These new findings clearly add fuel to the debate over whether transposable elements can be a beneficial component of eukaryotic genomes. At first glance, selfish gene models for transposable element maintenance do not predict that an element would be so indiscriminate in its choice of 3′ ends for retrotransposition. Transducing downstream sequences would be of little benefit to the element itself. One should consider, however, why L1 might find it advantageous to avoid its own poly(A) site. As pointed out by Moran *et al.*, the likely reason L1 elements have weak poly(A) signals is that it enables them to reside in the introns of a gene with little effect; strong poly(A) signals would disrupt expression of the gene. Thus, L1 is under conflicting pressure to retain its own poly(A) site, without that site being too "powerful." Although the occasional shuffling of an exon may be an advantage to the host, the element itself is simply increasing its chances of survival.

This work proffers the prediction that non-LTR elements in genomes with a high percentage of intron sequences will have weak poly(A) signals. Elements in genomes with a low percentage of introns will have strong poly(A) signals and will seldom transduce downstream sequences. It also suggests that it is not only Alu sequences and processed pseudogenes that may owe their origin to L1, but just about any insertion ending with an A-rich tail. The fraction of the human genome attributable to retrotransposition just got larger.

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PERSPECTIVES: MOLECULAR SPECTROSCOPY

Ultrafast Glimpses at Water and Ice

Edwin J. Heilweil

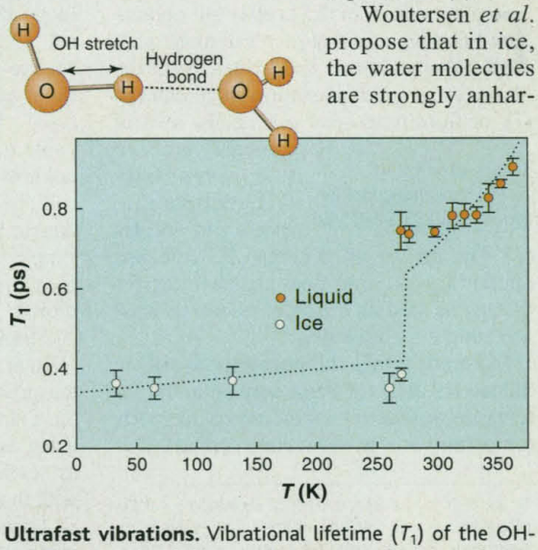
Even the properties of seemingly simple molecules can be rather elusive. Water—perhaps the most important medium for supporting chemical processes and biological functions—exhibits unusual properties, the origins of which remain a subject of debate. Compared with other molecular liquids and solids, water has a high dielectric constant and compressibility. Most notably, its density displays a maximum at several degrees above the freezing temperature (*1*). Now, modern spectroscopic techniques are beginning to decipher the origin of some of water's anomalous characteristics. Recent experimental and theoretical studies with transient infrared spectroscopy and molecular dynamics methods are providing interesting, although controversial, results on the microdynamics of water and ice that underlie the bulk properties.

Ultrafast mid-infrared spectroscopy (at wavelengths from 2 to 10 μm) has gained in popularity over the past 15 years because of its sensitivity to vibrational processes and orientation of molecules (*2*). A time-dependent infrared (IR) spectrum of a sample provides detailed information on molecular vibrational energy flow, conformational rearrangements, chemical reaction intermediates, and transitory tertiary structures of the system. For example, ultraviolet (UV) laser pulses with durations from picoseconds (1 ps = 10^{-12} s) to femtoseconds (1 fs = 10^{-15} s) tuned to a molecular electronic transition can cause that species to dissociate or react with other molecules. IR pulses of similar duration—either tuned to a discrete molecular vibration or broadband—can subsequently be used to probe the molecular absorptions originating from transient intermediates and stable products as a function of the delay between the earlier "pump" UV pulse and the subsequent "probe" IR pulse (pump-probe spectroscopy). Analysis of such time-dependent IR spectra allows one to assign the structure and monitor the time evolution of chemical species. Detailed mechanistic information and kinetic rates can thus be directly obtained for a dynamical system.

Such ultrafast IR technologies are now being used to study the microdynamics of liquid water and ice. Woutersen *et al.* recently published femtosecond IR measurements of the vibrational relaxation time (T_1) of the OH stretch in water and ice as a function of temperature (*3*). These results extended earlier spectroscopic and kinetics studies of room temperature water (*4, 5*).

Woutersen *et al.* reported vibrational population decay times (for the first excited, or $v = 1$ state) for the OH-stretching mode of HOD molecules diluted in D_2O (see figure) (*3, 4*). The decay time of vibrations depends on the molecular environment. For example, the OH vibrations may be coupled to other atomic motions in the system, such as hydrogen bonds between water molecules. The latter may take up the energy of vibrational modes. According to accepted theories (*6*), one would have expected the decay times to decrease with increasing temperature, because the number of lower, energy-accepting modes usually increases with temperature. However, Woutersen *et al.* observed a different behavior (see figure). They found that T_1 was nearly constant for the ice phase (30 to 270 K), abruptly increased at the solid-liquid phase-transition at 273 K, and then increased monotonically up to 363 K. Only a few inorganic condensed-phase systems are known to display such an inverted T_1 temperature dependence (*7*).

