Microwell Plate Integrated Microfluidics for Cell-Cell Interaction Screening

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Microfluidics improve control over the environments used in chemical synthesis, cell culture, and other biochemical assays, but these advantages can be offset by the complexity of the setup and control systems required. Experiments require many tubing connections to link each microfluidic inlet and outlet to a number of syringe pumps or liquid pressurized reservoirs. Inherently, these have multiple connection points that can leak or trap bubbles, compromising the experiment. In contrast, an ecosystem of fluid handling and imaging systems has developed around the use of microwell plates. These tools have made microwell plates a staple of any biology lab, and integrating microfluidics to this preexisting landscape encourages broader adoption of microfluidics by biologists. Joining microfluidics with the microwell plate removes the liquid tubing and many of the connection points required to carry out microfluidic experiments, while the refined architecture of the microfluidics can provide additional levels of control in an experiment. Control systems designed around well plate microfluidics are being developed commercially, providing further motivation for the integration of microfluidics and microwell plates.

The system described here integrates a custom microfluidic device onto the bottom of a commercial microwell plate. A four-chamber culture device with a nanoporous barrier between the chambers was integrated to the microwell plate for extended growth and interaction studies. This design was previously shown to physically isolate bacterial cells within a culture chamber while allowing nutrients to diffuse into the chamber[1]. *Figure 1* shows that adding an additional chamber allows spatially adjacent bacterial communities to communicate with one another chemically, without being in physical contact. The culture device is used to screen for interactions and dependencies between members of the oral microbiome. Fabrication was done using well-established soft lithography processes to construct a mold with the inlets and outlets aligned with a 48-well plate layout. *Figure **2*** shows the device design from the culture chamber, to the fluidic network, to the well plate. The resulting devices allow for 12 viewing areas and 48 addressable wells that can be routed together in any configuration.

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[1] P.G. Shankles, A.C. Timm, M.J. Doktycz, and S.T. Retterer, J. Vac. Sci. Technol. B, Nanotechnol. Microelectron. Mater. Process. Meas. Phenom. **33**, 06FM03 (2015).

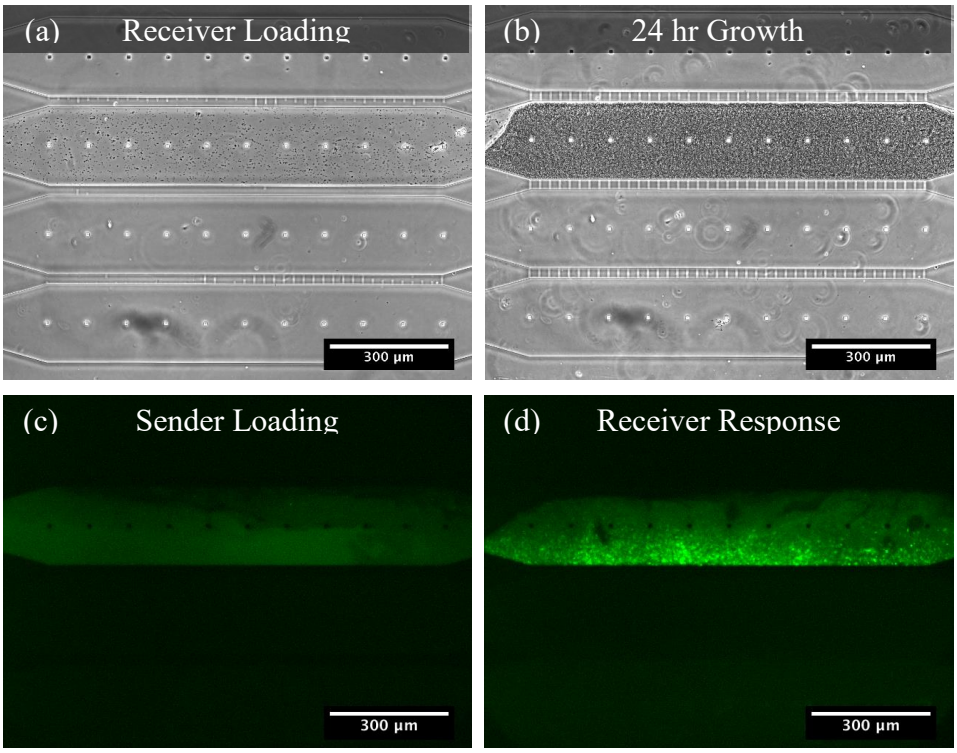

Figure 1 - (a-b) Receiver cells are loaded into the culture chamber and grown for 24 hours. (c-d) Sender cells are then loaded into the adjacent chamber and a response is seen over the following 24hrs.

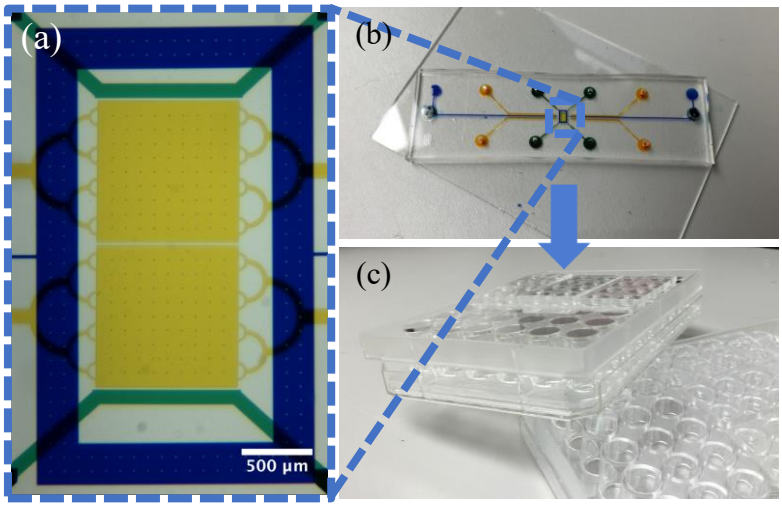

Figure 2 – (a) Two culture chambers and two support channels have a gas diffusion layer on top. (b) The inlets and outlets are designed to align with the wells of a microwell plate. (c) The device is bonded to the microwell plate using silicone.