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# A Computational Framework for Learning and Memory: Network Motif Evolution During LTP-Induced Plasticity

Xin Hu[†], Shahrukh Khanzada[†], Brett Addison Emery[†], and Hayder Amin[*], *Member, IEEE*

***Abstract*— Unraveling the complexity of network-level synaptic plasticity remains a challenge due to the dynamic and interconnected nature of neural circuits. In this study, we employ network motifs—recurrent, functionally specialized patterns of connectivity—as a framework to dissect long-term potentiation (LTP)-induced reorganization in hippocampal CA1-CA3 networks. Using network LTP recordings from high-density microelectrode arrays (HD-MEA), we systematically tracked motif evolution before and after high-frequency stimulation, assessing their roles in network stability, synaptic strength modulation, and criticality-redundancy trade-offs, linking these dynamics to firing synchrony and network potentiation. The Graph-theoretic analysis further demonstrated that LTP-induced reorganization follows a structured motif-guided trajectory, with early-phase motif recruitment optimizing efficiency, followed by phase-dependent refinement. These findings provide new insights into how structured connectivity enables network-level plasticity, balancing efficiency with stability, and offer a potential framework for understanding memory encoding mechanisms and their dysfunction in neurological disorders.**

## I. Introduction

Understanding how neural circuits reorganize during synaptic plasticity is critical for deciphering the mechanisms underlying learning and memory [1]. Long-term potentiation (LTP) serves as a well-established model for synaptic strengthening, driving persistent modifications in neural circuits and reshaping information flow [2]. However, capturing the principles governing network-wide reorganization remains a challenge due to the vast complexity of neural connectivity [3]. The brain's intrinsic structure comprises billions of neurons interconnected by trillions of synapses, exhibiting plasticity across multiple timescales—from milliseconds to days—making it difficult to identify coherent principles that dictate network adaptation [4]. Synaptic plasticity is an emergent behavior; therefore, integrating data from molecular, cellular, and network levels to form a coherent understanding adds to the complexity. While synaptic plasticity has been extensively studied at the molecular and synaptic levels, understanding how these changes translate to network-wide reorganization, structuring, and connectivity remains a significant challenge.

To address this challenge, network motifs offer a powerful framework for simplifying neural circuit complexity while preserving essential computational properties. Motifs represent small, recurring connectivity patterns that serve as functional building blocks of large-scale networks, enabling the identification of structured rules that govern plasticity-induced reorganization [5]. Recent studies have revealed that motifs are not randomly distributed but emerge preferentially during synaptic plasticity, influencing network stability, redundancy, and computational robustness [6], [7]. Different motifs may play distinct roles in neural processing; analysing these roles helps in understanding how neural circuits reorganize during plasticity. Furthermore, motifs can be used to test and extend Hebbian principles [8], by examining how co-activation of neurons within motifs leads to changes in synaptic strength and network connectivity. Despite this, the role of motif dynamics in shaping network-wide synaptic reorganization following LTP remains largely unexplored. While network motifs provide insight into localized patterns of synaptic connectivity, their role in large-scale adaptation can only be fully understood in the context of global network reorganization. Graph theory serves as a complementary framework that enables the quantification of topological changes at a broader scale, revealing how motif evolution aligns with shifts in network efficiency, criticality, and redundancy [3]. However, the utility of motifs and graph analyses in explaining network-wide plasticity hinges on the availability of large-scale high-resolution electrophysiological data to provide insights into connectivity changes.

In this study, we leverage unique large-scale recording capabilities of high-density microelectrode array (HD-MEA) [9] to capture large-scale hippocampal activity before and after LTP induction, systematically tracking motif reconfiguration and network-wide topology shifts [13]. LTP is a model for synaptic strengthening and a key proxy for studying plasticity [2]. Using high-density recordings, we track how network motifs reorganize, revealing their role in shaping connectivity. Motif analysis bridges synaptic changes to network adaptation, providing a structured approach to dissect plasticity dynamics. This framework offers insights into how neural circuits reorganize for learning and memory, aligning with Hebbian principles [11]. By capturing motif evolution, we establish a systematic model for understanding network plasticity and its role in brain computation.

## II. Materials and Methods

### A. *Extracellular Evoked-Synaptic Response Recording*

All experiments and animal procedures were conducted following the applicable European and national regulations (Tierschutzgesetz) and were approved by the local authority (Landesdirektion Sachsen; 25–5131/476/14). Acute, horizontal 300 µm thick hippocampal-cortical slices were obtained from 12-week-old female C57BL/6J mice (Charles

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*Corresponding author (Tel: +49351210463602 - E-mail hayder.amin@dzne.de).

