Time, Internal Clocks and Movement
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MODELS OF NEURAL TIMING

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ABSTRACT. That the central nervous system is capable of accurate encoding of time is obvious, as numerous human and animal experiments can demonstrate. But it is not at all clear how the phenomena of storage and processing of temporal information are achieved; it is in fact rather difficult to see how neurons can operate accurately over time scales of seconds or minutes, which must be required for controlling everyday behaviours. In this chapter I want to first describe what I consider to be the main difficulties in the neural encoding of time, then list some of the ways in which neurons, as we currently understand them, might actually be used to encode temporal information. Two models will then be described in more detail, that could be used for timing. Both are 'network' models in which a large population of neurons combines to encode a temporal interval. I will also briefly and selectively review some artificial neural network models that deal will time. The ideas presented here have been tested mainly through computer simulations, and so it remains to discover which, if any, of these methods are used in biological systems.

1. Introduction

The question of how to encode time in neural systems should perhaps be split into three parts. First there is the problem of the generation of temporal control signals for movement. Second is the problem of processing continuously variable signals, and extracting their temporal structure. Third, there is the problem of detecting, storing, and recalling discrete time intervals.

The first problem, of generating temporal control signals, for example to produce a finely timed motor response such as speech or a rhythmic voluntary limb movement, has being tackled successfully in several instances, especially in our understanding of central pattern generating circuits (Harris-Warwick et al., 1992; Selverston, 1993). It seems that intrinsic pacemaking neurons, complex membrane dynamics and reverbatory circuits are common to all well understood examples; it may well prove to be the same for less obviously 'patterned' outputs like voluntary limb movement. So the mechanisms by which such temporal activity are generated, while not yet certain, have at least been identified and can realistically be extrapolated from those well documented examples. The second problem was of dealing with continuously variable signals and using the temporal structure of these signals to extract, for example, image motion or to predict the path of a moving target. I emphasise prediction because this seems vital to overcome the delays associated with action. We know rather little of these sorts of processes. There are, of course, some good theories of how visual motion detectors could be constructed and the cortical areas concerned with visual motion processing have been localised. But, as far as I know, neither the mechanism nor the site of a predictor has yet been found. Third, there was the problem of how to detect, store, and recall discrete intervals of time bounded by marking events. In this category would fall, for example, estimating the time between two hand claps or the problem of timing an interval between presentation of a stimulus and the delayed response for a reward. This is the processing of time as an distinct quantity, separated from the physical or perceptual characteristics of the stimuli. It is this aspect of timing that we are most in the dark about, and this aspect that I believe is most difficult to propose a neural mechanism for. This is largely what I will discuss in this chapter.

1.1. BEHAVIOURAL AND NEURAL TIME SCALES

The nervous system operates over the range of microseconds (in the encoding and separation of sensory signals) to years (in memory and learning). At the finest scale, timing is dependent on and limited by the biophysical nature of neurons. Thus the quantal nature of membrane ion channels, the stochastic diffusion of neurotransmitters, the integration of post-synaptic events and the conduction velocity of active membranes set lower bounds to the time scale on which events can be accurately measured, processed or distinguished. When people are asked to estimate time over longer scales, perhaps tens of seconds, they try to count. We can in fact estimate well even if forced not to count, by being asked to complete some other task during the interval. However, the choice of a counting strategy implies that we are more accurate in estimating multiple small intervals than in estimating one long interval; hence use of a counting strategy may help us avoid the difficulty of pure time estimation by relying instead on the sorts of rhythmical pattern generators to which I alluded earlier. Over much longer scales of hours, days and years, we probably resort of estimating time with reference to other known time signals: the occurrence of an event relative to a mealtime, perhaps, or relative to some other remembered ('time-stamped') event. Hence at this range, time is not being handled as an explicit time varying neural signal, but as non-temporal, relational, knowledge about different episodes. However, we do routinely estimate intervals or durations ranging from hundreds of milliseconds up to several seconds, and can do so without resorting to tricks like counting in our heads (Macar et al., 1992). The mechanism or mechanisms responsible for this range of timing ability seem to be most difficult to resolve in terms of individual neurons or neural circuits.

There are two reasons why time keeping over these ranges is difficult. First, the intrinsic temporal range of many neurons is limited. A typical estimate for the membrane time constant is about 5 to 20 ms; synaptic and axonal delays within the vertebrate brain may add another 10-20 ms. Given this 'basic' operating range tens of milliseconds, it becomes difficult to extend the temporal scale to hundreds of milliseconds. There are of course a wide variety of complex membrane properties (with slow exponential decay of membrane potential, oscillatory or rebound behaviour, bistable membrane potentials and the like), which might be extend the time horizon. I will return to these possibilities further later on. However, I think it fair to say that those neurons within vertebrate circuits that are known to be important in temporal processing (e.g. prefrontal cortex or cerebellum) do not display obviously complex dynamics. The second difficulty is that neurons are inaccurate (although this does not necessarily mean that they are unreliable; cf. Bailek and Rieke, 1992). They operate stochastically, both at the level of the membrane and the synapse (Holden, 1976). We do not know the range over which synaptic weights normally vary with long term potentiation or depression, nor the precision with which they are set, nor the precision with which they transmit single impulses. However, the resolution of synaptic weights is probably quite low, perhaps 4–5 bits or 16–32 separable levels. There is also a limit to how accurately neurons can encode a quantity as a change in membrane potential, because of the signal-to-noise ratio of the signal; estimates of 4–7 bits (or 16–128 separable levels) are sometimes given (Laughlin, 1989; Attwell and Tessier-Lavigne, 1989). Spiking axons can only encode quantities as inter-spike intervals, and this sets a limit to the accuracy of reading the code. To read an interval with high precision requires some time to assess the mean firing rate, and also requires little or no temporal jitter at the synaptic junctions. Lastly, most neurons adapt to a steady input, and their firing rate falls with time. Together these factors mean that quantity cannot be represented with any great precision, either as the activation level of a single cell nor as a synaptic connection between cells.

