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Micromixing crowded biological agents by folding slugs through pillars

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Abstract

The natural state of the interior of a living cell is extremely dense with numerous molecules packed into a tiny amount of space. Such a physiological environment is known as “crowded” and can exert profound effects on the thermodynamic and kinetic properties of the molecules. In general most biochemical experiments involve low molecular concentrations and in the process, underestimate many reaction rates. This paper reports work on a microfluidic system fabricated using polydimethylsiloxane, and relied on chaotic advection to rapidly mix crowded biological solutions that have been isolated in droplets (slugs). By forcing the slugs through a pillar matrix, the slugs were compelled to stretch and fold repeatedly, creating unsteady fluid flows that rapidly mixed the slug contents in tens of milliseconds at Reynolds number in the order of 10^{-3}. Both straight and serpentine channels containing pillars were used for mixing the slug contents. Our results suggested that the pillars generated a significant amount of interfacial stresses on the slugs and in the process induced rapid mixing. This makes the system suitable for the study of reaction kinetics, which requires reactants to be mixed faster than the actual reaction time itself.
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1. Introduction

The interior of a living cell represents a teeming soup of soluble molecules. For example, a cube (100 nm on a side) of bacterial cytoplasm contains roughly 450 proteins, 30 ribosomes, 340 tRNA molecules, and several mRNA molecules. In between these macromolecules, we can find tens of thousands of smaller molecules that include amino acids, nucleotides, sugars, ATP, ions and others [1]. The concentration of a single molecular species is relatively low but collectively, these molecules can occupy a significant 20–30% of the total volume (typically 50–400 mg/ml). As such, a medium of this kind is termed as “crowded”, rather than “concentrated” [2,3]. Crowded conditions can also exist in extracellular environments such as blood plasma, which contains about 80 mg/ml of protein [2]. As macromolecules have the affinity for association in crowded environments, an important consequence is the formation of non-functional aggregates such as non-native proteins, the study of which is of great interest to biologists [4]. In addition, it has been known for the last 40 years that crowding can have profound effects on the thermodynamic and kinetic properties of the macromolecules [5].

Despite the dense physiological state of the *in vivo* cellular environment, experiments involving biochemical reactions are usually conducted in low macromolecular concentrations (1–10 mg/ml), in which the crowding effect is negligible. As a result, many estimates of reaction rates obtained using uncrowded solutions can differ from results of the same reactions that occur within crowded cellular conditions by several orders of magnitude [2]. The main requirement of the *in vitro* study of reaction kinetics is the reactants must be homogenously mixed faster than the occurrence of the reaction itself [6]. However, crowded media such as bovine serum albumin (BSA) and bovine hemoglobin (Hb) have high viscosities, strong adsorption to synthetic surfaces and diffusion coefficients that are one to two orders of magnitude lower

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than that of most liquids, making rapid mixing very difficult [7].

In many microfluidic applications that are targeted for biochemical analysis such as drug delivery, rapid mixing plays a very important role. Many biological processes such as enzyme reactions and protein folding begin through mixing of reactants in crowded *in vivo* environments. In *in vitro* environments, rapid mixing of fluids at the micro-scale is possible only when we are able to manipulate the fluids to increase the interfacial surface area between initially distinct fluid regions. Note that an increase in interfacial stresses usually precedes an increase in the interfacial surface area. As the flow in microfluidic channels is predominantly laminar, other mechanisms are needed to enhance the mixing process [8,9]. Furthermore, in spite of the small dimensions of microfluidic devices, to depend on molecular diffusion of macromolecules alone can take tens of minutes and this process is simply too slow [9]. However, to induce turbulence by randomizing fluid motion to improve mixing is not practical, since mixing by turbulence requires high sample consumption rates in the order of 1 ml/s [22]. Instead, deterministic mixing – that is, chaotic advection and chaotic mixing – are preferred for better control [10]. And in order to create chaos, we may for example generate helical fluid motions using surface patterns created on channel walls [11], confine reactants in droplets which are used as mixers [12], among other techniques.

