

immune suppression but also had an immediate practical impact on cyclosporin research, since the structure of the bound drug molecule was found to be turned inside-out when compared with the structure of free cyclosporin A¹⁹. Barely 10 days after the bovine spongiform encephalopathy (BSE) crisis in Great Britain had broken into the open in March 1996, we completed the NMR structure determination of the murine prion protein²⁰ in a collaboration with Rudi Glockshuber, who had joined our institute at the ETH Zürich as an Assistant Professor in 1994. The observation of a long flexible tail in prion proteins²¹ presents on the one hand a striking illustration of the unique power of NMR to characterize partially structured polypeptide chains in physiological milieus, and on the other hand indicates novel possible avenues for the transition of the benign cellular form of prion proteins to the disease-

related scrapie form. With the introduction of TROSY (transverse relaxation-optimized spectroscopy)²², the molecular weight limit for solution NMR spectroscopy has extended to ~500 kDa, and we may soon be able to obtain information on the structure of the disease-related, aggregated form of the prion protein.

Kurt Wüthrich is Professor of Biophysics at the Institute of Molecular Biology and Biophysics, ETH Zürich, CH-8093 Zürich, Switzerland, Fax: 41 1-633-1151, and Cecil H. and Ida M. Green Visiting Professor of Structural Biology at The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA, Fax: 1 858-784-8014.

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picture story

A force to be reckoned with

Bacteriophage DNA is packaged into protein capsids to near crystalline density. It was originally thought that the DNA was condensed first and the protein shell was built around it, until about 30 years ago when empty phage capsids, or proheads, were found to form first. This discovery presented the difficult question: how does a virus force its DNA into the tiny capsid? For the well-studied *Bacillus subtilis* bacteriophage $\phi 29$, ~19 kilobases of double stranded DNA (6.6 μm long) must fit into a prohead of 42 x 54 nm. The portal complex, the ATP-dependent protein and RNA motor responsible for this feat, must overcome substantial energetic barriers to package the DNA so tightly, but exactly how this is accomplished is not clear.

As reported in a recent issue of *Nature* (413, 748-752; 2001), Bustamante and colleagues use optical tweezers to measure the rates and forces involved in packaging $\phi 29$ DNA into individual phage heads. The unpackaged end of the DNA is attached to a polystyrene bead, which is held in an optical trap (left). At the other end of the DNA, the partly packaged phage head is attached to another bead and held in place with a pipette. Packaging resumes upon the

addition of ATP, and the beads move closer together. The experiment can be done in a 'constant force feedback' mode, keeping a predetermined tension in the DNA by moving the bead position, or the 'no feedback' mode, where the force is allowed to change but the beads are held in place.

The authors show that packaging is highly processive and efficient, with few pauses and slips. Despite this efficiency, the rate of packaging decreases as more DNA is packed into the head (middle), suggesting that pressure builds up inside the capsid. Using the 'no feedback' mode, the authors measured the decreasing rate of packaging as the tension between the tethered ends built up,

allowing them to quantitatively estimate the internal force produced by the DNA as it is condensed and packaged (right).

Interestingly, the internal force is quite small until ~50% of the genome is packaged, indicating that the DNA is initially packed fairly loosely, not in its condensed final state. The force then increases, reaching ~50 pN as the entire genome is packaged and making the packaging machinery one of the strongest molecular motors reported. As the authors point out, building up so much internal force may be useful for the phage during infection; the pressure may be used to partially inject the DNA into the host cell.

Julie Hollien