River Laboratories, Germany) and prepared following a previously established protocol [9], [10]. A large-scale high-density microelectrode array (HD-MEA) recording platform was utilized to record network-wide evoked responses. LTP was induced through a high-frequency stimulation (HFS), following a previously established stimulation-recording protocol [10]. Data points were collected during both the stability phase and post-tetanic potentiation (PTP) phases (PTP1–PTP4). The stability phase data were selected from the midpoint of the 20-minute period preceding HFS. Post-tetanic potentiation data were recorded at four distinct time points: the initial phase (PTP1) immediately after HFS, the short-term phase (PTP2) 15 minutes after HFS, the intermediate phase (PTP3) 30 minutes after HFS, and the sustained phase (PTP4) 1 hour after HFS.

### B. *Motif Identification and Detection*

We classified synaptic motifs into three primary types: feedforward, feedback, and bidirectional loops. Motif detection was performed using computational graph analysis and motif-specific algorithms [11], with occurrences normalized against stability-phase data. Comparisons were made between stability and PTP phases to assess motif recruitment, persistence, and modification following LTP induction.

### C. *Distribution of Network Synaptic Activation*

We analysed excitatory postsynaptic potential (EPSP) amplitudes using kernel density estimation (KDE) [12], providing a probabilistic model of synaptic strength changes. A probability density function (PDF) comparison was used to quantify deviations between stability and PTP phases. [13]

### D. *Network Topology Organization*

Graph-theoretic metrics, including node centrality, clustering coefficient, global efficiency, shortest path length, and assortativity, were computed to assess large-scale network modifications. We analysed whether LTP selectively enhances connectivity or leads to random reorganization. The impact of LTP on these metrics was evaluated to understand the contribution of motifs to network computation. A statistical threshold of $p < 0.05$ was applied for significance ANOVA testing. Data were presented as mean ± SEM.

### E. *Criticality of Network Motifs*

To assess the functional importance of network motifs, we applied a minimum dominating set (MDS)-based framework [14] to classify motifs as critical or redundant. The MDS approach identifies a minimal subset of nodes (motifs) that exert control over the entire network, determining which motifs are essential for maintaining network connectivity. A motif was classified as critical if its removal caused a significant disruption in network structure, while motifs with minimal impact were deemed redundant. This analysis was performed across stability and PTP1–PTP4 to track how motif criticality evolves following LTP induction.

## III. Results and Discussion

### A. *Network Motifs Underlying LTP-Induced Plasticity*

To investigate how network motifs reorganize following LTP induction, we analyzed the functional connectivity patterns within the hippocampal CA1-CA3 network before and after high-frequency stimulation (HFS). Using a motif detection algorithm (see method section), we systematically assessed all 13 possible types of connected three-node motifs (triplets). From this comprehensive analysis of our specific dataset (hippocampal CA1-CA3 network activity during LTP), only two patterns, here termed Motif A and Motif B, emerged as consistently present and significantly modulated across the different phases of plasticity (Fig. 1, a and b). These motifs do not reflect anatomical microcircuits (e.g., excitatory or inhibitory neuron types) but rather emerge from functional connectivity changes inferred from large-scale extracellular recordings. Fig. 1c quantifies the normalized counts of these motifs across different phases of synaptic plasticity. Under the stability phase (prior HFS), motif occurrences were low, indicating a relatively sparse motif engagement in baseline network activity. However, following LTP induction, both motifs exhibited a sharp increase at PTP1, reaching their peak engagement immediately post-tetanus. This early surge suggests an LTP-driven expansion of functional connectivity, increasing the prevalence of recurrent circuit motifs. Over time, the motif counts gradually declined across PTP2-PTP4, suggesting a refinement phase in which excess connections are pruned, returning the network toward a more stable configuration. Together, these findings illustrate a dual-phase reorganization, where Motif A enhances pathway-specific potentiation to strengthen functional connectivity, while Motif B contributes to network stabilization through recurrent dynamics. This structured adaptation ensures that LTP-driven plasticity supports both efficient information transfer and long-term circuit stability, preventing excessive excitation while preserving synaptic modifications critical for memory consolidation.

