Preprints of the 18th IFAC World Congress
Milano (Italy) August 28 - September 2, 2011

Sort-synchronization control in microfluidic loop devices with experimental uncertainties using a model predictive control (MPC) framework

Jeevan Maddala, Siva A Vanapalli and Raghunathan Rengaswamy [1]

Department of Chemical Engineering
Texas Tech university, Lubbock, Texas 79409

Abstract: Droplet microfluidic devices are being used in several applications. Increasing sophistication of these applications require precise control of the droplet behavior in such devices. However, it has been shown that even the simplest loop devices (a channel that splits into two arms and subsequently recombines) can demonstrate nonlinear behavior like period doubling, bifurcations and chaos. This behavior of the droplets makes control using traditional methods difficult. In this paper, a model based control algorithm is proposed for active sort-synchronization control in microfluidic devices. A recently proposed network model is used in this control. The control concepts are demonstrated on simulation studies using a prototypical loop device.

Keywords: Microfluidics, Model predictive control, sort-synchronization, loop device, active control, optimization

1. INTRODUCTION

Droplet microfluidic devices facilitate the use of materials at a scale of femto liters to micro liters providing precise control for conducting reactions and high throughput screening analysis. Droplet microfluidic devices have been widely used in protein crystallization (Zheng et al. (2004); Huebner et al. (2007)), biochemical assays (Haeberle and Zengerle III (2007)), high throughput screening of cells (Brouzes et al. (2009)), and fabrication of micro to nano particles (Song et al. (2006)). These applications require the following two key steps: (i) understanding droplet behavior in a network of narrow channels, and (ii) control of droplet traffic. Several studies have been performed to understand the dynamics exhibited by the droplets. Jousse et al. (2005) showed that the droplet motion even in a simple microfluidic loop device (a channel that splits into two arms and subsequently recombines) exhibit rich nonlinear dynamics. Fuerstman et al. (2007) characterized this dynamics using Poincaré maps; clusters in theses maps correspond to periodic and aperiodic behaviors of the droplets. This behavior of droplets was further explored by Prakash and Gershenfeld (2007), where nonlinearity introduced by hydrodynamic interactions between droplets is utilized for building logic gates and counters. The nonlinear dynamics exhibited by the droplets has been studied by Schindler and Ajdari (2008) using a simple network model. The decision making of the droplets at the bifurcations along with hydrodynamic interactions present among them were considered to be the sources of nonlinear dynamics. The network model has been widely used in literature to understand the dynamics exhibited by droplets in micro channels (Smith and Gaver III (2010); Labrot et al. (2009)).

Though reasonable amount of literature is available on understanding the droplet behavior, very little has been reported on control of droplets, which is a vital task in numerous applications. For instance, control is critical for sorting and mixing of droplets, which are important tasks in high throughput screening of single cells (Brouzes et al. (2009)) and reaction networks (Huebner et al. (2007); Song et al. (2006)). Let us first describe the sorting and synchronization tasks. Assume that a stream of white and black droplets arrive at the entrance of the microfluidic device (see Figure 1). The task of the microfluidic device is to merge pairs of black and white droplets at the exit. This would require that the black and white drops be reliably sorted into the two arms of the device; otherwise merging them at the exit is not possible. Once this sorting is achieved, the exit times of the leading droplets in the two arms have to be synchronized. This will ensure that the black and white droplets merge at the device exit. If the black and white droplets represent two reactants then such a microfluidic device can be thought of as carrying out reactions in precisely controlled quantities.

While the importance of this control problem is obvious, there are several challenges in achieving precise sort-synchronization control. These are: *(i)* nonlinear dynamics due to hydrodynamic interaction among droplets, *(ii)* bifurcations and chaotic behavior of droplets (behavioral change with respect to input and output conditions), *(iii)* disturbances in droplet generation, and *(iv)* existence of multiple steady states. Here, multiple steady states refers to the variations in the number of clusters in the Poincaré

