Development of an automatic, modularized and multiplexed heart-on-a-chip platform

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Abstract

Organ-on-a-chips (OoCs) are newly developed cell **culture microfluidic platforms. Cells in OoCs showcased more real tissue-like behaviors, due to** stimulations and dynamic controls, such as geometry confinements, physical enviroments, and chemical stimulations. Although OoCs are able to provide more information about real tissue, there is still a huge barrier of technical and background knowledge for end-user to operate them. In this project, I plan to develop a novel 3D cell culturing design and establish a highly integrated OoC platform to address the challenge. This platform can be divided into several parts: specialized cell culture units, fluid circuit broad (FCB), and integrated sensor arrays. The cell culture units with functional microstructures allows application of additional pressure and deformation, which are considered influential for physical stimulation-sensitive tissues (engineered heart tissue (EHT) in this case). The FCB for liquid perfusion and pressure control will be integrated with multiple micro valves and pumps, which can be actuated by programs automatically. The sensor array will be able to allow us to monitor cytokine expressed by EHTs in real time, helping us to understanding cell response to stimulations and environmental changes.

Introduction

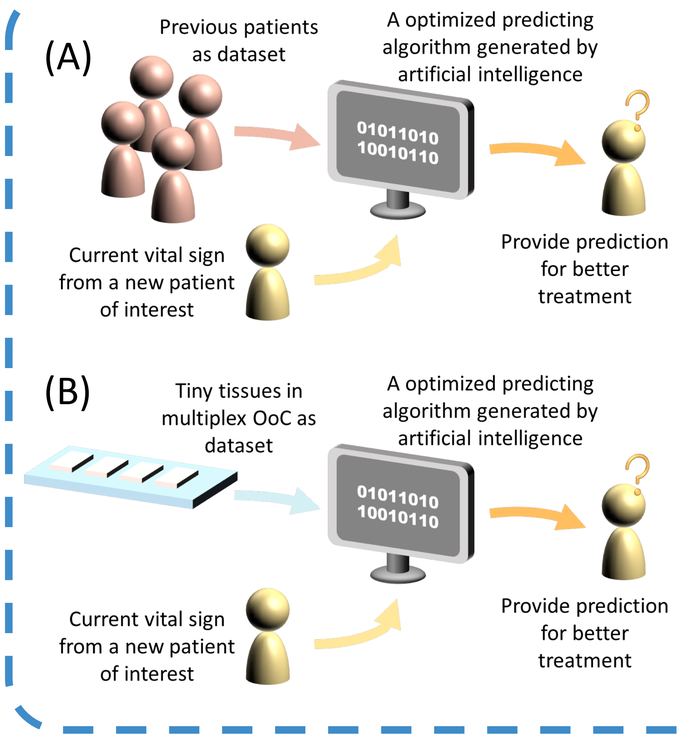


Figure 1: The importance of multiplex Organ-on-a-Chips.
As artificial intelligence has developed, researchers start to focus on the application to predict physical condition of patients. However, the accuracy is dependent on the size of the dataset, which is limited by the patient population. Besides, there are tissue responces difficult to observe from real patients. With multiplex Organ-on-a-Chip systems, we might be allowed to acquire more information to improve the decision by doctors.

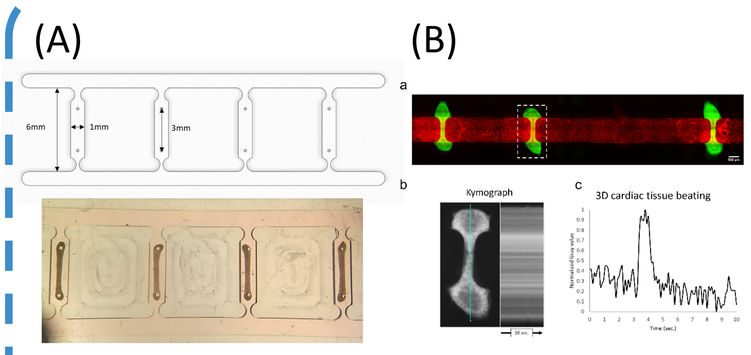


Figure 2: Current setups for 3D EHTs.
The figure shows current EHT-on-chip platforms, 3D EHTs were cultured in chambers with flexible pillars and in dumbbell-shaped chambers. After seeding, the cardiomyocytes spontaneously aggregated and formed compact tissues in the confined regions. However, both of these two systems mainly relied on low-throughout and time-consuming human operations. Besides, it is difficult to record responses of EHTs in real time.

