Optimal Fuzzy Sliding-Mode Control for Microcontroller-based Microfluidic Manipulation in Biochip System

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Abstract: In biometric and biomedical applications, a special transporting mechanism must be designed for the μTAS (micro total analysis system) to move samples and reagents through the microchannels that connect the unit procedure components in the system. An important issue for this miniaturization and integration is microfluid management technique, i.e., microfluid transportation, metering, and mixing. In view of this, this study presents an optimal fuzzy sliding-mode control (OFSMC) design based on the 8051 microprocessor and implementation of a complete microfluidic manipulated system implementation of biochip system with a pneumatic pumping actuator, a feedback-signal photodiodes and flowmeter. The new microfluid management technique successfully improved the efficiency of molecular biology reaction by increasing the velocity of the target nucleic acid molecules, which increases the effective collision into the probe molecules as the target molecules flow back and forth. Therefore, this hybridization chip was able to increase hybridization signal 6-fold and reduce non-specific target-probe binding and background noises within 30 minutes, as compared to conventional hybridization methods, which may take from 4 hours to overnight. In addition, the new technique was also used in DNA extraction. When serum existed in the fluid, the extraction efficiency of immobilized beads with solution flowing back and forth was 88-fold higher than that of free-beads.

Keywords: μTAS, optimal fuzzy sliding-mode control, 8051 microprocessor, biochip system, hybridization chip

1. INTRODUCTION

In recent years, research on biomedical or biochemical analysis miniaturization and integration has made explosive progress. For example, capillary electrophoresis (CE), sample preconcentration, genomic DNA extraction, and DNA hybridization have been successfully miniaturized and operated in a single-step chip. However, there is still a considerable technical challenge in integrating these procedures into a multiple-step system. In biometric and biomedical applications, a special transporting mechanism must be designed for the μTAS (micro total analysis system) to move samples and reagents through the microchannels that connect the unit procedure components in the system. Therefore, an important issue for this miniaturization and integration is microfluid management, i.e., microfluid transportation, metering, and mixing. In order to achieve microfluid management, this study presents the optimal fuzzy sliding-mode control (OFSMC) design based on the 8051 microprocessor and the complete microfluidic manipulated system implementation of biochip system with a pneumatic pumping actuator and a feedback-signal flowmeter.

However, the relationships among the pumping mechanisms, the operating conditions of the devices, and the transporting behavior of the multi-component fluids in these channels are quite complicated. To overcome the main disadvantages of mechanical valves using moving parts - the complexity and expense of fabrication, and the fragility of the components - a novel recursively-structured apparatus for valveless microfluid manipulation method based on a pneumatic pumping mechanism [1] is utilized in this study. The working principle of this pumping design on this device does not directly relate to the nature of the fluid components. The driving force acting on the microliquid drop in the microchannel of this device is based on the pneumatic pumping which is induced by a blowing airflow. Furthermore, the pneumatic pumping actuator should be independent of the actuation responsible for the biochemical analysis on the chip system, so the contamination of pneumatic pumping source can be avoided. The complete biochip mechanism consists of an external pneumatic actuator and an on-chip planar structure for airflow reception.

