The 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 for information storage or retrieval can be observed only as the tip of an iceberg of operational mechanisms occurring at a narrow window when sub-threshold activated (before learning) neurons fire during these events. Even firing of a set of neurons does not identify the location where information is stored due to the extreme degeneracy of inputs that can contribute potentials to cross the threshold and fire those neurons. In summary, it is necessary to identify initial locations where specific inputs to a neuron arrive where information is expected to make retrieval-efficient changes.

1   Introduction

Neurons were shown to have independent structural features by Santiago Ramón y Cajal by modifying the staining methods developed by Camillo Golgi. This led to the neuron doctrine (Shepherd, 1991). Neurons can be grown individually and synapses can be formed 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 examined to study almost all the higher brain functions including perception of different sensations (Zaidi et al., 2013). In recent years, specific sets of 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). Following this, large scale efforts are ongoing to record sets of neurons that fire during different brain functions. In these contexts, it is necessary to examine the relationship between neuronal firing and storage and retrieval of information.

Neurons in the cortical region on average has 2.4×10^4 to 8×10^4 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 generate nearly 40 to 50 excitatory postsynaptic potentials (EPSPs) at the synapses located 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 summation of potentials from nearly 140 randomly distributed synaptic inputs on a pyramidal neuron can fire that neuron when they arrive at the axon hillock. Later, modeling study using L2/L3 pyramidal cells having nearly 20,000 to 30,000 dendritic spines showed 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 can fire an excitatory neuron.

In this 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. Therefore, information needs to be stored to facilitate its retrieval as first-person internal sensations. 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 the firing of neurons (Selimbeyoglu and Parvizi, 2010). Another study has shown that the same cue stimulus results 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 concurrently with neuronal firing, it is necessary to provide a mechanistic explanation. From this, it is reasonable to expect to understand where and how information is stored.

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?" Main 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

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with the physiological time-scales at which learning takes place. Optogenetic techniques 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 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 (Munafò and Smith, 2018). To understand the information storage mechanism, these should be time-scale matched observations. The present work aims to examine how information can be stored in physiological time-scales of milliseconds for effective retrieval.

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) varies 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, the arrival of an EPSP fires a neuron that remains at a sub-threshold activated state when it is providing the nth EPSP required to trigger an action potential. But this is a very rare coincidence for any single 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 locations of origin 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. 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 $((1\text{x}10^4!)/(140! \text{ x } (1\text{x}10^4! - 140!))) = 2.79\text{x}10^{318}$ 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 $1.72\text{x}10^{244}$. Note that these calculations were done only for a 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. The extreme 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). The 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 the 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. An 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 a neuron 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. A 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 an action potential. These situations strongly indicate the necessary to search for a possible mechanism operating at the specific 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 contributes the vector component for the oscillating surface potentials, in a direction perpendicular 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). Calcium spikes generally contribute to a burst of action potentials (Major et al., 2013) and NMDA spikes enhance action potential generation during sensory input (Palmer et al., 2014). In this context, when information arriving at the inputs generates dendritic spikes first, followed by axonal spikes (neuronal firing), examination of neuronal firing alone will lead to loss of information.

2.5 Dilution of information as it passes through neuronal orders

Specificity of information reduced by the time sensory inputs reaches a neuron after propagating through few neuronal orders. In order to compensate for this loss, it is reasonable to expect that the memory retrieval process may have a mechanism to re-constitute the specificity back. Even if we find such a recovery mechanism, examining neuronal firing alone will still eliminate the friable pieces of information that reach after few neuronal orders. Since the 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 by just one input, if a neuron is at a baseline sub-threshold state short of small amounts of potentials to fire). How can an efficient information storage mechanism get evolved? Since the 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 to be examined. 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 to take place between associatively learned stimuli 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 the embryo. External factors can regulate its transcription and usage. In contrast, the nervous system is a storage device with very little information written in it at the time of birth 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 a mechanism to prevent overwriting of information. While most information gets lost within a few seconds following encryption (responsible for working memory), a small fraction of information will get stored for a long period of time. It should be possible to explain a continuum of mechanisms for storage of information for varying durations. To understand how specificity of information is retained, it is necessary to understand the structural changes that occur in 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. The extreme degeneracy of inputs in firing a neuron does not provide similar advantages when neuronal firing is examined **(Figure 2)**. In this context, we are likely missing an efficient mechanism that maintains motoric outputs of the system under conditions of damage of several of its inputs, which are expected during the lifespan of the system. Since the outputs are equally important, one may ask, "Why extreme degeneracy of inputs provides only one output (neuronal firing)?" This may be possibly due to the limited number of muscles that can be put into action for behavioral activity. Combinatorial use of these muscles can provide a large number of outputs, for example speech.