These arguments mean that single units may not be able to accurately encode long time intervals; there is an intrinsic trade-off between accuracy and firing duration or oscillation period, such that we can expect neurons to be most reliable at short intervals. Cells with very long oscillation periods would have slowly changing membrane potentials, and hence one would expect some scatter of the moment at which spiking initiates in each cycle. These arguments also imply some problems with networks of neurons, if high levels of accuracy are required for their combined processing. For example, if a recurrent network of neurons is to have stable oscillatory behaviour, the synaptic weights may need to be set with unrealistically high precision. Thus we should ask what mechanisms are feasible for single neurons, circuits or networks to encode time. We can therefore ask which mechanisms seem more likely (or perhaps less unlikely), and also compare these schemes with the techniques used in artificial computer models of timing. Neural network models have been criticised because of their 'biological implausibility'. But among the many different models there are useful insights into how large numbers of neurons can co-operatively solve tasks, tasks that pose almost impossible problems for small assemblies of neurons. Finally, it would be useful to develop guidelines that would allow us to experimentally distinguish between these various ideas and discover which mechanisms are used in real biological systems. The last aim is probably beyond the scope of this chapter.

2. Potential time codes

There have been many different mechanisms proposed for neural coding of time. In the Table I have loosely grouped the theories or mechanisms into those based on single cells (or at least serial connections between cells); those dealing with small circuits (where the individual members of the circuit may have rather specific roles); and those dealing with populations or

ble 1 Possible neural mechanisms for encoding time. A selection of neural properties are given, which may endow urons with the ability to encode temporal information. Theorertical proposals are then sorted in terms of both the mbers of neurons that might be involved, and how speciific is the role of individual neurons in the coding

Mechanism	**Single cells**	**Small neural circuits**	**Distributed population**
Intrinsic membrane dynamics [a]	pacemaker cells	oscillators; pattern generators	oscillators/beaters
Temporal integration	counter	pattern generators	
daptation	timer	pattern generators	
onduction delay	delay line	coincidence detector	
·naptic delay		tapped delay line	re-entrant loop models
ecurrent connections		pattern generators re-entrant loop models	
ctivation levels	counter		neural integrator; population activity model
ttern codes		coincidence detector	correlation models
patial codes	labelled lines		shifting activity wave

Dynamic membrane properties may also underlie temporal integration and adaptation, but are taken here to mean more nplex time varying behaviour such as spontaneous oscillations or plateau potentials.

networks of cells, where it is assumed that the individual neurons are less specific to the particular process.

The first mechanism is that based on single pacemaker neurons, which are certainly 'biologically feasible', as they are found in many different neural circuits. There is however a general problem in using intrinsic pacemakers to time arbitrary time intervals. One either needs a mechanism to adjust the period of the pacemaker, so that it can take on any periodicity (Torras , 1985, 1986), or one needs a large pool of different pacemakers from which one can select the appropriate individual. The alternative seems to be to have a fast pacemaker acting as an 'internal clock', and then solve the problem of counting the ticks of the clock. This brings me to the second mechanism, which is to use temporal integration (for example in the post-synaptic membrane) to sum up a temporal sequence of events. Here the post-synaptic potential represents the integrated quantity, until the spiking threshold is reached and the cell is activated. This 'integrate and fire' model is in fact widely used for a variety of models, and is again quite feasible. It also faces difficulties because to set up a versatile timer, one must either control the integration time of the membrane or the period of the internal clock, so that the post-synaptic cell reaches its firing threshold at the appropriate moment. A second possibility, based on the same principle, is that the neuron integrates supra-threshold activity; in other words the firing rate of the neuron reflects the integrated quantity. Again, this may be problematic for single neurons, as it poses high accuracy demands on the maintained firing rate, and on its interpretation by some other target neuron. I will discuss a population version of this scheme later, which largely avoids these difficulties. A third possibility is that a neuron fires a prolonged burst of action potentials, and the duration of the burst is self-terminated due to an adaptation mechanism. This seems a feasible mechanism, and makes no demands on the accurate decoding of the action potential bursts. The neuron might be 'switched on' with a supra-threshold activation, and a behaviour could easily be triggered at the end of the burst through disinhibition. To be flexible, one would need to adjust the adaptation rate of the neuron, or allow selection among many neurons.

