Principles for generation of reverberation

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Abstract

In modern neuroscience, memory has been postulated to stored in neural circuits as sequential spike train and Reverberation is one of the specific example. Former research has made much progress on phenomenon description. However, the mechanism of reverberation has been unclear yet.

In this study, combining electrophysiological record and numerical simulation, we confirmed a formerly unrealized neuron property that is necessary for the burst generation in reverberation.

Secondly, we find out the mechanism of sequential pattern generation which clearly explained by network topology and asynchronous neurotransmitter release. In addition, we also developed a pipeline that could design the network fire in manually set order.

Thirdly, we explored the dynamics of STDP learning and chased down the effects of STDP Rule in reverberation. With these understandings, we developed a STDP based learning rule which could drive the network to remember any presupposed sequence.

These results indicated that neuron circuit can remember malformation through STDP rule. Those information are stored in synapse connections. By this way, animals remember information as spike sequence pattern.

1 Introduction

Ever since neuroscience was born, the biological properties and basis of memory has been extensively studied for decades, especially on memory formation. Almost 70 years ago, Hebb’s study suggested that the synapses play a essential role in memory formation[1]. It is now widely accepted that a significant part of the memory is stored in the connections between neurons. In a organized neural network, information are mainly coded as synchronous activities in a repeating fire pattern.[2][3]. Sequential neuron activity pattern have been observed widely in vivo in a variety of behavioral context, including working memory[4], virtual-navigation decision task[5], bird songs[6][7], sleep[8]. But do research in vivo network is unpractical, because it is impossible to monitor such a great number of neurons and synapses at the same time.
To remember information, a learning rule is essential. In the past decades, researchers have made a great progress in understanding synapse plasticity theoretically and biologically in particular, spike-timing-dependent plasticity (STDP) which provide an operable learning rule and has been studied in detail. An interesting mode among these activities that postulate to be a form of memory called reverberation activity has been reported, where cultured neuron network active in two periods - active period and rest period. Most of the neurons in the network active in the active period and rest in the rest period. This repeated active-and-rest process can last for several seconds and are thought to be crucial to explore transmit memory formation. Furthermore, once the network formed, neurons would be activated in a certain spatiotemporal pattern. This repeated active-and-rest process can last for several seconds and are thought to be crucial to explore transmit memory formation. However, due to the limitation of current record technology level, direct analysis on reverberation become an dispiriting task. Although the interrelation between reverberation and memory has been demonstrated, little attention has been paid to why reverberation occurs and how reverberation record information. Hence, theoretical in depth research is necessary.

There have been several theoretical studies on reverberation. It’s has been proved that asynchronous transmitter release, which depend on the dynamic of residual synapti calcium, is necessary for maintaining reverberation activity. Apart from that, network size and the variance of synaptic input across neurons influence the stability of reverberation. The phenomenon of reverberation activity has been described clearly. Whereas, the theory and experiments are not sufficient to answer some basic questions, in particular: (1) what kind of neurons can be used to generate reverberation; (2) how the sequential pattern is generated; (3) is it possible for the network to learn a given sequence.

In this study, we combine electrophysiological recordings and model simulations to confirm the necessary conditions for the emergence and persistence of reverberation activities. Then with the simulations based on a well accepted model, we discovered that the spatiotemporal firing pattern is largely explained by total synaptic weight that every neuron received. With STDP learning rule, we observed the synapse dynamic process during reverberation and developed a model to explain how network form transmit memory.

2 Methodology

2.1 Cell cultures and Electrophysiological record

Hippocampal neurons culture were prepared follow the former study. For each network, there are around 100 neurons. Cultured cell were kept at 37°C and 7%CO₂. After 9-18 days in vitro, a voltage-clamp was applied to a single cell which participate in reverberation. A set of current stimuli were given to draw a I-F curve.
2.2 Numerical simulation

To investigate deeply into the dynamics of reverberation activity, we apply a model similar to Volman et al. [13] described with an optional NMDA current. The neuron membrane equation is modeled by Morris-Lecar (ML) model [16] and Izhikevich model [17]. Neurons are connected with Tsodyks–Markram (TM) synapses. The ML equations are:

\[
\begin{align*}
C \frac{dV_i}{dt} &= -g_L (V_i - V_L) - I_{ion,i} (V_i, t) + I_{app,i}(t) + I_{NMDA} \\
I_{ion,i} (V_i, t) &= \bar{g}_{Ca} m_\infty (V_i) (V_i - V_{Ca}) + \bar{g}_K W_i (V_i, t) (V_i - V_K) \\
\frac{dW_i (V_i, t)}{dt} &= \theta [W_\infty (V_i) - W_i (V_i, t)]/\tau_W (V_i)
\end{align*}
\]

where, the dynamic equation of calcium ion channel and potassium ion channel are:

\[
\begin{align*}
\tau_W (V_i) &= \left( \cosh \frac{V - V_3}{2V_4} \right)^{-1} \\
W_\infty &= \frac{1}{2} \left( 1 + \tanh \frac{V - V_3}{V_4} \right) \\
m_\infty &= \frac{1}{2} \left( 1 + \tanh \frac{V - V_1}{V_2} \right)
\end{align*}
\]

