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Modeling the Process of Rate Selection in Neuronal Activity

LARRY M. MANEVITZ*† AND SHIMON MAROM‡

†*Department of Computer Science, University of Haifa, Haifa, Israel* and ‡*Department of Medicine, Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel*

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We present the elements of a mathematical computational model that reflects the experimental finding that the time-scale of a neuron is *not* fixed; but rather varies with the history of its stimulus. Unlike most physiological models, there are no pre-determined rates associated with transitions between states of the system nor are there pre-determined constants associated with adaptation rates; instead, the model is a kind of "modulating automata" where the rates emerge from the history of the system itself.

We focus in this paper on the temporal dynamics of a neuron and show how a simple internal structure will give rise to complex temporal behavior. The internal structure modeled here is an abstraction of a reasonably well-understood physiological structure. We also suggest that this behavior can be used to transform a "rate" code into a "temporal one".

Introduction

Physiological studies have established that beyond the time envelope of a single action potential, neurons can demonstrate a huge range of activity time-scales, extending over several orders of magnitudes, from tens of milliseconds to many minutes which are manifested as temporal regularities.

Recent evidence suggests that the source of this richness stems from the cellular level (Lowen *et al.*, 1997, 1999; Tal *et al.*, 2001; Toib *et al.*, 1998) consistent with the idea that there are many forms of molecular interactions, each with its own time-scale (Marom, 1998; Millhauser *et al.*, 1988).

Nonetheless, the neuronal cell manages to select the appropriate time-scale for its current functionality. What is this mechanism of selection? Can it be effectively modeled?

Current computational models (e.g. the basic McCullough–Pitts, Perceptron, "Neural Network" school) do not address this question. More physiological models such as the basic Hodgkin–Huxley (Hodgkin & Huxley, 1952) model or more elaborated versions (e.g. Marom & Abbott, 1994; McCormick *et al.*, 1992) do have parameters allowing the inclusion of a limited number of fixed time-scales. This is standard, since systems in general, and biological systems in particular, are usually characterized in terms of a limited set of states and transition rates. The origin of these states and rates are usually beyond the scope of such rate-based models. Thus these models are *descriptive*, not *explanatory* regarding these time-scales in the sense that the scales are placed in the models by the parameters and thus there is no attempt at an

*Author to whom correspondence should be addressed.
E-mail: manevitz@cs.haifa.ac.il

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explanation as to how they might *emerge* from natural processing.

In this paper, we describe a computational model which shows the following.

1. The emergence of different time-scales in an adaptive fashion can be accounted for by the assumption of simple interactions between components of the neuron. We emphasize that these interactions do *not* have pre-described rates in the model. These components are based on an abstraction of known physiological facts.
2. These emergent time-scales can be non-monotonic (hence *a fortiori* nonlinear) functions of the history of the cell.
3. This mechanism has potential computational advantages; relating to (i) detection of periodic signals and (ii) conversion between "rate" and "temporal" neural codes (Gerstner, 1999).

Our model is deliberately both rather abstract and simple. This implies that this phenomenon of history-dependent non-montonic rate selection rather than being surprising, is to be expected unless some further mechanism is imposed to prevent it.

Description of Model

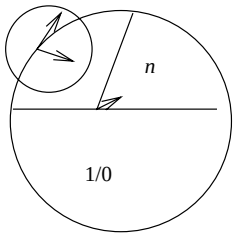
Cellular function is determined by biochemical reactions which can be abstractly described by the distribution between states and the rate of change between these states.

Thus, a change in the behavior of a cell must be the result of biochemical reactions that catalyse or impede the *rates* of other reactions.

Accordingly, the model presented here consists of basic components as an archetypical abstraction of catalysing and impeding reactions. Each of these components has its own rate which controls its ability to react to input from other components. Importantly, this rate is modifiable by other components.

The inter-relationships between the components can be represented by a directed graph; where each node has an internal structure and each directed connection has a magnitude.

