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. Evidence can be visible as the tip of an iceberg of operational mechanisms occurring only at a narrow window when sub-threshold activated (before learning) non-firing neurons fire during memory retrieval in response to a cue stimulus. Even this observation from a set of neurons does not identify the location where information is stored due to extreme degeneracy of inputs that can contribute potentials to cross the threshold and fire those neurons. In summary, it is necessary to identify locations of specific inputs where information is expected to make changes.

1 Introduction

Neurons were shown to have independent structural features by Santiago Ramón 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 (axonal spike or action potential) 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

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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 how neuronal firing imparts information to the system for the purpose of storing and retrieving that information.

Neurons in the cortical region on average has $2.4x10^4$ to $8x10^4$ input connections called postsynaptic terminals (dendritic spines or spines) (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. Even though it is theoretically possible to have nearly 40 to 50 EPSPs from synapses on the soma to fire a neuron, most of the time inputs arrive from randomly located synapses. There are two modelling studies that showed the number of inputs necessary to fire an action potential in a pyramidal neuron that receives tens of thousands of inputs. The first study showed that after providing sub-threshold synaptic inputs using 100 randomly distributed AMPA (alpha-amino-3-hydroxy-5-methyl-isoxazole propionic acid) and NMDA (N-methyl-D-aspartate) synapses over the entire dendritic tree, it was able to evoke somatic action potential with an additional 40 NMDA and AMPA synaptic inputs (Palmer et al., 2014). This shows that spatial summation of potentials from nearly 140 randomly distributed synaptic inputs on a pyramidal neuron as they arrive at the axon hillock can fire that neuron. Later, modeling study using L2/L3 pyramidal cells having nearly 20,000 to 30,000 dendritic spines show that nearly 135 synchronously activated excitatory axo-spinous synapses can generate an axonal spike (Eyal et al., 2018). It is to be noted that temporal (sequential arrival) summation of less number of EPSPs at the axonal hillock can also generate the same firing. For the purpose of this work, it is taken that nearly 140 randomly originating EPSPs fire the neuron.

In the above context, it is necessary to understand where information is stored and how neuronal firing is related to that information storage. Information arrives the nervous system from different sensory stimuli through sensory receptors. The stored information is retrieved as first-person inner sensations of memory. The following are some of the findings where internal sensations and neuronal firing are seen together. 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 Hebb's 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. In this view, an individual neuron takes part in different engrams due to their large number of synaptic connections. Since both storage of information during learning and retrieval of information during memory retrieval take place within milliseconds, it is necessary to search for a time-scale matched mechanism. However, until now it was not practically possible to undertake such studies. For example, one study that examined synaptic plasticity thesis (Hayashi-Takagi et al., 2015) used protein expression that does not match with the physiological time-scales at which learning takes place. 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

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studies used surrogate behavioral markers to assess the ability to retrieve stored information that in turn assessed 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 occurring at physiological time-scales during learning that can be used for generating first-person internal sensation of memory at physiological time scales. Only by triangulating as many observations as possible that we will be able to understand the operational mechanism of the system (Munaf and Smith, 2018). To understand the information storage mechanism, these should be time-scale matched observations.

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 5,600 (in a monkey visual cortex) and 60,000 (in a monkey 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 also increases (Stuart et al., 1997; Spruston, 2008; Major et al., 2013). Since spatial summation of nearly 140 EPSPs that are generated from randomly located synapses is required to elicit neuronal firing (axonal spike), further attenuation of EPSPs arriving from remote locations will require much more than 140 EPSPs to cause the same neuronal firing. This naturally leads to the question, "How can information be stored using attenuating EPSPs?" When threshold-operated neuronal firing is examined, an EPSP will find its most important function when it is providing the n^{th} EPSP required to trigger an action potential. But this is a rare event for any one EPSP arriving at the axon hillock. 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 140 spines are necessary to arrive at the axon hillock to get summated to generate one action potential at the axonal hillock of a neuron. Let us also assume that this neuron has 10,000 dendritic spines (inputs or postsynaptic terminals). If EPSPs arriving from exactly 140 of its dendritic spines can fire that neuron, then it shows that nearly $((1x10^4!)/(140!\ x\ (1x10^4!\ -\ 140!))) = 2.79x10^{318}$ sets of combinations of inputs are available from that neuron's dendritic spines to 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 $1.72x10^{244}$. Note that these calculations were done only for fixed number of 140 inputs. For a neuron with 10,000 inputs, when possible number of combinations of inputs that can fire that neuron for inputs ranging from 141 to 10,000 is calculated, then the sum of these combinations 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 (axonal spike or action potential) (*in vivo*, at physiological conditions), it is not at all specific with respect to its inputs. This extreme redundancy of inputs in firing a neuron will cause an abandoning of information residing within each input when neuronal firing is used for interpretations. Extreme

