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# An Integrative Account of Neural Network Interaction: Neuro-Messenger Theory

#### Tien-Wen Lee<sup>1,2</sup>

<sup>1</sup>The Neurocognitive Institute (NCI) Clinical Research Foundation, New Jersey, US

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# **Abstract**

Neural interaction is realized by information exchange. It seemed that the information amount does not keep constant and may be reduced during the travel between neural nodes. In addition, recent research of neural coding has suggested that neural information could be represented by parsimonious spiking pattern, named sparse coding. Based on the above observation, neuro-messenger theory (NMT) is proposed to explicate the communicative process between the source and the target neural nodes. Neuro-messenger is a sparse code which does not have to carry every detail of the dynamics in source node. Other formats of neural coding (e.g., temporal and rate coding) could be the precursors of neuro-messengers, and the repeated spatiotemporal patterns buried in the ongoing brain activities may be the circulated neuro-messengers from diverse origins. Referred to chaos/complexity theory, information can be recovered at target node where neuro-messenger serves as a facilitator to locate the trajectory at proper attractor, and hence the associated psychological entity. In contrast to conventional concepts of encoding and decoding, the processes of encoding in source node, issuing neuro-messengers, and recovering information at target node are summarized as "three-facet coding scheme". The design of neuro-messenger enables the brain to utilize energy in an efficient and economical way. NMT may have substantial implication in several major psychiatric disorders. Some psychiatric conditions could be mediated by abnormal neuro-messengers that coerce the regional neuro-dynamics to delve into maladaptive attractors and hence the characteristic symptoms.

## **Keywords**

Auditory Hallucination, Delusion, Neural Coding, Neuro-Messenger, Obsessive-Compulsive Disorder, Sparse Coding

<sup>&</sup>lt;sup>2</sup>Department of Psychiatry, Dajia Lee's General Hospital, Lee's Medical Corporation, Taichung, Chinese Taipei Email: dwleeibru@gmail.com

## 1. Introduction

Brainwaves flow around constantly in the central nervous system. It is natural to assume that information is loaded and carried in the neural activities. Recent neuroscience progress provides evidence to refine this naive scenario: the "information amount" may not keep constant in neural transmission. At first glance, this proposal seems counter-intuitive; however, it gains support from two perspectives. First, signal processing demands energy but neuroimaging scanning of brain metabolism, such as by positron emission tomography (PET), has revealed a distantly distributed and category-specific nodal pattern (contingent upon experimental tasks), instead of a (quasi-)continuous band of metabolic enhancement [1]. Second, recent research suggests that neural coding could be much more parsimonious than previously thought [2]. The evidence from the above two research fields is elucidated below.

In neuroscience, neural code or neural representation is used to characterize the relationship between (repeated and replicable) neural activities and stimulus. The nature and definition of neural code deserve some clarification. It is obvious that not every neural activity should be categorized as neural code; otherwise, the terms neural activity and neural code would be equivalent and redundant. "Code" has multiple definitions. In broad sense, "code" is anything that is used as an alternative representation of something; for example, neural activities in sensory cortex to represent the physical features of material world. In this case, neural code is a synonym of neural activity. A more specific denotation of code refers to a "vocabulary" system used for communication. Temporal coding and rate coding are generally indistinguishable from the neural response to stimuli, and in rigorous sense, only transmitted parsimonious neuro-pattern is the real neural code if "code" is obliged to serve the purpose of interaction and communication.

Supplementary to conventional models of encoding and decoding of neural information [3] [4], we propose neuro-messenger theory (NMT) to characterize the process of inter-regional neural interaction, where neuro-messenger is the "currency" exchanged between different brain regions. Note that the essence of neuro-messenger is not exactly the same as common currency or bitcoin because there is "qualitative" clue embedded in it, not just a quantity [5]. To avoid ambiguity, we invent a new term neuro-messenger and preserve the lingo of various neural coding strategies in neuroscience literature. Neuro-messenger addresses the interactive and communicative dimension (the strict definition of code), while neural coding (following its convention) indicates the conversion of psychological (e.g., anticipation) and physiological (e.g., retinal activity) attributes to neural activity (the broad definition of code).

