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Temporal computation by synaptic signaling pathways

Upinder S. Bhalla *

National Centre for Biological Sciences, GKVK Campus, Bangalore 560065, India

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Abstract

Synaptic signaling comprises a complex molecular network. Such networks carry out diverse operations such as molecular logic, signal amplification, memory and other aspects of cellular decision-making (Bray, 1995). The synapse in particular encounters complex input patterns that have different temporal sequences. Different input patterns to the synapse are known to give rise to a range of synaptic responses, including facilitation, depression and various forms of short and long-term potentiation. In many cases the stimuli that generate these disparate responses are tens of seconds or more in length, much greater than the typical time-courses of calcium dynamics. In this paper I propose that the synaptic signaling network can perform temporal computation operations such as tuning for stimulus duration or interval. Using simulation methods I show that the simple time-courses of individual signaling pathways combine in the network to give rise to different temporally selective responses. Downstream pathways that exhibit temporal integration or amplitude thresholding select different input patterns and thus perform temporal computation.

Keywords: Synaptic plasticity; Simulation; Tuning; Mitogen-activated protein kinase; Protein kinase A

1. Introduction

Temporally patterned synaptic input gives rise to multiple forms of synaptic change, such as short-term potentiation, multiple forms of long-term potentiation (Bliss and Collingridge, 1993; Cavus and Teyler, 1996; Grover and Teyler, 1990; Winder et al., 1999), synaptic depression and depotentiation (Barr et al., 1995; Bolshakov et al., 2000), and morphological change (Wu et al., 2001; LeMasson et al., 1993; Markram and Tsodyks, 1996; Turrigiano et al., 1994). To a large extent the difference between these responses is determined by the temporal pattern of the input stimulus (Abbott and Nelson, 2000). The discrimination between input patterns is probably a result of interaction between cellular biophysics especially calcium signaling, and synaptic signaling. The output effect of these patterns is mediated by a complex network of signaling molecules in interaction with protein synthesis machinery and cell biological processes such as receptor insertion into synaptic membranes. There is evidence that the pattern discrimination, especially on longer time-scales, involves the synaptic signaling network (Aszodi et al., 1991; Fields et al., 1997).

Synaptic signaling is relatively well characterized because the electrophysiological response provides an excellent assay for the role of different signaling molecules (Bliss and Collingridge 1993). Specific roles and functional interconnectivity of these pathways have been proposed by Lisman (1994), based on biochemical interactions as well as functional assays at the synapse. Using published biochemical data we have developed a model of some important synaptic signaling molecules that exhibits potentially interesting properties such as bistability, which we suggest may lead to protein synthesis independent short-term storage of information (Bhalla and Iyengar, 1999). I have recently considered temporal responses of the synaptic signaling network and propose that the signaling pathways can perform temporal tuning and filtering functions (Bhalla, 2002a,c). In this paper I examine how the output of these tuning pathways may be discriminated by downstream pathways. I consider amplitude thresholding and integrative functions of these downstream pathways and suggest that these, coupled with the tuning properties of signaling pathways, could give rise to temporal compu-

* Tel.: +91-80-363-6420x3230; fax: +91-80-363-6662.
E-mail address: bhalla@ncbs.res.in (U.S. Bhalla).

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tation operations such as pattern discrimination. I also show that these tuning properties are an emergent property of the network and apparently peripheral molecules may significantly affect tuning properties.

2. Methods

A signaling network of pathways based on the synaptic signaling literature was used as the basis for the model (Lisman, 1994). A network of 17 signaling enzymes and their regulators was modeled (Fig. 1) (Bhalla, 2002a; Bhalla and Iyengar, 1999). Each pathway block was represented as a number of mass-action chemical reactions and enzymatic interactions, based on biochemical data. The entire library of signaling models is publicly available on-line at a signaling database site http://doqcs.ncbs.res.in in accession number 16. The representation of each signaling pathway was based closely on biochemical experiments involving binding assays, response time-courses, enzymatic assays, and purifications from tissues. Most data are from mammalian brain preparations. The chemistry and kinetics of each individual pathway were defined independently to form a library of pathways. On average, each pathway definition involved 8.7 distinct molecular species, 4.9 reactions, and 3.8 Michaelis–Menten enzymatic steps. Pathways from this library were interconnected according to Fig. 1, again using known binding reactions and biochemically defined interactions between pathways. The overall model contains 148 molecular species, 84 reactions, 65 enzyme steps and can be represented as 199 differential equations. The details of the model development process have previously been described (Bhalla, 2000, 2002b).

