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Forum

A Postulate on the Brain's Basic Wiring Logic

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How should evolution and development build the brain to be capable of flexible and generative cognition? I wish to put forth a 'power-of-two'-based wiring logic that provides the basic computational principle in organizing the microarchitecture of cell assemblies that would readily enable knowledge and adaptive behaviors to emerge upon learning.

A divide-and-conquer strategy has thus far enabled neuroscientists to tackle many important questions about the brain. This has been accomplished via investigation of molecular and synaptic machineries or brain regions in great detail [1–4]. As several major BRAIN initiatives are just now getting under way, perhaps this is the right time to ponder the question: Imagine if all the molecular and cellular parts were made available, what is the basic design principle that evolution and development should employ in constructing brains?

Admittedly, it is entirely reasonable that neuroscientists may never solve this problem [5]. Yet, one can at least take a page from what architects or product-design engineers have routinely done – ask what the basic function of the structure or product is, then try to come up with the corresponding design blueprint to achieve it.

What is the central function of the brain? Humans and animals may encounter numerous events, objects, foods, and countless social interactions in a lifetime. As a result, the brain needs to cope with a world of uncertainties and infinite possibilities in order to survive and thrive. Therefore, the true mission of the brain is to discover relational patterns and knowledge about a complex, evolving world in the service of generating adaptive behavior.

With up to 30 000 synaptic connections per principal neuron and 8.6×10^{10} neurons in the human brain, attempts to establish general design principles via reconstruction of all anatomical connections (e.g., the 'connectome') will remain extremely challenging. The great variability in numbers of neurons and axonal/dendritic branching among individual brains and comparisons across species has already posed great obstacles. Currently, neuroscientists are unsure which biological details are crucial to the information processing capability of a brain and which can be safely abstracted away. This illustrates not only the complexity of the brain but also the need for a basic computational framework that would explain what the wiring logic of the brain is and how such connectivity would give rise to flexible and generative cognition.

Theoretically, the brain – as an information processing device – could potentially employ numerous connectomic strategies to carry out cognitive computing. For instance, it could use a 'one-to-one direct mapping' strategy, such as in some parts of the neuromuscular system [where information, (i), is matched to coding units, (n), or $i = n$]. At the other extreme end of the spectrum, the brain could use completely random wiring as a form of sparse code to register specific memories. However, overwhelming evidence demonstrates that this is not the case in real brains: experiments have demonstrated that connectivity is highly nonrandom [6–10], and faulty wiring inevitably gives rise to developmental lethality, intellectual disability, and neurological disorders.

In the case of computers, they use the combinatorial binary coding scheme ($i = 2^n$) in which 'n' is the number of transistors in an on-switch or off-switch state (1 or 0), whereas 'i' represents bits of information or input/output patterns (Figure 1A). This form of a power-of-two computer coding scheme offers immense storage capacity, but would be dynamically unstable in biological systems. Moreover, it lacks the intrinsic ability to discover conceptual knowledge.

Here, I wish to put forth a radically different wiring logic that provides the basic computational principle for organizing the microarchitecture of cell assemblies that can readily enable knowledge and adaptive behavior to emerge. The idea is based on what I term the power-of-two, specific-to-general combinatorial connectivity logic. Namely, I suggest the brain at its microscale is made of preconfigured, conserved 'functional connectivity motifs' (FCMs) across its central circuits. Each FCM consists of principal projection neuron cliques receiving specific inputs, as well as other principal projection neuron cliques receiving progressively more convergent inputs that are comprehensively and combinatorially arranged. The total number of neuron cliques with distinct input convergences follows the formula of $n = 2^i - 1$ [(i) is the number of distinct information inputs, and (n) is the number of neural cliques with all possible combinatorial connectivity patterns] (Figure 1B). In other words, each FCM is made of neural clique assemblies arranged from specific input-coding principle cell assemblies to sub-combinatorial and to general convergent input-coding cell assemblies. This 'power-of-two'-based, specific-to-general wiring logic has six basic properties or requirements, all of which should be subject to experimental inquiry.

