Exploring The Precision of Real Intelligence at Synapse Resolution

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Abstract

Synapses are the fundamental units of storage of information in neural circuits and their structure and strength are adjusted through synaptic plasticity. Hence, exploring different aspects of synaptic plasticity processes in the hippocampus is crucial to understanding mechanisms of learning and memory, improving artificial intelligence algorithms, and neuromorphic computers. The scope of this manuscript is to explore the precision of synaptic plasticity. Here we measured the precision of multiple synaptic features (Spine head volume, post synaptic density area, spine neck diameter, spine neck length and number of docked vesicles). Results show synaptic plasticity is highly precise and sub cellular resources such as mitochondria may have impact on it.

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1 Introduction

Synapses between neurons control the flow of information in neural circuits and their strengths are regulated by experience. While synaptic plasticity is well-established as an experience-dependent mechanism for modifying spine head volumes and other synaptic features, the precision of the mechanism is unknown. From an information theory point of view, there can be no information

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stored without precision – the more precise synaptic plasticity is, the more distinguishable synaptic strength states are possible and the greater amount of information that can be stored at the synapses in a particular neural circuit. Pairs of synapses from the same axon on the same dendritic branch (Called same-dendrite same-axon pairs (Bartol et al, 2015) or joint synapses on different dendritic branches (Motta et al., 2019; Dorkenwald et al, 2019) have highly correlated sizes due to common history of coactivation and consequently have similar spine head volumes, suggesting that changes in synapse structure are precisely modulated (Bartol et al, 2015; Kasthuri et al., 2015; Bloss et al., 2018). Joint synapses with up to 7 connections with same pre/post neurons were found (Motta et al., 2019; Dorkenwald et al, 2019). Studying these pairs can potentially guide us to the measurement of the precision of synaptic plasticity and the underlying molecular mechanisms.

2 Results

Until recently the measurement techniques did not have the potential to measure the precision of synaptic plasticity because the measurement error from the actual sizes of synapses were much higher than potential synaptic plasticity mechanism error. We analyzed high-resolution 3-dimensional electron microscopy (3DEM) reconstructed spine head volume, post synaptic density, spine neck diameter, spine neck length (Fig. 1) and number of docked vesicles in hippocampal area CA1 in rat (data from Bartol et al, 2015) and measured the precision of synaptic plasticity. Exploring same-dendrite same-axon synapse pairs for measuring precision of synaptic plasticity and information encoding in synapses is foundational to understanding mechanisms of learning and memory and studying aging and neurodegenerative diseases such as Alzheimer's disease as well as improving artificial intelligence algorithms and building neuromorphic computers.

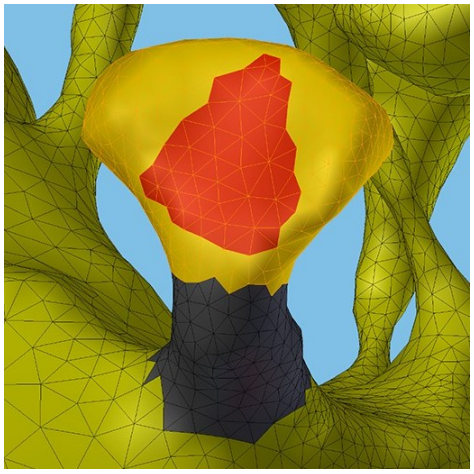

Figure 1: The spine heads fully captured in the reconstructed volume, displaying the PSD (red), spine head membrane (yellow), spine neck (black), dendritic shaft (yellow).

2.1 Precision Analysis

Precision is defined as the degree of reproducibility of a measurement and is often mistaken for accuracy, which is defined as the deviation of the average measurement from a reference value (Supplemental: Fig. 5). It is worth noting that the measurement error (done by 4 investigators) for 98% of the spine head volumes in our dataset is less than 10% (Supplemental: Fig. 6), which allows us to investigate the precision of synaptic plasticity mechanism.

The CV shown in equation (1) is a statistic that measures the variations within a sample, defined by the standard deviation (σ) equation (2), normalized by the mean of the sample (μ), making it a useful metric for measuring precision. Here we used N=2 in equation (2) because we analyzed SDSA pairs.