5 Introduction of a new concept of a "FIROME"

Observation of the extreme degeneracy of inputs in firing a neuron highlights the fact that there will be a significant apparent loss of information when neuronal firing is examined. For avoiding the error of ignoring the 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 specific 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 a 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, the 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 sensations 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

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
	30	not applicable	0	Few innately written information. Written during learning & retrieved during memory. Outputs are first-person inner sensations
Examples	140	$\sim 2.79 \times 10^{318}$	1	
	500	$\sim 2.53 \times 10^{860}$	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, the permutations are calculated to find the number of possible codons. The 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 spatial summation does not take into account the order of inputs, the combinations are calculated. Since there is only one output, the extreme degeneracy of inputs will result in the apparent loss of information when neuronal firing is examined. This directs examination to the location of the inputs for identifying 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 natural conditions, most EPSPs are expected to get attenuated by the time they reach the axon hillock. 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 that can generate neuronal firing.

spines). b) If two sensory inputs are to be associated to store information, it should take place at the level of dendritic spines in the locations of their convergence. c) For the duration that 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. Such a mechanism can be expected when the information storage and retrieval mechanism provides vector components to the oscillating potentials. e) Observing how one of the associatively learned stimulus uses the stored information to generate units of internal sensation is expected to reveal the operation of the system.

6   Neuronal firing is a marker of information processing only during a narrow window

What is the most likely input location for information storage? What is its relationship with neuronal firing? Attenuation of postsynaptic potential begins immediately as it propagates down from the spine head region due to the resistance at the spine neck (Koch and Poggio, 1983; Wilson, 1984). Therefore, it is necessary to examine the information storage mechanism occurring at the level of the spine head. For a neuron that continues to remain at either at sub-threshold or supra-threshold states, any information storage mechanism that occurs at its input level cannot be understood as long as it remains without neuronal firing. After learning, the only window to understand about learning-induced change is when that change adds additional input channels to a neuron that remains at a sub-threshold state to provide additional potentials to convert the non-firing state of the neuron to a firing state in the presence of one of the stimuli participated during learning (cue stimulus) **(Figure 3)**. An example is the observation of firing of additional neurons by the cue stimulus following learning (Schoenbaum et al., 1999; Tye et al., 2008). This indicates that the input level operational mechanism does not affect neuronal firing most of the time. 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.

7   Nature of information storage

The information is retrieved during memory retrieval as first-person internal sensations. Therefore, the storage of information is expected to encode information in such a specific manner that will enable one of the stimuli to induce first-person internal sensations of the second stimulus at the time of memory retrieval. For storing the 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 the physical properties of large number of items in the environment are shared, sharing the operational units of these items can provide efficiency in its operations. Since an infinite number of memories are expected to get generated using a finite number of neuronal processes, it is reasonable to assume that memory is formed from unitary mechanisms and their natural computation is occurring at physiological time-scales.
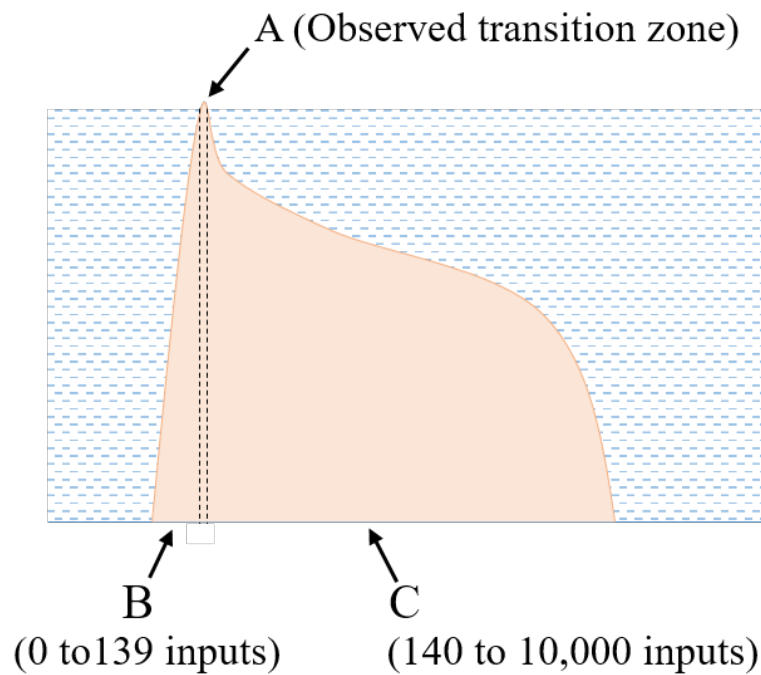
Figure 3: The firing of neurons in the presence of a cue stimulus after learning that were not firing before learning in the presence of the same cue stimulus can be compared to the tip (A) of a huge iceberg of learning-induced changes. What does it mean for a neuron that has 10,000 inputs? Since the 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 sub-threshold activation state (B) or supra-threshold activation state (C), there won't 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.

