between an electron's spin and an applied electric field is forbidden, if it is strong enough a quantum interaction known as spin–orbit coupling provides a means of controlling spins using oscillating electric fields, and is at the heart of the new field of 'spintronics'.

Special relativity requires that an electron moving through an electric field experiences an effective magnetic field that couples its spatial motion (orbit) to its spin. In the simplest picture, spin–orbit coupling is possible because, from the viewpoint of the electron, it is the electric field that is moving, and time-varying electric fields generate a magnetic field that splits the electron's spin states in energy. The detailed picture of spin–orbit coupling has played a key part in the formulation of quantum mechanics.

For semiconductors in a magnetic field, the spin–orbit interaction can be much stronger than in an atom, owing to the high electron velocities and strong electric-field gradients produced by nuclei in the semiconductor crystal lattice[12]. As is the case in Kouwenhoven and colleagues' experiment, careful choice of material system and device geometry can lead to spin–orbit coupling that is so strong that the electron's spatial state and its spin cannot be considered separately: they collectively form a quantum state that preserves the long-lived spin component while allowing for manipulation through electric fields[13,14].

The signature of spin–orbit control has previously been identified in gallium arsenide (GaAs) semiconductor quantum devices[15], but the strong coupling in the InAs nanowire devices allows both faster control and the potential for the exchange of quantum information between optical and solid-state electronic systems. Indeed, optoelectronic devices[16,17], such as semiconductor LEDs (light-emitting diodes), have recently been demonstrated in nanowire architectures that are similar to the authors' InAs nanowire, and the possibility of transferring the quantum state of a single spin to a single photon now seems viable. The creation of such hybrid quantum systems is pivotal because they allow the unique advantages of different quantum platforms to be combined to open up new quantum technologies. The iPhone provides the perfect example of how the tight integration of optical, mechanical and electrical devices can have a significant technological impact. In quantum mechanics, this kind of integration is not easy, owing, in part, to the nature of quantum measurement and the fragility of systems that manipulate quantum information.

For Kouwenhoven and colleagues' experiment[10], an important but perhaps unexpected result is that the spin coherence lifetime, measured by a technique known as the Hahn echo pulse sequence, is significantly shorter than in GaAs. The authors' hunch is that this may result from the larger nuclear spin moment of indium compared with gallium or arsenic, which couples uncontrollably to the electron spin. To what extent this short time presents a fundamental problem requires further research, but will undoubtedly drive fresh innovation in the science and engineering of quantum systems. ■

David J. Reilly *is in the School of Physics, The University of Sydney, New South Wales 2006, Australia.*
e-mail: david.reilly@sydney.edu.au

1. Datta, S. & Das, B. *Appl. Phys. Lett.* **56,** 665–667 (1990).
2. Loss, D. & DiVincenzo, D. P. *Phys. Rev. A* **57,** 120–126 (1998).
3. Elzerman, J. M. *et al. Nature* **430,** 431–435 (2004).
4. Petta, J. R. *et al. Science* **309,** 2180–2184 (2005).
5. Pioro-Ladrière, M. *et al. Nature Phys.* **4,** 776–779 (2008).
6. Barthel, C., Reilly, D. J., Marcus, C. M., Hanson, M. P. & Gossard, A. C. *Phys. Rev. Lett.* **103,** 160503 (2009).
7. Petta, J. R., Lu, H. & Gossard, A. C. *Science* **327,** 669–672 (2010).
8. Bluhm, H. *et al.* Preprint at http://arxiv.org/abs/1005.2995 (2010).
9. Barthel, C., Medford, J., Marcus, C. M., Hanson, M. P. & Gossard, A. C. Preprint at http://arxiv.org/abs/1007.4255 (2010).
10. Nadj-Perge, S., Frolov, S. M., Bakkers, E. P. A. M. & Kouwenhoven, L. P. *Nature* **468,** 1084–1087 (2010).
11. Koppens, F. H. L. *et al. Nature* **442,** 766–771 (2006).
12. Rashba, E. I. *Future Trends in Microelectronics: Up the Nano Creek* (eds Luryi, S., Xu, J. & Zaslavsky, A.) 28–40 (Wiley, 2007).
13. Golovach, V. N., Borhani, M. & Loss, D. *Phys. Rev. B* **74,** 165319 (2006).
14. Flindt, C., Sørensen, A. S. & Flensberg, K. *Phys. Rev. Lett.* **97,** 240501 (2006).
15. Nowack, K. C., Koppens, F. H. L., Nazarov, Y. V. & Vandersypen, L. M. K. *Science* **318,** 1430–1433 (2007).
16. Minot, E. D. *et al. Nano Lett.* **7,** 367–371 (2007).
17. van Weert, M. H. M. *et al. Nano Lett.* **9,** 1989–1993 (2009).