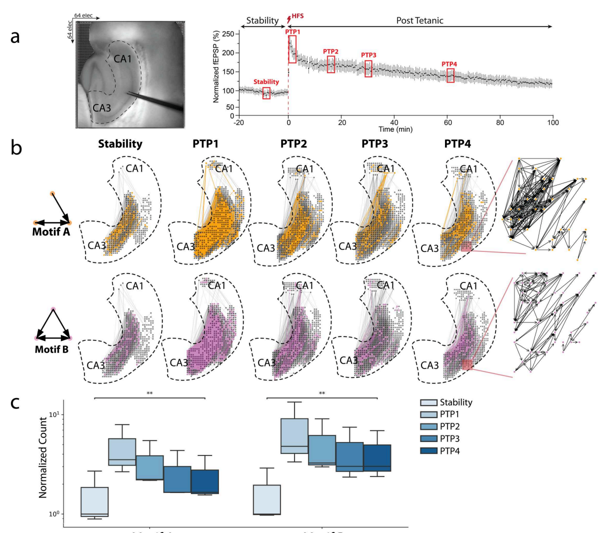


Figure 1. Motif Dynamics Following LTP Induction. (a) Experimental protocol highlighting data point intervals used in analysis. The left panel shows a schematic of the hippocampal slice with CA1 and CA3 regions labeled. The right panel displays the normalized amplitude (µV) of synaptic responses over time, highlighting stability and post-tetanic periods. (b) Network motifs A (orange) and B (purple) during stability and post-tetanic periods, with insets showing detailed connectivity patterns. (c) Box plots showing the normalized count of Motif A and Motif B during stability and post-tetanic periods (PTP1-PTP4). To highlight the relative dynamic changes in motif engagement driven by the plasticity protocol, the motif counts in the post-tetanic phases (PTP1-PTP4) were normalized to the baseline stability phase. (Stability vs. PTP1-PTP4, **p<0.01, *ANOVA*).

*B. Phase-Dependent Evolution of Network-Wide Synaptic Connectivity During LTP*

To quantify how network-wide synaptic activity evolves following LTP induction, we analyzed the distribution of evoked responses using kernel density estimation (KDE), a non-parametric method that provides a continuous representation of synaptic strength without binning constraints, allowing a more precise assessment of network-wide changes. Fig. 2a, and b present the probability density function (PDF) of synaptic activity and EPSP amplitude quantification across stability and PTP1–PTP4. At PTP1, the PDF shifts toward higher synaptic strength values compared to stability, indicating a transient increase in functional connectivity and synaptic potentiation. This heightened activity gradually declines from PTP2 to PTP4, suggesting a refinement process where potentiated connections are selectively maintained or pruned rather than reverting to baseline. A key feature of the PDF at PTP1 is the emergence of a longer-tailed distribution, which is absent in stability and later phases. This tail suggests that LTP induction temporarily drives the network toward a scale-free organization, where a subset of highly active synapses disproportionately contribute to connectivity. This transient reconfiguration likely enhances information transfer efficiency by amplifying key functional hubs within the network, optimizing synaptic communication. As potentiation stabilizes from PTP2 onward, the network shifts back toward a small-world topology, with connectivity becoming more evenly distributed, reducing hub dominance and restoring balanced network dynamics. These results indicate that LTP initially expands functional connectivity, transiently increasing hub-like activity within the network. However, over time, homeostatic mechanisms refine this connectivity, preserving potentiated pathways while preventing excessive excitation, ensuring an optimal balance between synaptic efficiency and network stability.