In order to achieve microfluidic manipulation in the microchannel of the biochip system, the pneumatic pumping controller plays an important role. Since it is difficult to set up a sensor on biochip in the biochip system for sensing the feedback signals of the position of the reagent in the microchannel of the biochip, the photodiode system should be utilized. Hence, according to the design of the biochip system, a design of the controller has been investigated by simulations and experiments in the present study. In the control structure of biochip system, first the mathematical model of the biochip mechanism is identified by ARX model for simulations. Second, according to the results of the biochip-mechanism identification, the control-algorithm design is developed. The simulation results of the biochip system with a feedback-signal photodiode system and flowmeter show the effectiveness of the developed control algorithm. Third, architecture of the control algorithm is integrated on a microprocessor to implement microfluidic manipulation. Since the mathematical model of the flow control mechanism in the biochip microchannels is a complicated nonlinear plant, the fuzzy logic control (FLC) design of the controller will be utilized. Design of the FLC based on the fuzzy set theory has been widely applied to consumer products and industrial process controls. In particular, they are very effective techniques for complicated, nonlinear, and imprecise plants for which either no mathematical model exists or the mathematical model is severely nonlinear. The FLC can approximate the human expert's control behaviors to work fine in such ill-defined environments. For some applications, the FLC can be divided into two classes 1) the general-purpose fuzzy processor with specialized fuzzy computations and 2) the dedicated fuzzy hardware for specific applications. Because the general-purpose fuzzy processor can be implemented quickly and applied flexibly, whereas dedicated fuzzy hardware requires a long time for development, this study used the general-purpose fuzzy processor-8051 microcontroller. Nevertheless, there are also systemic uncertainties and disturbance in FLC controller. Because sliding-mode control (SMC) is known as an effective approach to restrain the systemic uncertainties and disturbance, SMC algorithm was utilized. In order to achieve a robust control system, a microcontroller of the biochip system optimally combining FLC and SMC algorithms was developed. Therefore, an OFSMC based on an 8051 microcontroller has been investigated by simulations and experiments in this study. Microfluidic manipulation in the microchannel of the biochip system based on OFSMC has been implemented by using the 8051 microcontroller.

The paper is organized as follows. In Section 2, we introduce the structure of the biochip control system. In Section 3, the fundamental knowledge of OFSMC and the model of the biochip system are introduced, and we address the OFSMC scheme and the associated simulations. In Section 4, the OFSMC IC based on 8051 microprocessor is designed, and the results of the real-time experiment are presented. Finally, the conclusion is given in Section 5.

2. STRUCTURE OF BIOCHIP SYSTEM

The control structure of the biochip system (Fig. 1) contains six parts: an air compressor, two flow controllers and two flowmeters, a flow-control chip, a biochip, photodiodes system, and a control-chip circuit system. The flow-control chip is to design a pneumatic device with planar structures for microfluidic manipulation [1]. Pneumatic devices without any microfabricated electrodes or heaters are most suitable for μTAS. These devices do not generate electrical current or heat, so they have a minimal effect on biochemistry. To implement a pneumatic device, which can control the movement of microfluid without valves or moving parts, a pneumatic structure possessing the ability of bi-directional pumping should be utilized.

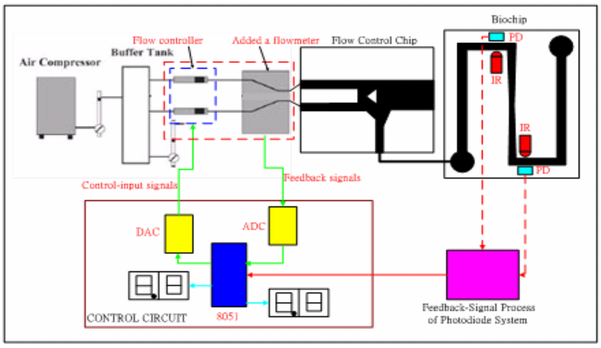

Fig. 1 Schematic diagram of biochip system for microfluidic manipulation.

The schematic diagram of the single pneumatic structure, which provides suction and exclusion by two inlets, is depicted in Fig. 2. When the air flows through inlet A only, the airflow at inlet A causes a low-pressure zone behind the triangular block and the suction occurs in the vertical microchannel. Furthermore, when the air flows through inlet B only, the airflow at inlet B is induced into the vertical microchannel to generate exclusion. According to [1], it illustrates the numerical and experimental results of the pressure and the stream tracers for the condition of the flow-control chip. Therefore, according to the principle of the flow-control chip, the microfluidic manipulation on the biochip is presented in this study by using OFSMC rule with two flow controllers and two flowmeters. Since the biochip in the biochip system is a consumer, the photodiodes system should be utilized for sensing the feedback signals of the position of the reagent in the microchannel of the biochip. Hence, DNA hybridization and extraction can be achieved in this study.