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degeneracy of inputs in firing a neuron compels us to search for a mechanism for information storage and its retrieval occurring at the locations where inputs arrive, before they get attenuated.

Figure 1: Comparison between minimum number of inputs needed to fire a neuron (in red) and all the possible inputs (in red and blue) that can arrive at a pyramidal neuron having 10,000 inputs (dendritic spines). Lengths of the lines represent 10,000 inputs. A: Number of EPSPs (nearly 50) needed (in red, at the left end) to elicit neuronal firing by spatial summation, if EPSPs originate from synapses on the soma. Note that in this situation, there will be nearly 2.9×10^{135} combinatorial possibilities of sets of exactly 50 inputs that can fire that neuron. B: Number of EPSPs (nearly 140) needed (in red, at the left end) to elicit neuronal firing by spatial summation if EPSPs are originating from randomly located synapses. Note that in this situation, there will be nearly 2.79×10^{318} combinatorial possibilities of sets of 140 inputs that can fire that neuron. Empty area at the right end represents those EPSPs that arrive from remote locations and 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 tens of thousands of inputs (dendritic spines). If 3000 inputs are activated simultaneously (supra-threshold activation) during the arrival of a sensory input, only one action potential will be elicited. Simultaneous arrival of 140 EPSPs from random locations at the axonal hillock is enough to induce that action potential. This means that when neuronal firing is examined, (3000 - 140) = 2860 EPSPs have to be viewed as wasted without having any functional use. In this context, it is necessary to examine means to preserve information that the system would have acquired while evolving. It is also necessary to preserve information when less than 140 EPSPs (sub-threshold activation) arrive at a neuron that do not result in eliciting and action potential. These situations strongly indicate the necessary to search for a possible mechanism operating at the individual locations where each input arrives.

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 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 regions. Calcium dendritic spikes contribute to surface potentials that are recorded as electroencephalogram (EEG) (Suzuki et al., 2017). It is not yet known what

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contributes a vector component, for the oscillating surface potentials, 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; Smith et al., 2013), it is reasonable to expect an operational mechanism that can explain both. Distal dendrites that generate spikes have a firing rate nearly five times greater than that occur at the cell body (Moore et al., 2017). Even though calcium spikes generally contributes to a burst of action potentials (Major et al., 2013) and NMDA spikes enhance action potential generation during sensory input (Palmer et al., 2014), when information arriving at the inputs generate these dendritic spikes first instead of axonal spikes (neuronal firing) examination of neuronal firing will lead to loss of information.

2.5 Dilution of information as it passes through few neuronal orders

There is already reduced specificity of information when 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 that can preserve all the information that reaches at the input locations of these neurons.

3 Systems organized to preserve information have evolved

In sections 2.2 and 2.3, we have seen examples of conditions in which a neuron can get fired by either all or a minor fraction (even just 1 input if a neuron is at a baseline subthreshold state short of small amount of potentials to fire). How can an efficient information storage mechanism get evolved within such a system? Since specificity of information is expected to get preserved in systems that evolve to adapt to a predator-prey environment, it is reasonable to expect a mechanism where by all the EPSPs are utilized. 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 EPSPs at the 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 different cue stimuli?" For this to occur, it is reasonable to expect interactive changes taking place at the input level of the neurons. This is 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.

