# CLASSIFICATION OF BRAIN-ON-CHIP MICROSYSTEMS

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**Introduction.** For a long period of time, 2D and 3D cultures, model animals have been used for experiments, but in recent years, organ-on-chip (OoC) technology has become more popular and it is rapidly gaining significant research attention (figure 1). The combination of the "laboratory-on-chip" with the methods of cell biology moderates the research methods and makes it possible to design physiological processes of the human body on models of multicellular human organs in vitro [1].

The aim of this article is to overview the most interesting and important OoCs, which recreate brain structures, the progress of creating those chips and their classification.

**Materials and methods.** Analytical overview of the latest articles and basic literature on the topics: organ-on-chip and brain-on-chip (BoC), their classification and latest innovations.

**Results and discussion.** OoC in general, and BoC in particular, is a multi-channel (tens or hundreds of microns in size) three-dimensional microfluidic in vitro platform that allows to model tissues, organs, their systems, replacing a living organism with a model. The reaction chambers of the device are filled with living cells, which are connected through the membranes and placed on opposite sides to simulate real organs.

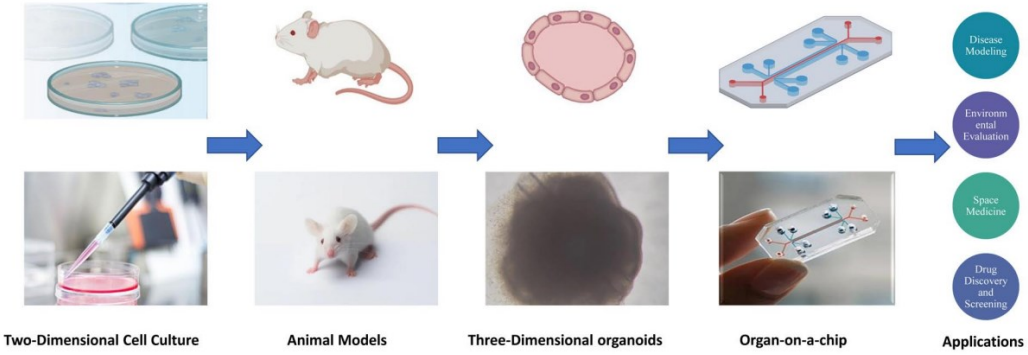


**Fig. 1. The experimental models' evolution [2].**

OoC can be useful for studying pathophysiological reactions, modeling the interactions of cells with metabolites, gases with circulating cells [3], the effect of various drugs on organs and tissues and determining their effectiveness or harness.

As the technology is quite young, there is no basic classification of BoCs, however, they can still be divided into categories depending on their design and functional purpose (figure 2).

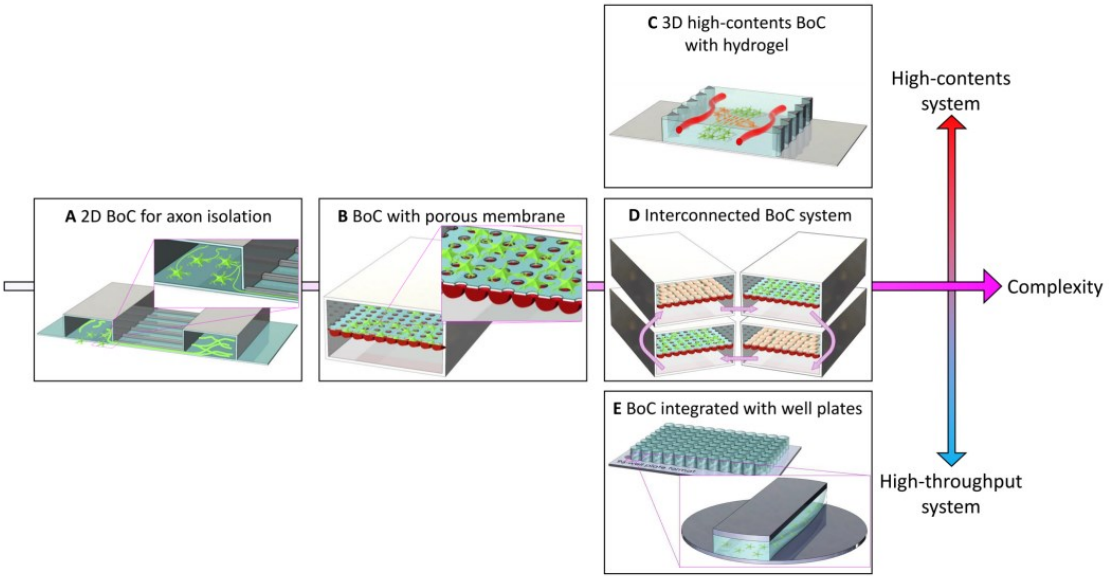


**Fig. 2. a - A 2D BoC for axon isolation; b - A BoC with porous membrane; c - A 3D high-content BoC with hydrogel; d - An interconnected multichip system; e - A BoC integrated with well plate [4]**

First group is 2D BoC for axon isolation. Within the single chip different height microchannels are created, which allows to separate neuron's axon and soma, so that only the axon can pass through the channels. It allows scientists to lead axon-specific drug testing, their regeneration after axotomy [5], growth [6] of the axon and their myelination.

The second group can be characterized by sandwiched between two microchannels porous membrane and various cells that are attached on different sides of it. It allows two different types of cells to communicate through the pores of membrane which creates a great possibility to study cell–cell communication or measure of transendothelial electrical resistance of blood-brain barrier (BBB) [7].

Third type of chips is able to mimic the brain tissue with different cell types and create in vivo-like microenvironment for the research of 3D neural circuit formation and key structures, such as the BBB and neurovascular units, neurons and their axodendritic synapses, and the additional role of oligodendrocytes, astrocytes and microglia [8]. Further development of hydrogels and recognition of in vitro models of BBB-on-chip based on hydrogel by regulatory and industrial authorities can lead to a shortened screening and help in the further development of the brain tumors.

The interconnected BoC system were developed to recreate interactions between various neural cells and look closer into changes in the metabolism of neurovascular unit. Moreover, this system is able to simulate the communication of various BoCs, which allows to link the brain to the liver, heart, kidneys and analyze the reaction of organs to different drugs. For example, Miller and Shuler [9] developed a system that represents 13 main parenchymal organs, including brain, and physiological barrier tissues.

And last but not least, BoC integrated with well plate is a fifth group that is created for high-throughput analysis and is compatible with conventional labwares. Merging of a traditional platform with a BoC can give us the ability to perform a high-throughput

quantification of cell responses [10]. For example, scientists were able to show the ability of the brain cancer chip to culture tumor-derived human GBM cells in microwells and tested the effectiveness of clinically used drugs (TMZ and BEV) for the treatment of tumors [11].

**Conclusion.** However, despite a great progress in this field of science, there are still certain disadvantages of these systems that should be improved in next enhancements. One of the typical issues is the materials selection for the creation of chips, which is difficult due to the need for high biocompatibility, the complexity of structure, manufacturing (in particular, for widespread usage in laboratories) and maintaining adequate prices or reuse possibility for commercial distribution. In addition, when creating BoC systems, it is important to correctly scale organelles in accordance with their human sizes, which is achieved with the help of mathematical modeling of microfluidic elements (channels/capillaries, vessels, circulatory systems and this aspect also needs to be improved. Moreover, attractive systems that combine many organs or parts of the brain itself also have their drawbacks, for example, the more parts they combine, the less sensitive the design becomes and the greater the risk of obtaining unreadable and inaccurate results is.

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