Serial chains of neurons acting as delay lines might be possible (Licklider, 1951) with each synapse adding a small delay to the signal, but few neurons in the vertebrate brain have synapses powerful enough to ensure signal transmission down a single neural chain. Another idea was to make use of the conduction delays in axons, to spatially map time as distance along an

axon (Jeffress, 1948), and this scheme is known to be used within the medial superior ovilary nucleus for detecting sub-millisecond interaural time delays (Carr and Konishi, 1988). Re-entrant (recurrent) pathways have also be proposed to form 'delay lines' (e.g. Longuet-Higgins, 1968), but because of the limits on neural accuracy mentioned before these schemes seem unlikely to me. The demands on maintaining an accurate representation of the signal as it repeatedly passes through many synapses seem too great.

2.1. OSCILLATORS AS TIMERS

An alternative possibility is to make use of the interactions between groups of oscillatory pacemaker neurons. The idea of using oscillators to store an arbitrary temporal sequence was fundamental to Longuet-Higgins' holophone (1968). Church and Broadbent (1990a,b) used a related scheme to model animals' time estimation in delayed-reward experiments. A fourth type of model invokes neurons with a broad range of membrane dynamics (Tank and Hopfield, 1987; Grossberg and Schmajuk, 1989), so that time can be mapped onto neurons with appropriate dynamics. In all these schemes, the oscillators have a broad frequency range, or even a regular hierarchy of oscillation periods. For example, in Church and Broadbent's model the pacemaker periods increased in powers of two (1, 2, 4, ... 256 seconds). In Longuet-Higgins' holophone a broad bank of neural filters was required, one tuned to each frequency. Thus they require that the population of pacemakers or the membrane time constants include at least one neuron with a duration as long or longer than the interval to be stored. This is not impossible in neural terms, and hierarchies of pacemakers have been suggested to underlie other long duration processes, for example, diurnal rhythms. A somewhat different scheme relied on the phenomenon of 'beating' amongst large networks of oscillating neurons (Miall 1989a, 1992). This model was shown to be robust, and made no unreasonable physiological demands, and I will briefly review it here.

I originally proposed a scheme which relied on a large population of pacemakers with only a narrow distribution of oscillation periods and which used a simple Hebbian learning rule to store long time intervals (Miall, 1989a). In this model a unique group of pacemakers could be selected that had the appropriate beat frequency to store any particular time interval. Consider a group of oscillators (pacemaker neurons), each with a slightly different frequency of oscillation, and each spiking for a brief part of each cycle (Figure 1). The beat frequency of any pair of these oscillators is then the frequency at which they spike simultaneously. Thus their beat frequency is much lower than their intrinsic oscillation frequency; it is given by the difference between the frequencies of the two cells. For a population of oscillators the beat frequency is given by the lowest common multiple of the periods of their oscillations. A group of a few hundred pacemaker cells, even with quite similar oscillation frequencies, could encode a wide range of time intervals and could recall the interval at a later time.

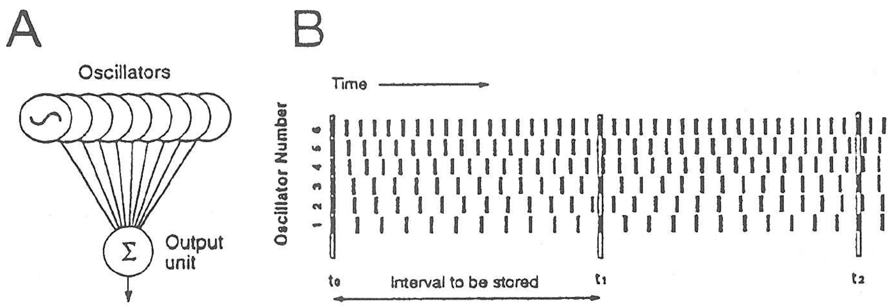

Figure 1: Storing time with oscillating neurons. A: The network: a heterogeneou population of oscillators mutually excite an output neuron, which sums incomin activity and fires when a threshold is reached. B: A schematic diagram of activit in 6 oscillators, indicated by short vertical bars. The interval t_0-t_1 can be encode by selection of those few oscillators active both at t_0 and at t_1 (oscillators 1, 2, 6) their beat frequency matches the test interval. Modified from Miall (1989a).

To demonstrate the basic model, the mechanism indicated in Figure 1 was simulated on a computer (Miall, 1989a). A population of up to 500 pacemaking units was defined, with oscillation frequencies between 5–15 Hz chosen using a random number generator to give an average frequency of 10 Hz (Llinas, 1988) and a standard deviation about the mean of 1.6 Hz. The output of each pacemaker was zero for 90% of each cycle, and 1 for the remaining 10%. All pacemaking units synapsed onto a single output unit via Hebbian synapses taking values of 1 or zero. The total input from the pacemakers was summed, and displayed as time histograms (Figure 2). Now, to store any specific interval, t_0-t_1, first all pacemaker units were synchronised at t_0 (as in Figure 1B). Those active at time t_1 were noted, and the strength of their synapses onto the output unit set to value 1. To test the specificity with which the selected units stored each interval, all the pacemakers were again re-synchronised, and the activity of the output unit monitored (Figure 2). The model has been tested with a population of between 10 and 500 pacemakers, with intervals ranging from 200 milliseconds to 10 seconds, and with the percentage of each cycle that a oscillator was considered to be active ranging from 50-99.9%.

The shortest interval that could be stored was set by the shortest period of any pacemaker in the population. The longest interval that could be stored was difficult to specify. It depends on the number of pacemakers, their activity thresholds, and the precise distribution of oscillation frequencies within the group. In simulations of 250 or 500 pacemakers, the upper time limit seemed to be at least 20 seconds.