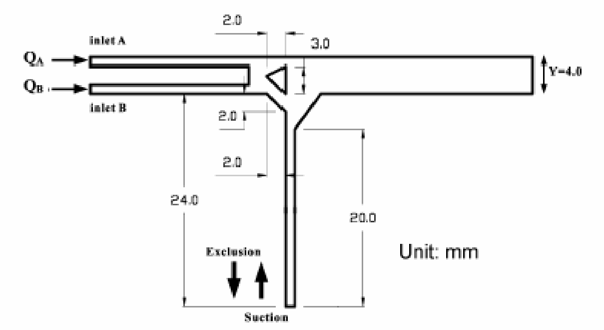

Fig. 2 Schematic diagram of the single pneumatic structure.

3. DESIGN AND SIMULATION OF OFSMC

3.1 Design of OFSMC

The biochip system depicted in Fig. 1 is a nonlinear system. Since the mathematical model of the flow control mechanism and biochip in the biochip microchannels is a complicated nonlinear plant, FLC design of the controller was utilized. The basic idea behind FLC is to incorporate the expert experience of a human operator in the design of the controller in controlling a process whose input-output relationship is described by a collection of fuzzy control rules. The heart of the fuzzy control rules is a knowledge base consisting of the so-called fuzzy IF-THEN rules involving linguistic variables rather than a complicated dynamic model. The typical architecture of a FLC, shown in Fig. 3, is comprised of four principal components: a fuzzification interface, a knowledge base, an inference engine, and defuzzification interface. The fuzzification interface has the effect of transforming crisp measured data into suitable linguistic values; it was designed first so that further fuzzy inferences could be performed according to the fuzzy rules. The heart of the fuzzification interface is the design of membership function. There are many kinds of membership functions - Gaussian, trapezoid, triangular and so on - of the fuzzy set. In this paper, a triangular membership function was utilized, as shown in Fig. 4. The inference engine is based on the compositional rule of inference with knowledge base for approximate reasoning suggested by Zadeh [2-3]. An inference engine is the kernel of the FC in modeling human decision making within the conceptual framework of fuzzy logic and reasoning. Hence, the fuzzification interface and fuzzy rules are designed completely before fuzzy reasoning. In this paper, since there are many structures of inference engine, fuzzy reasoning-Mamdani’s minimum fuzzy implication rule (MMFIR) method [4-8] was utilized, as shown in Fig. 5. Defuzzification is a mapping from a space of fuzzy control actions defined over an output universe of discourse into a space of crisp control actions. This process is necessary because fuzzy control actions cannot be utilized in controlling the plant for practical applications. Hence, the widely used center of area (COA) method, generates the center of gravity of the possibility distribution of a control action, was utilized. In the case of a discrete universe, this method yields

$$z_{COA} = \frac{\sum_{j=1}^{n} \mu_C(z_j) z_j}{\sum_{j=1}^{n} \mu_C(z_j)} \tag{1}$$

where n is the number of quantization levels of the output, z_j is the amount of control output at the quantization level j, and $\mu_C(z_j)$ represents its membership degree in the output fuzzy set C.

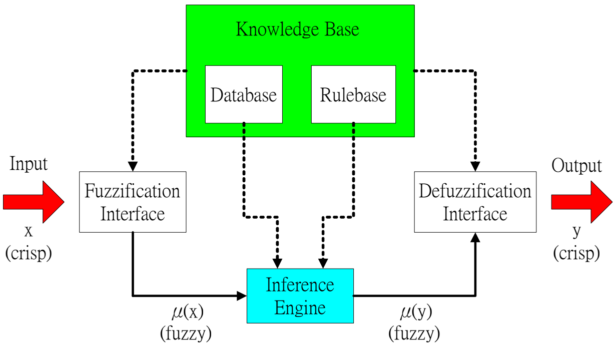

Fig. 3 Architecture of a fuzzy controller.

