

A Novel Tissue Bioreactor for Retinal Organoid Microenvironmental Control

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Abstract

Purpose : *In vitro* culture systems generally apply homogeneous stimuli and rely on intercellular signaling to guide growth of tissues. However, to derive complex tissue structures such as the human retina, a gradation of certain stimuli is required. The inner retina resides in a hypoxic environment (2% O₂) adjacent to the vitreous cavity. From there, oxygenation levels rapidly increase towards the outer retina (18% O₂) at the choroid. Here we developed a novel tissue bioreactor allowing the maturation of inner and outer retinal cell phenotypes within an O₂ gradient.

Methods : The bioreactor is assembled from a 75x25x3 mm acrylic slide, a PFA film, a cover glass, and double-sided adhesives, which were adjusted with computer numerical control milling and laser cutting (Fig. 1A). The 60 culture wells of 2 mm in diameter and 0.7 mm high each hold one retinal organoid. A nitrogen (N₂) tank provides the bioreactor with 5 mL/min N₂ gas and a dual syringe pump creates a 5 µL/min continuous flow of culture medium through the bioreactor (Fig. 1B). Gas diffusion through the PFA membrane and culture medium was predicted using computational modeling software for atmosphere (20.9% O₂) and incubator (18.6% O₂) conditions. O₂ concentration measurements were performed with O₂ sensors along the z-axis in 50 µm steps in atmospheric conditions.

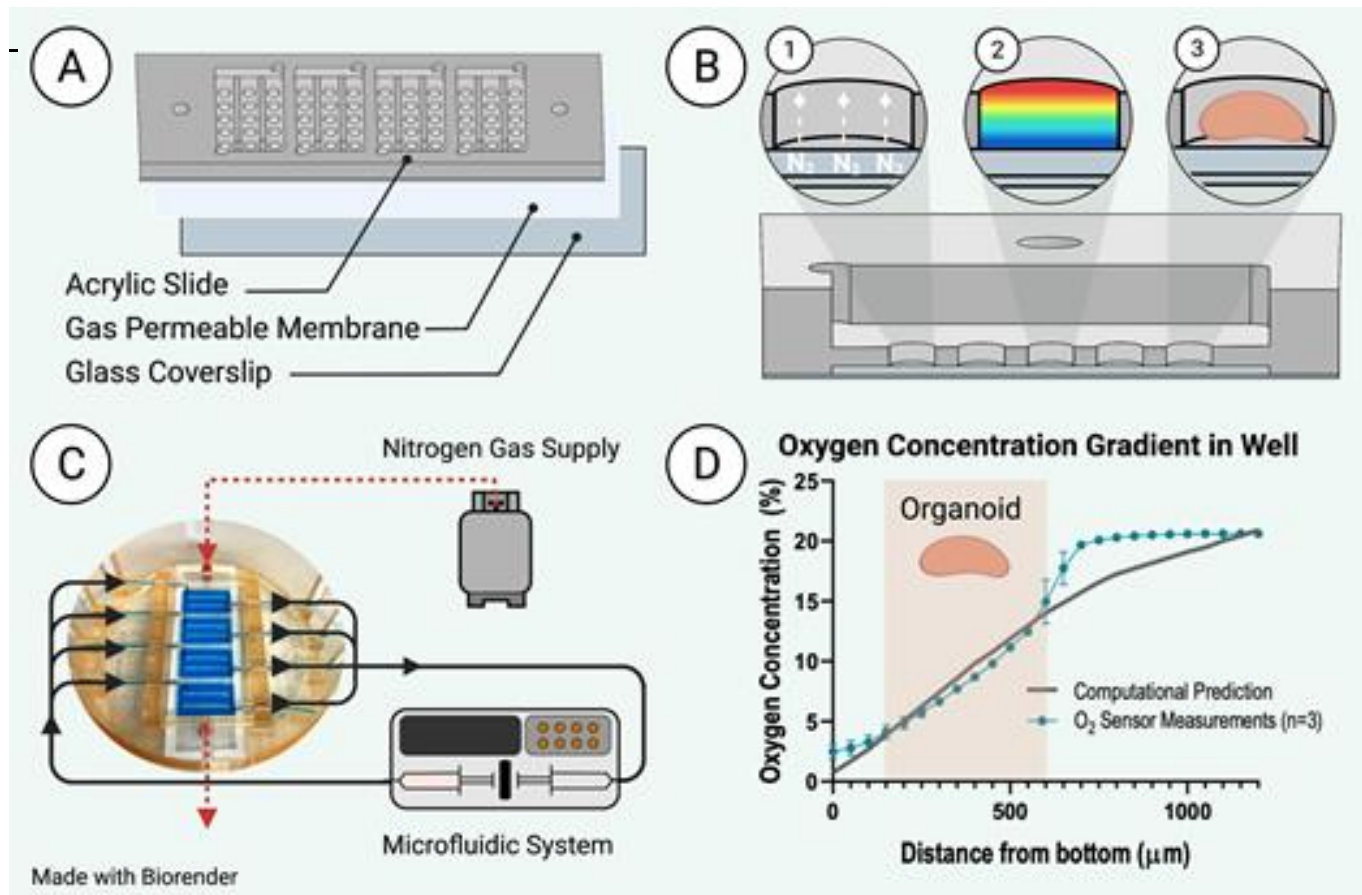
Results : The gas diffusion throughout the culture medium resulted in an O₂ concentration gradient along the z-axis (Fig 1C). The computational predictions in atmospheric conditions are in accordance with the measurements around the retinal organoid location in the bioreactor (Fig. 1D).

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Conclusions : This open-well bioreactor is easily accessible for downstream analysis, establishes a steep O_2 gradient and allows high-throughput retinal organoid culture. It will help retinal organoids mature into the complex structure to use them for disease modeling and drug testing.

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(A) The bioreactor is fabricated from three main components. (B) The culture system provides the bioreactor continuously with fresh culture medium and N_2 gas flow. (C) The cross section of the bioreactor shows (1) the N_2 chamber under the cell culture wells where N_2 diffuses upwards (2) to create an O_2 concentration gradient (3) which is used for retinal organoid culture. (D) The computational O_2 predictions throughout the culture medium compared to O_2 sensor measurements in room air condition.

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