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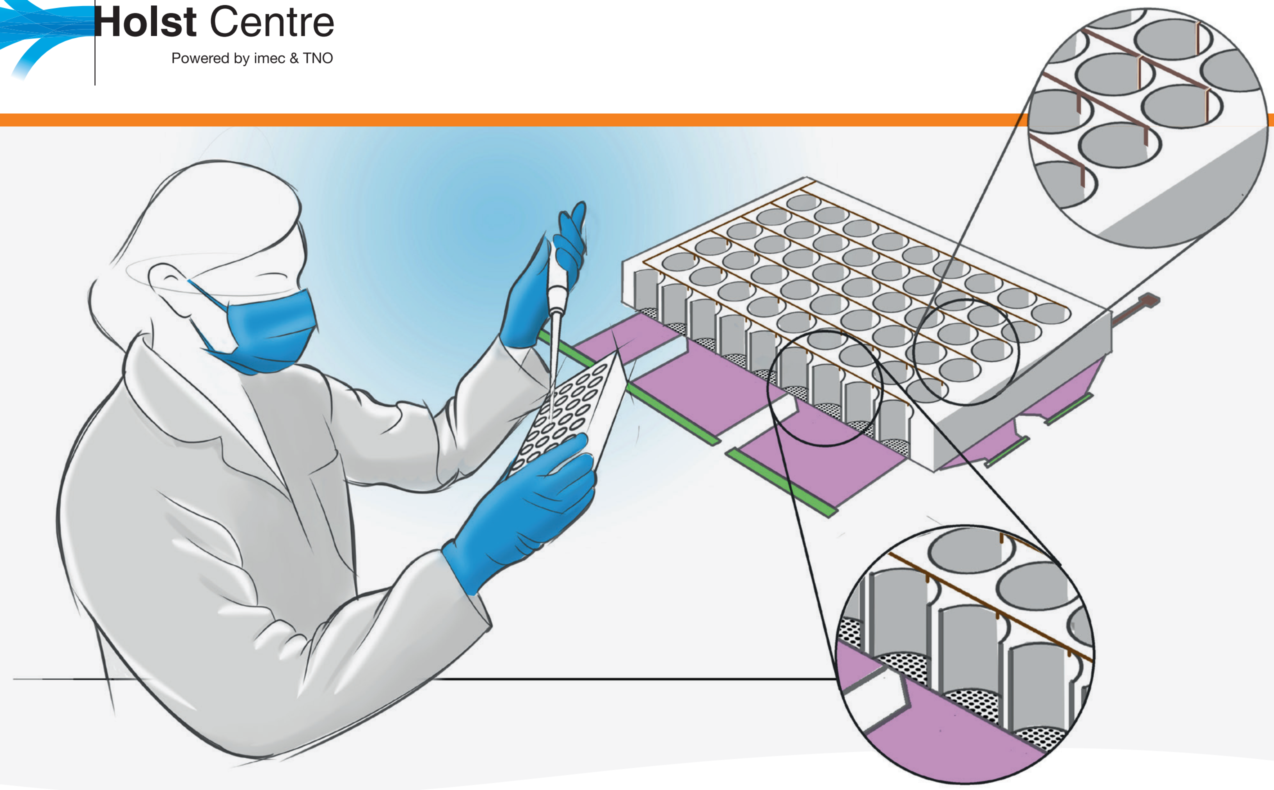

WHITE PAPER

Integrating Electronics in Organ on Chip: *can adoption be accelerated?*

Integrating electronics with organ-on-chip-related technologies can assist in the development of better medicines, such as those for neurodegenerative and cardiovascular diseases. Holst Centre looks to contribute its flexible electronics and manufacturing expertise to the ecosystem.

