The biology of time across different scales

Dean V Buonomano

Animals time events on scales that span from microseconds to days. In contrast to the technologies devised by humans to keep track of time, biology has developed vastly different mechanisms for timing across these different scales.

For both individuals and society as a whole, the ability to precisely track and tell time is critical across scales spanning over 15 orders of magnitude: from the nanosecond accuracy of atomic clocks used for global positioning systems to the tracking of our yearly trip around the sun. In-between these extremes we track the minutes and hours that govern our daily activities. It is noteworthy that the same technology can be used to measure time across these different scales; atomic clocks are used to time nanosecond delays in the arrival of signals from different satellites and to make adjustments to the calendar year. Similarly, digital wristwatches are used to time hundredths of a second and the days of the month.

In nature, animals also keep track of time over an equally impressive range of scales: from tens of microseconds, used for sound localization, to the anticipation of yearly seasonal changes, as well as the control of longer physiological events such as puberty and menopause. It is in-between these extremes that arguably the most sophisticated forms of timing occur. It is on the scale of milliseconds and seconds that complex forms of sensory and motor processing, which include speech recognition and motor coordination, take place[1,2]. The mechanisms by which animals tell time remain incompletely understood. Nevertheless, in contrast to human-made timing devices, it is clear that the biological solutions to telling time are fundamentally different across different timescales. The fact that there are numerous biological solutions to the problem of telling time likely reflects two factors. First, the biological components—be they biochemical reactions occurring within a cell or the emergent behavior of large networks of neurons—lack the digital precision of modern clocks. Second, the features required of a biological timer vary depending on whether its function is to process speech, anticipate when a traffic light will change, or control the circadian fluctuations in sleep-wake cycles.

The mechanisms biology has exploited to tell time provide insights not only into the function and importance of timing on different scales, but also into the relative limits and flexibility of different strategies. Based on the presumed underlying mechanisms and on didactic convenience, we can categorize timing into four different timescales: microseconds, milliseconds, seconds and circadian rhythms (**Fig. 1**).

Microsecond timing

The fastest scale of temporal processing occurs on the order of microseconds and allows animals to determine the interval it takes sound to travel from one ear to the other. For many vertebrates, localizing the source of a sound is essential to survival. For example, barn owls use sound localization to hunt rodents in the dark; rodents in turn use sound localization to avoid predators. One of the mechanisms underlying sound localization relies on the ability to discriminate very short temporal intervals[3]. In humans it takes sound approximately 600 μs to travel the distance between the left ear and the right ear. In barn owls this takes approximately 160 μs, and they can detect differences of approximately 10 μs (ref. 4). The ability to detect

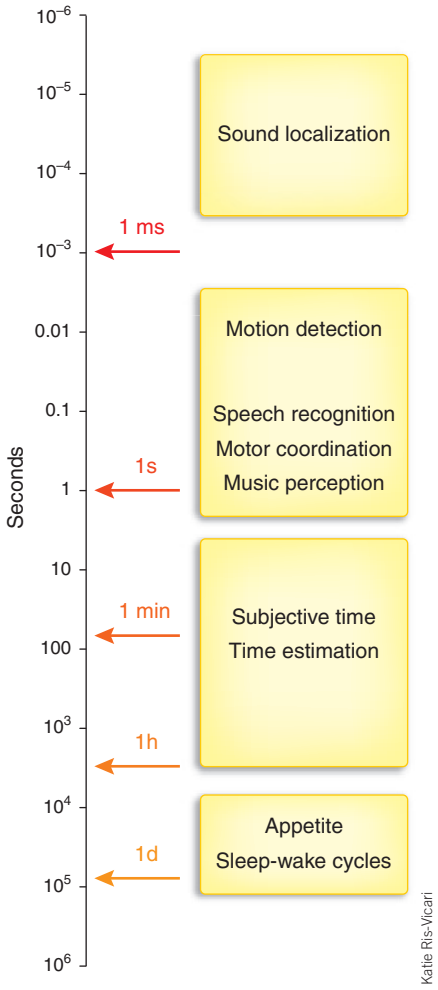

Figure 1 Scales of biological timing. Humans process temporal information over a wide range of timescales. On one extreme we detect the delay required for sound to travel from one ear to the other; these delays are on the order of tens to hundreds of microseconds. On the other extreme, we have daily physiological oscillations, such as our sleep-wake cycle. In-between these extremes temporal processing occurs on the scale of milliseconds and seconds. This intermediate range is critical to sensory processing, motor coordination, and our subjective sense of time that governs our daily activities. It is generally believed that timing in the range of tens to hundreds of milliseconds relies on mechanisms distinct from those responsible for timing seconds and hours. However, where the temporal boundary lies and how many neural mechanisms contribute to timing within these ranges is not known.