Each node is a triple $\langle n, m, q \rangle$ where n is a nonnegative integer; m is a nonnegative integer bounded by n and q is either 0 or 1. Each directed connection in the graph is labeled with an integer. The integer on the connections indicates the influence of a predecessor node on a successor; a positive value increases the successor's n value while a negative value decreases it.



A reaction is determined by its state (1/0); its waiting time (n) and the time remaining on the waiting time (indicated by a clock).

FIG. 1. The elements of a node.

Each node will also have an "integrating rule" which describes how the different influences of all of its active predecessors are combined to a total effect. This makes the entire structure a sort of "modulating automaton".

The intuition is that n sets the *rate* of reaction; i.e. by indicating the amount of time steps required between responses, m is an internal clock indicating how much time remains until the next response is possible, and q indicates whether the reaction is occurring or not. This structure is represented graphically in Fig. 1.

Informally, the node must be "ready" for reaction (i.e. $m = 0$); and be "triggered" (at least one of its predecessors is active, i.e. has value $q = 1$). The modification is then a functional combination of the values on all the connections from the active predecessors. In general, we can have a complex interconnection of such nodes; each affecting and being affected by others in different signs and magnitudes. See Fig. 2.

However, if we assume that each node can represent an abstraction of a myriad of reactions at the biochemical level, then we can simplify the above picture by considering only three such nodes where only one node can be affected by

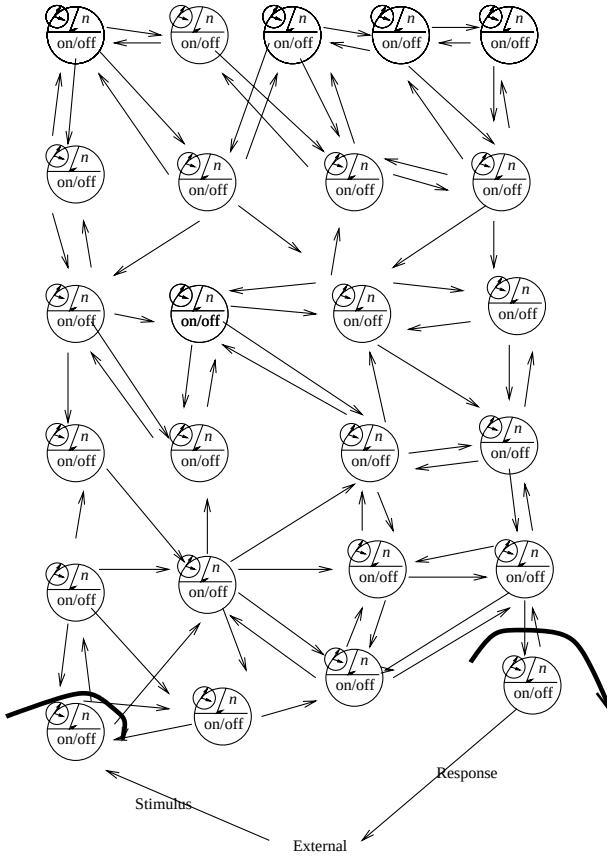
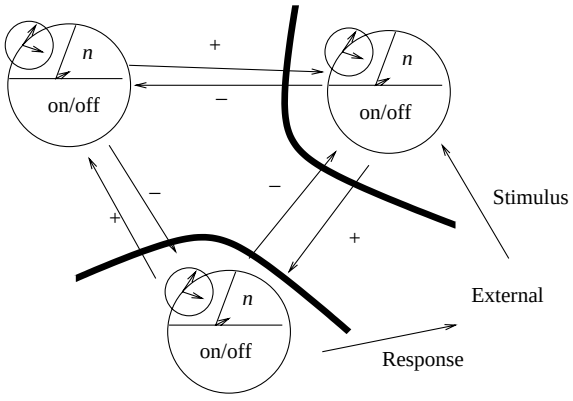


FIG. 2. A typical arrangement of nodes. The magnitudes of connections are not indicated in the diagram.

an external stimulus. (Three nodes are necessary to allow for balanced effects.)

