(incoherent) undulator radiation with an electron beam. As a beam of electrons passes through an undulator, the interaction of the beam with the radiation it emits causes it to be modulated into small groups (micro-bunches) separated by a distance equal to the wavelength of the radiation. In turn, these micro-bunches emit further radiation at a wavelength equivalent to this distance, causing them to contribute coherently to the growing radiation field. This process requires the generation of electron beams of extremely high current and small emittance and energy spread, and the construction of a precisely engineered undulator exceeding a hundred metres in length. For an FEL based on a conventional radiofrequency particle accelerator[9], this necessitates the use of a long, multistage bunch compressor called a 'chicane', which, as electrons bunch, compresses from an initial length of a few picoseconds to the order of 100 fs, to increase the current density of the electron beam up to the kiloampere level before injection into the undulator. But for the beams produced by a femtosecond-pulsed laser, such constraints are significantly relaxed.

The present understanding of the mechanism for the production of intense quasi-mono-energetic electron beams from laser-plasma accelerators is that plasma electrons are blown out to form a cavity known as a bubble[10] behind the laser pulse. The blow out of these electrons causes the development of a so-called 'wakefield', arising from the positive ions left behind in the tail of the bubble, which can generate immense electric fields of the order of teravolts per metre. This wakefield traps short packets of electrons and accelerates them to energies determined by the characteristics of the driving laser and its interaction with the plasma. Most significantly, the bunch size of the resulting electron beam is inherently much smaller than the bubble, which is equivalent to the plasma wavelength. And through appropriate control of the laser parameters, the relative energy spread may be minimized to the order of 0.1% for a 1-GeV beam, and a normalized emittance down to 0.1–1π mm mrad achieved. Such improvements should enable the production of a beam with an electron bunch length as short as 10 fs, and an effective beam current of up to 100 kA. As well as removing the need for a compression stage, this substantially reduces the required undulator length to just a few metres[11] — dramatically improving its ease of manufacture and cost.

The spontaneous emission of such a set-up in itself should be of sufficient brilliance to be of use to those who would otherwise have to wait for time on a conventional synchrotron to conduct their studies. The action of SASE, however, should boost this by some seven to eight orders of magnitude[12], enabling it to operate at a level comparable to a much larger and much more expensive FEL (see Fig. 1b). Coupled with steady progress in the performance and reduction in cost of the terawatt laser systems, this has the potential to put an FEL in every major university in the world, with momentous implications for the ability of physicists, chemists and biologists to study the dynamics of the natural world at the atomic scale.

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BIOPHYSICS

Cell commuters avoid delays

The rates of chemical reactions in a cell are limited by the time it takes the reactants to find each other through brownian motion. Thus diffusion determines the timescales of life — but can some reactions beat the diffusion limit?

Leonid Mirny

is in the Harvard–MIT Division of Health Sciences and Technology, and the Department of Physics, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139, USA.

e-mail: leonid@mit.edu

Practically all reactions within the biological cell are catalysed, or facilitated, by enzymes. DNA duplication is catalysed by polymerases; food digestion is catalysed by proteases; and the conversion of sugars into alcohol in catalysed by zymases, the first enzymes to be discovered. Although enzymes can accelerate the chemical reaction when the required reactants are present, they have little control over the supply of reagents. Most reagents diffuse freely in the cell until they collide with an enzyme and are chemically transformed. In 1917 Marian Smoluchowski[1] calculated the relationship between the rates of chemical reactions and the diffusion coefficient of the participating molecules, thus setting the diffusion limit of reaction rates.

The diffusion coefficients for biological molecules vary significantly depending on the size of the molecules, according to the Stokes–Einstein equation. Small molecules, of about 0.5 nm diameter (such as sugars and nucleotides), diffuse quickly with a diffusion coefficient, D, of about 100 $\mu m^2\ s^{-1}$; molecules of the size of a protein (3–5 nm) diffuse more slowly ($D \approx 3$–$10\ \mu m^2\ s^{-1}$), whereas larger vesicles (more than 10 nm in diameter) diffuse as slowly as $D \approx 0.1\ \mu m^2\ s^{-1}$, requiring hours to travel across a typical human cell (15 μm in diameter). Molecular crowding and stickiness of the cellular environment can lead to subdiffusion[2], threatening to make such journeys even longer and significantly slowing all the reactions in a cell. But molecules can in fact reach their targets faster than by simple diffusion — and