Compared with the equation described by Volman [13], here we add NMDA current to make the equation more suited to the way neuron perform. For the sake of reverberation occurrence condition, Izhikevich model was applied.

\[
\begin{align*}
v' &= 0.04v^2 + 5v + 140 - u + I_{app,i}(t) + I_{NMDA} \\
u' &= a(bv - u)
\end{align*}
\]

if \( v \geq 30\text{mV} \), then \( \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases} \)

NMDA current is given by:

\[
I_{NMDA} = \bar{g}_{NMDA} (1.2 \times \exp(\frac{-\delta t}{\tau_{NMDA,fast}}) - \exp(\frac{-\delta t}{\tau_{NMDA,slow}})) B(V) (V - V_{NMDA})
\]

where, \( B(V) = \frac{1}{1 + \exp(-0.062 V)([Mg]/3.57)} \)

two-component exponential function developed by Shouval et al. [18]. Additionally, the residual cytosolic calcium concentration driven by the spiking events was governed by the differential equation:

\[
\frac{d [Ca^{2+}]_{j,r}}{dt} = -\beta \left( [Ca^{2+}]_{j,r} \right)^n + I_p + \gamma \log \left( \frac{[Ca^{2+}]_{o}}{[Ca^{2+}]_{j,r}} \right) s_j(t)
\]
Calcium concentration will increase when an spike occurs and the extra-cell concentration of calcium is a constant in our model. The residual cytosolic calcium concentration affect the rate of asynchronous release, which represented by an independent Poisson process for every synapse in our model.

$$\eta\left([Ca^{2+}]_{j,r}\right) = \eta_{\text{max}} \frac{\left([Ca^{2+}]_{j,r}\right)^m}{k_a^m + \left([Ca^{2+}]_{j,r}\right)^m}$$

The pre-synaptic transmitters release evoked by pre-synapse spike and asynchronous release should satisfied:

$$\begin{cases}
\frac{dC_{X_{ij}}}{dt}(t) &= \frac{C_{Z_{ij}}(t)}{\tau_s} + \frac{C_{Z_{ij}}(t)}{\tau_r} - \mu \tanh [\alpha C_{X_{ij}}(t)] s_j(t) - \xi \tanh [\alpha C_{X_{ij}}(t)] s_{ij}^{\text{asyn}}(t) \\
\frac{dC_{Y_{ij}}}{dt}(t) &= \frac{C_{Z_{ij}}(t)}{\tau_r} + \frac{C_{Z_{ij}}(t)}{\tau_d} + \mu \tanh [\alpha C_{X_{ij}}(t)] s_j(t) + \xi \tanh [\alpha C_{X_{ij}}(t)] s_{ij}^{\text{asyn}}(t) \\
\frac{dC_{Z_{ij}}}{dt}(t) &= -\frac{C_{Z_{ij}}(t)}{\tau_r} + \frac{C_{Z_{ij}}(t)}{\tau_s} \\
\frac{dC_{S_{ij}}}{dt}(t) &= -\frac{C_{S_{ij}}(t)}{\tau_s} + \frac{C_{Z_{ij}}(t)}{\tau_r} + \frac{C_{Y_{ij}}(t)}{\tau_d}
\end{cases}$$

X,Y,Z,S stand for the recoverd, active, inactive, and super-inactive pre-synaptic vesicle pools respectively, with constraint $X+Y+Z+S = 1$. The Y fraction of neural vesicle pools delivers the released vesicle that determine the amplitude of post-synaptic current $I_{syn}$.

$$I_{syn} = g_{syn,i} (V_i - V_E)$$

$$g_{syn,i} = \sum_j w_{ij} Y_{i,j}$$

$I_{syn}$ current depends on both vesicle state and synapse weight. Here, STDP rule is applied to study how a network ‘remember’ external information.

$$J_{ij} \rightarrow J_{ij} + L(\tau)$$

$$L(\tau) = \begin{cases} 
A_+ e^{-\frac{\tau}{\tau_d}}, & \tau > 0 \\
-A_- e^{-\frac{\tau}{\tau_s}}, & \tau \leq 0 
\end{cases}$$

For other parameter, see supplementary material S1

### 2.3 Network generation

To investigate the impact of network structure, we adopt a method which allow us to build a serious network with increase topological heterogeneity. Firstly, we construct a regular network, where every neuron send certain number of synapse to adjacent neuron in orderly. Then, we rewire some edges with a certain probability. By adjusting the rewire probability, we can get network with different heterogeneity.