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Organ on Chip & Electronics: a quick review

Over the past decade, organ on chip (OoC) technology has become prominent in the world of drug development, with the first wave of OoCs already on the market. The second wave is expected to integrate electronics and sensors [1] and further impact the $7.8 billion preclinical research market [2]. With the integration of electronics, OoC-related technologies can assist in developing better medicines, such as those for neurodegenerative and cardiovascular diseases*, with brain and heart on chip devices. Involvement of all stakeholders is essential to realize the full potential of OoC-related devices, to which Holst Centre looks to contribute its flexible electronics and manufacturing expertise. This paper will touch on the industry's viewpoint, regarding the integration of electronics within in vitro devices, as well as the progress TNO at Holst Centre has made in creating solutions in this application domain.

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* It has been predicted that the market for neurodegenerative and cardiovascular medicines will reach $63 and $64 billion USD, respectively, by 2026 [3], [4].

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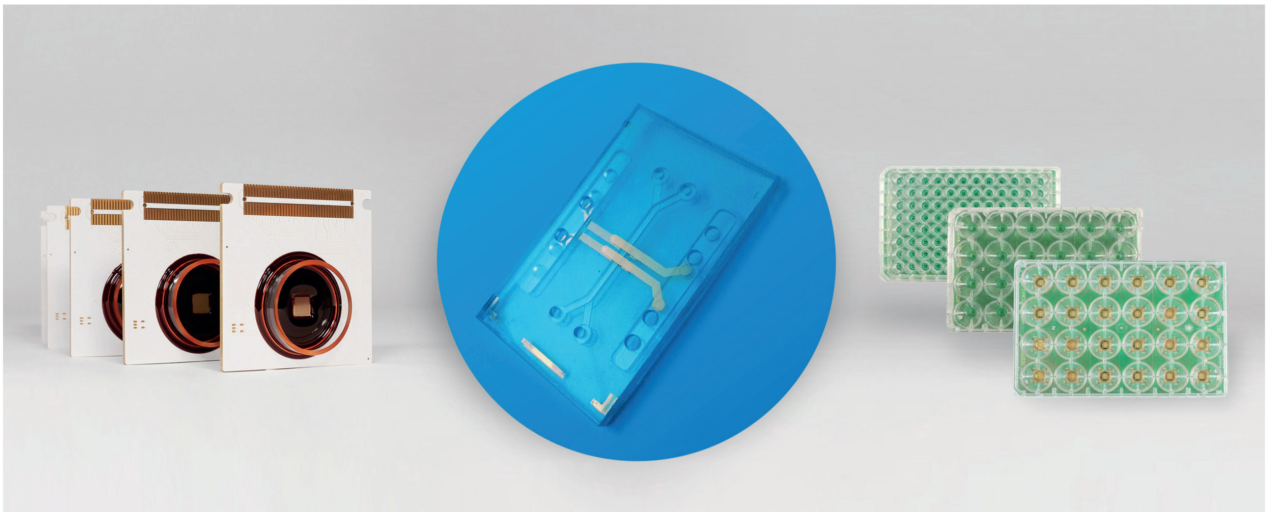


FIGURE 1 – OoC with integrated electronics, and related products with similar functionality. Left. 3Brain's high-density multielectrode array single wells. Right. Multi-electrode array multiwell plate from Multichannel Systems. Centre. OoC prototype with integrated TEER sensors from the Wyss Institute at Harvard University.

Integrating Electronics In OoC: why it's important, now

OoC may be new to Holst Centre, but it definitely isn't new to Holst Centre's founding partner, TNO. As stated in TNO's 2016 white paper on the topic, OoC technology holds promise to reduce animal testing and establish more efficient drug-discovery processes [5]. The technology may also prove useful for nutritional, diagnostic, cosmetic, chemical and environmental industries. Within the realm of pharmaceutical research, more human-specific compounds* are being developed. This means that traditional preclinical models, such as murine and other animal models, are not suitable for use with these compounds. Human cells must be used to test, validate and regulate said compounds; therefore, new tools are needed. Organoid, organ and lab on chip, and other in vitro devices, like smart multiwell plates (microplates), can close the gap between the findings of preclinical and clinical studies. There is an increased need for such devices as human-specific compounds become commonplace in the pharmaceutical world. Pharmaceutical companies are already working alongside regulatory agencies, to establish a bigger role for in vitro technologies in validation, safety and toxicology processes. Collaborations are also in place between OoC manufacturers and pharmaceutical companies, where both sides see an integral role for in vitro devices in the coming years [6], [7].