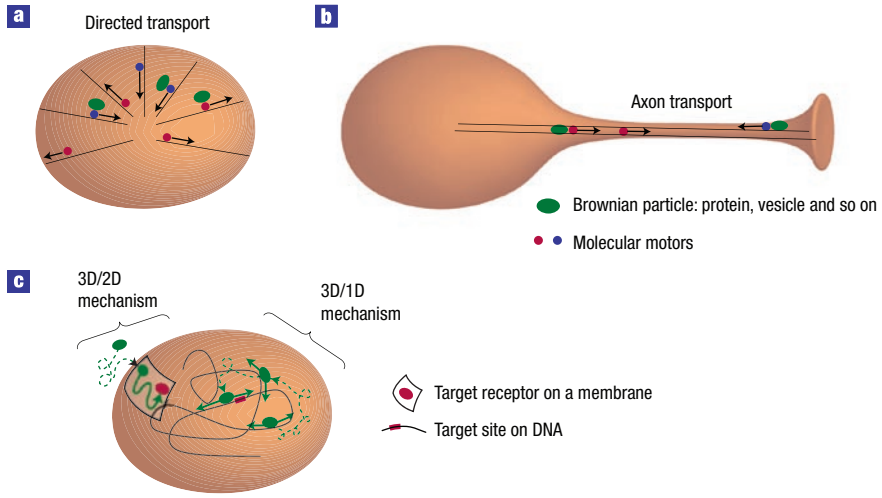

Figure 1 Transport network. **a–c**, The otherwise brownian motion of proteins and vesicles is accelerated when such a body hitches a ride on a 'molecular motor' moving along a filamentous track across the cell (**a**) — a mechanism that is also seen in neuronal axons (**b**). But this is an energy-consuming process, and in fact there are ways to speed up the diffusive motion of the particles without burning energy, such as by reducing the dimensionality of the search (**c**). A protein's 3D search for a receptor on the cell membrane is reduced to two dimensions if the protein binds to the membrane and then continues to seek its target; a 3D search for a target site on a strand of DNA is only a 1D problem if the protein binds somewhere on the strand and then hunts along its length. Loverdo *et al.*[3] show how an optimum combination of all of these mechanisms can accelerate transport, and hence reactions, in the cell.

on page 134 of this issue, Loverdo *et al.*[3] suggest a mechanism for doing so.

One way to speed up reactions is to establish a directed transport system to move molecules continuously in one direction, one that consumes energy without violating the second law of thermodynamics. To implement such transport, cells build tracks (long filaments that span across the cell) and use 'molecular motors'(proteins that consume energy and travel in a particular direction along these tracks) to carry molecules from one location to another (Fig. 1a,b). But not all the molecules have the luxury of riding on molecular motors. First, this is energetically expensive, and, second, most of the locations in the cell are not serviced by this transit authority, leaving most molecules at the mercy of diffusion.

Can diffusion be accelerated without energy consumption? In 1968 Adam and Delbrück[4] showed that a reduction of dimensionality solves the problem. For example, if a protein is searching for a membrane receptor, the process is much faster if the protein reduces the dimensionality of the search from three to two dimensions, by binding to the membrane and continuing its search along the membrane[4] (Fig. 1c). The idea of dimensionality reduction is particularly important in understanding protein–DNA interactions in which the target (a particular site on a long DNA molecule) needs to be bound by a protein that is freely diffusing inside a cell. To explain the faster-than-Smoluchowski binding rate that was observed experimentally, it was proposed[5,6] that the protein first binds DNA in a random place and then slides along it to the target, effectively performing one-dimensional diffusion, and thus reducing a 3D search to a 1D search. Diffusion is facilitated if the protein alternates between periods of 3D diffusion and 1D sliding along the DNA moelcule (Fig. 1c). This mechanism has been further developed in a number of theoretical studies[7–10], confirmed by biochemical experiments[8], and recently visualized on a single-molecule level *in vitro*[11], and *in vivo*[12]. Remarkably, if the time spent in 3D/1D phases is optimal, this mechanism can provide a 100–1,000-fold acceleration of binding[8,10].

Loverdo *et al.*[3] introduce a new mechanism of facilitated diffusion that combines the ideas of both the transport-driven and dimensionality-reduction mechanisms. Similar to the protein–DNA search method, a diffusing particle alternates between spatial diffusion and 1D motion. The latter, however, is not diffusive but directed: a particle associates with a motor moving in one direction along a track, which points in some random direction in the cell. This is similar to randomly hopping on and off trains in a commuter network and wandering between stations by a random walk; some trains may take you closer to your destination, others may take you further away. Loverdo *et al.* show that optimal partitioning of time spent between free diffusion and transport can lead to significant acceleration of binding reactions. Diffusion allows a thorough search of a small area, and transport can take a particle to a new area very quickly: finding a target in three dimensions means visiting every location in the cell, but transport along randomly directed tracks can help to stir particles around.

The nature of brownian motion depends on the dimensionality of the system. Diffusion in 1D and 2D is highly redundant — the same point or area will be visited repeatedly by a random walker — but 3D diffusion is not. Fast transport helps a particle to explore new locations, thus making the search less redundant and faster. Consistent with these arguments, Loverdo *et al.* show that 1D transport has a modest effect on the duration of 3D searches, but has a strong effect in 2D and 1D situations, which are actually quite common in cells. The motion of large vesicles in an almost flat cell can be considered to be a 2D process. An important biological example of an almost-1D process is molecular commuting in axons — the long projections of neurons that are typically less than a micrometre in diameter but more than a millimetre in length (with some axons in the body extending up to a metre).