Except for topology heterogeneity, synapse weight heterogeneity were also considered. The synaptic weights $w$ were sampled from a Gaussian distribution with a various variance of it’s mean. After sampling we scale it as a specific number to make sure every network has the same synapse weight summation.
2.4 Implementations

All the simulation programs are coded in Python using Numpy and figures are produced by the Matplotlib library module.

3 Result

3.1 Bounded firing rate is a critical condition for generation of reverberation

In all the theoretical work on reverberation, type I ML model seems like the only option.\([13, 14, 15]\) For a more general model, we decided to try Izhikevich model as the neuron membrane equation. The result shows that Izhikevich model can not generate reverberation.\([16]\) To find out the reason, we compared type one ML model and Izhikevich model’s I-F curve.\([51]\) ML model has a upper limit of firing rate which is different from most of models. To confirm this feature, we record I-F curve from a cultured reverberatory neuron network. From Fig2 B, it’s clear that cultured neurons has a firing rate upper limit. So, we add a refectory period in Izhikevich model to limit the fire rating below 20Hz. It’s works well and reverberation occurs.\([17, 18]\)

3.2 Dependency of sequential conservation and reverberation occurrence on Network heterogeneity

Data obtained from previous research shows heterogeneity help nerual network process signal and learn robustly.\([19, 20]\) For reverberation, it seems that reducing heterogeneity in synapse weight can stabilize reverberation in such network.\([14]\) In our study, reverberation occurrence and sequential conservation in different network were measured. Results were combined with network topology and synapse weight distribution to analysis the influence of network heterogeneity on reverberation. In Fig3 A, the occurrence of reverberation shows significant correlated with rewire probability \(P\). The parameter \(P\) actually define the heterogeneity of the degree of every neuron. With higher \(P\), the number of synapse every neuron connected distribute in a larger variance. Sequential conservation is another important indicator for reverberation functionality cause information are coded in the fire pattern. It can be observed that with the increasing of \(P\), the spike order become more clear and stable.\([13, 14]\) We also developed an indicator to measure the chaos of the spike order.

Another crucial network part is the synapse weight distribution. We observed similar phenomenon when we increase the variance of the synapse distribution in a topological fixed network.\([13, 14]\) In summary, the heterogeneity of the network has a positive effect on inducing reverberation and maintaining sequential conservation.
3.3 Mechanism of sequential firing pattern generation

It has been a long time that sequential firing pattern has been discovered, referred as “information trains” or "sequences". Former computational study suggested that spontaneously repeated spike pattern, termed "polychronous groups", is a common property in spiking networks with reentrant connection, axonal conduction delays and STDP. As for reverberation activity, spatiotemporal fire pattern is one of the important features. No matter in cultured network or simulated network, we all discovered this phenomenon. But there is no explanation for it. A intuitionistic thought is that fire pattern should be related to network topology. We observed that once the network has been fixed, the fire pattern would not change no matter which neuron stimuli to evoke reverberation. Hence, we analysis the relationship between network statistical indicators of every neuron and spike order. We found that the total input weight is highly correlated with fire order. To further clarify how total input weight influence spike order, we applied a Logistic Regression on different neuron parameters. By comparing the regression coefficient we confirm the asynchronous release is the approach. (Fig4 E) shows the integral of asynchronous release over 20ms before burst start and spike order. In conclusion, the asynchronous released not only determines the fire order with synapse weight but also maintain the reverberation. As mentioned before, the sum of input weigh determine the spike order of every neuron, which means we could design a network to make neuron in it fire as we want. Neurons in the network should has a sequential input weight as shown in Fig4 F and the adjacent matrix like Fig4 G. As we expected, neurons in the network fire as the sequence we designed. (Fig4 H)