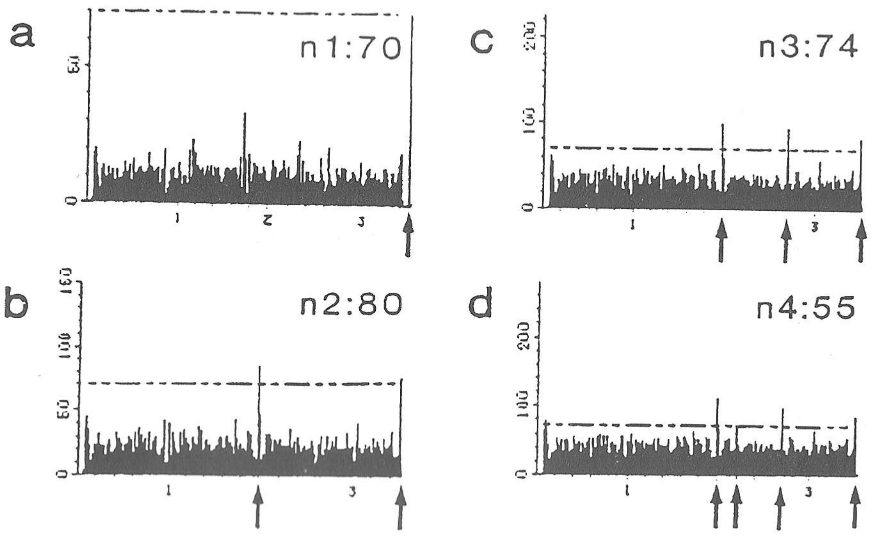

Figure 2: Records of the output unit's activation during recall of multiple random intervals. The horizontal line indicates the threshold for the output neuron to fire, set equal to the mean number of oscillator selected for each interval. **A:** Recall of the interval 3.5s; the threshold is crossed only after the target interval (arrow) **B-D:** Recall of two, three or four intervals (arrows) by the same network. As the number of stored intervals increases, the activation level approaches the threshold. The network's capacity was about 4 intervals. From Miall (1989a).

The basic mechanism can also be used to store more than one time interval simply be selecting additional pacemakers that encode for each additional time (Figure 2B). In the 1989 paper, I demonstrated how the simple Hebbian network could learn in a single trial but had relatively low storage capacity, so that a network of 500 or more oscillators would be required to accurately store a pattern of say 5 or 10 arbitrary time intervals. That model used synapses taking only integer values of 0 and 1, or 0, +1 and -1. In a biological framework it might be more realistic to assume that synapses could take values between 0 and 1, and would gradually move between these two limits on repeated presentations of a particular interval. In other words, a learning rule might only gradually increase the strength of selected synapses relative to the others. Thus in 1992 I extended my original scheme to a description of a temporal network using the perceptron learning rule to set its synaptic weights. Using a rule which allowed the synaptic weights to take on any integer value (which is functionally equivalent to allowing different levels between 0 and 1, a network of just 100 units could store at least 20 time intervals (Miall, 1992). With the optimum value of the activity threshold of the oscillators, about 70 cycles through the input set where required to learn such a sequence.

2.1.1. *Discussion of the oscillation model.* It is possible that the nervous system could use the basic mechanism proposed here in the perception of time, or in the production of long sequences of neuronal activity. The oscillatory components could be realised as individual pacemaker neurons, as entrained groups of pacemakers, or as reverbatory circuits containing several neurons. In the latter cases, any one cell in the circuit could make a synaptic connection to the output neuron. Each neuron or reverbatory circuit of neurons could have a relatively short oscillation period, as is frequently found in nervous tissue, while the whole ensemble could co-operate in behaviours with time courses hundreds or thousands of times longer. Evidence for such a scheme would be a group of rhythmically active cells forming synapses upon output units that sum activity over some selected subgroup of the ensemble. A strong requirement would be that the oscillators could be started synchronously, or phase-adjusted at the start of each input sequence.

Pacemaking units are found in a number of brain sites, and the figure of 10 Hz chosen for these simulations is biologically reasonable (Llinas, 1988). However, three weaknesses of the scheme were apparent as a model of biological time-keeping.

The most severe is that the network is intolerant of even very minor changes in the period of the whole population. If each oscillator's period was shifted by just 0·5 %, then recall was poor; if all the periods changed in the same direction then tolerance was improved but still low. Only if the units randomly fluctuated about a very stable mean period would the network be able to tolerate noise. In other words, if each unit showed some variation in activity threshold, so that for any one cycle there was uncertainly about its activity but it remained oscillating at the same period, then the system would be quite robust. The networks can be made less sensitive by a protocol of training them in the face of small random noise, as then the network continues to learn until it reaches a safety margin greater than the noise level. Then minor fluctuations in the oscillators have less effect during recall. A second failure to mimic biology is the relationship between interval duration and accuracy: The networks as modelled were either accurate or they failed. There was no distribution of responses about the desired time that might lead to the typical Weber's Law relationship between errors and duration. Again, by training with noisy oscillators, this would no longer be the case. In fact, Church and Broadbent (1990a,b) do just this to ensure that their models mimic the distribution of time-estimates shown in delayed-reward experiments. Their model is quite closely related to mine, in that it selects active oscillators from a population to encode an interval. The difference is that their scheme results in a binary code, as the oscillator periods increase in powers of two, requiring at least one oscillator with a period as long as the test interval. The remaining difficulty with the scheme presented here is that the group of selected units encoding a particular time interval or sequence needs to be synchronously reset to allow recall of the stored interval. This is possible, but would require some powerful reset signal to reach the entire group of oscillators.