First, as an evolutionarily conserved principle, this wiring logic should be implemented in many brain regions regardless of macroscale or mesoscale anatomical patterns, whether in the almond-shaped amygdala, the stratum of CA1 pyramidal cells, or the classic three- or six-layered cortex. This logic should also hold true for various animal species and for different cognitive computing (e.g., whether

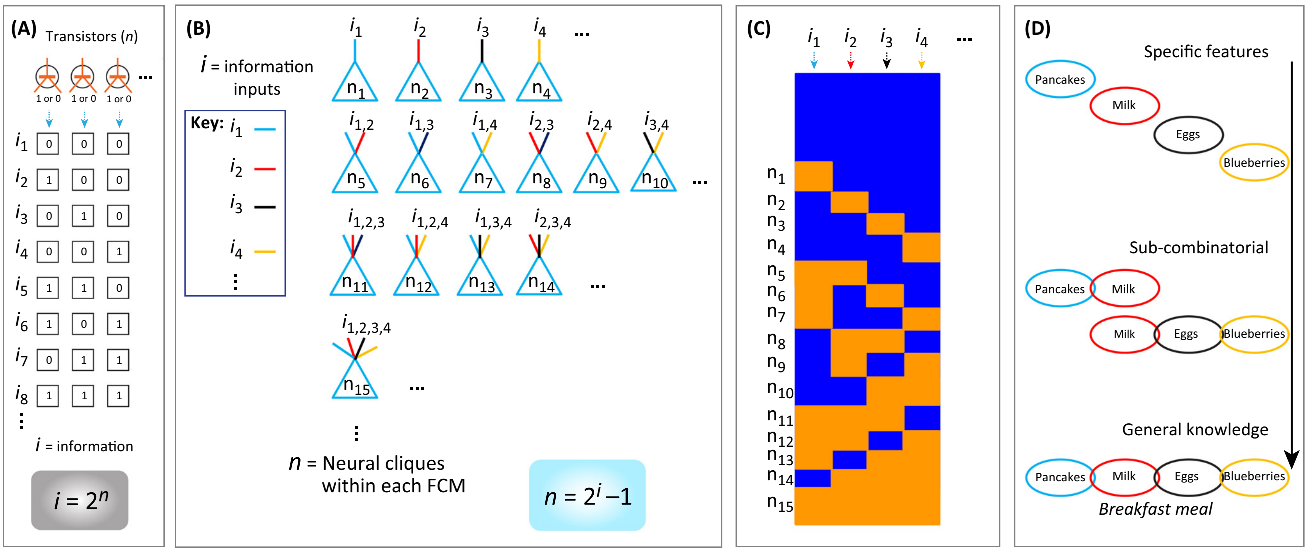

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Figure 1. Distinct Mathematical Logic for the Computer and the Brain. (A) 'Power-of-two'-based binary coding scheme is used in computers for maximal storage of information. Abbreviations: *i*, information; *n*, numbers of transistors. (B) By contrast, power-of-two-based, specific-to-general combinatorial connectivity logic is proposed for constructing microcircuits of the brain by evolution and development. Although the illustration uses only one cell for a given type of input connection, it should be viewed as a neural clique – a group of principal projection cells sharing similar tuning properties. This preconfigured wiring pattern within a functional connectivity motif (FCM) enables the neural networks to readily register not only specific information but also all possible relational patterns. (C) The schematic 'barcode' illustration of functional connectivity activation patterns of a given neural clique assembly (orange block represents active neural cliques) when processing four distinct inputs ($i = 4$). An FCM consisting of 15 distinct neural cliques (n_{1-15}) is required to represent all the possible connectivity patterns. This barcode-like motif gives rise to a specific-to-general feature extraction clique assembly. Abbreviations: *i*, information type with each distinct input; *n*, numbers of neural cliques within a given FCM. (D) A 'cognitive' example to illustrate flexible emergence of specific features, sub-combinatorial features, as well as the abstract concept of 'breakfast' from specific-to-general cell assemblies in the appetitive memory circuit.

processing appetitive behavior, social interactions, fearful events, etc.). Neurophysiologists can test these three key predictions by assessing functional connectivity patterns of cell assemblies using *in vivo* recording techniques, while animals receive cognitively important natural stimuli [9,10].

