

Neural Syntax: Cell Assemblies, Synapsembles, and Readers

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Footnotes

Note 1

Berkeley's dictum "Esse est percipi" ("To be is to be perceived") was a challenge to the British Empiricist philosophy. In his book 'A Treatise Concerning the Principles of Human Knowledge', published 300 years ago (1710/2010), Berkeley refutes the claims made by John Locke about the objective representation of the outside world by the mind. Although Berkeley is given much credit for this insight, he was surely not the first person to think about the relationship between subjective experience and objective reality. Here is a quote from a man of science almost a century earlier. "...if ears, tongues, and noses be taken away, the number, shape, and motion of bodies would remain, but not their tastes, sounds, and odors. The latter, external to the living creature, I believe to be nothing but mere names". These sentences were written by perhaps the most prominent champion of Aristotelian logic and the creator of dynamic physics, Galileo Galilei (1623; 1954 – Chapter: Two kinds of properties). The 'paradox' in Berkeley's question has to do with the definition of 'sound', which he defined by *sensation* of air vibration. The air vibrations caused by the falling tree acquire the meaning of sound only through a reader-interpreter mechanism. Perhaps nothing is more foreign to contemporary neuroscience than Berkeley's subjective idealism, yet the idea that in the absence of a 'reader-actuator' information *per se* does not exist well resonates with an engineering approach to brain function. Although the metaphor of the reader/interpreter/actuator admittedly has an element of spookiness, it captures the key feature of control theory of dynamical systems: a goal or desired output. The goal is achieved by manipulating the inputs to the system. Experiencing the surrounding world is an active process that begins with generating an action. To acquire experience, the brain scans the environment by controlling its sensors. By generating outputs, it acquires novel viewpoints as opposed to passive observation. This perspective is in contrast to the empiricist view of neuronal 'representation' of physical reality (James, 1890; Milner, 1996; Damasio and Damasio, 1994). In my view, representation has no real meaning unless the relationship between the outside world and the observing brain is calibrated through action-based experience. Acquisition of experience is possible only through actuator mechanisms (movement or other output), whose function is to modify the inputs by controlling the sensors. Without the ability to produce outputs, there is no biologically relevant meaning of inputs, there is no perception or cognition (Buzsáki, 2006; Llinás, 2001; Merleau-Ponty, 1945/1962; Noë, 2004), or as Sherrington (1924)

summarized more eloquently 'To move things is all mankind can do'. It is the ability of the brain to control its inputs is what makes it a system.

Note 2

The strength of Hebb's cell assembly hypothesis also appears to be its major weakness. The idea that changing constellations of neuronal firing patterns underlie our cognitive capacity is hardly falsifiable (save supernatural forces). Since there is no alternative hypothesis, the theory is hard to prove or disprove. Instead of trying to prove or refute Hebb's theory, my goal is simply to reexamine how the collective behavior of neurons can be objectively studied with current methods and suggest an alternative approach: classification of neuronal patterns by observing the output/impact they cause. While from the assemblies' point of view, such outputs may be conceived as 'goals' or 'desires', such a connotation disappears once the events are viewed as the actuator part of a system: outputs affecting the meaning of inputs. Hebb was not the first to conceive the assembly idea. Very similar, and even more explicit, suggestions were put forward by Nikolai Berstein (1947 in Russian; English translation 1967). But perhaps the real credit should go to Yves Delage (1919): "every modification engraved in the neuron's vibratory mode as a result of its co-action with others leave a trace that is more or less permanent in the vibratory mode resulting from its hereditary structures and from the effects of its previous coactions. Thus, its current vibratory mode reflects the entirely history of its previous participations in divers representations." (Translation by Frégnac et al., 2010). Delage thus already combined the advantages of oscillations and cell groupings. *Sub sole nihil novi est.*