Woutersen *et al.* propose that in ice, the water molecules are strongly anhar-



Ultrafast vibrations. Vibrational lifetime (T_1) of the OH-stretching mode of dilute HOD:D_2O as a function of temperature. The dashed curve is calculated by using the hydrogen-bond frequency from the OH-stretch redshift (*11*). [Reprinted with permission of the authors (*3*)]

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monically coupled and hydrogen bonded, and that this coupling has a similar strength in the ground state (populated at lower temperatures) as the first excited state (increasingly populated with increasing temperature). In such a situation, the occupation of accepting modes, and hence T_1, does not depend on temperature. Also, the density of ice does not change appreciably over the studied temperature range and that of pure water only increases by about 5% from 273 to 363 K. Thus, changes in bulk density or water-water interactions are considered to contribute negligibly to the observed temperature dependence of T_1.

In contrast, liquid water shows a strong dependence of hydrogen-bond strength on temperature. Earlier spectroscopic studies showed that with increasing liquid temperature, the hydrogen-bond strength decreases. In this situation, "if the hydrogen bond forms one of the accepting modes of the vibrational energy, this will lead to an increase of the vibrational lifetime" (*3*). Similar arguments were used to explain early measurements of T_1 in hydrogen-bonded systems with hydroxyl groups on silica and in micas (*8*), mixed acid-base complexes (*9*), and in zeolites (*10*).

Woutersen *et al.* incorporated the relative change in hydrogen-bond strength with temperature into an analytical hydrogen-bonding model (*11*) to estimate T_1 lifetimes for the water OH-stretch. The fit of the model results to the experimental data is excellent (see figure), suggesting that the T_1 temperature dependence may indeed be dominated by changes in average hydrogen-bond strength within the medium. Molecular dynamics simulations of liquid water as a function of density and temperature, using the best available potentials, have also obtained hydrogen-bond lifetimes of 10 ps or less (*12*), similar to measured lifetimes (*3–5, 13*).

Can we conclude then that their interpretation is correct? The answer is not simple. Other transient IR investigations of HOD:D_2O at room temperature (*5*) and up to 343 K (*13*) with longer IR pulses have also yielded T_1 lifetimes of about 1 ps. However, using sophisticated two-color IR pump-probe spectroscopy with 1- to 2-ps pulses, one finds that the high-frequency OH-stretch absorption (3200 to 3600 cm^{-1}) is actually composed of three sub-bands (about 45-cm^{-1} wide) from ice-like, dimeric, or extended species, which exhibit T_1 vibrational lifetimes of 0.8 to 1.5 ps and reorientation times in the 3- to 15-ps range. The extremely short, spectrally broad IR pulses used by Woutersen *et al.* (200 fs, 100 cm^{-1} full-width at half maximum) may mask the dynamics of such multiple substructures existing at short time scales because these studies trade spectral resolution for high time resolution.

We are beginning to elucidate the properties of bulk water and ice through measuring its ultrafast molecular dynamics with sophisticated laser techniques. However, further investigations will be required before we will fully understand the intriguing properties of this ubiquitous and important but complex system.

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PERSPECTIVES: BIOMEDICINE

Putting Stem Cells to Work

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Embryonic stem (ES) cells—pluripotential stem cells that give rise to all adult cell types—can be derived from the blastocyst, a preimplantation stage embryo (*1*), or from primordial germ cells, cells of the early embryo that eventually differentiate into sperm and oocytes (*2*). The derivation of human ES cells has opened up exciting new possibilities for therapy as well as a Pandora's box of legal and ethical controversies.

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Assuming that the currently available human ES cells (or those derived in the future) are similar to their mouse counterparts (an assumption by no means certain), it is likely that they will eventually be used in cell and tissue replacement therapy (*3*, *4*). Mouse ES cells are pluripotent—that is, they can differentiate into many cell types—but whether they are totipotent (capable of developing into all cell types) is unknown. The same is true for human ES cell differentiation. Although it is likely that human ES cells form various cell types and simple tissues, their capacity to build complex organs in culture is entirely unexplored. The judicious exploitation of cell and tissue interactions and the use of extracellular matrices should eventually enable the production of complex organs such as the kidney or lung. One can even imagine using existing organs (human or otherwise) as scaffolding, replacing the original cells with those derived from ES cells.

Using ES cells therapeutically carries inherent dangers. Mouse ES cells are tumorigenic, growing into teratomas or teratocarcinomas when injected anywhere in the adult mouse. There is no reason to believe that human ES cells will not be tumorigenic in humans. Whatever means we use to separate the undifferentiated ES cells from the desired, differentiated progeny to be injected, we will have to be absolutely sure that the separation is complete. As yet, we do not know the minimal number of ES cells necessary to form a tumor or the length of time necessary for tumor development. The answers to these questions will not come from experiments with mice because mice are too short-lived to provide an adequate test. It is entirely possible that we will have to provide some genetically designed fail-safe mechanism, a "suicide" gene, which will enable us to destroy transplanted cells if they become tumorigenic.

Many questions related to the possible therapeutic use of human ES cells have not been addressed in mouse ES cells simply because of the lack of interest. Fortunately, our understanding of the molecular pathways of differentiation and the molecules that mark specific cell types is extensive. This knowledge should help us to answer the following questions: Can human ES cells be forced to differentiate along a desired pathway? Can we make *all* ES cells

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