MAJOR ADVANCES IN MINI BRAIN BIOENGINEERING

1 BIOREACTORS

Maintaining organoids in culture allows them to mature and develop, but their growth and lifespan are limited because the larger they get the less access they have to nutrient diffusion, especially for cells in the inner core. Bioreactors—sterile vessels that gently stir contents, maintain temperature, pH, and oxygen levels, and disperse nutrients and biomolecular signals—help researchers control the environmental conditions of brain organoid cultures to maximize their size and lifespan. Researchers are exploring 3D printed and miniature bioreactors as application-specific, low cost, high-throughput, and reproducible alternatives to conventional bioreactors.[1,2]

2 MICROFLUIDICS

Microfluidic chips enable more precise fluid flow control to further optimize oxygen and nutrient exchange, and generate chemical gradients that guide cell differentiation and migration—addressing the limitation of large fluid volumes used to grow brain organoids in conventional bioreactors.[3] These chips can also accommodate complex, patterned co-cultures of various cell types—including nerve, blood vessel, and glial cells—using selective membranes and multiple chambers and channels, which simulate the structure and function of human brains and reduce heterogeneity between samples.[4,5] In doing so, researchers can create a cellular microenvironment that mimics different brain regions, the blood-brain barrier, and complex cell-cell interactions.

3 BIOMATERIALS

Researchers take advantage of a wide range of biological and synthetic biomaterials to mimic brain tissue's structure and molecular cues. For example, mini brains' growth and cellular patterning depends on the interaction of cells with extracellular matrix—a 3D biological network of molecules and minerals that supports tissue structure and provides biochemical cues to guide cell differentiation, migration, organization, and patterning.[6] Similarly, scaffolds made of synthetic polymers augment the extracellular environment of cultured stem cells to support 3D growth and organization.[7,8]

4 3D BIOPRINTING

3D bioprinting is a powerful method for mimicking the brain's tissue architecture with computer modeling and bioprinting technologies (e.g. inkjet, laser-assisted, extrusion-based, or stereolithography).[9] The ink used for bioprinting organoids contains stem cells plus various biomaterials such as extracellular matrix components that provide cells with appropriate biomolecular cues, architectural scaffolding, and mechanical support. Bioprinting mini brains enables researchers to control the spatial positioning of cell aggregates and ensure that the assembled tissue retains appropriate cell-cell interactions that mimic brain development.[10] Researchers also create structured scaffolds and patterned substrates to encourage stem cells to develop and interact within a topographical map.

5 MICROELECTRODES

As researchers develop increasingly complex brain organoids that exhibit advanced features such as rudimentary brainwaves and the ability to detect basic visual inputs, there is a growing need to characterize and monitor their neural activity. Researchers use specially designed microelectrode arrays—grids of tiny electrodes—to measure the electrical activity of 3D brain organoids.[11] Innovative 3D microelectrode arrays use flexible nanowires, novel materials, and unique customizable shapes to overcome the limitations of those traditionally used for 2D cultures by enabling simultaneous recordings across a 3D network, maximizing contact area, and minimizing physical disruption of the organoids.[12,13,14]

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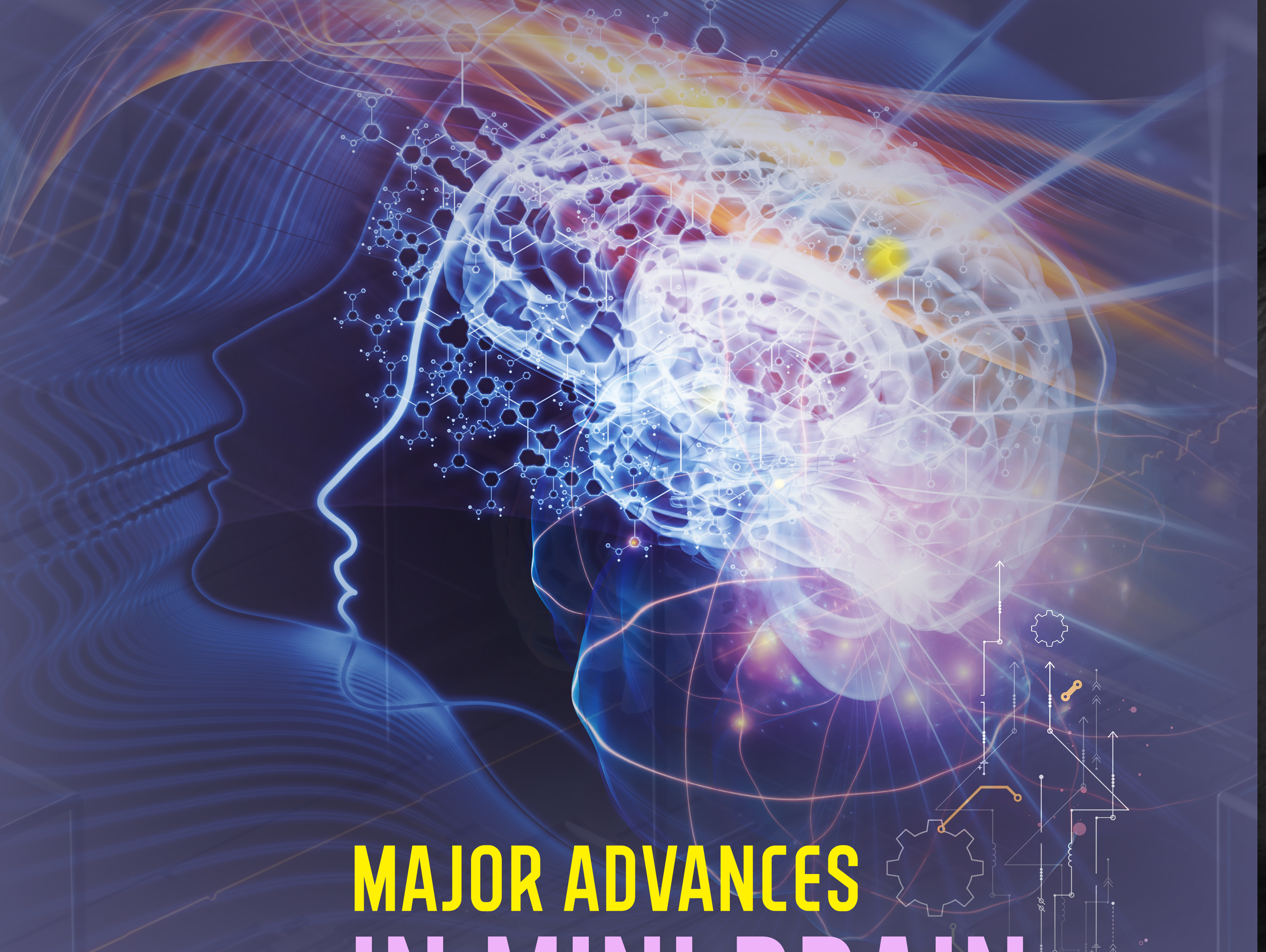

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