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Extreme degeneracy of inputs in firing a neuron leads to loss of information when neuronal firing is examined

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Abstract

Possible combinations of inputs in the order of 10^{100} can fire (axonal spike or action potential) a neuron that has nearly 10^4 inputs (dendritic spines). This extreme degeneracy of inputs that can fire a neuron is associated with significant loss of information when examination is limited to neuronal firing. Excitatory postsynaptic potentials (EPSPs) propagating from remote locations on the dendritic tree attenuate as they arrive at the axon hillock depending on the distance they propagate. Moreover, some EPSPs from remote locations will not even reach the axonal hillock. In this context, an operational mechanism at the location of origin of these EPSPs is necessary to preserve information for efficient storage. A similar mechanism is also expected at the location of origin of EPSPs generating dendritic spikes.

1 Introduction

Neurons were shown to have independent structural features by Santiago Ramn y Cajal using modification of staining methods developed by Camillo Golgi. This led to the neuron doctrine (Shepherd, 1991). Neurons can be grown individually and can make synapses between them in primary cell cultures, features that make them structural units of the nervous system. Effect of sensory stimuli on firing of sensory neurons and the role of firing of motor neurons for the contraction of muscle fibers are well understood. Examination of neuronal activity has been facilitated by the development of tools to observe and control neuronal firing more efficiently (Kramer et al., 2009). Since firing of a neuron is the most distinct single identifiable event in the nervous system, a general view is that neuronal firing is a unitary function of the system. Neuronal firing has been studied in almost all the higher brain functions including perception of different sensations (Zaidi et al., 2013). During recent years, neurons have been named after different functions. It was suggested that by recording every action potential from every neuron and by manipulating the activities of specific sets of neurons within a circuit, algorithm that generate a higher brain function can be understood (Alivisatos et al., 2013). In these contexts, it is necessary to examine what information does a neuronal firing impart?

Neurons in the cortical region on average has 2.410^4 to 810^4 input connections called postsynaptic terminals (Abeles, 1991); these numbers can vary substantially depending on the type of neuron and its location. While excitatory neuronal activities propagate towards the higher neuronal orders, the inhibitory neurons bring fine-control over such activity. In this context, excitatory neurotransmission is primarily examined. On an average, a pyramidal neuron that receives tens of thousands of inputs can fire an action potential by spatial (at the same time) summation of nearly 40 excitatory postsynaptic potentials (EPSPs) (Palmer et al., 2014) or temporal (sequential arrival) summation of much less number of EPSPs at the axonal hillock. Artificial stimulation of different brain areas can produce internal sensations of various sensory stimuli along with firing of neurons (Selimbeyoglu and Parvizi, 2010). It is known that the same cue stimulus resulted in firing of an additional set of neurons while generating internal sensation of fear memory after associative learning (Tye et al., 2008). In order to explain the occurrence of internal sensations of higher brain functions concurrent with neuronal firing, it is necessary to provide a mechanistic explanation.

In the above contexts, the present work seeks to answer the questions, Where is information stored in the nervous system? What is the substrate (engram) for storing information? Search began with Hebbs postulate (Hebb, 1949). One of its modifications namely synaptic plasticity and memory hypothesis (Martin et al., 2000) views engrams as spatially distributed synaptic weights within a network of neurons. An individual neuron takes part in different engrams due to their large number of synaptic connections. One study (Hayashi-Takagi et al., 2015) that examined synaptic plasticity thesis used protein expression that does not match with the time-scales at which learning takes place at physiological time-scales. Optogenetic techniques used to selectively mark individual neurons during memory encoding by concomitant activation of immediate early genes (Liu et al., 2012), whose expression times are far higher than milliseconds of time needed for associative learning also do not address the mechanism that takes place at physiological time-scales. Moreover, all the above studies used surrogate behavioral markers to assess memory that in turn assess the ability to learn. In these contexts, it is necessary to re-examine neuronal firing and tailor the focus to a specific mechanism of information storage during learning that can be used for generating first-person internal sensation of memory at physiological time scales. Only by interconnecting as many observations as possible that we will be able to triangulate (Munaf and Smith, 2018) them to discover the operational mechanism of the system.