[1] E-mail: raghu.rengasamy@ttu.edu

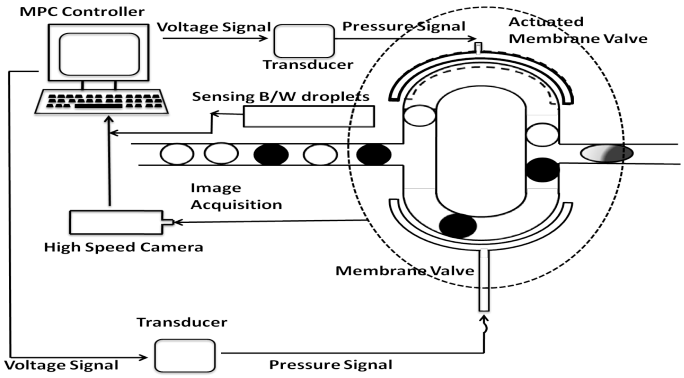

Fig. 1. A possible implementation of the proposed online feedback controller

map of exit times with changes in the inlet time periods of the droplets as discussed by Fuerstman et al. (2007). There has been some previous work in sort-synchronization of droplets using active and passive techniques. Passive techniques require precise control of droplet size, inlet flow (Jin et al. (2010)) or a cleverly engineered network structure (Cristobal et al. (2006)). Passive techniques provide the advantage of handling varied type of materials but lack in handling experimental uncertainties. Existing active control techniques require either an external electric field or valves to regulate the droplet traffic. The use of electric field for droplet control limits the application of this technique to materials that have high dielectric constant. Pressure driven micro-valve actuators can deliver precise actuation in most systems; the response time of such actuators might be slightly inferior to techniques based on electric fields. In terms of control algorithms, PI control using transfer function models has been investigated (Bhattacharjee and Najjaran (2010)). However, it is well established in the control literature that the PI algorithm cannot provide efficient control for processes which exhibit nonlinear dynamics, multiple steady states, and chaos; these are characteristic of microfluidic devices. In view of these challenges, in this paper, we evaluate a model-based active control strategy for sort-synchronization of droplets in a prototypical microfluidic device.

In our previous work (Maddala et al. (2010)), sort-synchronization control in a microfluidic loop was addressed using a Model Predictive Control (MPC) framework. The network model outlined in Schindler and Ajdari (2008) was used in the MPC algorithm. Elastomeric micro-valves (Abate and Weitz (2008)) were proposed as the final control elements that are manipulated through the MPC algorithm. The use of such valves for active sorting of droplets has already been discussed by Abate et al. (2010). The advantages of using MPC for sort-synchronization of droplets in a microfluidic device are: *(i)* the nonlinear droplet behavior can be captured using the network model, *(ii)* practical constraints arising due to the use of micro-valve actuators can be handled, and *(iii)* sorting and synchronization of droplets can be achieved for various input flows through continuous manipulation of the micro-valve actuators. While the MPC approach was shown to work satisfactorily, several simplifying assumptions were made. First, it was assumed that the droplets arrive at the entrance at precisely spaced intervals in the prototypical model. Second, it was assumed that the black and white droplets arrive in a precise BWBWBW... sequence at the entrance. In experimental systems both of these assumptions are likely to be violated. Pressure fluctuations at the inlet will result in fluctuations in the input arrival times of the droplets. Imprecisions in the upstream droplet generators can lead to droplets arriving out of sequence at the entrance. In this paper, we discuss an enhancement to our MPC work (Maddala et al. (2010)) to handle such inevitable experimental uncertainties. Simulation studies of the model predictive control strategy for sort-synchronization of droplets under these experimental uncertainties will be presented. The basic MPC concept that is used in this paper is similar to the one that was used in our prior work (Maddala et al. (2010)). This is shown in Figures 1 and 2. A high speed camera is assumed to capture images from the microfluidic loop device. These images are analyzed by the computer and the current droplet positions are then calculated, which serves as an input to the controller. The controller identifies the optimal valve actuations that the elastomeric valves should deliver to the microfluidic device. The actuations calculated by the controller respect the experimental constraints on the elastomeric valves. The rest of the paper is organized as follows. A summary of our previous MPC work on sort-synchronization control will be presented in section 2. In section 3, the problem that is addressed in this paper will be detailed along with the proposed solution approach. Results and discussions will follow in section 4.