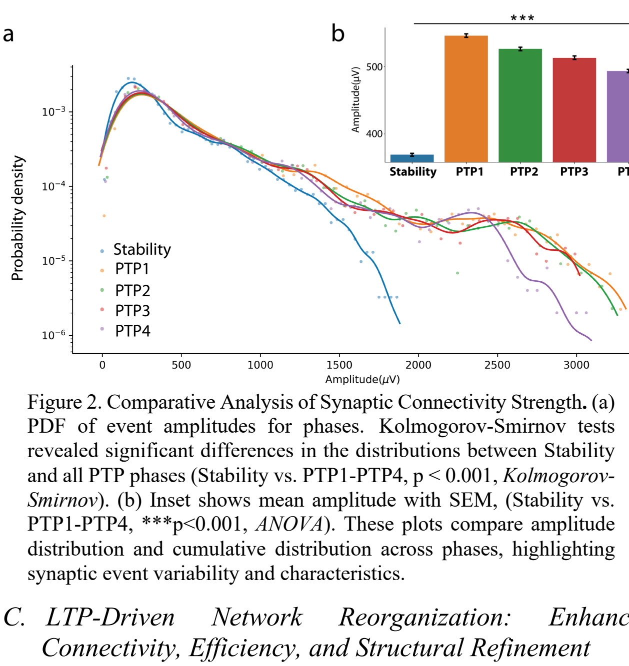


Figure 2. Comparative Analysis of Synaptic Connectivity Strength**.** (a) PDF of event amplitudes for phases. Kolmogorov-Smirnov tests revealed significant differences in the distributions between Stability and all PTP phases (Stability vs. PTP1-PTP4, $p < 0.001$, *Kolmogorov-Smirnov*). (b) Inset shows mean amplitude with SEM, (Stability vs. PTP1-PTP4, ***$p<0.001$, *ANOVA*). These plots compare amplitude distribution and cumulative distribution across phases, highlighting synaptic event variability and characteristics.

*C. LTP-Driven Network Reorganization: Enhanced Connectivity, Efficiency, and Structural Refinement*

To determine how LTP-induced activity reshapes global network organization and motif structure, we analyzed key graph-theoretic properties, focusing on node and edge dynamics, network topology, and motif-related connectivity changes. Fig. 3a shows that node counts increase from stability through PTP1 to PTP4, indicating progressive recruitment of active network elements following LTP induction. In contrast, edge count peaks at PTP1 and subsequently declines across PTP2–PTP4, suggesting that while more nodes become functionally engaged over time, network connectivity undergoes a refinement process, reducing redundant connections while maintaining critical pathways. Fig. 3b quantifies network reorganization through multiple metrics. Node density, global efficiency, centrality, and degree all exhibit their highest values at PTP1, with a gradual decrease from PTP2 to PTP4, yet remaining elevated relative to stability. This indicates that LTP initially enhances network integration, strengthening functional pathways and increasing overall communication efficiency. Average shortest path length is minimized at PTP1, suggesting that LTP reorganizes the network to facilitate faster signal propagation and optimize information transfer. Assortativity, which is lowest in stability, rises significantly from PTP1 to PTP4, indicating a shift toward preferential connectivity among similar-degree nodes, reinforcing structured network adaptation. These findings reveal a phased network reconfiguration following LTP induction. The early phase (PTP1) is marked by a peak in connectivity and efficiency, enabling rapid information transfer and motif engagement. The subsequent phases (PTP2–PTP4) reflect a progressive stabilization, where connectivity is selectively pruned while retaining an optimized structural organization. The sustained increase in node engagement and assortativity suggests a long-term refinement process that enhances functional clustering and network resilience. Together, this reorganization supports an LTP-driven transformation that increases network efficiency while ensuring stability, maintaining an optimal balance between adaptability and structured connectivity.

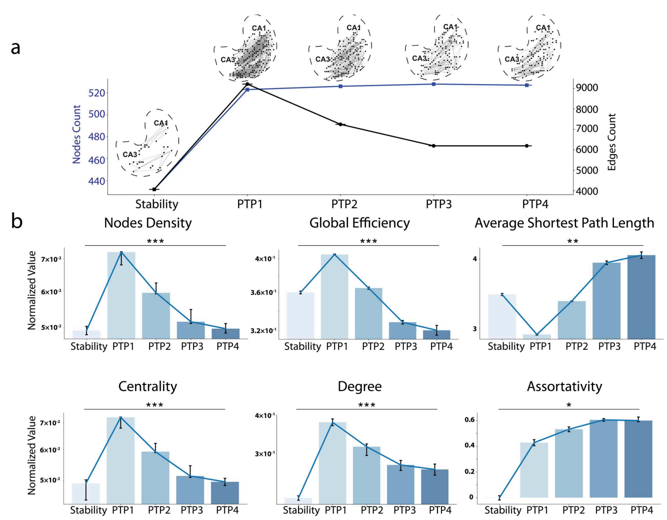


Figure 3. Network Analysis of LTP-induced Activity. (a) Network reorganization over phases shown by node (blue) and edge (black) counts. Insets highlight representative network connectomes (5% of all connections) for each phase in CA1 and CA3 regions. (b) Quantitative analysis of network properties (Node Density, Global Efficiency, Average Shortest Path Length, Centrality, Degree, and Assortativity) across phases, illustrating dynamic changes in network efficiency and regularity (Stability vs. PTP1-PTP4, *$p<0.05$, **$p<0.01$, ***$p<0.001$, *ANOVA*).