A Recipe for Adoption: what's important for the industry?

In order to reduce the time to adoption for OoC-related devices, it is of utmost importance to keep research workflows at the top of mind, and ensure certain design regulations and specifications are adhered to. Better alignment with existing clinical and pharmaceutical workflows will allow for testing, feedback, and adoption at earlier stages in the development of an in vitro device. Abiding by the SBS standardized footprint for multiwell plates, as well as other specifications, allow for new devices to integrate with the existing tools in a cell-related research laboratory. Additional sensors or electronics included in in vitro devices, should comply with existing technology within the laboratory. It is also likely that the involvement and use of OoC-related devices will introduce new techniques, approaches, and thus standards, that do not currently exist in the field.

* Human-specific compound: a highly species-specific drug candidate or medicine that cannot be tested on animal models (in vivo or in vitro) due to a lack of relevant human receptors, or otherwise, and can thus only be tested with human cells during experiments for all, or parts of, the development and drug-approval process.

Standardization comes as a result of solidified workflows, preexisting within the related research fields, and will also be important amongst OoC and smart-multiwell-plate manufacturers when reaching larger production volumes. This is not only true from a manufacturing perspective, as costs will decrease as repeatable, manufacturing standards are put into place, but also from the perspective of user adoption as the devices become more compatible and user friendly due to similar form factors. An interesting point to note, with respect to manufacturing, is that preclinical research has less stringent manufacturing regulations than further stages of the clinical-trial process. Therefore, medical-grade, good-manufacturing-practice (GMP) processes are not necessary when developing in vitro devices for preclinical purposes.

There are a few frontrunners with products currently on the market, that include integrated electronics. These products include wellplate-compatible TEER accessories, integrated multielectrode arrays (MEA) for stimulation and measurement, as well as others; some examples of these products can be seen in Figure 1. If categorized based on three main attributes: multiwell format, containing microfluidics, and possessing integrated electrodes, most devices would include two of three attributes, but no device has yet to integrate all three attributes within the device itself. Holst Centre would like to help the pioneers creating these products take the next step, in order to fabricate OoC-related devices using industry-proven manufacturing techniques from the world of flexible, printed circuit boards and displays. The field would benefit from economies of scale, and an institute familiar with the scale up of R&D to higher technology-readiness levels (TRL). TNO Unit, Healthy Living, can support in validation procedures with their extensive cell culture, biology, and OoC expertise.

Creating Solutions: what can Holst Centre offer?

Additional functionality, integrated into OoC-related devices, is now sought after to improve the experimental results and capabilities of in vitro devices [8], [9]. Customers are interested in the additional data points further functionality will provide, and are willing to pay for them—to a certain extent. The price point should not significantly increase beyond the 200€ – 500€ cost of a wellplate, today, which still gives ample room for the inclusion of electronics. Electrodes that stimulate and measure cell signals during experiments, would increase the quality of the experiments and the ability to recapitulate certain organs more accurately. Integrating small sensors that can measure temperature, pH, humidity, the sensing of specific molecules (glucose, lactate, etc.) and others noted in Figure 2, reliably over long periods of time, would allow for measurements to be taken during experiments with less inhibition. This would also provide continuous feedback and reduction of error-prone, time-dependent measurements.

FIGURE 2 – Important sensors and functionalities for inclusion in the next wave of OoC-related products. Larger circles represent sensors in higher demand within the field.