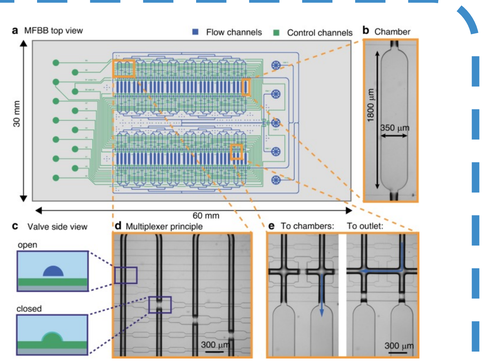
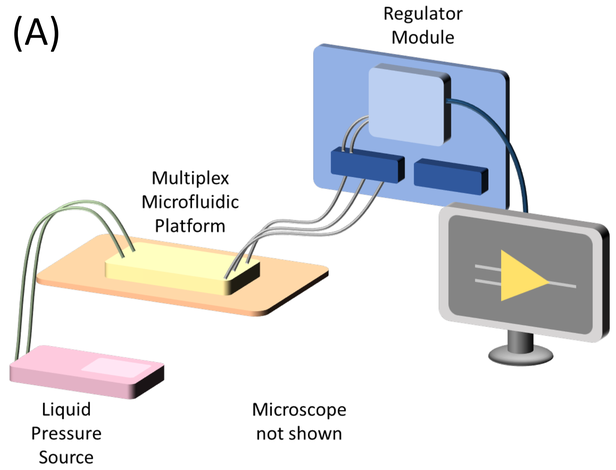
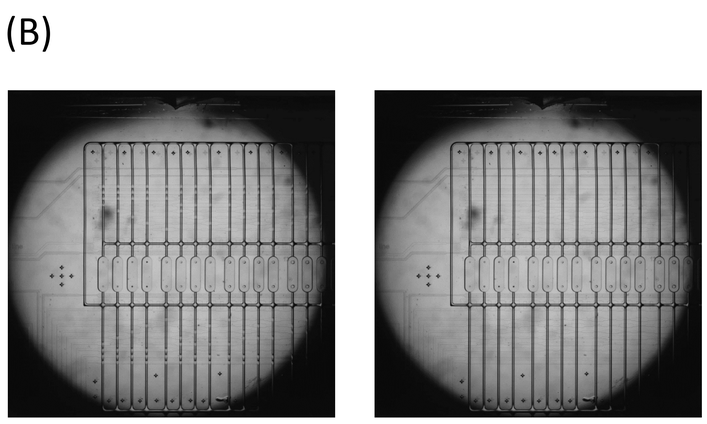


Figure 3: Multiplex and automatic platform for 2D cell culture.
Recently, researchers have developed a multiplex and automatic platform for 2D cardiomyocyte culturing with a high throughput. The network of the microfluidic elements helped selective introdution of stimuli of chemicals and cytokines.

New strategy





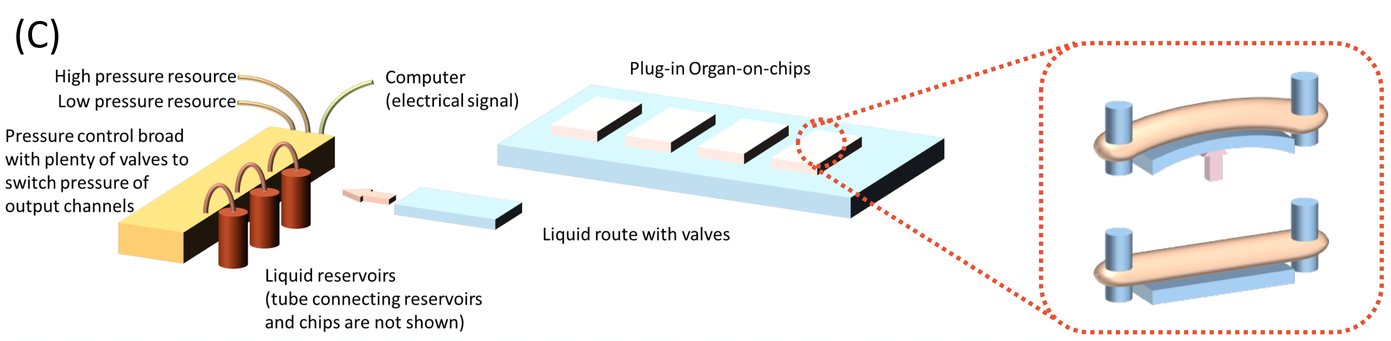


Figure 4: Overview of setup.
(A), the layout of the first generation of micro-EHT multiplex platform is shown. A microfluidic chip is connected to multiple pressure regulators to control the flow of fluids. The system is automatically executed based on a program.
(B) depicted the exact operations of a combination of peumatic microvalves. The demo chip was composed by two layers of PDMS. The top one was for channels (vertical lines) and culturing chambers. The bottom layers was for valves (horizontal lines). The interections of channels and valves were the places where the valves functioned. Pressure was applied to the channels in the left figure, making the valve deforming and blocking the channes, while the pressure was released in the right figure, so that the channels were reconnected.
(C) illustrated the overview of the modularized platform, which consists of a central pressure control broad, liquid reservoirs, a plug-and-play disposible microfluidic route and multiple tissue culturing chips.

Next steps

- To test and to optimize the 1st generation multiplex 3D micro-EHT chips
- To massively replicate and to introduce cytokines of interest
- To design the 2nd generation chip (with mechanical stimulations)
- To develop the modularized platform

References

Vivas, A. *et al*. (2022). *Lab on a Chip*, *22*(6), 1231-1243.
Vollertsen, A. R. *et al*. (2020). *Microsystems & nanoengineering*, *6*(1), 1-16.

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