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Codons	**Number of bases in mRNA**	**Number of bases in a codon**	**Number of possible permutations of triplet codons**	**Number of amino acids**	**Nature of information**
	4	3	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 of inputs that can fire a neuron with 10^4 input connections**	**Number of neuronal firing (outputs)**	**Nature of information**
Examples	30		not applicable	0	Few innately written information. Written during learning & retrieved during memory. Outputs are first-person inner sensations
	140		~ 2.79×10^{318}	1	
	500		~ 2.53×10^{860}	1	

Figure 2: Comparison between degeneracy of codons and degeneracy of inputs in firing a neuron. DNA has stable information and is heritable. Since repetition of bases within a codon is allowed and since bases can be arranged in any order, permutations are calculated to find the number of possible codons. Degeneracy of the codons helps to maintain information stable with biological variations and mutations. In contrast, in the nervous system only very less information is encoded innately. Since during spatial summation, repetition is not possible and since it does not take into account order of inputs, combinations are calculated. Since there is only one output, extreme degeneracy of inputs will result in apparent loss of information when neuronal firing is examined. This directs us to examine the location of inputs for an information storage and retrieval mechanism. Note: Only spatial summation of EPSPs arriving at the axonal hillock without attenuation is used in the comparison table. In addition to combinations that are calculated (for spatial summation), permutations can be calculated since temporal summation of lesser number of inputs can fire a neuron. This increases the number of possible ways to cause neuronal firing.

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, especially at the third position, has the important advantage to accommodate mutational changes and biological variations. Extreme degeneracy of inputs in firing a neuron does not provide similar advantages when neuronal firing is examined **(Figure 2)**. Instead, it directs us to examine the locations where inputs arrive for seeking an information storage and retrieval mechanism. Since outputs are equally important, one may ask "Why extreme degeneracy of inputs provides only one output (neuronal firing)?" This may be possibly due to limited number of muscles that can be put into action for behavioral activity.

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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 avoiding the error of ignoring huge amount of specific information contained in the inputs to a neuron and to understand 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 is called 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 EPSPs in FIROME-Ao undergo attenuation as they propagate towards the axonal hillock, sum of the values of EPSPs in FIROME-Ao will be much higher than in FIROME-A. Whereas, since FIROME-D is expected to occur at the origin of their EPSPs, it expected to be nearly equal to that of FIROME-Do.

5.1 Operational mechanism at the origin of FIROME

It is necessary to store information at the location of arrival of inputs at physiological time-scales that can be utilized at a later time to retrieve this information in the form of first-person internal sensation as needed. In this regard, the following observations are guideposts that can 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 to store information, it should take place at the level of dendritic spines at the locations of their convergence. c) If this storage mechanism is maintained, it should generate internal sensation of one of the stimuli when the second stimulus arrives and vice versa. d) 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 neuronal membranes, the information storage and retrieval mechanism is bound to the oscillating extracellular potentials. e) Observing how one of the associatively learned stimulus use the stored information to generate units of internal sensation is expected to reveal the operation of the system.

6 Extreme degeneracy of inputs affects interpretation of information processing

For a neuron that continues to remain at subthreshold state, any information storage mechanism that occurs at its input level cannot be understood since it does not fire. Similarly, if a neuron continues to remain at a supra-threshold state, any information storage mechanism that occurs at its input level cannot be understood by examining neuronal firing. The only window to understand about learning-induced change is when that change adds additional input channels to a neuron that allows it to change from a sub-threshold state to a firing state after learning in the presence of one of the stimuli participated during learning (cue stimulus). An example is the observation of firing of additional neurons by the cue stimulus following learning (Schoenbaum et al., 1999; Tye et al., 2008). What is the most likely input location for information storage? Attenuation of postsynaptic

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potential begins immediately as it propagates down from the spine head region due to resistance at the spine neck (Koch and Poggio, 1983; Wilson, 1984). Therefore, it is necessary to examine information storage mechanism occurring at the level of the spine head. In this section, a derived mechanism of information storage occurring at the spine head region is examined to understand how extreme degeneracy of inputs in firing a neuron can affect interpretations of experimental results. Only neuronal firing generated by spatial summation of EPSPs are examined.

6.1 A potential information storage mechanism at the input level

Initially by using logical arguments, a potential mechanism for a learning-induced mechanism taking place at the input level of the neurons capable of generating first-person internal sensations of memory at physiological time-scales of milliseconds was searched for (Vadakkan, 2007). Matching with the expectations that a biological mechanism for memory should 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 found at the location of convergence of inputs and was described previously (Vadakkan, 2013) (**Figure 3**). Large number of evidence was obtained by examining its suitability to operate by obeying constraints offered by large number of findings from several levels (Vadakkan, 2016).

