may, for example, form a section of a quantum computer—one must control the relevant optical and electronic resonances accurately. Here, multiple strongly coupled nanocavity-quantum dot systems are shown to interact. Each individual system is represented by the coupling between the oscillating electron states (horizontal lines linked by arrows) and the cavity resonance (orange torus).

of practical devices such as single-photon emitters and quantum computers.

Strong interactions between an emitter and a cavity are at the heart of quantum information processing, for example, in single-photon emission, optical logic, and quantum computing. Groundbreaking experiments with quantum systems have been performed, for example, with atoms suspended in a free-space cavity between two mirrors (4). However, realizing these experiments in the solid state is crucial for practical applications and is similar to the step change caused by the replacement of vacuum tubes with solid-state transistors.

It is thus not surprising that the recent all-solid-state demonstration of strong coupling between a single “atom-like” quantum dot

emitter and the optical nanocavity is embedded in (2, 3) caused much excitement. How does this approach work?

An excited emitter (such as a quantum dot) will emit a photon after a characteristic spontaneous-emission lifetime. If the emitter is in a suitable environment (such as a nanocavity that is resonant at the emitter’s wavelength), the emission will be enhanced. This “Purcell effect” reduces the spontaneous-emission lifetime, making the emission process more efficient. It is governed by the “ Q/V factor” of the system: The closer together the emitter and the cavity are in space (small volume V) and frequency (high quality factor Q), the stronger the interaction.

This is where the photonic crystal environment comes in. Photonic crystals are periodic dielectric structures (represented by the array of holes in the figure) through which light of a certain wavelength range cannot propagate; this light is therefore reflected. The high reflectivity allows one to construct cavities with extremely high Q (5). Furthermore, these high- Q cavities can be made very small, on the length scale of an optical wavelength in the material, which is several times 100 nm (1 nm = 10^{-9} m). Photonic crystals offer the highest Q/V factor of any cavity type known to date.

In the Purcell regime, the system is weakly coupled, that is, the properties of the emitter are modified but not fundamentally altered by the presence of the cavity. As the Q/V factor increases, the system enters a new regime, where the emitter and the cavity are so strongly coupled that they

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exchange energy and act like a coupled quantum system. In this strong-coupling regime, the system becomes sensitive to individual photons, that is, the cavity responds differently to an incoming photon depending on whether it is already occupied by a photon or not. This sensitivity opens up another new realm for photon-photon interactions, such as single-photon logic and single-photon emission. For comparison, photon-photon interactions in a conventional nonlinear optical device require $\sim 10^6$ or more photons.

However, because the cavity Q factors are so high (meaning very narrow spectral linewidths) and volumes so small, the strong coupling is difficult to control. To overcome this problem, most researchers fabricate so many cavities that the chance of finding one that contains a quantum dot of suitable resonance in the right place is high. Putting the dot in the right place is a rather important aspect that is easily overlooked; even though

the cavity is small, the light is not evenly distributed in it, and for maximum effect, the dot must sit at a peak of the cavity mode. Badolato *et al.* achieve this through the use of “marker dots” that accurately indicate the dot position; with the use of alignment markers, the cavity can then be placed lithographically at the right position (1).

If several such strongly coupled systems can be brought into close proximity, they can interact and “entangle” their states in a quantum system, which forms the basis for quantum computing. Here lies the true strength of the deterministic approach: It is difficult enough in the “chance” approach to find a single cavity and dot in resonance, but the chances of finding two or more next to one another is vanishingly small; controlling the resonances is the only viable option.

Badolato *et al.* have not actually demonstrated strong coupling in their cavities, but they are very close. Much stronger interactions could easily be achieved through the

use of cavity designs with higher Q (5). The strength of their result is therefore that two major mechanisms for controlling the coupling between quantum dot and cavity have been successfully demonstrated: the placement of the dot with respect to the cavity mode, and the tuning of the cavity resonance.