2 Causes for apparent information loss when neuronal firing is examined

2.1 Attenuation of EPSPs arriving from remote dendritic locations

The number of input connections (dendritic spines) vary widely among the neurons. It ranges from one (passive conductance of potentials between the initial orders of neurons of the visual pathway without generating action potentials) to approximately 5.6x10^3 (in a monkeys visual cortex) and 6x10^4 (in a monkeys motor cortex) (Cragg 1967). EPSPs get degraded as they propagate towards the axonal hillock. As the distance of the dendritic spine from the axonal hillock increases, attenuation of EPSPs will also increases (Stuart et al., 1997; Spruston, 2008; Major et al., 2013). This naturally leads to the question, How can information be stored using attenuating EPSPs? When neuronal firing is examined, an EPSP will find its most important function when it is providing the nth EPSP required to trigger the action potential. But this is a rare event for any one EPSP arriving at the axon hillock. Since spatial summation of nearly 40 EPSPs that are generated close to the soma is required to elicit neuronal firing (axonal spike), attenuation of EPSPs arriving from

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locations farther away from the axonal hillock necessitates much more than 40 EPSPs to cause the same neuronal firing. In this context, neuronal firing cannot be used to examine how information is processed in the system. Instead, it is reasonable to expect for the presence of a mechanism to preserve information at the origins of EPSPs.

2.2 Degeneracy of inputs in firing a neuron

To account for the attenuation of EPSPs, let us assume that on an average inputs from 100 spines are necessary to arrive at the axon hillock for the generation of one action potential at the axonal hillock of a neuron. Let us also assume that this pyramidal neuron has 10,000 dendritic spines (inputs or postsynaptic terminals). If EPSPs arriving from nearly 100 of its dendritic spines can fire that neuron, then nearly ((1x104!)/(100! x (1x104! - 100!))) = 6.5x10^{241} sets of combinations of inputs can fire that neuron (Figure.1). If we consider that a pyramidal neuron has only 3,000 dendritic spines, then the set of combinations will reduce to nearly 1.04x10^{189}. Note that these calculations were done only for 100 inputs. When all inputs ranging from 101 to either 10,000 or 101 to 3,000 are used to calculate, the sum of combinations of inputs that can fire a neuron reaches a very high value. This means that a gigantic number of combinations of inputs can cause the same neuronal firing. Therefore, when we see a neuron firing (somatic firing or somatic spike) (in vivo, at physiological conditions), it is not at all specific with respect to its inputs. This extreme redundancy will cause an abandoning of information residing within each input. Therefore, it is necessary to search for a mechanism for information storage without losing information. When neuronal firing is examined, it compels one to ignore all the sensory information arriving at the input level of that neuron and a potential mechanism of processing that takes place at that level for stable storage and their utilization during different higher brain functions.

Figure 1: Comparison between minimum number of inputs needed to fire a neuron (in red) and all the possible inputs (in red and blue) arriving at a pyramidal neuron having 10,000 inputs (dendritic spines). A: Number of EPSPs (nearly 40) needed (in red at the leftmost end) to elicit neuronal firing by spatial summation, if EPSPs originate close to soma. Note that in this situation, there will be nearly 1.13x10^{112} combinatorial possibilities of sets of 40 inputs that can fire a neuron. B: Number of EPSPs (nearly 100) needed (in red) to elicit neuronal firing by spatial summation if EPSPs originate away from soma. Note that in this situation, there will be nearly 6.5x10^{241} combinatorial possibilities of sets of 100 inputs that can fire a neuron. Empty area on the far right side represents those EPSPs that do not reach axonal hillock (these were not taken into account in the above calculations). Figure not to scale.