The fact that both learning and memory retrieval can take place only during a small range of frequency of oscillating extracellular potentials recorded from the extracellular matrix indicates that both information storage and retrieval are expected to contribute to the vector components of these oscillations. The induction of internal sensation occurring on physiological time scales of milliseconds requires explanation for a feasible cellular mechanism. The mechanism should also be able to generate virtual internal sensations responsible for inducing hallucinations as envisioned by Marvin Minsky (Minsky, 1980).

7.1 A potential information storage mechanism at the input level

An information storage mechanism at the input level is expected to have the following features. a) Storage and retrieval occur during both sub- and supra-threshold activations of a neuron without making changes of its firing status. b) Storage and retrieval occur at physiological time-scales. c) Retains specificity of stored information. d) Retrieves information as first-person inner sensations of sensory features by integration of units of internal sensations. e) One of the associatively learned stimuli should be able to activate just one input of a neuron and cause information retrieval with specificity, which 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 several other associative learning changes. g) Since information storage and retrieval mechanisms occur at a narrow range of frequency of oscillating extracellular potentials, these mechanisms are intricately associated with these oscillations.

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). Large number of evidence was obtained by examining its suitability to operate by the obeying constraints offered by a large number of findings from several levels (Vadakkan, 2016).

7.2 Firing of neurons in a neuronal order

The finding that a set of neurons fire neurons during various brain functions prompts one to ask the question, "What determines the neural population structure?" A report has shown that in tests for neuronal sets forming a null distribution by permuting each neuron's firing response by taking into account temporal, neuronal and conditional correlations, it becomes possible to examine true positive effects (Elsayed and Cunningham, 2017). Furthermore, this study also showed that lower order features are sufficient to explain basic large-scale phenomena. What low level feature can attribute to first-person internal sensations as well as population structure of firing neurons?

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 do 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). With this model, 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 the 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 a single 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 the 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 a 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 4**. 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, 2016).

