

Full-Hydrogel-based Real-Time Sensor and Drug Deliverer in Organ-on-Chip Devices

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Summary:

Integrating sensors into Organ-on-Chip devices is a crucial step toward fully exploiting these powerful platforms for biomedical research, especially in drug development. In this work, we used a custom stereolithography setup to embed hydrogels within a low-cost thermoplastic Organ-on-Chip. These micrometric hydrogels could absorb the drug, permitting a controlled release during the experiment. Moreover, the absorbed drugs acquired intrinsic fluorescence, which was exploited to train a machine learning algorithm, enabling quantitative tracking of absorption and release during the experiment.

Keywords: Hydrogel Sensor, Organ-on-Chip, Continuous Monitoring, Drug Delivery, Machine Learning

Background, Motivation and Objective

In recent years, the introduction of Organ-on-Chip technology into biomedical research has enabled this field to make significant strides [1]. These devices enable the replication of tissue and organ functions at the micrometric scale, allowing a deeper understanding of their biological mechanisms in a more realistic environment than in classical culture dishes. Moreover, in the context of a personalised medicine paradigm, it is crucial to understand the response of a patient's specific pathological tissue to a specific drug treatment.

However, obtaining useful information locally from the biological entity can be challenging, especially when done in real time [2]. In fact, continuous monitoring is crucial for a complete understanding of the dynamics of a certain phenomenon.

However, data coming from these real-time sensors can be difficult to interpret straightforwardly and to manipulate while maintaining the continuous monitoring paradigm. In this context, machine learning algorithms have proven their power by generating data-driven models that can correlate sensor inputs with known outputs. This initial information can subsequently be used during the dynamic monitoring of the biological entity in the Organ-on-Chip [3].

In this work, we present a technique for integrating hydrogel sensors using a custom stereolithographic approach. These hydrogels can absorb a drug or a combination of drugs and subsequently release them during the biological experiment. Using fluorescence imaging and a custom machine learning model based on hydrogel geometric features, we tracked in real time the evolution of this absorption/release process. In the meantime, we monitored the biological entity using brightfield microscopy.

We validated this technique by locally measuring the concentrations of doxorubicin and curcumin during a dynamic microfluidic experiment, revealing distinct absorption/desorption profiles for the drugs. We believe this technique will be extremely useful for local drug delivery and sensing in Organ-on-Chip experiments, especially to study personalised therapies for prostate cancer patients, where this drug combination could be more effective [4].

Methods

The Organ-on-Chip were laser-cut from Poly Methyl Methacrylate and Cyclic Olefin Polymer slabs using a Trotec Speedy 100 and adhered together using a biocompatible adhesive.

The Organ-on-Chip chambers were then filled with a prepolymer formulation consisting of Poly(ethylene glycol) diacrylate (PEGDA) and the LAP photoinitiator. A custom stereolithographic setup, obtained by mounting a commercial projector (E4500MKII, EKB Technologies Ltd) on the infinity port of an inverted microscope (Leica Dmi8), permitted the patterning of UV light on the surface of the Chip and locally generated the hydrogel (see Fig.1).

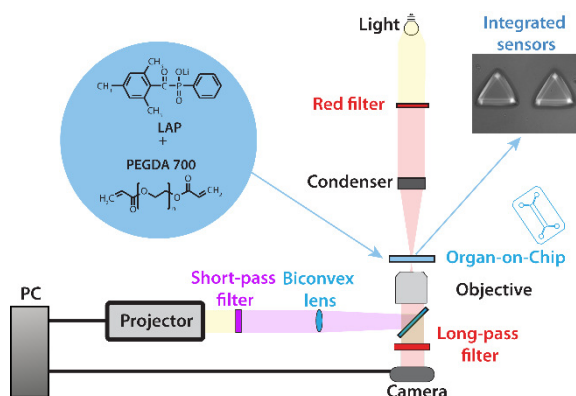


Fig. 1. A scheme of the concept of the experimental setup for integrating the hydrogel sensor and deliverer. The patterned UV light from the projector is focused on the Organ-on-Chip to crosslink the hydrogel. Red-filtered light from an inverted microscope enables monitoring their growth.

Fluorescence images of the sensors were acquired at different drug concentrations in the channels usually associated with FITC and RHOD. A machine learning algorithm was trained to recognise the sensors against the background, extract different geometric regions, and estimate the concentrations of doxorubicin and curcumin.

This model was then used to track drug delivery during a dynamic microfluidic experiment, in which the drugs were allowed to flow through the chambers using syringe pumps at a flow rate of 100 $\mu\text{L}/\text{min}$.

Results

Once the images of doxorubicin and curcumin absorption were obtained, we observed that both fluorescence channels were excited by the drugs. To better separate the information for the two case studies, we used a Partial Least Squares model, obtaining good predictive performance ($\text{RMSE} = 3.83 \pm 1.51 \mu\text{M}$ in a 10-fold test; see Fig. 2).

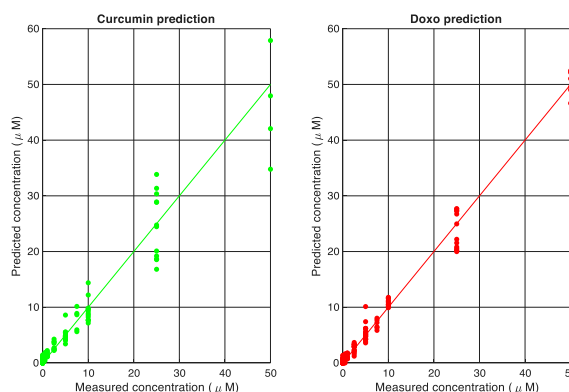


Fig. 2: The performances of prediction for curcumin and doxorubicin prediction using a PLS model. Performances are shown in test.

We could so exploit this model to track the absorption and release of the drugs within a dynamic microfluidic environment (See Fig. 3).

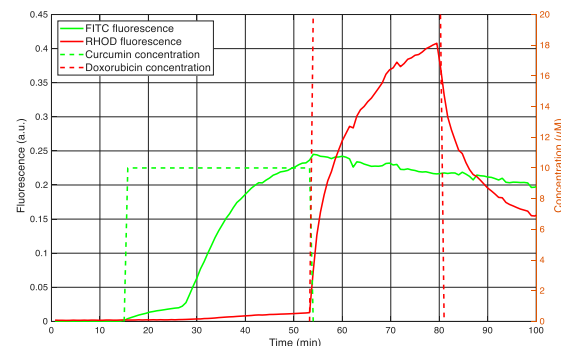


Fig. 3: The evolution of the absorbed/desorbed drugs during a dynamic drug experiment.

The developed model enabled real-time spatio-temporal monitoring of drug distribution within the chip, providing a quantitative description of the absorption and release dynamics during the experiment.

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