SAAP Journal of Integrative Physiology

https://www.thesaap.org/saap-journal ISSN 3121-410X (Online)

STUDENT ARTICLE | SJIP 2026

Physiological Basis of Organoid Intelligence

Raveen Hewage*

5th Year Medical Undergraduate, Faculty of Medicine, University of Ruhuna, Sri Lanka

Abstract

Organoid intelligence (OI) represents a paradigm shift in computation and neuropharmacology by integrating living human cortical neurons with digital interfaces to create synthetic, efficient biological computers. Utilizing high-density microelectrode arrays (HD-MEA), spatial data from simulated environments is encoded as electrical stimuli, prompting sodium influx and depolarization within *in vitro* neuronal networks. A closed-loop action-feedback system is thereby established, enabling real-time monitoring of extracellular field potentials. The fundamental driver of goal-oriented behavior in these isolated networks is the free energy principle, where neurons intrinsically act to minimize metabolic expenditure and unpredictable stimuli. The reality is, by selectively reinforcing predictable feedback through long-term potentiation and pruning chaotic connections via long-term depression, these cultures functionally learn spatial tasks to maintain homeostasis. Consequently, this framework offers immediate utility in advanced pharmacological screening, allowing researchers to evaluate therapeutic agents based on the restoration of active cognitive function rather than mere static cell viability. True computational innovation ultimately lies not in mimicking biology with silicon, but in directly harnessing the intrinsic, adaptive architecture of life itself.

Keywords: Biological computing, free energy principle, medical technology, organoid intelligence, synaptic plasticity

1. Introduction

Artificial intelligence (AI) is a branch of computer science where, instead of explicitly programming every step of a program, systems are designed that learn patterns from data and make decisions or predictions on their own. This method of computation is loosely inspired by how the human brain functions. However, compared to biological systems, traditional computers are based on microchips built with semiconductors made with silicon. Therefore, silicon-based AI requires massive amounts of energy for training, compared to the extreme metabolic efficiency biological neural networks require to function[1]. This distinction has led to the development of a domain called organoid intelligence (OI) which integrates primary cortical neurons with computational hardware to create synthetic biological systems[2]. The prototypical implementation, often termed *DishBrain*, involves culturing about 800,000 neurons on a high-density microelectrode array (HD-MEA)[1]. A microelectrode array (MEA) is a grid of microscopic electrodes that can both record extracellular electrical activity from neurons and deliver controlled electrical stimulation, allowing researchers to monitor and influence neural network behavior *in vitro* in real time[1].

The HD-MEA can be used to deliver stimulation patterns representing sensory input, and the tissue's electrical activity can be recorded as the network's output. One of the main principles driving this organization is called the free energy principle (FEP), which explains why the neurons modify their connectivity between each other in a way that minimizes the metabolic cost of unpredictable stimuli (Figure 1)[3].

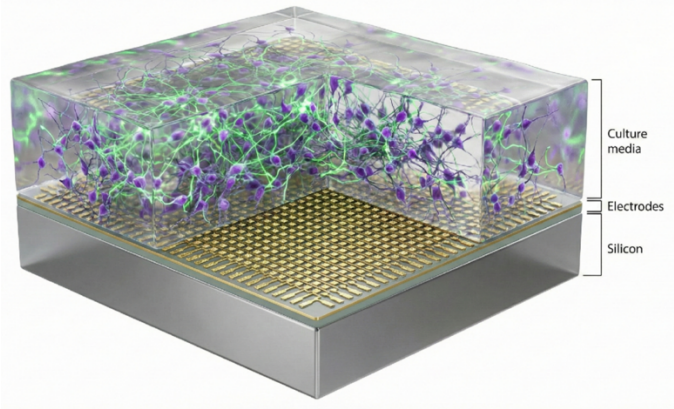

Figure 1: High-density microelectrode array (HD-MEA)

2. Physiology of the Interface

One of the biggest challenges in OI is to map digital logic into their biological imperatives. This is addressed in initial research by generating organoids from pluripotent stem cells[4] and culturing them as a sheet

Address for correspondence:
Raveen Hewage
Faculty of Medicine, University of Ruhuna, P.O. Box 70, Galle, Sri Lanka
E-mail: raveen6024@umed.ruh.ac.lk

How to cite this article: Hewage R. Physiological basis of organoid intelligence. SAAP J Integr Physiol. 2026;1(2): 27-29.

over the MEA, enabling the MEA to act as both the input and the output for the neuronal culture[1]. Later research has extended these systems into three-dimensional (3D) organoids exhibiting diverse cell types and complex network dynamics[5,6], with microfluidic perfusion further maintaining oxygen and nutrient delivery to prevent central necrosis[7].

When the system registers a variable, such as a position of a ball in a stimulated environment, direct transmission of complex sensory data (such as video) is impractical and noisy. Therefore, computationally encoded algorithms convert spatial coordinates into structured stimulation patterns that can be delivered through the MEA to the neuronal culture. These micropulses cause voltage-gated sodium channels on the cell membrane of neurons to undergo conformational changes and cause a sodium influx into the cell, inducing depolarization, essentially *writing* the pattern of electrical stimulation to the neurons[8].

