

Recognition of slow processes in rhythmic networks

Many behaviors depend on an accurate estimation of time for proper execution. Psychophysical studies in humans and other animals suggest the existence of an internal system in which time is represented in different regions of the brain, namely, cerebellum, basal ganglia and cortex (reviewed in Ref. 1). A key unresolved issue is how time is represented. In order to address this, two classes of models have been proposed. In clock-counter models, pulses generated by a pacemaker accumulate in a task-specific counter. The content of the counter is then read to extract time duration. In interval models, each time interval is represented in a distinct neuronal construct, which is specific for its duration. Which strategy is used by biological systems for temporal representation is still a matter of active debate¹.

The problem of temporal representation is much more complex when the cognitive task is not simple discrimination of time intervals but the recognition of repetitive temporal patterns. Numerous examples, such as locomotion and vocalization, show that detection of distinct patterns of low-frequency oscillations is an important aspect of neuronal function. Furthermore, patterned electrical activity has been shown to affect various neuronal processes, such as neurite growth, myelination and ion-current regulation^{2–11}. Recognition of rhythmic temporal patterns requires both the detection of differences and the identification of similarities. A simple computational approach would be to store the time intervals, compare them using subtraction operations and normalize them using division operations. Whether the nervous system uses a similar approach is questionable; however, neuronal networks do recognize slow temporal patterns. Therefore, a pivotal question is, 'What physiological mechanisms are employed for recognition of slow temporal patterns?'

In a recent paper, Hooper has proposed an elegant mechanism to answer this question¹². The essence of his proposal is that, rather than coding directly for long durations, a nervous system might first map events of long duration to short intervals, and then process or encode the short intervals using its available resources. Hooper was inspired by his experimental observations of the rhythmic activity generated by the pyloric network of the stomatogastric ganglion in the lobster, a model system for the study of central pattern generators. The output produced by the pyloric circuit is a motor pattern characterized by triphasic rhythmic bursting (Fig. 1)¹³. Depending on the environmental context, this rhythm

varies in cycle period, from 0.5 s to 2 s. In addition, the duty cycle (the ratio of burst duration to cycle period) of the different pyloric neurons also varies from 0.2 to 0.8. Hence, the pattern produced by the pyloric neurons is characterized by at least two parameters: the cycle period (or frequency) and the duty cycle.

Hooper observed that in response to intracellular injection of a periodic inhibitory current, the (six to eight) pyloric constrictor (PY) neurons of the pyloric network fire action potentials, upon release from inhibition, with a delay of several hundred milliseconds (Fig. 2A). This delay increased in a linear fashion when either period or duty cycle of the injected current was increased (Fig. 2B,C). Hence, the firing delay of each PY neuron is a linear function of both period and duty cycle:

$$\text{delay} = a \times \text{period} + b \times \text{duty cycle} + c$$

where the dependent variable 'delay' and the parameters a , b and c are obtained from data for individual PY neurons. However, the firing delays of different PY neurons do not respond to period and duty-cycle changes in exactly the same way. In fact, Hooper observed that the equations describing the dependence of the firing delay of the PY neurons on period and duty cycle are linearly independent (that is, the a , b and c values for different PY neurons are different). This linear independence could be used to detect the period and the duty cycle of the input pattern. By solving two equations of this form for two unknowns, explicit knowledge of the firing delays of two PY neurons is sufficient to code duty cycle and period. The problem remains that a neuronal mechanism for keeping track of delays of several hundred milliseconds has not been identified. However, in theory the relatively small difference in the firing delays, rather than the absolute value of the long firing delays, could be used to represent long time delays. Thus, two PY neurons would transmit their action potentials, through delay lines, to an array of coincidence detector neurons, which is similar to the model proposed by Jeffress for sound localization¹⁴. In one of the coincidence detectors, the action potentials arriving from the two PY neurons would coincide and the detector would fire. Because the detector is sensitive to the difference in firing delays, this process is equivalent to subtracting the equations representing the firing delays of the two PY neurons. This calculation, however, results in a single equation describing the difference in the firing delays in terms of

two unknowns: period and duty cycle. Therefore, infinite combinations of period and duty cycle produce the same delay in such a detector mechanism. This ambiguity, Hooper proposes, could be resolved with a 2D array of coincidence detector neurons, each of which receives coincident input from three (instead of two) PY neurons at a unique combination of period and duty cycle.