For storing infinite number of information using a finite number of neuronal processes, it is reasonable to expect that the system functions using combinations of operational units. Such a mechanism is expected to induce specific internal sensations in response to specific features of the cue stimulus. Since physical properties of large number of items in the environment are shared, sharing of the operational units for these items can provide efficiency in its operations. Since the operations at the input level can fire a neuron only when such changes enable the neuron to cross the threshold for firing, neuronal firing may be viewed as a path towards achieving behavioral motor actions. Input level operational mechanism does not affect neuronal firing most of the time. Information storage mechanism at the input level is expected to have the following features. a) Storage and retrieval occur at physiological time-scales. b) Retains specificity of stored information. c) Retrieves information as first-person inner sensations of sensory features by integration of units of internal sensations. d) Storage and retrieval occur during both sub- and supra-threshold activations of a neuron without making changes of its firing status. e) One of the associatively learned stimuli should be able to activate just one input of a neuron and cause information retrieval with specificity and may or may not cause its firing. f) Information retrieval mechanism is interlinked with corresponding behavioral motor actions, which should be under several regulatory controls based on other associative learning changes. g) Storage and retrieval mechanisms occur at a narrow range of frequency of oscillating extracellular potentials.

6.2 Firing of neurons in one neuronal order

Observation of firing of a set of neurons within a particular neuronal order in a specific brain region during a higher brain function implies that this set of neurons or their connections are associated with that function. More specifically, firing of a set of neurons is associated with generation of first-person internal sensation of a higher brain function with or without associated behavioral motor actions. Where does these functions come from? There are two major possibilities. The first possibility is - *One neuron receives inputs from two associatively learned stimuli through separate lower order neurons.* In agreement with this option, it was previously thought that dendritic branch receiving a cluster of inputs can have clustered plasticity (Govindarajan et al., 2006).

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There are three challenges for understanding information storage expected to occur in the nervous system. First, it does not explain a mechanism for the generation of internal sensation of memory of the second stimulus when first stimulus arrives after learning. Second, the time-scales needed for protein synthesis proposed during clustered plasticity change do not match with the time-scales of milliseconds by which mechanism of learning takes place. Thirdly, there is only one output. In a conditioning paradigm, if the neuronal output is common to two associatively learned stimuli then one stimulus will not be able to provide motor output reminiscent of the associatively learned second stimulus.

The second possibility is - *Two neurons each receive separate inputs from two associatively learned stimuli through separate lower order neurons*: Since each neuron receives separate inputs, it may appear that there is no possibility for any new function. Note that here each input has its own separate motor output. Now, since each input has separate motor outputs, we can ask the following question about the occurrence of a key incident when nervous systems were evolving. "Was it possible that there was an accidental coincidence that allowed a key change during learning that provided the ability to induce internal sensation of retrieved memory?"In other words, "What could have happened at one stage of evolution, as multiple sets of neurons connected through their synapses were present in certain order?"First, an accidental coincidence occurred that allowed pathways to cross over so that paths of two sensory stimuli converged at some point. Secondly, an interaction should have occurred at the location of convergence that enabled one of the stimuli participated in learning to induce first-person internal sensation of memory and motor action reminiscent of the arrival of second stimulus. This occurred by virtue of the unique features of the synaptically-connected neurons and special features at the location where convergence occurred. Obviously, this mechanism should be able to explain how it evaded our attention for so long. This condition can be satisfied if the abutted spines that belong to different neurons at which associated stimuli arrive can interact with each other, as shown in **Figure 3**. This inter-spine interaction can generate a new channel at the time of learning called inter-postsynaptic LINKs (IPLs) and can satisfy features of the system as explained by the semblance hypothesis (Vadakkan, 2007, 2013).

The inter-neuronal inter-spine interaction should satisfy firing of additional neurons by the cue stimulus following learning (Schoenbaum et al., 1999; Tye et al., 2008). In one of the studies (Tye et al., 2008), firing of additional neurons were explained as resulting from increased synaptic strength due to increased AMPAR (AMPA receptor) trafficking towards the postsynaptic membrane (Tye et al., 2008). Based on semblance hypothesis, AMPAR vesicle exocytosis provides membrane segments for membrane reorganization at the lateral spine head region that favors inter-spine interaction that can explain both generation of internal sensations and firing of additional neurons (Vadakkan, 2013, 2016).