## D. *Criticality and Redundancy in Network Motifs*

To evaluate how network motifs contribute to computational efficiency and redundancy reduction during LTP, we applied criticality analysis to determine which motifs play a dominant role in driving network reconfiguration. Using a minimum dominating set (MDS)-based framework, we classified motifs into critical (essential for network control) and redundant (dispensable for connectivity reorganization). Fig. 4a presents spatial maps of motif criticality, illustrating phase-dependent shifts in network organization across stability, PTP1, and PTP2–PTP4. Fig. 4b provides a schematic representation of criticality thresholding, mapping the transitions of motifs across stability and post-tetanic phases. At PTP1, a higher fraction of motifs reached the criticality threshold, indicating a transient period of maximal network influence. As LTP progressed, redundant motifs gradually increased, suggesting a network-wide stabilization process where initially engaged motifs were selectively preserved or pruned based on their functional relevance. Fig. 4c quantifies the normalized count of motifs A and B classified as critical or redundant across different phases. Motif A exhibited its highest criticality at PTP1, declining gradually through PTP4, while redundancy was lowest at PTP1 and progressively increased in later phases, converging with stability levels. A similar pattern was observed for Motif B, confirming a consistent phase-dependent reorganization in which both motif types undergo a transition from critical to redundant states as the network stabilizes. These findings demonstrate that LTP-induced motif engagement follows a structured criticality-refinement process. At PTP1, motifs play a dominant role in network-wide connectivity, optimizing computational efficiency by reducing processing delays and enhancing information flow. However, as the network transitions through later phases, a redundancy-pruning mechanism gradually reduces excess motif engagement, preserving only essential connectivity patterns. This adaptive reorganization ensures efficient network function while preventing excessive rewiring and maintaining a stable yet plastic synaptic architecture.

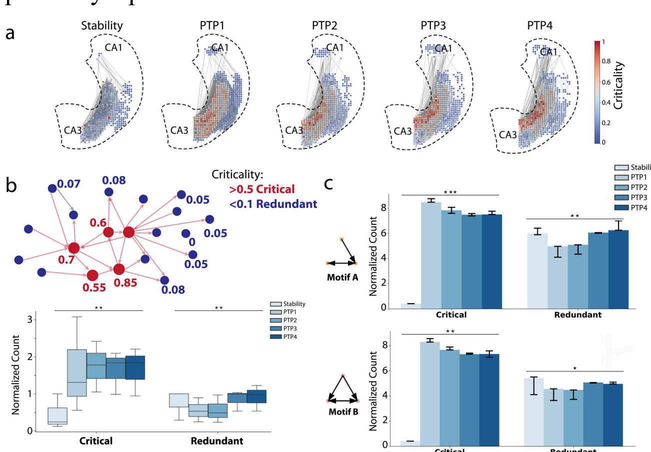


Figure 4. Criticality and Network Motif Analysis Across Phases**.** (a) Criticality maps in Stability, PTP1, PTP2, PTP3, and PTP4 phases, with a blue-to-red gradient indicating criticality values. (b) Network diagram showing nodes with criticality > 0.5 (red) and < 0.1 (blue), with edge numbers representing criticality values. Box plots below show normalized counts of critical and redundant nodes across phases. (c) Bar graphs of normalized counts of Motif A and Motif B in critical and redundant nodes across phases. (Stability vs. PTP1-PTP4, *p<0.05, **p<0.01, ***p<0.001, *ANOVA*).

# IV. Conclusion

This study presents a computational framework for analyzing synaptic plasticity through network motifs, offering a novel approach to studying LTP-induced network reorganization. Using high-density extracellular recordings and graph-theoretic analysis, we demonstrated that LTP initially enhances connectivity and motif engagement (PTP1), followed by a refinement phase (PTP2–PTP4) that stabilizes network architecture while preserving key functional pathways. By applying kernel density estimation, we quantified synaptic activity distributions, revealing scale-free-like connectivity at PTP1, optimizing information transfer. Graph-theoretic analysis confirmed transient efficiency enhancement, with progressive rewiring reinforcing structured connectivity. A minimum dominating set (MDS)-based framework further showed that early-phase motifs are critical for network processing, while later phases prioritize redundancy pruning for stability. This framework captures emergent properties of network-wide plasticity, bridging motif reorganization to optimized neural computation. Unlike traditional LTP models, it provides a scalable method for studying learning and memory through large-scale network adaptation, with implications for neuromorphic computing and neurological disorder research.

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