It is important to emphasize that the mechanism proposed in this article is not the way that the stomatogastric nervous system works, as Hooper himself indicates. This is a theoretical construct that explains temporal coding using specific properties found in the PY neurons, namely the direct relationship between the firing delay and the frequency or duty cycle. It should also be noted that an opposite relationship of response delay to period or duty cycle, or both, would equally satisfy the delay-line model. In fact, the issue is not the linearity of the responses of the individual neurons to period or duty cycle either; mere monotonicity of the responses is sufficient (see, for example, Ref. 15). The important message of Hooper's paper is that the linear independence of the responses of a few

Jorge Golowasch
Volen Center for Complex Systems,
Brandeis University,
Waltham,
MA 02454, USA.

Yair Manor
Life Sciences Dept
and Zlotowski
Center for Neuroscience,
Ben-Gurion
University of the
Negev, Beer-Sheva
84105, Israel.

Farzan Nadim
Dept of
Mathematical
Sciences, NJIT,
and Federated
Department of
Biological Sciences,
Rutgers University,
Newark,
NJ 07102, USA.

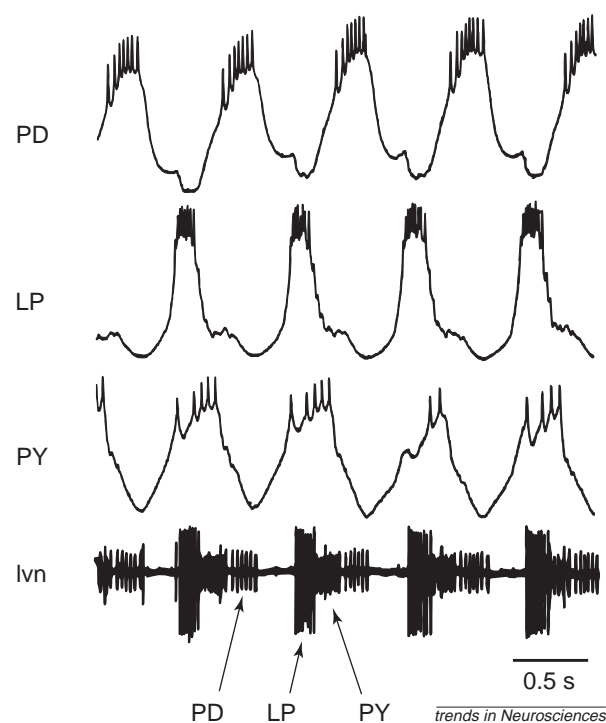


Fig. 1. Rhythmic activity of the pyloric network demonstrated by simultaneous intracellular and extracellular recordings. Intracellular recordings of three pyloric neurons: the pyloric dilator (PD) neuron (which is part of the pacemaker group that generates the rhythm), the lateral pyloric (LP) neuron and the PY neuron. Extracellular recording of the nerve lvn, which contains the axons of these three neurons. The sequence PD→LP→PY is maintained under a large range of conditions and frequencies.