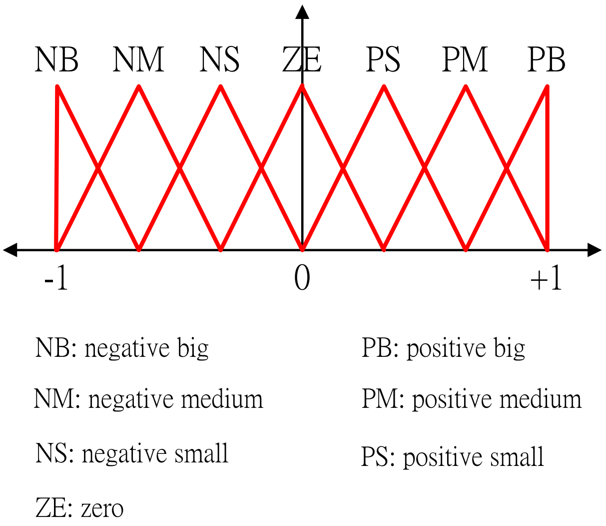

Fig. 4 Membership function.

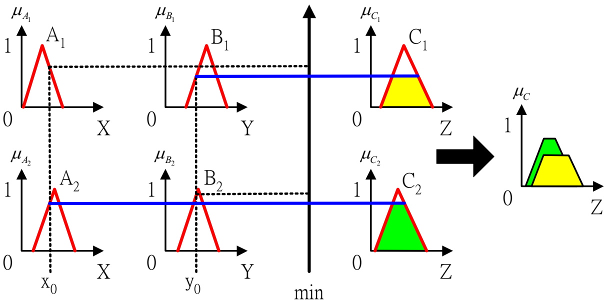

Fig. 5 Fuzzy reasoning of MMFIR method.

The biochip system depicted in Fig. 1 is a nonlinear system that has been used as an application to study real world nonlinear control problems by different control techniques [9-11]. The model of the biochip system is identified by ARX model, as

$$\begin{cases} X(k+1) = A_zX(k) + B_zu(k) \\ y(k) = C_zX(k) \end{cases} \quad (2)$$

where $X(k) \in R^n$ is the state variables of system, $u(k) \in R^m$ is the input voltage of the flow controller and $y(k) \in R^r$ is the assumed model output related to the position of the reagent in the microchannel of the biochip. The system is controllable and observable.

Since sliding mode control is robust and insensitive to disturbances, an SMC controller can perform well in systems with model uncertainty, disturbances and noises. In this paper, in addition to FLC controller, SMC controller was utilized to design the control input voltage of the flow controller. To design SMC controllers, a sliding function is designed first. The proposed SMC controller is based on pole placement [12], since the sliding function can be designed by pole placement. Some conditions are prepared for the sliding vector design in the proposed sliding mode control:

1. $\mathrm{Re}\{\lambda_i\}<0$, $\alpha_j \in R$, $\alpha_j < 0$, $\alpha_j \neq \lambda_i$.
2. Any eigenvalue in $\{\alpha_1,\ldots,\alpha_m\}$ is not in the spectrum of A_z.
3. The number of any repeated eigenvalues in $\{\lambda_1,\ldots,\lambda_{n-m},\alpha_1,\ldots,\alpha_m\}$ is not greater than m, the rank of B_z.

where $\{\lambda_1,\lambda_2,\ldots,\lambda_{n-m}\}$ are sliding-mode eigenvalues and $\{\alpha_1,\alpha_2,\ldots,\alpha_m\}$ are virtual eigenvalues.