One feature of the proposed model, which I originally thought of as a flaw, is that individual neurons within the group of oscillators, and indeed the output unit itself, would show little of no evidence of being related to the task in hand. In other words, it would be very difficult to detect such a scheme by single unit recording techniques (Figure 2, and also Miall, 1989). It is therefore interesting to see recent data on correlated high frequency oscillators in between pairs of cortical neurons (Gray et al., 1989; Engel et al., 1992). A recent report (Vaadia et al., 1995) has demonstrated that frontal neurons may show no overall change in firing rate, while the correlation between the pairs activity changes significantly and can differ between go and no-go trials in a delayed response task. This is just the sort of difficult detection problem that I had originally worried about, and its solution implies that one might indeed be able to detect the mechanism that I had proposed.

2.2. POPULATION INTEGRATION FOR TIMING

Having described the oscillatory models, I want to turn now to a rather different aspect of timing. There is considerable psychophysical and behavioural evidence for some form of counter, used in timing tasks, so that any given interval can be estimated by accumulating or integrating the ticks of a internal clock, and compared with a reference value (Gibbon and Allan, 1984). Neurons in frontal areas of the cortex show a gradual increase or decrease in their averaged activity during delayed response tasks, as expected of cells functioning as an integrator or counter (Niki and Watenabe, 1979). As mentioned previously, I would not expect any single cell to be able to integrate accurately over long periods, and in general the activation of these frontal neurons can be quite erratic even within any one trial. A population of neurons may be much more robust, however. Thus a possible integration mechanism is to simply consider the total activity within a population of noisy neurons, none of which can individually accumulate or integrate (Miall, 1993).

Consider a group of neurons, all receiving the inputs from an internal clock which is periodically emitting a pulse of activity. Imagine that each neuron has only a low probability of being activated by any one clock tick, but once switched on, it remains on. Further, we can also add a small probability that each active unit will switch itself off at any moment. Hence, the trial by trial activation of individual neurons will be erratic, and show no clear increase or decrease in activity with time. However, the total activity within this population monitored, for example by assuming that each of these neurons projects an excitatory input to another neuron or network of neurons, could represent the accumulated measure of time. Obviously this measure of total activity should rise or fall monotonically with the number of clock ticks. I consider here only the case of monotonic increase. On the first tick, a small number of units will be activated, and some will be inactivated. At the second tick, more of the inactive units will be activated, and a few active ones turn off, and so on. As the number of time steps increases, the number of active units asymptotes towards a fixed limit. Hence the network will have an upper boundary on the number of time steps it can encode. Figure 3A shows the averaged results from 10 runs of a simple computer simulation. The net had either 250, 500 or 1000 units; the probability of each unit switching on was 0.05 per clock tick, and the probability of each one turning off was 0.0001 per iteration of the model. Since the clock ticks arrived every 100 iterations, $p_{off} = 0.25 p_{on}$. The total activity did indeed increase with time, but the variance also rises over the first 6-10 time steps. So the fidelity of the system depends on the incremental increase in activity with each clock tick (Figure 3B), but this must be with respect to the variance at each step. Figure 3C plots the ratio of the change in mean to the standard deviation of the mean. A cut-off threshold of 1.96 is shown which represents the 95% confidence limit for accurate detection of the increase in activity per time step. For the largest net, this limit is reached after about 13 clock ticks, whereas the smaller nets fail earlier, after 9 or 5 clock ticks.

2.2.1. *Discussion of the integrator model.* It is clear that a population of 'low quality' neurons can form the accumulator required for an internal timer or to count randomly timed events. In this simple simulation the individual units were either on or off, all synaptic weights were fixed (and uniform), and all neurons were random both in their activation and inactivation. One could easy add more power to the network, for example allowing low resolution changes in activation level; even if only two or three separable activity levels were allowed (for example, low medium or high activity), this would have the effect of increasing the population size 2–3 fold. Note that it is only the source of the input that determines whether the network output reflects time or quantity; and thus the same network could be used to time or to count (Figure 3 C,F). It also means that timing is feasible with irregular clock pulses, as allowed for by scalar timing theory (Church and Gibbon, 1982) or behavioural timing theory (Killeen and Fetterman, 1988). The total activity in the net correlates with the passing time or number of events. However, no obvious clue to the timing ability of the network would be gained by recording from any one neuron on any one trial.