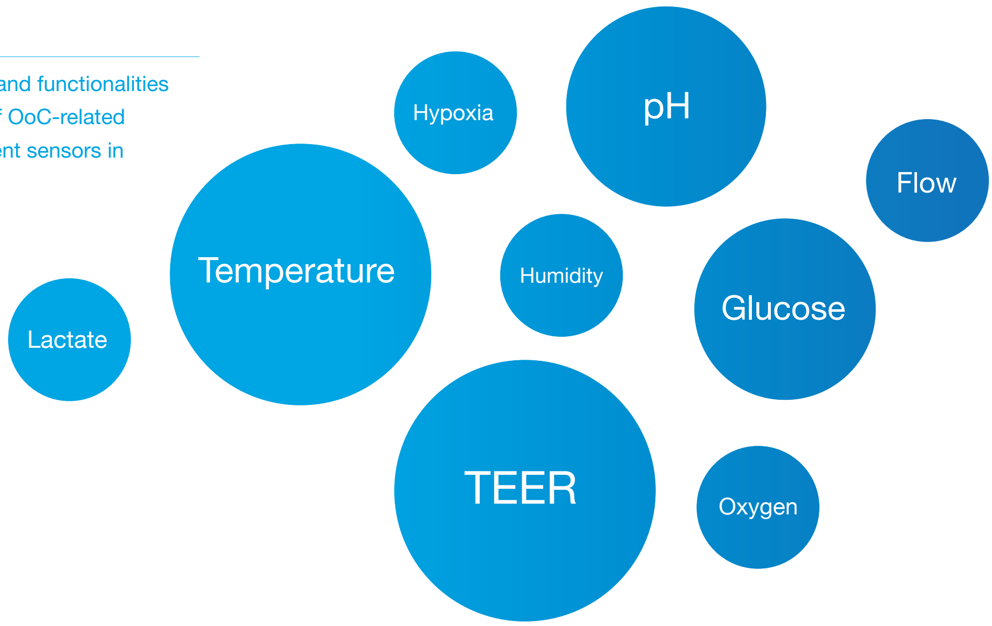
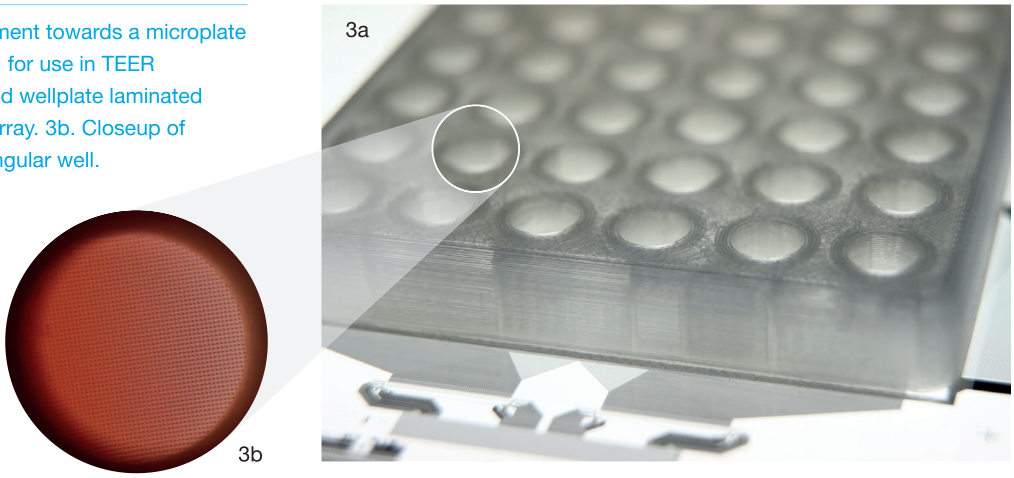


FIGURE 3 – Initial development towards a microplate with integrated electrodes, for use in TEER applications. 3a. 3D-printed wellplate laminated atop a 200 ppi electrode array. 3b. Closeup of electrode array within a singular well.



