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Control of a microfluidic separation process governed by the Zweifach-Fung effect

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Abstract: This paper presents a microfluidic process of separation of a fluid containing particles. The control input is the ratio of flowrates in the two daughter channels of a bifurcation, which due to the Zweifach-Fung effect, has a direct but nonlinear effect on the particle volume fractions in the channels. The dead-volumes of the device and its capillary tubings cause an input-varying delay of hydraulic type. The paper presents several control problems of practical importance and formulates some concise problem statements for future research along with first simulation results.

Keywords: Microfluidics, device integration technologies, process control applications, control of micro- and nano-systems, control of particulate processes, delay systems, non-smooth and discontinuous optimal control problems

1. INTRODUCTION

This article presents an example of a microfluidic system using the Zweifach-Fung effect to enrich or filter a fluid containing particles in suspension. The aim of the article is to present several control problems that are challenging and of practical interest.

Microfluidics is the science of manipulating and controlling fluids at Reynolds numbers under 1 in very small quantities (microliters to picoliters), in arrays of channels whose diameters are much smaller than 1 mm (from a few tens to a few hundreds of micrometers), see e.g. Tabeling (2005). Microfluidic systems are used in process engineering, chemistry and biotechnology among others. In these domains their ability to handle small volumes with high precision is an essential asset. Microfluidics is an enabling technology for many lab-on-a-chip applications, such as molecular analysis, chemical synthesis, biomanufacturing, drug screening, organ and tissue modeling, clinical diagnostic testing, virus detection and manipulation, etc. Microfluidic microsystems typically consist of complex arrays of channels, used to handle fluids in a way that allows them to interact, be mixed, measured, or encapsulated within each other, according to a desired process scheme. The network of channels consists of inlets, zigzag, cross, split, traps, pillars, among others typical architectures, see Paratore et al. (2021) for a state-of-the-art overview. The fluid mechanics at stake in microfluidic systems is highly dependent on the complex geometry of the network. A phenomenon that has received particular attention in this field is the Zweifach-Fung effect (see Fung and Zweifach (1971)), a.k.a. *bifurcation law*. It can be described as follows (see Doyeux et al. (2010, 2011)): when a suspension of particles reaches an asymmetric bifurcation, the particles volume fractions in the two daughter branches are not equal. In details, for branches of comparable geometrical characteristics, but receiving different flowrates, the volume fraction in particles increases in the high flowrate branch.

Interestingly, this effect can serve to engineer sorting or purification devices, see e.g. Yang et al. (2006). In such systems, channels have square section of 40 µm, lengths of 20 mm. Volumes to be treated are 30 µL over 30 min and the purification requirements are s.t. concentration must be handled with an accuracy of 1 %. Many studies have concentrated on establishing empirical and theoretical laws describing the separation of particles in the two daughter branches of the main channel. Depending on various parameters such as widths, angles of the branches and size of particles, several semi-analytical laws have been proposed to describe the particle volume fraction in the two branches as a function of the flowrate ratios between them, see e.g. Dellimore et al. (1983); Guibert et al. (2010). One can refer to Doyeux et al. (2010) for a comprehensive analysis of these laws.

This paper exposes some control challenges worth investigating for controlling such a process governed by the Zweifach-Fung effect. The simplest microfluidic set-up one can consider is pictured in Fig. 1. A main channel is used to transport a suspension contained in a (inlet) reservoir. Then, it reaches a bifurcation consisting of two equal dimension daughter branches. The bifurcation at stake is a T-shaped bifurcation (alternatively a Y-shape could be considered without loss of generality, see again Doyeux et al. (2010)). The main channel and its daughter branches are contained in a single microfluidic chip . The inlet of the main channel and the outlets of the branches are connected through capillary tubings to three reservoirs. The pressures at the three ports of the microfluidic chip are controlled (because the reservoirs are pressurized with a high level of accuracy, and the fluid is incompressible) so that the flowrates can be chosen. In the control problems under consideration in this article, the output of interest is the volume fraction in one of the output reservoirs, which can be controlled by changing the ratio between the flowrates of the daughter branches.

The paper is organized as follows. In Section 2, we briefly detail the model, and present a concise set of equations governing the system. The key properties of the dynamics is that it is nonlinear, mostly due to the Zweifach-Fung effect, and are subjected to an input-varying delay of hydraulic type. In Section 3, we illustrate some of its surprisingly complex behavior, in open loop. In Section 4 we expose the main challenges for application of optimization based techniques such as Model Predictive Control.