2. SUMMARY OF PREVIOUS WORK

The MPC approach proposed in our previous work (Maddala et al. (2010)) breaks the problem down into two steps, one for sorting and the other for synchronization. The sorting of droplets is achieved as an interrupt using model calculations. Whenever a droplet is at the device entrance, the sensor detects the droplet and the control algorithm changes the resistances in the two arms so that the entering droplet proceeds to the preferred arm of the loop device. The synchronization calculations minimize the mismatch in the exit times of the leading droplets. Both sorting and synchronization require a model of the device for the control actuations to be calculated. In our previous work (Maddala et al. (2010)), a network model (Schindler and Ajdari (2008)) was used. The network model describes the device behavior using an equivalent electrical circuit concept for calculation for droplet choices and the flow rates in the branches. We will now explain the network model. Consider the prototypical loop device shown in Figure 1. When a droplet enters the device it has one of two paths to take. A model needs to decide which one the droplet will take. The network model assumes that the droplet will take the arm which has maximum instantaneous flow. The instantaneous flows in the two arms are calculated using two equations. The first is the flow balance at the entrance; that is the inlet flow should equal the summation of the two flows in the upper and lower arms. The second is based on the fact that the pressure drop across the two arms should be the same (similar to voltage drop being the same between two points in an electrical network). The pressure drop in an arm is assumed to be equal to the product of the flow in the arm and the resistance offered to that flow (similar to the product of current and resistance). Each droplet in a branch is assumed to add to the intrinsic

resistance of a branch by a value R_d (resistance of the droplet). The velocity of the droplet once it enters a branch is assumed to depend linearly on the flow rate as follows:

$$V_d = \beta Q \tag{1}$$

In the equation above V_d is velocity of the droplet, β is the proportionality constant and Q is the bulk phase flow. Therefore, the network model has two parameters R_d and β; these parameters are optimally chosen to match the experimental data. The experimental data consists of the droplet entrance and exit times and the choices that the droplets make. Given the entrance times, the model predicts the droplet decisions and the exit times. In our previous work it was shown that the network model works quite well for different experimental scenarios. The experimental scenarios are characterized through the number of clusters in the Poincaré maps. The model was able to accurately characterize two periods (clusters), three period (clusters) and aperiodic (large number of clusters) behavior. The model was then used in lieu of the actual device for simulation studies of the MPC performance. For MPC studies, the prototypical model is assumed to have two elastomeric valves on the two branches which are actuated according to the given controller signal. The installed camera captures images and are analyzed to obtain the current positions of the droplets. These are given as inputs to the controller which iteratively solves for optimum valve actuations as shown in figure 2. These actuations are implemented by the elastomeric vlaves to achieve sort-synchronization. The proposed MPC algorithm consists of four conceptual components: *(i)* prediction step, *(ii)* optimization step for synchronization, *(iii)* synchronization actuation, and *(iv)* sorting actuation. In the prediction step, future droplet positions are predicted based on the current droplets in the loop using the network model. An important assumption here was that the input frequency of the droplets is constant. In the optimization step, the objective function, which is the sum squared error in the exit times of droplet pairs (upper and lower) was minimized. The limitations on the valves were included as constraints in the optimization problem. Unlike traditional MPC where the prediction horizon remains constant, in our prior MPC work the prediction horizon is defined as the time taken for two pairs of droplets to exit the loop. Therefore the prediction horizon varies with time. The control horizon is set as $3T_s$, where T_s is the sampling time. The sampling time is calculated using

$$T_s = max(5.5ms, \frac{\tau}{20}) \tag{2}$$

where τ is the average residence time of the droplets in the device. This ensures that the MPC implementation studies are realistic as $5.5ms$ is the minimum actuation time for the elastomeric valve(Abate and Weitz (2008)). The sorting actuation step is implemented as an interrupt to the controller. As mentioned before, another assumption in our prior work is that a constant sequence of black and white droplets enter the loop device. As a pair of droplets exit the loop due to synchronization the number of droplets in the upper and lower branches are either equal or differ by one droplet. Remarkably, this automatically allows the droplets to sort if the valves are not actuated. This is because the initial loop configuration repeats for every pair for droplets. Therefore, whenever a droplet is detected the valves are set to have zero actuation, thereby ensuring sorting.

