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Stepwise waveform generator for autonomous microfluidic control

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ABSTRACT

Controlling fluidic stepwise waveforms is important in many applications of medical science, biology, and chemistry. However, such a control is implemented by automated, yet expensive, dynamic controllers hindering broad use of these systems. This study presents a stepwise waveform generator (SWG) that achieves stepwise pressure variation using constant water-head pressure only. SWG consists of a microfluidic oscillator and a diode pump, autonomously converts constant pressure to pulsatile pressure via the oscillator, and then generates stepwise increasing or decreasing pressures via the diode pump. The step size, and duration time of the pressure step, can be set independently to take values within the range of 215–431 Pa and 26–181 s, respectively. With the use of additional valves, SWG can regulate flow rate, wall shear stress, and reagent concentration, in a stepwise manner, thereby opening new avenues for the applicability of this self-controlled device.

1. Introduction

Stepwise increases or decreases of reagent concentration, fluidic pressure, and shear stress, are extensively used in medical science applications, including studies of liver stiffness, and optic nerve elasticity [1,2], cell-matrix adhesion assays in biology [3–7], and biomolecular purification and separations in chemistry [8–10]. Stepwise control of these variables in such applications, however, is mainly achieved using automated dynamic control systems that are costly, and that require expertise for their setup and operation. For example, high-speed counter-current chromatography using stepwise elution requires stepwise increases in the reagent concentration using dynamic controllers that precisely regulate the concentration increment and injection interval [9,10]. This is typically performed by computerized dynamic controllers using pressure regulators. If users manually operate the settings, the control process may be proven laborious and time-consuming, and sometimes impossible. Thus, it is envisaged that if a device exists to regulate such a process in an autonomous manner, and without the use of any dynamic external controllers, the device would be extensively used.

To implement such a device, we can rely on new operational principle, whereby a device autonomously converts constant pressure, such as water-head pressure, to a stepwise varying pressure. Although microfluidic devices that mimic the functions of electronic circuits have generated time-varying pressure outputs using constant pressure or flow rate as inputs [11–19], the outputs only alternate between a high- and low-pressure state in a periodic manner. The output does not generate a stepwise pressure change. Generation of a stepwise varying pressure from a constant pressure input requires a different approach, and has not been achieved yet.

In this study, we implement a microfluidic stepwise waveform generator (SWG) that converts a constant pressure to stepwise increasing or decreasing pressures (Fig. 1). Importantly, SWG performs this process without the use of any dynamic external controllers using only a constant input pressure. In SWG, a microfluidic oscillator and a diode pump are serially connected. When a constant pressure input is applied to the oscillator, the oscillator generates pulsatile pressures, and the diode pump then converts the pulsatile pressure to stepwise increasing or decreasing pressures (Fig. 1a). In this way, SWG only uses the constant pressure to generate the stepwise increasing or decreasing pressures. Furthermore, we show that the step size and the duration of the pressure step can be independently controlled. With the connection of additional valves, we demonstrate that SWG can control the reagent concentration, flow rate, and shear stress, in a stepwise manner.

2. Experimental section

2.1. Device fabrication

The devices were fabricated using soft lithography. We fabricated master molds using negative photoresists (Model SU-8 2025, 2075, MicroChem) and silanized them with trichloro-

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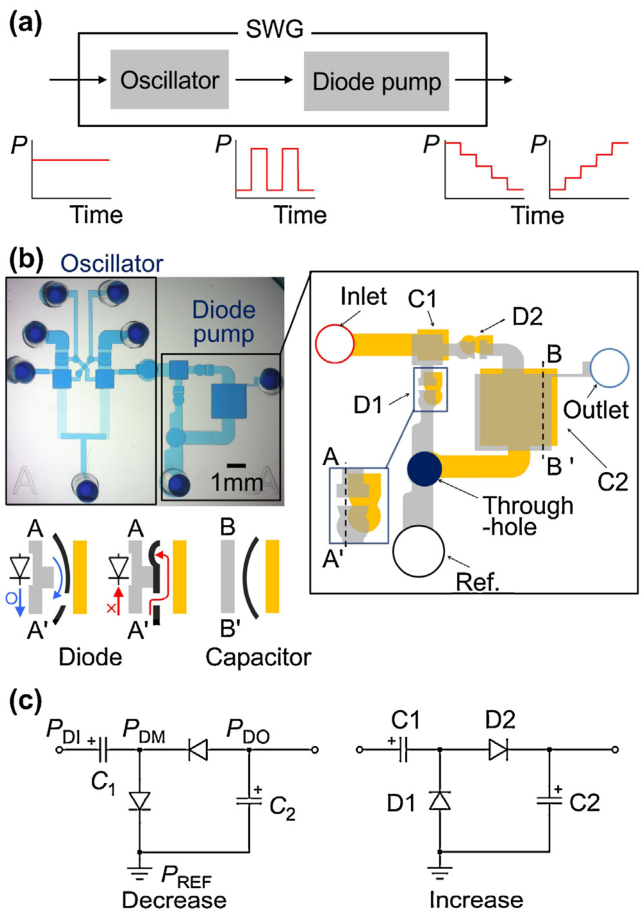