We call this structure a "triad". The simplest such triad will have in each node a predecessor to the other two nodes, one with connection value $+1$ and one with connection value -1. In addition, an external stimulus affects one node with connection value 0. Such a non-trivial arrangement (which is the one we use henceforth in this paper) is depicted in Fig. 3.‖ Table 1 gives the complete integrating rule for the modification of any of the nodes.

‖ This arrangement reflects the intuition that the sum of all connection values entering a node should be zero; any substantial deviation from such a balance would result in passing to a trivial case. For example, if all connections to a node were $+1$ then n can only increase which eventually seems as if the node were disconnected from the graph. If all connections were -1, then eventually it would act as a simple one-step delay between predecessor and successor nodes.



A "triad" of reactions; external stimulus may affect one or more of the reactions; response is read from the state of one of the reactions. Reactions affect each other either with impedance (–) or catalysation (+).

FIG. 3. A standard "triad".

Results

SIMPLE PERIODIC INPUT

We first examine the response of the triad to the simplest periodic stimuli. We use one member of the triad to "receive" the input; and we record the state of a different member as the response, as in Fig. 3. The choice of which member of the triad is chosen as "input" and as "output" does not affect the time-scales that are evolved, but can have an affect on the complexity of the perceived generated pattern .

Fig. 4 shows the response to these inputs.

Traces representing the response over time to one stimulus per period are displayed for periods 1–9. In each case, the response settled down to cyclic behavior after an initial transient period. This is the case in all experiments with periodic input; even with a more complex stimulus pattern, the balanced triad always settles down to cyclic behavior.

In each trace, the transient behavior and the first complete cycle are indicated.

The time-scales of the system are manifested via the length of the transient, the length of the cycle, and the internal structure of the specific spike pattern. Even a superficial examination of this raw data shows that although the triad system started in each case from the same initial conditions with no pre-determined rates, the time-scales vary substantially. That is, quite

TABLE 1
Rules of change for standard triad

Event					Consequence		
Stimulus			Timing		Timing		
External	Internal	State (q)	Wait (n)	Remain (m)	State (q)	Wait (n)	Remain (m)
Any	Any	1/0	n	$m \neq 0$	0	n	$m-1$
Yes	No	1/0	n	0	1	n	n
Any	+ only	1/0	n	0	1	$n+1$	$n+1$
Any	− only	1/0	n	0	1	$n-1$	$n-1$
Any	+ & −	1/0	n	0	1	n	n