2.3 Ignoring large number of EPSPs during supra- and sub-threshold activations

Since firing of a neuron takes place by an all or none process, EPSPs responsible for sub-threshold or supra-threshold activations of neurons are not taken into account when neuronal firing is examined (Figure 1). Let us examine one pyramidal neuron (excitatory neuron) with thousands of inputs (dendritic spines). If 3600 inputs are activated simultaneously (supra-threshold activation) during the arrival of a sensory input, only one action potential will be elicited. Simultaneous arrival of 40 EPSPs of full strength at the axonal hillock is enough to induce that action potential. This means that when neuronal firing is examined, (3600 - 40) = 3560 EPSPs have to be viewed as wasted without having any functional use. In this context, it is necessary to think about means to preserve information. It is also necessary to preserve information when less than 40 EPSPs (sub-threshold activation) arrive at a neuron that do not result in eliciting and action potential. These findings indicate the necessary to search for a mechanism associated with all the inputs.

2.4 Some EPSPs are used to generate dendritic spikes

Similar to spikes at the axonal hillocks (neuronal firing), there are spikes occurring at the dendrites, which are called dendritic spikes. Depending on the channels involved there are different types of dendritic spikes. Based on the strength of summated potentials, a rough estimate shows that they constitute synchronous activation of up to 50 neighboring glutamatergic synapses triggering a local regenerative potential (Antic et al., 2010). It was found that distal dendrites generating spikes have firing rate nearly five times greater than at the cell body (Moore et al., 2017). It is known that the surface positive potentials are generated mainly by synaptic inputs from other cortical and subcortical regions to the pyramidal neurons located between L2/3 to L4 regions (Douglas and Martin, 2004). These input locations can be information processing locations. Calcium dendritic spikes contribute to surface potentials that are recorded as electroencephalogram (EEG) (Suzuki et al., 2017). The oscillating nature of the surface potentials need a vector component operating in a perpendicular direction to the synaptic transmission occurring between orders of neurons arranged in one direction. Since dendritic spikes are related to both behavior and cognitive function (Xu et al., 2012), it is reasonable to expect the presence of a mechanism that can explain both. Even though NMDA spikes enhance action potential generation during sensory input (Palmer et al., 2014) and calcium spikes generally contributes to a burst of action potentials (Major et al., 2013), when information arriving at the inputs generate these dendritic spikes first instead of axonal spikes (neuronal firing) examination of neuronal firing will lead to concealment of information.

2.5 Dilution of information as it pass through few neuronal orders

There is already reduced specificity of information after sensory inputs reach neurons located after few neuronal orders. In order to compensate for this loss, memory retrieval process is expected to have a mechanism to bring specificity back. Even if we find such a recovery mechanism, examining neuronal firing will eliminate the friable pieces of information that reach after few neuronal orders. Since information is already getting diluted as they propagate through few neuronal orders, it is necessary to search for a mechanism for preserving information at the level of inputs.

3 Systems organized to preserve information survived and evolved

We have seen examples of conditions in which a neuron held at its baseline state can get fired by all, a minor fraction or even just 1 input. In what context can such a mechanism evolve in comparison to other mechanisms? How did it evolve to retrieve information within the mind? Since evolution would not maintain a mechanism where vast majority of EPSPs do not serve a purpose, the functions of these currently unaccounted EPSPs need re-examination. Moreover, since very large number of EPSPs from apical dendrites do not reach the soma (Spruston, 2008) to induce a spike, the functional relevance of evolutionary conservation of apical dendrites also needs re-examination. This leads to the question, What mechanism of operation can retain information so that it can deliver this information in a specific manner in response to specific inputs by a cue stimulus. For this to occur, it is reasonable to expect interactive changes taking place at the input level of the neurons. This can be possible only when inputs at the location of convergence of sensory stimuli interact with each other to leave a signature at the time of learning.