Fig. 1. Stepwise waveform generator (SWG). (a) Conceptual diagram showing the process of generating stepwise pressure. In SWG, a microfluidic oscillator and a diode pump are serially connected. (b) Photograph of SWG and schematic of the diode pump attaining stepwise decrease in pressure. The diode pump consists of two microfluidic diodes (D1, D2), two different capacitors (C1, C2), and microchannels. The cross-sections of diode 1 (section A-A′) and capacitor 2 (section B-B′) show the presence of the top layer (gray), bottom layer (orange), and the thin membranous middle layer (black). (c) Circuit diagrams of diode pumps with stepwise decreasing (left) and increasing (right) pressures. C_1 and C_2 are the capacitances of capacitors 1 and 2 ($C_1 < C_2$). P_{DI}, P_{DO}, and P_{DM}, are the pressures of the input, output, and the position between capacitors 1 and diode 2, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(1H,1H,2H,2H-perfluorooctyl)-silane (Product number 448931, Sigma-Aldrich) in a vacuum desiccator for periods > 4 h to promote facile demolding of casting material [20]. The casting material was poly(dimethylsiloxane) (PDMS) (Sylgard 184, Dow Corning) at a mixing ratio of 10:1 (base-to-curing agent), and was used for the devices. The devices consisted of three layers. The top and bottom layers, which have the features of microfluidic components, were cast using molds at a curing temperature of 65 °C overnight. To secure enough space for membrane deflection, the chamber heights of the microfluidic capacitors were increased by digging manually the chamber surfaces. The middle, thin membranous layer was spin-coated on a silanized glass slide, and was then cured at 120 °C for 20 min. Each layer was bonded using a plasma machine (Model Cute-1MP, FemtoScience) for 30 s. We injected cell culture medium (DMEM, D5671, Sigma-Aldrich) and maintained it for 24 h to reduce the adhesive properties of PDMS, thereby decreasing the opening threshold pressure of the valves [14]. It also helped the microvalves used in Fig. 4 to effectively function as variable fluidic resistors by preventing their attachments on their valve seats.

2.2. Device connection

To control the oscillation period easily, we used modular fluidic resistors [19] in the oscillators. We mounted the modular resistors onto the oscillator with connectors made of properly cut pipette tips (Pistons 25 μL, Rainin Bioclean). Reference and input wells were hung on a stand and were connected with tubes to the inlets of the devices, thereby providing constant water-head pressure. Pulsatile oscillator pressures [17–19] were applied to the diode pumps, and the stepwise pressures of the diode pumps were then applied to the valves with variable fluidic resistances (See Fig. S1 in Supplementary data for more details about device connection). The working solution was deionized water that was mixed with food dyes for flow visualization.

2.3. Fluidic parameters including pressure, flow rate, and concentration

The output pressures of the diode pumps were measured using the pressure sensors (Model PX309-015G5 V, Omega Eng). The pressure data were recorded with a sampling time of 0.2 s, using commercial software (LabVIEW8.5, National Instruments). To obtain the flow rates for Fig. 4b, we measured the pressure at the position between the valve and its downstream channel (Fig. S1, Supplementary data), and converted it to a flow rate using Poiseuille's law. We calculated the wall shear stress using $\tau_w = 6\,\mu Q/(wh^2)$, where μ and Q are the viscosity and flow rate, respectively, and w and h are the width and height of the microfluidic channel, respectively. For this shear-flow experiment, the step size ($\Delta P_{DO}{}^{(n)}$) and pressure duration time (T_D) of SWG were −280 Pa and ∼55 s, respectively. The inlet (P_{In}) and outlet (P_{Out}) pressures were 3.2 and 0 kPa, respectively. The high (P_H) and low (P_L) pressures of the oscillator were 7.6 and −8.6 kPa, respectively. To quantify the concentration of the fluorescent solution (Product number F6377, Sigma-Aldrich), we captured fluorescent images of a microfluidic channel with a microscope (Model Ti-U, Nikon) and an sCMOS camera (Model pco.edge 5.5, PCO). The exposure time was 200 ms and the frame rate was 1 fps. The grayscale values of pixels within selected regions-of-interest were averaged and converted to one concentration value by using calibration curves. We respectively set the absolute concentrations of 0 and 1 mM fluorescein as 0 and 100% concentrations. For the concentration experiment, $\Delta P_{DO}{}^{(n)}$ and T_D were −200 Pa and ∼55 s, respectively, and P_{In}, P_{Out}, P_H, and P_L, were 1, 0, 7, −10.7 kPa, respectively. For the sequential opening of valves, $\Delta P_{DO}{}^{(n)}$ and T_D were −206 Pa and ∼40 s, respectively, and P_{In}, P_{Out}, P_H, and P_L, were 3.2, 0, 8.2, and −8.6 kPa, respectively.

3. Results and discussion

3.1. Device structure and working process

Regarding the SWG, we explain herein the diode pump structure and the operational principle. The oscillator's structure and working mechanism were explained in our previous publications [17–19]. As illustrated in Fig. 1b, the diode pump consists of microfluidic resistors (channels), two different capacitors (chambers with membranes), and two microfluidic diodes [12] (check valves) that allow unidirectional fluidic motion. Each diode (diodes 1 and 2) consists of three layers, including a top channel (gray) with protrusion, a bottom chamber (orange), and a thin membranous middle layer (black) with a hole. When liquid moves in the forward direction at the top channel of the diode (cross-section A-A′ in Fig. 1b), the membrane of the diode moves downwards, and the liquid can thus move along the top channel. However, if the liq-