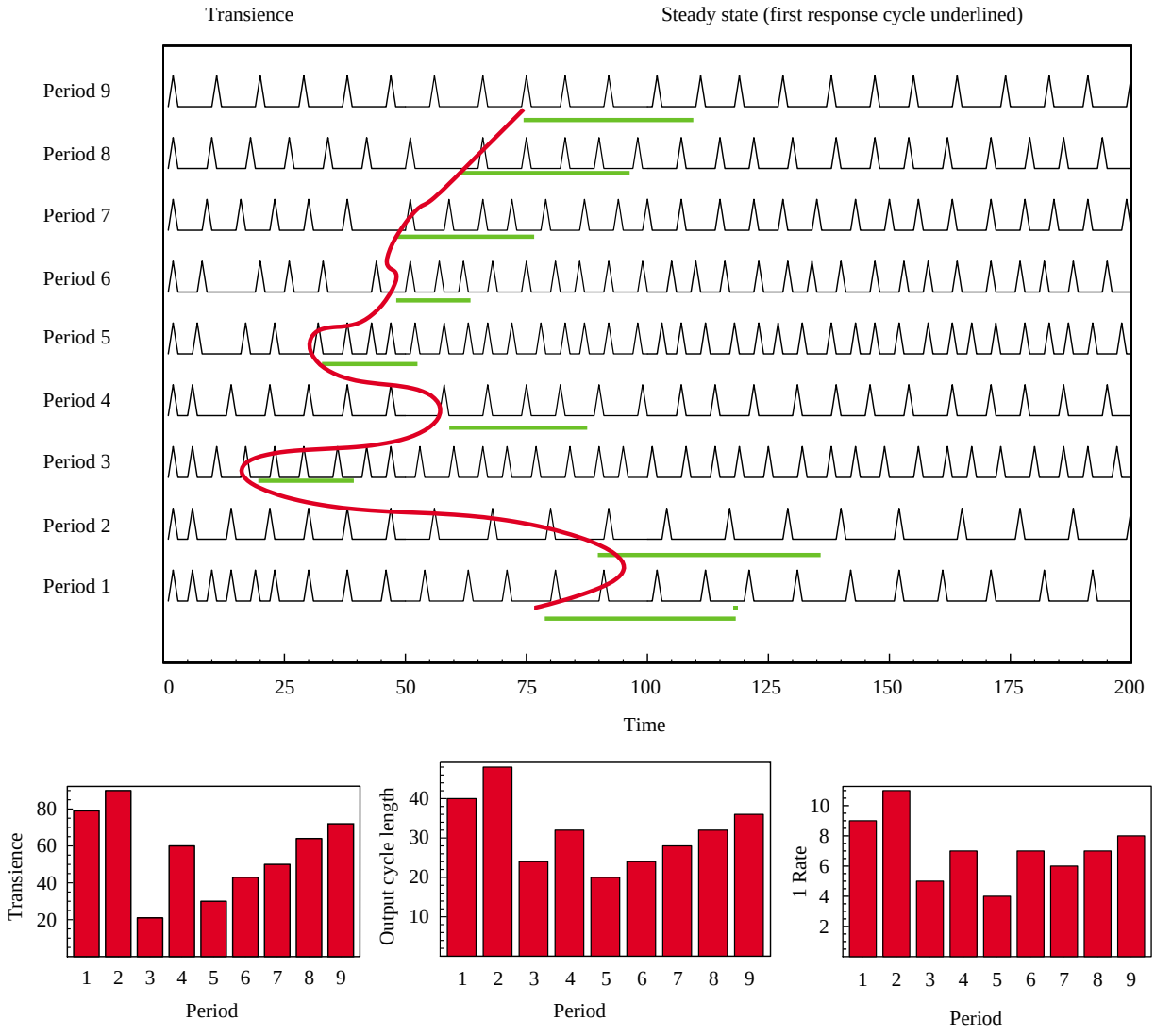


FIG. 4. Time graph of spike response of triad under different simple periodic inputs.

different time-scales are determined as a function of the *history* of the triad.

Figure 5 shows the evolution of three of the traces (periods 2, 9, 5) displaying the n values of a specific element of the triad. Note the separation of these time-scales over the different periods; and that these are non-monotonic in the stimulus period, *a fortiori* nonlinear. This

nonmonotonicity can also be seen in the cycle length, the average ISI response rate inside a period after transience and the transient length (see Fig. 4). Note that this non-monotonicity is an intrinsic aspect of the system as a whole. For example, if the output is measured from one of the other two elements, the transience, and cycle measurements are of course identical. Less trivially, while the specific ISI pattern varies substantially between nodes, the non-monotonicity of response is retained.

We investigated the stability of the response by varying both the initial settings of the individual nodes of the triad (i.e. the n, m and q values) as well as the complexity of the cyclic input pattern. The overall picture is not affected by these parameters. The cycle length, while having some variance, is quite stable. Moreover, most variance is reflected in multiples of the period. The variance of the internal ISI structure is more complex. However, the output patterns fall into a limited selection for a given input frequency.

If we examine a given response cycle, we see that it further has a structure (i.e. the complexity of the spike pattern) besides the cycle length and the average ISI response. Note that the internal ISI structure varies substantially between different input frequencies. Figure 6 shows four of these structures based on different inputs.

