

These studies use a technique called chromatin immunoprecipitation to capture from cells a particular transcription factor along with its bound short DNA strings. These DNA strings are then identified by hybridization to DNA microarrays (9, 10).

Using this approach, Borneman *et al.* examined binding of two transcription factors in three yeast species. In only about 20% of cases did a transcription factor bind to the same site (meaning, approximately the same position with respect to the target gene) in all three species. In some cases, the absence of binding corresponded to a loss of the appropriate binding site. Surprisingly, in other cases, the absence of binding in one species occurred despite conservation of the DNA sequence. In a similar study that compared transcription factor binding between human and mouse genomes, Odom *et al.* (11) found that 41 to 89% of cis-regulatory regions bound in one species were not bound in the other. Even when the same gene region was bound by a particular transcription factor in both species, the precise position of the bound site with respect to the target gene often differed between species.

Do all of these evolutionary switches in transcription factor binding sites cause phenotypic differences? For two reasons, it seems likely that many do not. First, change of a sin-

gle site may not alter gene expression. Transcription factors often bind to multiple sites within the same cis-regulatory region and act synergistically to regulate gene expression (3) (see the figure). Thus, individual binding sites may be gained and lost during evolution while the phenotype remains the same (12, 13). Second, the phenotype is robust to some changes in gene expression (14). For example, changes in enzyme concentration often have little effect on the output of a metabolic pathway (15).

Thus, while the new results support a major role for cis-regulatory mutations in evolution, they leave us little closer to the question we first posed: Which DNA changes make species different? The definitive way to identify the mutations causing phenotypic differences is to perform a genetic cross between species, and then trace the association between genomic locations and phenotypes in offspring. But most species pairs are too diverged to mate and produce viable offspring, and this approach is morally untenable for humans and chimpanzees. Therefore, the discovery of the specific genomic changes that make species different will rely largely on computational and experimental searches for putative functional differences.

The experimental approach discussed here begins to identify the DNA differences

that may influence gene expression. The large number of changes discovered, however, emphasizes the difficulty of the problem. Distinguishing between DNA changes that merely alter transcription factor binding and those that actually alter the phenotype requires innovative approaches for inferring the phenotypic consequences of molecular switches.

References

1. The Chimpanzee Sequencing and Analysis Consortium, *Nature* **437**, 69 (2005).
2. A. R. Borneman *et al.*, *Science* **317**, 815 (2007).
3. R. J. White, *Gene Transcription: Mechanisms and Control* (Blackwell Science, Oxford, 2001).
4. M. C. King, A. C. Wilson, *Science* **188**, 107 (1975).
5. G. A. Wray, *Nat. Rev. Genet.* **8**, 206 (2007).
6. S. W. Doniger, J. C. Fay, *PLoS Comput. Biol.* **3**, e99 (2007).
7. A. M. Moses *et al.*, *PLoS Comput. Biol.* **2**, e130 (2006).
8. The ENCODE Project Consortium, *Nature* **447**, 799 (2007).
9. V. R. Iyer *et al.*, *Nature* **409**, 533 (2001).
10. B. Ren *et al.*, *Science* **290**, 2306 (2000).
11. D. T. Odom *et al.*, *Nat. Genet.* **39**, 730 (2007).
12. M. Z. Ludwig, C. Bergman, N. H. Patel, M. Kreitman, *Nature* **403**, 564 (2000).
13. A. P. McGregor *et al.*, *Evol. Dev.* **3**, 397 (2001).
14. J. L. Hartman IV, B. Garvik, L. Hartwell, *Science* **291**, 1001 (2001).
15. H. Kacser, J. A. Burns, *Genetics* **97**, 639 (1981).

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CHEMISTRY

Molecules Take the Heat

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Problems of heating and heat transfer are ubiquitous in everyday life, from planning efficient air conditioners to dealing with overheated car engines. Such heat transfer is also of critical importance for the stability and performance of the extremely small systems considered in nanotechnology applications. In this regime, new scientific questions arise. In particular, advances in molecular electronics (where molecules are active components in nanometer-scale electronic circuits) require heating and heat transport to be understood and controlled on the molecular scale. On page 787 of this issue, Dlott and co-workers (1) report an important step in this direction. The authors describe and apply a novel method for measuring heat conduction through a monomolecular layer.