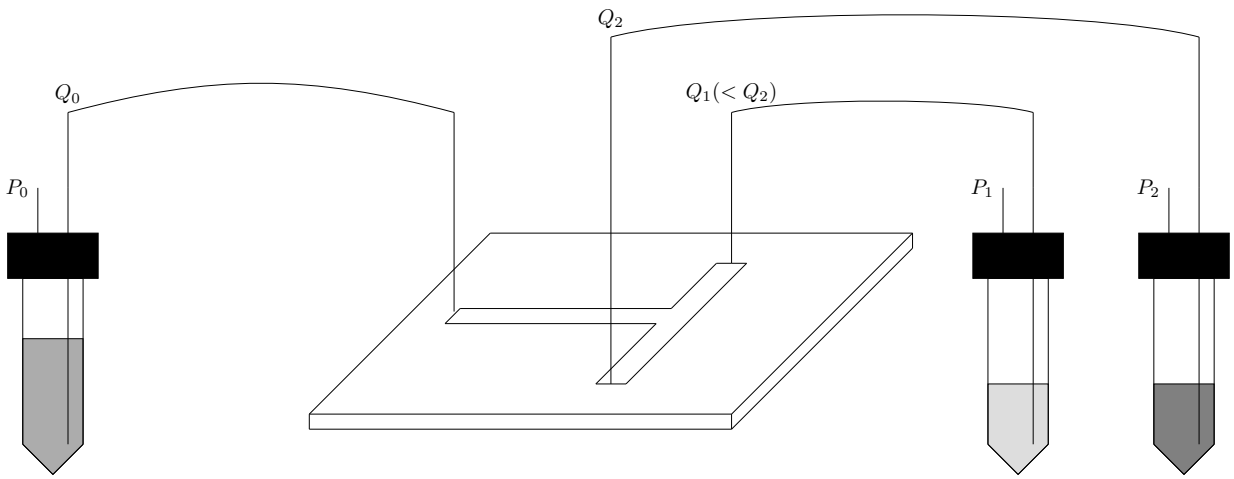

Fig. 1. Separation process using the Zweifach-Fung effect. A fluid containing particles flows from the inlet reservoir through a microfluidic device within which it reaches a bifurcation and finally flows to the outlet reservoirs. The flowrates Q_0, Q_1, Q_2 are controlled by the pressures P_0, P_1, P_2 in the reservoirs.

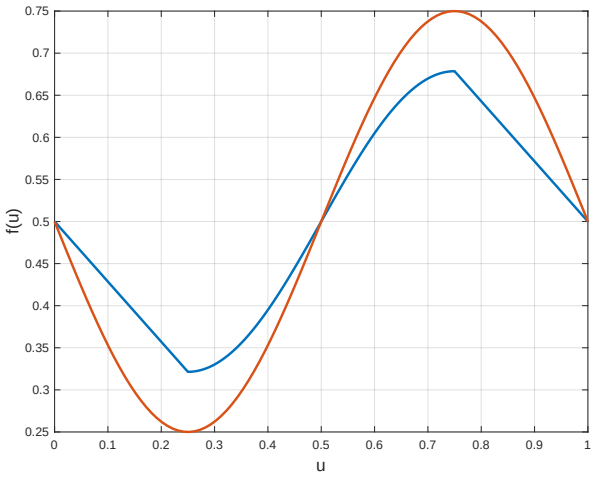

Fig. 2. Two examples of possible functions bifurcation laws f. Blue: (adapted from Doyeux et al. (2011). Red: (sinusoidal) simplified version.

In Section 5, we discuss closed-loop stabilization. Some conclusions and perspectives are given in Section 6.

2. MODEL OF THE DYNAMICS

Consider the system pictured in Fig. 1. Note Q_0, Q_1, Q_2 the (volume) flowrates in the input, and two daughter (output) channels (1 and 2). The fluid (suspension) contained in the reservoir consists of a solvent and particles. Using pressure controllers, it can be considered that the ratio

$$u = \frac{Q_1}{Q_0} \in [0,\, 1]$$

is a control variable while Q_0 is kept constant. Conservation of volume implies that $Q_2 = Q_0 - Q_1$. When u is changed, then the volume fraction after the bifurcation point is altered. Define $f(u)$ the volume fraction in channel 1 (right after the bifurcation). Its graph is of the form presented in Fig. 2 (adapted from Doyeux et al. (2011)). Because the daughter channels have similar geometries, the function f is symmetric.