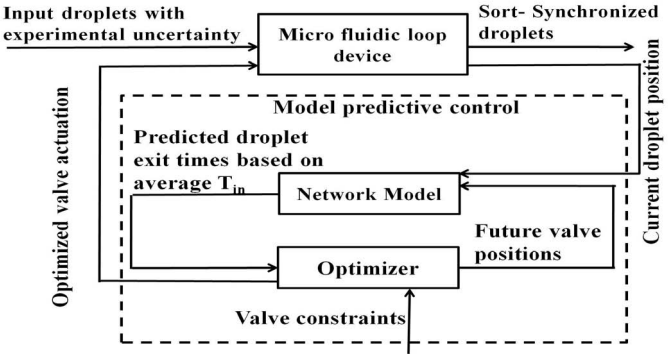

Fig. 2. Block diagram of MPC implementation. The dashed box contains the various components of MPC

We will now briefly summarize the MPC results from our prior work (Maddala et al. (2010)). It is shown that the proposed MPC works extremely well for a broad range of droplet dynamics. The MPC was tested on three different scenarios: *(i)* three period behavior without entrance time fluctuations (as observed from Poincaré map of the exit times), *(ii)* aperiodic period behavior, and *(iii)* three period behavior with input timing fluctuations(preliminary results). In the three period case, at any instant, two droplets travel in the lower branch and one droplet in the upper branch. After implementation of the controller, the droplets alternate between the lower and upper branches and are synchronized at the exit. 35 pairs of droplets were synchronized in a span of $3.3s$ with upper and lower branch actuation of 204 and 113 times respectively. In the second case the droplets choose the branches in a random fashion, resulting in aperiodic behavior in the Poincaré map. In this case, to synchronize 35 pairs of droplets, the upper and lower branches were actuated about 162 and 165 times respectively over a span of $4.2s$. In the third case, the prototypical model was simulated using the experimental inlet times, whereas MPC uses an average value of the inlet times. This demonstrated that MPC is an attractive approach for control of nonlinear discrete bubble microfludic systems. It has to be remarked that simple controllers such as PI will not be viable for this sort-synchronization control problem.

3. CONTROL OF MICROFLUIDIC LOOP DEVICE

As discussed in the previous section the two important assumptions are: *(i)* constant input droplet frequency (no disturbance) and *(ii)* constant input sequence. However, in real experimental situations, these assumptions may not be valid. In this work we study the robustness of the MPC approach to input disturbances in inlet droplet arrival times. We also develop enhancements to the MPC framework to address variations in the input sequence.

(I) Handling droplet inlet time variations: Inlet time variations need to be addressed in the prediction step of MPC. Since predictions are performed for a future time horizon, the exact droplet arrival times will become unavailable to MPC. We address this issue by assuming that all the future droplets (within the prediction horizon) arrive at a constant frequency that is the based on an average droplet

spacing of the prior droplets. No other modifications to the MPC algorithm are needed to handle this case. It is interesting to note that our approach will automatically introduce a model-plant mismatch that is unavoidable in stochastic systems.

(II) Input sequence anomaly: In experiments anomalies can occur that can disrupt the droplet sequence. Therefore, the MPC algorithm has to perform robust sort-synchronization in cases where the droplet sequence changes. In this paper we will show results for two anomalous sequences. The first case has one extra white or black droplet in the sequence ,*i.e.*, the sequence is (B, W, B, W... W, B, B, W...B, W, W, B...). In the second case two black droplets are followed by two white droplets (are vice versa), *i.e.*, the sequence is (B, W, B, W... W, B, B, W, W, B...B, W, W, B, B, W...). We propose enhancements in both the sorting and synchronization steps to address this problem.

(II.a) Sorting step enhancement: In the previous work as the droplets are assumed to alternate in the input sequence sorting is automatically addressed by the synchronization step. This is not the case now as the droplet sequence changes. Assume that the white and black droplets are to be synchronized into upper and lower branches. Consider two cases for a white droplet entering the device (similar arguments hold for a black droplet entering the device):

Case(i): The upper branch resistance is less than the lower branch.