The inter-neuronal inter-spine interaction can 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 was explained as resulting from increased synaptic strength due to increased AMPA receptor trafficking towards the postsynaptic membrane (Tye et al., 2008). Based on the semblance hypothesis, exocytosis of vesicles containing AMPA receptor subunits 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).
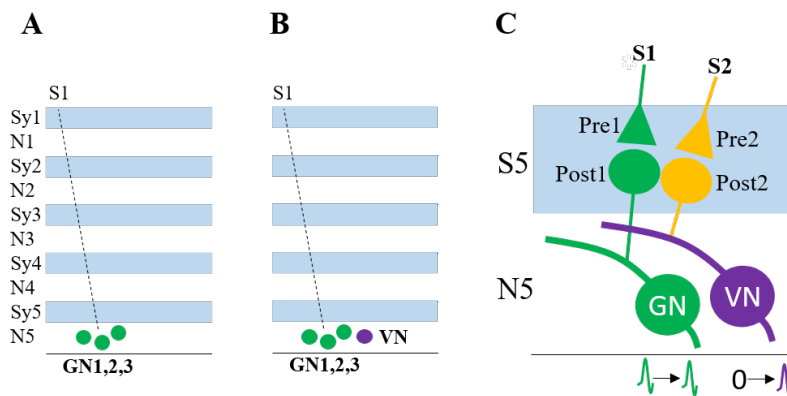
Figure 4. A testable mechanism for information storage at the input level capable of retrieval of information when one of the stimuli (cue stimulus) is presented. The diagram shows five neuronal orders (N1 to N5) starting from the sensory receptor level (Sy1: area dense in sensory receptors; Sy2-Sy5: 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 the 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 in sub-threshold activation state before learning. Change induced by associative learning provides a route for the 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 104 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 (nth 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 post1-post2 inter-spine connection. After learning, stimulus S1 is able to provide nth EPSP (through the newly formed inter-spine connection) to neuron VN and make it fire. As long as the inter-spine electrical interaction of post1-post2 persists after learning, arrival of stimulus S1 can continue to fire neuron VN. 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. This is the induction of semblance. Unique circumstances that lead to semblance generation was explained previously (Vadakkan, 2013). The lifespan of post1-post2 interaction determines the duration for which units of internal sensations can be induced, which can explain working, short-term and long-term memories. Below figure C, zero and trace of a spike are shown to denote absence or presence of spike respectively before (blunt end of the arrow) and after (pointed end of the arrow) learning. Size of spines (post1 and post2) and neuronal somata (GN and VN) are not scaled and are not to be compared.

7.3   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 a 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 state of a neuron when it is already receiving a 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 re-activation of IPLs at its dendritic spines makes any change in the firing of that neuron (**Figure 5A**). In addition, the presence of inhibitory blanket over the excitatory neurons in the cortical region (Palmer et al., 2012) prevent neuronal firing even when the IPL operations at the dendritic spines take place to increase the number of inputs from 139 to 140 (**Figure 5D**). 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 5**).
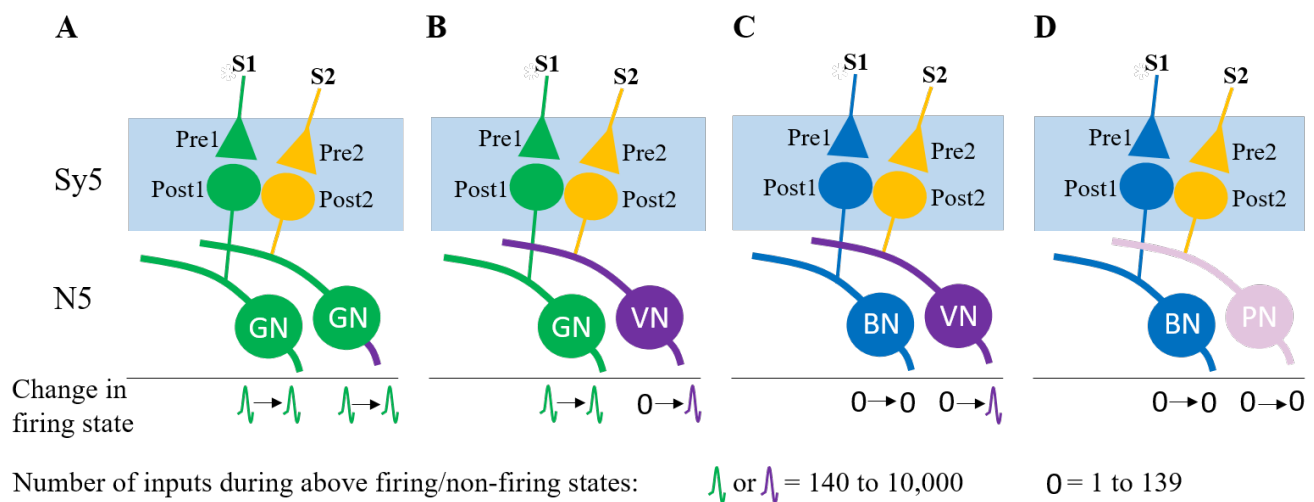

Figure 5. Most of the time, firing or non-firing state of a neuron does not reflect on a potential information processing mechanism at the input level. This figure shows different types of changes in the state of the neurons following learning that generated and a post1-post2 IPL and in the presence 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 neurons (GN), any information processing occurring at the input level does not change their firing states. Both GN neurons fire both before and after learning in the presence of stimulus S1 (cue stimulus) even though a learning event 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 units of internal sensation of memory at the inter-LINKed spine post2.