The outlet of channel 1 flows in an incompressible manner, with no back mixing, into a reservoir. The reservoir contains a volume v of particles which dynamics is

$$\dot{v} = f(u(t - D(t)))\, Q_0\, u \tag{1}$$

where D is a hydraulic delay corresponding to the volume V_0 of channel 1 (from the bifurcation to the reservoir, thought the capillary tubing). As for many systems involving transportation of material, see e.g. Bresch-Pietri and Petit (2016); Chèbre et al. (2010), a delay appears in the dynamics which is defined through an implicit integral equation [1] . Such delays are referred to as *hydraulic delays*. In Eq. (1), this delay is visible on the volume fraction as it propagates without being altered in the channel (there is no back mixing), but not to the flowrate which is uniform in the channel due to incompressibility. The implicit equation is

$$\int_{t-D(t)}^{t} u(\tau)d\tau = \Gamma \triangleq \frac{V_0}{Q_0} > 0 \tag{2}$$

The output of interest is the volume fraction in the reservoir. Assuming it is empty at $t = 0$, one has

$$y(t) = \frac{1}{Q_0}\frac{v}{\int_0^t u(\tau)d\tau} = \frac{\int_0^t f(u(\tau - D(\tau))u(\tau)d\tau}{\int_0^t u(\tau)d\tau}$$

In practice, y can be measured. A cytometer is located at the outlet of channel 1, after the hydraulic delay. These notations allow us to formulate a first problem of practical interest for this microfluidic separation system.

Problem 1. Consider the two states systems $\dot{x}_1(t) = f(u(t - D(t))u(t)$, $\dot{x}_2(t) = u(t)$, with single output $y(t) = x_1(t)/x_2(t)$ and single input $u(t) \in [0,\, 1]$, find a closed loop controller able to asymptotically stabilize any feasible setpoint.

3. OPEN LOOP BEHAVIOR

The system described in Problem 1 has a surprisingly complex behavior. For example, its transient responses to a positive step and to a negative step vastly differ (parameter Γ was set to 1). These differences are illustrated in Figs. 3 and 4 using square inputs signals. Short durations

[1] This equation stems from an exact resolution of the transport partial differential equation with variable velocity, (Bresch-Pietri and Petit, 2016, Lemma 1.1).

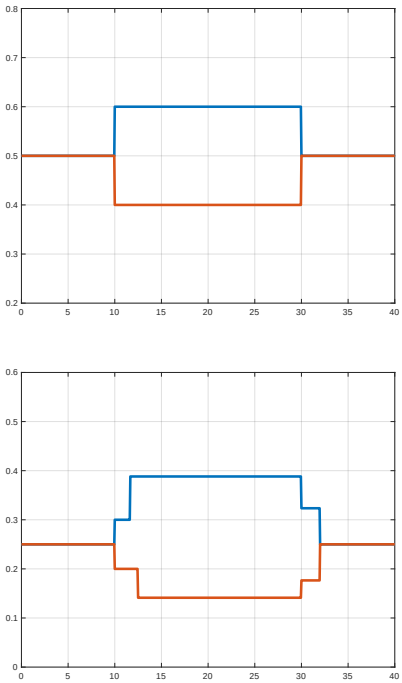

Fig. 4. Long-duration square signals showing a non symmetric responses to step signals (top: input signals, bottom: right-hand sides of the first state differential equation).

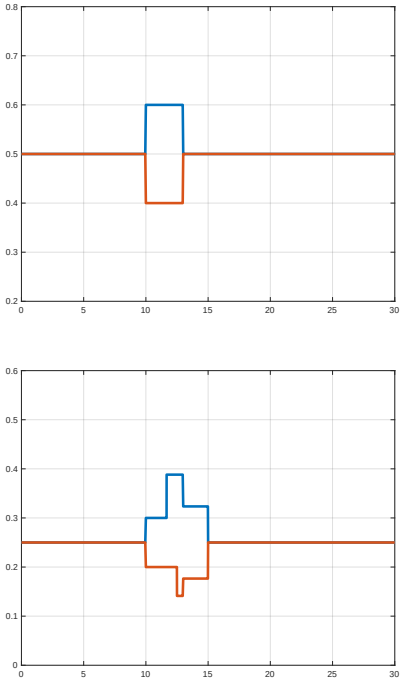

Fig. 3. Short-duration square signals showing a non symmetric responses to step signals (top: input signals, bottom: right-hand sides of the first state differential equation).

are below the typical settling time of 5 s for this system setup. The figures report the right-hand sides of the first state differential equation in response to various square signals. The two culprits of the observed dissimilarities are the nonlinearity f (generating an expected nonlinear asymptotic gain, visible in Fig. 4) and the time-varying delay depending on the input whose effects include the possible appearance of a strong peak when the delay is reduced (see Fig. 3). These simulation results are obtained using a method discussed below.

