reduces its activity. Third, why does Sog activate Dpp signalling only at a distance? Can alternative forms or complexes of Sog diffuse to a greater or lesser extent? Finally, why is the border between the domains with high Dpp activity, and those with low activity, so sharp? Does some kind of 'secondary' refinement contribute to the stable sub-division of the dorsal domain? It is clear that the Soga will continue. □

Ethan Bier is in the Department of Biology, University of California at San Diego, 9500 Gilman Drive, La Jolla, California 92093-0349, USA.
e-mail: bier@biomail.ucsd.edu

1. Ashe, H. L. & Levine, M. *Nature* **398,** 427–431 (1999).
2. Zusman, S. B., Sweeton, D. & Wieschaus, E. F. *Dev. Biol.* **129,** 417–427 (1988).
3. Ferguson, E. L. & Anderson, K. V. *Development* **114,** 583–597 (1992).
4. François, V., Solloway, M., O'Neill, J. W., Emery, J. & Bier, E. *Genes Dev.* **8,** 2602–2616 (1994).
5. Biehs, B., François, V. & Bier, E. *Genes Dev.* **10,** 2922–2934 (1996).
6. Padgett, R. W., St Johnson, R. D. & Gelbart, W. M. *Nature* **325,** 81–84 (1987).
7. Rusch, J. & Levine, M. *Curr. Opin. Genet. Dev.* **6,** 416–423 (1996).
8. Bier, E. *Cell* **89,** 681–684 (1997).
9. Hemmati-Brivanlou, A. & Melton, D. A. *Cell* **88,** 13–17 (1997).
10. Marques, G. *et al. Cell* **91,** 417–426 (1997).

Microbiology

Millennium bug

R. S. Siew

So, naturalists observe, a flea
Hath smaller fleas that on him prey;
And these have smaller fleas to bite 'em,
And so proceed ad infinitum.
Thus every poet, in his kind,
Is bit by him that comes behind.

Jonathan Swift's ditty is true even for those smallest of parasites, the viruses. For example, adeno-associated virus is a parvovirus (parvo means small), which cannot replicate without its larger companion. Similarly, the hepatitis delta agent (an RNA genome related to plant viroids) depends on hepatitis B (a DNA virus) for encapsidation[1], the process in which the viral nucleic acid is packaged in protein.

In the era before antibiotics, phages were thought to be ideal viruses to control bacterial infections. Now evidence is emerging that a satellite RNA phage[2] with retrovirus-like properties first colonizes *Salmonella enteriditis* in chickens and then transmits its genome to cells of the chicken itself[3]. This agent — named bellophage after Hilaire Belloc, who came behind Swift to muse on microbes — could thus act as a shuttle vector moving gene sequences between bacteria and their animal hosts[4]. The findings have stimulated debate among microbiologists and evolutionary biologists, and are attracting the attention of both the biotechnology industry and environmentalists.

Bellophage has a tiny 1-kilobase genome encoding a nucleocapsid protein, a replicase component and an integrase[2]. The replicase is minute but serves as a reverse transcriptase, and it was a puzzle how such a small protein could perform the complex polymerase and RNaseH functions. Recently it became apparent that, rather like the replicase of the RNA phage Qβ, it binds to host DNA polymerase to change the enzyme's specificity so that the complex acts as an RNA-directed DNA polymerase[5]. The newly formed DNA genome then becomes inserted as prophage into the host genome with the aid of integrase. The nucleocapsid also has intriguing properties. It is essentially a leucine zipper, a structural motif that features in many protein–protein interactions, with a carboxy-terminal basic domain which brings the bellophage RNA to associate with the capsid protein of its DNA helper phage, omega[2].

The claimants to the discovery of bellophage[6,7] agree on its remarkable ability to adopt new helper viruses and indeed new hosts. Although the main reservoir appears to be omega-phage-carrying *Salmonella* in the gut of chickens, there is growing evidence that it can be packaged by adenovirus and even influenza capsid proteins (in birds, both of these viruses also persist as gut infections). Transcapsidation by the animal viruses, however, requires that the bellophage genome transfers from *Salmonella* to the gut epithelium itself. The capacity of the bellovirus, as we must now call it, to mobilize different helper viruses is correlated with hypermutation in the leucine zipper region of its nucleocapsid, generated by the lack of editing in the reverse transcription step in its life cycle. Moreover, a crucial Y2K mutation allows the provirus to remain latent in the host until its activation triggers programmed cell death[8].

