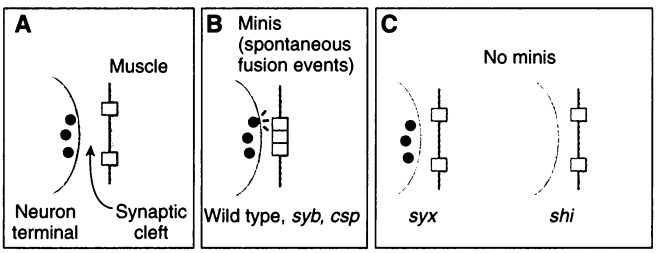
mate receptor clustering is prevented when sodium channel activity is blocked in a temperature-sensitive fly mutant (*6, 8*). Intriguingly, at the restrictive temperature (34°C), minis were mostly absent in this temperature-sensitive fly mutant. Unfortunately, wild-type NMJ activity is also severely impaired at the restrictive temperature, making these experiments difficult to interpret. Thus, neural activity seems to be required for clustering of postsynaptic glutamate receptors in the developing *Drosophila* NMJ, but the nature of this neural activity is still unclear.

Saitoe *et al.* (*4*) now demonstrate that spontaneous fusion, but not fusion evoked by action potentials, is required for glutamate receptor organization in the NMJ postsynaptic membrane. They observed that *Drosophila* mutants with defective synaptic vesicle proteins such as Syntaxin or Dynamin had neither evoked nor spontaneous fusions and did not show refinement of glutamate receptor clustering. In contrast, clustering was essentially normal in flies with defective Synaptobrevin or Cysteine String Protein—mutants that exhibit spontaneous fusion but not action potential–dependent fusion. In these mutants, activation of glutamate receptors did not seem to be important for clustering, because ionotrophic glutamate receptor blockers did not interfere with this process. Thus, spontaneous fusion is likely to be important for refining postsynaptic receptor clustering in the *Drosophila* NMJ. It is possible that spontaneous fusion induces the secretion of unknown factors that are required for glutamate receptor clustering.

How does the clustering of postsynaptic glutamate receptors in the developing fly NMJ compare to the clustering of acetylcholine receptors in the NMJ of the developing mouse embryo? Acetylcholine receptor clustering in the developing mouse NMJ depends on the secreted protein agrin and its postsynaptic receptor MuSK (*9, 10*). Interestingly, postsynaptic acetylcholine receptors localize and cluster normally in the developing mouse NMJ in the absence of both evoked and spontaneous fusion events (*11*). Therefore, spontaneous fusion does not seem to be required for clustering of mouse NMJ acetylcholine receptors.

Glutamate receptors are the most common receptors in the vertebrate brain, but how they cluster in the postsynaptic membrane is still not well understood. Recently, a protein called Narp (neural activity–regulated pentraxin) secreted by cultured mouse presynaptic neurons, perhaps through spontaneous fusion, was found to induce the clustering of glutamate (AMPA) receptors (*12*). Interestingly, proteins similar to Narp exist in *Drosophila* and may evoke similar postsynaptic effects in fly NMJs.

Spontaneous fusion events may operate not only during glutamate receptor clustering in the developing fly NMJ, but also at other synapses, indicating their importance in many different aspects of neuronal communication.



What a mini can do. **(A)** During development of NMJs in the fruit fly, glutamate receptors become localized to broad presumptive fields of nerve contact in the absence of neural activity. **(B)** Spontaneous fusion of a single synaptic vesicle with the presynaptic membrane generates a mini in the postsynaptic membrane and provokes clustering of postsynaptic glutamate receptors. In *synaptobrevin* (*syb*) and *cysteine string protein* (*csp*) fly mutants, there is still glutamate receptor clustering because only vesicle fusion evoked by action potentials and not spontaneous fusion is abolished. **(C)** In the *syntaxin* (*syx*) and *dynamin* (*shi*) fly mutants, which have neither evoked nor spontaneous fusion, glutamate receptors do not cluster but stay dispersed in the NMJ postsynaptic (muscle) membrane. In the *syx* mutant there is an absolute block in neurotransmitter release, whereas in the *shi* mutant there is depletion of synaptic vesicles.

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PERSPECTIVES: ELECTRON TRANSFER

Sometimes You Can Go Home Again

Christopher Bardeen

From simple nucleophilic substitution reactions in organic chemistry to photosynthesis, electron transfer is a basic element of chemical reactions in liquids (*1*). The theoretical framework for understanding electron transfer rates in systems near equilibrium was developed by Marcus and verified experimentally by many workers. The advent of ultrafast lasers has provided physical chemists with a tool for studying how these systems evolve under nonequilibrium conditions. Such studies have revealed molecular details of how electrons move in dense media. On page 462 of this issue, Martini *et al.* go one step further, providing evidence that femtosecond pulses may be used not only to observe electron transfer dynamics but to control them as well (*2*).

The system we are concerned with here is an electron embedded in a molecular liquid. An electron is arguably the simplest possible reactant in a condensed phase environment because it lacks the intramolecular vibrational modes of a molecular solute. A dissolved electron can be prepared by a variety of methods in a variety of solvents, but its essential characteristics remain the same.

At equilibrium, the electron is nestled in a solvent cavity, kept in place by the solvent dipoles. Absorption of a photon excites the electron into a delocalized state, whose wave function may then relocalize to different sites in the solvent that are spatially separated from the original low-energy site. As time goes on, many electrons will lose energy and find their way back to their original cavities, a process known as recombination. But some will escape into the solvent, never to return.