6.3 Most IPL operations are independent of neuronal firing

In threshold-operated neuronal firing, neuronal firing can only be used to assess a function when that function makes that neuron to just cross the threshold for firing. Let us take a neuron having 10,000 inputs that has threshold for firing when inputs from 140 randomly originating inputs arrive to get spatially summated at the axon hillock. This means that neuronal firing will become visible only when the number of inputs increases from 139 to 140. This means that operational function can occur at the input level even without causing neuronal firing during the following conditions. a) IPL operation does not make any change in the firing of a neuron when it is already receiving threshold number of inputs for firing. Thus, when the above neuron that already receives inputs anywhere between 141 and 10,000, neither formation of new IPLs nor reactivation of IPLs at its

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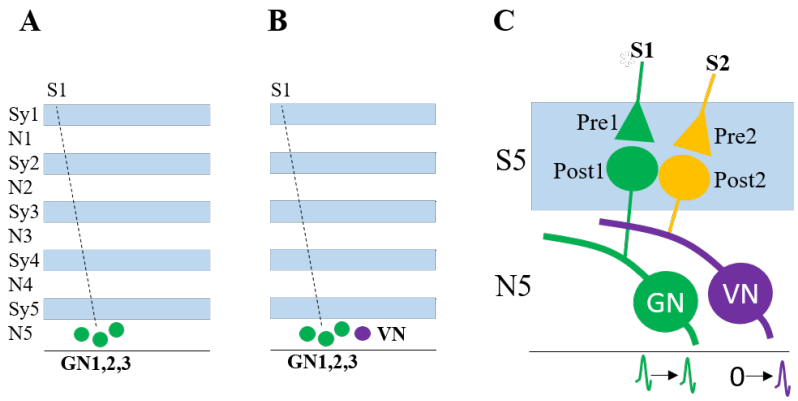

Figure 3.A testable mechanism for information storage at the input level capable of retrieval of information when one of the stimuli (cue stimulus) is presented. Diagram shows five neuronal orders (N1 to N5) starting from the sensory receptor level (Sy1: area dense in sensory receptors; Sy2-Sy5: area dense with synapses; N1-N5: area with neuronal soma). Note that each neuron is expected to fire an action potential on receiving nearly 140 EPSPs from randomly located synapses on its dendritic tree. A) Before learning, arrival of sensory stimulus S1 leads to firing of a set of 3 neurons (GN1, 2, 3) (in green). B) After associative learning, arrival of stimulus S1 (cue stimulus) alone causes firing of neuron (VN) (in violet) that did not fire before learning, in addition to previously fired three neurons (GN1, 2, 3). This indicates that learning has opened a new channel through which EPSPs from neuronal circuitry activated by stimulus S1 arrive at an additional neuron VN. Formation of a new channel should have occurred 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 a route for arrival of additional EPSPs to neuron VN resulting in its firing. This is expected to take place most likely between the synapses at synaptic region S5 where stimuli S1 and S2 converge. C) Inter-spine interaction: Neurons GN and VN are shown only with one of their spines each out of nearly 10^4 spines. When stimulus S1 alone reaches at synapse (pre1-post1) on the spine of neuron GN, neuron GN fires both before and after learning. This shows that neuron GN is receiving supramaximal inputs for firing during both conditions and learning does not change its firing status. After learning when stimulus S1 alone reaches at synapse (pre1-post1) on the spine of neuron GN, it fires neuron VN in addition to firing neuron GN. This shows that neuron VN receives one EPSP (n^{th} EPSP) from stimulus S1 after learning. Searching for the route through which this occurs indicates one possibility. When dendritic spines post1 and post2 at which stimuli S1 and S2 arrive respectively are abutted to each other (before learning), they undergo structural change during learning to generate an electrical connection between them. This is expected to take place at physiological time-scales of milliseconds. Information is stored in the form of this inter-spine connection. After learning, stimulus S1 is able to provide n^{th} EPSP (through the newly formed inter-spine connection) to neuron VN and make it fire. As long as inter-spine electrical interaction persists after learning, arrival of stimulus S1 can continue to 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 that it is receiving sensory stimulus from stimulus S2. Unique circumstances that lead to this was explained previously (Vadakkan, 2013). Below figure C, zero and trace of a spike denote absence or presence of spike respectively before (blunt end of arrow) and after (pointed end of arrow) learning. Size of spines and neuronal somata are not scaled.

