tions, whether these transitions be developmental or adaptive. If stochasticity is a fact of life, states are by definition metastable, and fluctuations can cause transitions between them. We are comfortable with the notion that antigenic phase variation in bacteria is stochastic (*10*), but might not stochastic mechanisms equally underlie the well-orchestrated, seemingly deterministic progression of states we call organismal development? We recognize the importance of the stochastic genetic mechanisms that generate diversity in the immune system. When coupled to suitable feedback mechanisms, such as the clonal amplification of cells expressing a particular antigen, these constitute a powerful means of learning, of crafting appropriate responses to unforeseen situations. Will we discover an analogous role for stochastic gene activation?

Stochasticity is inherent in all biological processes and it can be argued that the proliferation of both noise and noise-reduction systems is a hallmark of organismal evolution. One of us (*11*) has suggested that the reason it took so long to figure out that most genomes, including our own, are stuffed with transposons is because they "jump" from one chromosomal site to another so rarely that they are almost invisible genetically. Genome growth, dependent on the stochastic processes of gene duplication and transposition, may well have necessitated the prior invention of ways to suppress the inevitable countervailing deletions and genome scrambling caused by homologous recombination. Adrian Bird (*12*) has suggested that the inherent imprecision of gene regulation also sets an upper limit upon gene numbers. He has argued that the jump in gene numbers that accompanied the prokaryotic-eukaryotic transition was made possible by the accretion of multiple transcriptional noise-reduction mechanisms including chromatin, DNA methylation, the separation of the transcriptional from the translational apparatus, and the introduction of a complex quality control machinery into the production of mRNAs. And so the question is this: To what extent is the seemingly inexorable increase in complexity that we call evolution driven by the counterpoint of noise and noise reduction, of chance and the necessity of inventing and accumulating mechanisms to render coherent its random gifts?

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PERSPECTIVES: PHYSICS

Resolving Physical Processes on the Attosecond Time Scale

Maciej Lewenstein

Many molecular and atomic processes occur on a femtosecond time scale (1 fs = 10^{-15} s), which can be probed with coherent laser excitation. Now physicists are reaching for the next frontier. On page 1144 of this issue, Kienberger *et al.* (*1*) lead the way toward resolving physical processes on the even faster attosecond scale (1 as = 10^{-18} s).

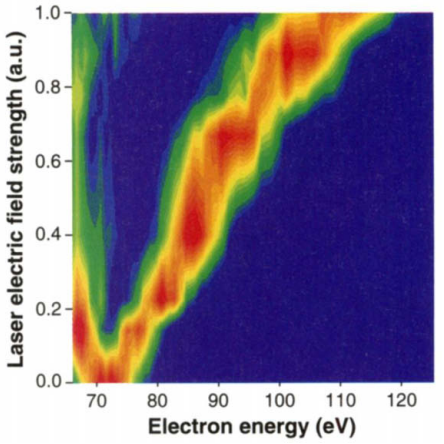
To achieve fast time resolution, the duration of the laser pulse must be controlled. With two short laser pulses, one can perform "pump-probe" experiments, in which the first pulse excites the system and the second pulse probes the resulting dynamics. For this method to work, the pulses must be shorter than the characteristic time scale of the dynamics in question.

A laser pulse cannot be shorter than the oscillation period of the electromagnetic field in the pulse. Hence, for a laser with a wavelength λ of ~800 nm, the shortest pulse duration is ~4 to 5 fs. In time-resolved spectroscopy, such femtosecond pulses are used, for instance, to monitor the dynamics of molecular reactions. However, tightly bound electrons in atoms and ions cannot be observed with femtosecond techniques, because their dynamics occur typically on the attosecond time scale.

To decrease the pulse duration beyond the femtosecond time scale requires coherent sources of ultraviolet and soft x-ray radiation. A method called high order harmonic generation (HHG) (*2*) offers a possibility of realizing this task. When an atomic gas is irradiated with an intense femtosecond pulse, the gas produces harmonics of the laser field. The frequencies of these harmonics are odd integers of the laser frequency (ω_L) and extend up to few hundred ω_L (*3*). They reach wavelengths of a few nanometers and periods in the attosecond regime.

In a macroscopic medium, HHG requires constructive interference (phase-matching) between the contributions of individual atoms. According to the "simple man's model" (*4*, *5*), the HHG process occurs in three steps. First, the laser field causes an electron to tunnel to those regions in space where interactions with its nucleus are practically negligible. It then oscillates in the laser field as a free charge. If it comes back to the nucleus, it may recombine, emitting harmonics. This model has a solid quantum mechanical basis (*6*); in particular, it incorporates quantum mechanical interferences between various electronic trajectories.

Antoine *et al.* predicted (*7*) that the harmonics, generated in a macroscopic medium under phase-matching conditions, are locked in phase. Twice in a laser period T_L, groups of neighboring harmonics interfere constructively for a very short time interval, producing a train of attosecond pulses separated by $T_L/2$. The first indirect evidence that HHG generates at-



How to steer electrons. The shift of this photoelectron energy spectrum toward higher energies with increasing laser field represents "steering" of the electronic wavepacket. [From (*1*)]

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tosecond pulse trains was reported by Papadogiannis *et al.* (*8*). Last year, de Paul *et al.* measured a train of 250-as pulses directly in the time domain (*9*).