$$\begin{aligned} &if\ C_{in} = \text{`}white\text{'}\ \&\ R_U < R_L \\ &\alpha_{L,new} = \alpha_{L,old} \\ &\alpha_{U,new} = \alpha_{U,old} \end{aligned} \tag{3}$$

where R_U and R_L are the resistances of upper and lower branches respectively and C_{in} is the color of the entering droplet. The resistance of a micro channel with droplets is calculated as:

$$\begin{aligned} R_U &= R_{C,U} + n_d R_d + \alpha R_{C,U} \\ R_{C,U} &= \tfrac{12\mu L}{h^3 w}\left[1 - \textstyle\sum_n^\infty \tfrac{1}{n^5}\tfrac{192}{\pi^5}\tfrac{h}{w}\tanh(\tfrac{n\pi w}{2h})\right]^{-1} \end{aligned} \tag{4}$$

In the equation above $R_{C,U}$ is the resistance of the upper rectangular channel, n_d is the number of droplets in the channel, α is the valve actuation parameter and is less than 0.68 (Abate and Weitz (2008)), h, w, and L are the height, width and length of the branch respectively. μ represents the viscosity of the bulk phase and n is the series index which takes only odd values. Similar equations define the resistance of the lower branch.

Case (ii): The lower branch offers less resistance than the upper branch. In this case, the upper branch actuation is reduced to zero and the lower branch resistance is increased in multiples of R_d until the lower branch resistance becomes higher than the upper branch.

$$\begin{aligned} &if\ C_{in} = \text{`}white\text{'}\ \&\ R_U > R_L \\ &until\ R_U < R_L \\ &\alpha_{U,new} = 0 \\ &\alpha_{L,new} = \tfrac{(kR_d)}{R_U} + \alpha_{L,old} + \tfrac{(R_U - R_L)}{R_U} \end{aligned} \tag{5}$$

In the above equation k is an integer that is incremented from 0 to k until the resistance condition is satisfied.

(II.b) Synchronization enhancement: In our previous work, as white and black droplets are assumed to alternate, synchronization was achieved by minimizing the error in exit times of alternate droplets. In this case because the alternate droplets may not be black and white, the objective function is modified with a penalty function. A penalty term that represents two black droplets or two white droplets exiting the loop is added to the objective function. This penalty term ensures that synchronization occurs.

$$\begin{aligned} \min_{\alpha_{(1,2,3),L},\alpha_{(1,2,3),U}} E \quad = \quad & \sum_{D=i}^{i+1}\{[T^D_{exit,L} - T^D_{exit,U}]^2 + \\ & \delta(C^D_L - C^D_U) * P\} \\ 0 \le\ & \alpha_{1,L}, \alpha_{1,U} \le\ 0.6 \\ 0 \le\ & \alpha_{2,L}, \alpha_{2,U} \le\ 1 \\ 0 \le\ & \alpha_{3,L}, \alpha_{3,U} \le\ 1 \end{aligned} \tag{6}$$

In the above equation E is sum of the squared errors of differences in exit times of i^{th} and $(i+1)^{th}$ pair of droplets, *i.e*, two from the upper branch and two from the lower branch and the penalty function. $T^i_{exit,L}$ and $T^i_{exit,U}$ are the exit times of i^{th} droplet in upper and lower branches respectively. C^D_L, C^D_U are the colors of the droplets exiting in the upper and lower branches. P is a large positive constant. δ is the Kronecker delta function; therefore, when the colors in the upper and lower branches are equal the value is 1, otherwise the value is zero.

4. RESULTS AND DISCUSSION

The enhanced MPC is implemented with input time disturbances and anomalies in the input sequence. Robustness of the proposed algorithm to input disturbance is shown for a aperiodic dynamics case. To demonstrate robustness to sequence anomaly, results for a three period case with two different anomalies are presented. Consider Figure 3 (A), which shows sorting in the presence of input disturbances. The droplets without actuation choose the branches randomly, whereas in the actuated case the droplets alternate between the upper and lower branches consistently. Figure 3 (B) shows the Poincaré map with and without actuation; the chaotic multi-period Poincaré map reduces to a simple two period map after the implementation of MPC. This is due to the synchronization of droplets which reduces the exit time difference between alternate pairs of droplets. The inset shows the synchronization error as a function of droplet index pair. It is observed that efficient synchronization is achieved after the implementation of MPC. The trajectories of droplets traveling in the upper and lower branches are shown in Figure 3 (C). As the droplets travel to the exit of the loop the distance between the droplets decrease and they merge at the exit of the microfluidic loop device. The actuation required to achieve this sort-synchronization is presented in Figure 3 (D). It is seen that both the upper and lower branches are actuated consistently unlike the case with no disturbance where the actuation is constant for large swaths of time (Maddala et al. (2010)). The periodic dips in the inset of Figure 3 (D) that are calculated by the MPC algorithm are necessary for sorting the droplets. The next result that we present is for anomalous input sequences. Two specific anomalies are considered as discussed in the previous section. The sorting results for the first anomalous sequence is presented in Figure 4(A). The circled area shows the sorting of two white droplets into the upper branch and two black droplets into the lower