4 A comparison with the degeneracy of codons

DNA contains stable information with the formation of embryo. External factors can regulate its transcription and usage. In contrast, nervous system is a storage device with very little information written in it at the time of birth that are responsible for innate behavior. The findings presented in this work argues for the presence of a writable storage device at the origins of inputs to a neuron. There should be mechanism to prevent overwriting of information. While most information gets lost following encryption, some information will get stored for long period of time. It should be possible to explain mechanisms for these. To understand how specificity of information is retained, it is necessary to understand the structural changes that occur at the region of inputs during learning and passive reactivation those learning-induced encryptions during memory retrieval. Provision for degeneracy at the level of the codons has the important advantage to accommodate mutational changes and biological variations especially at the third position (Figure 2). Extreme degeneracy of inputs in firing a neuron does not provide similar advantages. Instead, it directs us to examine the origin of inputs for seeking an information storage and retrieval mechanism.

5 Introduction of a new concept of a FIROME

Observation of extreme degeneracy of inputs in firing a neuron highlights the fact that there will be significant apparent loss of information when neuronal firing is examined (Figure 2). For reducing loss of information associated with examining neuronal firing in understanding the operation of the system, a new term FIROME is introduced. FIROME is a set of EPSPs that are summated to generate a spike at the location of spike generation. There are two types of FIROMEs. One for axonal spike, which can be named as FIROME-A and the second one that generates dendritic spike, which is called as FIROME-D. Since EPSPs attenuate as they propagate towards the location of spike generation, especially for axonal spike, examining them at the location of their origin is necessary to find the information storage mechanism. Therefore, FIROME-A at the locations of their origin is called as FIROME-Ao. Since these EPSPs undergo attenuation as they propagate towards the axonal hillock, sum of the values of EPSPs in FIROME-Ao will be much higher than FIROME-A. Whereas, since FIROME-D is expected to occur at the origin of their EPSPs, it expected to be the same as FIROME-Do.

5.1 Operational mechanism at the origin of FIROME

For preventing loss associated with information storage, as information arrive at a neuron, it is necessary to store information at physiological time-scales. Therefore, it is necessary to search for a mechanism operating at this level that can utilize this stored information to generate first-person internal sensation as needed. In this regard, the following observations are guideposts that can

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Codons	**Number of bases in mRNA**	**Number of possible triplet codons**	**Number of amino acids**	**Nature of information**
	4	4^3	20	Innately stored & stable. Outputs can be observed by third-person
Example	A, U, C, G	AGA, AGG, CGA, CGU, CGC, CGG	Arginine	

Firing of a neuron (axonal spike)	**Number of inputs to a neuron**	**Number of possible combinations that can fire a neuron**	**Number of neuronal firing (outputs)**	**Nature of information**
	~ 10^3 to 10^4	~ 10^{112} to 10^{241}	1	Few innately written information. Written during learning & retrieved during memory. Outputs are first-person inner sensations
Examples	30	none	0	
	40	~ $1.13\text{x}10^{112}$	1	
	8000	~ $1.47\text{x}10^{108}$	1	

Figure 2: Comparison between degeneracy of codons and degeneracy of inputs in firing a neuron. DNA has stable information that are inherited. In contrast, in the nervous system only very less information is encoded innately. The area of inputs is a writable medium where learning writes information and memory retrieval retrieves them. Both extreme degeneracy and apparent loss of information is clearly evident when neuronal firing is examined. This suggests that in order to preserve information, information storage should be taking place at the level of inputs (dendritic spine) to a neuron. Degeneracy provides beneficial effect of maintaining information in DNA stable to a certain extent when it undergoes mutational changes. Degeneracy of inputs in firing a neuron does not provide similar advantages. Instead, it directs us to examine the origin of inputs for an information storage and retrieval mechanism. Only spatial summation of EPSPs arriving at the axonal hillock without attenuation is used in the comparison table.