Mixing of crowded agents confined in droplets (or slugs) has been demonstrated in serpentine-shaped micromixers with bumpy channel walls [6], which enhance the mixing of droplet contents by exaggerating flow asymmetry within the droplet. Hereafter, the term ‘slug’ will be used to describe an aqueous sample which occupies an elongated stretch of the flow channel compared to its effective diameter. One advantage of confining reactants to a small volume is that they will mix faster than by diffusion alone, and the transport is achieved with minimal axial dispersion (Taylor dispersion) [12,13]. However, we can further exaggerate the flow asymmetry by introducing more profound stretching and folding of the slug. This capability is provided by our passive micromixer (Fig. 1a) which incorporates a simple pattern of pillars that induced chaotic mixing of slug contents by surface shearing the slugs to induce interfacial stresses. Moving through the pillars, the slugs are subjected to a cyclical split–stretch-fold-recombine action, which is a hallmark and represent the simplest effective possible case of chaotic mixing [14,15]. By ‘split’, we refer to the engulfment of the pillar by the slugs.

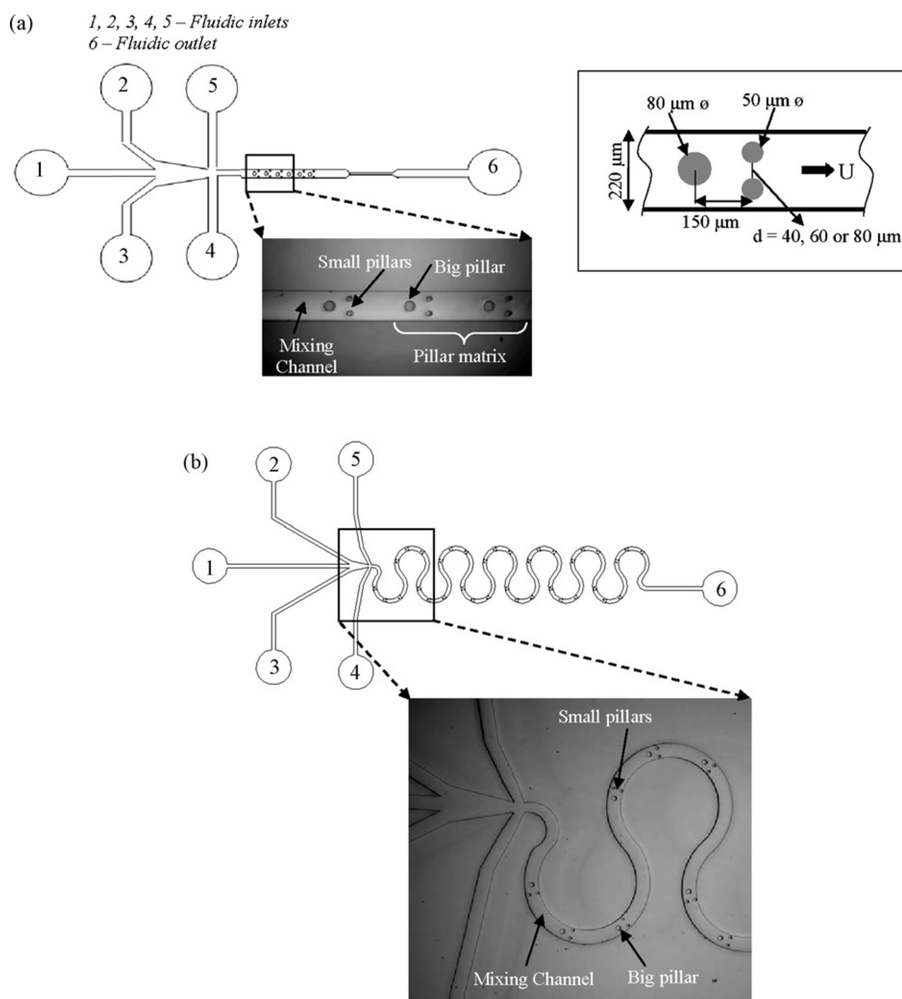

Fig. 1. (a) Schematic and photomicrograph of our micromixer device and (b) schematic and photomicrograph of a smooth serpentine channel with pillars.

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