Numerical simulation of the dynamics

To obtain reliable simulation results of the input-dependent varying delay dynamics, special care is required on the numerical side. As noted in Clerget (2017), delays require specific tools in their numerical simulation. A rich body of literature has long studied the numerical simulation of delay-differential algebraic equations (DDAE). Useful references can be found in Banks and Kappel (1979), Karoui and Vaillancourt (1994) or Ascher and Petzold (1995).

A classic idea is to replace it with the underlying transport equation governing the system (*e.g.* Shi et al. (2016)). Formally, this change of representation does not generate any approximation (equation (2) is the exact solution of the PDE, see Bresch-Pietri (2012)).

In turn this requires the discretization of the transport PDE. It is well-known that good numerical schemes can be obtained for transport phenomena using finite volumes methods (see Leveque (2004)). Classically, space is divided into a set of cells over which averaged properties are defined.

The approach described in Agarwal (2010) based on the use of the Method of Lines (MOL) by discretizing the PDE only with respect to space into a set of ordinary differential equations can be used. It is a second-order accurate scheme defined over a regular mesh.

Comparable results can be obtained using a full discretization approach (both w.r.t. time and space) using the following a second order accurate scheme. To obtain reliable results, it should be remembered that this type of finite volumes numerical schemes is stable only if the Courant-Friedrichs-Lewy (see e.g. Allaire (2007)) condition is verified (bearing on Δt the step size and Δx the spatial resolution). This condition is instrumental in setting up the numerical scheme.

4. OPTIMIZATION BASED-CONTROL

Considering the relative simplicity (more precisely the conciseness) of the formulation of Problem 1, it is tempting to try to solve it with a classic Model Predictive Control methodology, see for example Sbarciog et al. (2008) for a typical application to a related problem. Even if the discussion about the non symmetric nature of the system behavior near equilibrium presented in Section 3 might stress some possible difficulty, a main obstruction has not been discussed yet.

The system controllability remains to be established although the first part of the dynamics has already been studied and be shown to be controllable in a very general sense. This point is discussed below in Section 4.1. However, a more hidden pitfall is that any general optimal control problem formulated for the dynamics of problem 1 is (most likely) non smooth and will therefore reveal particularly troublesome for numerical solvers in its present form. This point is covered in Section 4.3.

4.1 Motion planning

The dynamics under consideration is actually close to the dynamics of blending (or dilution dynamics) studied

in other contexts. Adding functions composition and inversion to the usual algebraic computation rules, it was shown in Petit et al. (1998) that such systems are controllable in the sense of Willems (1991), i.e. that their trajectories could be explicitly parameterized in the sense of flat systems (see Fliess et al. (1999)) so that from a prescribed past trajectory on $]-\infty, 0]$ a trajectory could be constructed on $[0, T]$ for some $T > 0$ connecting to a future trajectory over $[T, +\infty[$. In these systems, the flat output under consideration is

$$Y(t) = \int_0^t u(\ell) d\ell$$

This variable serves to parameterize several of the variables at stake here. Indeed

$$Y(t) - Y(t - D(t)) = \Gamma$$

which gives

$$D(t) = t - Y^{(-1)}(Y(t) - \Gamma)$$

which is legit as Y can be assumed strictly monotonic when $u > 0$, and thus is invertible. Here, the two additional states x_1 and x_2 can be defined by integration (up to some initial condition) of right-hand sides solely defined by Y past values.

$$\dot{x}_1 = f(\dot{Y}(Y^{(-1)}(Y(t) - \Gamma))\,\dot{Y}(t), \quad \dot{x}_2 = \dot{Y}(t)$$

to account for the initial conditions in the reservoir. Motion planning can be readily addressed by means of scheduling a smooth and monotonic trajectory for Y, the end points and the transient of which being determined according to the desired target in the reservoir.

The relation above also shows that the delay can be easily bounded by assumptions on Y and its inverse. It gives, under some appropriate assumptions, see again Petit et al. (1998), that the transient is achieved in finite time. In practice this controllability result is only a first step, and optimal transients are desired. This is discussed next.

4.2 Two optimal control problems of practical interest

A first problem of practical interest is to reach a desired concentration in the reservoir in minimum time. The solution might not be a simple as one can anticipate it due to the properties of the function f governing the separation at the bifurcation point.

Problem 2. Consider the input-output description of Problem 1 and some initial conditions for x_1, x_2, and some past values for u. Let $y^{\text{sp}} \in (0, 1)$, solve $\min T$, where T is s.t. $y(T) = y^{\text{sp}}$.