Dean V. Buonomano is in the Departments of Neurobiology and Psychology, Brain Research Institute, University of California, Los Angeles, Box 951761, Los Angeles, California 90095, USA. e-mail: dbuono@ucla.edu

such short intervals is surprising in a system in which even the fastest events, such as an action potential, last a few hundred microseconds. The biological solution to detecting short intervals lies in using the time it takes action potentials to propagate down an axon as a physical delay line. Axons in the auditory brain stem conduct action potentials at a speed of approximately 3 mm ms^{-1} (ref. 5); thus, a 300-μm distance can serve as a 100-μs delay. In the same manner that the intersection of two cars that started at fixed points heading toward each other provides a measure of their relative starting times, the brain uses the intersection point between action potentials coming from the different ears to determine which started first. The key to this strategy is that some neurons are able to detect the simultaneous occurrence of inputs from the left and right ears. This is termed 'coincidence detection' and is something neurons are inherently well designed to do. Although they are an effective mechanism for detecting extremely short intervals, axonal delay lines evolved to solve the highly specialized problem of sound

Box 1 Interval selectivity in simple neural circuits

Theoretical and experimental work suggests that neurons may be inherently capable of telling time on the scale of tens to hundreds of milliseconds as a result of the interaction between short-term synaptic plasticity and circuit dynamics. In **Figure 2a**, a computer simulation shows how interval-selective neurons can be generated from a simple neural circuit (right) composed of an excitatory neuron (Ex) and an inhibitory neuron (Inh). There are five synapses: Input → Ex, Input → Inh, Inh_{fast} → Ex, Inh_{slow} → Ex and Inh_{slow} → Inh. The excitatory synapses exhibit paired-pulse facilitation (the second excitatory postsynaptic potential is stronger than the first). The three sets of traces to the left (red, green and blue) represent the voltage traces from the Ex and Inh cells for three different sets of synaptic strengths (the sharp high-amplitude deflections represent action potentials, whereas the longer low-amplitude events are subthreshold excitatory postsynaptic potentials). Each group consists of three simulations (overlaid traces) in response to a 50-, 100- and 200-ms interval. By changing the strengths of the Input → Ex and Input → Inh connections in parallel it is possible to tune the Ex unit to respond selectively to either interval. Specifically, with relatively weak inputs to both the Ex and Inh cells (red traces), the Ex neuron can respond selectively to the 50-ms interval, thus functioning as an interval detector. Further increases in the excitatory synaptic weights can shift the selectivity to 100 (green) or 200 (blue) ms, in the absence of any changes in the temporal properties of the synapses or neurons. **Figure 2b** shows interval selectivity as a function of 'synapse space'. The strength of the Input → Ex and Input → Inh were parametrically varied over a range of weights. The results are represented as an RGB plot, which permits visualization of the selectivity to the three intervals while varying two dimensions. As color-coded in **Figure 2a**, red represents regions of synapse space in which the Ex unit fires exclusively to the second pulse of a 50-ms interpulse interval (IPI), but not to the 100- or 200-ms IPI; that is, red represents the Ex unit as a 50-ms interval detector. Similarly, green and dark blue areas represent regions of synapse space in which the Ex units respond only to the 100- or 200-ms interval, respectively. All other colors represent the summation of the primary colors (see color cube inset); thus, white areas correspond to regions that respond to all the intervals but not to the first pulse. Black areas represent regions in which the cell was not interval selective—not firing at all or firing only in response to the first pulse. The three unfilled white squares show the areas of synapse space of the traces in **Figure 2a**.