# Methods Used to Explore Neuronal/Neural Interactions: Empirical and Computational Approach

The appearance of brain activities and neural interactions seem complicated, no

matter at whatever scales. There are many ways to indicate neuronal/neural activities, such as neuron membrane potential and conductance, open and close of ion channels, ion flow into and out of cells, cascade of biochemical reaction, cortico-electric potential and electricity flow, oxygen consumption, glucose metabolism, blood flow, etc. The methods of electrophysiology and optical imaging (e.g., calcium imaging) are frequently adopted to quantify neuronal activity. Within a volume of brain tissue, the electrical current flowing along dendrosomatic axis of pyramidal neurons constitutes local field potential (LFP, within 0.25 to 0.5 mm in radius around the recording tip). At large scale, the manifestation of population activity also depends on the applied imaging modalities; to name a few: electrical oscillation and event-related potential (ERP) in electroencephalography (EEG), blood-oxygen-level-dependent signal (BOLD) in functional magnetic resonance imaging (fMRI), flow and metabolism indicated by radioactivity in positron emission tomography (PET) and in single-photon emission computed tomography (SPECT), and oximetry in near-infrared spectroscopy and so on. Each research method possesses advantage and limitation and is equipped with innate noise structure to take care of.

In addition to experimental approach, computational simulation may complement our understanding of brain principles. It is particularly pertinent when the theoretical models are constructed based on physiological constraints so that the rationality is endorsed by empirical evidence and in turn, the derived neural model may provide prediction, unveil more detail, help forming hypotheses, and guide future experiments. Commonly employed biophysical neuronal/neural models include Hodgkin-Huxley model, FitzHugh-Nagumo model, Hindmarsh-Rose model, and non-leaky integrate-and-fire model, to name a few [6] [7] [8] [9] [10]. Bridging several neuronal/neural nodes together may define a neural network. It is noteworthy that with proper adjustment of parameters, the network may be situated at the state of multi-stability and criticality, may demonstrate various behaviors (e.g., self-similarity across scales, spike train and oscillation), and may accommodate regularity and chaos [5] [11]. Extension of the artificial neural network model to fMRI simulation by way of Balloon model has been explored and the results were with face validity [12]. The relationship between experimental and theoretical perspectives of neuroscience thus can be regarded as mutually informative, and these two disciplines are equally appreciated in their contribution to our understanding of neuronal/neural interaction.

## 2. Evidence of NMT

## 2.1. Evidence of NMT from Energy Expenditure Perspective

In the central nervous system, encoding and decoding are two fundamental and complementary operations to recognize the world. Take perception as an example, encoding can be regarded as a process that transforms external stimuli to neural representations, whereas decoding re-constructs sensory information from the neural activities to engender percept. The brain has abundant neurons

to register (encode) detailed features of the environment, such as line orientation, color, motion, angle, etc. Along the processing stream, receptive fields increase, and neurons may respond to global feature, such as face, place, or house. It is obvious that not every detail of the sensory stimuli is transmitted along the processing stream since the higher order neurons do not respond to fundamental sensory attributes. Why do we propose NMT in addition to encoding and decoding? Assume a simplified PET study of face perception in which the activation blobs appear in primary visual cortex and fusiform face area (neural correlates executing a particular neuropsychological function tend to aggregate together). Most researchers just focus on the two activated regions but why the brain regions in between (e.g., letter recognition) or other fusiform region (e.g., object recognition) do not show prominent activation? Since the brain cannot foretell whether the upcoming neural events are faces, letters, words, objects, or something else, if without other mechanism, the message amount needs to keep constant along all the possible information routes, and the relay stations would consume similar quantity of energy to catch and pass the information delivered from upstream. We thus regard that neural information transmitted between neural nodes are not just propagating synfire chains but neuro-messengers [13]. The detailed features relevant to faces are registered in primary visual cortex by neural encoding of stimuli, and the output is converted to certain parsimonious neuro-messengers (so the energy expenditure is low); then the transmitted neuro-messengers identified and caught by fusiform face area trigger the trajectory to suitable attractor correspondent with face perception in "virtual brain space" (note: "attractor" will be explained in section 3, and the mathematical space hosting the attractor is named virtual brain space); at this stage, energy consumption re-boosts, and hence activation blob shows up at fusiform face area. The above conjecture was supported by a recent report that the local glucose metabolism and the fractality (an index of attractor) of the neural signal are highly correlated [14]. We name these processes "three-facet coding scheme". Different versions of neuro-messengers may be transmitted to superior temporal sulcus for gaze detection and to emotion center for emotion recognition. Other classes of broadcasted neuro-messengers may reach mirror neuron system to issue motor command or may gather at dorsolateral prefrontal cortex (together with neuro-messengers from different brain regions) to feed material for cognitive computation.