A second problem of interest expresses an optimal output tracking problem while limiting the variations of the control. To formulate this, a state extension is considered.

Problem 3. Consider the input-output description of Problem 1 and some initial conditions for x_1, x_2, and some past values for u. Further consider the extra dynamic $\dot{u} = v$. Let $y^{\text{sp}} \in (0, 1)$, solve $\min \int_0^T ||y(t) - y^{\text{sp}}||^2 + w||v(t)||^2 dt$ for some fixed parameters $w > 0$ and $T > 0$.

4.3 Non smoothness related to hydraulic delays

Strictly speaking, the study of the calculus of variations for optimal control problems subject to time-varying delays in the dynamics is not a new subject. At first, it seems that the historical results of Banks (1968); Asher and Sebesta (1971), which can be seen as an extension to Hughes (1968) given for fixed delays, could be applied to solve Problem 2 and Problem 3. Indeed in this seminal work, necessary stationarity conditions were derived for a system subject to multiple fixed time-varying delays (i.e. depending once for all on t only and not on the state nor the control).

However, the dependency of the delay on the input make these results incomplete and some extra terms, possibly non-smooth appear. By expressing all the mutual interactions between the variables, it was shown in Clerget and Petit (2020) under which condition such an optimal control problem for a system subjected to a hydraulic delay is Gâteaux differentiable. It was also shown that this input dependency of the delay generally make the system violate these conditions.

To treat such optimal control problems, it was suggested to introduce a (smooth) regularized version of the problem and derive its stationarity conditions. The regularization can be shown to converge, i.e. it produces a sequence of solutions converging in a functional sense to the actual non-smooth solution when the regularization parameter is gradually reduced. Interestingly, this latter result can be seen as a refinement of the results of the pioneer work of Asher and Sebesta (1971) to the case of an hydraulic delay, under regularization. The sequence consists of fixed time-varying delayed optimal control problems. Each of these problems is defined using a sensitivity analysis stemming from the adjoint equations defined by the calculus of variations. A penalty term prevents the control from deviating too much between the two consecutive problems in the sequence, and a strong convexity results guarantees convergence.

The general optimal control problem covered by the previously described study is as follows. We recall it to highlight the role of the delay dependency.

Let $\phi : \mathbb{R}^p \to \mathbb{R}_+^*$ be a smooth function. Take some initial conditions (over a finite past) $(u_0, x_0) \in C^1_{pw}([r_0; 0], \mathbb{R}^p) \times D^1([r_0; 0], \mathbb{R}^p)$, $r_0 < 0$ with $\int_{r_0}^0 \phi(u_0(\tau))\, \mathrm{d}\tau = 1$. Consider the optimal control problem with input-dependent delays

$$\begin{aligned} \min_u \int_0^T L(t, x(t), u(t))\, \mathrm{d}t + \psi(x(T)) \triangleq J_0(u) \\ s.t. \quad \forall t \in [0; T],\ \dot{x}(t) = f(t, x(t), x(r_u(t)), u(t), u(r_u(t))) \\ x_{[r_0;0]} = x_0,\ u_{[r_0;0]} = u_0 \end{aligned}$$

where r_u is defined by the relation $\int_{r_u(t)}^t \phi(u(\tau))\, \mathrm{d}\tau = 1$. The following useful preliminary result stresses the main issue of general non-differentiability

Proposition 1. Sensitivity of hydraulic delay w.r.t. input variations Clerget and Petit (2019) For any $t \in [0; T]$, $(u, h) \in C^1_{pw}([0; T], \mathbb{R}^p)^2$ and $s \in \{-1; 1\}$, we have

$$\lim_{\substack{\delta \to 0 \\ s}} \frac{r_{u+\delta h}(t) - r_u(t)}{\delta} =$$

$$\frac{1}{\lim\limits_{\substack{\tau \to r_u(t) \\ s'}} \phi(u(\tau))} \int_{r_u(t)}^t \frac{\partial \phi}{\partial u}(u(\tau)) h(\tau)\, \mathrm{d}\tau$$

where

$$s' = \operatorname{sign}\left(s \cdot \int_{r_u(t)}^t \frac{\partial \phi}{\partial u}(u(\tau)) h(\tau)\, \mathrm{d}\tau \right)$$

In particular, if u is continuous at $r_u(t)$, the Gâteaux derivative of $r_u(t)$ w.r.t. the input at point u in the direction h is

$$\begin{aligned} D_h r_u(t) &\triangleq \lim_{\delta \to 0} \frac{r_{u+\delta h}(t) - r_u(t)}{\delta} \\ &= \frac{1}{\phi(u(r_u(t)))} \int_{r_u(t)}^t \frac{\partial \phi}{\partial u}(u(\tau)) h(\tau)\, \mathrm{d}\tau \end{aligned}$$