Simulations were carried out using the Kinetikit interface to the simulator GENESIS (Bhalla 2002b; Bower and Beeman 1998). Computations were performed on PCs running Linux. The exponential Euler integration method was used for numerical integration. All pathways were represented using mass-action chemistry for binding and enzyme-catalyzed reactions:

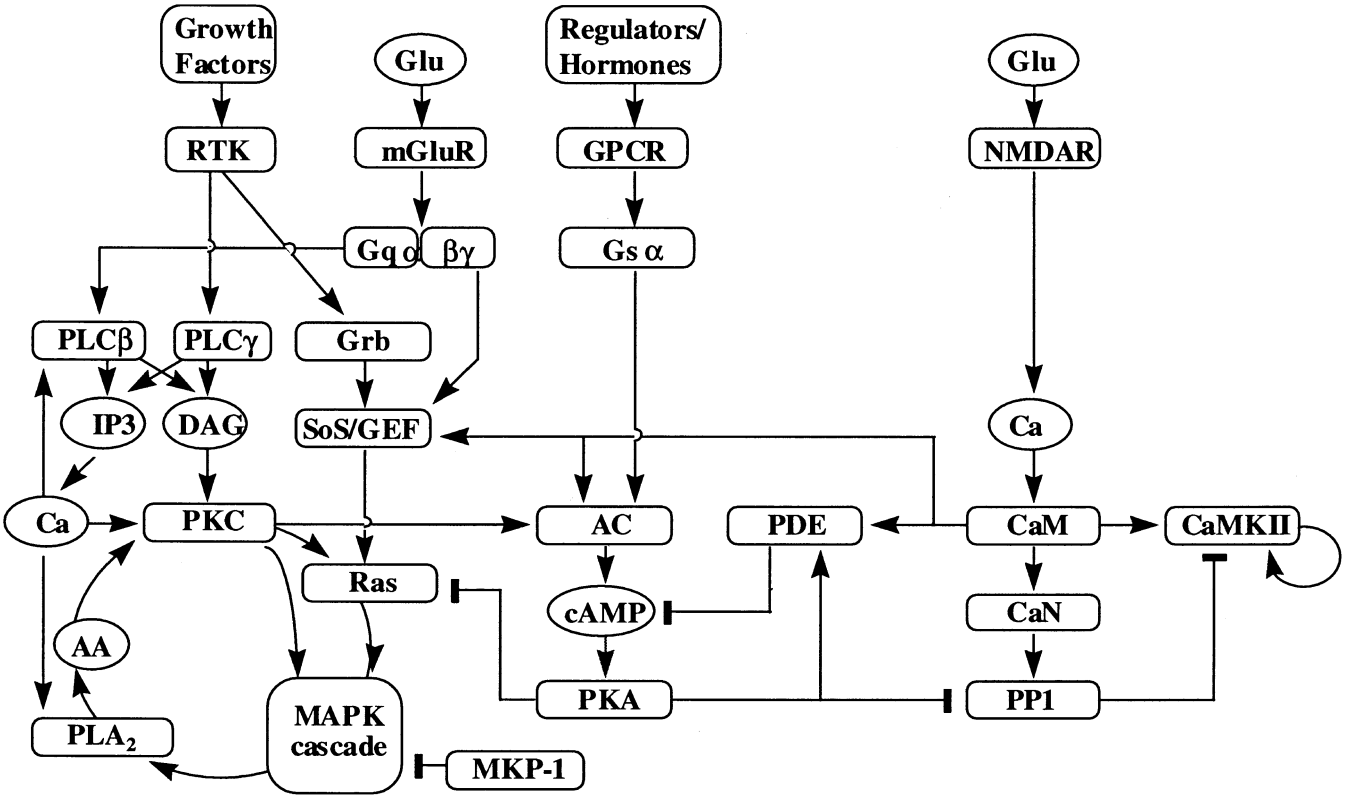

Fig. 1. Block diagram of signaling pathways in model. Reproduced with permission from J. Comput. Neurosci. (Bhalla 2002c). Each block was modeled in terms of several binding and enzyme reactions. The complete network of pathways was modeled for all simulations. Abbreviations: RTK: receptor tyrosine kinase; mGluR: metabotropic glutamate recptor; GPCR: G-protein coupled receptor; NMDAR: *N*-methyl D-aspartate Receptor; Gq: G-protein type q; Gs: G-protein type s; PLCβ: phospholipase C β; PLCγ: phospholipase C γ; IP3: inositol trisphosphate; DAG: diacylglycerol; Sos/GEF: Son of Sevenless/guanine nucleotide exchange factor; Ca: Calcium; PKC: protein kinase C; AC: adenylyl cyclase; PDE: phosphodiesterase; CaM: calmodulin; CaMKII: calcium calmodulin kinase type II; cAMP: cyclic adenosine monophosphate; CaN: calcineurin; AA: arachidonic acid; PLA_2: phospholipase A2; MAPK: mitogen activated protein kinase; MKP-1: MAP-Kinase phosphatase type 1; PKA: protein kinase A; PP1: protein phosphatase type 1.

