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Design of multi-functional microfluidic ladder networks to passively control droplet spacing using genetic algorithms

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ABSTRACT

Accelerated progress in the use of droplet-based microfluidics for high throughput screening and biochemical analysis will require development of devices that are robust to experimental uncertainties and which offer multiple functionalities. Achieving precise functionalities in microfluidic devices is challenging because droplets exhibit complex dynamic behavior in these devices due to hydrodynamic interactions and discontinuities that are a result of discrete decision-making at junctions. For example, even a simple loop device can show transitions from periodic to aperiodic/chaotic behavior based on input conditions. Hence, rational design frameworks that handle this complexity are required to move this field from labs to industrial practice. Two main challenges that need to be confronted in the realization of such a rational design framework are: (i) computational science related to rapid simulation of very large networks; development of predictive models that will form the basis for characterizing droplet motion through interconnected and intricate large-scale networks, and (ii) conceptualization of a design approach that is generic in nature and not very narrowly defined limiting its application potential. In this paper, we develop a GA approach for the design of ladder networks that are used to control the relative droplet distance at the exit. Through several case studies, the potential of the proposed GA approach in designing exquisite ladder structures for multiple functions is demonstrated. A recently proposed network model is used as the basis for all the computational studies reported in this paper.

1. Introduction

The ability to control small volumes of fluids through droplet-based microfluidics has revolutionized conventional biochemical analysis (Ho, Chakrabarty, & Pop, 2011; Su, Chakrabarty, & Fair, 2006). Recent advances in this area have led to the development of devices with basic functionalities such as sorting (Christopher et al., 2009; Cristobal, Benoit, Jaonicot, & Ajdari, 2006; Hatakeyama, Chen, & Ismagilov, 2006), merging (Jin, Kim, Lee, & Yoo, 2010), synchronization (Prakash & Gershenfeld, 2007) and storing (Boukellal, Selimovic, Jia, Cristobal, & Fraden, 2008; Laval, Crombez, & Salmon, 2009; Shim et al., 2007). Using these basic devices it is now possible to design massively parallelized large-scale architectures for lab-on-chip applications. The current state-of-the-art is that these devices are developed using a bottom up approach *i.e.* by rigorous experimentation to find optimal designs for a given objective. Advanced computational techniques have the potential to accelerate this design discovery process through a top down approach *i.e.*, rigorous simulations to discover optimal designs for the given task, which could then lead to experimental validation. Reliable computational approaches can have a tremendous impact in this area similar to the impact of simulations in the electronics industry.

Two main challenges that need to be confronted in the realization of such a computational framework are: (i) computational science related to rapid simulation of very large networks; development of predictive models that will form the basis for characterizing droplet motion through interconnected and intricate large-scale networks, and (ii) conceptualization of a design approach that is generic in nature and not very narrowly defined limiting its application potential. Development of predictive models will have to address the inevitable complex nonlinear dynamics of droplet-based microfluidic systems (Cybulski & Garstecki, 2009; Epstein, 2007; Sessoms, Amon, Courbin, & Panizza, 2010). For example, it has been shown that binary decisions that droplets make at bifurcations can lead to fascinating nonlinear dynamics, including chaos and fractal behavior. Nonetheless, rapid progress is being made in characterizing the dynamic behavior related to the various phenomena that occur in droplet-based microfluidic devices. On the other hand, there is very limited work that can be found on rational design approaches for discovering large-scale microfluidic networks. To address this gap, we propose a genetic algorithm based design framework in this paper.

While the ultimate vision is the development of a design discovery process for very general and complex microfluidic networks

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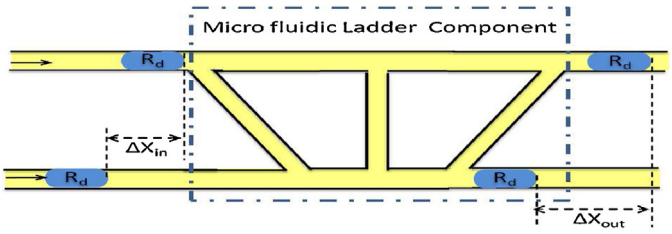

Fig. 1. Ladder network with a combination of backward, vertical and forward bypasses.

that incorporate several design elements, as a first step towards this goal, we develop and demonstrate our approach for a novel structure, the ladder networks. We begin with a brief introduction to the ladder networks, the importance of this structure, and the design questions that need to be answered. We then discuss the proposed approach, which consists of two components: (i) a model for ladder networks and (ii) a design algorithm. The network model that is used to simulate the dynamics of the ladder networks and a customized genetic algorithm (GA) approach for design are discussed subsequently. The capability of the proposed GA formulation is demonstrated through three case studies: (i) synchronization of droplets for a particular input spacing (ii) synchronization of droplets for a range of input spacing, and (iii) realization of constant delay between droplets exiting the ladder network.