Note 3

To facilitate the discovery process in a rigorous manner, according to the representational paradigm, the presented stimuli first should be 'simple', such as vertical and horizontal gratings or beeps of particular frequencies. As the data are collected and interpreted, neuronal responses to increasingly more 'complex' stimuli are searched for. In the process, we understand more and more and the expectation is that eventually one should be able to explain e.g., how an object is represented in the brain and how it is separated from its background and other objects. According to the representational framework, objects that share similar attributes are bound together by coherently active cell assemblies, whereas different objects should evoke distinctly unique assembly patterns. Unfortunately, which attributes are shared and which are independent is not a fixed property of the inputs but depend on a classifier-interpreter mechanism. Judgments of 'similar' or 'different' are subjective (i.e., reader-dependent) and cannot be objectively derived from the spatio-temporal firing patterns of neurons alone unless the firing patterns are evaluated against an output. It may be edifying to compare the promise of the 'bottom up' combinatorial strategy with opinions in another field. 'I know one approach that will fail, which is to start with genes, make proteins from them and to try to build things bottom-up.' (Sydney Brenner; in Novartis Foundation, 2001). Nevertheless, my general comments should not be interpreted that the stimulus-response paradigm is not a useful approach. On the contrary, the empiricist-representational approach has generated most of our

available knowledge about sensory coding and continues to be an important strategy (Rieke et al., 1997; Friston, 2009). However, when studying more central parts of the brain involved in cognition, the limitations of the stimulus-neuronal response strategy become apparent.

Note 4

The time constant τ is the product of the resistance r_m and capacitance c_m of the membrane ($\tau = r_m c_m$) and represents a duration within which the membrane potential relaxes to approximately 37% ($= e^{-1}$) of its initial value after a voltage step. Therefore, neurons with a longer τ can integrate postsynaptic potentials for longer time periods (Johnston and Wu, 1995; Koch et al., 1996). The time constant can vary extensively, depending on the state of the network in which the neuron is embedded.

Note 5

Neural syntax, cell assemblies and the classifier mechanisms discussed in this review of course apply to all parts of brain organization, including the spinal cord. Because historically the cell assembly hypothesis has been discussed primarily in connection with the cooperative activity of cortical neurons, most of the discussion here, naturally, relates to the cerebral cortex. I apologize for this myopic vision to all enthusiasts of non-cortical organization.

Note 6

Non-synaptic interactions, due to electrical coupling or ephaptic effects, local changes in ion concentration, can also contribute to fast recruitment of local neurons, provided that the anatomical arrangements are ideal. For example, the dipole moments generated by nearby pyramidal cells can, in turn, influence other neurons to spike (Jefferys 1995; Anastassiou et al., 2010; Fröhlich and McCormick, 2010; Ozen et al., 2010).

Note 7

A related concept to the cell assembly is the population vector, defined as the weighted contributions of spiking activity of a given constellation of neurons in sequential time windows (Georgopoulos et al., 1986). In the definition of the population vector there is no reference to synaptic connectedness. What matters is which neurons fire together in a given time window. However, in contrast to the reader-centric definition of the cell assembly, the time windows in the population vector are arbitrary. Population vector is also related to neuronal trajectory. Each 'state' of the trajectory corresponds to a time step in the population vector. In case of movement control, the population vector of motor neurons is congruent with the direction of arm movement, illustrating that the ultimate reader mechanism is reaction of the arm muscles. The population vector of hippocampal neurons reliably predicts the spatial position of the rat in a 2-dimensional environment (Wilson and McNaughton, 1993).

Note 8

Letters explicitly define the fundamentals of the syntax of written language. In spoken language, however, the sound fundamentals are less explicit and often depend on the preceding sound(s) and vowels are much more important for comprehension than in written text. Similarly, in neural syntax the fundamental cell assemblies are less explicit because the exact constellation of neurons, which effectively discharge the reader neuron, varies from trial-to-trial and depends on the spiking history of both the reader and the assembly members (Truccolo et al., 2010). For a precise characterization of the assembly, in addition to the constellation of spiking activity (population vector), the exact distribution of synaptic strengths between assembly members and the reader neuron is also needed.