Second, the specific-to-general connectivity pattern is ideal to account for how categorical and hierarchical knowledge emerges at the microarchitecture level. The specific neural cliques should represent unique features about perspective stimuli, whereas the subgeneral and general neural cliques extract categorical or combinational relationships among features and knowledge, in the form of a 'barcode' (Figure 1C). For a 'cognitive' example, when a person consumes pancakes, milk, eggs, and blueberries – either separately, combinatorially or together ($i = 4$) – existence of all 15 types of principal neural cliques in an appetitive association circuit can readily capture various specific and/or combinational relationships, ranging from neural representation for 'milk only' or 'milk with pancakes', to 'milk together with pancakes and eggs' or the general concept of 'a breakfast meal' (Figure 1D). This specific-to-general barcode logic, implemented at the cell assembly level, intrinsically enables the microcircuits to discover potentially all sorts of cognitively important patterns; consequently, giving rise to categorical knowledge at the macroscale network level. By conforming to this simple mathematical logic, $n = 2^i - 1$, at the cell assembly level, evolution and development afford the brain to carry out flexible cognition.

Third, although the concept of cell assembly was first coined by Hebb in 1949, its wiring patterns or organizing principles remain unknown. A random wiring-based mechanism can be potentially employed to generate combinatorial connectivity, if given sufficient convergence and divergence in a microcircuit. However, I would argue that executing this wiring logic should be via a nonrandom mechanism for multiple reasons. This nonrandom mechanism can be confirmed or rejected in several ways. For example, I anticipate that the specific-to-general neural clique assembly should exhibit first-order specific, nonrandom connectivity patterns, yet the combinatorial arrangement would conform to a second-order statistical principle that intrinsically enables the circuit to generate a variety of possible relational connectivity patterns. One can use statistical approaches, such as the independent connectivity model and the second-order correlation model, to test the connectivity distribution. The proposed wiring logic should fit perfectly with the second-order correlation model, which permits hierarchical code to emerge instantaneously within a microcircuit cell assembly, rather than the classical two-level code models (i.e., simple cells versus complex cells in V1 or place cells versus grid cells in CA1–medial entorhinal cortex).

Fourth, this specific-to-general feature extraction computation can explain the functional purposes of cortical layers. In expanding the prediction about the non-random wiring mechanism, I further propose that the classic three- or six-layered cortex is an ideal microarchitecture to execute this power-of-two-based wiring logic. Specifically, I propose that input cortical layers should host most of the specific neural cliques and simple subgeneral neural cliques, whereas deep layers accommodate more subgeneral and general neural cliques. In addition, subgeneral and general feature coding neural cliques from the output layer of a lower cortical FCM may also act as presynaptic cells projecting to the specific cliques located in the next level cortical FCM (feed-forward knowledge generation) or subcortical sites for modulation of the global cognitive states including consciousness, motor and motivational control. In general, the neurons belonging to the same sets of FCMs should exhibit more coherent correlations and coupling than those belonging to the different FCMs.

Fifth, this power-of-two mathematical logic confines the total numbers of distinct inputs (i) coming into a given microcircuit in order to best utilize the available cell resources. For instance, as a result of its exponential growth, at a mere $i = 40$, the total number of neurons (n) required to cover all possible connectivity patterns within a microcircuit would be more than 10^{12} (already exceeding the total number of neurons in the human brain). For *Caenorhabditis elegans* – which has only 302 neurons, limiting i to 8 or less at a given neural node makes good economic sense. Furthermore, by employing a submodular approach (e.g., using a set of four or five inputs per subnode), a given circuit can greatly increase the input types it can process with the same number of neurons. This cost–benefit factor may also explain the macroscale and mesoscale modular and hierarchical organization in the brain. Computational neuroscientists may use this logic to explore the wiring efficiency at each network [11].