Can such pulse trains be used for time-resolved attosecond spectroscopy? Salières *et al.* proposed in 1996 to use them for monitoring processes that occur with the period $T_L/2$ of the train. Candidates for such processes are harmonic generation itself or above threshold ionization (*2*), a laser-induced ionization process in which electrons absorb more photons than they need to be released. All of these processes can be described by "simple man's models" (*10*). Unfortunately, today's attosecond pulses are not sufficiently intense to realize time-resolved attosecond spectroscopy of these processes.

Although HHG is now an established source for attosecond pulse trains, it has one major limitation. Applications of time-resolved spectroscopy to dynamics that do not occur with the $T_L/2$ period require single isolated attosecond pulses. But there may be a way around this problem. For laser pulses shorter than 10 fs, the resulting individual harmonics fall below the femtosecond limit. Because the laser pulse lasts for only a few T_L, the harmonics cannot develop; instead, a soft x-ray attosecond pulse should be generated.

Krausz and co-workers (*11*) generated such an isolated attosecond x-ray pulse ($\lambda \approx 14$ nm) by irradiating a very short laser pulse ($\lambda \approx 750$ nm) of ~5-fs duration on a krypton gas sample, and filtering the outgoing radiation to a 5-eV range around 90 eV. They then irradiated the target krypton sample simultaneously with the x-ray pulse and a laser pulse of visible light of a few laser cycles duration. The x-ray pulse ionized the krypton atoms. The energy spectrum of the photoelectrons depended on the phase of the laser pulse at the moment of the electron's detachment. When the authors changed the relative delay between the laser and the soft x-ray pulse, a modulation of the spectral width appeared, allowing the duration of the x-ray pulse to be estimated as ~650 as.

Krausz and co-workers now describe (*1*) the first genuine application of isolated attosecond pulses for time-resolved attosecond spectroscopy. They study the absorption and emission of laser photons by electronic wavepackets created by soft x-ray radiation. Normally, the photoelectron energy spreads as a result of the photon absorption or emission (*12*). If, however, the emitted electron wavepacket is temporally confined to a fraction of T_L, its energy spectrum may be up- or down-shifted by several laser photon energies without broadening. The laser light can then "steer" the electron wavepacket like a classical particle. The results of such "steering" depend on the timing of the attosecond x-ray pulse relative to the absolute phase of the laser (see the figure), offering a simple, single-shot tool for time-resolved attosecond spectroscopy.

Attophysics has moved from dream to reality. One can expect fruitful applications of time-resolved attosecond spectroscopy to HHG or to above threshold ionization processes induced by ultrashort laser pulses, in which the absolute phase of the laser pulse plays a crucial role (*13*). Attosecond spectroscopy will provide diagnostics and perhaps new ways of controlling these processes, in particular to obtain better ways of short x-ray coherent pulse generation.

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PERSPECTIVES: NEUROSCIENCE

It Takes More Than Two to Nogo

Clifford J. Woolf and Stefan Bloechlinger

The environment of the adult mammalian central nervous system (CNS) is hostile to the growth of axons and is a major contributor to the inability of injured neurons to regenerate. Much of this inhibition is caused by myelin, the insulating lipid and protein material that is wrapped around axons, ensuring rapid transmission of electrical signals along central nerve fibers. In the CNS, myelin is produced by supporting glial cells called oligodendrocytes. These cells also make growth-inhibitory proteins that become embedded within the myelin sheath.

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Injured nerve fibers that make contact with CNS myelin cease to regenerate. At least three growth-inhibitory proteins have been identified so far: Nogo-A, named for its inhibitory action on axonal growth; myelin-associated glycoprotein (MAG); and oligodendrocyte myelin glycoprotein (OMgp). Although Nogo-A is known to bind to the Nogo receptor (NgR), the receptors for MAG and OMgp have remained elusive. Now, in an extraordinary and unexpected convergence reported by several groups including Liu *et al.* (*1*) on page 1190 of this issue, all three molecules appear to bind to the same receptor, NgR (*2–4*). This discovery opens up exciting new possibilities for overcoming axonal growth inhibition, a vital step in neuronal regrowth after brain or spinal cord injury.

During the development of the nervous system and in neurons grown in culture, the extension of axons from the cell body begins with the formation of small processes whose active tips have a specialized structure called the axonal growth cone. The growth cone interacts with the environment to determine the direction and rate of axon elongation. When the growth cone contacts CNS myelin, its cytoskeletal structure is altered, causing it to collapse and resulting in cessation of axonal growth. Nogo-A, MAG, and OMgp all contribute to the inhibitory action of CNS myelin on axonal growth and regeneration.

Nogo-A, a member of the reticulon family of proteins, has two inhibitory domains: a cell surface domain called Nogo-66 (*5*), and a long amino-terminal region (*6*) (see the figure). The Nogo-66 domain on the oligodendrocyte surface binds to NgR, a leucine-rich repeat protein that is attached to the extracellular surface of the neuronal membrane by glycophosphatidylinositol (GPI) (*4*). The location of the inhibitory amino-terminal domain of Nogo-A may be cytoplasmic, although this remains unclear (*5, 6*). If this is the case, then the amino-terminal domain of Nogo-A can inhibit axonal growth only when myelin is disrupted by injury. No receptor