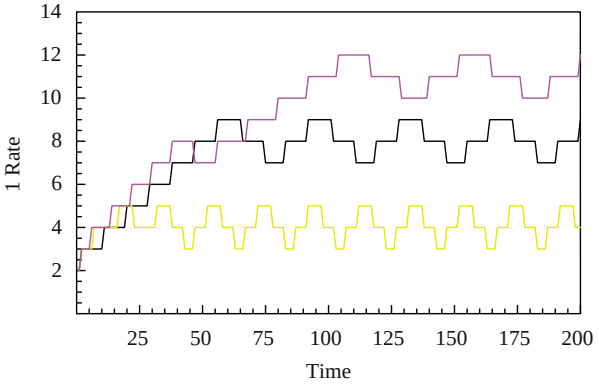


FIG. 5. The evolution of rates of neuronal responses under different periodic inputs (periods 2, 9 and 5).

COMPLEX PERIODIC INPUTS

It is interesting to see what happens when a triad is stimulated by a more complex periodic code (i.e. as opposed to a simple one stimulus per period). This might happen if the input was the output of some other triad.

To test this, we stimulated the triad with all possible periodic inputs with period of up to 8. The full data set can be accessed at (http://cs.haifa.ac.il/~manevitz/triad_data).

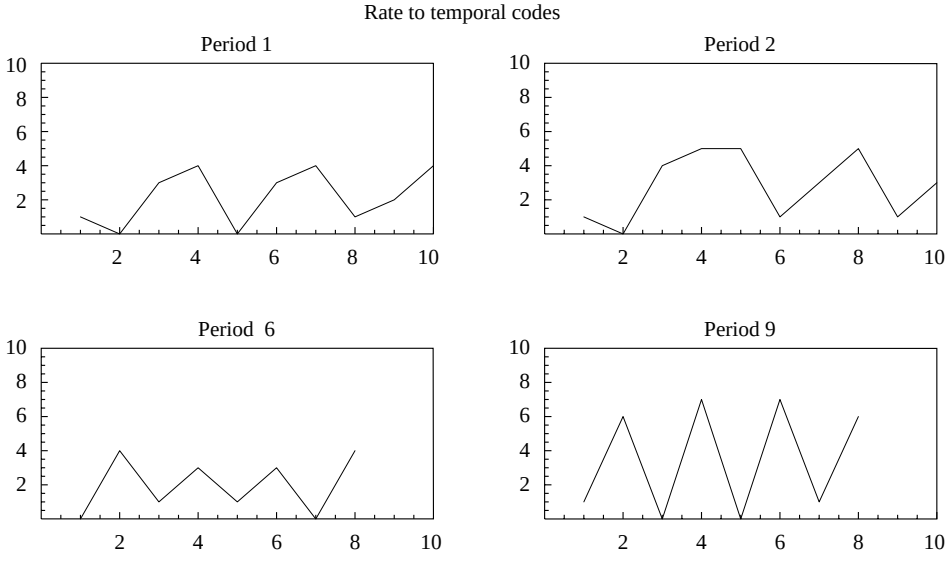


FIG. 6. Different ISI responses based on different simple periodic inputs. This can be interpreted as a transformation from rate codes to pulse or temporal codes.

Overall, there is in fact very little variance in the output ISI codes. A small sample of the table of different stimuli with 3 stimulii in a period of length 8 is given below

Note that: (1) all codes are of output period 32 or 64. (This is true for all stimuli with period 8, regardless of the number of pulses in the input as can be seen in the full data set.) (2) Most of the period 64 codes are simple padding with 8 s (the period of input) of a period 32 code. (3) There are extremely few (6) distinct ISI codes altogether for the entire approximate 2**8 set of possible stimuli inputs. (Approximate because we should not count stimuli which are actually of period 1, 2 or 4.)

Thus we can think of these codes as ''attractors''. The extremely small number of distinct codes means that such encodings are relatively robust to noise.

Nonetheless, in rare cases, as can be seen by the entries marked ** in the table below, which attractor a stimulus falls into can, in fact, depend on the initial conditions of the triad. This can be seen as over the long term, the entries marked ** are the same cyclic input; the difference occurs only in terms of where the triad starts in the cycle. This is equivalent to starting the triad in a different initial condition.