In summary, we first determined that the measurement error between investigators of the same spine head volumes was smaller than the variability between the measured spine head volumes of the SDSA spine pairs. Then we could measure the precision of 5 post synaptic features (Spine head volume,

post synaptic density area, spine neck diameter, spine neck length and number of docked vesicles) of the SDSA pairs to explore the precision of synaptic plasticity as these features dynamically are modified during learning and memory processes. We calculated the CV of all SDSA pairs for each of the 5 features (Fig. 2). None of the correlations between the CV values and mean of feature's pair values for the SDSA pairs were significant (except for the noted weak correlation, Fig. 2C and D). These outcomes suggest that the synaptic plasticity based on co-activation history among small spines is as precise as it is for large spines in control condition. Our statistical analysis on 3D dimensions of the 5 aforementioned pre/post synaptic features (Fig. 2) confirmed dendritic spine head volumes with median CV value of 0.12 ± 0.046 can be used as the surrogate of synaptic weight as it is also showed by electrophysiology (Dobrunz et al., 1997) that it is highly correlated with synaptic strength. It is worth nothing that the median CV of 10000 random pairs sampled from the 288 spine head volumes is 0.42 supporting our finding of spine head volumes size adjustment being highly precise.

$$CV = \frac{\sigma}{\mu} \tag{1}$$

$$\sigma = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i - \mu)^2} \tag{2}$$

2.2 Role of sub cellular resources on precision of synaptic plasticity

Our results demonstrated that sub cellular resources such as mitochondria may play role on the adaptation of synaptic plasticity precision. Mitochondria play a significant role on synaptic transmission through production of ATP, sequestration of calcium and synthesis of glutamate (Smith et al, 2016). Here we investigated potential role of Mitochondria on the correlation of SDSA pairs. As illustrated in (Fig 3.A) for the SDSA pair that Mitochondria observed only in the presynaptic bouton of one of the spines (upper spine synapsed with an axon that contains 2 Mitochondria at the presynaptic axonal bouton), CV=0.12. It is 1 order of magnitude higher than the CV of the SDSA pair in the (Fig 3.B) that represents the case of no Mitochondria observed at the presynaptic bouton with the value of 0.016. We checked the existence of Mitochondria at presynaptic axonal bouton of all 10 SDSA pairs. We found that 5 out of 10 pairs have Mitochondria at presynaptic bouton of only one of the spines within the pair and showed this scenario with red filled circles in (Fig. 4). The average CV value for the imbalance appearance of mitochondria at presynaptic bouton is 0.4 versus 0.1 for the cases that either both spines had mitochondria at presynaptic bouton or none was observed. Larger datasets from different brain region is needed to confirm our hypothesis on the role mitochondria on the precision of synaptic plasticity. (In this section, CV is calculated with equation 1 for the SDSA pair's spine head volumes only)

3 Conclusion

Our analytic method constitutes a new biomarker for synapses that can be used to assess differences between brain area in different species, between different behavioral conditions and different brain disorders. Results from the analysis also have important implications for the precision of the molecular mechanisms underlying learning and memory at synapses. For the future direction of this research we would like to further explore the impact of the appearance of mitochondria across hippocampal regions (Samavat et al, 2022) and cortex.

Furthermore, quantifying precision of synaptic plasticity is a key factor for discovering the number of distinguishable states of synapses explored in (Bartol et al, 2015; Samavat et al, 2022).