The electrophysiological finding of long-term potentiation (LTP) that has shown a large number of correlations between LTP and memory can be explained in terms of IPL formation (Vadakkan, 2019). Specifically, LTP is accompanied by an increased probability of neuronal firing and a reduced firing latency (Andersen et al., 1980). This can occur secondary to the formation of IPLs during LTP stimulation, which can be explained as an experimental correlate of the changes occurring during natural learning (Vadakkan, 2019). In summary, neuronal firing can be used to correlate a function only when that function provides potentials that allow the neuron to cross the threshold for firing. In a neuron that has 10,000 inputs, this means that operations taking place while a neuron receives 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 receiving more than 140 inputs is removed by that function. In other words, most IPL-operations are not associated with the firing of the neurons of the LINKed spines.

8   Conclusion

The present work that has examined only spatial summation of EPSPs generating neuronal firing has explained the importance of extreme degeneracy of inputs in firing a neuron. This allows us to view every neuronal firing event as a highly non-specific event 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. A testable mechanism of information storage that can take place at the level of the initial location of inputs (spine heads) and its relationship with neuronal firing is explained.

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

References

Abeles M (1991) Corticonics: Neural Circuits of the Cerebral Cortex. Cambridge University Press.

Alivisatos AP, Chun M, Church GM, Deisseroth K, Donoghue JP, Greenspan RJ, McEuen PL, Roukes ML, Sejnowski TJ, Weiss PS, Yuste R (2013) Neuroscience. The brain activity map. Science **339**(6125):1284-1285. https://doi.org/10.1126/science.1236939

Andersen P, Sundberg S.H., Sveen O Swann, J.W., Wigström H (1980) Possible mechanisms for long-lasting potentiation of synaptic transmission in hippocampal slices from guinea-pigs. J. Physiol. **302**:463-482.

Antic SD, Zhou WL, Moore AR, Short SM, Ikonomu KD (2010) The decade of the dendritic NMDA spike. J Neurosci Res. **88**(14):2991-3001. https://doi.org/10.1002/jnr.22444

Cragg BG (1967) The density of synapses and neurones in the motor and visual areas of the cerebral cortex. J Anat. **101**(Pt 4):639-654.

Douglas RJ, Martin KA (2004) Neuronal circuits of the neocortex. Annu Rev Neurosci. **27**:419-451. https://doi.org/10.1093/cercor/bhq290

Elsayed GF, Cunningham JP (2017) Structure in neural population recordings: an expected byproduct of simpler phenomena? Nat. Neurosci. **20**(9):1310-1318.

Eyal G, Verhoog MB, Testa-Silva G, Deitcher Y, Benavides-Piccione R, DeFelipe J, de Kock CPJ, Mansvelder HD, Segev I (2018) Human cortical pyramidal neurons: From spines to spikes via models. Front Cell Neurosci. **12**:181. https://doi.org/10.3389/fncel.2018.00181

Govindarajan A, Kelleher RJ, Tonegawa S (2006) A clustered plasticity model of long-term memory engrams. Nat Rev Neurosci. **7**(7):575-583. https://doi.org/10.1038/nrn1937

Hayashi-Takagi A, Yagishita S, Nakamura M, Shirai F, Wu YI, Loshbaugh AL, Kuhlman B, Hahn KM, Kasai H (2015) Labelling and optical erasure of synaptic memory traces in the motor cortex. Nature. **525**(7569):333-338. https://doi.org/10.1038/nature15257

Hebb (1949) Organization of behavior (Wiley, New York).

Koch C, Poggio T (1983) A theoretical analysis of electrical properties of spines. Proc R Soc Lond B Biol Sci. **218**:455. https://www.jstor.org/stable/35802

Konur S, Rabinowitz D, Fenstermaker VL, Yuste R (2003) Systematic regulation of spine sizes and densities in pyramidal neurons. J Neurobiol. **56**(2):95-112. https://doi.org/10.1002/neu.10229

Kramer RH, Fortin DL, Trauner D (2009) New photochemical tools for controlling neuronal activity. Curr Opin Neurobiol. **19**(5):544-552. https://doi.org/10.1016/j.conb.2009.09.004

Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, Deisseroth K, Tonegawa S (2012) Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature. **484**(7394):381-385. https://doi.org/10.1038/nature11028

