subunit, which help to anchor the subcomplex.

Procession of RNA polymerases along a DNA template is facilitated by a closed-clamp component. The structures of Pol I reveal that the A43–A14 subcomplex, which comprises a fixed stalk (Fig. 1), contributes to a permanently closed state of the clamp and, therefore, to the high processivity of Pol I. By contrast, the clamps of other RNA polymerases are mobile elements. In Pol II, for example, attachment of the Rpb4–Rpb7 stalk locks the clamp in a closed state over the complex of RNA and DNA template during transcription, but this stalk is detachable[9,10].

Intriguingly, both teams' crystals are dimers of Pol I, in which the stalk of each Pol I inserts into the DNA-binding cleft of the other Pol I, through the A43 C-terminal 'connector' domain, thus making extensive contacts with the cleft and the coiled-coil motif of the clamp. The dimers have an unusually wide cleft (Fig. 1), perhaps partly because of this A43-connector insertion.

The cleft is too wide to anchor the complex of RNA and DNA template, particularly near the active site. This widening contributes to further rearrangements near the active site. (For example, crucial 'aspartate-loop' interactions are configured differently from those in Pol II; the 'bridge' helix contributing to DNA movement through the active site is unfolded in the middle and kinked; and there is partial blockage of the gate to the exit channel for newly synthesized RNA.) Furthermore, the wide cleft is occupied by a Pol I-specific extended loop of A190, which the authors refer to as the expander[3] or DNA-mimicking loop[2]. Because of its location, this loop would interfere with DNA loading at the active site. In one of the three Pol I structures presented by Fernández-Tornero *et al.*, no loop is detectable at the active site, hinting that it is unlikely to be essential for stabilization of the expanded cleft, although not excluding a role in its establishment.

Fernández-Tornero and colleagues' crystals display varying degrees of cleft widening. Comparative structural modelling of RNA polymerases suggests that the Pol I cleft widens as a result of relative pivoting of 'core' and 'shelf' modules (which are formed mainly by the largest subunits, A135 and A190) at the base of the cleft, near the active site[2,3] (Fig. 1). Engel *et al.* draw parallels to similar domain pivoting in inhibitor-bound or paused bacterial Pol, in which a pivoted or ratcheted state is associated with cleft opening and coupled rearrangements of domains near the active centre, inactivating the polymerase[11,12].

Because the new structures imply that the DNA template must be loaded into Pol I that has a closed clamp, perhaps the open or shut status of the cleft contributes to DNA-loading efficiency. It is possible that binding of the DNA template in the open cleft of a Pol I monomer triggers cleft closure, potentially coupled with relocation of the expander loop, rendering the enzyme active. Cleft closure by pivoting of the core and shelf modules presumably occurs concomitantly with refolding of the bridge helix, opening of the RNA-exit gate and the approach of A135 to anchor the DNA template in the active site. An understanding of the exact rearrangements will hinge on structural analysis of Pol I engaged in transcript elongation and, therefore, in complex with DNA and RNA.

Engel *et al.* propose that regulatory factors binding at the core–shelf interface might facilitate cleft closure. They speculate that Rrn3 (a factor that tethers Pol I to proteins bound specifically to promoter DNA sequences) triggers cleft closure by binding Pol I near the RNA-exit channel[3,13]. This attractive possibility awaits confirmation, perhaps through analysis of a Pol I–Rrn3 co-crystal. Conversely, factors that terminate transcription by Pol I might induce cleft opening. In all probability, the regulation of transcription by modulation of the core–shelf interface, which is seen in bacterial Pol, is also a feature of eukaryotic RNA polymerases[3].