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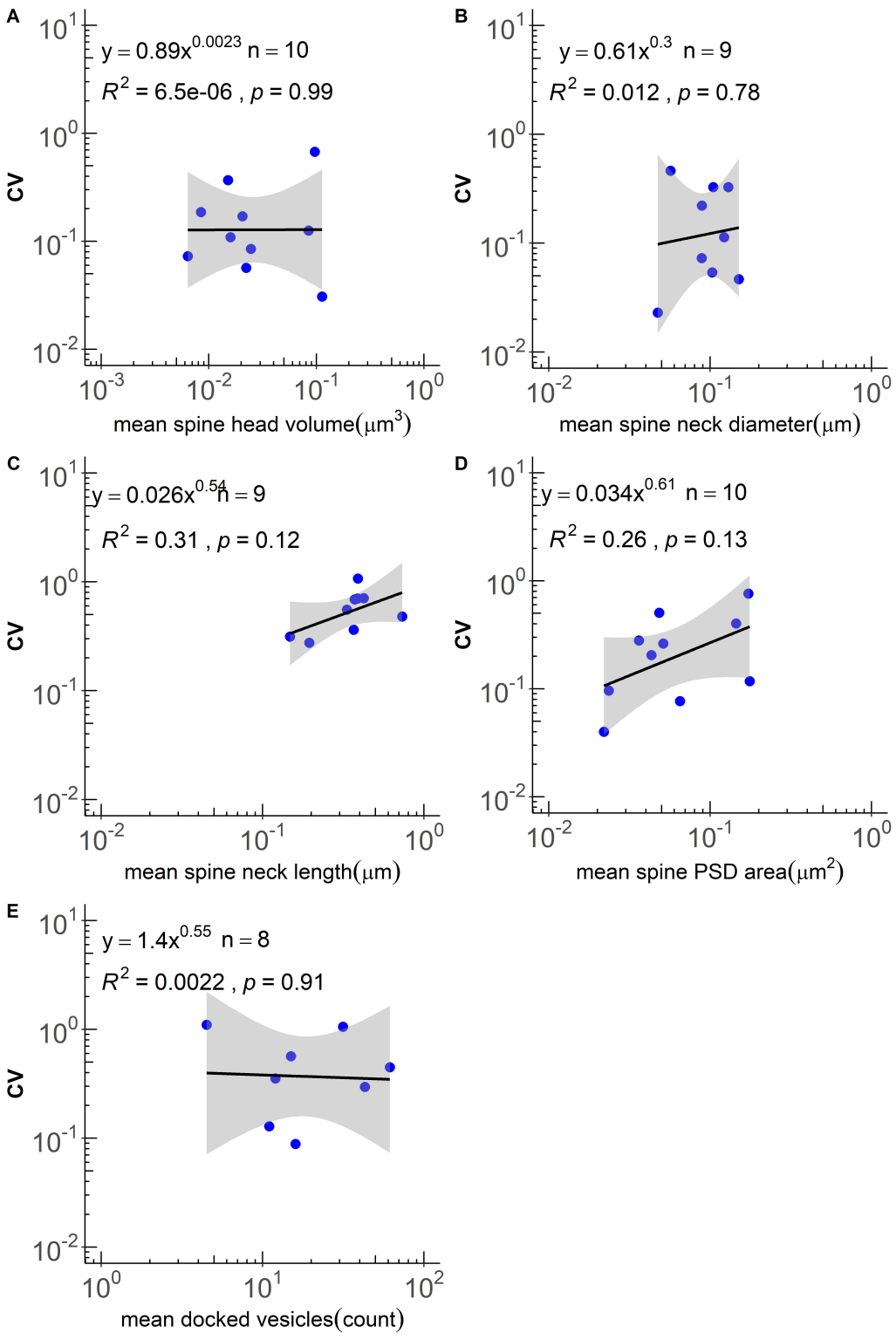

Figure 2: (A-E) Same-dendrite same-axon (SDSA) pairs were analyzed for each post synaptic feature. The regression line, p value and R^2 for the CV of n SDSA pairs are shown for each feature .The gray region is the 95% confidence interval for each regression line. The Y axis is the CV for each SDSA pair depicted by blue. The X axis shows the mean value of the post synaptic feature, on a log scale, for each SDSA pair.

