frontiers | Frontiers in Science

TYPE Frontiers in Science Viewpoint
PUBLISHED 28 February 2023
DOI 10.3389/fsci.2023.1150594

EDITED AND REVIEWED BY
Richard S. Frackowiak,
Swiss Federal Institute of Technology
Lausanne, Switzerland

*CORRESPONDENCE
Gary W. Miller
Gary.Miller@columbia.edu

RECEIVED 24 January 2023
ACCEPTED 06 February 2023
PUBLISHED 28 February 2023

CITATION
Miller GW. Organoid intelligence: smarter than the average cell culture.
Front Sci (2023) 1:1150594.
doi: 10.3389/fsci.2023.1150594

Organoid intelligence: smarter than the average cell culture

Gary W. Miller[1,2]*

[1]Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, United States, [2]Department of Molecular Pharmacology and Therapeutics, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, United States

KEYWORDS

organoid, organoid intelligence, artificial intelligence, synapse, long-term potentiation

A Viewpoint on the Frontiers in Science Lead Article
Organoid intelligence (OI): the new frontier in biocomputing and intelligence-in-a-dish

Key points

- Advances in synthetic biology have allowed complex neuronal processes to be reliably studied in cultured organoids.
- The intelligence capabilities possessed by brain organoids demand careful consideration of the ethical challenges posed by these systems.
- Brain organoids represent an important model for studying how environmental factors disrupt components of neuronal function, including memory and cognition.

Organoid. (or·ga·noid/'ôrgə,noid/noun): an artificially grown mass of cells or tissue that resembles an organ.
Intelligence. (in·tel·li·gence/in'teləj(ə)ns/noun): the ability to acquire and apply knowledge and skills.

For more than a century, scientists have cultured living cells to study biological processes. In the laboratory, scientists can provide the key nutrients and conditions that allow cells to undergo cell division, and even postmitotic cells can be kept alive for many weeks under the right conditions. Rapidly dividing cancer cell populations are especially amenable to being cultured. Indisputably the study of cultured cells has yielded extraordinary insights and a variety of therapeutic products, from insulin to adrenaline. And yet the ignominious origin of culturing human cells [see the Immortal Life of Henrietta Lacks (1)] serves as a strong reminder that technological and scientific advancement must be accompanied by equally robust ethical deliberations and protections. The article by Smirnova and colleagues in this issue (2) showcases the advances that have been made with brain organoids, to the point where we must start addressing the science and ethics of what they term "organoid intelligence" (OI).

Progress in brain organoid culturing

For many years, researchers favored the study of rapidly dividing cell populations derived from a single cell. Clonal cell populations provide consistency over time, and non-clonal cells were often viewed as contaminants. However, the benefits of studying heterogenous populations of different cell types are now clear. For example, neurons tend to fare better in the presence of some of their supporting glial cells. Cytochrome p450-expressing hepatocytes in the liver interact closely with the immune-based Kupffer cells (3). Indeed, labs have used 3D printing to build cellular layers of liver tissue that replicate some of the plumbing and connectivity observed in the liver (4). When multiple cell types are combined in a dish, the result is more analogous to the organ itself, thereby offering important advantages over the individual cellular components. These self-organizing 3D collections of cells that replicate organ-level features are called “organoids.”

Slices of brain can allow more detailed study of neuronal connections, but tissue slices tend to be short-lived owing to the damage incurred from their removal and the difficulty in achieving oxygen and nutrient perfusion to a depth sufficient to sustain them. Scientists have been interested in how neurons make synaptic connections and, by combining pre- and post-synaptic cellular populations, have used such models to study neuronal activity. Again, the supportive glial cells tend to make the system stronger by providing growth factors and other key components (5). One key aspect of neurons is how much better they conduct electrical activity when they are myelinated. The myelin generated by oligodendrocytes provides critical insulation and allows saltatory conduction that greatly accelerates nerve conduction (5). The systems described by Smirnova and coworkers exhibit all of the components needed for synaptic transmission along myelinated axons (2), which marks an exciting development for the field.

A role in regulatory testing

Induced pluripotent stem cells (IPSCs) have been used widely to study the effects of gene mutations on select populations of cells, but there is a need to study complex environmental exposures in a manner that retains the 3D architecture of the system. Brain organoids display the key features needed to allow the systematic analysis of chemicals of concern (i.e., multicellularity, neurons and glia, synaptic connections, and myelination). Given recent changes in regulatory policy in the European Union and the United States, brain organoids are well-positioned for toxicological testing and can allow examination of fundamental processes involved in neuronal function that underlie complex human functions, such as cognition. Although there are many challenges involved in studying complex mixtures, the reality is that in the vast majority of situations, humans are exposed to mixtures of chemicals. Therefore, if we want to study the effects of the environment on brain processes such as cognition, brain organoids are an ideal model to systematically interrogate simple and complex chemical mixtures.

