opportunities for exploitation in the development of novel heparin-based therapeutics (*10*–*12*). Synthetic chemistry and chemoenzymatic approaches represent interrelated pathways that could deliver such compounds for clinical evaluation. Modular approaches to the full chemical synthesis of small libraries of tetra- and hexasaccharides have been described (*13*–*15*), and increasingly larger individual target structures are being synthesized (*16*, *17*).

The key questions now for LMW heparin production as anticoagulants are whether the new chemoenzymatic processes can be scaled up to meet industrial production levels (an estimated 10 to 20 tonnes per year worldwide) and can compete on cost with the natural product route. Although the chemoenzymatic approach can in principle be extended to make larger heparins and more structurally diversified "heparan sulfate–type" compounds, the heparin saccharides generated by Xu *et al.* took advantage of natural specificities of some of the enzymes, which imposes some limitations on product range. Careful design of the sequence of modifications, and perhaps additional chemical control strategies, will likely be needed to permit generation of some of the structural variants that may be required. Nevertheless, the prospects for fully defined heparin and related compounds seem very bright, with huge potential to secure safe production routes for replacement of animal-derived heparins, as well as providing a novel class of compounds with important therapeutic applications.

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PHYSICS

Plasmonics Goes Quantum

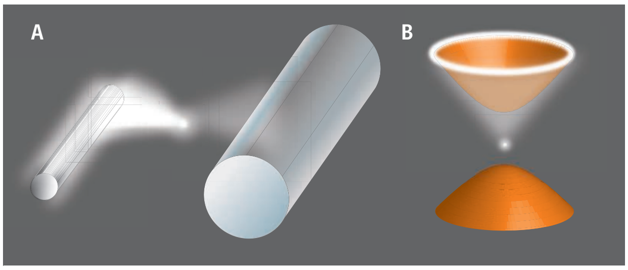
A combined plasmonics and metamaterials approach may allow light-matter interaction to be controlled at the single-photon level.

Zubin Jacob[1] and Vladimir M. Shalaev[2]

Light in a silica fiber and electrons in silicon are the backbones of current communication and computation systems. A seamless interface between the two can guarantee the use of light to overcome issues related to the resistive time delay of electrons within integrated circuits. However, a fundamental incompatibility arises between photonics and nanometer-scale electronics because light breaks free when confined to sizes below its wavelength. Instead, coupling light to the free electrons of metals can lead to a quasiparticle called a plasmon, with nanometer-scale mode volumes. The resulting possibility of efficiently interfacing photonics and nanoelectronics has been the impetus for the field of plasmonics (*1*). Recent work has shown that these nanoscale plasmons, which can transmit classical information with unprecedented bandwidth, are also naturally conducive to quantum information processing (*2*).

Tiny light emitters like quantum dots and molecules interact exceptionally well with low–mode-volume plasmons, but not with the photonic modes of a conventional optical fiber (*2*). Although a host of nanoscale metallic particles can exhibit localized plasmonic behavior at a particular resonant excitation frequency, the nanowire supports a single propagating plasmon mode for a wide range of frequencies. It is similar to a single-mode optical fiber, but with the advantage that the mode is confined to the nanoscale dimensions of the wire. This leads to strong coupling with isolated broadband emitters at room temperature. An excited quantum dot near a metallic nanowire will almost always spontaneously emit a single photon into this fundamental plasmonic mode. Such robustness is central to reliable technological exploitation of quantum-mechanical rules that are otherwise governed by probabilities (see the figure, panel A).

The quantum properties of this single plasmonic oscillation were demonstrated with antibunching statistics (*2*) as well as wave-particle duality (*3*). This is not surprising because plasmons have been shown to preserve quantum information in the light used to generate them. Experiments have conclusively proven that conventional plasmons on a nanohole array or a gold metal strip can show exotic quantum properties such as entanglement (*4*) and squeezing (*5*).



Make it quantum. Building blocks of an integrated nanoscale quantum information system. **(A)** The nanowire supports a single plasmonic oscillation conceptually similar to a single-mode optical fiber. However, the nanoscale mode volumes of the plasmon lead to strong coupling with the quantum emitter. **(B)** An unorthodox approach of enhancing light-matter interaction is by tailoring the dielectric constant of a medium so that it is dielectric in one direction and metallic in another. The resulting hyperboloidal dispersion relation supports infinitely many electromagnetic states for channeling light into a single-photon resonance cone.

Remarkably, despite the decoherence expected due to collisions, the millions of electrons making up the plasmon conspire to carry the quantum bit originally encoded in the photon (*6*). Furthermore, this nonclassical information survives the photon-to-plasmon-to-photon conversion and can be faithfully recovered (*5*). There is little doubt that the plasmon is uniquely poised to play a role in future nanoscale quantum information processing.