#### 2.2. Evidence of NMT from Neural Coding Perspective

To map a myriad of attributes of the physical world onto neural activities, several coding strategies have been devised. Neural codes are brief spatio-temporal spike trains (transients) as observed in intra-cellular or extra-cellular recordings, in vitro or in vivo. Among the neural coding proposals, temporal and rate coding enjoys the longest history, both with substantial physiological support [15] [16]. Temporal coding addresses the temporal structure/pattern of spike trains,

while rate coding emphasizes the spike number within a time window, thus also named frequency coding. The demand of precision in spike timing is different between the two coding strategies. With fixed number of spikes within a time frame, the number of possible codes for rate coding is limited to one, while that for temporal coding is huge. In other words, slight variation in the timing of spikes may constitute different temporal codes but may not affect rate coding. Nevertheless, rate coding captures an outstanding property—the neural firing rate may increase with the intensity of stimuli.

Despite the popularity of temporal and rate coding, recent evidence has suggested the existence of sparse coding. Electrophysiological recording reveals that the structure of neuronal transients can be quite frugal [17] [18]. In auditory cortex, neurons may even show binary responsiveness regardless of the duration and frequency of tone pips [19]. Here, "binary" means either only one or zero spike to each trial of auditory input, also named binary coding. Binary coding is the most basic form of sparse coding, equipped with low variability and high fidelity. Evidence of sparse coding also comes from vision research, even in the early stage of visual system. There are many linear and non-linear algorithms to decompose natural images into various basis function sets. Olshausen and Field first discovered that incorporation of the constraint of maximizing sparseness may fractionize natural scenes into composite images that satisfied cardinal properties of visual receptive fields (spatially localized, oriented, and band-passed) [2]. Their discovery is appreciated because it bridges physical properties of visual stimuli and physiological properties of striate neurons, and it implies that the brain may encode sensory information using smaller number of neurons-physiological denotation of sparseness. The sparse-coding strategy has gained support from theoretical, computational and experimental perspectives in different sensory modalities, motor system, and higher cognitive function (e.g., associative memory and hippocampus) [20] [21] [22]. Like rate and temporal coding, sparse coding is also a generic coding strategy in the brain.

From the inference of energy consumption, it is reasoned that neuro-communication could be mediated by simplified format. Sparse coding, on the other hand, endorses that thrifty neuro-communication is tenable. The two discourses altogether provide physiological plausibility of NMT. Then, how could the reduced content of information flow recover at proper neural node? What is the consequent benefit of this design? These issues are the central themes of NMT, introduced below.

# 3. Hypotheses of Neuro-Messenger Theory (NMT)

Unlike traditional two-stage processes of decoding and encoding, we propose that there are three facets to complete neuro-communication: stimuli encoding, transmitted parsimonious coding—neuro-messenger, and neural decoding to recover information. Neuro-messenger system may possess the property of HTTP (internet communication protocol) so that it can be differentiated from

spurious noise or irrelevant information. In addition, neuro-messenger is conceptually encrypted so that only target brain region may recognize and decrypt the content (*i.e.*, region specificity). Neuro-messenger is akin to messenger-RNA, which is transcribed in cell nucleus and then at proper place translated to peptide. Analogous to the doctrine in genetics, neuro-messenger is "transcribed" by source neural node, disseminated between relay stations, and is translated at destination neural node. NMT provides an integrative account to bridge different neural coding schemes.

