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Design keys for paper-based concentration gradient generators

Federico Schaumburg [a], Raúl Urteaga [b], Pablo A. Kler [c,d,*], Claudio L.A. Berli [a,**]

[a] Instituto de Desarrollo Tecnológico para la Industria Química (INTEC, UNL–CONICET), Colectora RN 168 Km 472, S3000GLN Santa Fe, Argentina
[b] Instituto de Física del Litoral (IFIS Litoral, UNL–CONICET), Güemes 3450, S3000GLN Santa Fe, Argentina
[c] Centro de Investigación de Métodos Computacionales (CIMEC, UNL–CONICET), Colectora RN 168 Km 472, S3000GLN Santa Fe, Argentina
[d] Departamento de Ingeniería en Sistemas de Información, FRSF-UTN, Lavaise 610, S3004EWB Santa Fe, Argentina

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ABSTRACT

The generation of concentration gradients is an essential operation for several analytical processes implemented on microfluidic paper-based analytical devices. The dynamic gradient formation is based on the transverse dispersion of chemical species across co-flowing streams. In paper channels, this transverse flux of molecules is dominated by mechanical dispersion, which is substantially different than molecular diffusion, which is the mechanism acting in conventional microchannels. Therefore, the design of gradient generators on paper requires strategies different from those used in traditional microfluidics. This work considers the foundations of transverse dispersion in porous substrates to investigate the optimal design of microfluidic paper-based concentration gradient generators (μPGGs) by computer simulations. A set of novel and versatile μPGGs were designed in the format of numerical prototypes, and virtual experiments were run to explore the ranges of operation and the overall performance of such devices. Then physical prototypes were fabricated and experimentally tested in our lab. Finally, some basic rules for the design of optimized μPGGs are proposed. Apart from improving the efficiency of mixers, diluters and μPGGs, the results of this investigation are relevant to attain highly controlled concentration fields on paper-based devices.

1. Introduction

Microfluidic paper-based analytical devices (μPADs) is nowadays a well established technology, as demonstrated in different topical review papers [1–4]. Nevertheless, several aspects related to transport of species in the porous substrate are still to be improved to reach higher levels of efficiency. For example, the amount of analyte effectively transported by the flow and the details of sample distribution in complex geometries are central issues for analytical operations implemented on μPADs [5]. In particular, the generation of concentration gradients is a key operation in microfluidic platforms for drug discovery, bacterial growth, cell culture, and chemotaxis studies [6]. Actually, several of these procedures are being implemented on μPADs [7–10]. However, scientific reports on the generation of concentration gradients on paper are still a few: the conventional tree-like network [11], co-flow in Y-shaped channel [12], and multiple co-flows in a wide single channel [13], to the best of our knowledge. Closely related works are those dealing with mixing operations [14,15], where the transverse dispersion of species is also involved. In this context, the design of effective and versatile microfluidic paper-based gradient generators (μPGGs) deserves further investigation, and this is precisely the goal of the present work.

A central aspect here is that solute dispersion in porous media is mostly due to mechanical dispersion, a mechanism inherent to the random character of the pore network [16]. Although this effect is well documented in the literature related to transport in porous media [17,18], the subject has not been considered in the field of paper-based microfluidics until a topical work [19], where we have discussed the physical basis of transverse solute dispersion in filter paper by theory and experiments. The outcome of this study is essential for the accurate design of operations requiring precise spatial distribution of analytes or reactants, notably the generation of concentration gradients. To put this knowledge in perspective, it is worth to briefly review the conventional methods.

Microfluidics gradient generators fabricated with conventional microchannels may be divided in two main categories: statics and dynamics. In the first case, the concentration gradient is gener-

* Corresponding author at: Centro de Investigación de Métodos Computacionales (CIMEC, UNL–CONICET), Colectora RN 168 Km 472, S3000GLN Santa Fe, Argentina.
** Corresponding author at: Instituto de Desarrollo Tecnológico para la Industria Química (INTEC, UNL–CONICET)., Colectora RN 168 Km 472, S3000GLN Santa Fe, Argentina.
E-mail addresses: kler@cimec.unl.edu.ar (P.A. Kler), cberli@santafe-conicet.gov.ar (C.L.A. Berli).

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ated in a chamber with stagnant flow, which is constantly feed with fresh reactants from opposite side ports, so that controlled diffusion-based gradients are achieved, including sophisticated spatio-temporal distributions [20–22]. Dynamic generators also rely on molecular diffusion, though in this case the species diffuse across parallel flow streams with different initial concentrations, thus a concentration gradient orthogonal to the flow is formed at a certain downstream distance [23,24]. Further, this transverse mixing taking place after T- or Y-shaped junctures is the elementary process used to generate gradients at larger scales by using microchannel networks, such as the tree format for linear gradients [25,26], or asymmetric configurations for non-linear gradients [27,28] and serial dilutions [29,30].

In the gradient generators mentioned above, a balance between diffusive and advective transports has to be found to optimize mixing performance. Thus, the design is constrained by the molecular diffusivity of species, the desired flow rate, and microchannel length. In contrast, the underlying mechanism of transverse dispersion in paper is substantially different, since it is dominated by mechanical dispersion in the pore space. More precisely, the gradient formation is independent on fluid velocity and fully determined by the paper microstructure [19]. This information reveals that the design of μPGGs requires strategies different from those used for conventional microchannels. Indeed, a change of paradigm is envisioned for the rationalization of gradient generators in paper-based devices [13]. The present work investigates the problem by numerical simulations based on the appropriate theory for species transport in porous media. A set of novel, versatile, and easy-to-build μPGGs were designed in the form of numerical prototypes. After running virtual experiments, physical prototypes were constructed and tested to prove the concepts. Finally, some basic rules to be considered for the design of effective and optimized μPGGs are proposed.

