PHYSICS

Electrons catch light pulses on the fly

Energy exchange between electrons and photons enables ultrafast probing of materials

By **Albert Polman**[1] and **F. Javier García de Abajo**[2,3]

Although free electrons are widely used as probes to analyze the morphology, atomic structure, and optical properties of nanoscale materials using transmission or scanning electron microscopy, they can also interact strongly with light and, thus, sample the distribution of optical fields in and around those materials with high spatial resolution (*1*–*3*). Specifically, in photon-induced near-field electron microscopy (PINEM), intense light fields bring an electron into multiple energy states simultaneously—a quantum-mechanical superposition state—which are then measured with an electron spectrometer. On page 168 of this issue, Yang *et al.* (*4*) report the use of PINEM to examine the creation of special light pulses known as solitons in an optical integrated circuit. The electron–soliton interaction shapes the electron's probability distribution in space and time, thereby enabling new ways to probe ultrafast dynamics in matter with an electron microscope.

In quantum mechanics, a free-space electron is described as a wave packet characterized by a spatiotemporal distribution of probability density—the likelihood of an electron being present at a given position in space as a function of time. A distinct feature of PINEM is that, by tailoring the light field, electron–light interaction enables control over this distribution of the electron probability density. Starting with an incident electron of energy E_0 and a smooth spatial density distribution curve, its interaction with light expands the energy spectrum, creating energy states (sidebands) that are separated from E_0 by positive and negative multiples of the photon energy $\hbar\omega$. After the initial observation of PINEM and associated electron sideband spectra (*1*), a well-defined coherence relation was established between the electron waves at different sideband energies for every electron (*2*, *3*). This coherence has important implications for propagation of the electron because sidebands with different energies have different electron velocities, and therefore, the electron wave packet that is formed by the superposition of all sidebands undergoes a spatiotemporal reshaping as the electron propagates (*3*). Specifically, the probability density distribution of each electron takes the shape of a train of pulses of short duration compared with the period of the light, which is a few femtoseconds in the visible regime. PINEM thus pushes the combined spatiotemporal resolution of electron microscopes to the subfemtosecond and nanometer (sub-fs/nm) regime. Besides reshaping the electron probability density, the sideband amplitudes provide a direct measure of the intensity associated with the optical near field traversed by the electron. Yang *et al.* leveraged this effect to measure the intensity associated with the generation of solitons.

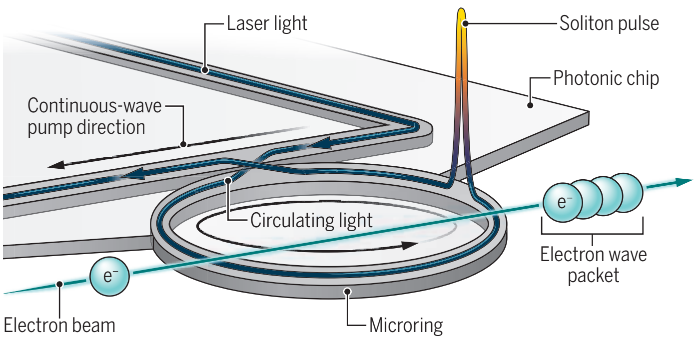
The creation of strong electron–light interactions in PINEM requires intense optical fields, which are commonly achieved by using ultrashort intense laser pulses under far-field illumination conditions (*5*). Intense fields are also achieved by using optical microring waveguides made of highly transparent silicon nitride and fabricated on a silicon chip through lithographic techniques (*6*). When light is injected into a microring, it circulates hundreds of times inside the ring cavity, thereby increasing the light intensity to a high value and enabling PINEM to be performed with a low-power continuous-wave laser light source (*7*). This capitalizes on the ability of integrated optical circuits to combine waveguides, multiplexers, and other optical components to process information entirely using light, rather than using electrons as in common electronic integrated circuits.

Yang *et al.* exploited a fascinating property of some optical materials such as silicon nitride—a relatively strong nonlinear optical response. The speed of light in silicon nitride depends on light intensity even for moderate laser powers. Above a certain power threshold, such nonlinearity causes light to propagate in complex ways. This includes the formation of Kerr solitons (*8*), light pulses generated from a continuous laser that circulate in the microring cavity.

Yang *et al.* brought together free electrons and nonlinear optics by using PINEM with 200-keV electrons to probe Kerr solitons in a silicon nitride microring of hundreds of micrometers in diameter. This established a disruptive approach to explore electron–light interactions and to shape the free-electron probability density. The structure is pumped with a continuous-wave laser at a wavelength commonly used for on-chip telecommunication applications (1.55 µm). The authors aligned the electron beam (which travels in vacuum along a straight path) and the ring such that the electron interacts twice along the cavity circumference, thereby probing the optical field at two different moments in time (see the figure). The delay between the two interactions is controlled by the electron beam distance from the cavity center (i.e., zero delay when the beam is tangent to the ring, and a maximum delay determined by the ring diameter when the beam intersects the ring center). This provides a means to examine the temporal propagation and phase of light as it circulates the ring cavity. In particular, the phase is proportional to the delay, thus allowing Yang *et al.* to observe characteristic Ramsey interference patterns of light as the distance between the two points of light–electron interaction is gradually changed.