According to the proof by Sinswat and Fallside [13], if the condition (3) in the above is established, the control system matrix $A_z - B_zK$ can be diagonalized as

$$A_z - B_zK = \begin{bmatrix} V \\ F \end{bmatrix}^{-1} \begin{bmatrix} \Phi_V & 0 \\ 0 & \Gamma_F \end{bmatrix} \begin{bmatrix} V \\ F \end{bmatrix} \quad (3)$$

where $\Phi_V = diag[\lambda_1,\lambda_2,\ldots,\lambda_{n-m}]$, $\Gamma_F = diag[\alpha_1,\alpha_2,\ldots,\alpha_m]$, and V and F are left eigenvectors with respect to Φ_V and Γ_F, respectively. Hence, Eq. (3) can be rewritten as

$$\begin{cases} V(A_z - B_zK) = \Phi_V V \\ F(A_z - B_zK) = \Gamma_F F \end{cases} \quad (4)$$

Rearranging Eq. (4) yields

$$FA_z - \Gamma_F F = (FB_z)K \quad (5)$$

According to Chang [12],

$$rank(FA_z - \Gamma_F F) = rank(F) \quad (6)$$

Since F contains m independent left eigenvectors, we have $rank(F) = m$. From Eqs. (5) and (6), it is also true that $rank(FA_z - \Gamma_F F) = rank((Fb_z)K) = rank(F) = m$. In other words, FB_z is invertible. With the designed left eigenvector F above, the sliding function $S(k)$ is designed as

$$S(k) = FX(k) \quad (7)$$

The second step is the discrete-time switching control design. According to Gao et al. [14], a different but much more expedient approach is adopted here. This approach is called the reaching law approach that has been proposed for continuous VSC systems [15-17]. In this approach, a reaching law is first specified in two procedures of sliding mode, as shown in Fig. 6, are always satisfied. This control law is synthesized from the reaching law in conjunction with a plant model and the known bounds of perturbations. For a discrete-time system, the reaching law is [14]

$$S(k+1) - S(k) = -qTS(k) - \varepsilon T\,\mathrm{sgn}(S(k)) \quad (8)$$

where $T>0$ is the sampling period, $q>0$, $\varepsilon>0$ and $1-qT>0$. Therefore, the switching control law for the discrete-time system is derived based on this reaching law. From Eq. (7) and pole-placement method, $S(k)$ and $S(k+1)$ can be obtained as, in terms of sliding vector F,

$$\begin{cases} S(k)=FX(k) \\ S(k+1)=FX(k+1)=F(A_z-B_zK)X(k)+FB_zu(k) \end{cases} \tag{9}$$

where $K\in R^n$ is a gain matrix obtained by assign n desired eigenvalues $\{\lambda_1,\dots,\lambda_{n-m},\alpha_1,\dots,\alpha_m\}$ of $A-BK$.

It follows that

$$S(k+1)-S(k)=F(A_z-B_zK)X(k)+FB_zu(k)-FX(k) \tag{10}$$

From Eqs. (8) and (10),

$$S(k+1)-S(k)=-qTS(k)-\varepsilon T\,\mathrm{sgn}(S(k))$$
$$=F(A_z-B_zK)X(k)+FB_zu(k)-FX(k)$$

Solving for $u(k)$ obtains the switching control law

$$\begin{aligned} u(k)=-(FB_z)^{-1}[&F(A_z-B_zK)X(k) \\ &+(qT-1)FX(k)+\varepsilon T\,\mathrm{sgn}(FX(k))] \end{aligned} \tag{11}$$

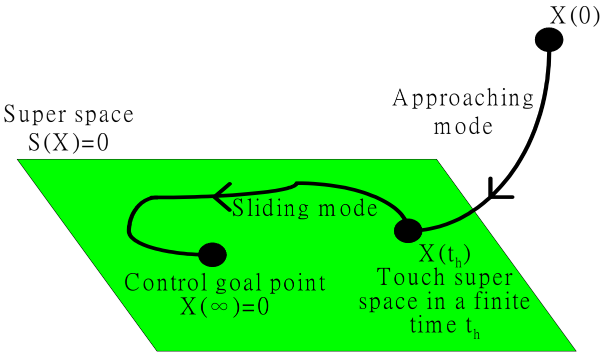

Fig. 6 Generation of sliding mode.