$$A + B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} C \quad (1)$$

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_3}{\rightarrow} E + P \quad (2)$$

Both these equations can be expressed as differential equations of the form:

$$d[A]/dt = -k_f[A][B] + k_b[C] \quad (3)$$

The enzyme reactions in Eq. (2) are equivalent to two reactions in sequence, the second reaction having a zero value for k_b.

Temporal patterns of input to the model were delivered as Ca^{2+} pulses of appropriate amplitude, duration and spacing.

3. Results

3.1. Time-course of responses to different input patterns

I first simulated the time-course of responses of the network to different input patterns of Ca^{2+} input. Two simple patterns were chosen: calcium input pulses of fixed total flux, but different duration, and paired calcium pulses each of 1 s duration, but different intervals between pulses (Fig. 2). More complex patterns could be regarded as composites of these two basic patterns. In both cases the total calcium flux is unchanged from pattern to pattern, so the response changes are purely a function of time-course of the input. The outputs from two representative signaling molecules were monitored: protein kinase A (PKA) and the mitogen-activated protein kinase (MAPK).

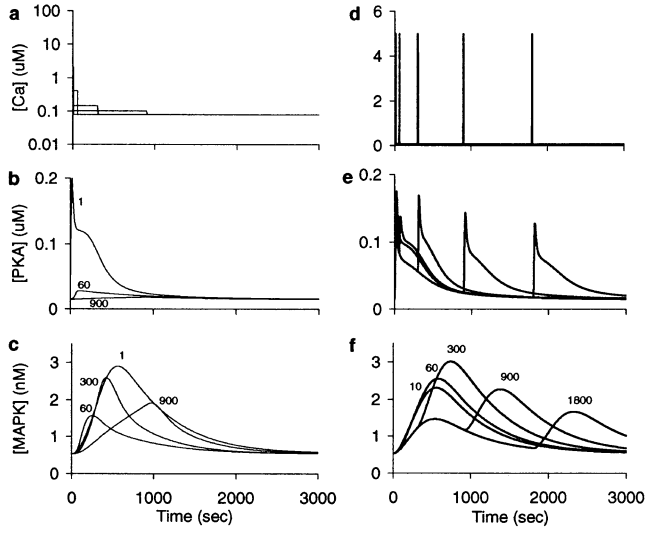

Fig. 2. Time courses of Ca^{2+}, PKA and MAPK activity. (a) Ca^{2+} stimulus delivered for different durations, such that duration × amplitude is constant at 20 μM s. (b) PKA responses to the Ca^{2+} stimulus. The response to the 1 and 10 s stimuli are almost identical and are both large, the remaining responses are small. (c) MAPK responses to the Ca^{2+} stimulus. Response profiles vary considerably with amplitude and duration. (d) Paired-pulse Ca^{2+} stimulus. The first pulse is always at $t = 0$, and the second pulse is at varying intervals following the first pulse. (e) PKA responses to paired-pulse stimuli. There is a gradual decline in response amplitude as interval increases. (f) MAPK responses to paired-pulse stimuli. The largest response is for an interval of 300 s. Reproduced with permission from Biophys. J. (Bhalla 2002a).

In Fig. 2a–c, calcium inputs of different durations are delivered such that the total flux remains constant. As flux = amplitude × duration, this means that a brief input has a high amplitude and a long input has a lower amplitude. PKA responds strongly to a brief input, but weakly to a longer one. This is due to the high threshold for calcium activation of calmodulin (CaM), acting through type 1 adenylyl cyclase (AC1) and cyclic adenosinemonophosphate (cAMP): Ca → CaM → AC1 → cAMP → PKA

MAPK, on the other hand, responds both to brief and to prolonged inputs. The activation of MAPK is also very slow compared to PKA. Thus MAPK acts as a slow integrator whereas PKA responds well to brief stimuli.

In Fig. 2d–f, calcium inputs were delivered as two successive pulses. Each pulse was 1 s in duration and 5 μM in amplitude. The interval between pulses was varied. PKA shows some buildup of responses especially at short time-intervals. MAPK builds up as well, but at rather longer intervals. Thus in this respect as well, PKA and MAPK differ and MAPK tends to slower responses.