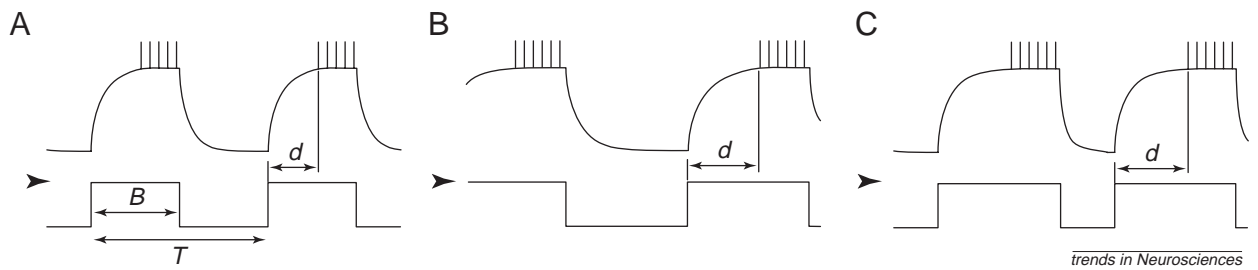


Fig. 2. Schematic representation of the firing delay, d , of PY neurons as reported by Hooper¹². Traces in (A)–(C) represent PY neuron membrane potential (top) and external current injection (the input signal; bottom). The arrowheads denote zero current. B and T , respectively, denote the ‘bursting’ phase and the period of one cycle, and d is the delay. (A) Control traces, duty cycle (B/T) of the input signal = 50%. (B) Increasing the period of the input signal increases d . (C) Increasing the duty cycle of the input signal also increases d .

biological elements to period and duty cycle could provide a biological basis for coding of slow temporal patterns.

Other, more-involved models have been suggested for control and detection of temporally patterned inputs (as opposed to simple durations). These models range from analog model neural networks based on ‘grandmother-cell’ sequence recognizers¹⁶, to nonlinear, saturating input–output transformations¹⁵. The elegance of the Hooper model is that any collection of biological responses that are sensitive to period and duty cycle and linearly independent of each other could potentially serve as a basis for a temporal pattern-coding mechanism. Examples of such biological responses include short-term plasticity mechanisms such as use-dependent regulation of voltage-gated ionic conductances and synaptic strengths.

Many temporal and even spatial processes at the cellular level might also be involved in coding slow temporal patterns. Neurotransmitter release¹⁷, Ca^{2+} currents^{8,10},

intracellular Ca^{2+} levels^{17,18}, myelination¹¹, gene expression^{11,19} and electrical activity of individual neurons^{3,7} are all regulated by stimulation frequency, although the sensitivity to other parameters (such as duty cycle) was not assessed in these studies. Outgrowth of neurites, elimination of synapses, myelination and gene expression have been shown to be regulated by stimulation with patterned activity (patterns determined by both period and duty cycle)^{2,4–6,9,11,19}.

The ideas proposed by Hooper could be implemented in various ways, and not only through different firing times of neurons transmitted through delay lines onto coincidence detectors. Let us consider an equally hypothetical construct that uses the same principles, although not the same cellular ingredients. Short-term synaptic plasticity, such as facilitation and depression, could provide the mechanisms necessary for detection of slow temporal patterns. This has been shown theoretically to be feasible in the cerebellum’s role in the classically conditioned nictitating-membrane response¹⁷. Moreover, studies of the stomatogastric nervous system have shown that both frequency and duty cycle strongly influence the strength and temporal properties of graded synapses²⁰. This influence comes about via a mechanism of synaptic depression with a time course of several hundred milliseconds to seconds. Such a mechanism suggests the following temporal pattern-coding scheme. Suppose that a collection of neurons, A_i , is entrained by a periodic input and, further, that each A_i neuron affects neuron B via independent synaptic contacts whose amplitude and dynamics are sensitive to frequency and duty cycle (Fig. 3). Similar periods and duty cycles in A_i neurons produce different synaptic responses in neuron B . The firing properties of neuron B will reflect the combined effects of independent inputs from A_i neurons and, therefore, encode the temporal properties of the input. Thus, if there is a change in the period or duty cycle of the input to A_i neurons, this change could be detected by the synaptic properties of these neurons and integrated by neuron B (Fig. 3). The response of A_i neurons and neuron B , in turn,

result in changes in behavior through their effectors. A single neuron B does not necessarily code for all periods and duty cycles, but a small network of neurons receiving inputs from a set of A_i neurons might. Such a detection mechanism would be intrinsic to the network itself, and would not require an extrinsic coincidence detector.