3.4 A STDP based sequential learning scheme

Experiments in cultured network shows that paired-pulse stimulation( SSP ) could persistent reverberation in some nascent circuits, in which brief single-pulse stimuli could not evoke a long-lasting reverberatory activity. After PPS trails, single pulse stimuli could elicit reverberation successfully. It’s proved that synapse plasticity participate in reverberation formation. In simulated system, we generate a random network with a lower synapse weight to model an immature network. As expected, single-pulse stimuli only induce a transient activity. With STDP rule, after PPS training, reverberation can be provoked robustly. To explore reverberation more comprehensively, we also introduce a Temporal-Sequential Learning task. Begin with a full-connected random network, we add a Poisson noise on every neuron and stimuli neuron in a RNN-like way that every time we stimuli former neuron and current neuron. For example, there are 80 neurons. First time we stimuli No. 0 neuron. Second time we stimuli No.0 and No.1 neuron. The rest can be done in the same manner. Fig5 C show the adjacency matrix before and after STDP training. By this way, the network can remember certain sequence. (Fig5 D)
For STDP learning details, synapse project from former spike neuron with larger receive weight to later spike neuron would increase, as a result, the later spike neuron receive more input synaptic current and spike prior. In contrast, former spike neuron would spike later. In consequence, the burst would narrow.

4 Discussion

Prior work has documented the physiological function of reverberation in memory formation and the feature of it. However, these study have either focus on the reason why reverberation would act in such way, or have not taken synapse plasticity into consideration to explore the mechanism of transient memory formation. In this study we combine electrophysiological record and numerical simulation to investigate the dynamic character of reverberation. Further more, including synapse plasticity we explore the learning mechanism.

We found that only with a upper-limited fire rate, reverberation can occur. The reverberation fire pattern decided by the sum of every neuron input weight. In addition, using STDP rule we can train network spike in a certain order. These findings extent the memory formation theory, confirming that how a network record sequence information. This study therefore indicates that spike pattern in reverberation is determined by network topology and synapse weight distribution and sequential information can be stored in structure of the network by training with STDP rule. Most notably, this is the first study to our knowledge to investigate spike order in a neuron network. However, some limitations are worth noting. Although our hypotheses were supported statistically, there is no in vivo or in vitro experiment have trained a certain fire order successfully. Future work may depend on more high throughput neuron signal record method to observe the network activity during behavioral experiment.

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Figure 1: A: Calcium imaging of a complete neuron network.; B: Raster plot of the reverberation. After high-speed calcium imaging, neuron segmentation and deconvolution were applied to get the accurate spike time.
Figure 2: A: Voltage trace of ML model.; B: Voltage trace of Izhikevich model without refractory period.; C: I-F curve of reverberation neuron in cultured network.; D: Voltage trace of Izhikevich model with refractory period.
Figure 3: A: The rewire probability $P$ effect on the occurrence probability of evoked reverberation. Horizontal axis 0–7 represented rewire probability $P$ from low to high. Error bars represent SEM. ; B: From (1) to (3), the randomness of the network topology become higher and higher and the conservation of the reverberation sequence go higher as well.; C: The synapse weight distribution variance effect on the occurrence probability of evoked reverberation.; D:The synapse weight distribution variance effect on the occurrence probability of evoked reverberation. Reverberation occurrence probability showed an upward tendency.
Figure 4: A: the randomness of cultured network activity. We record every neuron fire position in every event and draw a histogram for every neuron to show the neuron’s firing order distribution. Then, we sort the neurons by their firing order’s median. Next, we draw the histogram in heat gram style by the order has been sorted before. If those neuron fire in a certain sequence, there would be a bright diagonal line in the picture.; B: the randomness of simulated network activity.; C: the randomness of two times simulated activity. We reorder the first time result by the second time firing order’s median. There also a bright diagonal line in the heat map. D: Relationship between fire order and input synapse weight for every neuron. The abscissa denotes the fire order statistical interval and Y axis represents the neuron number which rearranged by the input weight of every neuron.; E: Relationship between fire order in every event and received asynchronous release over 10 ms for every neuron. The abscissa denotes the asynchronous release strength and Y axis represents the neuron fire order. Different colors mean in different event. F: Received weight for every neuron. G: The network we generate with a decreasing sequence of receive weight. H: Relationship between fire order and the order we designed.
Figure 5: A: The voltage trace of a nascent circuits. Brief single-pulse stimuli only evoked several scattered spike.; B: The voltage trace of a nascent circuits after STDP trained.; C: Relationship between fire order and stimuli order. The abscissa denotes the stimuli order and Y axis represents the neuron fire order. A bright counter-diagonal indicates that the fire order is in verse of stimuli order.
5 Supplementary Material