Conversely, the electrodes detect and record the extracellular field potentials produced when neurons fire. These signals arise from the rapid influx of sodium ions into the neurons, which creates a transient negative voltage change in the surrounding extracellular environment.

This system creates an action-feedback loop with sub-millisecond latency. This is crucial because if the duration between the action and the feedback is not tightly coupled temporally, the neurons cannot associate their internal firing states with external consequences, rendering learning impossible. This precise temporal synchronization defines spike-timing-dependent plasticity (STDP)[9].

3. Free Energy Principle

One of the most important questions in OI is to understand not just how the neurons process data but to understand why an *in vitro*, isolated collection of cortical neurons exhibit goal-oriented behavior at all. There are a few theories behind this, and the FEP is considered a prominent guiding theory supported by empirical functional mapping[10].

The FEP states that all self-organizing biological systems strive to minimize *surprisal* (variational free energy) to maintain homeostasis. To put this in the context of *DishBrain*, the system is made to stimulate the neuronal culture in two distinct patterns. When the culture successfully *hits* the ball, it is stimulated with a predictable, rhythmic, and synchronous stimulus, and conversely, when it *misses* the culture is *punished* with a chaotic, high-entropy stimulus with unpredictable frequency and amplitude[1].

Physiologically, chaotic stimulations are disruptive to the synaptic connections between neurons and also metabolically expensive. In order to minimize the *surprise*, the neurons rearrange their connections with each other, which is called synaptic plasticity. This is executed primarily through long-term potentiation (LTP) and long-term depression (LTD). LTP states that when a pre-synaptic neuron repeatedly stimulates a post-synaptic neuron, the connection strengthens. LTD states that, conversely, if the firing is uncorrelated, the connection weakens[11].

By synapsing with each other in such a way that ensures predictable feedback (the *hit*) and pruning the ones that lead to chaotic feedback (the *miss*), the network *learns* how to do the task, which in this case is hitting a ball in a stimulated environment. The *learning* is an intrinsic biological by-product of the culture attempting to minimize its entropy and maximize the predictable stimulus (Figure 2)[6].

4. Applications of Organoid Intelligence

Immediate application of OI methods lies in pharmacology. Currently, drug screening relies on static cell cultures that cannot represent functional cognition, or animal models that often fail to properly translate to human physiology. Organoid intelligence offers a third paradigm, namely, the *in vitro* patient. By culturing neurons derived from induced pluripotent stem cells (iPSCs) of patients with specific neurological disorders, such as Alzheimer's disease or epilepsy, researchers can create functional organoids capable of measurable outputs[12]. These networks can then be challenged with cognitive tasks and observed how their learning rate degrades over time or in response to neurotoxic stressors. Conversely, potential therapeutic agents can be screened to see if they restore synaptic plasticity and information processing capabilities in real-time. This moves the metric of drug success from simple *cell survival* to the restoration of *functional intelligence*.

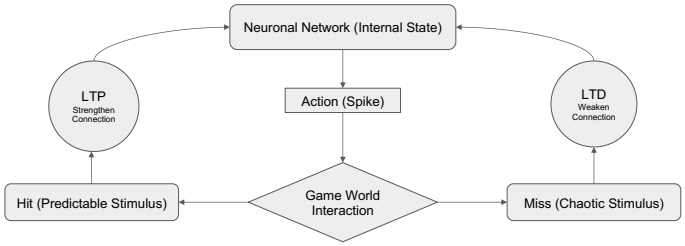

Figure 2: Mechanism of action of neuronal networks aiming to minimize entropy

5. Challenges and Prospects

It should be noted that realizing the clinical and computational potential of these synthetic systems requires overcoming profound physiological hurdles. The reality is, current organoids lack intrinsic vascular networks and essential neuroimmune components like microglia, which strictly limits their physical scale, longevity, and accurate representation of human neuroinflammation[13]. Therefore, scaling these micro-brains for complex processing or extended disease modeling necessitates advanced microfluidic perfusion to prevent central necrosis[7]. Recent empirical advances have demonstrated that integrating human brain organoids with engineered functional vascular-like systems significantly reduces hypoxia and apoptosis in the core[14]. Furthermore, *in vivo* implantation models have successfully achieved host-derived vascularization, promoting extended functional maturation and neuronal survival[15]. Incorporating these microfluidic and vascular bioengineering solutions into HD-MEAs is critical. Without these structural supports, the sustained metabolic demands of continuous LTP during goal-oriented tasks will induce rapid cellular degradation, neutralizing their utility as enduring biological computers. Furthermore, as these biological constructs demonstrate increasingly sophisticated goal-oriented behavior, the ethical boundaries of *in vitro* cognition and plasticity must be rigorously defined. Consequently, advancing this field requires an integrated approach to ensure these models serve strictly as predictive therapeutic and computational tools without crossing into unregulated sentience.

