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Microfluidic Chemical Integrated Circuits Based on Stimuli-Responsive Hydrogels for On-Chip Flow Control

Philipp Frank

von der Fakultät Elektrotechnik und Informationstechnik der
Technischen Universität Dresden

zur Erlangung des akademischen Grades eines

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Abstract

Microfluidics exhibits great capability in various research fields such as biology, chemistry or medicine. The lab-on-a-chip technology brings tremendous advantages over the conventional methods as it increases reaction kinetics, reduces reagent consumption and provides high throughput and parallelization capability. The aspect of parallelization on a large scale requires a powerful control paradigm where a large number of devices need to be manipulated by a small number of inputs.

Even though, microfluidics has produced a variety of different platform technologies utilizing the most different physical effects the majority of technologies lack the ability to act on direct feedback from the process liquid. This results in a sophisticated external control unit off-chip which directly hinders high degrees of parallelization respectively integration.

This work presents a microfluidic platform concept, which utilizes the volume phase transition of stimuli-responsive hydrogels on-chip to actively switch between fluid streams in a discrete operating manner. The volume phase transition combines the sensing and acting functionality in one component. Smart hydrogels are utilized in a transistor-like device which is capable to autonomously make switching decision exclusively depending on the chemical content of a fluid. The content comprising molecules and ions that exist simultaneously in a solution is viewed as carrier of chemical information. Thus, the chemo-fluidic transistor couples the molecular content of the liquid with the fluidic behavior of the system.

The combination of the chemo-fluidic transistor and the analogy between electronics and microfluidic allowed the development of discrete basic circuits such as the logic gates AND, OR, NOT, and their negated counterparts rendering a complete computation. By consequently following the electronic paradigm more sophisticated modules are demonstrated such as an RS flip-flop or a chemo-fluidic oscillator circuit. The chemo-fluidic oscillator exhibits an autonomous oscillation in flow rate and concentration. The system architecture and circuitry allows a decoupling of the excitation stimulus and the emission concentration enabling future biological and medical application.

This work discusses a novel concept for the implementation of microfluidic integrated circuits. Main aspects are examined such as technological requirements, the theoretical background, the signal variability and biological application of the system.

Kurzfassung

Mikrofluidik zeigt enormes Potential in den Forschungsbereichen der Biologie, Chemie oder auch Medizin. Die Lab-on-a-Chip Technologie bringt dabei herausragende Vorteile gegenüber konventionellen Methoden wobei Reaktionskinetiken beschleunigt, Reagenzienverbrauch verringert und Hochdurchsatzsysteme und Parallelisierung ermöglicht werden. Der Aspekt der Parallelisierung in einem großen Maßstab setzt allerdings ein skalierbares Steuerkonzept voraus, wobei eine große Anzahl an aktiven Bauelementen mit einer kleinen Anzahl an Steuereingängen beeinflusst wird.

Obwohl sich eine Vielzahl von mikrofluidischen Plattformtechnologien entwickelt hat, sind die wenigsten Technologien in der Lage eine direkte Rückkopplung aus dem Prozessmedium zu nutzen. Diese Technologien sind auf eine Reihe von externen technischen Aufbauten außerhalb des Chips angewiesen, die einer systematischen Miniaturisierung entgegenwirken.

Diese Arbeit präsentiert ein mikrofluidisches Plattformkonzept, das stimuli-responsive Hydrogele auf der Chip-Ebene nutzt um aktiv und diskret Fluidströme zu schalten. Diese smarten Hydrogele vereinen sensorische und aktorische Funktionalität und sind demzufolge in der Lage autonom auf physikochemische Änderungen in ihrer Umgebungen zu reagieren. Hydrogele eingesetzt in einem transistorartigen Bauelement ermöglichen ein autonomes Steuern von Fluidströmen, das ausschließlich von der chemischen Zusammensetzung des Fluides abhängt. Das Fluid setzt sich aus Lösungsmittel und darin gelösten Ionen und Molekülen zusammen und kann somit als Träger von chemischer Information betrachtet werden. Der chemo-fluidische Transistor ist somit in der Lage, die molekulare Zusammensetzung einer Lösung mit dem fluidischen Verhalten des Mikrosystems zu koppeln.