permit discovering the mechanism. a) Since maximum information is contained at the origin of the inputs, a mechanism to retain this information is expected to take place at the level of the inputs (dendritic spines). b) If two sensory inputs are to be associated, it should take place at the locations of their convergence. If the mechanism generated at the level of the dendritic spines during learning is maintained, it should allow internal sensation of one of the stimuli when the second stimulus arrives and vice versa. c) Narrow range of frequency of oscillating extracellular potentials at which all the higher brain functions are taking place indicate that oscillating potentials impart a binding property to the systems operations. Since oscillating extracellular potentials reflect ionic changes taking place at the membranes of neurons, the information storage and retrieval mechanism is likely contributing to the oscillating extracellular potentials. d) Observing how one of the associatively learned stimulus can lead to the generation of units of internal sensation is expected to understand the operation of the system.

5.2 Nature of information storage at the input level

It is necessary to deduce the operational mechanism of information storage at the input level using available observations. One key observation is the firing of additional neurons by the cue stimulus following learning (Schoenbaum et al., 1999; Tye et al., 2008). With this knowledge, how can an information storage mechanism get operated? Using constraints offered by all the findings at different levels and by using the idea that if a mechanism X can explain all the findings, then that mechanism should be correct, it was possible to derive a mechanism (Figure 3). Since a biological mechanism for memory is expected to have a component for eliciting hallucination (an apparent perception of something not present) (Minsky, 1980), a suitable mechanism that allows the stored information to get retrieved as first-person internal sensation was searched. A suitable mechanism was found at the location of information storage at the origin of input region and was described previously (Vadakkan, 2013).