But the size of particles also counts, and small particles that can diffuse sufficiently quickly do not benefit from the motor rides. The authors show that transport significantly speeds searching for particles larger than 10 nm, suggesting that the proposed mechanism applies mostly to organelles and cargo vesicles that otherwise diffuse very slowly. These two aspects — low dimensionality of the diffusive process and large size of the particle — distinguish the proposed mechanism from the 3D/1D diffusion that works for individual DNA-binding proteins. Despite this limitation, the study by Loverdo *et al.* can be applied in a number of biological situations.

Their mechanism is consistent with our understanding of transport in axons and dendrites, where individual molecules are packed into cargo vesicles that are transported by molecular motors along microtubules (Fig. 1b). Such transport,

however, is believed to be directional: vesicles are labelled for travel from the centre of the cell to the periphery, or *vice versa*. A significant acceleration can be achieved even if vesicles hop onto inbound or outbound motors at random. This mechanism may be particularly relevant for dendrites where microtubules are not oriented and thus motors of the same type travel both inbound and outbound, thus making it impossible for a commuting molecule to say where a particular motor goes. Such non-directional transport can be tested experimentally by single-molecule tracking of individual vesicles or by their affinity for both dynein motors that move inbound and kinesin motors that move outbound in axons.

Another implication is for intracellular transport of large organelles using motors that move along a network of actin filaments. Although organelles are known to be moved by molecular motors, it is assumed that this transport is directional and motors deliver their cargo to a final destination. The study by Loverdo *et al.* opens an intriguing possibility that such transport could be, in part, non-directional and is another mechanism to speed up diffusion — like stirring a teaspoon in a cup of coffee.

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SUPERCONDUCTIVITY

Bring on the real resonance

The relationship between high-temperature superconductivity and the pseudogap state is further probed by an atomic-scale study that shows that what was believed to be a signature of the superconducting state exists in both states.

Wei-Sheng Lee & Zhi-Xun Shen

are in the Departments of Applied Physics and Physics, and SLAC Photon Science, Stanford University, Stanford, California 94305-4045, USA.

e-mail: wslee@stanford.edu; zxshen@stanford.edu

A phase transition is one of the most interesting and profound phenomena in nature. On a temperature change through a critical value T_c, matter changes its state from one to another. The nature of these states is often encoded in the way they evolve through the thermodynamic transition. However, the copper-oxide-based high-temperature superconductors exhibit a transition from the superconducting state that is anything but conventional; some properties show little change across T_c, whereas others, such as the resistivity, change abruptly. This behaviour has led to the speculation of an intimate relation between superconductivity and the 'pseudogap' state directly above it in temperature. Several recent temperature-dependent spectroscopy measurements across T_c have already revealed startling new information[1–4].

A trademark of high-T_c superconductors is the prominent role of local physics, in the range ~1 nm, driven by the strong interactions. As such, atomically resolved spectroscopy such as scanning tunnelling microscopy (STM) has had a vital role in unravelling the mystery of high-T_c physics[5]. Scanning tunnelling microscopy investigations have revealed a wealth of phenomena at low temperatures. However, it has been a technical challenge to keep the fine tip (only a few ångströms in size) 'space-registered' against the thermal expansion and fluctuation caused when varying the temperature. Only recently, researchers managed to overcome this difficulty to perform space-registered temperature-dependent STM measurements[1–4]. Using this improved capability, Chatterjee *et al.*[1] report on page 108 of this issue how the electrons in a high-T_c superconductor behave when scattering from an impurity that serves as a 'marker' of the electronic wavefunction. Surprisingly, these authors found that the scattering pattern and the associated spectra from the impurity do not change across the critical temperature. As the presence or absence of change across T_c is often the hallmark of the underlying physics, their finding will undoubtedly fuel debates in the field, especially on the contested relationship between the superconducting state and the pseudogap state.

The central question of high-T_c superconductivity is how the superconducting state forms. In conventional superconductors, the electron is in a metallic state at a temperature higher than T_c, which is generally referred to as a 'normal' state where the density of states near the Fermi level, E_F — the uppermost energy level of the ground-state electrons — is smooth and generally treated as featureless. Below T_c, the metallic state is no longer the ground state of the electrons; the electrons tend to bind into 'Cooper pairs' and the system changes from a metal to a superconductor. As a result, the superconducting phase transition is accompanied by the opening of a gap in the density of states at the Fermi level, which is a measure of the binding energy of a Cooper pair. The situation in a high-T_c superconductor is quite different; its normal state is not normal at all. Instead, it is known as the pseudogap state[6], which exists in a wide range of chemical composition and temperature in the phase diagram. In contrast with a typical metallic state, the pseudogap state also displays a gap or spectral weight suppression near the Fermi energy, and shares many similarities with the superconducting gap below T_c. The nature of this pseudogap is another key question in the high-T_c saga.

Scanning tunnelling microscopy is capable of measuring the local density of states, and has been used to measure energy gaps in high-T_c superconducting cuprates[5]. The persistence of an energy gap above T_c in STM spectra is an important part of the phenomenology establishing the presence of the pseudogap. Furthermore,