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dendritic spines make any change in the firing of that neuron (**Figure 4A**). In addition, presence of inhibitory blanket over the excitatory neurons in the cortical region (Palmer et al., 2012) shows that IPL operations at the dendritic spines can take place even when the number of inputs increase from 139 to 140 (**Figure 4D**). b) Inter-spine interaction forming IPL can take place even when the above neuron receives less than 139 inputs that allows it to remain without firing. Other possibilities are also described (**Figure 4**).

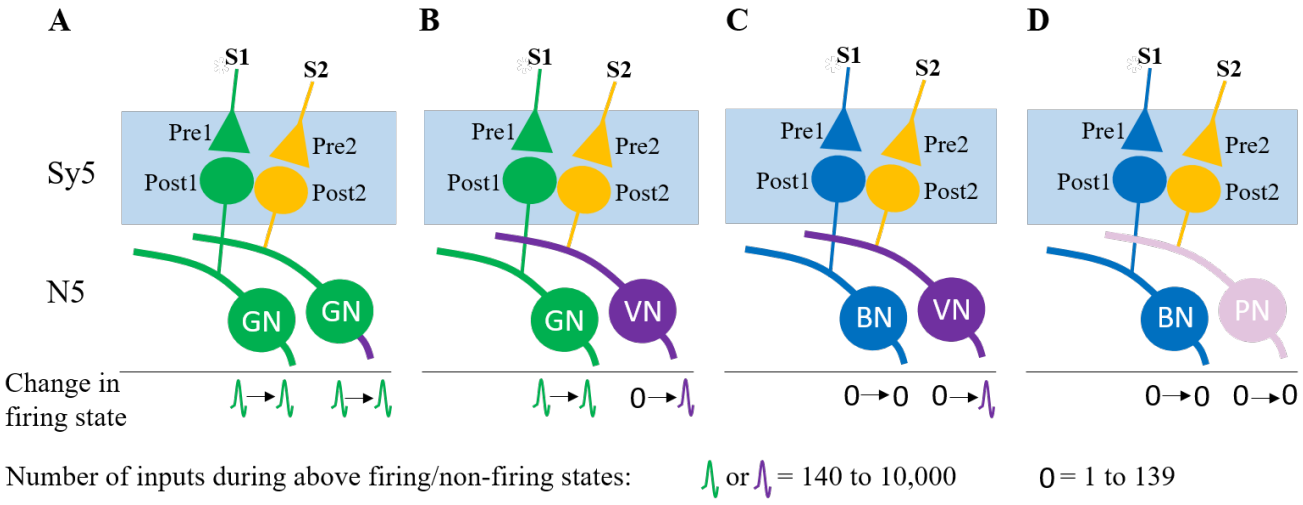

Figure 4. Most of the time, firing or non-firing state of a neuron does not reflect on a potential information processing mechanism at the input level. This figure shows different types of changes in the state of the neurons before and after learning in the presence of one of the stimuli, S1. Learning has made an inter-spine interaction (IPL) between spines post1 and post2. A) At supra-threshold state of a neuron (GN), any information processing occurring at the input level does not change its firing state. Both GN neurons fire both before and after learning in the presence of stimulus S1 (cue stimulus) even though learning has generated a change at the input level between post1 and post2. B) Learning generated IPL between post1 and post2 causes inter-LINKed spine's (post2's) neuron VN to change from sub-threshold to threshold state in the presence of stimulus S1 after learning. C) Here, both neurons BN and VN do not fire before learning. However, after learning, inter-LINKed spine's (post2's) neuron VN changed from sub-threshold state to threshold state and fire in the presence of stimulus S1. D) Both neurons BN and PN do not fire either before or after learning in the presence of stimulus S1, even though learning has generated a change at the input level between post1 and post2. Note that in all the above conditions, after learning, stimulus S1 induces internal sensation at the inter-LINKed spine post2. Below each figure change in firing state from before learning (blunt end of arrow) and after learning and during memory retrieval (pointed end of arrow) is shown.