The prospects for organoid intelligence

While many intelligent people have been involved in the development of neuronal or brain organoid cultures, historically there has not been a discussion of the intelligence of the organoids themselves. The cultured systems exhibited synaptic activity and adaptation, but for many years they were relatively simplistic, making it difficult to envision complex processes like long-term potentiation. Now, as neuronal and brain organoids advance [as described by Smirnova and colleagues (2)] we face a point in time when we must consider if these complex cell culture systems can acquire or possess intelligence. On the surface, this seems like a ridiculous and unlikely scenario. How could a cluster of cells possess intelligence? Yet, when we consider the basic biology of intelligence and examine the primary constituents, it becomes less far-fetched.

We have watched the development of artificial intelligence (AI), waiting for the point of “singularity.” When will computers pass the Turing test? Some argue we are just about there. ChatGPT can effectively synthesize information available from the internet, but it does not exhibit intelligence *per se*; rather, it is an exceptional gatherer and synthesizer of written information. It cannot react to a change in temperature or a chemical signal, something even the most basic cultured cellular system can do. As the brain organoid models become more sophisticated and complex, will they eventually be able to pass a biological Turing test?

As a child of the 1970s, I recall when Pong was introduced – a simple game with simple controls. This was followed by classic arcade games such as Breakout, Space Invaders, Missile Command, Galaga, and Pac-Man. If the evolution of OI follows a similar pace, it will not be long before organoids are playing Space Invaders and even becoming worthy adversaries in the strategy board game Go. Why does it matter if a brain organoid can play a video game? Clearly, the goal is not merely to play video games, but these games do serve as useful surrogates of complex problem-solving. In 1997, the IBM computer Deep Blue was able to duel with chess grandmasters such as Garry Kasparov; this paralleled the more practical advances in data analysis for which the system was designed (6). Moreover, the ability to respond within these games to diverse signals, adapt to the rapidly changing environment, and apply that knowledge to future endeavors represents key aspects of intelligence and sentience.

What if we could train a brain organoid to store and organize information within its DNA? Even though the DNA system relies on a simplistic 4-code alphabet, we have learned that it is an incredibly efficient means of storing information. (Even the brains of small children outperform high-performance computers in many domains). From a power efficiency perspective, biology is far superior to a computer. A brain organoid farm has the potential to deliver the storage and computational power of a conventional silicon-based server farm that uses a million times more energy. Indeed, an intelligent organoid farm for data storage and computation may be one of the most exciting future applications of OI. Perhaps a fusion of brain organoid and silicon-based computing and storage will harness the best of both worlds.

Smirnova et al. (2) have made the case for the uniqueness of the field of OI. The convergence of elegant brain organoid systems, technological innovation, learning and memory pathways, and ethical issues requires a focused and methodical process, proceeding with caution and optimism. The field of OI conjures up images of science-fiction fantasy but also forces us to consider the scientific reality. Brain organoid systems could exhibit key aspects of intelligence and sentience. This demands a robust examination of the ethical implications of the technology, in which ethicists must be included. We must ensure that each step of the process is conducted with scientific integrity, while acknowledging that the larger issue is the potential impact on society. OI blurs the line between human cognition and machine intelligence, and the technology and biology are advancing at a speed that could outpace the ethical and moral discussions that are needed. This emerging field must take a vigorous approach to addressing the ethical and moral issues that come with this type of scientific advancement and must do so before the technology crashes into the moral abyss.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Skloot R. *The immortal life of Henrietta lacks*. New York: Broadway Paperbacks, Random House (2011).

2. Smirnova L, Caffo BS, Gracias DH, Huang Q, Morales Pantoja IE, Tang B, et al. Organoid intelligence (OI): the new frontier in biocomputing and intelligence-in-a-dish. *Front Sci* (2023) 1:1017235. doi: 10.3389/fsci.2023.1017235

3. Hall JE. *Guyton and hall textbook of medical physiology. 13th ed*. Philadelphia: Saunders Elsevier (2015).

4. Norona LM, Nguyen DG, Gerber DA, Presnell SC, LeCluyse EL. Modeling compound-induced fibrogenesis *in vitro* using three-dimensional bioprinted human liver tissues. *Toxicol Sci* (2016) 154(2):354–67. doi: 10.1093/toxsci/kfw169

5. Kandel ER, Koester JD, Mack SH, Siegelbaum SA. *Principles of neural science. 6th ed*. New York: McGraw-Hill (2021).

6. IBM. *IMB 100 - Deep Blue* (2011). Available at: https://www.ibm.com/ibm/history/ibm100/us/en/icons/deepblue/.