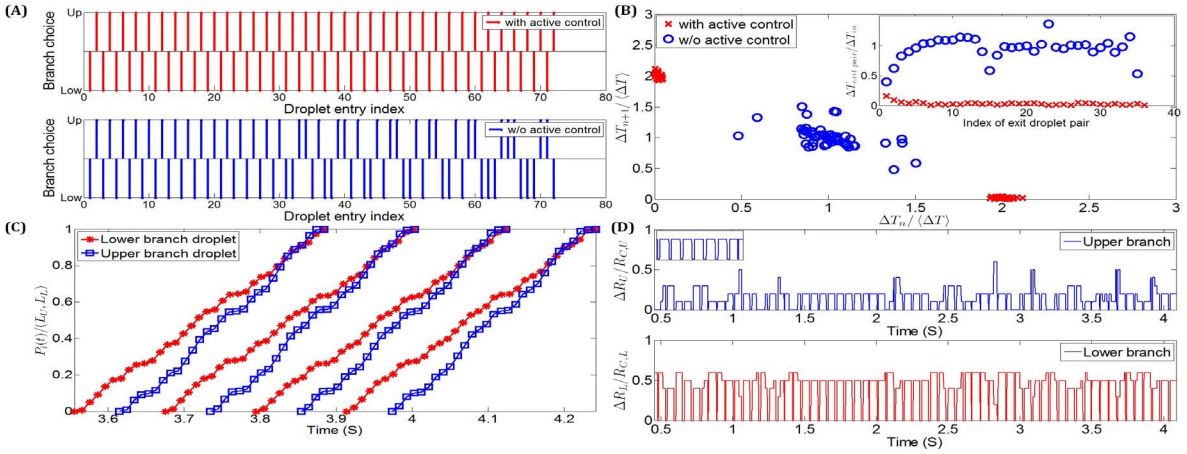

Fig. 3. Disturbance handling in the aperiodic case (A) Representation of droplet choices with respect to droplet index with and without actuation (B) Poincaré map for with and without actuation, the inset figure shows the plot of synchronization (C) Trajectories of upper and lower branch droplets (Position of the droplet normalized with the total length vs time) (D) Actuation (normalized with total resistance) as a function of time, the periodic dips in the actuation are seen in the inset