In order to achieve the output tracking control, a reference command input $r(k)$ is introduced into the system by modifying the state feedback control law $u_p(k)=-KX(k)$ with pole-placement design method [18] to become

$$u_p(k)=N_ur(k)-K(X(k)-N_xr(k)) \tag{12}$$

where

$$\begin{bmatrix} N_u \\ N_x \end{bmatrix}=\begin{bmatrix} A_z-I & B_z \\ C_z & 0 \end{bmatrix}^{-1}\begin{bmatrix} 0 \\ I \end{bmatrix} \tag{13}$$

The proposed SMC input, based on Eq. (13), is assumed to be

$$u_s(k)=u_p(k)+u=N_ur(k)-K(X(k)-N_xr(k))+u \tag{14}$$

Substituting Eq. (11) into (14) gives the proposed SMC input as

$$\begin{aligned} u_s(k)=N_ur(k)&-K(X(k)-N_xr(k)) \\ &-(FB_z)^{-1}[F(A_z-B_zK)X(k) \\ &+(qT-1)FX(k)+\varepsilon T\,\mathrm{sgn}(FX(k))] \end{aligned} \tag{15}$$

The pole-placement SMC design method utilizes the feedback of all state variables to form the desired sliding vector. In practice, not all state variables are available for direct measurement. Hence, it is necessary to estimate the state variables that are not directly measurable. Such estimator is commonly called state observer.

In practice, a discrete linear time-invariant system sometimes has system disturbances and measurement noise. Hence, here linear quadratic estimator (LQE) will be applied to estimate optimal states in having system disturbances and measurement noise.

According to Eq. (2), consider a system plant as

$$\begin{cases} X(k+1)=A_zX(k)+B_zu(k)+G\nu(k) \\ y(k)=C_zX(k)+\omega(k) \end{cases} \tag{16}$$

where $X(k)\in R^n$ is the state variable, $u(k)\in R^m$ is the control input voltage , $y'(k)\in R^r$ is the assumed plant output related to the XY stage position, and $\nu(k)\in R^n$ and $\omega(k)\in R^r$ are system disturbances and measurement noise with covariances $E[\omega\omega^T]=Q$, $E[\nu\nu^T]=R$ and $E[\omega\nu^T]=0$. The system investigated in this study is controllable and observable.

The objective of LQE is to find a vector $\hat{X}(k)$ which is an optimal estimation of the present state $X(k)$. Here "optimal" means that the cost function

$$J=\lim_{T\to\infty}E\left\{\int_0^T(X^TQX+u^TRu)dt\right\} \tag{17}$$

is minimize. The solution is the estimator as

$$\begin{cases} \hat{X}(k+1)=A_z\hat{X}(k)+B_zu(k)+K_f(y(k)-C_z\hat{X}(k)) \\ \hat{y}(k)=C_z\hat{X}(k) \end{cases} \tag{18}$$

where K_f is the "optimal kalman" gain $K_f=PC_z^TR^{-1}$ and P is the solution of the algebraic Riccati equation

$$A_zP+PA_z^T-PC_z^TR^{-1}C_zP+Q=0 \tag{19}$$

The combination of FLC, SMC, and LQE is the so called optimal fuzzy sliding-mode control (OFSMC) that was utilized to control input voltage of the flow controller. The LQE block diagram is shown in Fig. 7, and OFSMC block diagram with LQE is shown in Fig. 8. The simulation results and discussion are presented in Section 3.2.

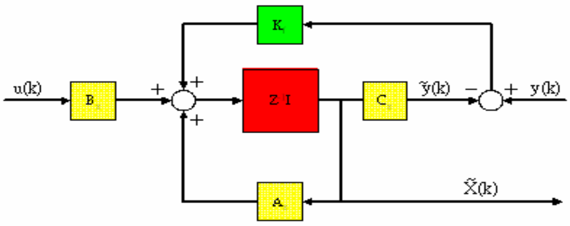

Fig. 7 LQE block diagram.