Other signaling pathways (data not shown) also exhibit a variety of distinctive responses that include rapid responses (e.g. phospholipase-C β), slow build-up (e.g. type II calcium–CaM activated protein kinase) and combinations of rapid and slow components of the response (e.g., protein kinase C) (Bhalla, 2002a,c).

3.2. Amplitude and pattern thresholding

These qualitative assessments of pathway responses to different stimulus duration were quantified using two measures: average activation and peak. First, the average activation of each pathway was assessed. This was calculated as the average of the ratio of the pathway activity to its baseline activity. Second, the peak amplitude of activation was found. The calculation of average activation and peak was made from the time of the beginning of the stimulus, till 3000 s following the end of the stimulus. The period of 3000 s was chosen as it exceeds the time-course of all the pathway responses of the system so they would be expected to settle within this time.

Using these measures, it is seen that there are distinctive tuning profiles for PKA (Fig. 3). PKA responds selectively to short duration stimuli as described above (Fig. 3a and b). Both the average

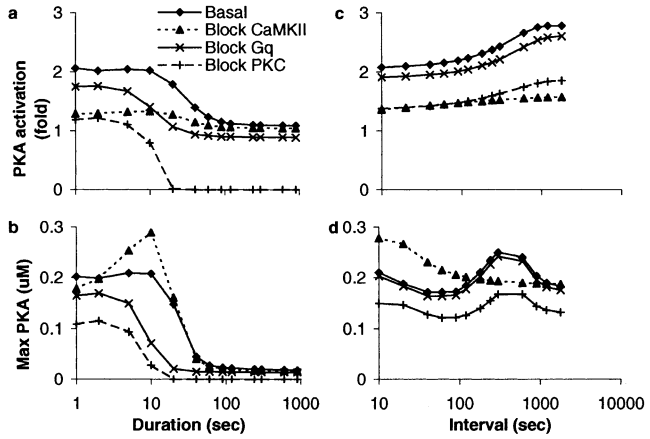

Fig. 3. Temporal pattern selectivity of PKA. In each panel four plots are shown: Diamonds: Basal activity; triangles: CaMKII enzyme removed; ×: Gq removed; +: PKC removed. Calcium stimuli are as in Fig. 2. (a) Average activation as a function of Ca^{2+} stimulus duration. The basal activation declines by 50% starting at about 10 s stimulus duration. (b) Peak amplitude of PKA response as a function of Ca^{2+} stimulus duration. There is a very large decline in basal response amplitude again starting at about 10 s stimulus duration. (c) Activation as a function of Ca^{2+} inter-pulse interval according to Fig. 2d. There is a small rise in basal activation for intervals of over 300 s. (d) Peak amplitude of PKA response as a function of inter-stimulus interval. There is a peak in basal response between 300 and 900 s. In each panel, removal of other pathways leads to changes in tuning as well as in amplitude of responses.

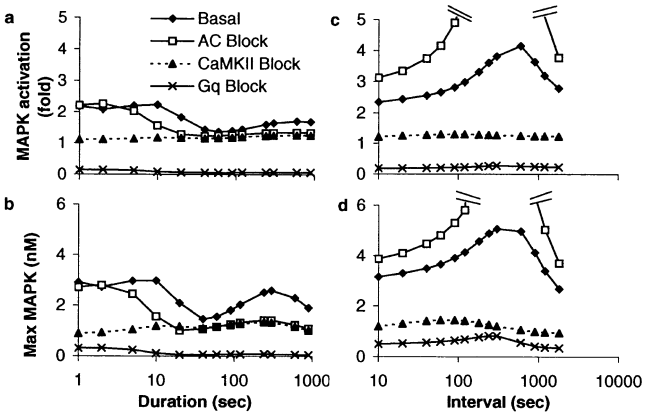

Fig. 4. Temporal pattern selectivity of MAPK. In each panel four plots are shown: Diamonds: Basal activity; open squares: AC removed; triangles: CaMKII enzyme removed; ×: Gq removed. (a) Basal activation as a function of Ca^{2+} stimulus duration as per Fig. 2a. There is a small dip at around 60 s for the basal response. (b) Peak amplitude of basal MAPK response undergoes a reduction again around 60 s stimulus duration. (c) Average basal activation as a function of inter-pulse interval for paired Ca^{2+} pulses, as per Fig. 2d. There is a peak at around 600 s. (d) Peak amplitude of basal MAPK response also has a peak at 600 s inter-pulse interval. In each panel, removal of pathways alters tuning as well as amplitude of responses. Removal of AC releases inhibition of MAPK response, giving rise to very large amplitude responses in the 180–600 s interval range.

activation and the peak response follow the same pattern, and the response drops at around 10 s. The response of PKA to different pulse intervals is more interesting. The average response of PKA rises with increasing inter-pulse interval (Fig. 3c). However, the maximal response is a complex function of inter-pulse interval and has two peaks: one at very short intervals (10 s) and another at intermediate intervals (300 s) (Fig. 3d). Thus a pathway downstream of PKA would exhibit different tuning depending on whether its response builds up in a slow integrative way (average response) as opposed to amplitude thresholding (maximal response).