I should try to describe what form of input (clock) or output (threshold device) this mechanism would use. As a timing device, a synchronous pulse is required at all neurons in the net; for counting the net should receive discrete pulses from the sensory system detecting the events to be counted. But only a fraction of the population of neurons should be activated by each input pulse. One possibility would be to require coincident input from the timer and from another independent input. For example, each neuron might receive an independent series of action potentials uncorrelated with the common timer input, then only those neurons with coincident arrival of both inputs would become activated. Alternatively, one might imagine that the whole population of neurons has asynchronous sub-threshold oscillatory behaviour. Then the additional excitatory timing input arriving in-phase with this oscillation could switch them to their active state; again, if the population oscillations were uncorrelated, the selected group would be just those few at the peak phase of their oscillation period. Hence this has links with the mechanism suggested in Section 2.1, for the selection of a subset of oscillators amongst a larger population. The output side requires a threshold mechanism. The accumulating activity within the network should only trigger the delayed response when the correct number of timing pulses have been integrated; this threshold device should receive an equally weighted input from every member of the integrator population (to avoid biasing the statistics of the count). One possibility, which would avoid difficulties raised early regarding the limits to accurate threshold setting in single neurons (Section 1.1), would be for the accumulating activity to switch on – or off – another group of neurons. If these were mutually excitatory, then the threshold for switching within the whole group could be robust, despite individual neurons behaving erratically. The principle here, as in the main integrator population, is of averaging across many neurons. A mutually excitatory group would therefore switch rather abruptly from low to high activity, as the input drive from the accumulating counter reached the threshold for explosive positive-feedback driven excitation. In principle, this threshold feature could even co-exist within the integrative population. One could have a number of excitatory interconnections which, when the total activity reached some critical point, would cause rapid mutual firing of the whole group. To vary the threshold value, one would add slight inhibition or excitation from another source. Hence the neural mechanics of this whole scheme are quite easy to imagine.

The net displays initially increasing variance with increasing events or time, and t herefore approximates the psychophysical data on behavioural

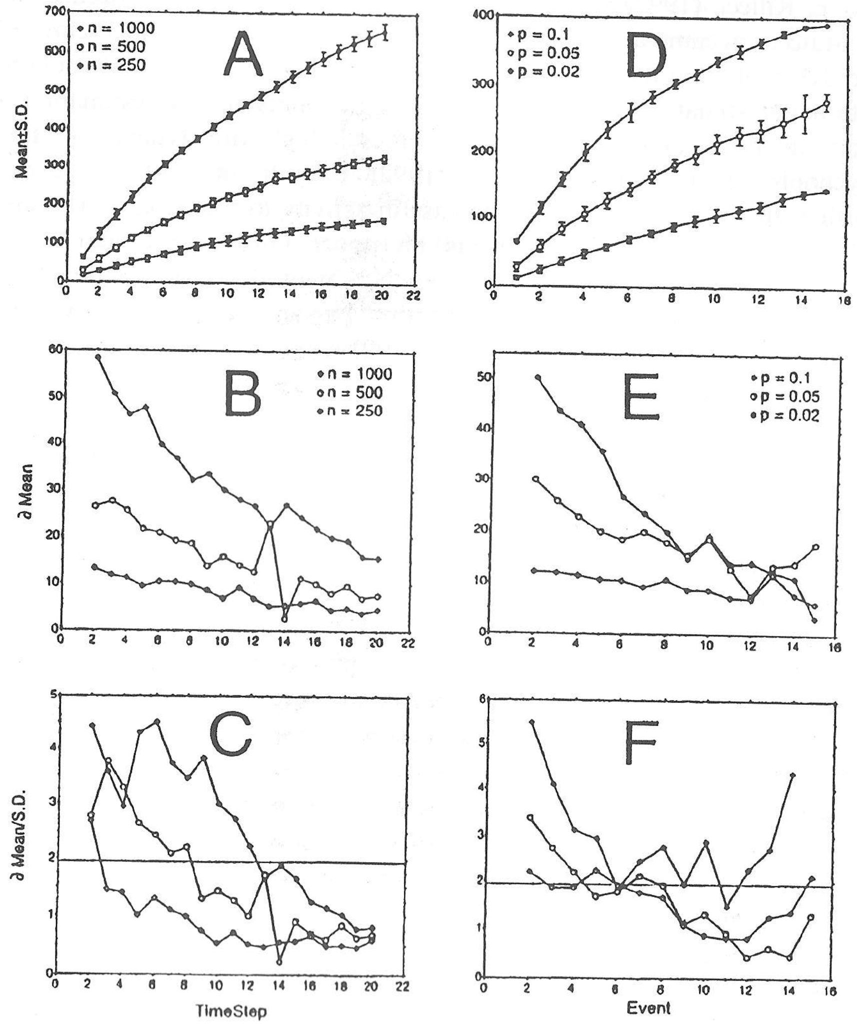

Figure 3: Timing and counting. A-C: Timing. A: Mean number (± SD) of active units against number of time steps. The input is from a regularly ticking clock. **B:** The increment in mean activity per clock tick. C: The ratio of incremental increase to standard deviation. The horizontal line is at 1.96 (95% confidence limit). D-F: Counting. D: Mean activity against event number. A 500 unit network received. irregular inputs arriving with a probability of 0.005 per iteration. The probability that each unit would be activated by an event was varied from 0.1, 0.02 to 0.05. E: Incremental activity; F: Incremental increase over standard deviation.

timing; Killeen (1992) reviews evidence that the counter may indeed be inaccurate in accumulating clock ticks. The asymptotic curves in Figure 3A and 3D imply that there would be systematic errors of timing and counting with underestimation of long intervals or high counts and overestimation of short intervals and low counts, features which are typical of time psychophysics (see again Killeen, 1992; Church and Gibbon, 1982). Further, the ratio of differential increase in activity to the variance (Figures 3C and 3F) implies that there is an upper limit to the number of accumulated clock intervals or the number of events that can be distinguished. This again approximates the human behavioural evidence (Kristofferson, 1980), while Gallistel (1990) reviews evidence that animals may also count their own behavioural responses, although with considerable variance.