Die Kombination aus chemo-fluidischem Transistor und der Analogie zwischen Elektronik und Mikrofluidik ermöglicht die Entwicklung von diskreten Basisschaltungen wie die Logikgatter UND, ODER, NICHT und deren negierte Entsprechungen. Unter Verwendung elektrischer Paradigmen konnten komplexere mikrofluidische Schaltungen entwickelt werden, wie am Beispiel des RS Flip-flops oder des chemo-fluidischen Oszillators gezeigt wird. Die Systemarchitektur ermöglicht hierbei ein Entkoppeln des Anregungsstimulus und des abgegebenen Mediums, was sich vorteilhaft für biologische Anwendungen erwieß.

Von diesem neuartigen Konzept zur Implementierung von mikrofluidischen integrierten Schaltungen werden Aspekte wie technologische Voraussetzungen, theoretische Hintergründe, Signalvariabilität und die biologische Anwendung des Systems beleuchtet.

Contents

List of Symbols

Symbol	Description	Unit
v	Velocity	$\mathrm{m\,s^{-1}}$
ρ	Density	$\mathrm{kg\,m^{-3}}$
L	Length	µm
μ	Viscosity	Pa s
Re	*Reynold* number	-
Q	Flow rate	$\mathrm{\mu l\,min^{-1}}$
w	Width	µm
h	Height	µm
g	Gravitational acceleration	$\mathrm{m\,s^{-2}}$
σ	Surface tension	$\mathrm{J\,m^{-2}}$
Bo	*Bond* number	-
We	*Weber* number	-
Pe	*Peclet* number	-
D	Diffusion coefficient	$\mathrm{m^2\,s^{-1}}$
t	Time	s
u	Velocity	$\mathrm{m\,s^{-1}}$
p	Pressure	mbar
r	Radius	µm
ϕ	Angle	°
R_{H}	Hydraulic resistance	$\mathrm{mbar\,min\,\mu l^{-1}}$
I	Electric current	A
U	Voltage	V
R	Electric resistance	Ω
r_h	Hydraulic radius	µm
A	Area	$\mathrm{\mu m^2}$
P	Perimeter	µm
m	Mass	kg
D_{Coop}	Cooperative diffusion coefficient	$\mathrm{m^2\,s^{-1}}$
τ	Characteristic time constant	s
ϑ	Temperature	°C
ω	Rotational velocity	rpm
V	Volume	$\mathrm{m^3}$
c	Concentration	wt. %

Symbol	Description	Unit
w_a	Aperture width	µm
d	Thickness	mm
E_{Exp}	Exposure energy	$\mathrm{mJ\,cm^{-2}}$
R^2	Determination coefficient	-
k	Compliance factor	-
$1-k$	Compliance factor	-
f	Frequency	Hz
f_0	Fundamental frequency	Hz
b	Growth rate	$\mathrm{h^{-1}}$
t_d	Doubling time	min

1. Introduction, Motivation and Scope

1.1. An Introduction to Microfluidics

Microfluidics researches physical fluid phenomena on the micro scale and is directly related to *Lab-on-a-Chip* (LOC) technology which aims to utilize these phenomena in microsystems. LOC technology develops and implements methods and paradigms to fabricate and operate fluidic microsystems. The systematical scale down of dimensions reduces reagent consumption, increases reaction kinetics, facilitates parallelization and, therefore, enables high throughput experiments. Microfluidics finds application in the fields of chemistry, medicine, biology and biotechnology. Typical microfluidic applications are *DNA sequencing* [64, 73, 88, 97], *single cell analysis* (SCA) [12, 147, 156, 159] and *point of care* (POC) diagnostics [108, 140].

Microfluidics from its beginnings has always had a strong connection to electronics – especially to microelectronics. This connection arises from the fact that most fabrication techniques utilized for the manufacturing of microfluidic devices originate from microelectronics. In the early stages microelectronics provided a rich portfolio of methods to structure silicon or glass substrates in order to synthesize fluidic chips. Also, the integration of electro-conductive elements was straight-forward bringing electrokinetic phenomena like electrophoresis or electro-osmosis for flow generation into focus [51, 83, 84]. Connected to this background *Manz* in 1990 introduced the concept of the *Miniaturized Total Chemical Analysis Systems*, short µ-TAS [84]. The µ-TAS concept discusses the benefits of spatial miniaturization and a prospective parallelization for chemical analysis. The concept established and predicted guidelines for the development of future microfluidic systems.