Lastly, as an evolutionarily conserved principle, this wiring logic should be already present as preconfigured, genetically programmed patterns prior to learning. In the literature, there are two major theories on how networks generate representations. One is known as the Selectionism Theory of Learning, or Neural Darwinism, which is based on synapse overproduction during development and followed by regressive selection via learning [12,13]. The other is known as the Constructivism Theory of Learning, which postulates that learning interacts with the growth of neural connections over the developmental period to gradually construct representational networks [14]. As a result of the lack of knowledge on functional connectivity patterns of cell assembly, researchers have resorted to synaptic plasticity driven by learning to explain the emergence of representational patterns from unknown, presumably random or disordered, local connectivity [4]. However, all models built on random or disordered connectivity are difficult to explain why the innate cognitive abilities in infants can still emerge without apparent learning [15]. Local randomness is also used in Deep Learning algorithms, which inevitably require exhaustive training. By contrast, the wiring logic postulated here offers a primeval form of specific-to-general connectivity landscape from which categorical knowledge can be readily sculpted and dynamically updated by learning. This preconfigured wiring logic can be confirmed by uncovering the specific-to-general response patterns and/or pre-existing correlations of these neural cliques in naive animals without prior training.

In short, I propose a power-of-two-based, specific-to-general wiring logic that provides the basic computational principle for how the brain should be structured at its cell assembly level. This genetically programmed, preconfigured wiring logic can inherently enable knowledge and adaptive behaviors to emerge much more readily upon learning. If attested, this design principle may also offer a new path towards artificial general intelligence.

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References

1. Hubel, D.H. and Wiesel, T.N. (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J. Physiol.* 160, 106–154
2. Bliss, T. and Collingridge, G. (1993) A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361, 31–39
3. Tang, Y.P. *et al.* (1999) Genetic enhancement of learning and memory in mice. *Nature* 401, 63–69
4. Rothschild, G. and Mizrahi, A. (2015) Global order and local disorder in brain maps. *Annu. Rev. Neurosci.* 38, 247–268
5. Adolphs, R. (2015) The unsolved problems of neuroscience. *Trends Cogn. Sci.* 19, 173–175
6. Song, S. *et al.* (2005) Highly nonrandom features of synaptic connectivity in local cortical circuits. *PLoS Biol.* 3, e68
7. Förster, E. *et al.* (2006) Laminating the hippocampus. *Nat. Rev. Neurosci.* 7, 259–267
8. Barbas, H. (2015) General cortical and special prefrontal connections: principles from structure to function. *Annu. Rev. Neurosci.* 38, 269–289
9. Guven-Ozkan, T. and Davis, R.L. (2014) Functional neuroanatomy of *Drosophila* olfactory memory formation. *Learn. Mem.* 21, 519–526
10. Lin, L. *et al.* (2006) Organizing principles of real-time memory encoding: neural clique assemblies and universal neural codes. *Trends Neurosci.* 29, 48–57
11. Stevens, C.F. (2012) Brain organization: wiring economy works for the large and small. *Curr. Biol.* 22, R24–R25
12. Changeux, J.P. and Danchin, A. (1976) Selective stabilization of developing synapses as a mechanism for the specification of neuronal networks. *Nature* 264, 705–712
13. Edelman, G.M. (1993) Neural Darwinism: selection and reentrant signaling in higher brain function. *Neuron* 10, 115–125
14. Quartz, S.R. and Sejnowski, T.J. (1997) The neural basis of cognitive development: a constructivist manifesto. *Behav. Brain Sci.* 20, 537–596
15. Carruthers, P. *et al.*, eds (2005) *The Innate Mind: Structure and Contents*, Oxford University Press