2.3. OTHER CODING SCHEMES

One can of course invent an infinite variety of temporal coding schemes, and if the two schemes described here have any merit, I suggest that it is that they are both fundamentally simple. They make limited demands on the properties of the individual neurons, and require only a simple algorithm to select or train the appropriate member or synapses within the population. Before finishing, therefore, I will briefly speculate about one or two remaining possibilities (Table 1).

I have discussed the possibility of delay lines; while a simple delay line does not seem to be feasible, except for very short time scales, the principle of the spatial mapping of time does have its attractions. Would it be possible to spatially map time in a cortical sheet? There seem to be two possibilities. First, time might be mapped locally, such that each neuron might represent a particular time or interval. Individual neurons might have more or less sharply defined 'temporal receptive fields', and there could be considerable overlap between neighbouring neurons. If so, the passing of time would reflect the movement of neural activity across this cortical sheet, until some critical location was reached, and the time taken to traverse the map would be the target interval. This is in essence the same idea as a delay line, but extrapolated to two dimensions. It has an interesting parallel in the recent work of Abbott and Blum (1995). They have explored the spatial mapping of dynamic stimuli (for example the passage of a visual stimulus across a retinotopically organised visual map), and have shown through computer simulations that temporal asymmetry in the rules governing Hebbian learning between neighbouring neurons can lead to a temporal shift in the retinotopic map. This is analogous to a short term prediction of the motion of the stimulus (cf. Montague and Sejnowski, 1994)

The second alternative is that the wave of activity over the cortex has no fixed path, and may even pass the same areas of cortex more than once, but the overall spatio-temporal pattern of neural activity has a particular structure. For instance, it is thought that cortical activity waves may behave in a very complex (Wright et al., 1992), even chaotic manner, so that after some initial stimulus a complex reverberation or activity wave may pass backwards and forwards over a set if interconnected neurons (Milton, Chu and Cowan, 1993). It might be possible to derive timing schemes based on this model, if the activity wave were reproducible. If one could select just those neurons that were active at each particular moment after the initial event, one would then have a distributed, overlapping set of neurons coding for each time interval.

3. Timing in artificial neural networks

In this final section, I will very briefly review coding techniques employed in artificial neural networks. It is first worth mentioning how digital computer models can deal with the time dimension at all, and then look at those neural network models that have sought to represent time, limiting my choice to a few networks that explicitly aim to encode temporal events.

There are a large class of 'neural mimics', which are the most physiologically accurate models of individual neurons, modelling membrane properties with cable equations or with compartmental models, and thus accurately modelling the dynamics of the membrane potential of the neurons (review: Koch and Segev, 1989). These are computationally demanding, and there have been very few models of large networks of neurons. Few have been tested on the sorts of learning tasks for which discrete artificial neural networks are so popular (Buhmann and Schulten, 1986; Pearson, Finkel and Edelman, 1987; see also Koch and Segev, 1989).

At a simpler level, neurons can be simulated with sets of continuous differential equations (Pineda, 1987; Pearlmutter, 1989). These models still have dynamic, time-dependent properties and can represent the behaviour of neurons as if they were non-spiking devices. They have continuously variable activation values, with dynamics analogous to the membrane, synaptic and adaptation conductances (Amari, 1978), but have no spatial dimensions. There are also discontinuous versions which add an instantaneous impulse representing an action potential. The action potential is triggered by, and resets the membrane potential, while synapses transmit the action potential (Perkel, 1964; Miall, 1989b; Amit, Evans and Abeles, 1990; Judd and Aihara, 1993).

Finally, at the most simple level, there are 'digital' models in which a computer simulation is iteratively calculated, and at each calculation the activity or synaptic weights of the elements are changed (Rumelhart and McClelland, 1986). These models encode time as a discrete sequence of states governed by the iteration rate of the model. As an approximation to neurobiology, activity within the network can be treated as representing average neural firing rates, measured over large enough units of time that the individual action potentials and membrane time constants can be ignored (Hopfield, 1984).These models cope rather poorly with the temporal dimension, as the encoding is largely forced into the iterated pattern of inputs or outputs. The most simple way to extend a network from a static to a temporal representation is therefore to map sequential samples from the inputs into a 'spatial pattern' and thus train the network to recognise certain regular features in this sequence of changing spatial patterns. The vast majority of published examples of artificial networks are simulated with this form of iterative process. These networks can therefore be powerful tools, when combined with a pre-processor to converts the incoming temporal signal into a discrete set of inputs which can then be treated as a spatial pattern.