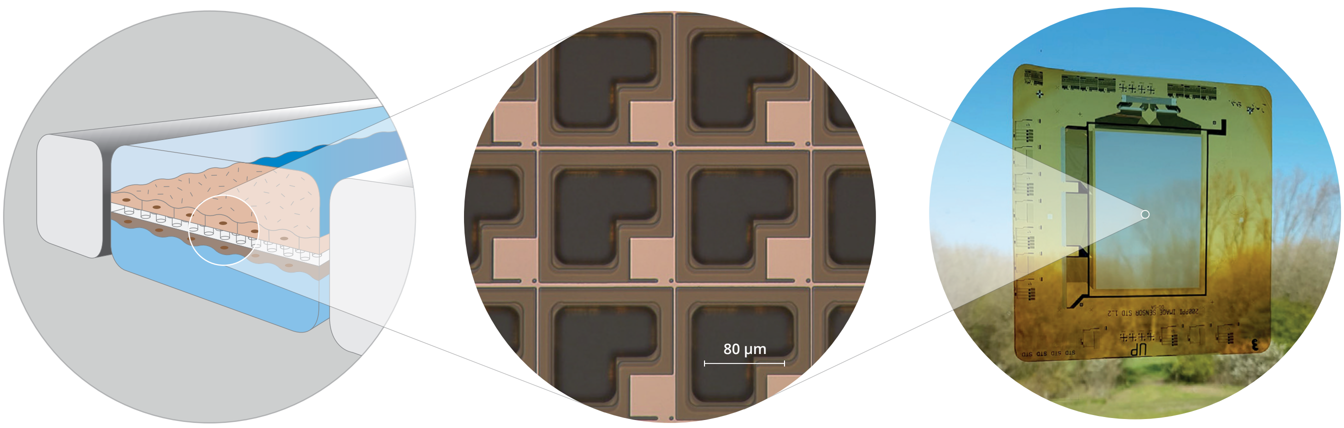
Don’t Shed a TEER: integrating electrodes within an OoC platform

In the realm of OoC, Holst Centre is working towards the acceleration of drug screening with the development of autonomous, connected OoC platforms and has begun to develop a number of technologies. One of the first steps, is an integrated transepithelial electrical resistance (TEER) device. Traditionally, TEER measurements are carried out using chopstick electrodes [10], dipped into medium on both sides of a Transwell® insert or other form of membrane. Holst Centre is exploring the use of thin-film electrodes, spatially dispersed over large area on ultrathin substrates, for use in TEER applications. Holst Centre’s initial development towards a smart wellplate with integrated TEER electronics is shown in Figure 3. The included MEA can also be manufactured optically transparent, retaining the ability to perform optical readouts and measurements with standardized laboratory equipment. Regardless of the implementation method, the desired result is unique in-well TEER measurements continuously provided throughout an experiment.

Diffusion for the Win: unobstructed flow with continuous measurements

Many OoC experiments involve diffusion through a cell or tissue layer—the layer is often supported with a membrane of some kind. Holst Centre has developed a transparent, flexible, active-matrix mesh-electrode array, which would allow for the diffusion of molecules to be unobstructed by the array. The semi-permeable, membrane-like structures with active-matrix electronics were designed to reduce surface area. The electrode

FIGURE 4 – Right and center images show Holst Centre’s active-matrix mesh-electrode (AMME) array. The AMME array could be utilized within membranes of an OoC device as the voids between electrode pixels allow for diffusion of molecules through the membrane, as suggested in the illustration of the left image.



arrays possess sensor pixels at specific positions, while voids between pixels allow for full permeability of molecules and culture medium between the sensors (with a pore size of ≈ 10 μm). A photograph and micrograph of the mesh electrode is provided in Figure 4. The mesh electrode array could therefore be utilized within a membrane layer, to obtain measurements and readings, while allowing the diffusion of molecules and chemical messengers to occur naturally. The use of membranes is currently an essential piece of the OoC puzzle, and further functionalizing them while reducing their influence on the culture, will improve the capabilities of such devices as a whole. As the mesh electrode arrays are also optically transparent, they will not disturb any inspection required via microscopy.