It is a natural concern that neuro-messenger may fail to represent the detail—complicatedness and heterogeneity of internal and external world. Is neuro-messenger really inadequate to reflect the varied and complicated reality? The answer could be no. So profuse and affluent, the ongoing dynamics of each neural node endorsed by local neural computation is equipped with tremendous, if not infinite, possibilities, which has been tuned to be an optimal representation of the external and internal environment through the processes of evolution and development [23] [24] [25]. Even a single neuron can be equivalent to an artificial neural network, a known universal approximator [26]. In other words, the detail has already been "here" (inside the target nodes), rather than from "there" (from other nodes). Chaos/complexity theory has been applied to describe complicated neural dynamics, fostering a well-established discipline in neuroscience [27] [28]. Conventionally, chaos is defined as "aperiodic" and "bounded" dynamics in a "deterministic" system that is "sensitive to its initial condition" and may converge to attractors (p.27 - p.28 in [29]). Take a double scroll attractor as an example of chaos, which is described by a set of three nonlinear ordinary differential equations and a 3-segment piecewise-linear equation. This chaotic attractor is known as the double scroll because of its shape in three-dimensional space, which is like two Saturn-like rings connected by swirling lines, see Figure 1 for illustration. The trajectory may stay in one wing for a while, then jump to the other wing for another while and so on. Together with the chaos theory that has been applied to brain research, neuro-messenger may initiate the neural trajectory to fix on one attractor to reach a psychological certainty (i.e., selecting one out of many or infinite possibilities) [30], not necessarily having to carry every detail processed in the source neural node. We name it

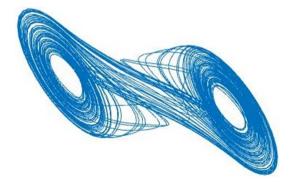


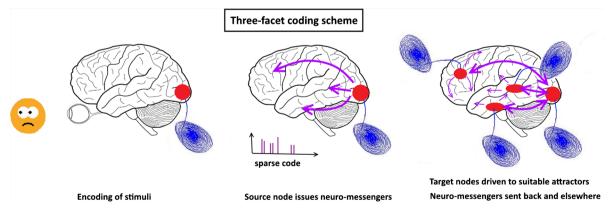
Figure 1. Double scroll attractor as an example of chaos. Two attractors are demonstrated.

"code driving complexity hypothesis". In this regard, neuro-messenger is not only translated (like messenger RNA) but can be viewed as a facilitator to ascertain a structure of high-dimensional neural dynamics in virtual brain space [5].

The properties of neuro-messenger are summarized below:

- 1) A neural node may issue different versions of neuro-messenger to reflect its state and content. If there is a universal version of neuro-messenger, the communication to one region could be intercepted by other regions, interference could occur, and the fidelity of distant communication could be jeopardized.
  - 2) Neuro-messenger has signature of its own generator.
- 3) Neuro-messenger is innately sparse; however, it is not equivalent to the sparse coding that registers sensory input. The distinguishing role of neuro-messenger is for inter-regional interaction (communication at a distance).
  - 4) Other coding schemes could be the precursors of neuro-messengers.
- 5) The repeated spatiotemporal patterns buried in ongoing brain activities may be the circulated neuro-messengers from diverse origins [31].
- 6) Not every arrived neuro-messenger is fully utilized. Capture of a particular neuro-messenger is a region-specific process and may demand the participation of attention function. There may be several different safety valves to turn on and off the processing of neuro-messengers.
- 7) In code-driving-complexity hypothesis, the "code" generally refers to neuro-messenger.

It seemed reasonable to assume that the neural codes distributing in the brain must carry the same amount of information as the given sensation or situation. Accordingly, some research applied non-linear filter to neural spikes to reconstruct waveform as similar to the physical features of external stimuli as possible (how a neuron achieved the non-linear filtering was really hard to contrive) [4]. NMT overturns previous assumption with three-facet coding scheme (summarized in Figure 2) and endows decoding process with novel physiological denotation: decoding corresponds to locating regional neuro-dynamics at proper attractor(s). NMT may explain why information may be processed in parallel without interference, such as working memory.



**Figure 2.** Illustration of three-facet coding scheme. Red: enhanced neural activities in source and target neural nodes. Purple: distribution of neuro-messengers. Blue: trajectory of neuro-dynamics (attractors).