MAPK also exhibits distinctive tuning profiles (Fig. 4). MAPK average activation is high for short and long stimuli, and low at around 60 s both in terms of average activation and amplitude (Fig. 4a and b). The amplitude response shows a greater reduction at 60 s, and also declines at very long stimulus durations (900 s). When inter-pulse interval tuning is considered, the MAPK response builds up to a peak for stimulus intervals of 600 s (Fig. 4c). The MAPK amplitude response also has a similar peak, occurring at almost the same interval of 300 s (Fig. 4d). Thus a pathway downstream of MAPK would respond well to short duration as well as long-duration stimuli, but relatively poorly to 60 s duration stimuli. If repetitive stimuli were given a downstream pathway would be preferentially activated for stimulus durations of around 600 s.

The entire signaling network exerts a complex control over the tuning responses. In Fig. 3 and Fig. 4, various key signaling molecules were removed from the model to examine their roles in tuning. Even molecules such as Gq and CaMKII, which do not exert direct control over either PKA or MAPK, strongly affect their tuning responses through cross-talk in the network. The tuning responses therefore do not arise in any particular subset of the signaling network, but are emergent properties of the network as a whole. Regulatory inputs to the network via hormonal, growth factor, or G-protein coupled receptor inputs have also been shown to strongly modulate responses (Bhalla, 2002a,c).

4. Discussion

4.1. Temporal computation and learning

Natural stimuli are characterized by complex timing. This is reflected in many studies of learning, where complex causal sequences of events are necessary to give rise to robust conditioning (Gallistel and Gibbon, 2000). Electrophysiological properties of neurons may form the basis for some aspects of temporal pattern recognition at short time-scales (Hooper, 1998). Network properties

can also give rise to some aspects of temporal decoding (Buonomano, 2000). The current paper considers temporal tuning properties of signaling pathways and suggests that these may give rise to temporal pattern selectivity at time-scales of seconds to tens of minutes. This form of computation is especially interesting in the context of learning for two reasons. First, the same set of synaptic signaling molecules are also implicated in synaptic plasticity. Second, the time-scales of their temporal selectivity is in the same range as natural stimuli leading to learning. It is also intriguing that such molecular tuning circuits may be present at all synapses, thus forming a highly distributed substrate for temporal computation.

4.2. Synaptic consequences

The current model includes several signaling pathways at the synapse which are stimulated by Ca^{2+}. The inputs to the simulations are therefore Ca^{2+} pulses of different duration and interval. The output of the model is considered in terms of the activity of key signaling molecules, but the assumption is that these would feed into downstream effector processes leading to synaptic change. For example, PKA and MAPK activity leads on the one hand to phosphorylation of cytoskeletal components and signaling molecules that may be involved in restructuring the synapse and insertion of new receptors. The other effect of both PKA and MAPK is to induce transcription of proteins, many of which may contribute to synaptic plasticity. In the simulations we explicitly consider the signaling effects on downstream pathways that act as integrators or threshold detectors for signaling activity. The prediction is that such downstream pathways would be selectively stimulated for distinct patterns of input (Ca^{2+}) activity to the synapse. Thus the signaling network performs a temporal computation leading to synaptic change.

4.3. Model interpretation

In this and other modeling studies, it is clear that we are only able to model a subset of signaling molecules with imperfect accuracy. The major approximations in our model are incompleteness, reaction kinetics, and spatial considerations. To the extent that test-tube biochemistry can approximate cellular signaling, we feel confident that the model represents the basic signaling effects, as the biochemistry is tightly constrained by experiments. Thus we would suggest that such models are semi-quantitative given the limitations of current techniques and knowledge about signaling. The key point is that even this small subset of molecules interacting in very simple, spatially homogenous approximations, gives rise to complex and biologically interesting computational properties. Thus we propose that this model, by showing that signaling pathways can perform temporal computations, may provide insights into the far richer signaling computations occurring at the synapse and other cellular systems.

Acknowledgements

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