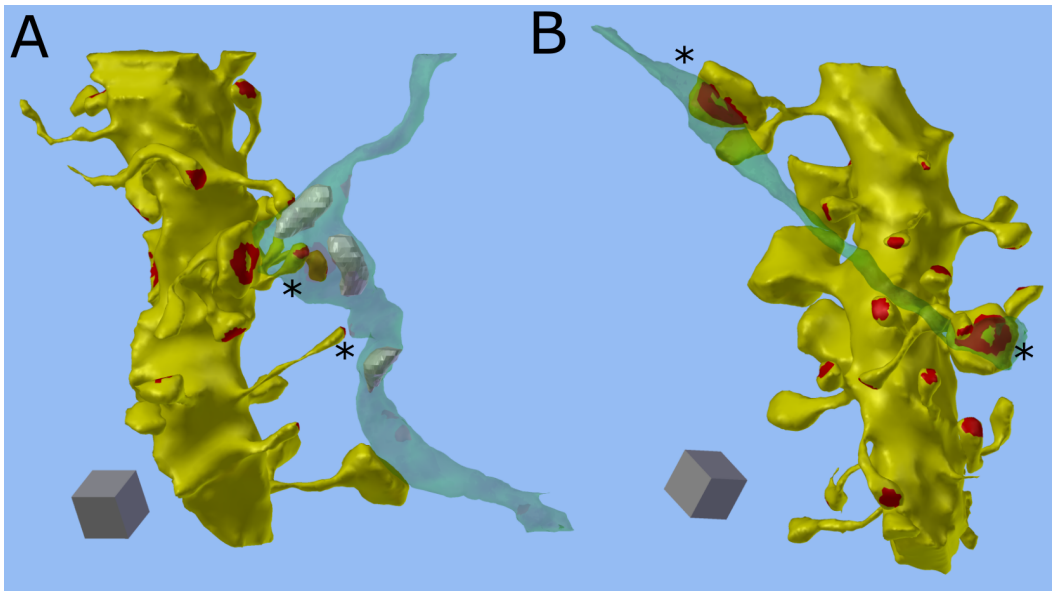

Figure 3: The spine heads fully captured in the reconstructed volume, displaying the PSD (red), spine head membrane (yellow), axon in light green and mitochondria in gray. (A) Represents the SDSA pairs with mitochondria obsreved only in the presynaptic bouton of one of the spines (upper spine surrounded with 2 Mitochondria at the presynaptic axonal bouton) with CV=0.12 and (B) illustrate the case of no mitochondria observed at the presynaptic bouton with CV=0.016 that is one order of magnitude smaller.[Scale cube: 0.125 μm^3, SDSA spines are labeled by a star sign next to them.]

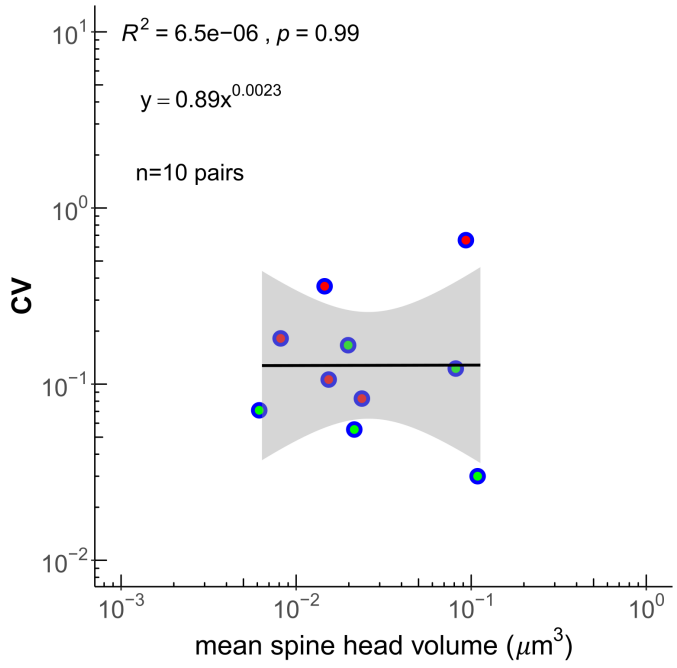

Figure 4: The red filled circles represents the SDSA pairs with mitochondria obsreved only in the presynaptic bouton of one of the spines (We call this scenario an imbalanced appearance of mitochondria) and green filled circles for the cases that either both presynaptic boutons had mitochondria or no mitochondria observed.(We call this scenario balanced appearance of mitochondria)