# 4. Evaluation of Neuro-Messenger Hypotheses

Previous sections have introduced the motivation of NMT, and herein we will highlight the germane evidence from empirical and computational neuroscience. The pre-requisite for NMT and "code driving complexity hypothesis" to be valid depends on that neuronal events may trigger drastic change in population neural activities. Even-related synchronization and desynchronization phenomenon in the cortex provides preliminary support [32]. Computational simulation of two interconnected oscillators reveals that external cue may stabilize the trajectory of chaos and create an "attentive" state [33]. The research by Tsodyks *et al.* is particularly pertinent which verifies that neural codes have close relationship with the population dynamics [25], depicted below.

Tsodyks et al. combined optical imaging and single-unit recording to establish the relationship between population activities and single neuron spikes to external stimuli, and then to explore the relationship between evoked and spontaneous neural activities [25]. In detail, optimal drifting grating stimuli were delivered to cat eyes and simultaneously, population voltage changes and single neuron spikes were both recorded. Analysis of optical imaging data revealed "preferred cortical state" (PCS) to the grating, which was an averaged spatial voltage pattern. Based on the similarity to PCS, a predictive algorithm that generated spike trains was constructed to approximate the behavior of the recorded single neuron. The validity of the prediction was assured based on the mathematically defined relationship between population and single neuron activities. Then, the reverse procedure was applied to spontaneous neural activities. It was noticed that the spatial pattern of voltage distribution in resting condition can be very similar to that in evoked condition once in a while. In those moments, spontaneous spike trains engendered by the predictive algorithm (via similarity to PCS) were amazingly similar to what was recorded instantaneously of the selected neuron. Their results implicated a reliable relationship between neuronal spikes (codes) and neural population.

It is noteworthy that the Tsodyks *et al.*'s research cited above only addressed a coincident relationship, *i.e.*, the relationship between neuron spikes and population activities [25]. However, NMT and "code driving complexity" demand a causal influence of neural codes on the behavior of neural population, which can be examined experimentally. For example, we can adopt a dynamic neural network model (e.g., using NEST from <a href="https://www.nest-simulator.org/">https://www.nest-simulator.org/</a>, or pyNN from <a href="https://www.nest-simulator.org/">https://www.nest-simulator.org/</a>, endow it with appropriate features, and test the hypothesis in an ideal situation. If NMT is supported by neural modelling, it is feasible to deliver organized spike trains (surrogate of neuro-messenger) to stimulate neural tissue and then analyze the consequent patterns of population activities. Since the nature of neuro-messenger is still not clear, the method of Tsodyks *et al.* may be adopted to retrieve physiologically meaningful spike trains, which can then be programmed as electronic pulses to stimulate the prepared neural tissue. The population neural activities derived from the retrieved

spike trains can be compared with randomly administered counterparts. Application of chaos analysis may disclose whether attractor structure exists. We predict that the fractal indices in the population activities of the former would be higher than that of the latter.

## **Potential Accountability of NMT**

NMT may have profound implication in psychiatric disorders. Take auditory hallucination (AH) and delusion as cardinal examples. Psychiatric patients with AH generally do not have hearing impairment. Nevertheless, neuroimaging research observed enhanced neural activities in primary auditory cortices during active AH [34], indicating that AH is something being heard, not being thought. Psychiatric patients with delusion are frequently associated with cognitive impairment, such as in schizophrenia and organic mental disorders. However, impaired cognition is not a premise for delusion to occur, and a typical example is delusional disorder. We thus infer that psychotic symptoms actually reflect the aberrance in neuro-messenger system, not necessarily the target neural nodes of symptoms, namely the neural correlates of hearing (auditory cortex in AH) or thought (prefrontal cortex in delusion). Abnormal neuro-messengers may coerce the neural trajectory in auditory cortex to repeatedly converge to the attractors that lead the patients to hear something not existent. Similarly, maladaptive neuro-messengers may facilitate the fronto-striatal network to aggregate to the attractors that constantly make the patients feel being threatened (i.e., persecutory delusion). As to the prefrontal cortex abnormality and the impaired cognition in schizophrenia, evidence has suggested their relevance to negative symptoms (note: positive symptoms used to refer to AH and delusion, while negative symptoms generally indicate functional deterioration and social withdrawal) [35]. Dopamine antagonists targeting at mesolimbic system may alleviate positive symptoms by modulating dysfunctional neuro-messengers, rather than by affecting auditory cortex to treat AH or prefrontal cortex to treat delusion.