Note 9

Various species of cetaceans produce complex sounds. The portrayal of humpback whale sound sequences as “songs” has captured the imagination of both scientists and the public (Frazer and Mercado, 2000). Humpback whale songs are often interpreted as advertisement displays used to convey information about sexual fitness or, by others, as means for echolocation. Since humpback whales sharing the same waters have similar songs and modify their songs based on what they hear from other humpback whales, they must be continuously monitoring and learning about the songs of their conspecifics (Payne and Payne, 1985). Unfortunately, nothing is known about the neuronal mechanisms underlying whale songs and sound communication.

Note 10

Even though the Zebra finch generates only a single rigid song, its brain is capable of recognizing and differentiating several songs of other territory-competing males (Clayton 1988). Similarly, children can interpret human speech before uttering syntactically correct sentences. Adults learning a foreign language can interpret syntax earlier than actively using it. These and similar examples may be interpreted to support the view that neuronal substrates underlying syntactic rules may preexist prior to linking them to an overt output (Chomsky, 1986; but see also Pulvermüller, 2003; 2005, 2010). A potential counterargument is that discriminating between neuronal trajectories does not require decoding entire trajectories but it is sufficient to detect differential single cues.

Note 11

A fixed action pattern is generally defined as an inherited or ‘instinctive’ behavioral sequence, which, when elicited, runs to completion. The behavioral sequences are stereotypical and released in response to a sign stimulus or ‘releaser’ even the first time the organism encounters the relevant stimulus (typically appearance or action of other animals; Tinbergen 1951). It is perhaps interesting to point out that while ethologists were thinking about the organization of stereotypic action patterns, Karl Lashley (1951) also argued that complex sequential behavior does not necessarily depend on continuous proprioception but by a central, hierarchically organized program.

Note 12

Even very regular neuronal sequences are not always associated with an obvious motor output, making the verification of the suspected cause-effect relationship difficult. For example, place cell activity, phase precession and other complex patterns are consistently displayed by hippocampal neurons under conditions that do not require the hippocampus (e.g., running back and forth on a linear track; O'Keefe and Recce, 1993). However, such pattern generation may be essential. Hippocampal networks can be conceived as a vigilant 'sentinel', which is constantly monitoring and documenting the activity of cortical circuits, and acting only when unusual, unexpected patterns emerge, much like security cameras/recorders whose content may become indispensable for a single critical episode in the sea of irrelevant daily routine patterns.

Note 13

The theta time scale constraints of distance resolution may also apply to the grid cells of the entorhinal cortex. Barry and colleagues (2007) reported that the spatial scale of the grid in layer II entorhinal grid cells varied parametrically with changes to a familiar environment's size and shape. The problem of scaling in both hippocampus and entorhinal cortex, of course, is this: how does the brain allocate its temporal resources and determine the appropriate spatial scaling in a given environment? For this, some a priori knowledge about the approximate size of the environment to be explored is needed (O'Keefe and Burgess, 1996). When the rat is placed into environments of different sizes (e.g., a small box or a football field), it needs to estimate the distances of the boundaries and landmarks to 'plan' a travel from its current location. The theoretically postulated 'boundary vector cells' (Burgess et al., 2000) in the subiculum (Lever et al., 2009) and/or the recently discovered 'border cells' of the entorhinal cortex (Solstad et al., 2008) may be critical in such a computation.

Note 14

Since the limited capacity of working memory (Miller 1956) is usually considered a property of neocortex, particularly the prefrontal cortex (cf. Fuster 1980; Goldman-Rakic, 1995), objections can be raised against the role of hippocampal theta-gamma coupling as a relevant mechanisms (Lisman and Idiart, 1995). Working memory in the laboratory is typically tested by presenting a list of items prior to testing short-term recall. However, long-term memory may also need a short-term buffer. It is impossible to recall the content of an entire book with all the details at once. Instead, long-term recall may take us back mentally to a specific spatio-temporal context and load a limited amount of information in the working memory buffer. The cooperation of long-term and short-term memory mechanisms then can propel forward detailed recall with sufficient resolution. Hippocampal theta phase-entrainment of prefrontal gamma oscillations may serve such a function (Sirota et al., 2008).