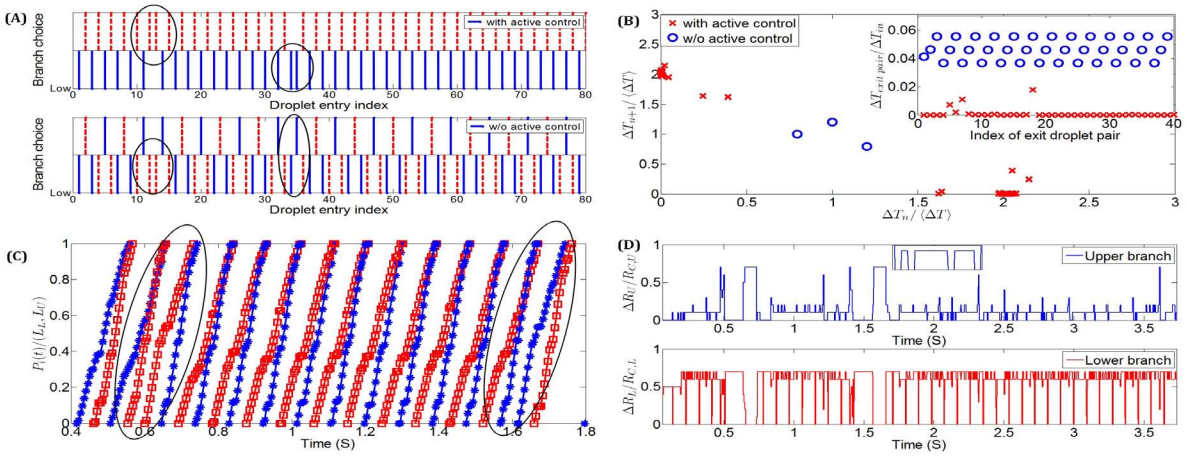

Fig. 4. Result for the first anomalous sequence(A) Representation of droplet choices with respect to droplet index with and without actuation (B) Poincaré map for with and without actuation, the inset figure shows the plot of synchronization (C) Trajectories of upper and lower branch droplets (Position of the droplet normalized with the total length vs time) (D) Actuation (normalized with total resistance) as a function of time, the magnified plot of the actuation is seen in the inset

branch respectively in the actuated case. Without actuation, the white and black droplets choose the branches randomly. Figure 4(B) shows the Poincaré maps. It is seen that efficient synchronization is achieved. The trajectory of these droplets is shown in Figure 4(C). The branches are actuated in such a way that the two white droplets are synchronized with the adjacent black droplets and vice-versa. Figure 4 (D) shows the actuation as a function of time; unlike the previous case there are less periodic dips in the actuation profile. Close to the sequence anomalies drastic resistance increase or decrease is required to achieve perfect sorting. It is also observed that the actuation is still within experimental constraints, which in this case is set as 70% Consider the second anomalous input sequence. This requires much more rigorous actuation as compared to the previous case. Figure 5(A) shows the sorting of the droplets with and without actuation. The white and black droplets with actuation are sorted consistently to the upper and lower branches respectively whereas without actuation the droplets are not sorted. The Poincaré maps with and without actuation are presented in Figure 5 (B). It is observed that the error increases near the input sequence change but the error is much less compared to the unsynchronized case. The trajectories of black and white droplets are shown in Figure 5 (C). It is seen in the circled area that the controller performs exceptionally well in handling the input sequence changes for sorting and synchronization. Figure 5 (D) shows the actuation as a function of time. It is seen that the actuation in the upper branch is intermittently on the constraint boundary. This is to achieve sorting of the droplets. This can be contrasted with the disturbance case where regular dips are necessary for sorting.

5. CONCLUSIONS

In this paper, the problem of sort-synchronization control in a prototypical microfluidic loop device was addressed. The control is achieved using a MPC framework. It was shown that the MPC performs exceptional sort-

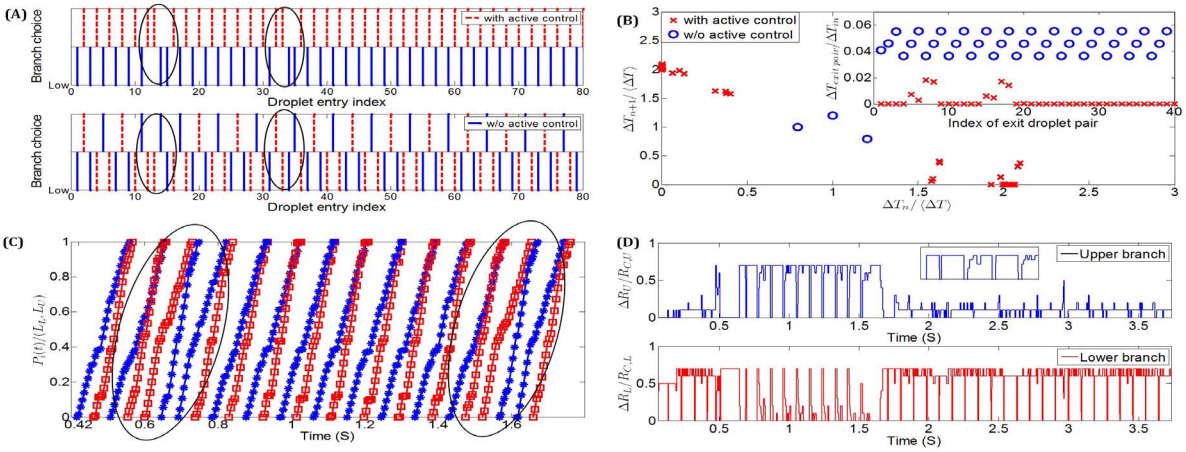

Fig. 5. Result for the second anomalous sequence (A) Representation of droplet choices with respect to droplet index with and without actuation (B) Poincaré map for with and without actuation, the inset figure shows the plot of synchronization (C) Trajectories of upper and lower branch droplets (Position of the droplet normalized with the total length vs time) (D) Actuation (normalized with total resistance) as a function of time, the magnified plot of the actuation is seen in the inset