Most known cellular and synaptic mechanisms involved in short-term plasticity depend on intracellular Ca^{2+} levels^{2,3,7,8,10,11,21}. Regulation of intracellular Ca^{2+} levels might, therefore, have a significant role in mediating the processes of recognition and generation of temporal patterning (see Ref. 17). De Koninck and Schulman have shown that Ca^{2+} /calmodulin-dependent protein kinase II, an enzyme that is involved in numerous cellular processes, is sensitive to the frequency of applied Ca^{2+} pulses²². Gene expression has also been shown to be regulated as a function of the temporal dynamics of intracellular Ca^{2+} (Refs 2,23,24). In the pyloric system, synaptic release is a graded function of membrane potential and intracellular Ca^{2+} levels, and synaptic efficacy is sensitive to the frequency, duty cycle and exact waveform of the membrane potential of the presynaptic neuron²⁰. Thus, it is highly likely that the frequency, duty cycle and waveforms of many types of neurons involved in temporal pattern representation and production influence their cellular dynamical processes. These processes could, in turn, affect transmitter release from the neuron. Thus, part of the temporal encoding process could, in fact, occur at the subcellular level.

The neuronal networks that perform temporal pattern coding possibly involve a complex dynamical interplay of temporal (and spatial) properties of cells and synapses. These complexities should be explored from all perspectives, in different systems and with all techniques at hand. Hooper’s work demonstrates elegantly that coding slow temporal patterns could involve very simple neurobiological mechanisms such as firing delays of individual neurons. As such, this model is a stepping-stone towards the discovery of other simple biological substrates of temporal pattern coding in the nervous system.

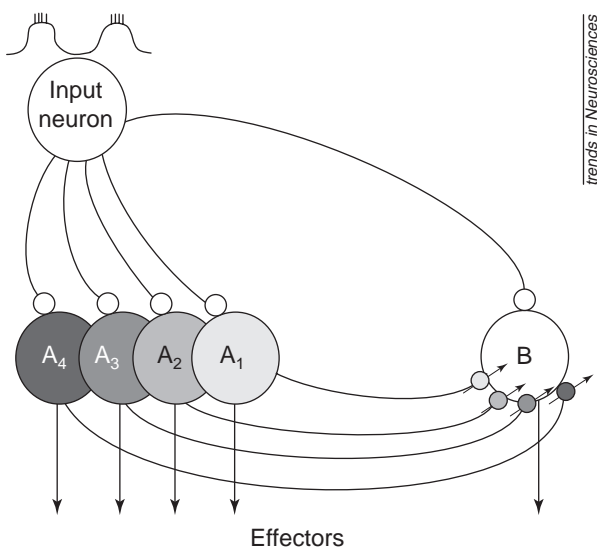


Fig. 3. Schematic diagram of a temporal coding network based on synaptic plasticity. The input neuron generates rhythmic activity (shown above) characterized by its bursting frequency and duty cycle. Arrows through synaptic contacts indicate temporal dynamics of the synapse. Different shades of gray indicate different properties of the A_i to B synapses. Downward arrows from neurons A_i and B are outputs of the network.

Selected references

- 1 Ivry, R.B. (1996) *Curr. Opin. Neurobiol.* 6, 851–857
- 2 Fields, R.D., Neale, E.A. and Nelson, P.G. (1990) *J. Neurosci.* 10, 2950–2964
- 3 LeMasson, G., Marder, E. and Abbott, L.F. (1993) *Science* 259, 1915–1917
- 4 Nelson, P.G. et al. (1993) *J. Neurobiol.* 24, 1517–1530
- 5 Sheng, H.Z., Fields, R.D. and Nelson, P.G. (1993) *J. Neurosci. Res.* 35, 459–467
- 6 Lin, P.X., Fields, R.D. and von Agoston, D. (1993) *Dev. Brain Res.* 76, 95–103
- 7 Turrigiano, G., Abbott, L.F. and Marder, E. (1994) *Science* 264, 974–977
- 8 Hong, S.J. and Lnenicka, G.A. (1995) *J. Neurosci.* 15, 3539–3547
- 9 Itoh, K. et al. (1995) *Science* 270, 1369–1372
- 10 Li, M. et al. (1996) *J. Neurophysiol.* 76, 2595–2607
- 11 Stevens, B., Tanner, S. and Fields, R.D. (1998) *J. Neurosci.* 18, 9303–9311
- 12 Hooper, S.L. (1998) *Nat. Neurosci.* 1, 720–726
- 13 Selverston, A.I. and Moulins, M. (1987) *The Crustacean Stomatogastric System*, Springer-Verlag
- 14 Jeffress, L.A. (1948) *J. Comp. Physiol. Psych.* 41, 35–39
- 15 Brezina, V., Orekhova, I.V. and Weiss, K.R. (1997) *Proc. Natl. Acad. Sci. U. S. A.* 94, 10444–10449
- 16 Tank, D.W. and Hopfield, J.J. (1987) *Proc. Natl. Acad. Sci. U. S. A.* 84, 1896–1900
- 17 Fiala, J., Grossberg, S. and Bullock, D. (1996) *J. Neurosci.* 16, 3760–3774
- 18 Zirpel, L., Lippe, W.R. and Rubel, E.W. (1998) *J. Neurophysiol.* 79, 2288–2302
- 19 Fields, R.D. et al. (1997) *J. Neurosci.* 17, 7252–7266
- 20 Manor, Y. et al. (1997) *J. Neurosci.* 17, 5610–5621
- 21 Liu, Z. et al. (1998) *J. Neurosci.* 18, 2309–2320
- 22 De Koninck, P. and Schulman, H. (1998) *Science* 279, 227–230
- 23 Dolmetsch, R.E., Xu, K. and Lewis, R.S. (1998) *Nature* 392, 933–936
- 24 Li, W. et al. (1998) *Nature* 392, 936–941