Solving the crystal structure of the complete Pol I complex is a triumph, providing a wealth of information with which to build a picture of the specific mechanisms and control of rRNA-gene transcription in eukaryotes and also to explore the general mechanisms of transcription by all RNA polymerases. Another tour de force will be necessary to solve the structure of Pol I in transcription-elongation mode and, further, that of the complete Pol I pre-initiation complex, incorporating Rrn3, the core promoter-binding factors (Rrn6, Rrn7 and Rrn11 with TBP) and the rDNA promoter sequences. Such structures, together with those presented by Fernández-Tornero *et al.* and Engel *et al.*, will yield information that is vital for establishing when and where crucial protein and DNA contacts are made, disrupted and rearranged as Pol I steps through the transcription cycle. ■

Joost Zomerdijk *is at the Centre for Gene Regulation and Expression, College of Life Sciences, University of Dundee, Dundee DD1 5EH, UK.*
e-mail: j.zomerdijk@dundee.ac.uk

1. Russell, J. & Zomerdijk, J. C. B. M. *Trends Biochem. Sci.* **30,** 87–96 (2005).
2. Fernández-Tornero, C. *et al. Nature* **502,** 644–649 (2013).
3. Engel, C., Sainsbury, S., Cheung, A. C., Kostrewa, D. & Cramer, P. *Nature* **502,** 650–655 (2013).
4. Werner, F. & Grohmann, D. *Nature Rev. Microbiol.* **9,** 85–98 (2011).
5. Cramer, P. *et al. Annu. Rev. Biophys.* **37,** 337–352 (2008).
6. Vannini, A. & Cramer, P. *Mol. Cell* **45,** 439–446 (2012).
7. Kuhn, C.-D. *et al. Cell* **131,** 1260–1272 (2007).
8. Geiger, S. R. *et al. Mol. Cell* **39,** 583–594 (2010).
9. Armache, K.-J., Kettenberger, H. & Cramer, P. *Proc. Natl Acad. Sci. USA* **100,** 6964–6968 (2003).
10. Bushnell, D. A. & Kornberg, R. D. *Proc. Natl Acad. Sci. USA* **100,** 6969–6973 (2003).
11. Tagami, S. *et al. Nature* **468,** 978–982 (2010).
12. Weixlbaumer, A., Leon, K., Landick, R. & Darst, S. A. *Cell* **152,** 431–441 (2013).
13. Blattner, C. *et al. Genes Dev.* **25,** 2093–2105 (2011).

QUANTUM PHYSICS

Single electrons pop out of the Fermi sea

The ability to control individual electrons in an electronic conductor would pave the way for novel quantum technologies. Single electrons emerging from a sea of their fellows in a nanoscale electrode can now be generated. SEE LETTER P.659

CHRISTIAN FLINDT

Splashing water in the bath usually leads to small waves, splashes and droplets. Similarly, applying a voltage pulse to the sea of electrons in a nanoscale electrode produces a complex quantum state involving several electrons that have been kicked out of the sea, as well as holes — or missing electrons — left behind. On page 659 of this issue, Dubois *et al.*[1] report the first experimental voltage-pulse generation of just a single electron, not several, emerging on top of an electronic sea*.

*This article and the paper under discussion[1] were published online on 23 October 2013.

A nanoscale electrode is a reservoir of electrons, often referred to as a Fermi sea. Applying a voltage to the electrode amounts to changing the sea level by either pouring more electrons into the electrode (thus increasing the sea level) or emptying out electrons (thereby decreasing the sea level). A voltage that varies with time typically stirs up the Fermi sea and causes waves and splashes of electrons. This effect led Levitov and colleagues[2–4] to investigate theoretically how a time-dependent voltage affects a Fermi sea. Surprisingly, and quite remarkably, they found that a particular shape of voltage pulses should excite just a single electron onto the surface of the Fermi