Major G, Larkum ME, Schiller J (2013) Active properties of neocortical pyramidal neuron dendrites. Annu Rev Neurosci. **36**:1-24. https://doi.org/10.1146/annurev-neuro-062111-150343

Martin SJ, Grimwood PD, Morris RG (2000) Synaptic plasticity and memory: an evaluation of the hypothesis. Annu Rev Neurosci. **23**:649-711. https://doi.org/10.1146/annurev.neuro.23.1.649

Minsky M (1980) K-lines: a theory of memory. Cogn Sci. **4**:117-133. https://doi.org/10.1207/s15516709cog0402_1

Moore JJ, Ravassard PM, Ho D, Acharya L, Kees AL, Vuong C, Mehta MR (2017) Dynamics

of cortical dendritic membrane potential and spikes in freely behaving rats. Science. **355**(6331). https://doi.org/10.1126/science.aaj1497

Munafò MR and Smith GD (2018) Repeating experiments is not enough. Nature. **553**(7689):399-401 https://doi.org/10.1038/d41586-018-01023-3

Palmer L, Murayama M, Larkum M (2012) Inhibitory regulation of dendritic activity in vivo. Front Neural Circuits. **6**:26. https://doi.org/10.3389/fncir.2012.00026

Palmer LM, Shai AS, Reeve JE, Anderson HL, Paulsen O, Larkum ME (2014) NMDA spikes enhance action potential generation during sensory input. Nat Neurosci. **17**(3):383-390. https://doi.org/10.1038/nn.3646

Schoenbaum G, Chiba AA, Gallagher M (1999) Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning. J. Neurosci. **19**:1876-1884. https://doi.org/10.1523/jneurosci.19-05-01876

Selimbeyoglu A, Parvizi J (2010) Electrical stimulation of the human brain: perceptual and behavioral phenomena reported in the old and new literature. Front Hum Neurosci. **4**:46. https://doi.org/10.3389/fnhum.2010.00046

Shepherd GM (1991) Foundations of the neuron doctrine. Oxford University Press ISBN 978-0-19-506491-9.

Smith, SL, Smith IT, Branco T, Hausser M (2013) Dendritic spikes enhance stimulus selectivity in cortical neurons in vivo. Nature **503**: 115-120. https://doi.org/10.1038/nature12600

Spruston N (2008) Pyramidal neurons: dendritic structure and synaptic integration. Nat Rev Neurosci. **9**(3):206-221. https://doi.org/10.1038/nrn2286

Stuart G, Schiller J, Sakmann B (1997) Action potential initiation and propagation in rat neocortical pyramidal neurons. J Physiol. **505**(Pt 3):617-632. https://doi.org/10.1111/j.1469-7793.1997.617ba.x

Suzuki M, Larkum ME (2017) Dendritic calcium spikes are clearly detectable at the cortical surface. Nat Commun. **8**(1):276. https://doi.org/10.1038/s41467-017-00282-4

Tye KM, Stuber GD, de Ridder B, Bonci A, Janak PH (2008) Rapid strengthening of thalamo-amygdala synapses mediates cue-reward learning. Nature. **453**:1253-1257. https://doi.org/10.1038/nature06963

Vadakkan KI (2013) A supplementary circuit rule-set for the neuronal wiring. Front Hum Neurosci. **1**;7:170. https://doi.org/10.1038/nature06963

Vadakkan KI (2016) The functional role of all postsynaptic potentials examined from a first-person frame of reference. Rev Neurosci. **27**(2):159-84. https://doi.org/10.1038/nrn2286

Wilson CJ (1984) Passive cable properties of dendritic spines and spiny neurons. J Neurosci. **4**:281. https://doi.org/10.1523/jneurosci.04-01-00281.1984

Xu NL, Harnett MT, Williams SR, Huber D, O'Connor DH, Svoboda K, Magee JC (2012) Nonlinear dendritic integration of sensory and motor input during an active sensing task. Nature. **492**(7428):247-251. https://doi.org/10.1038/nature11601

Zaidi Q, Victor J, McDermott J, Geffen M, Bensmaia S, Cleland TA (2013) Perceptual spaces: mathematical structures to neural mechanisms. J Neurosci. **33**(45):17597-17602. https://doi.org/10.1523/jneurosci.3343-13.2013