A common form of pre-processor, which may also be used on connections within a network, is the tapped delay line. Imagine a set of regular samples from a time series, perhaps speech, each passed into a delay line which delays the signal by a different amount. If the early samples are delayed the most, and the later samples delayed the least, they can exit the delay line simultaneously, and provide a spatially distributed snapshot of the time series (Lang, Waibel and Hinton, 1990). Typically a tapped delay line, from which the delayed signal can be read off at many different points, or multiple delays lines of various lengths are employed. More complex varieties of delay line are worth mentioning – dispersive, Gaussian and adaptive delays. In dispersive and Gaussian delay lines, the output is a time-weighted version of the input. So, if the input is a discrete pulse, the output may be a temporally blurred version whose output rises and falls around some median time delay (review: de Vries and Principe, 1992). Adaptive delays have also been used, in which the delay time or the parameters of the dispersion are modified, again avoiding prior knowledge of the optimal form (review: Mozer, 1993). And lastly, nets have been designed with 'slow' and 'fast' synapses, the slow ones delaying signals between neurons (Sompolinksy and Kantor, 1986; Kleinfeld and Sompolinksy, 1988).

The overall architecture of the neural network is also of great importance, and one can distinguish between 'feedforward' networks, with information flowing in only one direction, and 'recurrent' networks in which connections within the network feed activity back from outputs to inputs. This gives recurrent networks dynamic scope, as activity within the net is no longer governed simply by the inputs (whether or not delayed) but can be self-sustaining. Imagine a unit with a self-excitatory connection – if the strength of this connection is high enough then activity in the unit in response to a pulse input will feedback and re-excite itself, and this activity will be maintained long after the input pulse has ended. Thus a recurrent network can have behaviour similar to that of a dispersive delay line, but can also have more complex dynamic behaviours. The timing of the network is again often implicit in the iteration rate of the model (Jordan, 1986). These recurrent networks have been used widely for signal processing, motor control, sequence production and the like; very many applications can be found in Neural Information Processing Systems (Touretzky et al. 1989-1995).

A few final properties of artificial neural networks should be mentioned. There are nets that incorporate dynamic activation thresholds (Horn and Usher, 1989; Heskes and Gielen, 1992), so that their responses vary with constant inputs. The parameters controlling the threshold can endow the network with very rich behaviour. A trivial example might be an oscillatory threshold, so that the unit acts much like a pacemaker; another could be a bistable membrane, switching from one state to another. Alternatively, the synapses may adapt over time (Dong and Hopfield, 1992) or with activity from 'modulators' (Dahaene, Changeux and Nadal, 1987). The level of activity within one set of synapses thus sets the moment-to-moment weight of another set of connections (Dahaene et al., 1987; Schmidhuber, 1992).

In summary, artificial neural networks (those other than neural mimics of the biophysical properties of neurons) encode time in three basic ways. They use 'hard-wired' devices such as delay lines or spatio-temporal preprocessors; they endow the networks with a variety of explicit temporal features; or they use the dynamics of recurrent connections within the network. The first and second of these three have biological counterparts, but also have some problems when mapped onto real neurons. The third, based on dynamic recurrent behaviour, may also have biological correspondence, but may suffer from its demand for high resolution in activation levels or in the precision of synaptic weights.

4. Conclusions

The aim of this chapter has been to address what I perceive to be the difficulties of mapping time onto biological neural networks. I have reviewed a number of possible encoding schemes, but described just two of these in any detail. Both are very simple models and how closely they approach reality is far from clear. However, they do highlight some interesting points. The first is that networks of neurons can operate on time scales very different from the time scale of their constituent parts. Hence the mismatch between the temporal horizon of individual neurons and the timing of everyday behaviour may be overcome by considering population based models of timing. Second, neither scheme would display an obvious 'timing function' if accidentally overheard with a recording electrode. So the fact that we are still ignorant of how the brain times events may be revealing in itself. It implies that a distributed code is used, that can only be decoded by observing many different neurons simultaneously. Third, both schemes operate with what might be considered 'low quality' neurons, and this emphasises the power of neural networks. Many very simple units can contribute to a powerful and robust network; the whole definitely exceeds the sum of the parts.

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NEURONAL MECHANISMS OF BIOLOGICAL RHYTHMS

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ABSTRACT. Rhythmicity is an inherent property in many biological systems. Regular variations are known to occur in the level of physiological functions and the nervous system plays a key role in the generation and integration of the various physiological rhythms. Neuronal ensambles are capable of generating rhythmic activity in a wide range of frequencies from 1 KHz in fast firing neurons to circannual rhythms in neurosecretory activity. Various mechanisms at the cellular and molecular level underlay the generation of these rhythms: a) alternancy of ionic currents resulting in rhythmic fluctuation of membrane potential in endogenously pacemaking neurons. b) interactions between elements of neuronal networks, being rhythmicity an emergent property of the network. c) rhythmic changes in the biosynthesis of neurotransmitters, neurohormones, secondary messengers and membrane proteins. A given rhythm may be the end product of the interplay of different mechanisms. Endogenous rhythms are also under entraining influences, either of mutual nature between different oscillators, or from external sources.

1. Introduction

The various biological functions undergo rhythmic changes within a wide range of frequencies, from nearly 1 KHz, as in the discharge of action potentials in some neurons, to yearly periods in seasonal rhythms

The various rhythms in an organism maintain constant phase relations among them. This has led to the notion of an integrated system of biochronometry; actually, the precise temporal coupling of the body functions is a requirement for a healthy condition. The medical implications of biochronometry are a well known and still growing field. Susceptibility to physical or chemical hazards, or the effectiveness of therapeutic manipulations, vary depending on the hour of day, and seasonal differences in propensity to some diseases are known since Hippocratic times. The