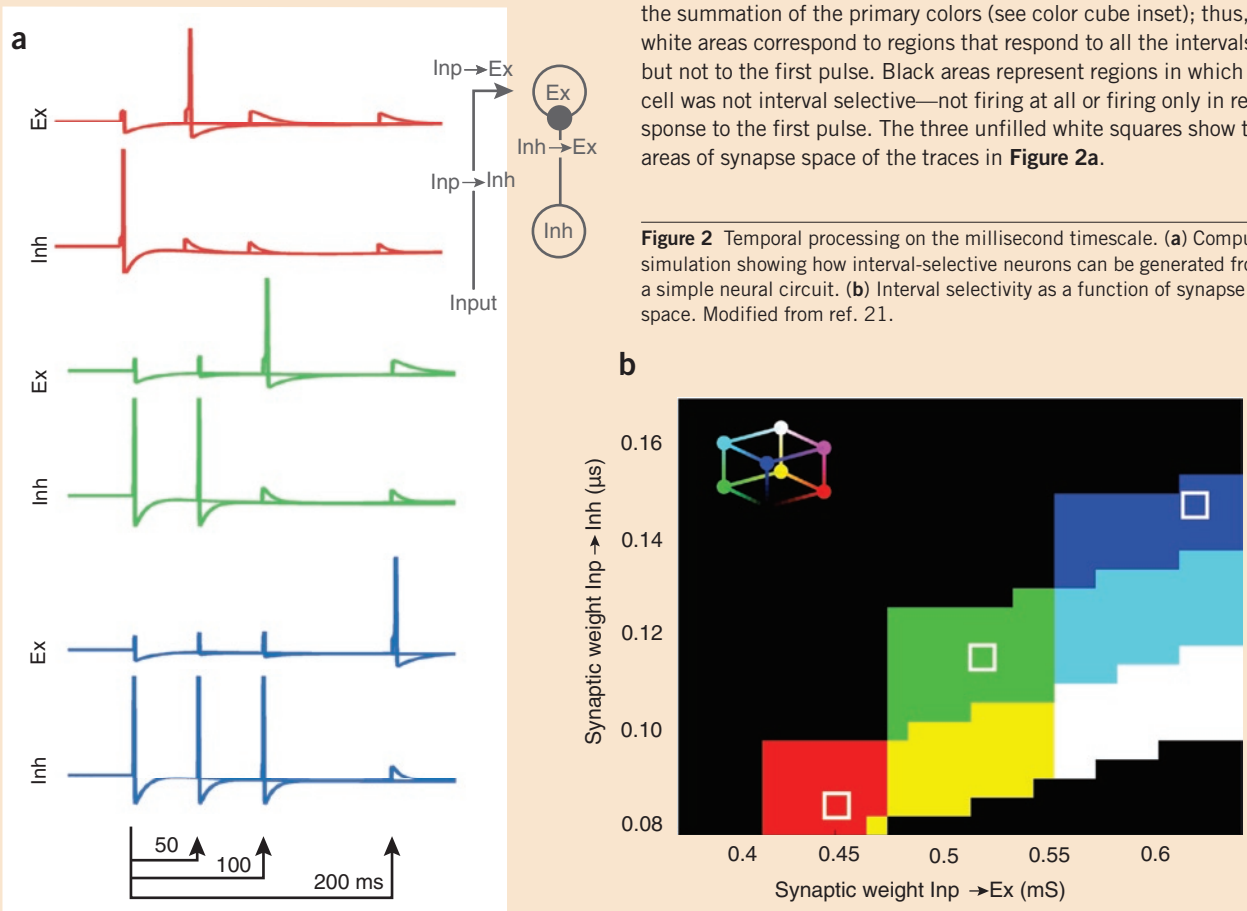

Figure 2 Temporal processing on the millisecond timescale. (**a**) Computer simulation showing how interval-selective neurons can be generated from a simple neural circuit. (**b**) Interval selectivity as a function of synapse space. Modified from ref. 21.

localization. There is little evidence that similar mechanisms are used to time longer intervals, or even that such a delay line strategy is sufficiently flexible or powerful to underlie other forms of timing.

Millisecond and second timing

Perhaps the most sophisticated example of temporal processing in biological systems occurs on the timescale of tens to hundreds of milliseconds. This is the range in which most animals generate and decipher the complex temporal structure of auditory signals used for communication. In human language, the duration and interval between different speech segments is critical for speech recognition and for the determination of prosody[6,7]. For example, the pauses between words contribute to the disambiguation of 'black bird' versus 'blackbird', or of the mondegreen 'kiss the sky' versus 'kiss this guy'. The brain's ability to process complex temporal patterns on this timescale is well demonstrated by the fact that language can be reduced to a purely temporal code, as occurs in Morse code. In addition to processing on this subsecond scale, animals predict and anticipate events on the scale of seconds and minutes[8]. It is this range that we associate with our subjective 'sense' of time, and that is responsible for anticipating when a traffic light will change or how long we have been waiting in line.