A related question is about what happens in the limit of a

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large ensemble of emitters near a metallic nanoparticle. The preferential emission into a single plasmonic mode also makes possible the concept of a spaser, an amplifier and coherent generator of plasmons (*7*). To understand plasmons in complex nanoparticle architectures for spasers or other applications such as single-molecule detection, it is important to incorporate a quantum-mechanical model of the electron density in the analysis. Effects such as tunneling of electrons between coupled nanostructures can considerably affect the nature of plasmons (*8*). Such a microscopic approach will be critical to develop a complete understanding of quantum plasmonics.

Efforts in quantum optics have been directed toward overcoming decoherence effects and achieving scalability of quantum bits (qubits) for practical applications. One approach is to achieve parallelism and communication between quantum bits of different nature (e.g., spin qubits and photonic qubits; akin to our current use of optoelectronics for computation and communication). The nitrogen-vacancy (NV) center in diamond is a promising choice for the robust solid-state quantum bit because it can show single-photon emission as well as long spin coherence times (*9*). The ability to make these two degrees of freedom interact rests on efficient single-photon emission beyond that available in bulk diamond NV centers. Resonant cavity approaches to enhancing the optical emission are incompatible with these sources, which have a broad emission spectrum. The broadband enhancement of spontaneous emission enabled by nanoplasmonic approaches allows the possibility of coupling to such emitters, which was otherwise difficult to achieve by conventional quantum optical techniques (*10*).

Another unorthodox approach of enhancing the nanoscale light-matter interaction in a broad bandwidth is to provide the quantum emitter with a plethora of electromagnetic states (*11*). Current nanofabrication technologies allow the engineering of the dielectric constant with metamaterials, transforming the space perceived by light to be metallic in one direction and dielectric in another. This lifts the restriction on the well-known closed spherical dispersion relation of an isotropic medium into a hyperboloid, leading to electromagnetic states unique to the metamaterial (*12*, *13*). An infinite number of metamaterial states can lie on this hyperboloid (in the low-loss, effective-medium limit), increasing the interaction with the quantum emitter while simultaneously channeling the light into a subdiffraction single-photon resonance cone (*12*) (see the figure, panel B). Currently, losses present a formidable challenge to practical applications, but the new class of alternate plasmonic materials can lead to quantum-vacuum engineered devices with these "hyperbolic" metamaterials (*14*).

The future of nanophotonics is bright, with many possibilities of interfacing with quantum optics to address challenges of qubit scalability and communication. One topic to be addressed in the near future is single-photon switching and routing. Single photons do not talk to each other, but efforts are under way to use plasmon-mediated interactions for this purpose (*15*). It is quite likely that the hybrid excitation that combines photons and electrons will be the carrier of choice in future quantum information systems.

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BIOCHEMISTRY

How Proteins Fold

Computational and experimental results provide support for defined protein folding pathways.

Tobin R. Sosnick[1] and James R. Hinshaw[2]

Two reports in this issue probe single protein chains as they spontaneously unfold and refold. On page 517 of this issue, Lindorff-Larsen *et al.* (*1*) use state-of-the-art molecular dynamics (MD) simulations to elucidate the folding mechanisms of 12 different proteins. On page 512 of this issue, Stigler *et al.* (*2*) study the folding and unfolding of single calmodulin domains with single-molecule force spectroscopy. The results provide remarkable views of the folding process and address basic questions, such as whether proteins fold along pathways.

The Shaw group previously succeeded in modeling the folding of a 35-residue protein in the presence of water molecules (*3*). Lindorff-Larsen *et al.* now show that these methods are suitable for probing the folding of larger, more complex proteins. In addition to matching experimental folding rates, the authors obtain native-like models for 12 proteins, which contain helices and sheets and are up to 80 residues long. For most of the proteins, the trajectories contain discrete transitions between the native and unfolded states. This behavior is consistent with barrier-limited cooperative folding, the hallmark of the experimental folding reaction.

Whether folding occurs along a diverse set of routes elicits diverse opinions, with many researchers favoring extensive pathway heterogeneity due to the complexity of the system (*4*). Yet, Lindorff-Larsen *et al.* find that for nine of their proteins, heterogeneity is minimal, with the routes typically sharing over 60% of their native contacts. They conclude that these routes are best viewed as variations of a single folding pathway. This lack of pathway diversity is consistent with experimental studies where transition state heterogeneity was not observed (*5*). However, in the simulations of two β sheet–containing proteins, the order of strand formation can vary. For a protein G variant, the observation of two pathways is consistent with experimental work, which found that the folding order of the two hairpins can be manipulated (*6*). Generally, symmetric (*7*, *8*) and multidomain proteins are strong candidates for multiple pathways, because different portions can form first.

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