STRUCTURAL BIOLOGY

Proteins in dynamic equilibrium

Protein molecules in solution exist as an equilibrium of different conformations, but the sizes and shifts of these populations cannot be determined from static structures. A report now shows how they can be measured in solution.

PAU BERNADÓ & MARTIN BLACKLEDGE

Technologies for determining protein structure have contributed immensely to our understanding of molecular biology, providing us with three-dimensional models at atomic resolution to explain the molecular basis of physiologically important interactions between biochemically active molecules[1]. But as we emerge from a decade of massive investment in structural genomic projects, it is becoming increasingly clear that a complete description of biomolecular activity also requires an understanding of the nature and role of protein conformational dynamics. Reporting in the *Proceedings of the National Academy of Sciences*, Yang *et al.*[2] describe a method that could provide us with just such an understanding — a combination of computational simulations and experimental X-ray scattering data enables the observation of shifts in the equilibrium population of protein conformational states.

Proteins must be able to move in order to function. Such motion can be on a small scale — involving atomic fluctuations around an average structure — or can involve large-scale reorganization of molecular machinery[3]. Experimental data for proteins normally represent average values for the entire ensemble of conformations, but structural determinations routinely represent a single, static structure. The dynamic trajectories of protein movement can be invoked, by trapping and observing active or inactive conformational states and deducing the pathway that connects them. But direct access to functionally important protein motions requires new experimental and analytical tools that can accurately map conformational equilibria.

In recent years, structural biologists have risen to this challenge by developing techniques to describe dynamic systems in terms of ensembles of structures, thus providing information about the importance of molecular motion for biological function[4,5]. For example, nuclear magnetic resonance (NMR) spectroscopy provides ensemble-averaged experimental parameters that describe the intrinsic conformational dynamics that control molecular recognition[6]. Changes in global orientations of protein domains, or in the shape and size of molecular assemblies, are more difficult to characterize using NMR alone, but these can be determined using a method known as small-angle X-ray scattering (SAXS)[7,8].

It is gradually becoming established that the most appropriate way to define proteins' conformational disorder is to explicitly identify the

ensembles of conformations that coexist and rapidly interconvert in dynamic equilibrium. Because of the vast number of conformations that can potentially be adopted by flexible proteins, accurate identification of these ensembles presents an ill-defined 'inverse problem' — how can the ensembles be identified from acquired data? The solution requires the development of robust statistical approaches to determine the probability that any particular multi-conformational equilibrium will exist[9]. A true statistical mechanical description of an ensemble also requires a quantitative assessment of the weighting of each conformation in the Boltzmann probability distribution of conformations. Yang *et al.* elegantly address both of these considerations in their study[2].

The authors used SAXS to study a multi-domain tyrosine kinase enzyme known as Hck, which belongs to the Src family of kinases. Src kinases are thought to be involved in the signalling pathways that govern cell growth and proliferation, and are implicated in many human diseases, most notably cancer. The regulation of Src kinases is known to involve large-scale reorientation of the proteins' domains.

Activation of these enzymes has been proposed to be a two-step process. In the first step, two small domains (SH2 and SH3) form intramolecular interactions with the carboxy and amino termini of a larger, catalytic domain to form a compact, inactive 'assembled' conformation. In the second step, the release of the intramolecular interactions destabilizes the compact structure, causing the formation of a more open, 'disassembled' state (the active conformation). This model of regulation has been delineated from crystal structures of different Src proteins at the end points of the activation process[10,11]. Crucially, however, the dynamic flux between these states was poorly understood — until Yang *et al.* published their report[2].

The authors studied Hck in solution, both in its free form and in complex with SH2- and SH3-binding peptides. First, they used coarse-grained (low resolution) molecular dynamics simulations to extensively explore and sample accessible conformations of the protein in a physically meaningful way. Next, they used a clustering analysis on the resulting data to obtain a set of sub-states for the protein, which they used to interpret their experimentally obtained SAXS curves.