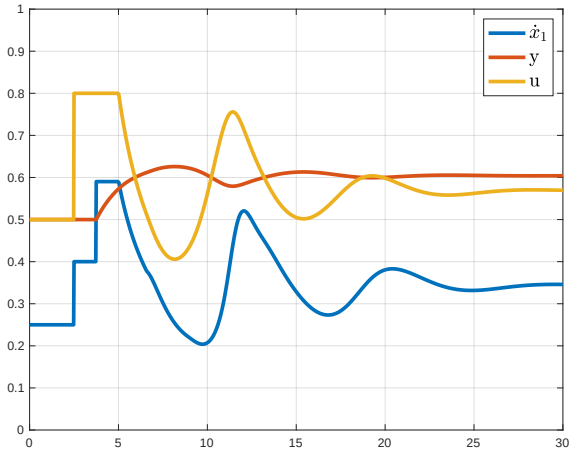

Fig. 5. Closed-loop performance on Problem 1.

Similarly, for any $t \in [0; r_u(T)[$

$$\lim_{\substack{\delta \to 0 \\ s}} \frac{r_{u+\delta h}^{-1}(t) - r_u^{-1}(t)}{\delta} =$$

$$- \frac{1}{\lim\limits_{\substack{\tau \to r_u^{-1}(t) \\ s'}} \phi(u(\tau))} \int_t^{r_u^{-1}(t)} \frac{\partial \phi}{\partial u}(u(\tau))h(\tau)\,\mathrm{d}\tau$$

where

$$s' = \mathrm{sign}\left(-s \cdot \int_t^{r_u^{-1}(t)} \frac{\partial \phi}{\partial u}(u(\tau))h(\tau)\,\mathrm{d}\tau \right)$$

and if u is continuous at $r_u^{-1}(t)$ (which is not need), the Gâteaux derivative is given by

$$D_h r_u^{-1}(t) = -\frac{1}{\phi(u(r_u^{-1}(t)))} \int_t^{r_u^{-1}(t)} \frac{\partial \phi}{\partial u}(u(\tau))h(\tau)\,\mathrm{d}\tau$$

This last expression can be checked to see the jumps.

On the algorithm side, the resolution of the successive problems can be performed using a direct collocation transcription method (see e.g. Biegler (1984)), with AMPL as algebraic modeling language and IPOPT as NLP solver (see details in Clerget (2017)). Adjoint equations are resolved through a discretization scheme and used to formulate the next problem in the sequence.

5. CLOSED-LOOP CONTROL

This last section finishes the panorama of basic questions of control interest for the separation process under consideration.

5.1 Stabilisation by means of small gains

To a desired reference for the output, there corresponds a constant value for $\dot{x}_1$ and one (possibly several depending on the function f) setpoint for u. Problem 1 can be treated, using a small gain controller, in a vicinity of the initial conditions. Indeed, assuming that the initial conditions correspond to a non zero value of the derivative of f, then the dynamics of x_1 can be approximated, for some $\alpha > 0$, $\epsilon \neq 0$

$$\dot{x}_1 = (\alpha + \epsilon u(t - D(t))u(t), \quad \dot{x}_2 = u(t) \tag{3}$$

$$y(t) = x_1(t)/x_2(t) \tag{4}$$

A linearizing feedback can be easily derived so that x_1 tracks any given feasible and constant reference. Because this reference is not varying, then it can be shown that the linearizing feedback strategy is always feasible. A sequence of cascaded inequalities could be established, as in Bresch-Pietri et al. (2018), to prove that, in turn, the delay remains within some specified bounds. These bounds can serve to define a sequence of time intervals over which uniform w.r.t. time bounds can be established. A conservative bound on the initial condition is usually sufficient to grant asymptotic convergence, by breaking the inter-dependency of the cascade of inequalities. It serves to bound the value of ϵ and to use this bound in the definition of the initial condition on the states x_1. However, to account for the second state x_2 in the definition of y it is necessary to bias the reference signal of x_1 or to increase the gain over time. This causes more advanced difficulties.

An example of performance obtained with a linear saturated controller is pictured in Fig. 5 for a step change of the output setpoint to $y^{\mathrm{sp}} = 0.6$.

