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# Three-phase microfluidic reactor networks – Design, modeling and application to scaled-out nanoparticle-catalyzed hydrogenations with online catalyst recovery and recycle

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ABSTRACT

We present a design framework for the robust, self-regulating long-term operation of parallelized multiphase microfluidic reactor networks without the use of any active flow control elements. A fluidic circuit-based design scheme is developed for the feed manifolds in a general multiphase microfluidic reactor network where an inline, fluidic capacitance element allows autonomous damping of periodic and aperiodic flow disturbances, in combination with a fluidic resistance-based strategy for even flow distribution into the network. A dynamic model for the fluidic capacitance element is derived, numerically solved and validated with experiments on model time varying feed flows. This model sheds new light on important network-level design considerations for stable long-term operation. Finally, our design scheme is applied to present the first demonstration of a robust eight-fold parallelized three-phase segmented-flow reactor network for platinum nanoparticle-catalyzed hydrogenation of nitrobenzene, a model substrate, at an approximately constant substrate conversion of ~80% under ambient conditions, with continuous online recovery and recycle of the colloidal catalyst phase over five hours of operation.


## 1. Introduction

Multiphase catalytic reactions such as oxidation, hydrogenation and halogenation are integral to the pharmaceutical and fine chemical industries. These reactions involve the contacting of gases, liquids and solids, and are conventionally carried out in stirred batch reactors, at high stirring rates and under harsh reaction conditions of elevated temperature and pressure to overcome severe heat and mass transfer limitations. Continuous-flow microreactors offer tremendous heat and mass transport acceleration, in addition to the prospect of facile phase separation, and are of considerable interest as platforms for conducting multiphase reactions in recent years (Murphy et al., 2007; Günther and Jensen, 2006). Several demonstrations of biphasic organic syntheses in various microreactor configurations have reported significant improvements in product yield, selectivity and reaction times (Murphy et al., 2007; Rahman et al., 2006; Bourne et al., 2013; Noël and Hessel, 2013; Yeong et al., 2003; Park and Kim, 2010). For example, gas-liquid segmented flow, in which the gaseous reactant and the liquid plug containing the substrate and the catalyst flow alternately, provides direct contact between the two phases with enhanced interfacial gas-liquid mass transfer (Murphy et al., 2007; Rahman et al., 2006). Membrane microreactors have also been used as platforms for biphasic organic syntheses by allowing for the independent infusion of gaseous and liquid phase reactants (Bourne et al., 2013; Noël and Hessel, 2013; Park and Kim, 2010). We have previously introduced a triphasic segmented flow reactor for rapid nanoparticle-catalyzed reactions, (Yap et al., 2014a,b; Khan et al., 2014) where the compartmentalization of catalyst in a separate immiscible fluid phase allows facile catalyst recovery and recycle, and the provision of a large interfacial area for the dissolution of gaseous reactant enables an order of magnitude reduction in the reaction time compared to batch reactors. We have demonstrated the application of this reactor scheme in the hydrogenation of a variety of substrates, using different catalysts, with enhanced yields and selectivities under near ambient conditions.

These advantages notwithstanding, the productivity of single micro-/millifluidic reactors is limited by their low volumetric throughputs (Al-Rawashdeh, 2013; Woitalka et al., 2014). The exploitation of micro/millireactor technologies for larger production volumes can be achieved by a combination of scaling *up*, i.e. an increase in reactor dimensions to the 'milli' scale or 'meso' scale, to the extent possible without sacrificing the accelerated interphase heat and mass transport properties, and scaling *out*, i.e. the operation of multiple identical reactors in parallel (Woitalka

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et al., 2014; Al-Rawashdeh et al., 2012; Adamo et al., 2016; Nightingale et al., 2013; Riche et al., 2016; Zhang et al., 2014; Su et al., 2016).

There are two crucial engineering challenges in the design and operation of a parallelized *multiphase* flow reactor system. The first crucial challenge is the equal routing of the multiple fluid phases into the various arms of the parallelized flow network that is immune to variations or temporal fluctuations in pressure drop in any of the individual branches. Even distribution of fluids into a parallelized reactor system by means of pressure-drop (or 'barrier') channels as flow distributors has been well demonstrated for both gas-liquid and liquid-liquid reactor networks (Al-Rawashdeh et al., 2012, 2012, 2013; de Mas et al., 2005). The basic idea is for the distributor channels to have fluidic resistances much greater than those of the reactor channels; the high pressure drop across these distributor channels is thus able to effectively diminish the effects of any fluctuations or variations in pressure drop within the arms of the reactor network.

The second crucial challenge is to have uninterrupted, smooth, and pulse-free delivery of all fluids supplied to the network. While syringe pumps are often the preferred choice for the operation of single micro/millireactors due to their ability to provide fluid flow at a constant volumetric flow rate, the finite capacities of syringes limit the use of these pumps in continuous long-term production. Uninterrupted flows can be achieved by means of pumps that are able to continuously withdraw feed from a reservoir, such as peristaltic pumps, high performance liquid chromatography (HPLC) pumps and displacement pumps, among others. However, these pumps introduce both periodic and aperiodic pressure pulsations into the fluid streams, resulting in the injection of feed with time varying flow rates into the reactor network. When left unresolved, such pressure pulsations dramatically influence the stability of a multiphase reactor network, since the morphology of multiphase flows (i.e. the observed flow regimes) in small scale flowing reactors is typically highly sensitive to small changes in flow conditions (Yue et al., 2014; Kreutzer et al., 2005).