A common problem with statistical analyses is over-fitting, which occurs when a statistical model describes noise, rather than the desired underlying relationship. Yang *et al.* intelligently avoided over-fitting by evoking only the minimum number of states that could be distinguished from their SAXS data. In addition, and equally importantly, the authors used a Bayesian statistical analysis of these states to accurately determine their fractional populations under different experimental conditions that change the conformational equilibrium.

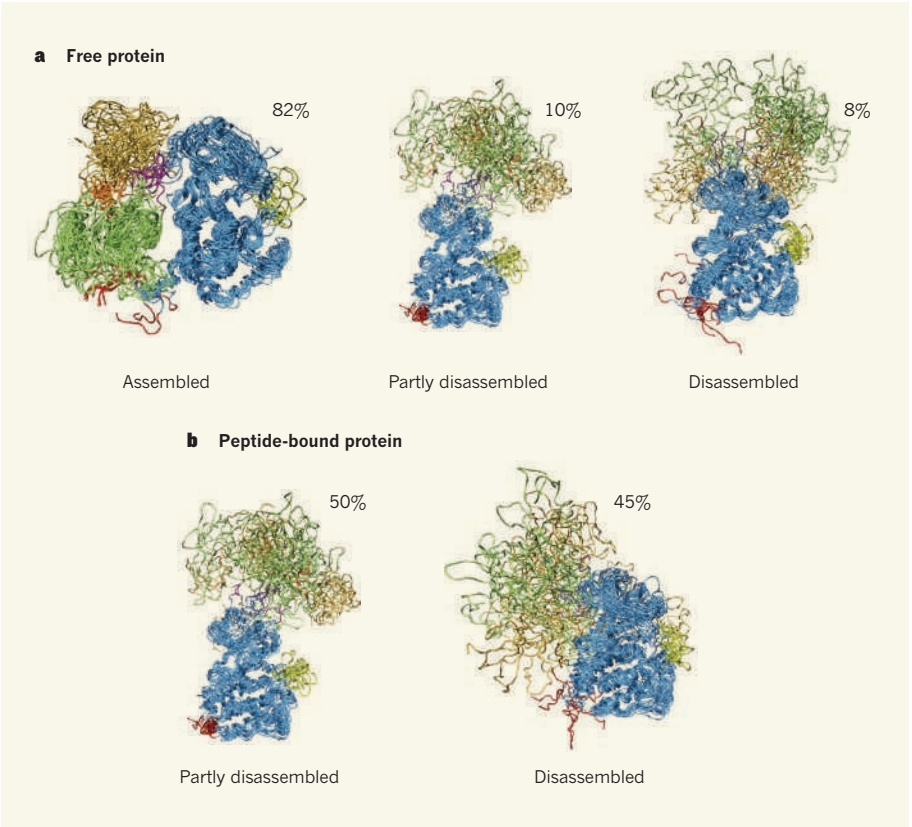

Figure 1 | Conformational states of the Hck enzyme in solution. The multidomain enzyme Hck can adopt several conformational states in solution, ranging from a compact 'assembled' state to partially assembled and disassembled states. Different domains are shown in different colours. **a**, Yang *et al.*[2] used a combination of molecular dynamics simulations with small-angle X-ray scattering (SAXS) data to show that, in solution, free molecules of Hck divide into different populations of these states, existing in a dynamic equilibrium with each other. The percentages indicate the fraction of the molecular population that exists in a particular state. **b**, The authors also charted major population shifts in response to the binding of peptides (not shown) to the SH2 and SH3 domains. The 5% of the population unaccounted for in the figure is divided between several other conformational states. (Figure adapted from ref. 2.)

Yang *et al.* demonstrated that several assembly states in equilibrium — not just two —must be considered to properly understand the conformational landscape that is crucial to the regulation of Hck (Fig. 1). The authors found that the enzyme is predominantly in the inactive, assembled conformation (82% of enzyme molecules), but is in dynamic equilibrium with partially and fully disassembled states. The assembled conformation predominates even in the absence of a phosphate group on the carboxy terminus of the catalytic domain. This is notable because phosphorylation of the carboxy terminus was thought to anchor Src enzymes in the assembled state, with dephosphorylation triggering disassembly to the active state.

