A microfluidic platform with integrated traction force microscopy enabling mechanobiology under controlled flow

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We present the development of a platform that enables mechanobiology studies under controlled shear and hydrodynamic pressure loadings, through the integration of traction force microscopy (TFM) in a microfluidic device.

TFM is a versatile measurement technique for quantification of cellular forces at the cell-matrix interface.[1] We implemented TFM for studying the behavior of endothelial cells (ECs) under flow. First, ECs attach and form a monolayer on a hydrogel containing fluorescent beads, which emulates the extracellular matrix. During the measurement, the displacements of the beads are determined and subsequently used to calculate the traction forces that the cells apply onto the hydrogel, knowing the stiffness of the gel (Figure 1). Therefore, it is important to control the mechanical properties of the hydrogel.

For the successful implementation of TFM, we developed a modular microfluidic device with a single base and separate top chambers for two modes of operation. In the first mode, the device serves as a culture chamber for casting the hydrogel while controlling its mechanical properties, coating of protein on the hydrogel, and growing the EC monolayer. In the second mode, the device provides a closed flow chamber for applying different shear and pressure loadings in an uncoupled way (Figure 2).

To create flow, we developed a hybrid positive displacement and pressure driven pumping approach, which is based on the regulation of high and low pressures at the inlet and the outlet, respectively, and allows for the decoupling of flow rate and pressure, i.e. setting them independently (Figure 3).

Combining these novel elements, our platform allows mimicking physiological and pathological conditions for any part of circulatory system as extreme (low and high) values for shear stress and pressure can be reached and matched at any combination. The platform is designed to be interfaced with a fluorescent microscope with environmental control, thus providing a total system that can be used for live cell imaging under flow coupled to TFM.

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[1] L. Boldock, C. Wittkowske, C.M. Perrault, Microcirculation 24, (2017), e12361.

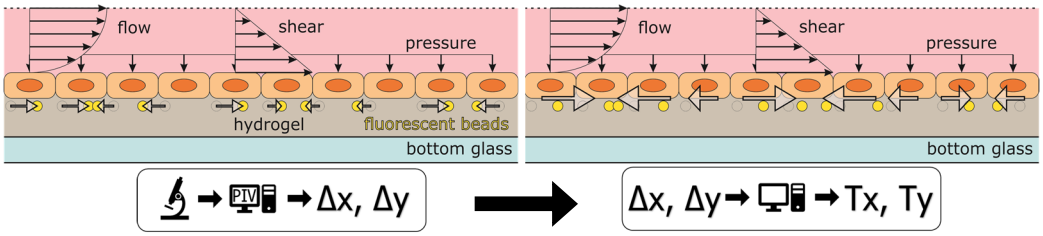

Figure 1: TFM working principle: (left) The displacements of fluorescent beads are recorded using microscopy and the displacement field is calculated via PIV (Particle Image Velocimetry). (right) These displacements are used to calculate the traction forces using the known stiffness of the hydrogel.

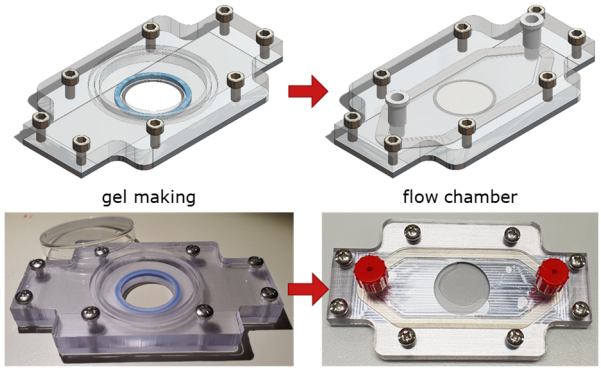

Figure 2: Modular device for two modes of operation: (left) Gel casting and cell growth. (right) Flow experiments with a closed chamber with single inlet and outlet design. Leak-tight assembly is secured by silicone gaskets.

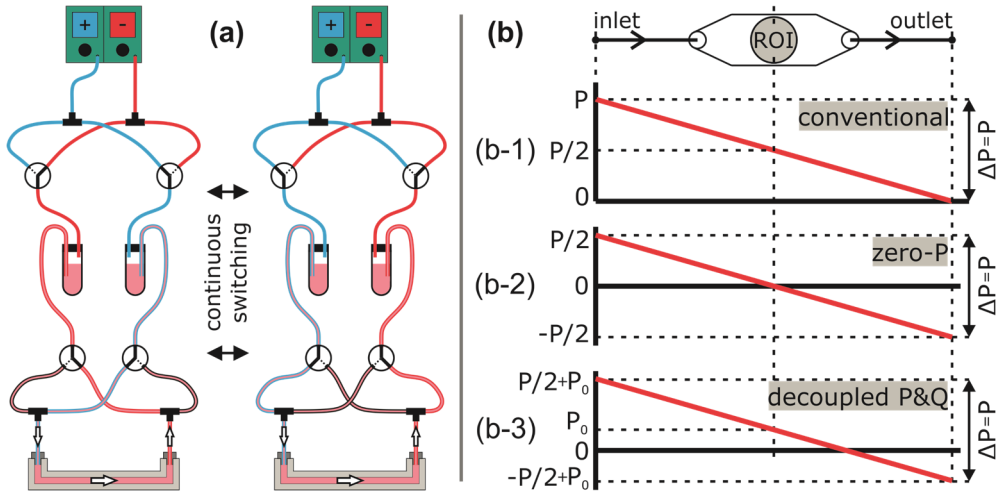

Figure 3: New pumping system working principle: (a) The high and low pressures are created to pressurize sample reservoirs, and the medium is guided for its recirculation while preserving the unidirectional flow. (b-1) When a total pressure drop of ΔP is created, the pressure at the measurement zone (ROI) equals half of the set pressure drop ($P/2$) for conventional method. (b-2) If we apply positive and negative pressures with identical magnitudes ($\pm P/2$) to create ΔP, a zero-pressure zone (pure shear case) is obtained at the ROI. (b-3) To set he pressure of the ROI to any desired level, P_0, we apply an offset of P_0 on the applied pressures in zero-pressure setting. In all these cases, the flow rate, Q (hence the shear stress), which is defined by ΔP over the system, is not affected by P_0 and is controlled independently by ΔP only.