NMT may also account for other psychiatric disorders characterized by stereotyped behaviors and/or thoughts. For example, the key features of obsessive-compulsive disorder (OCD) include repeated intrusive thoughts and action routines (called "rituals", such as checking things repeatedly). It is noticed that the cognitive and motor functions of OCD patients are generally within normal range, just like hearing in schizophrenia and cognitive capability in delusional disorder. Even if there is mild deviation (e.g., subtle decline in working memory or soft neurological sings), it is definitely inadequate to explain the devastating psychiatric symptoms. Similar to the application of NMT to psychosis, anomalous neuro-messenger may trigger the neuro-dynamics of normal neural substrates to delve into maladaptive attractors to cause OCD. The explanatory power of NMT to psychopathology is tremendous, which reconciles the observation that the relatively normal brain tissue may behave abnormally. The development and research of NMT may ultimately yield neuroscientific definition of several

major psychiatric disorders, as exemplified above.

The adult human brain occupies around 2 percent of body weight, but it takes up 20 percent of total body oxygen consumption and 25 percent of total body glucose utilization [36]. Although the brain expends disproportionate energy relative to its size, it actually has organized itself to be efficient and economic. Around 15 - 20 watts only is consumed by human brain, which could be 10 million watts using modern chip technology with comparable intricacy [37]. Further, it was estimated that the average firing rate of the cortical neurons is less than 1 Hz and only one fifteenth of cortical neurons are affordable to be simultaneously active [38] [39]. The energy constraint urged Olshausen and Field to infer that "sparse code would seem to be a necessity" [22]. The design of neuro-messenger may contribute substantially to both the efficiency and the frugality in the energy expenditure of the brain.

Although neuro-messenger is sparse, its capacity in representation could be extremely huge. Two main reasons are elucidated here. First, it is noted that shorter coding sequences may union to form longer motifs (cortical songs), whereas the subsets of a particular spatiotemporal pattern may re-organize themselves to form other patterns [31]. The re-combination of spiking sequences may have to do with the coding of binding and context effects, and more importantly, may greatly enrich the manifestation of neural codes (and hence neuro-messengers). Second, chaos theory (sensitive to initial condition) ratifies that mild variation in neuro-messenger may cause radical change in the dynamics of the target neural node, and hence the relevant psychological content, named code driving complexity in this article.

Recent research unveiled that the intrinsic activities in resting brain comprise the neural spikes in evoked condition [5] [23] [25]. If the proposal of neuro-messenger and complexity is valid, the brain must endow itself with the capability to generate percept in the absence of external stimuli—that is what happens in the dream, meditation, or sensory deprivation. The source neural node sends feedforward neuro-messenger to target neural node, and conversely, the target neural node may respond to source neural node with feedback neuro-messenger (*i.e.*, feedback connection). Completion of the bi-directional interaction is essential for conscious perception, and the configuration and the focus of attractor may determine what pops up in our aware experience. The neuro-dynamics of source and target nodes resonance in virtual brain space and hence integrate as a holistic conscious experience. The bi-directional NMs may explain why our experience is integrated seamlessly despite that accumulated temporal lag is expected between neural processing of different attributes (e.g., color and motion) [40].

#### 5. Conclusion

Earlier EEG and neurophysiological research noticed continuous propagation of brain waves, and it was natural to assume that the neuro-electric flows carried the circulated information. Information definitely travels between brain regions, but it appears that its amount does not keep constant during the tour. Between neural nodes, the information seems compressed or down-sampled, while at proper neural nodes, the information de-compressed and recovered. If this is not the case, energy consumption will be unaffordable. Later studies supported sparse coding, which may help to refine the mechanism of neural interaction. Referred to chaos/complexity theory, information can be recovered at target node where sparse code serves as a facilitator to locate the trajectory at proper attractor, and hence the associated psychological entity, dubbed neuro-messenger theory of neural network interaction. Three-facet coding scheme is proposed to explicate the roles of neuro-messenger as an "estafette" to substantiate functional integration and interaction.

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#### **Conflicts of Interest**

The author declares no conflicts of interest regarding the publication of this paper.

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