as more such factors are affinity-purified, cloned and eventually synthesized in bulk. The second may be less straightforward. So far, none of these factors has been shown to be very tissue specific or to increase transcription even 100-fold *in vivo* or *in vitro*, yet the expression of eukaryotic genes can vary from tissue to tissue over many orders of magnitude. Even the factor NF-κB[6], which binds to the immunoglobulin κ enhancer and seemed to be confined by κ-producing cells, now appears to be inducible in HeLa cells by phorbol ester treatment[7] (although it differs in several ways from the Sp1-type factors described here).

The possibility therefore remains that almost all the *trans*-acting factors uncovered in the remarkable discoveries of the past three years constitute a mechanism for the fine-tuning of transcription in a given cell, and that the availability of a particular gene for transcription is determined by a separate class of *trans*-acting factors working in a different and unexplored way. □

1. Jones, K. A., Kadonga, J. T., Rosenfield, P. J., Kelly, T. J. & Tjian, R. *Cell* **48**, 79–89 (1987).
2. Briggs, M. R., Kadonga, J. T., Bell, S. P. & Tjian, R. *Science* **234**, 47–52 (1986).
3. Takahashi, K. *et al. Nature* **319**, 121–126 (1986).
4. de Vries, E., van Driel, W., van den Heuvel, S. J. L. & van der Vliet, P. C. *EMBO J.* **6**, 161–168 (1987).
5. Prijn, G. J. M., van Driel, W. & van der Vliet, P. C. *Nature* **322**, 656–659 (1986).
6. Sen, R. & Baltimore, D. *Cell* **46**, 705–716 (1986).
7. Sen, R. & Baltimore, D. *Cell* **47**, 921–928 (1986).

Nicholas J. Short is at the Department of Biophysics, King's College London (KQC), 26-29 Drury Lane, London WC2B 5RL, UK.

Drosophila genetics

Love-song and circadian rhythm

Michael Ashburner

BIOLOGICAL clocks allow organisms to synchronize their activities with the predictable cycle of day and night, giving them a sense of time, so that even in the absence of external cues an organism's behaviour changes during the day as it would under normal conditions. A population of the fruitfly *Drosophila*, for example, entrained to a 12-h light:12-h dark cycle, will continue to hatch just after dawn, and only then, even in constant darkness. At least six different genes are known in *D.melanogaster* to affect circadian rhythms. The best studied of these is the *per* gene, discovered by Ron Konopka when a graduate student at Caltech. New results reported by Yu and colleagues on page 765 of this issue[1] suggest a mechanism by which this gene mediates two different effects.

Mutation of *per* abolishes completely all circadian behaviour, not only the hatching rhythm but also the rhythm of spontaneous locomotor activity of adult flies. Other mutations of this gene can increase the period of the rhythm from 24 to 29 h (per^l) or decrease it to 19 h (per^s). Mutations of this gene also have remarkable effects on a rhythm with a very different periodicity — the oscillation in the interval between the bursts of sound that characterize the love-song male *Drosophila* sing to potential mates. This interval varies around a mean of 34 ms in *D.melanogaster* with a period of about 55 s in the wild type. In per^l males this period is 80 s, in per^s it is 40 s and in per^0 there is no rhythmicity in the variation in interpulse interval.

The temporal characteristics of the male love-song are highly species-specific. For example, in the closely related species *D.simulans* the mean interval between pulses of song is 49 ms, fluctuating with a period of 40 s. Females are excited by a song characteristic of their own species, not that of another. More strikingly, hybrid females prefer the (simulated) song of hybrid males[2]. This raises two questions. The first is the role of the *per* gene in the female; does it perhaps encode an oscillator against which incoming song is measured? If so, then this would neatly explain the genetic coupling between the male's stimulus and the female's response. The second is how the product of one gene can affect a species-constant circadian rhythm and a rhythm that is not only variable between species but whose very variation is concerned with species isolation.

Whether *per* encodes a component of the fundamental oscillator or a component of the black box that lies between the oscillator and the behaviour is not yet known. Perhaps molecular studies of *per* and its gene products will help[3,4]. These studies are certainly providing fascinating insights into the genetic control of behaviour. As reported by Yu *et al.* in this issue[1] the effects of *per* on the very short period rhythms of the love-song and on circadian rhythms can be experimentally distinguished. Judging from its DNA sequence, *per* encodes a very large protein of 1,218 amino acids. These include a run of alternating glycine and threonine residues. The length of the Gly–Thr run varies between different wild-type *per* alleles: in some stocks it is 17 Gly–Thr repeats, in others 20 or 23. It is not known whether or not these different alleles are functionally different. We would certainly like to know whether males with these different alleles show the same periodicity characteristics of their love-songs. By some nifty cutting and splicing Yu *et al.*[1] constructed a *per* gene that lacks the DNA encoding the Gly–Thr repeat region and used it to transform per^0 flies. The surprising result is that this mutant construct can rescue the circadian rhythm phenotype to normality but that the flies have a very short love-song rhythm. The per^0 flies transformed with a normal *per* gene have a love-song periodicity of about 60 s; when transformed by the Gly–Thr deletion they have a periodicity of about 40 s. In principle, this result gives a mechanism by means of which the periodicity of the love-song can evolve without affecting the control of circadian rhythms.

The love-song of per^0 flies transformed with the deleted gene shows the same periodicity, about 40 s, as that of per^s, known to be a single amino-acid substitution about 100 residues amino-terminal to the Gly–Thr region[5,6]. The periodicity of circadian rhythms in *per* transformants is negatively correlated with amount of *per* messenger RNA[6], although periodicities shorter than 24 h have not yet been achieved by over-expression. It is possible to reconcile these observations in a single model if we assume that the circadian oscillation depends on the absolute amount of *per* gene product and that the song rhythm depends on variations in *per* protein concentration. As a first approximation it is easy to see how the amount of *per* protein could oscillate around a mean if, for example, the protein is unstable and blocked the translation of its own messenger RNA. Then a change in its stability (for example, by a change in the number of Gly–Thr repeats) will change the periodicity of oscillation of protein concentration. Such speculation is, however, probably premature. Although we know that the *per* protein is a proteoglycan-like molecule[3,7], there are also clear indications that the *per* gene encodes at least three different but related proteins[4] that may be involved in different aspects of its function. Complementary DNAs encoding two of these proteins can rescue the circadian phenotype of per^0 flies. Moreover, there remains a large black box between *per* and its proteins and the behavioural phenotype and there is plenty of room for other genes and their products to interact with those of *per*. That having been said, we are but on the threshold of an exciting analysis of the genetic and molecular basis of a very fundamental behavioural pattern. □

1. Yu, Q. *et al. Nature* **326**, 765–769 (1987).
2. Kyrlacou, C.P. & Hall, J.C. *Science* **232**, 494–497 (1986).
3. Jackson, F.R., Bargiello, T.A., Yun, S.-H. & Young, M.W. *Nature* **320**, 185–199 (1986).
4. Citri, Y. *et al. Nature* **326**, 42–47 (1987).
5. Yu, Q. *et al. Proc. natn. Acad. Sci. U.S.A.* **84**, 784–788 (1987).
6. Baylies, M.K., Bargiello, T.A., Jackson, F.R. & Young, M.W. *Nature* **326**, 390–392 (1987).
7. Reddy, P., Jacquier, A.C., Abovich, N., Petersen, G. & Rosbash, M. *Cell* **46**, 53–61 (1986).

Michael Ashburner is at the Department of Genetics, University of Cambridge, Downing Street, Cambridge CB2 3EH, UK.