Yang and colleagues also observed that the population equilibrium among the various states responds to the presence of signalling peptides that, on binding to the SH2 or SH3 domains, break specific intramolecular interactions in the enzyme. Taken together, their results demonstrate the link between the regulation of Hck and the complexity of its conformational-energy landscape, and exemplify the inability of single structural images to fully describe such an intricate molecular process.

The development of quantitative approaches for characterizing highly fluctuating conformational equilibria on the basis of experimental data measured in solution is essential if we are to develop true statistical mechanical images of the potential-energy landscapes intrinsic to dynamic biomolecular systems. It is becoming clear that structural biology is experiencing a paradigm shift, with the realization that excited or partially populated states are crucial to biological function[12], and that the determination of single structures from ensemble-averaged experimental data can miss vital conformational fluctuations or population changes that may be essential for biological activity. Ensemble approaches to the interpretation of SAXS and NMR data will inevitably reveal further secrets of the role of intrinsic conformational dynamics in protein function, as structural biology continues its inexorable shift towards a richer and more dynamic equilibrium. ■

Pau Bernadó *is at the Institute for Research in Biomedicine, 08028-Barcelona, Spain.*

Martin Blackledge *is at the Institute de Biologie Structurale Jean-Pierre Ebel, Commissariat à l'Energie Atomique, CNRS, Université Joseph Fourier, Grenoble 38027, France.*
e-mails: pau.bernado@irbbarcelona.org; martin.blackledge@ibs.fr

1. Chandonia, J.-M. & Brenner, S. E. *Science* **311,** 347–351 (2006).
2. Yang, S., Blachowicz, L., Makowski, L. & Roux, B. *Proc. Natl Acad. Sci. USA* **107,** 15757–15762 (2010).
3. Henzler-Wildman, K. & Kern, D. *Nature* **450,** 964–972 (2007).
4. Mittermaier, A. K. & Kay, L. E. *Trends Biochem. Sci.* **34,** 601–611 (2009).
5. Zhang, Q. *et al. Nature* **450,** 1263–1267 (2007).
6. Markwick, P. R. L. *et al. J. Am. Chem. Soc.* **131,** 16968–16975 (2009).
7. Putnam, C. D., Hammel, M., Hura, G. L. & Tainer, J. A. *Q. Rev. Biophys.* **40,** 191–285 (2007).
8. Bernadó, P., Mylonas, E., Petoukhov, M. V., Blackledge, M. & Svergun, D. I. *J. Am. Chem. Soc.* **129,** 5656–5664 (2007).
9. Bertini, I. *et al. J. Am. Chem. Soc.* **132,** 13553–13558 (2010).
10. Sicheri, F., Moarefi, I. & Kuriyan, J. *Nature* **385,** 602–609 (1997).
11. Cowan-Jacob, S. W. *et al. Structure* **13,** 861–871 (2005).
12. Baldwin, A. J. & Kay, L. E. *Nature Chem. Biol.* **5,** 808–814 (2009).

EXTRASOLAR PLANETS

A giant surprise

The discovery of an inner giant planet in the unusually massive solar system around the star HR 8799 creates an ensemble of planets that is difficult to explain with prevailing theories of planet formation. SEE LETTER P.1080

LAIRD CLOSE

The solar system around the star HR 8799 should not exist. This system is unlike any other known: it is a massive system that has multiple massive planets, with each giant planet containing many times the mass of all the planets in our Solar System combined. However, on page 1080 of this issue, Marois and collaborators[1] present new images of HR 8799 in which yet another equally massive planet is visible*.

Previous work[2] had imaged three planets around HR 8799, and now we have the surprise discovery of a fourth, HR 8799e, an inner, massive planet (about 10 Jupiter masses) located some 14.5 astronomical units from the star (1 AU is the average distance from Earth to the Sun). One might question the importance of the discovery of another extrasolar planet when more than 500 are known. But the HR 8799 system is the only solar system known to have multiple outer planets (the other three planets, HR 8799b, HR 8799c and HR 8799d, orbit respectively at approximately 68, 38 and 24 AU from the host star, and have estimated masses of about 7, 10 and 10 Jupiters).