Internal clock model. The mechanisms underlying even a simple temporal task such as discriminating whether a tone lasted 100 or 200 ms, or the timed anticipation of the next ring of a telephone, are not known. However, the dominant model of timing on these scales has been the internal clock model, which proposes that action potentials from neurons oscillating at some fixed rate are counted by an integrator to provide a linear metric of time[9]. Indeed, oscillatory behavior is commonly observed in many neurons, and it is established that changes in the period of oscillations control the timing of many periodic behaviors, such as breathing or locomotor control. However, in periodic behaviors there is not generally an integer integration of each cycle to provide a metric of time on a scale that far exceeds the period of the oscillator. Thus, though there are abundant examples of oscillators and pacemakers in the nervous system, there is currently little evidence that these oscillations are 'counted' to provide a linear measure of time. However, some oscillator-based models do not require integration of events, but rather rely on detection of coincident activity between a large number of oscillators beating at different frequencies[8]. Although early internal clock models generally assumed that timing on the millisecond and second scales relies on the same 'central' clock, it has become increasingly clear that these scales depend on distinct mechanisms and systems[10–12].

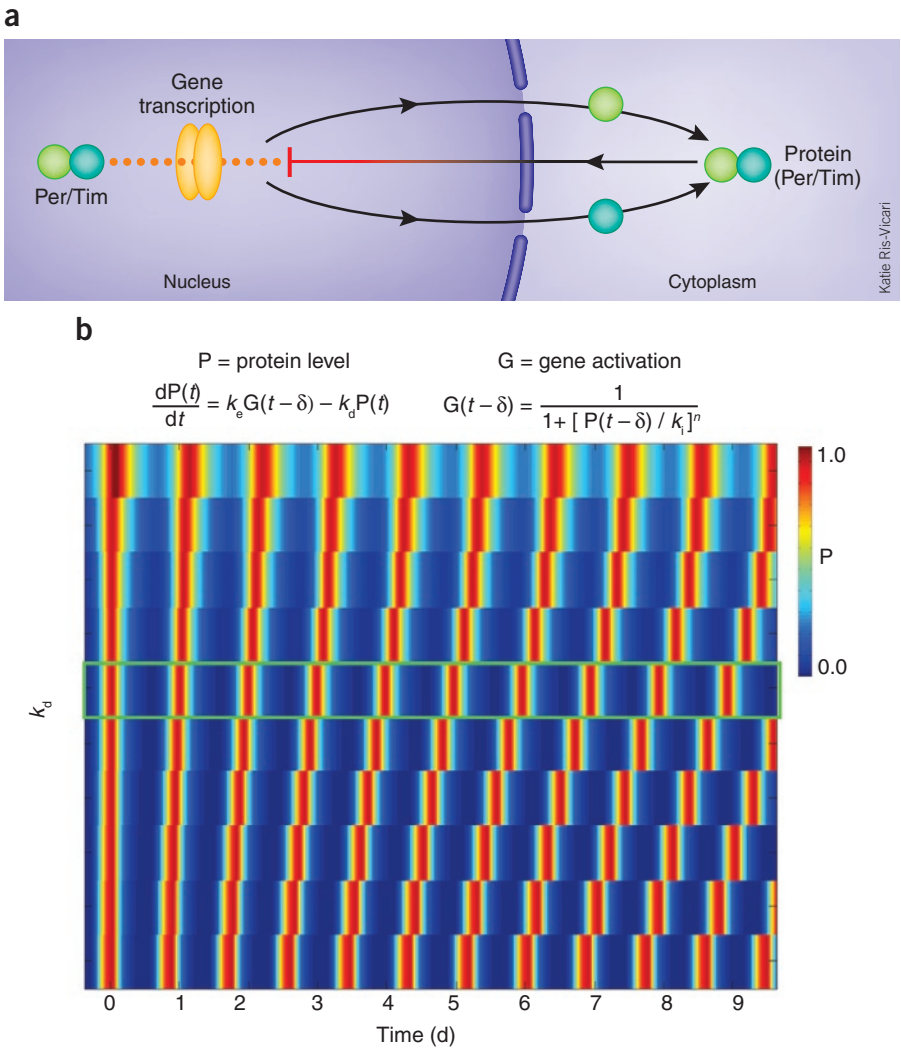

Figure 3 Controlling the period in a biochemical clock. Oscillations can be created in a number of biochemical systems. (**a**) The oscillatory behavior observed in single cells, including those in the suprachiasmatic nucleus, is the result of complex autoregulatory transcription-translation feedback loops. (**b**) A simplified description of this process is captured in these equations, in which the tonic transcription of a gene (G) is translated into a protein (P) that inhibits its own transcription[22]. A constant delay (δ) is a critical component of the model and is meant to capture the time involved in nuclear cytoplasmic transport and protein synthesis. The lower panel shows the results of simulations in which the period of the oscillation is adjusted by changing the decay rate constant (k_d) corresponding to degradation of P. Ten different values of k_d are used. Each line represents the fluctuation in the concentration of P, represented in color (peak value of P is normalized to 1). The green outline represents an oscillation in which the concentration of P shows a 24-h period. k_e, expression rate constant; k_i, inhibition rate constant; n, the Hill coefficient.

State-dependent networks. A distinct class of models proposes that timing does not depend on a clock *per se*, but rather on time-dependent changes in the state of neural networks. In other words, much like the ripples on a pond could be used to determine how long ago a pebble was thrown in, networks of neurons could tell time as a result of a rich repertoire of time-dependent neuronal properties[10,13]. Consider the discrimination of a 100-ms interval between two brief tones. The first tone activates a population of neurons in the cortex and triggers a series of time-dependent changes in neuronal properties, such as the strength of synapses (synaptic efficacy changes in a use-dependent fashion, a phenomenon called short-term synaptic plasticity). Thus, though the same tone will arrive in the same network 100 ms later, the state of the network will be significantly different—in other words, the short-term changes in synaptic