Both types of events are examples of electron transfer from one solvent site to another, and both can be followed by observing the transient absorption spectra of the electron because its wave function, which depends on its spatial extent and environment, also determines its spectral behavior. By using femtosecond pulses, one can ob-

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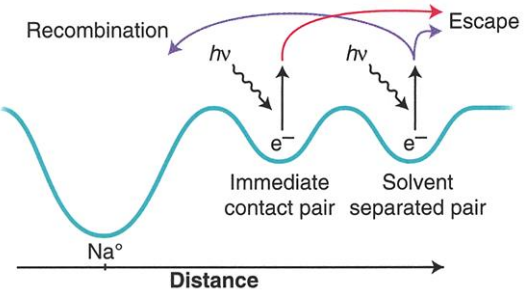
serve the creation, relaxation, and recombination of the wayward electron in detail.

The apparent simplicity of the solvated electron has made it the subject of many studies. Pioneering work by Eisenthal and Antonetti established that electrons created by direct ionization of simple solutes in water undergo a complex relaxation process that involves distinct solvation states [reviewed in (*3*, *4*)]. More recent studies (*5*–*10*) have concentrated on the dynamics of electron recombination in water under a variety of conditions. In particular, Barbara and co-workers at the University of Texas have clarified the nature of the electron's excited states by quantifying their spatial extent and relaxation times in water (*9*). Very recently, they have demonstrated how recombination can be suppressed by direct excitation of the solvated electron to very delocalized conduction band states (*10*).



Wayward electrons. In the sodide/tetrahydrofuran system, the initially excited electron can exist in an immediate contact pair or a solvent-separated pair. Electrons in immediate contact pairs will leave when the control pulse is applied, but some solvent-separated pairs recombine with the sodium atom.

In Martini *et al.*'s experiment, the electron is originally localized in a cavity that it shares with a sodium atom, forming a "sodide" ion in room temperature tetrahydrofuran. As in water, the escape probability of the electron can be enhanced by providing extra energy from a second pulse. But the authors do not stop there. They show that by delaying the second pulse an appropriate amount of time, one can enhance the rate of recombination as well.

To accomplish this, the authors exploit a subtlety of the sodide/tetrahydrofuran system, namely that the initially excited electron can exist in two different sites: a closely held immediate contact pair and a more distant solvent-separated pair (see the figure). The two species have different relaxation times, and the key is to wait long enough so that the control pulse excites only the more separated sites. Electrons that originally stayed close to home in immediate contact pairs will leave when the control pulse is applied, but some that originally ventured farther afield in solvent-separated pairs can be persuaded to return more quickly. The authors have thus found an experimental handle to control whether an electron continues to wander off into the solvent or returns home to its original solvent cavity.

It is important to point out that the observed enhancement in recombination rate is small and that the net effect of adding energy to the system with the control pulse, no matter what the delay, is to enhance the escape probability. In other words, the control pulse provides a transient acceleration of the recombination rate, but the time-integrated reaction yield only changes in one direction—toward enhanced escape.

In some sense, this is academic because the main goal of the research is the characterization of the electron's dynamics in liquids. The authors point out that this "control" experiment confirms their previous hypothesis about the existence of two states of the electron. But to what extent can electron dynamics in complex fluids be controlled?

Wasielewski and co-workers have demonstrated that femtosecond pulse sequences can be used to turn electron transfer on and off in designed molecular assemblies (*11*). And recent advances in pulse shaping and feedback control have demonstrated impressive results in the control of gas phase molecular dissociation (*12*). Can such an approach be extended to find a combination of pulse delays and excitation wavelengths that will create and then turn off a delocalized electron state in a liquid, in effect creating an ultrafast polarizable switch? The results reported here suggest that it may be worth trying.

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PERSPECTIVES: BIOMEDICINE

Huntingtin—Profit and Loss

Yvon Trottier and Jean Louis Mandel

An aberrant expansion of glutamines in the protein huntingtin causes Huntington's disease (HD), a neurodegenerative disorder that strikes in middle age. It has been presumed that mutant huntingtin with its extra glutamines is toxic to neurons possibly because it has a tendency to form aggregates (*1*). In HD, there is selective destruction of the medium-sized spiny neurons in the striatum of the brain, which has been attributed either to the accumulation of mutant huntingtin aggregates or to the continued expansion of glutamine repeats (*1*, *2*). On page 493 of this issue, Zuccato *et al.* (*3*) present evidence that mutant huntingtin affects cortical neurons producing brain-derived neurotrophic factor (BDNF), which is necessary for the survival of striatal neurons. They propose that partial loss of the beneficial effects of wild-type huntingtin combined with the toxicity associated with mutant huntingtin conspire to selectively destroy the striatum of the brain.

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Huntingtin is a widely expressed protein that resides in the cell cytoplasm and may be important for transport of vesicles in the endosomal and secretory pathways, and for preventing cells from undergoing apoptosis (*4*). Mutant huntingtin is proteolytically processed, and the resulting amino-terminal fragments containing the glutamine expansions form aggregates, which are deposited in nuclear and cytoplasmic inclusions in the brains of HD patients and HD mice. It is still not clear whether the primary cause of HD pathology is the soluble or aggregated form of mutant huntingtin.

BDNF is a key player in the maintenance of nerve cells. Like other neurotrophic factors, it is secreted by one group of neurons, and is then taken up by the axons and nerve endings of other neurons (retrograde transport) that require this factor for survival. BDNF is also a neuromodulator that moves by anterograde transport along nerve axons and is released when neurons become depolarized, moving across the synapse and triggering action potentials in target cells (*5*). BDNF produced by cortical and nigral neurons