The introduction of *Soft Lithography* in 1998 by *Whitesides* [151] led to a tremendous change in microfluidics. The advantages of this technique such as fabrication speed, ease, biocompatibility and inexpensiveness evoked the emerging of polymer-based microfluidics. *Quake* in 2000 extended *Soft Lithography* by introducing multiple structured layers [138]. Multi-layer *Soft Lithography* utilizes monolithically integrated, flexible membranes in combination with pneumatic pressure to facilitate valves and pumps. *Soft Lithography* provided access to microfluidic devices for a brought audience. The technique since then became one of the most popular fabrication methods in the research community and still is today. Though, the technology is mostly used in the laboratory environment rather than for commercialization.

1.2. Motivation for Microfluidic ICs

Microfluidics, when it first emerged, was predicted to have a similar progression as electronics had shown before. The miniaturization of chemical analysis and medical diagnosis was supposed to enable autonomous and mobile devices, which would embed into everyday life. However, the technology has not yet met the expectations of the prophecy, as discussed by *Whitesides* in his review in 2006 [148]. One of the reasons is the lack of an active device capable of making autonomous switching decisions, a device much like the transistor in electronics [33]. The electronic transistor enabled the development of an integrated circuit (IC) concept and consequently broke ground for large-scale integration (LSI) platforms that facilitate integrated function and independent control of the chip.

In contrast LOC systems of today rely on a multitude of external and typically bulky equipment restricting the flexibility and application [20, 42, 87]. External equipment consists of sensors, actuators and a processing unit (PC) and is imperative to facilitate microfluidic chip control. Hence, the microfluidic chip is tied to the laboratory environment rendering it to be a computer controlled machine rather than an integrated microsystem. A transistor-like device with the capability of autonomous decision making would enable the development of a working IC concept and eventually lead to complex circuits. Complex, sophisticated circuits are key in order to facilitate both an integrated control and function on the chip level. The integration of control elements on the chip results in location-independence, more flexibility for applications, and ultimately a prospective LSI concept that facilitates functional and technological scalability. Electronics serves not only as source of fabrication methods but also as paragon of what is in reach of the technology.

But the commonality between electronics and microfluidics is entrenched deeper. Through an analogy described by *Schönfeld* in 1954 [119] and by *Rodriguez* in 1979 [115] electronic circuits can be transferred into microfluidic networks and vice versa. These descriptions discuss the parallels between the electronic domain and the fluidic respectively the hydraulic domain. *Perdigones* in 2014 connected the microfluidic domain with electronics even further by expanding the analogy [103] considering the boundary conditions as constituted by the dimensionless numbers such as the *Reynolds* number Re or the *Bond* number Bo. The benefit of a circuit analogy lies in the possibility to transfer circuits and functionality from the rich knowledge base of electronics into microfluidics without the need to re-invent already existing paradigms.

For instance, the extremely high density of integration in combination with expensive and sophisticated fabrication processes in todays electronic IC technology are vastly incalculable for a single individual to oversee. The complexity of design and fabrication processes produced a series of advanced software tools that are capable to model and simulate products before production. Microfluidics would benefit greatly if the existing software tools could be applied to microfluidic circuits.

1.3. The Scope of this Work

Microfluidics produced a variety of different platform technologies that utilize the most different physical effects to facilitate small fluid volume manipulation. Despite a considerable functional diversity most technologies lack the ability to act on direct feedback from the process medium. Thus, the need for a sophisticated external control unit off-chip is imperative. External equipment, addressing issues, and increasing complexity limit the technological as well as the functional scalability and lead to bulky setups rendering a mobile use of the technology impossible. Smart hydrogels as intrinsically active actuators provide a solution as they are capable of sensing chemical information in the process medium in form of molecules and ions and are capable of acting on this information accordingly. This chemical information serves as an instruction for the fluidic control, that is executed by the gel particle.

The work at hand aims to develop an active microfluidic device capable of making switching decisions autonomously and to employ said device in circuit-based modules comparable to the IC concept from electronics. The modules are to execute basic functions and to work widely independently so they can be freely interconnected to form more complex units. In order to face the addressing problems that are encountered with increasing system complexity stimuli-responsive hydrogels are utilized. These *smart* hydrogels facilitate the coupling of the chemical domain with the hydraulic domain as they react to molecular changes in a fluid mechanically with a volume change. The chemical information exist in form of stimuli that can be processed by hydrogels and transmitted from one circuit to the next one enabling signal propagation. The utilization of feedback in form of chemical information enables the development of a whole new circuit paradigm in microfluidics. The technology breaks ground for a new functionality and better scalability in contrast to the technologies accessible today.