synchronization control in the face of severe disturbances affecting the droplet input behavior. The true promise of the proposed MPC approach can be judged only through implementation in real experimental systems. While we expect similar performance in experimental systems as in the simulation studies, online optimization calculations that are required to be performed in a time frame of milliseconds will pose significant challenges.

REFERENCES

Abate, A.R. and Weitz, D.A. (2008). Single-layer membrane valves for elastomeric microfluidic devices. *Applied Physics Letters.*, 92, 243509(1)– 243509(3).

Abate, A.R., Agresti, J.J., and Weitz, D.A. (2010). Microfluidic sorting with high-speed single layer membrane valves. *Applied Physics Letters.*, 96, 203509(1)–203509(3).

Bhattacharjee, B. and Najjaran, H. (2010). Droplet position control in digital microfluidic systems. *Biomed Microdevices*, 12, 115–124.

Brouzes, E., Medkova, M., Savenelli, N., Marran, D., twardowski, M., Hutchison, J.B., Rothberg, J.M., Link, D.R., Perrimon, N., and Samuels, M.L. (2009). Droplet microfluidic technology for single-cell high throughput screening. *PNAS*, 106, 14195–14200.

Cristobal, G., Benoit, J.P., Jaonicot, M., and Ajdari, A. (2006). Microfluidic bypass for efficient passive regulation of droplet traffic at a junction. *Applied Physics Letters.*, 89, 034104(1)–034104(3).

Fuerstman, M.J., Garstecki, P., and Whitesides, G.M. (2007). Coding/decoding and reversibility of droplet trains in microfluidic networks. *Science*, 315, 828–832.

Haeberle, S. and Zengerle III, R. (2007). Microfluidic platforms for lab-on-chip applications. *Lab Chip.*, 7, 1094–1110.

Huebner, A., Srisa-Art, M., Holt, D., Abell, C., Hollfelder, F., deMello, A.J., and Edel, J.B. (2007). Quantitative detection od protein expression in single cells using droplet micrfluidics. *Chem. Commun.*, 1218–1220.

Jin, B.J., Kim, Y.W., Lee, Y., and Yoo, J.Y. (2010). Droplet merging in a straight microchannel using droplet size or viscosity difference. *J. Micromech Microeng*, 20, 035003(1)–035003(3).

Jousse, F., Lian, G., Janes, R., and Melrose, J. (2005). Compact model for multi-phase liquid-liquid flows in microfluidic devices. *Lab Chip.*, 5, 646–656.

Labrot, V., Schindler, M., Guillot, P., Colin, A., and Joanicot, M. (2009). Extracting the hydrodynamic resistance of droplets from their behavior in microchannel networks. *BioMicrofluidics.*, 3, 012804(1)–012804(16).

Maddala, J., Srinivasan, B., Bithi, S.S., Vanapalli, S.A., and Rengaswamy, R. (2010). Design of a model-based feedback controller for active sorting and synchronization of droplets in microfluidic loop. *article submitted to AIChE Journal.*

Prakash, M. and Gershenfeld, N. (2007). Microfluidic bubble logic. *Science*, 315, 832–835.

Schindler, M. and Ajdari, A. (2008). Droplet traffic microfluidic networks: A simple model for understanding and designing. *Physical Review Letters.*, 100, 044501(1)–044501(4).

Smith, B.J. and Gaver III, D.P. (2010). Agent-based simulations of complex droplet pattern formation in a two-branch microfluidic network. *Lab Chip.*, 10, 303–312.

Song, H., Chen, D.L., and Ismagilov, R.F. (2006). Reactions in droplets in microfluidic channels. *Angew. Chem. Int. Ed.*, 45, 7336–7356.

Zheng, B., Tice, J.D., and Ismagilov, R.F. (2004). Formation of droplets of alternating composition in micrfluidic channels and applications to indexing of concentrations in droplet based assays. *Anal Chem.*, 76, 4977–4982.