strength can act as a memory of what happened 100 ms ago. Because the network is in a different state the response to the stimulus will reflect the interval between the tones. A simple model of how short-term synaptic plasticity could allow neurons to respond selectively to specific intervals is shown in **Box 1**. Because the strength of a synapse can increase as a function of the amount of time that has elapsed since the previous presynaptic action potential, a synapse that was not strong enough to elicit a postsynaptic action potential at time 0 may elicit one at 100 ms. In a circuit, short-term synaptic plasticity occurs at both excitatory and inhibitory synapses; thus, there is a dynamic balance between excitation and inhibition. It is this interplay between the short-term changes in synaptic strength and the balance between excitation and inhibition that can be used to 'tune' a neuron to fire in response to specific intervals (**Fig. 2**).

Another mechanism that may underlie timing in the range of hundreds of milliseconds and seconds (particularly for motor responses) is changes in the firing rates of a population of neurons. Experiments in which neurons were recorded while animals performed a timing task reveal that the firing rate of some cortical neurons can increase or decrease as a function of time, thus potentially encoding time[14]. Additionally, dynamic changes in the firing rate of neurons have been proposed to underlie the ability of the cerebellum to generate precisely timed motor responses[15]. Given the diversity of temporal processing across sensory and motor domains, it is likely that there are multiple independent mechanisms responsible for timing within the millisecond and second scales.

Circadian rhythms

On a longer scale animals track time through circadian rhythms. These daily cycles allow animals to anticipate changes in their environment, including light levels, temperature, the availability of food and the presence of predators. The ability to anticipate daily changes in the environment is not, however, unique to animals. Plants and single-cell organisms also have circadian rhythms. For example, the opening of stomata on leaves and the pathways involved in photosynthesis are modulated by a biological clock, and they continue to cycle at an approximately 24-h rhythm in constant darkness[16]. Thus, unlike the more rapid scales of timing, it is clear that the biological clock on the timescale of hours does not rely on the specialized skills of neurons.

The circadian biological clock does much more than oscillate at the same period as the Earth's rotation; it must be able to be entrained to the changes in diurnal phase that occur across different seasons and longitudes. Additionally, the clock must be insensitive to changes in temperature. For these reasons, the precise molecular underpinnings of the biological clock are complex. However, the underlying principles are well understood: biological clocks rely on autoregulatory translation-transcription feedback loops. Specific proteins (termed Per and Tim in *Drosophila melanogaster*) are synthesized, and as these proteins accumulate in the cytoplasm they are translocated to the nucleus, where they inhibit further transcription of the genes that encode them[17,18]. The precise mechanisms underlying the biological clock in single cells involve dozens of proteins and remain incompletely understood. However, the essence of the circadian clock can be captured by an autoinhibitory translation-transcription model, in which the synthesis of a protein inhibits the transcription of its gene after a fixed delay. Furthermore, changes in a single parameter, such as the decay rate of a protein, can control the period of the oscillation (**Fig. 3**).

