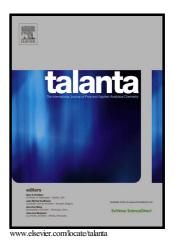
## Author's Accepted Manuscript

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### **ACCEPTED MANUSCRIPT**

## Local surface modification at precise position using a chemical pen

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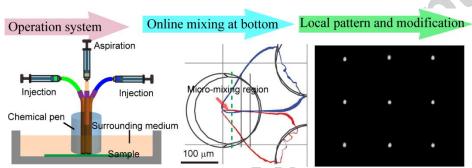
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#### ABSTRACT

Push-pull cannula system, which was first proposed by Gaddum, has grown to be an important method for the perfusion of brain and region-selective surface treatment. However, reported push-pull cannula systems only concerned on single reagent applications. Microfluidic system was then an exciting tool for multi-reagent treatment on substrate in closed microchannels. Nowadays, it is still a challenge to apply online mixing and reaction for surface pattern in an open environment. Here, we present a novel method using a chemical pen that enables region-selective online chemical reactions for the micro-surface modification/patterning. We utilized this method to fabricate labeling protein array using an online labeling strategy. Moreover, the device was applied for local modification of biomaterials surface by using a three-component reaction at precise position. This tool was the first demonstration of design to perform online reaction of two different reagents on a real solid sample in an open environment. It was demonstrated a useful method for protein array fabrication with online labeled protein.

#### Graphical abstract



We present a novel method using a chemical pen that enables region-selective online chemical reactions for the micro-surface modification/patterning. The new pen was successfully applied for online labeled protein patterning and local modification at precise position.

#### Keywords:

Microfluidics; Flow control; Bioreactor; Bio-interface; Analytical methods

#### 1. Introduction

Microfluidic mixing system based on microfluidics technology [1-3] is an outstanding method for region-selective chemical modification because of the enhanced mass transport resulting from the induced diffusion distance maintaining a laminar flow. Previous studies regarding fluid mixing in microfluidic devices were realized in Y-channel [4, 5], 2D-network [6, 7], or 3D-network [8] based on diffusion effects. Both the mixing region and the mixture have been widely used in physical and chemical modifications [9, 10], liquid-liquid extraction [11, 12] and cell stimulation [13, 14]. However, when the mixing fluid is restricted to the small closed micro-channels, this will result in a high flow stress, high flow resistance, and even clogging. More importantly, such mixing systems need to combine with the substrate to perform modification. As a result, closed micro-channel systems limit the target substrate and makes interfacing the microfluidic mixing systems difficult for use in the case of macroscopic solid objects.

Push-pull perfusion system is also a very famous method for surface treatment. A push-pull cannula system was firstly proposed by Gaddum [15] for circumscribed perfusion of brain. After that, substantial researches were reported on the perfusion of brain based on such push-pull cannula system that was structured using dual glass pipettes [16-20].

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