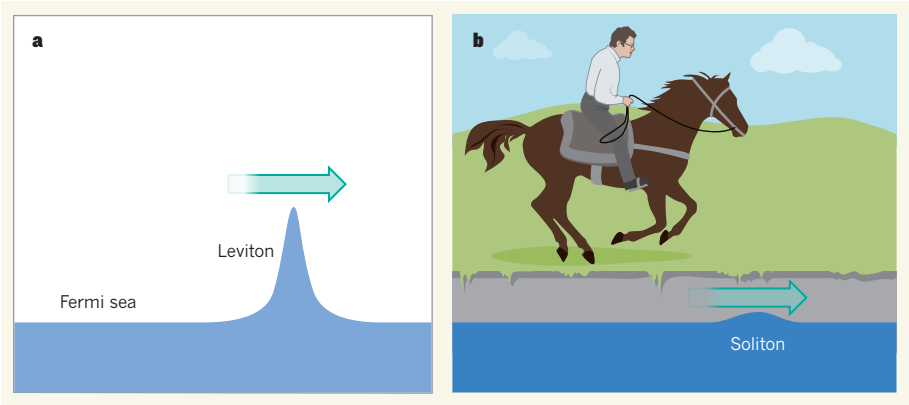

Figure 1 | Spotting solitons and levitons. **a**, Dubois *et al.*[1] have experimentally realized Levitov and colleagues' proposal[2–4] that a carefully engineered voltage pulse would bring just a single electron to the top of the Fermi sea of electrons in a nanoelectrode; they have named the resulting single-electron wavepacket a leviton. **b**, Levitons resemble solitons, waves that keep their shape while travelling at constant speed and which were first observed in Edinburgh's Union Canal by John Scott Russell while on horseback.

sea, leaving no traces behind. This job would be done by a voltage pulse that changes in time according to the mathematical function called a Lorentzian.

In their experiment, Dubois *et al.* realize the proposal by Levitov and colleagues, and they name the resulting single-electron wavepacket a leviton, because it resembles a soliton in certain ways. Solitons were first observed in the nineteenth century by the Scottish engineer John Scott Russell who noticed that a boat brought to a sudden stop in the Union Canal running into Edinburgh generated a single, localized wave of water that travelled several kilometres without changing its shape or slowing down (Fig. 1). Such self-sustained waves are now known as solitons, and they occur in a variety of systems described by non-linear wave equations.

Just like solitons, levitons of different heights, widths and creation times can be superimposed in a controllable manner and travel unhindered on top of a Fermi sea. To produce levitons, Dubois *et al.* used a nanoscale circuit consisting of two electrodes connected by a small conductor. They applied Lorentzian-shaped voltage pulses on one electrode to generate levitons that travel through the conductor to the other electrode.

Whereas Russell observed solitons in the Union Canal from the back of his horse, the observation of levitons requires sophisticated experimental techniques. To observe them, the temperature must be as low as it can get to make the Fermi sea as quiet as possible. Dubois and colleagues managed to cool their sample down to 35 millikelvin, close to absolute zero. A sequence of Lorentzian-shaped pulses should yield a noiseless flow of levitons without electrical fluctuations[2–4]. The authors measured the electrical noise[5] and found only the background noise caused by tiny thermal fluctuations. Next, they used a narrow constriction in the conductor — a quantum point contact — to filter out a fraction of the levitons. By measuring the increased noise due to the filtering, they could infer the number of emitted levitons and demonstrate that each pulse produces exactly one leviton, with no additional disturbances.

To corroborate their findings, the research team performed a Hong-Ou-Mandel experiment known from optics[6]. Here, a semi-transparent mirror randomly reflects or transmits photons into two different output arms. However, if two identical photons simultaneously hit each side of the mirror, they always exit into the same output arm. The photons are said to 'bunch', as is typical for the class of particles called bosons. Levitons, by contrast, are fermions, which 'anti-bunch' by exiting into different output arms[7]. Dubois *et al.* generated levitons in both electrodes and caused them to interfere at the quantum point contact, which acts as a semi-transparent mirror. Levitons arriving simultaneously at the quantum point contact were found to anti-bunch, confirming their fermionic nature.

Dubois and colleagues' work demonstrates unprecedented control of single electrons in the Fermi sea of a nanoelectrode, and it opens up a plethora of applications and directions for fundamental research. One can envisage future quantum electronics with levitons — levitonics — in which single levitons are emitted into a circuit architecture with edge states (formed in a strong magnetic field) that function as rails for the levitons by guiding them to beam splitters and interferometers for further processing, borrowing ideas and concepts from quantum optics.