Heat flow into or out of a macroscopic system can easily be monitored by measuring the change in the system temperature with a conventional thermometer. Carrying out such measurements on the molecular scale is much more difficult. First, in a heat-conducting molecular wire, local temperature may change along the molecule, requiring temperature to be gauged with submolecular resolution. Second, the thermal response may need to be detected at the picosecond ($1 \text{ ps} = 10^{-12} \text{ s}$) time scale that characterizes molecular relaxation processes. Finally, researchers have to guard against artifacts associated with noise and cope with competing energy transfer processes to and from the surrounding macroscopic environment.

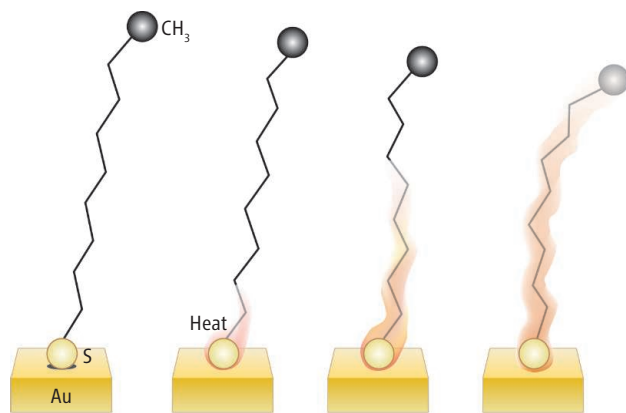
Schwab *et al.* have previously scaled thermal measurements down to a few micrometers (2), and Kim *et al.* have measured the heat transport properties of carbon nanotubes of

Advances in understanding how heat is transported through molecules will help to guide the development of molecular electronic devices.

similar length (3). Dlott and co-workers now take a bottom-up approach, studying heat transport through monomolecular hydrocarbon layers of varying chain lengths with 6 to 24 carbon atoms. In these insulating systems, heat transport is dominated by vibrational motions.

R. Y. Wang *et al.* have previously reported experiments in which a monomolecular layer connects gallium arsenide and gold surfaces via sulfur end groups. They inferred the thermal conduction of the layer from the electrical resistance to an oscillatory driving current on the gold (4). Dlott and co-workers use a different approach: They attach the molecules at one end via sulfur bonds to a gold layer deposited on glass; the other ends, terminated by methyl groups, point outward. These methyl ends form a two-dimensional surface, situated above the gold substrate at a distance determined by the length of the molecular

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How molecules heat up. In the experiments reported by Dlott and co-workers, heat is transferred from the heated gold substrate along the molecular chain, causing the chain to become increasingly disordered.

chain and its tilt with respect to the surface. The authors use a short laser pulse to heat the gold substrate to an estimated temperature of 800°C and measure the rate at which thermal energy reaches the methyl end of the molecules (see the first figure). They do so by using a method called sum-frequency generation to follow the disorder that develops as the methyl groups heat up.

Analysis of the observed time evolution yields two characteristic times, both proportional to the molecular chain length. Dlott and co-workers interpret the time delay, t_0 , between the heating laser pulse and the onset of disorder at the methyl end of the monomolecular layer as the time it takes for the heat pulse to travel between the hot gold substrate and that methyl end. Its linear dependence on chain length indicates the ballistic (that is, interruption-free) nature of this travel. The other time, τ , governs the relaxation of this energy pulse and the evolution of thermal disorder; its dependence on molecular length reflects the fact that the rate of temperature increase in the monomolecular layer is inversely proportional to its heat capacity and, therefore, to its thickness.

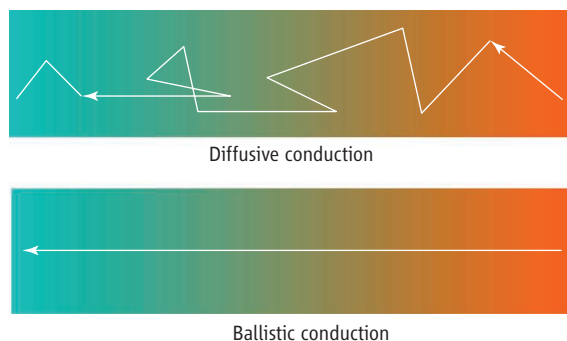
The ballistic heat transfer observed in (1, 4) is similar to the free propagation of energy along a chain of beads connected by harmonic springs after the first bead is pushed (see the second figure, bottom panel). In contrast, macroscopic heat conduction is an energy-diffusion process (see the second figure, top panel), governed by collisions with impurities and anharmonic interactions, in which heat spreads like a drop of ink inserted into water.