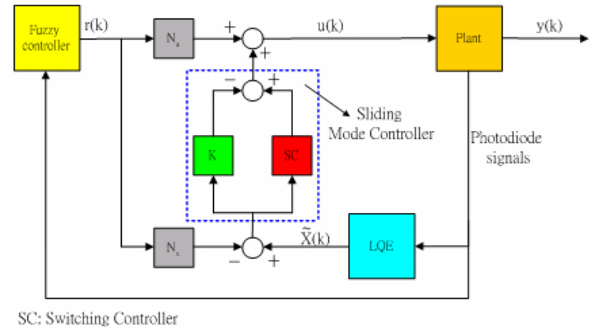

Fig. 8 OFSMC block diagram.

3.2 Simulation of OFSMC

This section deals with a system plant described by Eq. (2) and defines a reference command input $r(k)$, which is a input voltage of the flow controller by fuzzy controller with designed photodiode signals. From Section 3.1, the pole-placement algorithm is utilized to determine a sliding vector. In this study, Ackermann's Formula is used to determine the pole-placement feedback gain matrix K. In practice, because not all state variables are available for direct measurement, it is necessary to estimate the state variables that are not directly measurable. Hence, the full-order state observer designed by Ackermann's Formula and LQE will be utilized in this study.

Based on Section 3.1, [14] and [19], Fig. 9 simulate respectively biochip system model based on FLC and OFSMC with the LQE by using the MATLAB and Simulink. In the Figure, solid lines represent reference command input whereas the dashed lines are the system output.

Analysis of the simulation results from Fig. 9 raises the following points:

1. In the figure, every turning of the curve represents a reversal of the flowing reagent during its back and forth flow in the microchannel on the biochip. The biochip system model based on OFSMC controller with LQE performs better than that based on FLC controller.
2. For the simulation results, it is certain that the OFSMC control method is capable of manipulating the position of the reagent in the microchannel on the biochip robustly and successfully. The experimental results of microfluidic manipulation on biochip system with OFSMC controller based on 8051 microprocessor will be shown in Section 4.

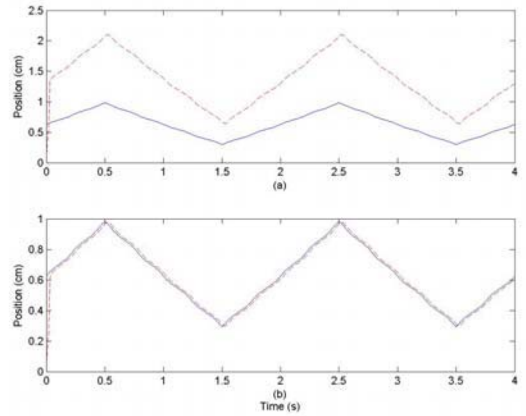

Fig. 9 Simulation results of biochip system model based on (a) FLC and (b) OFSMC with the LQE.

4. EXPERIMENTAL RESULTS

4.1 Experimental results of OFSMC

The control block diagram of the biochip system described in Section 2 and 3 is shown in Fig. 10. In this study, in order to provide a quick-useful product for non PC-based systems, the microfluidic manipulation is implemented by 8051 microprocessor. In addition to 8051 microprocessor, the A/D and D/A chips are utilized to convert the photodiode or flowmeter feedback analog signals into digital signals for the microprocessor, and convert digital signals into analog signals for the flow-controller. Then, the circuit of the photodiode-signal process should be designed. Assembly language was utilized to program the OFSMC control rules to embed into 8051 microprocessor, and the flow chat of the program is shown in Fig. 11. The experimental results of microfluidic manipulation on biochip system with OFSMC controller based on 8051 microprocessor are shown in Fig. 12.

From the experimental results, it is certain that the OFSMC control method is capable of manipulating the position of the reagent in the microchannel on the biochip robustly and successfully.

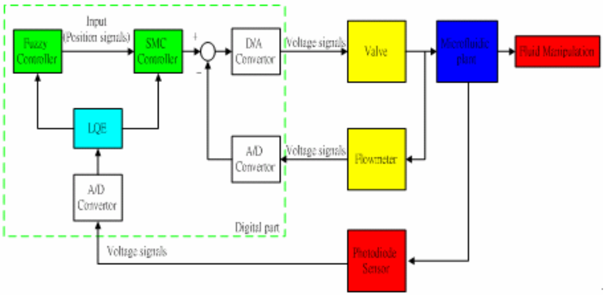

Fig. 10 Control block diagram.