2. Numerical simulations

2.1. Theoretical background

This section briefly discusses the physical basis of the model and the main equations used to solve the transport of species in paper substrates. Firstly, the capillary-driven fluid dynamics is solved by using an effective medium approach, as recently reported for nitrocellulose and similar porous substrates [31]; further explanations are given next in Section 2.2. A macroscopic velocity field $\mathbf{u}$ is obtained, which is defined by fluid viscosity, porosity, permeability, and the geometrical boundaries of the fluid domain. Coupled to this velocity field, the macroscopic species concentration field (that already considers the local porosity) C is governed by the following equation:

$$\frac{\partial C}{\partial t} = \nabla \cdot \mathbf{J} \tag{1}$$

where the $\mathbf{J}$ is the total mass flux for the species. For weakly concentrated species in the porous matrix, $\mathbf{J}$ is introduced as the linear superposition of advective, diffusive and mechanical-dispersive transport mechanisms, respectively [32,33],

$$\mathbf{J} = \mathbf{u}C - D_0 \nabla C - s|\mathbf{u}|\nabla C \tag{2}$$

where D_0 is the molecular diffusion coefficient and s is the dispersivity constant, which represents a characteristic dimension of the fiber network microstructure. The last term in Eq. (2) is characteristic of porous media, where the alternating variation of pore-level fluid velocity, in both magnitude and direction, produces a mechanical dispersion. This mechanism is normally characterized by a mechanical dispersion coefficient D_m, which can be differentiated in the longitudinal, $D_{m,L} = s_L u_L$, and transverse $D_{m,T} = s_T u_L$, directions

[16–18]. In these expressions, s_L and s_T are the dispersivities in the longitudinal and transverse directions, respectively, and u_L is the average fluid velocity in the longitudinal direction of the flow. It is known that s_L is larger than s_T, however, as this work is focused on μPGGs, where the solute dispersion transverse to the flow is the main concern for the design, the isotropic formulation $s|\mathbf{u}|\nabla C$ is considered to be adequate, and hereafter we use $s = s_T$. This coefficient was measured to be $s = 30\,\mu m$ for the transverse dispersion of solutes in Whatman grade 1 filter paper [19]. It is worth noting that, for the typical fluid velocities developed in paper-based microfluidics, $s|\mathbf{u}| \gg D_0$, thus transverse solute dispersion is predominantly driven by the mechanical process. Molecular diffusion contributes to the total dispersion when fluid velocity decreases up to the critical value $|\mathbf{u}|_c = D_0/s$. Of course, if $|\mathbf{u}| \to 0$, there is no advection in the pore space, and molecular diffusion is the only active mechanism.

In order to gain more insight on the problem, following we introduce an analytical solution of Eq. (1) for steady 1D flows, which was already studied in [19] and will be also used next for model validation. The flow domain for this basic problem is schematically shown in Fig. 1a: it represents a porous substrate with co-flowing streams of average velocity u_y, one of them transporting a given species of initial concentration C_0. For constant u_y, this problem is equivalent to that with stagnant flow and molecular diffusion in the x-direction, considering that the time-evolution of $C(x, t)$ is observed at each transect $y = u_y t$ along the flow path. Then the concentration profile $C(x, y)$ is governed by,

$$u_y \left(\frac{\partial C}{\partial y} \right) = D \left(\frac{\partial^2 C}{\partial x^2} \right) \tag{3}$$

which derives form Eq. (1) via the change of variable $t = y/u_y$ and a generic coefficient D that condenses diffusive and dispersive effects. Besides, in flow conditions where molecular diffusion is negligible compared to mechanical dispersion, the coefficient can be included directly as $D = s u_y$, and the governing equation results,

$$\frac{\partial C}{\partial y} = s \left(\frac{\partial^2 C}{\partial x^2} \right). \tag{4}$$

Given the boundary conditions $[C(x \to -\infty) = C_0,\ C(x \to \infty) = 0]$ for the problem stated, the solution of Eq. (4) is [34],

$$\frac{C(x, y)}{C_0} = \frac{1}{2} erfc \left[\frac{x}{2(sy)^{1/2}} \right] \tag{5}$$

It is worth noting that the concentration field predicted by Eq. (5) becomes independent of the fluid velocity field. Therefore, three relevant corollaries emerge from Eq. (5): (i) the dispersion width $\sigma_x = (sy)^{1/2}$ is independent of fluid velocity and species characteristics, (ii) the gradient formation is fully determined by the dispersivity s (paper microstructure), and (iii) the transverse solute dispersion is several times larger than the one expected for molecular diffusion.

Concerning the range of validity of this modeling, it should be mentioned that for capillary-driven flows in uniform strips, $u_y = c/y$, where c is the dynamic coefficient that characterizes each paper substrate [35]. Thus the hypothesis of dominant mechanical dispersion is satisfied at distances shorter than $y_c = cs/D_0$. For aqueous solutions in Whatman 1 paper, this critical distance is around 1 m, which means that Eqs. (4 and 5) are fairly valid in paper-based microfluidics. The flow regimes can be also characterized by the Peclet number, which is defined at the pore level as $Pe = su_y/D_0$ [16,17]. In this context, mechanical dispersion prevails over diffusion when $Pe \gg 1$, which is largely the case for Whatman 1 filter paper [19]. These concepts will be used along this work to generate the design rules for μPPGs summarized in the conclusions.