Note 15

The longer time processing in the waking brain may be needed for recruiting multiple networks, a prerequisite for conscious experience. From stimulation experiments of

the human brain, Libet (2004) concluded that cortical assemblies should be active and coordinated for a minimum of 0.5 sec for the subject to become aware of the stimulation (Libet's 'mind-time' concept). Hebb (1949) also emphasized that cognitive processing requires some minimum duration of neuronal activity. "What I have in mind, in emphasized half a second or so as the duration of a reverberatory activity, is the observed duration of a single content in perception (Pillsbury, 1913; Boring, 1933). Attention wanders, and the best estimate one can make of the duration of a single 'conscious content' is of this time order." (p. 74; 1949). Human psychophysical experiments suggest that intervals shorter than 0.5 sec are sufficient for formation of a percept but temporal processing of intervals longer than 0.5 sec is cognitively mediated (Michon, 1985).

Note 16

Support for such a conjecture comes from experiments in humans exposed to partially solved problems prior to sleep. Sleep facilitated problem solution significantly more than a similar amount of waking time (Wagner et al., 2004). Off-line states are often regarded anecdotally as being critical for creativity (Andreasen, 2005).

Note 17

An illuminating technical analogy here is the sensor arrays of digital cameras. The resolution of the camera depends on the number of observers (i.e., picture elements or pixels); the more pixels, the higher the resolution of the image. For discriminating simple features (e.g., horizontal vs. vertical lines or small and large objects) sparsely distributed pixels (say 10 by 10) would be not only good enough but highly economical in terms of wiring, processing and maintenance costs. Adding more pixels (more wiring, more processing, larger buffer memory, more energy cost) would result in strong local correlations, redundancy, and no added benefits for such simple tasks. However, for recognizing the difference between the growth or shrinkage of a few spines in the jungle of dendrites in two successively taken images of the cortex would require multiple megapixels. For such a task, the investment is worth it. Neuronal networks are capable of flexibly allocating only a few or very large numbers of observers for solving simple and complex tasks because the task goals can 'tune' the circuits and mobilize the necessary and sufficient resources effectively.

Note 18

The hierarchy of parallel observers appears to be effective in analyzing multiple aspects of the same input in machine learning as well. 'Watson', IBM's supercomputer, ready to be a star on the US Quiz Show Jeopardy, uses more than a hundred algorithms (i.e., observers/integrators) at the same time to analyze a question (i.e., the same input) and compare it with its enormous acquired memory (i.e., the reference material fed to it by humans). The next level of observers in Watson's e-brain then ranks the answers by their likelihood to be correct.

Note 19

The hippocampus-entorhinal cortex circuit illustrates the importance of reader

mechanisms. A general principle of this complex circuit is that strongly recurrent excitatory networks (i.e., layers 2 and 5 of entorhinal cortex, CA3) are sandwiched between layers with largely parallel organization (i.e., layer 3 of entorhinal cortex, dentate gyrus, CA1). The advantage of such organization is that in successive layers the neuronal representations can be iteratively *segregated* (at parallel stages) and *integrated* (at recursive stages; Buzsaki, 2010). As discussed in the main text, the number of resolvable trajectories (e.g., putative recoverable memories) depends on the number of discrete readers. The importance of the large reader population is illustrated by the relative increase of the segregating layers in the mammalian evolution. For example, the ratio of the number of neurons in CA1 and CA3 regions in the rat is ~1.1:1, whereas in the human brain this ratio is 2.5:1 (Seress 1988).

Note 20

Reading of neuronal trajectories (i.e., evolving population vectors) can be illustrated by the control of hand movement. At each instant of time a different motor neuron group is active and as time proceeds, the constellation of sequential assembly members vary (Georgopoulos et al., 1986). Each hand muscle is a reader-integrator of the population activity and the number of potentially differentiable assembly patterns depends on the number of muscles (readers) involved. However, this simple scenario is modified by the fact that muscles are not independent readers because they are anchored to the skeleton and can affect each other's responding abilities. If the activity of the same motor neuronal population was read by a large neuronal pool, instead of the limited numbers of muscles, many more differences in the trajectory could be differentiated. That is the number of differentiable states in any given trajectory depends on the resolution of the reader pool. Similarly to the muscle readers, reader neurons are also not independent since neurons are always embedded in networks. However, with the help of inhibition, neurons can be functionally isolated from the influence of other excitatory inputs, thereby effectively increasing the entropy of the reader population. The larger their entropy, the more patterns can the reader population discriminate.

