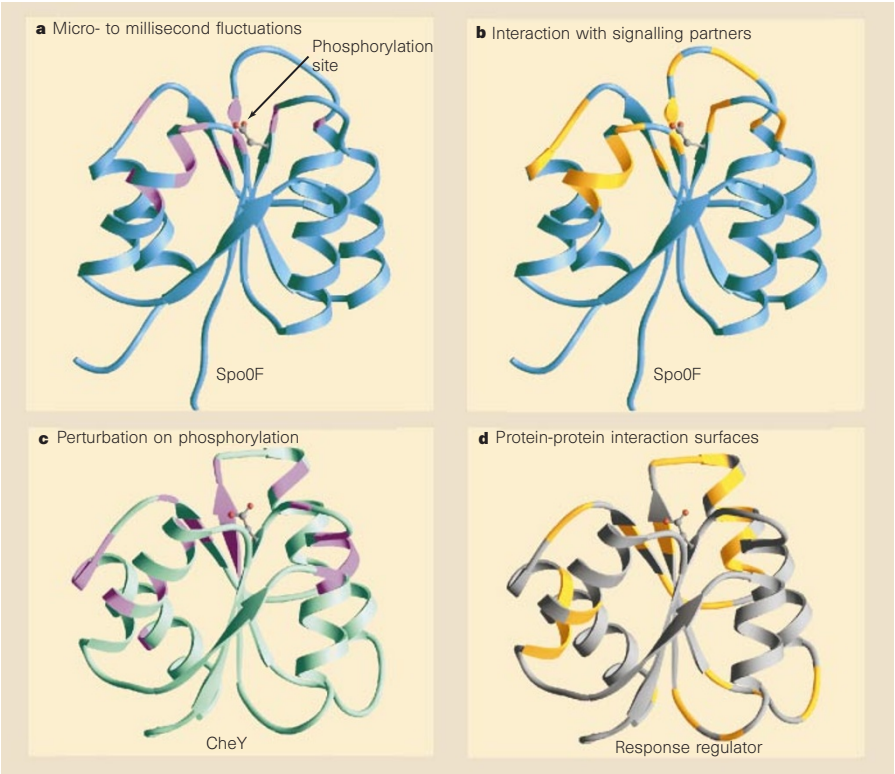

Figure 1 **Dynamic regions in response-regulator proteins.** a, **Spo0F, a signalling protein that participates in the phospho-relay pathway controlling sporulation in *Bacillus subtilis*. Magenta regions indicate residues that Feher and Cavanagh[2] find have motions in the microsecond to millisecond timescale.** b, **These residues are compared to a surface of Spo0F that has previously been identified as important for interactions with other signalling partners[3,4] (gold).** c, **Residues in the response regulator CheY that show large chemical-shift changes on phosphorylation[8] (magenta).** d, **Residues involved in protein–protein interactions in the response regulators CheY, CheB, NarL and PhoB (gold) mapped onto a representative domain as described previously[12].**

may facilitate binding of different partners. They also suggest that different entropic contributions in the bound and free states may contribute to modulation of binding affinities. (Advances in analysing dynamics at macromolecular interfaces should give a more detailed assessment of these entropic contributions.) Alternatively, the mobility in Spo0F may be related to the conformational changes associated with phosphorylation. The structural fluctuations could reflect the many conformational substates of Spo0F, one of which probably corresponds to the active conformation.

It may not be feasible to distinguish the relative contributions of dynamics to each of these functional features of Spo0F, because phosphorylation-induced conformational changes and protein–protein interactions are intertwined in the family of response-regulator proteins. Take, for example, NMR chemical-shift-perturbation studies of two other response regulators, CheY and NtrC, which indicate that phosphorylation induces a propagated conformational change that extends over one face of the domain[8,9]. Protein–protein interaction surfaces identified in several different response regulators overlap with this region (Fig. 1). Perhaps unsurprisingly this surface corresponds with the flexible regions in Spo0F, and the fundamental strategies for its functioning will probably turn out to be common to all response-regulator proteins. In the meantime, the forthcoming structural characterization of Spo0F complexed with its partners[10], as well as the structural and dynamic characterization of a phosphorylated response regulator[11], should increase our understanding of this functionally and structurally dynamic surface in response-regulator proteins. □

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1. Kay, L. E. *Nature Struct. Biol. NMR Suppl.* 513–517 (1998).
2. Feher, V. A. & Cavanagh, J. *Nature* **400,** 289–293 (1999).
3. Tzeng, Y.-L. *et al. Biochemistry* **37,** 16538–16545 (1998).
4. Tzeng, Y.-L. & Hoch, J. A. *J. Mol. Biol.* **272,** 200–212 (1997).
5. Hoch, J. A. & Silhavy, T. J. *Two-Component Signal Transduction* (Am. Soc. Microbiol. Press, Washington DC, 1995).
6. Burbulys, D., Trach, K. A. & Hoch, J. A. *Cell* **64,** 545–552 (1991).
7. Clore, G. M. *et al. J. Am. Chem. Soc.* **112,** 4989–4991 (1990).
8. Lowry, D. F. *et al. J. Biol. Chem.* **269,** 26358–26362 (1994).
9. Nohaile, M. *et al. J. Mol. Biol.* **273,** 299–316 (1997).
10. Varughese, K. I., Sen, U., Zapf, J., Madhusudan, M. & Hoch, J. *Am. Crystallogr. Assoc. Meeting* Abstr. 40 (1999).
11. Kern, D. *et al. Keystone Symp. Frontiers of NMR in Mol. Biol. VI* Abstr. 76 (1999).
12. Goudreau, P. N. & Stock, A. M. *Curr. Opin. Microbiol.* **1,** 160–169 (1998).

Daedalus

Reason to be cheerful

The ultimate goal of civilization is, perhaps, maximizing the sum of human happiness. Most governments interpret this as raising the standard of living. In fact, happiness correlates fairly weakly with economic affluence. For most of us, it is pretty much set by our inherent temperament, sunny or gloomy, modified by the triumphs or disasters of the past six months or so. Even lottery winners and bankrupts relax back to their normal mental state in under a year.

So Daedalus wants to lift our spirits directly. 'Cosmetic psychopharmacology' — the use of anti-depressant or narcotic drugs — has serious social side-effects. But Daedalus recalls the story of a patient with a fairly non-invasive pancreatic tumour. Despite his unenviable plight, the man was permanently cheerful. It turned out that the tumour generated a steady stream of endorphins, the hormones that mediate our feelings of satisfaction. This suggests that our inherent personality differences merely reflect the different endorphin levels maintained by our bodies.

Few people would want to boost their happiness by means of an implanted tumour, however non-invasive. Gene therapy seems more promising. Some of the subject's own cells would be extracted, loaded with the genes for his own endorphins, and then re-implanted into him. Dermal cells would be a good choice. They are easy to get at, and can be reimplanted by simple tattoo technology. If the subject remained gloomy, more cells could be inserted; if he developed a dangerously manic optimism, some could be removed.

Gene therapy, of course, is in its infancy. It is tricky to insert the right genes into the chosen cells, and trickier still to switch them on. But resources put into developing Daedalus' scheme should bring far greater returns of happiness than any amount of economic growth. Governments should rush to fund the project and offer its benisons to the people, starting with the most disgruntled and resentful citizens: criminals and the underclass. Infused with calm self-satisfaction, they would cease to be so troublesome. Later, the long-term unemployed and the more clamorous political activists would be added; later still, the rest of us. As contentment spread through society, the drive and restless ambition that fuel, not only crime, but innovation and economic growth, would falter and fade. But that, of course, would no longer matter.

David Jones