1.1. Microfluidic ladder networks

Several papers have studied the ladder networks in detail. The ladder networks are important in their own right and have been used in microfluidic networks for synchronization. Synchronization is an operation that is used to maintain a zero or relatively small time difference between two events such as droplets exiting two arms of a ladder. That is, droplets entering the two arms of the ladder at different times but leave the ladder at the same time. A microfluidic ladder network (MLN) device contains a pair of parallel channels interconnected with bypasses. Droplets are transported through the parallel channels, whereas the bypass channels are inaccessible to the droplets. Fig. 1 represents an example ladder network, the first bypass slopes backward, and is defined as a backward slant; similarly, the middle and the last bypasses are called as vertical and forward slants, respectively. The bypasses of the MLN are defined based on their structural orientation—in reference to the direction of motion of the droplets.

The spacing transformation achieved by a ladder network is defined as its functionality. Fig. 1 shows a pair of droplets entering the ladder network with an inlet spacing of ΔX_{in}, this spacing is transformed to ΔX_{out} as the pair of droplets exit the ladder network. The change in droplet spacing is due to the change in the relative velocity between the two droplets. The change in the relative velocity is a result of redistribution of flow across the bypasses. Symmetric ladder networks, *i.e.*, networks with equally spaced vertical bypasses are shown to reduce the droplet spacing (Prakash & Gershenfeld, 2007) whereas asymmetrical ladder networks are shown to expand, contract, flip or synchronize the droplets (Maddala, Wang, Vanapalli, & Rengaswamy, 2012). In general, symmetric ladder networks offer less flexibility in terms of functionality compared to asymmetrical ladder networks. Additionally, asymmetric ladder networks have more parameters to optimize as compared to the vertical ladder networks.

While the underlying physical principle of the ladder networks is deceptively simple, yet trying to design a robust ladder network with minimal device foot-print under unavoidable experimental constraints is not trivial. For example, in the pursuit of a ladder network for robust synchronization, one might ask what is the optimal number of bypasses that is needed and how does this number depend on droplet hydrodynamic resistance and velocities? What degree of experimental uncertainties can be tolerated while still achieving acceptable synchronizer functionality? Are there alternative and more efficient structural configurations for the synchronizer than that implemented by Prakash and Gershenfeld (2007)? Going beyond the synchronizer, is it possible to design a ladder network for multiple functions such as input delay dependent behavior? Are there any advantages that can be accrued by slanting the arms of the ladder either in the forward or backward directions? To answer these questions, currently neither systematic efforts have been devoted nor rational approaches have been developed. Our proposed approach addresses such questions, specifically in the context of ladder networks. More generally, we view our approach as a first step towards the development of a rational tool for the design of complex microfluidic networks.

2. Proposed approach

The ladder design problem comprises both structural and real variables. The structural elements of the problem are related to the topology such as the number of bypasses in the network. The continuous variables are the cross-sections of the bypasses and the positions of the bypasses on the main channels. This combination of structural and continuous variables will be a characteristic of almost all microfluidic design problems. The other important characteristic is the presence of constraints and bounds on the variables. These constraints could arise when minimum bypass separations are specified or if one forbids the bypasses to cross. The objective function has to reflect the goal of the design. The definition of the objective function for general microfluidic designs will be problem-specific.

Optimization approaches to process design have been well studied in chemical engineering. Structural optimization problems are solved using combinatorial algorithms and continuous variable optimization approaches are largely gradient-based. Based on the problem characteristics described above, mathematical formulations for microfluidic design in general and the synchronizer problem in particular will be of the Mixed Integer NonLinear Programming (MINLP) variety. Branch-and-bound is an effective approach to solve large-scale MINLP problems (Parker & Rardin, 1988). One difficulty in using a standard MINLP formulation for microfluidic design would be the lack of closed form analytical expression for the objective function for typical design problems. The objective function has to be calculated through numerical simulations using a model such as the one discussed subsequently. This would make repeated gradient evaluations extremely numerically cumbersome.

In the paper, we pursue the use of alternate non-gradient approaches for microfluidic design. In particular, we will explore the use of GAs. While other alternatives such as simplex search algorithms exist, GAs have been shown to solve combined structural and continuous variable problems efficiently, for example, in heat and mass exchange network design (Garrard & Fraga, 1998; Ravagnani, Silva, Arroyo, & Constantino, 2005). Another often cited advantage of GAs is that several acceptable designs are identified due to the principle of hyperplane sampling (Whitley, 1994). Further, in general it is reasonably straight-forward to setup a GA search (Goldberg, 1989; Holland, 1975). The general principles that underlie GAs are loosely based on ideas from evolution. In a genetic search, from an initial population of chromosomes, a set of best fit chromosomes (elitist selection) are chosen for reproduction. The parameters in an optimization problem are genes in a chromosome. These genes or parameters can be real numbers, integers or