Additional experiments might investigate the statistical properties of levitons, including the fluctuations in the number of levitons (full counting statistics[8]) and the distribution of waiting times between levitons[9]. A leviton can contain more than one electron and may even carry just a fraction of the electron charge if implemented in a one-dimensional system

50 Years Ago

During the past year, reports of a remarkable case of 'digital vision' have percolated into Britain from the U.S.S.R. … The subject … whose personality is admittedly abnormal, is said to have trained herself to distinguish colours and forms by means of her fingers and to be able to read books and newspapers by digital scanning alone … It has been shown, for example, that her reading is not impaired by interposing a plate of glass between the print and her fingers or by projecting the print on to a ground glass screen to exclude tactile sensation. It might, therefore, seem that the girl's fingers are genuinely sensitive to light … The lack of any image-forming device and the relative poverty of the nerve supply to the fingers in comparison with that of the eye constitute seemingly fatal objections to the hypothesis of 'digital vision'.
From *Nature* 2 November 1963

100 Years Ago

Vorlesungen über die Theorie der Wärmestrahlung. By Dr. Max Planck — The first edition of this book, which appeared in 1906, was reviewed in Nature … The many and varied contributions to our knowledge of radiation phenomena that have been published in the ensuing years have made it necessary for Dr. Planck to rewrite and modify the book to a considerable extent … As before, the object of the book is to apply the statistical methods previously used in the kinetic theory of gases to the phenomena of radiation … The treatment is largely based on the remarkable assumption which the author designates as the "quantum-hypothesis." … This is analogous to the electron theory, which assigns a definite magnitude to the electron or "elementary quantum" of electricity.
From *Nature* 30 November 1913

of interacting electrons known as a Luttinger liquid. Atomic levitons may also be realized in Fermi gases of cold atoms. Further down the road, one can imagine solid-state qua ntum computers with levitons acting as the fundamental carriers of quantum information. The realization of on-demand levitons is a major step forward in the attempts to realize quantum electronics with timed emissions of single electrons into a nanoscale quantum circuit. There are plenty of promising prospects ahead. ■

Christian Flindt *is in the Department of Theoretical Physics, University of Geneva, 1211 Geneva, Switzerland.*
e-mail: christian.flindt@unige.ch

1. Dubois, J. *et al. Nature* **502,** 659–663 (2013).
2. Levitov, L. S., Lee, H. & Lesovik, G. *J. Math. Phys.* **37,** 4845–4866 (1996).
3. Ivanov, D. A., Lee, H. W. & Levitov, L. S. *Phys. Rev. B* **56,** 6839–6850 (1997).
4. Keeling, J., Klich, I. & Levitov, L. S. *Phys. Rev. Lett.* **97,** 116403 (2006).
5. Blanter, Y. M. & Büttiker, M. *Phys. Rep.* **336,** 1–166 (2000).
6. Hong, C. K., Ou, Z. Y. & Mandel, L. *Phys. Rev. Lett.* **59,** 2044–2046 (1987).
7. Bocquillon, E. *et al. Science* **339,** 1054–1057 (2013).
8. Nazarov, Y. V. (ed.) *Quantum Noise in Mesoscopic Physics*, NATO Science Series (Kluwer, 2003).
9. Albert, M., Haack, G., Flindt, C. & Büttiker, M. *Phys. Rev. Lett.* **108,** 186806 (2012).

BIOPHYSICS

Rough passage across a barrier

The dynamics of chemical reactions in solution are described by Kramers' theory, but the parameters involved have eluded direct measurement. A study of protein folding reveals how this problem can be overcome. SEE LETTER P.685

BENJAMIN SCHULER & JANE CLARKE

Proteins fluctuate between different conformations to perform their sophisticated tasks. The random motion of water molecules around proteins provides an inexhaustible reservoir of thermal 'kicks', which act as the molecular driving forces of such conformational dynamics. Counterintuitively, the same thermal motions of the solvent also limit the speed of biomolecular motion, an effect known as solvent friction. But it has become increasingly clear that, in some important cases, friction within a protein molecule might be the dominant impediment to its molecular dynamics. In this issue, Chung and Eaton[1] (page 685) report one of the most impressive studies so far in which the contribution of such internal friction to dynamics is quantified for protein molecules caught in the act of folding. Remarkably, the results have implications far beyond protein folding*.

