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Organoid Intelligence: The Crossroads of Biology and Artificial Intelligence

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Although new artificial intelligence (AI) tools like ChatGPT are constantly emerging, scientists are already working on modern AI's likely successor: organoid intelligence (OI). OI aims to leverage the computational power of the human brain by growing cells that resemble neurons. By doing this, scientists are literally "growing intelligence." In addition to using OI to solve traditional computational problems with a system that emulates the plasticity of the human brain, OI has the potential to improve our understanding of neurologic conditions with complex pathophysiologies such as autism and Alzheimer's disease. While prospective OI technology has yet to undergo clinical testing, organoids have been successfully validated and utilized to study various human diseases in the laboratory for over a decade. Critics of OI warn that advanced organoids could eventually exhibit human-like sentience.

Organoids are self-organizing and interconnected cell cultures grown in highly specialized environments, where they are genetically programmed to express the identical characteristics of a particular organ, such as a heart, lung, or even a brain. These "mini-organs" capture the full complexity of the original organ, including creating specific parenchymal cells, but on a microscopic scale. As a reconstruction of *in vivo* organs, organoids are considered superior to immortalized cell lines in replicating 3D cyto/histoarchitecture, cell function, and heterogeneity of human organs. The unique abilities of organoids have allowed researchers to overcome many of the challenges of studying live human organs, bridging the gap between developmental biology and medicine. A study conducted by the Canadian Cancer Society

Research Institute demonstrated the value of organoids derived from patients with non-small cell lung cancer. The authors discovered that these organoid cultures accurately reproduced the tumorigenicity, genetic mutations, sensitivity to targeted drug treatments, and gene expression profiles observed in the original tissue.

Expanding on previous organoid research, a recent study published in Frontiers in Science proposed the integration of organoids in biological computing. Biological computing refers to harnessing the power of biologically derived molecules, such as those found in organoids, to perform storage, retrieval, and processing. Human neurons are capable of incredible information processing thanks to the microscopic size of their densely packed computational units with trillions of hyperdense synapses and high metabolic efficiency. Moreover, these cells have the remarkable ability to regenerate and repair themselves continuously, similar to a computer system that operates without the need for external maintenance. Dr. Thomas Hartung, one of the authors of the Frontier study, said to CNN, "The brain is still unmatched by modern [silicon] computers." For example, the 8,000-pound Frontier supercomputer, which claims to exceed the computational speed of the human adult brain, can only do so by consuming a million times more energy. However, with new advancements in organoids, future machine learning could harness the computational efficiency and power of the brain.

Currently, researchers can synthesize enhanced organoids that have the potential to mimic the computational and cognitive capabilities of an in-vivo brain. A laboratory-grown brain organoid is characterized by high levels of myelination, a greater abundance of support cells, and a capacity for spontaneous neural activity, representing a substantial advancement from earlier iterations that lacked such physiological complexity. With these synthesized mini-brains, the

Frontiers study proposes using available 3D microelectrode arrays (similar to EEG) to perform external electrophysiological recordings of these organoids to perform tasks such as learning, memory, and other cognitive functions. Other studies have shown latent diffusion models can reconstruct regional brain activation under fMRI, thereby decoding visual stimuli into high-fidelity images. Just as AI can be trained, OI could be taught to recognize and respond to specific environmental stimuli, potentially surpassing the performance of any modern computer. With the help of sensory units from organoids, OI may even be able to display decoded neural outputs on a digital screen, offering a novel way to understand complex biological processes. With the combined development of AI and OI, technology that leverages both systems could surpass the human brain as a superior information processing device. Hartung hopes "there will be a beneficial communication channel between AI and OI that would allow the two to explore each other's capabilities."

With the incorporation of both OI and brain organoids, there is tremendous potential to revolutionize the study of human neurological disease. Previous clinical trials for neurologic conditions such as Alzheimer's disease, autism, and schizophrenia have exhibited poor success rates, possibly attributed to the poor translation of research findings from animal models to human pathophysiology. Brain organoids, which are created by reprogramming a small sample of a patient's skin cells, offer a non-invasive method to test brain tissue without the need for extracting tissue from living specimens. Access to these recapitulated brains may allow for novel biomarker discovery using "omics" during initial disease stages, which could lead to innovative and personalized therapeutics.

Aside from examining the microscopic pathology, OI can be leveraged to understand specific cognitive dysfunctions and how to treat them. Dr. Hartung states, "We could compare

memory formation in organoids derived from healthy people and Alzheimer's patients and try to repair relative deficits. We could also use OI to test whether certain substances, such as pesticides, cause memory or learning problems." Organoid models replicate the induced stem cells of the host and can compare neurologic condition manifestations between patients. To ensure that cognitive improvement is observed, the patient's predictive organoid can help assess the efficacy of various treatments. Through new avenues for preclinical research, it is proposed that OI-based research models may serve as the first human-based preclinical models that can aid in understanding and developing treatments for a broad range of devastating neurological conditions.

Despite the expected benefit of this technology, there has been much controversy surrounding its ethics. A primary concern regarding organoids derived from stem cells is the notion that manipulating pluripotent cultures violates beliefs about how organisms are created. Along with creating these intelligent, human-like brains, some consider the possibility of organoids autonomously developing sentience, awareness, or pain perception. In this case, critics argue that highly intelligent animals such as chimpanzees and dolphins should not be tested, and such organoids should be granted a similar exemption. In the event that organoids were involved in such experiments, there would need to be a rigorous protocol with strict experimental regulations such as duration of treatment, organoid sense perception, boundaries, and proper disposal. Similarly to AI, OI carries ethical issues such as the possibility of being fed biased or harmful information as well as concerns regarding cost, privacy and data mining, equity among users, intellectual property protections, and disruption of human-occupied jobs. To overcome these relevant issues surrounding OI, researchers suggest performing a comprehensive ethical analysis that includes a review from diverse groups to foster responsibility, accountability, and

trust with the stakeholders. To ensure the successful integration of this technology, unmet limitations will need to be addressed first.

Currently, the main limitation of OI and brain organoids is the discrepancy in complexity compared to actual human brains. Today, brain organoids are below 500 micrometers in diameter and have less than 100,000 cells. These relatively non-complex models fail to show the developmental asymmetry nor the predictable anatomy that is needed to supplement preclinical trials of neurological conditions. As a result, decades of work will likely be necessary to develop organoids advanced enough to replace modern AI. Moreover, additional time is needed to develop the technology required for fully transmitting the computations of the organoid to a digital interface before it can practically convey clinically relevant information. Despite these hurdles, the proposition of OI "intelligence-in-a-dish" is an exciting new field that will surely attract more research. Complex brain organoids pose beneficial applications for understanding the development and treatment of neurological diseases. A long road of rigorous testing and embedded ethical mediation will be required before OI and brain organoids reach their potential. However, this emerging discipline offers a unique approach to integrating human organs into both biotechnology and medicine and will be exciting to follow in the coming years.

The authors have no conflicts to report