5.2 Sampled measurement feedback

Measurement of the concentration y is usually performed using one of the current cytometry technique, among which are image cytometers, flow cytometers and time-lapse cytometers, see e.g. McKinnon (2018); Han et al. (2016). These techniques all have relatively long processing times, and can only treat fluid samples outside of the reservoir, causing an additional lag. Therefore, a formula representing these specifities and limitation is to model the measurement of y as follows

$$y^{\mathrm{meas}}(t_i) = y(t_i - D_m(t_i)) + \varepsilon_i$$

where information is only available at instants t_i (forming an increasing sequence going to ∞, almost ideally spaced over a regular time grid) and $D_m(t_i)$ is a measurement delay, which can be considered as randomly distributed as in Kong and Bresch-Pietri (2020) or depending on the value of y itself as in Bekiaris-Liberis and Krstic (2013b,a). A stochastic framework to model the noise ε_i is required, see e.g. Min et al. (2019). The fact that the delay in the dynamics changes when the control changes complexifies significantly the analysis beyond what is usually considered, see e.g. Choi and Lim (2009).

6. CONCLUSION AND PERSPECTIVES

The purpose of this paper is to highlight a simple yet surprisingly rich and difficult to control nonlinear dynamics under input varying delay of hydraulic type. This microfluidic system has some great interest in the community of lab-on-chips and there is little doubt that controlling it with a high level of performance, fast transients and strong disturbance rejection capabilities could be very beneficial in many situations where the handled fluids have very high costs, such as stem cells for example as is done in many biological applications Zhang et al. (2012); Zhang and Austin (2012). It is believed that a sophisticated predictor-based controller could solve Problem 1. On the other hand Problem 2 and Problem 3 could be directly addressed by the recent results on optimal control of such systems. Microfluidics devices handle very tiny volumes but their time constants are macroscopic (of the order of 1 or 2 sec), so it is not unlikely that online optimization should be possible. Finally, the sampling issue discussed in Section 5.2 remains vastly opened but of critical importance at the light of current measurement systems noises.

REFERENCES

Agarwal, A. (2010). *Advanced Strategies for Optimal Design and Operation of Pressure Swing Adsorption Processes*. Ph.D. thesis, Carnegie Mellon University.

Allaire, G. (2007). *Numerical analysis and optimization: an introduction to mathematical modelling and numerical simulation*. Oxford University Press.

Ascher, U.M. and Petzold, L. (1995). The numerical solution of delay-differential-algebraic equations of retarded and neutral type. *SIAM Journal on Numerical Analysis*, 32(5), 1635–1657.

Asher, R.B. and Sebesta, H.R. (1971). Optimal control of systems with state-dependent time delay. *International Journal of Control*, 14(2), 353–366.

Banks, H.T. (1968). Necessary conditions for control problems with variable time lags. *SIAM Journal on Control*, 6(1), 9–47.

Banks, H.T. and Kappel, F. (1979). Spline approximations for functional differential equations. *Journal of Differential Equations*, 34(3), 496–522.

Bekiaris-Liberis, N. and Krstic, M. (2013a). Compensation of state-dependent input delay for nonlinear systems. *IEEE Transactions on Automatic Control*.

Bekiaris-Liberis, N. and Krstic, M. (2013b). Nonlinear control under delays that depend on delayed states. *European Journal on Control, Special Issue for the ECC13*.

Biegler, L.T. (1984). Solution of dynamic optimization problems by successive quadratic programming and orthogonal collocation. *Computers & chemical engineering*, 8(3-4), 243–247.

Bresch-Pietri, D. (2012). *Robust control of variable time-delay systems. Theoretical contributions and applications to engine control*. Ph.D. thesis, Mines ParisTech.

Bresch-Pietri, D., Mazenc, F., and Petit, N. (2018). Robust compensation of a chattering time-varying input delay with jumps. *Automatica*, 92, 225–234.

Bresch-Pietri, D. and Petit, N. (2016). Implicit integral equations for modeling systems with a transport delay. In *Recent Results on Time-Delay Systems*, 3–21. Springer.

Choi, H.L. and Lim, J.T. (2009). Output feedback regulation of a chain of integrators with an unknown time-varying delay in the input. *IEEE Transactions on Automatic Control*, 55(1), 263–268.

Chèbre, M., Creff, Y., and Petit, N. (2010). Feedback control and optimization for the production of commercial fuels by blending. *Journal of Process Control*, 20(4), 441–451.

Clerget, C.H. (2017). *Contributions to the control and dynamic optimization of processes with varying delays*. Ph.D. thesis, PSL University.

Clerget, C.H. and Petit, N. (2019). Dynamic optimization of processes with time varying hydraulic delays. *Journal of Process Control*, 83, 20–29.