Conclusion

The mechanisms discussed above indicate that biological systems have evolved a diverse set of solutions to the important problem of telling time. Each one of these solutions has distinct characteristics. For example, the biological clock controlling circadian rhythms is very precise; in the absence of external cues the period varies by less than 2% (ref. 19). However, it is not particularly flexible—it cannot be rapidly reset to a new phase (thus the phenomenon of jet lag). In contrast, our ability to time durations on the order of milli-seconds, or anticipate the change of a traffic light, is generally less precise—on the order of 10% (ref. 2)—but these timers are considerably more flexible since they can be reset at will and further tuned as a result of learning[20].

The diversity of the solutions to the problem of telling time reflect the fundamental importance of keeping track of time on multiple different scales. Significant progress has been made toward understanding some of these mechanisms, particularly in the lower and upper extremes of the biological time ranges. However, the mechanisms underlying timing in the range of milliseconds and seconds remain poorly understood; indeed, it remains to be established how many different solutions to the problem of telling time evolution has devised.

ACKNOWLEDGMENTS

This work was supported by a US National Institutes of Health grant (MH060163). I would like to thank T. Carvalho for helpful comments on an earlier version of this manuscript.

COMPETING INTERESTS STATEMENT

The author declares no competing financial interests.

1. Ivry, R.B. & Spencer, R.M.C. *Curr. Opin. Neurobiol.* **14**, 225–232 (2004).
2. Mauk, M.D. & Buonomano, D.V. *Annu. Rev. Neurosci.* **27**, 304–340 (2004).
3. Carr, C.E. *Annu. Rev. Neurosci.* **16**, 223–243 (1993).
4. Moiseff, A. & Konishi, M. *J. Neurosci.* **1**, 40–48 (1981).
5. Overholt, E.M., Rubel, E.W. & Hyson, R.L. *J. Neurosci.* **12**, 1698–1708 (1992).
6. Shannon, R.V., Zeng, F.G., Kamath, V., Wygonski, J. & Ekelid, M. *Science* **270**, 303–304 (1995).
7. Schirmer, A. *Brain Res. Cogn. Brain Res.* **21**, 269–287 (2004).
8. Buhusi, C.V. & Meck, W.H. *Nat. Rev. Neurosci.* **6**, 755–765 (2005).
9. Gibbon, J. *Psychol. Rev.* **84**, 279–335 (1977).
10. Karmarkar, U.R. & Buonomano, D.V. *Neuron* **53**, 427–438 (2007).
11. Lewis, P.A. & Miall, R.C. *Curr. Opin. Neurobiol.* **13**, 250–255 (2003).
12. Rammsayer, T.H. Q. *J. Exp. Psychol. B* **52**, 273–286 (1999).
13. Buonomano, D.V. & Merzenich, M.M. *Science* **267**, 1028–1030 (1995).
14. Leon, M.I. & Shadlen, M.N. *Neuron* **38**, 317–327 (2003).
15. Medina, J.F., Garcia, K.S., Nores, W.L., Taylor, N.M. & Mauk, M.D. *J. Neurosci.* **20**, 5516–5525 (2000).
16. McClung, C.R. *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **52**, 139–162 (2001).
17. Panda, S., Hogenesch, J.B. & Kay, S.A. *Nature* **417**, 329–335 (2002).
18. King, D.P. & Takahashi, J.S. *Annu. Rev. Neurosci.* **23**, 713–742 (2000).
19. Herzog, E.D., Aton, S.J., Numano, R., Sakaki, Y. & Tei, H. *J. Biol. Rhythms* **19**, 35–46 (2004).
20. Karmarkar, U.R. & Buonomano, D.V. *Learn. Mem.* **10**, 141–147 (2003).
21. Buonomano, D.V. *J. Neurosci.* **20**, 1129–1141 (2000).
22. Lema, M.A., Golombek, D.A. & Echave, J. *J. Theor. Biol.* **204**, 565–573 (2000).