VIEWPOINT

Paracrine neurotransmission in the CNS: involvement of 5-HT

Melissa A. Bunin and R. Mark Wightman

While GABA and glutamate have an established synaptic function in the CNS, recent evidence suggests 5-HT neurotransmission is predominantly paracrine. As the amino-acid neurotransmitters interact with receptors that produce effects rapidly, electrophysiological approaches can be used to assess the time delay between transmitter release and the postsynaptic response directly. However, this approach cannot be used for studies of 5-HT-mediated neurotransmission, because the majority of its receptors react more slowly, so anatomical and voltammetrical approaches have been used to provide insight into 5-HT-mediated events. These studies have revealed that extrasynaptic receptors and transporters for 5-HT exist, and that 5-HT escapes readily from the synaptic cleft. Attenuation of 5-HT binding by 5-HT-receptor antagonists and 5-HT-uptake inhibitors does not affect the synaptic efflux elicited by transient stimuli, although the effects of such drugs are apparent at later time points. Once it is extrasynaptic, 5-HT has a concentration that is similar to those estimated to be optimal for receptor and transporter activation, and it can diffuse a few micrometers until removed by its transporter. These properties of 5-HT raise the possibility that it can act on receptors that are distant from its release site and function as a paracrine transmitter.

Trends Neurosci. (1999) 22, 377–382

THE CONCEPT that neurotransmitters relay information in a synaptic manner predominates modern views of chemical communication in the brain¹. Synaptic neurotransmission is initiated by exocytotic release of neurotransmitters followed by their diffusion across the nanometer dimensions of the synaptic cleft and their activation of postsynaptic receptors. This process enables rapid communication between neurons and ensures that information flows in an orderly fashion. Examination of these events at GABAergic and glutamatergic synapses in the CNS has revealed many of the details of synaptic neurotransmission². However, the question still remains as to whether extrasynaptic, or paracrine³, neurotransmission also occurs. In this article, the term paracrine transmission is used to describe communication by neurotransmitters that diffuse into the

brain extracellular space and act on receptors that are remote from the release site. This type of communication might occur over a range of only a few micrometers, but this distance is much greater than the width of the synaptic cleft. The possibility of paracrine neurotransmission has far-reaching consequences for the interpretation of information processing in the brain. When neurotransmission is restricted to the synaptic cleft it renders a hardwired system, with specific junctions between neurons that determine the way in which information flows. In contrast, the presence of paracrine neurotransmission would allow information flow to a variety of targets over a much wider spatial area (Fig. 1).

Paracrine communication can occur if receptors are located extrasynaptically and if released neurotransmitter reaches the extrasynaptic space at a sufficiently

Melissa A. Bunin and R. Mark Wightman are at the Dept of Chemistry and Neurobiology Curriculum, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-3290, USA.