Conclusions, Discussion and Future Directions

In this paper, we have suggested an abstract mechanism capable of explaining the occurrence of multiple time-scales in neurons. These multiple time-scales have been observed in *in vivo* experiments; yet are not truly addressed in current computational models of neurons where the rates do not emerge, but are a part of the ''hard-wiring'', so-to-speak, of the model.

Our model shows that the simple idea of multiple reactions inside a neuron, which interact to impede or speed up other reactions can, in principle, account for this phenomenon. This shows that a non-rate-based model can evolve appropriate rates as a result of interactions between its components and its input. The simplicity of this idea, means that rather being surprising, history-dependent rate selection should always occur unless there is an elaboration of the mechanism to suppress it.

We note that processes of rate selection have been observed in various neural systems *in vivo* Teich *et al.*, 1997, and *in vitro* Lowen *et al.*, 1997 and in various levels of organizations from molecular (Toib *et al.*, 1998) to cellular (Tal *et al.*, 2001) to behavioral (Ebbinghaus, 1885; Wixted & Ebbesen, 1997). Interestingly, while this paper was under review, Fairhall *et al.*

Stimulii	Tran	Per	ISI	
11100000	164	64	8 1 7 8 1 7 8 2 6 8 2 6	
10110000	41	32	6 1 7 1 7 2 6 2	
10011000	185	64	8 1 7 8 1 7 8 2 6 8 2 6	
10001100	165	64	8 1 7 8 1 7 8 2 6 8 2 6	
10000110	166	64	8 1 7 8 1 7 8 2 6 8 2 6	
10101000	58	32	1 7 2 6 2 6 1 7	
10100100**	31	32	1 4 2 4 1 4 2 3 2 4 1 4	
10100010	167	64	8 1 7 8 1 7 8 2 6 8 2 6	NOTE: not the same as 10101000
10010100**	204	64	6 1 4 5 6 1 4 5 6 2 3 5 6 2 3 5	
10010010**	183	64	6 1 4 5 6 1 4 5 6 2 3 5 6 2 3 5	
10001010	165	64	8 1 7 8 1 7 8 2 6 8 2 6	NOTE: not the same as 10101000
10000101	166	64	8 1 7 8 1 7 8 2 6 8 2 6	

Note: ** is a rare example where initial conditions DO matter; over the long term the cyclic input is the same, but where one starts in the cycle made a difference.

(2001) have demonstrated the rate selection phenomenon in a specific motion-sensitive neuron in the fly visual system and have analysed how this selection process serves to optimize the information encoded in the neural response. Our model offers a basic insight into such observations.

This model, which is based on basic physiological considerations, has the following characteristics:

1. It always relaxes to a periodic solution given periodic input.
2. The nature of such a solution is dependent on the input period in a non-monotonic (hence, *a fortiori*, non-linear) fashion.
3. The solution does not vary much with changes in the initial conditions of the model. Note that these points have been observed in real neurons (Tal *et al*., 2001; Teich *et al*., 1997)

Further we noted:

4. The solution is remarkably insensitive to the internal structure of a periodic input. This means that one can interpret the system in general as a frequency detector; wherein it is sensitive to the lowest frequency in the input.

In addition, we speculate that such a mechanism might have computational consequences. In particular: (1) it is possible that it could be used to transform "rate" codes to "pulse" codes (Gerstner, 1999). In recent years, there has been much discussion (Softky, 1995; Shadlen & Newsome, 1994, 1998), supported by physiological data, indicating that both forms of representation occur in the nervous system; a fact that necessitates the existence of such functionality. (2) Point (4) above implies that the system can in fact function as an efficient period detector. Whether the neural system uses this capability is unknown.

In summary, we have shown that a system wherein no pre-determined rates are imposed can naturally adapt to its inputs by a process of rate selection. At the end of this adaptation, the system evolves into a system that is working with a small fixed set of rate constants. That is, the constants that are imposed in a Hodgkin–Huxley style model are in fact generated by the system itself as a function of its input history.

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