4.2 Application results

According to experimental results of Section 4.1, the microfluidic manipulation based on the microcontroller could be utilized in biotechnology, as it successfully improved the efficiency of the molecular biology reaction. First, the new technique was used in DNA hybridization. There are two methods to improve the efficiency of the nucleic acid hybridization in this study. The first method is to increase the velocity of the target nucleic acid molecules, which increases the effective collision into the probe molecules as the target molecules flow back and forth. The second method is to introduce the strain rates of the target mixture flow on the hybridization surface. This hybridization chip was able to increase hybridization signal 6-fold and reduce non-specific target-probe binding and background noises within 30 minutes, as compared to conventional hybridization methods, which may take from 4 hours to overnight. Second, it was used in DNA extraction. When serum existed in the fluid, the extraction efficiency of immobilized beads with solution flowing back and forth was 88-fold higher than that of free-beads. When the number of Escherichia coli (E. coli) cells was 10^3 to10^4 in 25 μl of whole blood, the extraction efficiency of immobilized beads with solution flowing back and forth was much (10^2 to10^3 fold) larger than that of free beads. When the number was 10^4 to 10^6, the extraction efficiency of immobilized beads was 10^1 to 10^2 fold.

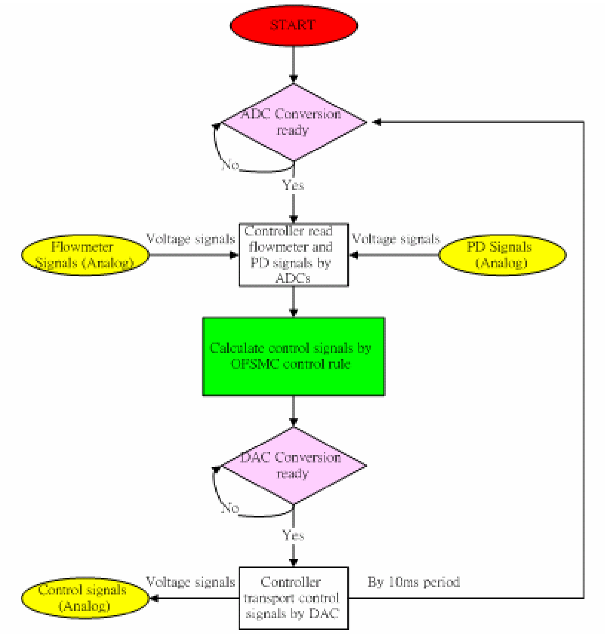

Fig. 11 Flow chat of the program.

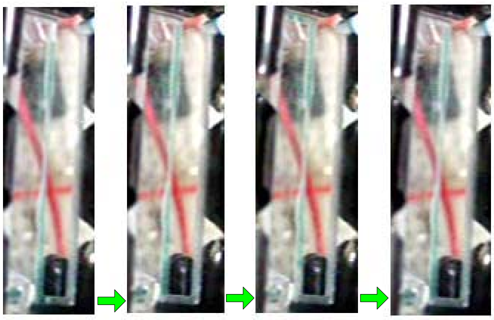

Fig. 12 Experimental results of microfluidic manipulation (A period from (a) to (d)).

5. CONCLUSIONS

In biometric and biomedical applications, an important issue for miniaturization and integration is microfluid management. In order to achieve this, this study presented the optimal fuzzy sliding-mode control (OFSMC) design based on the 8051 microprocessor and the complete microfluidic manipulated system implementation of biochip system with a pneumatic pumping actuator, a feedback-signal photodiodes and flowmeter. The newly developed microfluid management technique was successfully utilized to improve the reaction and extraction efficiency of a molecular biology reaction.

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