6. Conclusion

Organoid intelligence establishes a fundamentally new frontier at the intersection of cellular neurophysiology and computational logic. By leveraging the innate thermodynamic drive of living neural networks to minimize free energy, researchers can harness authentic biological plasticity rather than merely simulating it with semiconductors. However, the trajectory from rudimentary models to highly predictive biological computers demand solving critical limitations in tissue vascularization and the long-term metabolic maintenance of 3D cultures. The reality is, mastering these physiological constraints will ultimately dictate the viability of OI in accelerating translational neuropharmacology. Consequently, refining the microelectrode interfaces and microfluidic perfusion systems remains the immediate scientific priority. True mastery of biocomputing lies not in overriding cellular biology, but in precisely orchestrating its intrinsic drive for equilibrium. Achieving this balance will require interdisciplinary collaboration to realize the full cognitive potential of living systems.

Disclosure

The AI tool, Gemini 3.1 Pro was used for writing the abstract.

References

1. Kagan BJ, Kitchen AC, Tran NT, Habibollahi F, Khajehnejad M, Parker BJ, et al. In vitro neurons learn and exhibit sentience when embodied in a simulated game-world. Neuron. 2022;110(23):3952-69.e8. DOI: 10.1016/j.neuron.2022.09.001.
2. Bakkum DJ, Chao ZC, Potter SM. Spatio-temporal electrical stimuli shape behavior of an embodied cortical network in a goal-directed learning task. J Neural Eng. 2008;5(3):310-23. DOI: 10.1088/1741-2560/5/3/004.
3. Isomura T, Kotani K, Jimbo Y. Cultured cortical neurons can perform blind source separation according to the free-energy principle. PLoS Comput Biol. 2015;11(12):e1004643. DOI: 10.1371/journal.pcbi.1004643.
4. Lancaster MA, Renner M, Martin CA, Wenzel D, Bicknell LS, Hurles ME, et al. Cerebral organoids model human brain development and microcephaly. Nature. 2013;501(7467):373-9. DOI: 10.1038/nature12517.
5. Giandomenico SL, Mierau SB, Gibbons GM, Wenger LMD, Masullo L, Sit T, et al. Cerebral organoids at the air-liquid interface generate diverse nerve tracts with functional output. Nat Neurosci. 2019;22(4):669-79. DOI: 10.1038/s41593-019-0350-2.
6. Quadrato G, Nguyen T, Macosko EZ, Sherwood JL, Yang SM, Berger DR, et al. Cell diversity and network dynamics in photosensitive human brain organoids. Nature. 2017;545(7652):48-53. DOI: 10.1038/nature22047.
7. Cho AN, Jin Y, An Y, Kim J, Choi YS, Lee JS, et al. Microfluidic device with brain extracellular matrix promotes structural and functional maturation of human brain organoids. Nat Commun. 2021;12(1):4730. DOI: 10.1038/s41467-021-24775-5.
8. Huang Q, Tang B, Romero JC, Yang Y, Elsayed SK, Pahapale G, et al. Shell microelectrode arrays (MEAs) for brain organoids. Sci Adv. 2022;8(33):eabq5031. DOI: 10.1126/sciadv.abq5031.
9. Markram H, Lübke J, Frotscher M, Sakmann B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science. 1997;275(5297):213-5. DOI: 10.1126/science.275.5297.213.
10. Trujillo CA, Gao R, Negraes PD, Gu J, Buchanan J, Preissl S, et al. Complex oscillatory waves emerging from cortical organoids model early human brain network development. Cell Stem Cell. 2019;25(4):558-69.e7. DOI: 10.1016/j.stem.2019.08.002.
11. Bi GQ, Poo MM. Synaptic modifications in cultured hippocampal neurons: Dependence on spike timing, synaptic strength, and postsynaptic cell type. J Neurosci. 1998;18(24):10464-72. DOI: 10.1523/JNEUROSCI.18-24-10464.1998.
12. Choi SH, Kim YH, Hebisch M, Sliwinski C, Lee S, D'Avanzo C, et al. A three-dimensional human neural cell culture model of Alzheimer's disease. Nature. 2014;515(7526):274-8. DOI: 10.1038/nature13800.
13. Ormel PR, de Sá RV, van Bodegraven EJ, Karst H, Harschnitz O, Sneeboer MAM, et al. Microglia innately develop within cerebral organoids. Nat Commun. 2018;9(1):4167. DOI: 10.1038/s41467-018-06684-2.
14. Cakir B, Xiang Y, Tanaka Y, Kural MH, Parent M, Kang YJ, et al. Engineering of human brain organoids with a functional vascular-like system. Nat Methods. 2019;16(11):1169-75. DOI: 10.1038/s41592-019-0586-5.
15. Mansour AA, Gonçalves JT, Bloyd CW, Li H, Fernandes S, Quang D, et al. An in vivo model of functional and vascularized human brain organoids. Nat Biotechnol. 2018;36(5):432-41. DOI: 10.1038/nbt.4127.