At a symposium in Sri Lanka, held last month, virologists and evolutionary biologists discussed whether bellovirus has newly emerged as an animal parasite. Free-living bacteria often exist in complex biofilms[9] that also contain single-cell eukaryotes, such as algae and protozoa, and this may long have provided an opportunity for viruses to shuttle between bacterial, plant and animal host kingdoms. Mathematical biologists have become fascinated by bellophage[10] — computer modelling demonstrates how the evolutionary dynamics of bellophage hypermutation yield strikingly different outcomes in *Salmonella* and chickens, the virus seemingly oscillating between extreme virulence and aggressive symbiosis.

As to which came first, so to speak, the chicken or the phage, the answer has come from another quite unexpected feature of the bellovirus life cycle. In chicken cells the provirus does not integrate into nuclear DNA, but rather into mitochondrial DNA[11]. The mitochondrial genome is of course related to bacterial DNA, especially of intracellular parasites such as *Rickettsia*[12]. This is the first example of viral genome insertion into mtDNA as a kind of retrotransposon and it may explain why bellovirus can cross host kingdoms. Comparative studies of mtDNA reveal traces of bellovirus-related sequences in some host species but not in others. For example, integrase sequences have been detected in both human and chimpanzee mtDNA, but not in that of orang-utans[13]. This analysis of mitochondrial 'Eve' not only confirms that the Garden of Eden really was in Africa, but also indicates that bellovirus-like transposition has occurred among apes as well as chickens.

While academics ponder co-evolution versus genetic mobility, the biotechnology industry has been quick to see more profitable opportunities. A start-up company in Britain, Oxgal, is testing Bellovir, a nucleoside analogue which blocks bellophage reverse transcription[14] (though preliminary data indicate that Bellovir also inhibits telomerase, resulting in feather loss in chickens treated with high doses of the drug). Another company, Tomannos, has patented a bellovirus variant that integrates into chloroplast DNA as a possible vector for genetically modified plants.

It is hardly surprising that public health officials and environmentalists will wish to keep a close watch on bellophage. Manipulation of such a versatile virus could allow it to escape in undesirable ways that with hindsight might make us appear foolish. Belloc may have foreseen this 101 years ago when, inspired by Samuel Butler[15], he ended his poem, *The Microbe*:

But scientists, who ought to know,
Assure us that this must be so.
Oh! let us never, never doubt
What nobody is sure about! □

R. S. Siew is at the Windeyer Institute, University College London, 46 Cleveland Street, London W1P 6DP, UK.
e-mail: windinst@ucl.ac.uk

1. Carman, W. F. & Trautwein, C. in *HIV and the New Viruses* (eds Dalgleish, A. G. & Weiss, R.) 415–460 (Academic, London, 1999).
2. Ffowl, A. *Phil. Trans. Acad. Sci.* **237,** 1951–1970 (1999).
3. Lagado, R. S. *J. Chem. Biol.* **88,** 10001–10006 (1998).
4. Chesterton, G. K. *et al. Protista* **6,** 123–130 (1997).
5. Nimet, M. H. & Inatuzim, S. *J. Enzymol.* **391,** 121–125 (1998).
6. Issounis, F. B. *et al. Avian Virol.* **41,** 525–535 (1997).
7. Ollag, C. R. *et al. Nature* **394,** 967–974 (1998).
8. Sisir, C. & Lainnellim, K. *Silico* (in the press).
9. Brown, M. R. W. & Barker, J. *Trends Microbiol.* **7,** 46–50 (1999).
10. Yam, R. & Kawon, M. *Ecneics* **284,** 60–64 (1999).
11. Silugram, L. *et al. Plastid* **16,** 232–230 (1999).
12. Gray, M. W., Burger, G. & Lang, B. F. *Science* **283,** 1476–1481 (1999).
13. Prash, P. & Nhah, H. *Nature* **394,** 1999–2001 (1998).
14. Doh, D. & Eroom, J. *Tecnal* **335,** 871–872 (1998).
15. Butler, S. *Erewhon* (Trübner, London, 1872).