In summary, neuronal firing can be used to assess a function only when it crosses the threshold for firing. In a neuron that has 10,000 inputs, this means that operations taking place while a neuron receive inputs between 1 and 139 or 141 and 10,000 do not show any change in neuronal firing. Increase in neuronal firing observed in experiments (Schoenbaum et al., 1999; Tye et al., 2008) occurred during two conditions a) when the number of inputs increased from some value at or below 139 to 140 or more, and b) when the inhibitory control over a neuron that is already

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receiving more than 140 inputs is removed by that function. In other words, most IPL-operations are not linked with neuronal firing.

6.4 Firing of neurons in two consecutive neuronal orders

When one neuron in a neuronal order fires, it indicates that it is receiving inputs from firing of a set of neurons at the lower neuronal order. When a set of neurons within a neuronal order fires, it indicates that different sets of neurons in the lower neuronal order fire. From this, can we get enough information to synthesize an operational mechanism? Can manipulation of firing of specific sets of neurons inform about a higher brain function? The main reasons that prevents us from obtaining valuable information are the following. 1) Neuronal firing occurs when the total number of inputs change from 139 to 140, crossing the threshold. This can occur when few additional channels are created at the input level during a higher brain function. These additional channels can form at any combination of inputs. This will be observed in experiments as the tip of an iceberg of large number of such operational units taking place without affecting neuronal firing state (**Figure 5**). 2) It is necessary to discover the mechanism that generates first-person internal sensations occurring at physiological time-scales of milliseconds during higher brain functions.

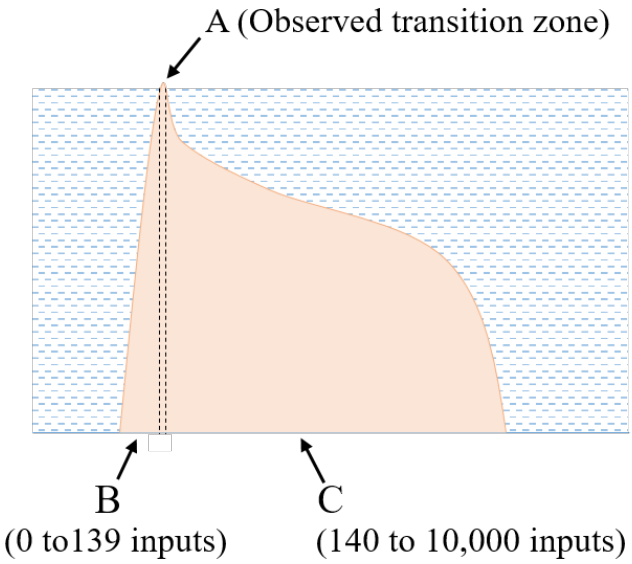

Figure 5. Firing of neurons in the presence of a cue stimulus after learning that were not firing before learning in the presence of the same cue stimulus can be compared to the tip (A) of a huge iceberg of learning-induced changes. What does it mean for a neuron that has 10,000 inputs? Since the same tip of the iceberg will be visible for nearly 2.79×10^{318} combinations of inputs, it means that same number of different learning events can show the same tip of that iceberg of multiple learning-induced changes. This change in firing occurs only when learning makes certain changes that can allow a sub-threshold activated neuron to fire. If learning-induced changes occur at the input level either when that neuron continue to maintain its subthreshold activation state (B) or supra-threshold activation state (C), there wont be any observed changes in either non-firing or firing state of that neuron. Note that only spatial summation of EPSPs that fire a neuron is examined here.

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7 Conclusion

Extreme degeneracy of inputs in firing a neuron makes every single neuronal firing event highly non-specific with respect to the identity of the inputs, and therefore information. Usage of the word "degeneracy" fits with the condition explained in this work since the potentials are in fact degenerating (attenuating) as they propagate towards the soma. This leads to a state where minute fractions of postsynaptic potentials will determine when a neuron is going to cross its threshold state. This will shift all the calculations made in this work towards severe loss of information than anticipated when neuronal firing is examined by giving full value to each EPSP. Most of the information storage and retrieval take place either in the absence of neuronal firing during its sub-threshold activation state or without making any changes in the firing of a neuron during its supra-threshold state. These 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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