There are two general approaches to address the issue of flow pulsations – *passive* capacitance-based flow regulation and *active* regulation via the use of mass flow controllers (MFCs) and/or the integration of complex control algorithms with the pumping hardware (Advanced Energy Industries Inc., 2015). The use of passive capacitance-based damping has been applied in the engineering of large, 'macroscale' fluid flow networks; (Macek et al., 2011) typical dampers consist of an assembly of capacitances and resistances in series, with pipes of suitable length and diameter acting as hydraulic resistors, and vessels with a gaseous headspace above the flowing liquid serving as pneumatic capacitors, or devices with variable pressure-dependent volumes (e.g. elastic walls) acting as hydraulic capacitors. However, both general approaches have drawbacks that limit their use in complex micro-/millifluidic reactor networks involving multiphase flows. Thus, for example, the passive approaches typically involve large dead volumes, as in the case of pneumatic dampers, while active approaches involve flow through complex geometries, which dramatically increases the possibility of fouling, especially for the flow of solid suspensions (such as colloidal nanoparticle catalysts as used in our work). Furthermore, while the latter is able to provide active regulation in simple flow circuits, its ability to regulate highly branched and multiphase flow networks with time-varying feed flow rates is limited, and increases in complexity with the number of fluid phases fed into the system.

In this paper, a quantitative fluidic circuit-based design framework for parallelized multiphase micro-/millifluidic reactor networks that combines resistance-based fluid distribution and capacitance-based autonomous flow regulation that overcomes the key challenges highlighted above is presented. The paper is divided into two parts. First, the design of fluid supply manifolds in a general multiphase micro-/millfluidic reactor network, where a simple, passive capacitance-based method allows autonomous damping of both periodic and aperiodic flow pulsations in combination with the resistance-based strategy for flow distribution, is presented. We derive and present a model for the dynamics of fluidic damping, and validate it with experiments on model pulsed flows; the availability of a model for the damping dynamics also sheds light on important *network-level* design considerations. In the second part of the paper, this framework is applied to present the first demonstration of an eight-fold parallelized triphasic segmented-flow reactor system for platinum nanoparticle-catalyzed hydrogenations of nitrobenzene, a model substrate, with continuous catalyst recovery and *online* recycle.

## 2. Materials and methods

### 2.1. Fluidic damper assembly and testing

Two different elastic tubes, each of 4.76 mm inner diameter (ID), were used in the construction of simple capacitance-based fluidic damping schemes - (i) polytetrafluoroethylene (PTFE) tube (Cole Parmer, 6.35 mm OD) and (ii) #25 silicone tube (Masterflex, 7.94 mm OD). The fluidic damper consisted of a 5 cm long 101.6 μm ID polyether ether ketone (PEEK) tube, an 8 cm long 4.76 mm ID elastic tube followed by another 5 cm long 101.6 μm ID PEEK tube assembled in series. Water was infused into the series of tubes by means of a peristaltic pump (Leadfluid BT-50S, YZ-15) at an average flow rate of ~267 μL/min and a liquid flow meter (Sensirion, SLI-1000) connected at the end of the fluidic damper was used to measure the variation of liquid flow rate with time.

### 2.2. Fluid distribution manifold assembly and testing

A one-to-eight fluid delivery manifold incorporating a fluidic capacitance-based damping strategy was used to supply the two liquids (organic substrate and aqueous catalyst) into our reactor network. In both cases, 0.5 mm ID PEEK T-junctions were used at all bifurcations in the fluid lines. The gas distributor did not include a damper, and simply consisted of eight parallel 15 cm long 63.5 μm ID PEEK tubes assembled by successive bifurcations of the delivery line. Liquid flow distributors were designed as follows. The aqueous phase distributor consisted of a 230 cm long 254 μm ID fluorinated ethylene propylene (FEP) tube connected to an 8 cm long 4.76 mm ID silicone tube prior to branching by bifurcation into eight parallel lines, each consisting of a 5 cm long 101.6 μm ID PEEK tube. Similarly, the organic phase distributor consisted of a 40 cm long 101.6 μm ID PEEK tube connected to an 8 cm long 4.76 mm ID viton tube prior to branching into eight parallel lines consisting of a 5 cm long 63.5 μm ID PEEK tube. To calibrate the gas lines, flow rate of nitrogen gas (Soxal, purified) was measured via the water displacement method in an inverted 50 mL burette. Nitrogen gas was introduced into the main line, and the volume of water displaced by nitrogen gas in each parallel line within 5 min was then measured. The volumetric flow rate for the respective line was subsequently calculated. The aqueous lines were calibrated by infusing ultrapure water into the aqueous distributor at a gauge pressure of 1.31 atm using a peristaltic pump and measuring the average flow rate in each of the eight lines. The calibration of the organic lines was similarly carried out by infusing diisopropyl ether at a gauge pressure of 1.33 atm using a peristaltic pump into the organic phase distributor and measuring the mass of diisopropyl ether (Sigma, ⩾98.5%) dispensed into individual vials at the outlets over time. An average flow rate of 40 μL/min and 20 μL/min was achieved for each of the lines in the aqueous

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