Integrating the Possibilities

Additional sensors, such as temperature, are also sought after for cell-culture experiments—as previously seen in Figure 2. Flexible and stretchable Holst Centre sensors, could be utilized within this context [11]. Whether incorporated into a flexible membrane or moulded onto a plastic substrate, this would provide unique, in-well temperature measurement rather than relying on the thermostat of an incubator. Increasing the precision and capabilities of in vitro devices and cell-culture setups, will provide increased insight regarding the state of cells in culture and thus more merit for further use of these items in a regulatory context.

The Take-Home Message

If the integration of electronic functionality in OoC-related devices is to achieve its full potential, continued collaboration is essential, between both industry and academia, specifically pertaining to the realm of preclinical research and device developers. Additional electrical components should not interfere with current research workflows and should instead align with current conventions. Manufacturing routes should be selected based on their potential to be upscaled cost effectively. Holst Centre looks to contribute expertise in the domain of flexible electronics and manufacturing to the OoC ecosystem, while also utilizing the vast realm of OoC knowledge within the Netherlands. This will also require the involvement of multiple stakeholders such as OoC companies, electronics and sensor technology enterprises, institutes such as hDMT and EUROoCS (both of which TNO is a member), pharmaceutical companies, and preclinical research organizations. Holst Centre can play a crucial role, as an internationally-renowned independent research institute, in bringing these various stakeholders together.

INFORMATION

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REFERENCES

* The contents and insights of this report come from interviews and conversations with pharmaceutical companies, clinical research organizations, device manufacturers, research institutes and other industry and academic experts in the field, as well as internal findings within TNO

[1] U. Marx et al., "Biology-inspired microphysiological systems to advance patient benefit and animal welfare in drug development," ALTEX, Feb. 2020.

[2] "Preclinical CRO Market Size, Share & Trends Analysis Report By Services (Bioanalysis & DMPK Studies, Toxicology Testing), By End Use (Biopharmaceutical Companies, Medical Device Companies), And Segment Forecasts, 2020 – 2027," Grand View Research, Mar. 2020.

[3] "Neurodegenerative Diseases Drugs Market Size, Share and Industry Analysis By Drug Class, By Disease Indication, By Route of Administration, By End User and Regional Forecast 2019-2026," Fortune Business Insights, Jun. 2019.

[4] "Cardiovascular Drugs Market Size, Share & Industry Analysis, By Drug Type, By Disease Indication, By Distribution Channel, and Regional Forecast, 2019-2026," Fortune Business Insights, Nov. 2019.

[5] G. Grootaers et al., "THE 3 DIMENSIONS OF ORGAN- ON-A-CHIP," TNO, The Netherlands, Oct. 2016.

[6] M. Mastrangeli, S. Millet, T. ORCHID partners, and J. van den Eijnden-van Raaij, "Organ-on-chip in development: Towards a roadmap for organs-on-chip", ALTEX, vol. 36, no. 4, pp. 650-668, Oct. 2019.

[7] D. Huh, G. A. Hamilton, D. E. Ingber, "From 3D cell culture to organs-on-chips," Trends in Cell Biology, vol. 21, no. 12, pp. 745-754, Dec. 2011.

[8] L. M. Griep, F. Wolbers, B. de Wagenaar, et al., "BBB ON CHIP: microfluidic platform to mechanically and biochemically modulate blood-brain barrier function," Biomed Microdevices, vol. 15, pp. 145–150, Sept. 2012.

[9] O. Y. F. Henry et al., "Organs-on-chips with integrated electrodes for trans-epithelial electrical resistance (TEER) measurements of human epithelial barrier function," Lab Chip, vol. 17, pp. 2264-2271, May 2017.

[10] K. Benson et al., "Impedance-based cell monitoring: barrier properties and beyond," Fluids Barriers CNS, vol. 10, no. 5, Jan. 2013.

[11] Hybrid Printed Electronics, Holst Centre. Accessed on: May 2020. [Online]. Available: https://www.holstcentre.com/technologies/hybrid-printed-electronics/

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