Dlott and co-workers find that t_0 and τ extrapolate to essentially zero at chain lengths

shorter than four carbon atoms. If we think of the molecule as a collection of ballistic pathways for energy transfer (called normal modes), most of these pathways appear to be operational for chains shorter than four atoms but become blocked (localized) beyond this length. These observations are consistent with calculations (5) and earlier observations (6) of chain-length dependence of vibrational energy transfer in alkane molecules.

These studies (1, 4) continue a string of recent exciting experiments on heat transport in nanojunctions, which demonstrated the existence of a fundamental quantum unit of heat transport (that is, a limit on the maximum conductance per pathway) (2, 7), thermal rectification (that is, preferred conduction in one direction) (8) and a transistor-like nanorefrigerator (9). These experiments raise important issues regarding the nature of heat conduction in such junctions, including molecular junctions.

First is the analogy between energy transfer and electronic transport in such systems. In their ballistic regimes, both of these transport phenomena can be described by Landauer's



theory for electronic conduction. For example, the quantum unit of heat conduction has the same origin as the analogous unit in electronic conduction. Considerations of molecular heat rectification (8, 10) were motivated by earlier studies of rectification in molecular-conduction junctions. Ge *et al.* (11) have reported first steps toward addressing the relation between structure and function in molecular heat conduction, a problem much studied in electronic conduction.

Second is the realization that a full description of molecular conduction junctions requires consideration of both electronic and heat conduction, which together determine

the temperature rise in such systems under operating conditions. Theoreticians have only recently targeted this important problem (10), and a first attempt to determine junction temperature was recently made (12). The same framework can be used to discuss the thermoelectric effect in molecular junctions (13, 14), whose first experimental manifestation was recently published (15).

Next is the observation that molecular (vibrational) heat transport is closely related to the long-studied problem of molecular vibrational energy redistribution, which determines the amount of energy available to the reaction in many chemical processes. Future efforts to elucidate energy transfer pathways and identify efficient carrier modes in molecular heat conduction will benefit from experience gained in these earlier studies.

Finally, the ballistic heat transport on the molecular scale must become diffusive in larger systems, where anharmonic interactions and external collisions become effective. The role played by such interactions and the nature of this change are other important issues for future studies.

Thermometry, heat conduction, and thermoelectricity are old problems that pose new fundamental questions and experimental challenges when studied on the molecular scale. Heating issues in molecular electronics and visions of future applications to molecular heat engines and nanorefrigerators add a strong technological motivation for these studies. The experiment of Dlott and co-workers and other recent advances (4, 7–9, 11, 12, 15) are first important steps in what promises to be an exciting endeavor.

References

1. Z. Wang *et al.*, *Science* **317**, 787 (2007).
2. K. Schwab, E. A. Henriksen, J. M. Worlock, M. L. Roukes, *Nature* **404**, 974 (2000).
3. P. Kim, L. Shi, A. Majumdar, P. L. McEuen, *Phys. Rev. Lett.* **87**, 215502 (2001).
4. R. Y. Wang, R. A. Segalman, A. Majumdar, *Appl. Phys. Lett.* **89**, 173113 (2006).
5. D. Segal, A. Nitzan, P. Hanggi, *J. Chem. Phys.* **119**, 6840 (2003).
6. D. Schwarzer, P. Kutne, C. Schroder, J. Troe, *J. Chem. Phys.* **121**, 1754 (2004).
7. M. Meschke, W. Guichard, J. P. Pekola, *Nature* **444**, 187 (2006).
8. C. W. Chang, D. Okawa, A. Majumdar, A. Zettl, *Science* **314**, 1121 (2006).
9. O.-P. Saira *et al.*, *Phys. Rev. Lett.* **99**, 027203 (2007).
10. M. Galperin, M. A. Ratner, A. Nitzan, *J. Phys. Cond. Mat.* **19**, 103201 (2007).
11. Z. Ge, D. G. Cahill, P. V. Braun, *Phys. Rev. Lett.* **96**, 186101 (2006).
12. Z. F. Huang, B. Q. Xu, Y. C. Chen, M. Di Ventra, N. J. Tao, *Nano Letters* **6**, 1240 (2006).
13. M. Paulsson, S. Datta, *Phys. Rev. B* **67**, 241403 (2003).
14. D. Segal, *Phys. Rev. B* **72**, 165426 (2005).
15. P. Reddy, S.-Y. Jang, R. A. Segalman, A. Majumdar, *Science* **315**, 1568 (2007).

10.1126/science.1147011