Note 21

This idea is somewhat related to the 'handshaking' mechanism in telecommunications and information technology. When a computer is about to communicate with a modem, network server, printer or another device it needs to first establish a connection prior to information transfer.

Supplemental References

Anastassiou CA, Montgomery SM, Barahona M, Buzsaki G, Koch C (2010) The effect of spatially inhomogeneous extracellular fields on neurons. *J Neurosci* 30:1925-1936.

Andreasen NC (2005) *The Creating Brain: the Neuroscience of Genius*. New York: Dana Press.

Barry C, Hayman R, Burgess N, Jeffery KJ (2007) Experience-dependent rescaling of entorhinal grids. *10(6):682-684*.

- Berkeley G. (2010) *A Treatise Concerning The Principles Of Human Knowledge*. Kindle Edition. Amazon.com
- Bernstein NA (1947/1967) *The coordination and regulation of movements*. Pergamon Press, London.
- Boring, E. G. (1933) *The physical dimensions of consciousness*. New York: Century.
- Burgess N, Jackson A, Hartley T, O'Keefe J (2000) Predictions derived from modelling the hippocampal role in navigation. *Biol Cybern* 83:301–312.
- Buzsáki, G. (2006). *Rhythms of the brain*. New York: Oxford University Press.
- Buzsáki G. (2010) Hippocampal microcircuits – physiology. In: *Handbook of Brain Microcircuits* (eds: S Grillner, and G. Shepherd). Oxford University Press, NY.
- Chomsky N (1986) *Knowledge of Language: Its Nature, Origin, and Use*, Praeger, New York.
- Clayton NA (1988) Song discrimination learning in zebra finches. *Anim Behav* 36: 1016–1024.
- Damasio AR, Damasio H (1994) Cortical systems for retrieval of concrete knowledge: the convergent zone framework. In: *Large-scale neuronal theories of the brain* Ed. C. Koch, J.L. Davis. Cambridge, MA: MIT Press.
- Delage Y (1919). *Le Réve. Etude psychologique, philosophique et littéraire*. Paris: Presses Universitaires de France.
- Frazer LN, Mercado E, III (2000) A sonar model for humpback whale song. *IEEE J. Oceanic Eng.* 25: 160–182.
- Frégnac Y, Carelli PV, Pananceau M and Monier C (2010) Stimulus-driven coordination of subcortical cell assemblies and propagation of Gestalt belief in V1. In: *Dynamic coordination in the brain: from neurons to mind* (Eds: C. von der Malsburg, W.A. Phillips and W. Singer). MIT Press, Cambridge, MA.
- Friston KJ. (2009) Modalities, modes, and models in functional neuroimaging. *Science* 326:399-403.
- Fröhlich F, McCormick DA (2010) Endogenous electric fields may guide neocortical network activity. *Neuron* 67:129-143.
- Fuster JM (1980) *The prefrontal cortex: Anatomy, physiology, and neuropsychology of the frontal lobe*. Raven Press, New York.
- Galilei G (1623) *Il Saggiatore* (The Assayer) English Translation: A. C. Danto. Introduction to *Contemporary Civilization in the West* (2nd ed.; New York: Columbia University Press, 1954), vol. I. (quoted text on p. 721).
- Georgopoulos AP, Schwartz AB, Kettner RE (1986) Neuronal population coding of movement direction. *Science*, 233: 1416-1419.
- Goldman-Rakic PS (1995) Cellular basis of working memory. *Neuron* 14:477-485.
- Hebb DO (1949) *The Organization of Behavior*. New York: JohnWiley & Sons.
- Jefferys JG (1995) Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. *Physiol Rev* 75: 689-723.
- Johnston D, Wu SM (1995) *Foundations of cellular neurophysiology*. Cambridge, MA: MIT Press (Bradford Books)
- Koch C, Rapp M and Segev I (1996) A brief history of time (constants). *Cerebral Cortex* 6:93-101.
- Lashley KS (1951) The problem of serial order in behavior. In *Cerebral Mechanisms in Behavior*, The Hixon Symposium, edited by L. A. Jeffress; Wiley, New York. pp. 112–