Figure S1: (a) A: I-F Curve of Izhikevich model neuron. The abscissa denotes injected synaptic current and Y axis represents spike rate. (b) B: Curve of Morris Lecar (ML) model neuron.
Figure S2: A: The relationship between degree centrality and the median of every neuron’s fire order in an event for a whole reverberation activity. B: The relationship between eigenvector centrality and the median of every neuron’s fire order in an event for a whole reverberation activity. C: The relationship between in degree centrality and the median of every neuron’s fire order in an event for a whole reverberation activity. D: The relationship between out degree centrality and the median of every neuron’s fire order in an event for a whole reverberation activity. E: The relationship between initial output weight value and the median of every neuron’s fire order in an event for a whole reverberation activity. F: The relationship between initial output weight VAR value and the median of every neuron’s fire order in an event for a whole reverberation activity. G: The relationship between initial receive weight value and the median of every neuron’s fire order in an event for a whole reverberation activity. H: The relationship between initial receive weight VAR value and the median of every neuron’s fire order in an event for a whole reverberation activity.
Figure S3: A Schematic diagram of the dynamic STDP and reverberation.
Table S1: Parameters used in simulations

| Parameter | Value          | Description                                      |
|-----------|----------------|--------------------------------------------------|
| $g_{Ca}$  | 4.4 mS/cm²     | Conductance of Ca²⁺ channel                      |
| $g_K$     | 8 mS/cm²       | Conductance of K⁺ channel                        |
| $g_L$     | 2 mS/cm²       | Conductance of leak channel                      |
| $V_{Ca}$  | 120 mV         | Equilibrium potential of Ca²⁺ channel            |
| $V_K$     | -84 mV         | Equilibrium potential of K⁺ channel              |
| $V_L$     | -60 mV         | Equilibrium potential of leak channel            |
| $V_1$     | -1.2 mV        | Turning point of the voltage-dependent function  |
|           |                | of activation variable m                         |
| $V_2$     | 18 mV          | Span of the voltage-dependent function of activation variable m |
| $V_3$     | 2 mV           | Turning point of the voltage-dependent function  |
|           |                | of activation variable W                         |
| $V_4$     | 30 mV          | Span of the voltage-dependent function of activation variable W |
| $V_E$     | 0 mV           | Equilibrium potential of excitatory neuron       |
| $q$       | 0.04           | Reference frequency                              |
| $C$       | 2 mF/cm²       | Membrane capacitance                             |
| $\tau_d$ | 10 ms          | Time constant of post synaptic currents decrease  |
| $\tau_r$ | 61 ms          | Time constant of inactive state vesicle transform|
|           |                | to recovered state                               |
| $\tau_l$ | 1250 ms        | Time constant of inactive state vesicle transform|
|           |                | to super-inactive state                          |
| $\tau_{us}$ | 10 s          | Time constant of super inactive state vesicle    |
|           |                | transform to recovered state                      |
| $m$       | 0.25           | The quantity of neurotransmitter release per     |
|           |                | spike                                            |
| $x$       | 0.00625        | The quantity of neurotransmitter release per     |
|           |                | asynchronous release                             |
| $a$       | 2.5            | The ratio of neurotransmitter every spike release|
|           |                | to neurotransmitter in recovered state           |
| $h_{max}$ | 0.95 kHz       | Max asynchronous release frequency                |
| $k_a$     | 0.10 mM        | When $[Ca^{2+}] = k_a$, asynchronous release speed is half of the max speed |
| $m$       | 4              | Measures the sensitivity of asynchronous release  |
|           |                | speed to Ca²⁺ concentration                      |
| $k_r$     | 0.2951 mM      | When $[Ca^{2+}] = k_r$, Ca²⁺ pump active transport speed is half of the max speed |
| $b$       | $1.25 \times 10^4 mM/ms$ | The effective rate of pumping depends upon pre-synaptic Ca²⁺ concentration |

Continued on next page
| Parameter | Value       | Description                               |
|-----------|-------------|-------------------------------------------|
| $n$       | 2           | The degree of the cooperation required to activate the pump |
| $[Ca^{2+}]$ | $2 \times 10^4$ mM | The concentration of residual cytosolic calcium |
| $g$       | 6.5 $\times 10^{-3}$ mM/ms | Increment of residual Ca2+ per spike |
| $I_p$     | 0.002 $\times 10^{-3}$ mM/ms | Passive diffusion Ca2+ current |
| $I_{app}$ | 3.5 mA      | Background current input in neurons       |
| $g_{NMDA}$ | 2 mS/cm2    | Conductance of NMDA channel               |
| $\tau_{NMDA,fast}$ | 46 ms | Fast time constant of NMDA channel |
| $\tau_{NMDA,slow}$ | 46 ms | Slow time constant of NMDA channel |