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Appendix

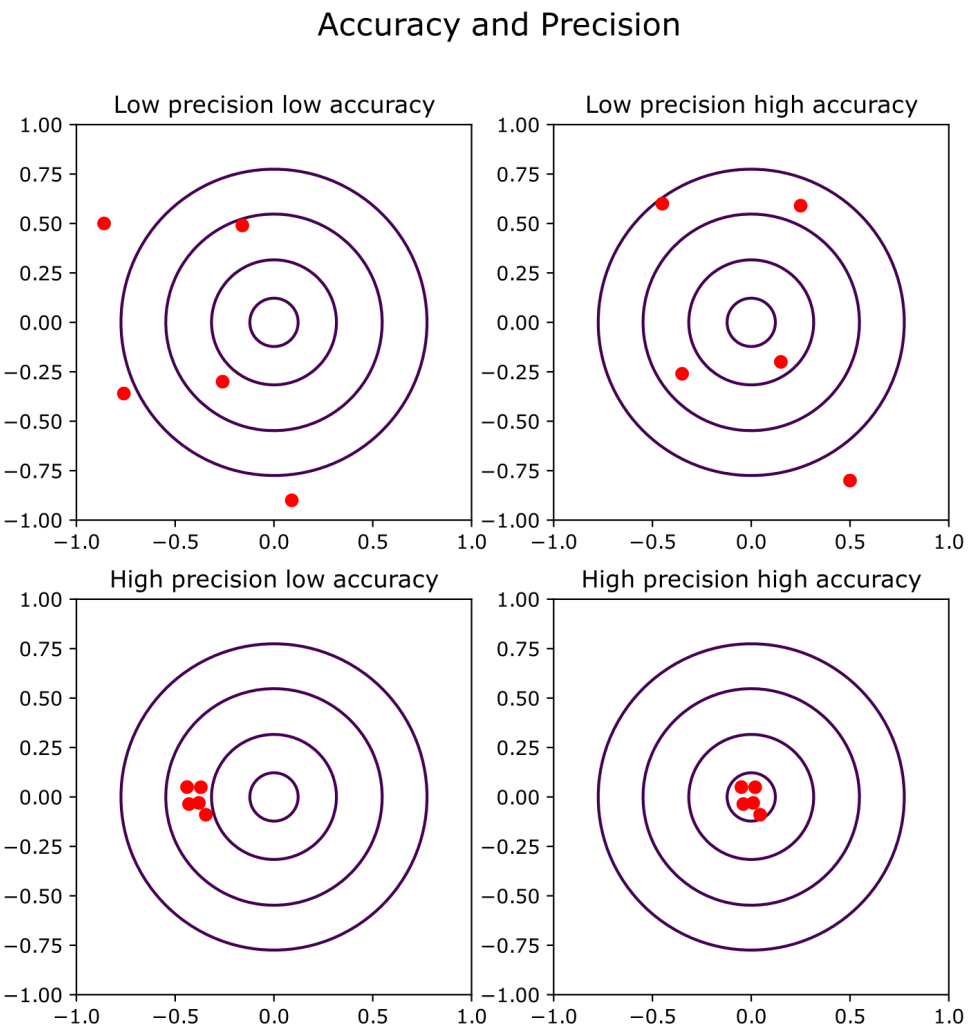

Figure 5: Dart precision versus accuracy. Precision concerns the degree of reproducibility of a process. When a process or system is repeated with the same input the amount of variation in the output shows the precision level of the process. For accuracy there is a reference frame with which the average value of measurements is compared. The graphs illustrate a low precision and low accuracy outcome (top left), low precision and high accuracy (top right; the average of the positions is almost on the bull's eye), high precision and low accuracy (bottom left), and high precision and high accuracy (bottom right).

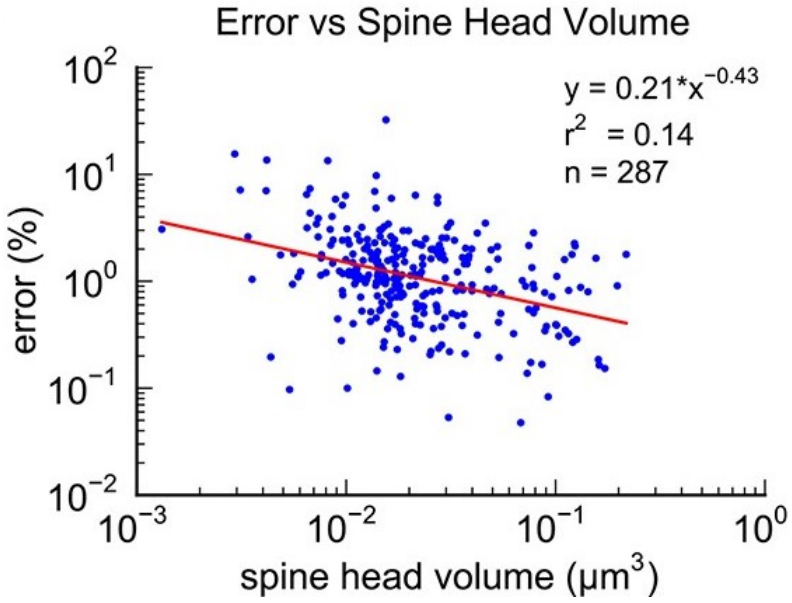

Figure 6: Measurement error plotted against spine head volume.

Algorithm 1 Bootstrap Algorithm for Estimating the Standard Error of Median

Require: $n \geq 1$

Let $X_1, \ldots, X_n$ be some data and $\hat{\theta}_n = t\left(X_1, \ldots, X_n\right)$

For $b = 1, \ldots, B$

Simulate $X_1^{*(b)}, \ldots, X_n^{*(b)} \overset{iid}{\sim} F_n$ by sampling with replacement from $\{X_1, \ldots, X_n\}$

Evaluate $\hat{\theta}_n^{*(b)} = t\left(X_1^{*(b)}, \ldots, X_n^{*(b)}\right)$

$$\hat{\sigma}_{n,B}^2 = \frac{1}{B}\sum_{b=1}^{B}\left(\hat{\theta}_n^{*(b)} - \frac{1}{B}\sum_{b=1}^{B}\hat{\theta}_n^{*(b)}\right)^2$$

Return the bootstrap estimate of standard error of median

$$\hat{\sigma}_{n,B}$$