- Lever C, Burton S, Jeewajee A, O'Keefe J, Burgess N (2009) Boundary vector cells in the subiculum of the hippocampal formation. *J Neurosci* 29:9771-9777.
- Libet B (2004) *Mind Time: The temporal factor in consciousness*. Cambridge MA: Harvard University Press 2004.
- Lisman JE, Idiart MA (1995) Storage of 7 +/- 2 short-term memories in oscillatory subcycles. *Science* 267:1512-1515.
- Llinás, R (2001) *I of the Vortex: From Neurons to Self*. MIT Press, Cambridge, MA.
- Merleau-Ponty, M (1945/1962) *Phenomenology of Perception*, translated by Colin Smith (Routledge & Kegan Paul: London).
- Michon, J.A. (1985) The compleat time experiencer. In J.A. Michon and J.L. Jackson (eds) *Time, Mind, and Behavior*, pp. 20-52. Berlin: Springer-Verlag.
- Miller, G. A. (1956). "The magical number seven, plus or minus two: Some limits on our capacity for processing information". *Psychological Review* 63: 81-97
- Milner PM (1996) Neural representations: some old problems revisited. *J. Cog. Neurosci.* 8:69-77.
- Noë A (2004) *Action in Perception*. Cambridge, MA: MIT Press.
- Novartis Foundation (2001) *Complexity in Biological Information Processing*, Wiley, Chichester.
- O'Keefe J, Recce ML (1993) Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3:317-330.
- O'Keefe J, Burgess N (1996) Geometric determinants of the place fields of hippocampal neurons. *Nature* 381:425-428.
- Payne K, Payne RS (1985) Large scale changes over 19 years in songs of humpback whales in Bermuda," *Z. Tierpsych.* 68:89-114.
- Pillsbury WB (1913) "Fluctuation of attention" and the refractory period. *J. phyl. Psychol. Sci. Meth.* 10:181-185.
- Pouille F, Scanziani M (2001) Enforcement of temporal fidelity in pyramidal cells by somatic feed-forward inhibition. *Science* 293:1159-1163.
- Pulvermüller F (2003). *The neuroscience of language*. Cambridge: Cambridge University Press.
- Pulvermüller F (2005) Brain mechanisms linking language and action. *Nat Rev Neurosci* 6:576-582.
- Pulvermüller F (2010) Brain embodiment of syntax and grammar: Discrete combinatorial mechanisms spelt out in neuronal circuits. *Brain Lang.*
- Rieke F, Warland D, de Ruyter van Steveninck R, Bialek W (1997) *Spikes: Exploring the neural code*. MIT Press, Cambridge MA.
- Sherrington, C.S. (1924) Problems of muscular receptivity. *Nature* 113:892-894.
- Seress L (1988) Interspecies comparison of the hippocampal formation shows increased emphasis on the regio superior in the Ammons's horn of the human brain. *J Hirnforschung* 29, 335-340.
- Sirota A, Montgomery S, Fujisawa S, Isomura Y, Zugaro M, Buzsáki G. Entrainment of neocortical neurons and gamma oscillations by the hippocampal theta rhythm. *Neuron*. 2008; 60:683-97.
- Solstad T, Boccara CN, Kropff E, Moser MB, Moser EI (2008) Representation of geometric borders in the entorhinal cortex. *Science* 322:1865-1868.

- Tinbergen, N. (1951) *The Study of Instinct*. Oxford University Press, New York.
- Truccolo W, Hochberg LR, Donoghue JP (2010) Collective dynamics in human and monkey sensorimotor cortex: Predicting single neuron spikes. *Nat Neurosci* 13:105–111.
- Wagner U, Gais S, Haider H, Verleger R, Born J (2004) Sleep inspires insight. *Nature* 427:352-325.
- Wilson MA, McNaughton BL (1993) Dynamics of the hippocampal ensemble code for space. *Science* 261:1055–1058.