Clerget, C.H. and Petit, N. (2020). Optimal control of systems subject to input-dependent hydraulic delays. *IEEE Transactions on Automatic Control*, 66(1), 245–260.

Dellimore, J.W., Dunlop, M.J., and Canham, P.B. (1983). Ratio of cells and plasma in blood flowing past branches in small plastic channels. *American Journal of Physiology-Heart and Circulatory Physiology*, 244(5), H635–H643.

Doyeux, V., Podgorski, T., Peponas, S., Ismail, M., and Coupier, G. (2010). Behavior of flowing bodies near a bifurcation: Elucidating the Zweifach-Fung effect. In *2nd European Conference on Microfluidics*, 1–17.

Doyeux, V., Podgorski, T., Peponas, S., Ismail, M., and Coupier, G. (2011). Spheres in the vicinity of a bifurcation: elucidating the Zweifach–Fung effect. *Journal of Fluid Mechanics*, 674, 359–388.

Fliess, M., Lévine, J., Martin, P., and Rouchon, P. (1999). A Lie-Bäcklund approach to equivalence and flatness of nonlinear systems. *IEEE Transactions on automatic control*, 44(5), 922–937.

Fung, Y. and Zweifach, B. (1971). Microcirculation: mechanics of blood flow in capillaries. *Annual Review of Fluid Mechanics*, 3(1), 189–210.

Guibert, R., Fonta, C., and Plouraboué, F. (2010). A new approach to model confined suspensions flows in complex networks: application to blood flow. *Transport in porous media*, 83(1), 171–194.

Han, Y., Gu, Y., Zhang, A.C., and Lo, Y.H. (2016). Imaging technologies for flow cytometry. *Lab on a Chip*, 16(24), 4639–4647.

Hughes, D.K. (1968). Variational and optimal control problems with delayed argument. *Journal of optimization theory and applications*, 2, 1–14.

Karoui, A. and Vaillancourt, R. (1994). Computer solutions of state-dependent delay differential equations. *Computers & Mathematics with Applications*, 27(4), 37 – 51.

Kong, S. and Bresch-Pietri, D. (2020). Constant time horizon prediction-based control for linear systems with time-varying input delay. *IFAC-PapersOnLine*, 53(2), 7665–7670.

Leveque, R.J. (2004). *Finite Volumes Methods for Hyperbolic Problems, Cambridge texts in applied mathematics*. Cambridge University Press.

McKinnon, K.M. (2018). Flow cytometry: an overview. *Current protocols in immunology*, 120(1), 5–1.

Min, H., Xu, S., Zhang, B., and Ma, Q. (2019). Output-feedback control for stochastic nonlinear systems subject to input saturation and time-varying delay. *IEEE Transactions on Automatic Control*, 64(1), 359–364.

Paratore, F., Bacheva, V., Bercovici, M., and Kaigala, G.V. (2021). Reconfigurable microfluidics. *Nature Reviews Chemistry*, 1–11.

Petit, N., Creff, Y., and Rouchon, P. (1998). Motion planning for two classes of nonlinear systems with delays depending on the control. In *Proc. of the 37th IEEE Conference on Decision and Control*, 1007–1011.

Sbarciog, M., De Keyser, R., Cristea, S., and De Prada, C. (2008). Nonlinear predictive control of processes with variable time delay. a temperature control case study. In *2008 IEEE International Conference on Control Applications*, 1001–1006. IEEE.

Shi, J., Biegler, L.T., and Hamdan, I. (2016). Optimization of grade transitions in polyethylene solution polymerization processes. *AIChE Journal*, 62(4), 1126–1142.

Tabeling, P. (2005). *Introduction to microfluidics*. OUP Oxford.

Willems, J.C. (1991). Paradigms and puzzles in the theory of dynamical systems. *IEEE Transactions on automatic control*, 36(3), 259–294.

Yang, S., Ündar, A., and Zahn, J.D. (2006). A microfluidic device for continuous, real time blood plasma separation. *Lab on a Chip*, 6(7), 871–880.

Zhang, Q. and Austin, R.H. (2012). Applications of microfluidics in stem cell biology. *BioNanoScience*, 2(4), 277–286.

Zhang, W., Kai, K., Choi, D.S., Iwamoto, T., Nguyen, Y.H., Wong, H., Landis, M.D., Ueno, N.T., Chang, J., and Qin, L. (2012). Microfluidics separation reveals the stem-cell–like deformability of tumor-initiating cells. *Proceedings of the National Academy of Sciences*, 109(46), 18707–18712.