For the dream of quantum computers based on optical cavities (see the figure) to become reality, further control needs to be exercised, for example, in the creation of quantum dots with deterministic emission wavelength. The work by Badolato *et al.* is nonetheless a major step forward in exercising control over quantum systems in the solid state.

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MOLECULAR BIOLOGY

A Renewed Focus on Transfer RNA

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Translation of the genetic code occurs through base-pairing interactions between the codon on messenger RNA and the anticodon on transfer RNA (tRNA) that are mediated by the ribosome, the molecular machine that catalyzes protein synthesis. Even before the complete elucidation of the genetic code, it was clear that the accuracy of protein synthesis is too high to be accounted for by codon-anticodon pairing alone (1). The discovery that it could be affected by antibiotics and ribosomal mutations suggested that the ribosome has a decoding site that inspects codon-anticodon interactions (2). Hence, the discovery of a mutant tryptophanyl tRNA (“Hirsh suppressor”) that could suppress the termination of protein synthesis was a puzzle (3). A G24A mutation on this tRNA, although quite distant from the anticodon at positions 34 to 36 (see the figure), nevertheless conferred on the mutant tRNA the ability to pair with the UGA stop codon in addition to the wild-type UGG codon. How does this tRNA recognize UGA and evade proofreading by the ribosome? Now, decades after the discovery of the Hirsh suppressor, its secrets are being

revealed. On page 1178 in this issue, Cochella and Green (4) show how the kinetic properties of the mutant tRNA allow it to decode stop codons.

Aminoacyl-tRNA is initially brought into the ribosome as a complex with elongation factor Tu (EF-Tu) and guanosine 5'-triphosphate (GTP) (see the figure). Upon GTP hydrolysis, EF-Tu is released. In a view of decoding termed kinetic proofreading (5, 6), incorrect tRNAs can dissociate from the ribosome either before or after EF-Tu release, with the overall selectivity being as much as the product of both selection steps. Experimental evidence for proofreading came when it was shown that near-cognate tRNAs (which contain a single subtle mismatch between codon and anticodon) require more GTPs hydrolyzed per amino acid incorporated than do cognate tRNAs (7, 8). In this view, the ribosome merely provided a passive platform for tRNA selection, with mutations and antibiotics altering accuracy by affecting the rate of GTP hydrolysis by EF-Tu. In principle, mutations distant from the codon-anticodon pairing could also affect the rate of GTP hydrolysis.

More recent work points to a direct role for the ribosome and its associated players in tRNA selection. Careful studies on the

stability of RNA helices show that the free-energy differences from a base-pairing mismatch can account for a factor of 5 to 10 in selectivity (9) rather than the factor of 100 assumed previously. This is too low to account for the accuracy of protein synthesis even with proofreading. Pre-steady-state kinetic experiments show that the forward rates of GTPase (guanosine triphosphatase) activation (the rate-limiting step in GTP hydrolysis) and accommodation (movement of tRNA into the peptidyl transferase center) are dramatically higher for cognate tRNA than for near-cognate tRNA (10, 11). Thus, cognate tRNA is likely more efficient at inducing a productive ribosome conformation, consistent with results from nuclear magnetic resonance studies on a portion of the decoding site (12). Crystallographic studies on the 30S ribosomal subunit showed that, in the productive conformation, the ribosome directly monitors the geometry of base pairing at the minor groove of the first two positions (but interestingly not at the wobble position) between the codon and anticodon (13).

Several other key pieces of evidence helped to clarify things further. Kinetic studies showed that intact tRNA is required to transmit the signal from codon recognition in the 30S subunit to the GTPase center in the 50S subunit (14). Cryoelectron microscopy demonstrated that in the ribosome, the tRNA in complex with EF-Tu has a bend in the anticodon stem-loop: The region around the anticodon loop is in nearly the accommodated orientation, while the bend allows the rest of the tRNA to remain in the orientation presented by EF-Tu (15, 16). Crystal structures revealed

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