The rate at which chemical reactions proceed is most commonly conceptualized in terms of a barrier-crossing process. In the simplest case considered in most chemistry textbooks, this barrier might correspond to the energy required to break a single chemical bond in a molecule in the gas phase. The generalized concept of barrier crossing, developed by the Dutch physicist Hans Kramers and published[2] in 1940, can also be applied to much more complex processes[3], including reactions in solution, and even protein folding[4].

The formulation of such a simplified description of reaction kinetics requires two key ingredients: the shape of a suitable 'free-energy surface' that describes the energetic and entropic properties of a system at equilibrium, and the magnitude of the frictional forces that determine how fast the system can move around on its free-energy surface. Any molecule will spend almost all of its time in free-energy valleys (minima of the free-energy surface). In the case of protein folding, these valleys correspond to the folded and the unfolded states (Fig. 1).

The probability of a molecule passing from one valley to another — that is, how frequently the reaction takes place — is dominated by the height of the barrier between the valleys. The most interesting event, however, which contains essentially all of the information about the sequence of molecular steps in the reaction, is the actual crossing of the barrier. The molecules spend only a tiny fraction of their time in this transition-state region, and information about their passage is correspondingly hard to get hold of.

Chung, Eaton and colleagues last year succeeded[5] in measuring these microsecond transition-path times by recording the fluorescence from individual protein molecules and analysing the signal photon by photon, using a clever, previously reported method[6]. They have now taken these investigations a crucial step further by probing the dynamics of a small helical protein in the transition-state area in unprecedented detail.

For protein folding, information about the structural properties of molecules at the top of the barrier has previously been inferred from investigations of how individual changes in a protein's amino-acid sequence affect its folding kinetics[7]. The timescales of barrier crossing have been studied in laser-induced temperature-jump experiments[8]

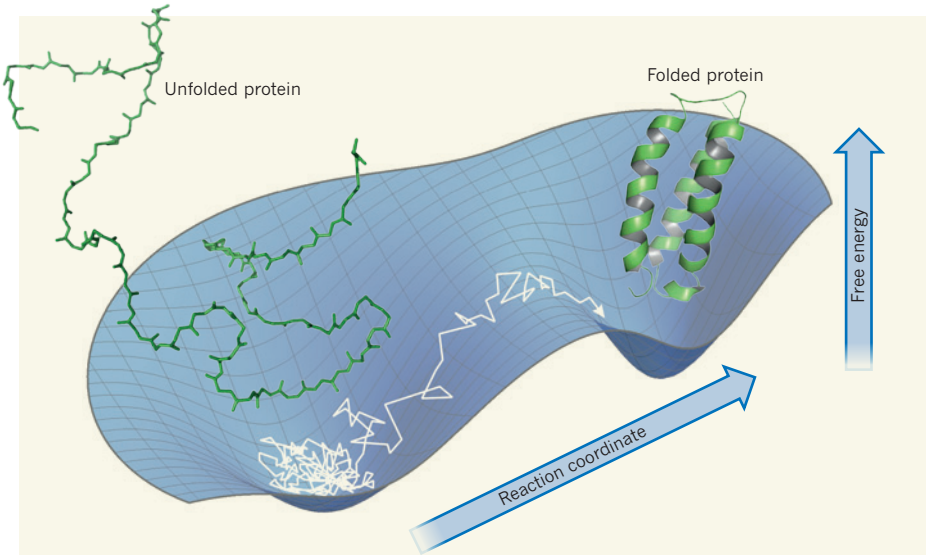

Figure 1 | Barrier crossing in protein folding. Many molecular processes can be described in terms of the diffusion of a particle on a free-energy surface, which depicts how the combined effects of energy and entropy change along a suitably chosen coordinate that represents the progress of a reaction. Here, a protein in its unfolded state corresponds to a basin on a free-energy surface; the protein must cross a free-energy barrier to reach its folded state, which constitutes another basin. The white arrow indicates the diffusive passage of the protein across the surface. Chung and Eaton[1] have used optical single-molecule experiments to probe the dynamics of the process at the top of the barrier.

*This article and the paper under discussion[1] were published online on 23 October 2013.