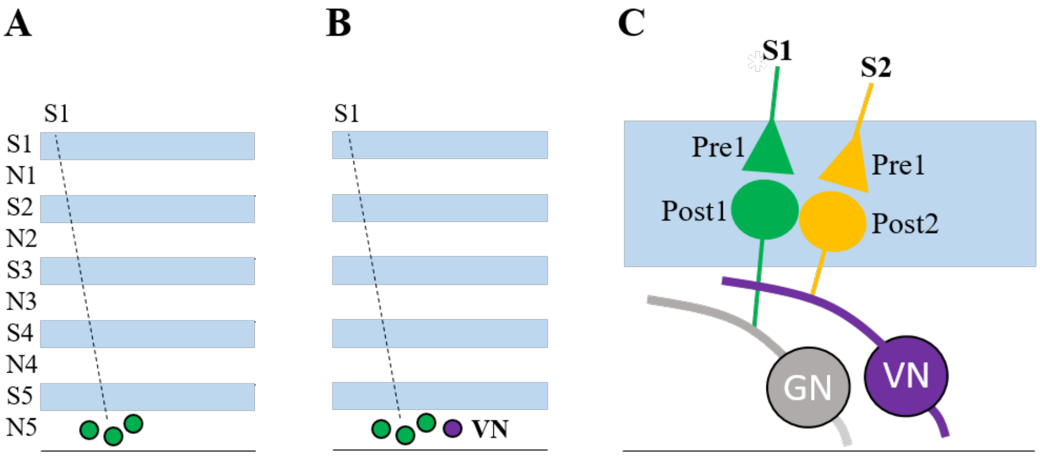

Figure 3. Information storage at the input level capable of retrieval when one of the stimuli (cue stimulus) is presented. Diagram shows five neuronal orders starting from the sensory receptor level (S1: zone dense in sensory receptors; S2-S5: zone dense with synapses; N1-N5: zone dense with neuronal soma). Note that each neuron is expected to fire an action potential on receiving nearly 40 EPSPs of full strength. A) Before learning, arrival of sensory stimulus 1 leads to firing of a set of 3 neurons (in green). B) After associative learning, arrival of stimulus 1 (cue stimulus) alone causes firing of previously fired three neurons (in green) and an additional neuron (VN in violet). This indicates that learning has opened a new channel through which EPSPs from neuronal circuitry activated by stimulus 1 arrive at the additional neuron. This mechanism should be occurring between the synapses of the two converging stimuli at physiological time-scales. Neuron VN most likely would have been remaining at sub-threshold activation state before learning. Change induced by associative learning provides additional EPSPs to neuron VN resulting in its firing. A mechanism for learning should be able to provide an explanation for the arrival of additional potentials to VN. This is expected to take place most likely between the synapses at synaptic region S5 where stimulus 1 and 2 convergence. C) Two neurons (GN and VN) each with only one dendritic spine out of their total number of spines of the order of 10^4 are shown. Neuron VN fired by the cue stimulus (stimulus S1) is expected to have remained at a subthreshold state before learning (alternatively, it could have been remaining inhibited by the action of inhibitory interneurons). Stimulus S1 synapse to the spine of a neuron GN, which is not firing. Stimulus S2 synapse on to the spine of neuron VN and is providing the $(n\text{-}1)^{th}$ EPSP to it. Stimulus S2 wont fire neuron VN because even with stimulus S2, VN is short of one EPSP to fire. Spines at which stimuli S1 and S2 arrive are abutted to each other such that during learning they undergo structural change to generate an electrical connection between them. Information is stored in the form of this inter-spine connection. After learning, stimulus 1 can provide both $(n\text{-}1)^{th}$ (through the inter-spine connection) and n^{th} EPSPs to neuron VN and cause it to fire. As long as inter-spine electrical interaction persists after learning, arrival of stimulus S1 can fire neuron VN. In addition, arrival of stimulus S1 that depolarizes dendritic spine post2 from its lateral side is expected to

spark a hallucination at spine post2 at physiological time-scales that it is receiving sensory stimulus from stimulus S2. Unique circumstances that lead to this was explained previously (Vadakkan, 2013). Size of the spines (post1 and post2) and neuronal somata (GN and VN) are not scaled and are not to be compared.

Associatively learned sensory stimuli reach specific inputs of a neuron that form only a minute fraction of its total inputs of the order of 10^4. In this context for retaining specificity, associative learning should have unitary mechanism of operation at the input level. Since physical properties of large number of items in the environment are shared, sharing of the operational units by these items can provide an efficient operational mechanism. Furthermore, using combinations of unitary mechanisms provide opportunity to represent infinite number of items or events in the environment including those with complex features. For efficient storage of information, it should have the features described in Table 1.

1. Storage occurring at physiological time-scales
2. One of the associatively learned stimuli can activate just one input and cause both firing of a neuron and at the same time store information with specificity
3. Retains specificity of stored information
4. Retrieves information as first-person inner sensations of sensory features
5. Occurs at a short range of frequency of oscillating extracellular potentials
6. Retrieves information by integration of units of internal sensations at physiological time-scales
7. Operates to store and retrieve information at physiological time-scales
8. Information storage and retrieval operates during both sub- and supra-threshold activations of a neuron
9. Information storage and retrieval should have a provision for a mechanism to interlink with corresponding behavioral motor actions

Table 1. Expected features of an information storage mechanism that provides constraints to arrive at a mechanism.

6 Conclusion

The systems property of oscillating extracellular potentials at a specific range of frequency is expected to compute all the units of internal sensations to generate sensory qualia of retrieved information as a system property. Any derived information storage mechanism that can explain all the previous observations is expected to be correct and compels to verify the operational mechanism using artificial systems in an engineered system. Extreme degeneracy of inputs in firing a neuron and the finding that interaction between inputs of different neurons is the only means to reach a solution that satisfies all the constraints indicate that neuronal firing does not contain specificity anticipated of a mechanism for information storage.

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Conflict of interest: U.S. patent: number 9477924 pertains to an electronic circuit model of the inter-postsynaptic functional LINK.

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