As HR 8799 is the only known example of a wide (greater than 25 AU) solar system with multiple giant planets, astronomers were curious to know whether the star's planets could have formed by gravitational collapse[3] — one of the most popular theories of outer-planet formation. This theory posits that outer giant planets form from the fragmentation of the disk of gas and dust that develops around stars when they are young. In a process rather like the way binary stars form, a gravitational instability in the disk fragments it and quickly (on a timescale of 10,000 years) leads to the formation of gas-giant planets[3]. But the discovery of an inner planet such as HR 8799e at 14.5 AU poses a tricky puzzle. At this distance, the disk was neither cold enough nor rotating slowly enough to fragment and undergo gravitational collapse *in situ* to form HR 8799e[3].

To explain the formation of this latest planet, Marois *et al.*[1] appeal to the dominant theory of giant-planet formation: a slower process than gravitational collapse (about 3.5 million years at a distance of 10 AU) in which solid dust grains conglomerate into solid cores of tens of Earth masses and then gravitationally accrete disk gas to grow to Jupiter masses. Such a 'core-accretion' process itself is only marginally fast enough at 14.5 AU to build up HR 8799e's roughly 10 Jupiter masses before the disk gas accretes onto the star in less than 10 Myr. This formation timescale problem[3] becomes even more vexing if one considers that, at about 2.6 times the distance HR 8799e is from the host star, HR 8799c would require about 20 times longer (more than about 200 Myr) to grow to the same mass at 38 AU — long after the disk has lost all its gas. What's more, at 68 AU, HR 8799b's formation is truly problematic, requiring an even longer timescale (many times the age of the star) to have formed *in situ* by core accretion. Hence, neither of the two favoured theories of giant-planet formation can explain how all the planets around HR 8799 formed: HR 8799e is too close to have formed by gravitational collapse, and HR 8799c and HR 8799b are too far out to have formed by core accretion (Fig. 1).

Perhaps all of these massive planets formed at much larger distances (more than at least 50 AU) by the gravitational collapse of an unusually massive disk and then migrated quickly inwards to their current positions, somehow sweeping into a dynamically stable set of 1:2:4 orbital resonances[1] (where, for every one orbit of planet c, there are two of d and four of e). This does not really help the situation, however, because it is unlikely

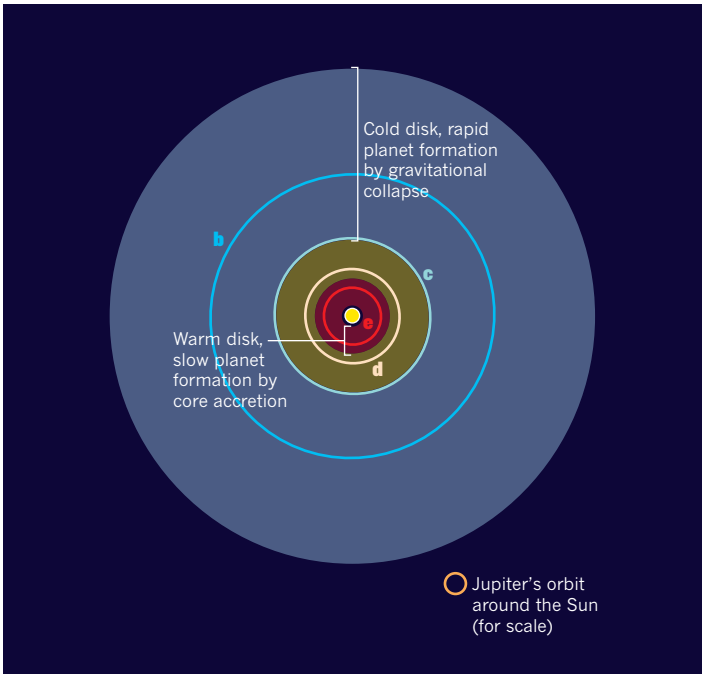

Figure 1 | The HR 8799 planetary system. When star HR 8799 formed, a massive circumstellar disk of gas and dust probably existed from which the star's four massive planets formed; the planets' approximate current orbits are overlaid and labelled b–e. The outer part of the disk was very cold and rotated slowly, and so might have collapsed through gravitational instabilities to quickly form outer planets such as 'b'. The newly discovered 'e' planet[1] is in a very different zone, where the disk was much warmer and the planet is likely to have formed in a slow, two-step 'core-accretion' process. Neither theory of planet formation — gravitational collapse or core accretion — can explain the whole family of four planets.

*This article and the paper under discussion[1] were published online on 8 December 2010.