Probing electron–light interaction

A high-energy beam aligned with a microring cavity can probe the ultrafast evolution of optical soliton pulses. Strong electron–photon interaction tailors the production of quantum-mechanical electron wave packets in space and time.



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These patterns evolve between constructive and destructive interference as the delay-induced phase varies from 0 to π. The soliton signature emerges as a broad background signal superimposed on the Ramsey pattern and involves higher light intensities (optical fields accumulated in the pulse-shaped soliton) that, consequently, produce higher-order sidebands.

Nonlinear optical behavior can also be observed through the formation of chaotic light fields, trains of solitons, or individual solitons, depending on how the input light wavelength and its power are tuned. These phenomena are driven by the silicon nitride nonlinear optical response (*5*, *8*). As the laser wavelength and power were varied, Yang *et al.* could probe the transitions between nonlinear optical regimes because of the strong sensitivity of PINEM to the light field intensity and its distribution around the ring. The data of Yang *et al.* could be explained through a combination of well-established theoretical models for both the nonlinear optical response of microcavities (*9*) and the electron–photon interaction (*2*, *3*). Simulations based on these models were in good quantitative agreement with the authors' experiments.

The interaction of electrons with enhanced light fields enabled by the microring geometry creates opportunities to obtain previously inaccessible information on light propagation inside integrated optical circuits. This includes the degree and spatial distribution of coherence associated with nonlinearly generated light pulses such as solitons. Furthermore, electron–soliton interaction enables a disruptive approach to shaping the electron probability density in space and time. Also, solitons circulating the microring cavity can interact with a continuous electron beam at a high repetition rate approaching the terahertz, which is inaccessible with current ultrafast optics technology. The resulting electron modulations could be synchronized with the optical excitation, presenting new ways to perform electron microscopy and probe ultrafast dynamics in material systems with sub-fs/nm spatiotemporal resolution. ■

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MEDICINE

Practical challenges for precision medicine

The prediction of individual treatment responses with machine learning faces hurdles

By **Frederike H. Petzschner**

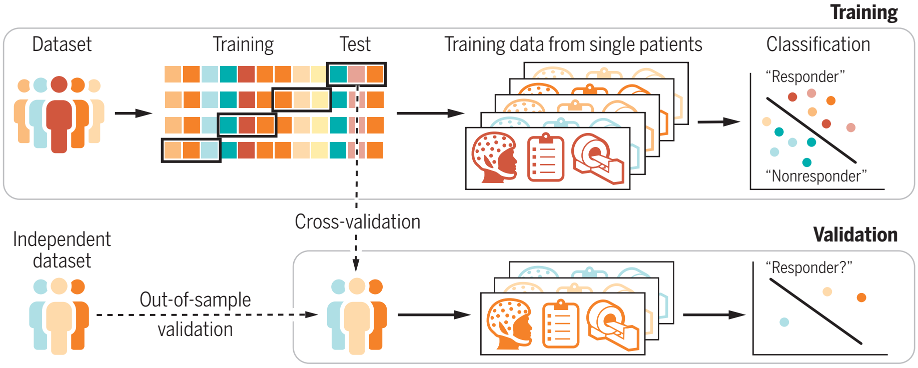
Precision medicine promises treatments tailored to individual patient profiles. Machine learning models have been heralded as the tools to accelerate precision medicine by sifting through large amounts of complex data to pinpoint the genetic, sociodemographic, or biological markers that predict the right treatment for the right person at the right time. However, the initial enthusiasm for these advanced predictive tools is now facing a sobering reality check. On page 164 of this issue, Chekroud *et al.* (*1*) show that machine learning models that predict treatment response to antipsychotic medication among individuals with schizophrenia in one clinical trial failed to generalize to data from new, unseen clinical trials. The findings not only highlight the necessity for more stringent methodological standards for machine learning approaches but also require reexamination of the practical challenges that precision medicine is facing.

What predicts whether a patient will benefit from a particular treatment? The answer may lie in their genetics, biology, sociodemographic background, social environment, past experiences, or a myriad of other potential factors. Machine learning techniques have the capacity to analyze large datasets and identify the most effective combination of features that accurately predicts a variable of interest. They thus offer a promising avenue for discovering relevant features or biomarkers that predict individual treatment responses. Typically, this involves training the model on a dataset for which the outcome, such as the response to a given treatment, is already known. This is known as supervised learning. One common pitfall of this method is overfitting. Overfitting occurs when a model is too flexible relative to the data it is trained on, which limits its generalizability. A sign of overfitting is when the model accurately predicts outcomes on the data it was trained on but performs poorly on new, unseen data. To address the issue of overfitting, it is essential to validate models on unseen data. Cross-validation is a widely used technique for this purpose. It involves repeatedly dividing the data into subsets, training the model on one subset, and then evaluating its prediction accuracy on the remaining "held-out" data (see the figure).

However, cross-validation is not infallible. Chekroud *et al.* revealed that models trained to predict responses to antipsychotic medication in schizophrenia within a specific clinical trial using cross-validation failed to predict treatment responses in other independent

Individual treatment prediction using machine learning

Supervised machine learning for individual treatment prediction is based on the development of classifiers. To prevent overfitting, model validation is crucial, typically achieved through cross-validation or out-of-sample validation. Out-of-sample validation requires a completely independent dataset and is more resource-intensive, but this approach is less susceptible to overfitting and can provide more generalizable results.



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