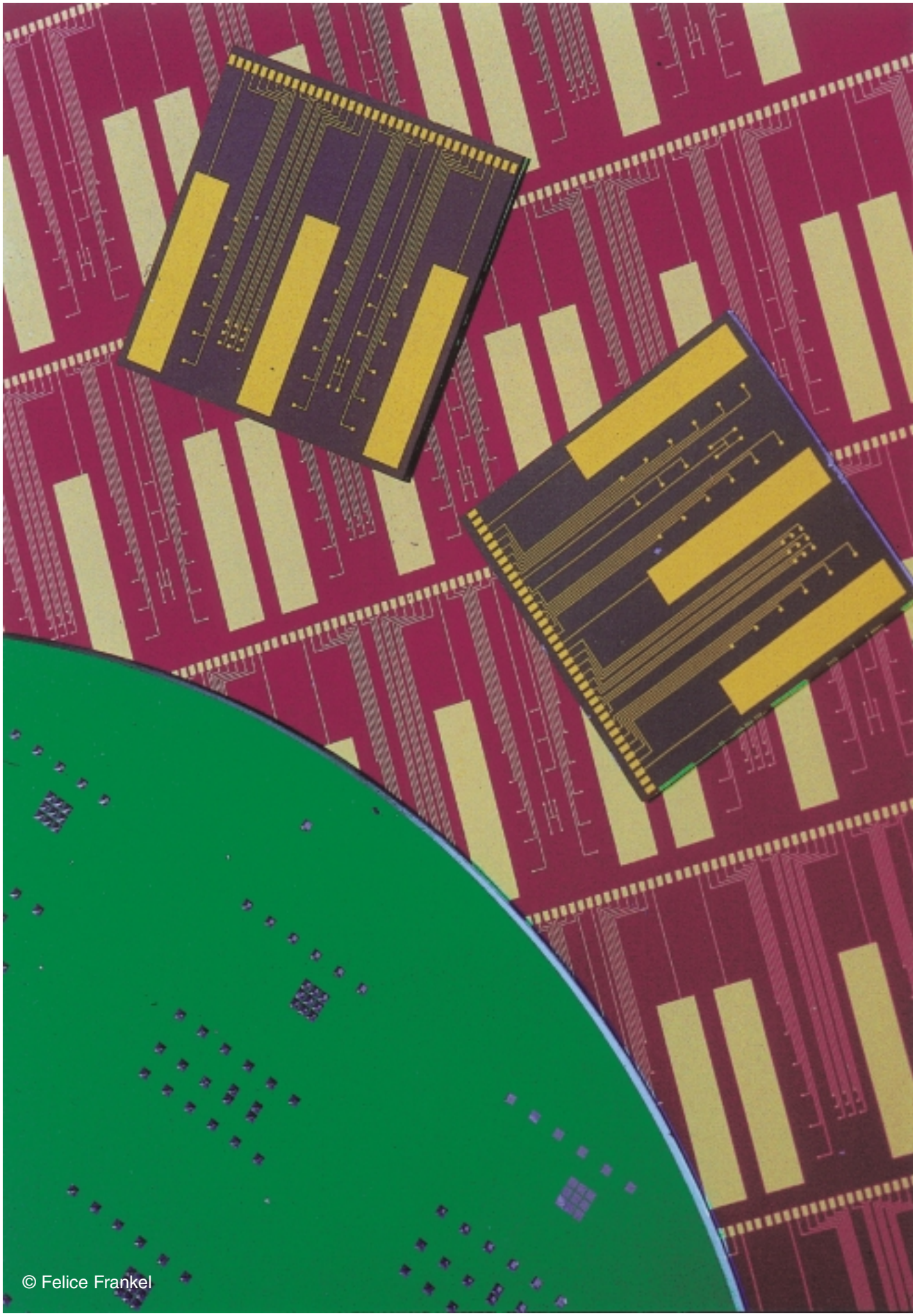

Microchips with reservoirs for chemicals that can be filled from the back (lower left part) and electrodes at the front for opening the reservoirs.

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Microchips as Controlled Drug-Delivery Devices

John T. Santini, Jr.,* Amy C. Richards, Rebecca Scheidt, Michael J. Cima,* and Robert Langer*

Controlled-release systems are common in a number of product areas, including foods, cosmetics, pesticides, and paper. Microencapsulated systems, for example, are used for the release of flavors and vitamins in foods, fragrances in perfumes, and inks in carbonless copy paper. Controlled-release systems for drug delivery first appeared in the 1960s and 1970s. In the past three decades, the number and variety of controlled release systems for drug-delivery applications has increased dramatically. Many of these use polymers having particular physical or chemical characteristics such as biodegradability, biocompatibility, or responsiveness to pH or temperature changes. However, recent advances in the field of microfabrication have created the possibility of a new class of controlled-release systems for drug delivery, namely, that of small, programmable devices. Their small size, potential for integration with microelectronics, and ability to store and release chemicals on demand could make controlled-release microchips useful in a number of areas, including medical diagnostics, analytical chemistry, chemical detection, industrial process monitoring and control, combinatorial chemistry, microbiology, and fragrance delivery. More importantly, drug-delivery microchips resulting from this convergence of controlled release and microfabrication technologies may provide new treatment options to clinicians in their fight against disease.

Keywords: controlled release · drug delivery · drug research · microchips · microreactors

1. Introduction

Microelectronic devices have become an integral part of our lives. They are present in our automobiles, cellular phones, and personal computers. This review examines an emerging new field: the application of microfabrication technologies to the development of devices for the controlled release of chemicals, including drugs. To provide the proper background for understanding this new field, we begin with an overview of the field of controlled release and then briefly discuss relevant work from the field of microfabrication. The remainder of the article reviews our recent work on the development of controlled-release microchips for chemical- and drug-delivery applications.

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2. Overview of Controlled Release

Controlled release, as used in this review, refers to materials or devices for controlling the release time of a chemical, the release rate, or both. Controlled release has proved useful in areas such as foods, cosmetics, and pesticides,[1] but it has had its largest impact in the field of drug delivery.[2]

The method by which a drug is delivered can have a significant effect on its therapeutic efficacy.[3] Some drugs have an optimum range of concentrations within which the maximum therapeutic benefit is derived. Drug concentrations above or below this range can be toxic or produce no therapeutic benefit. Conventional drug-delivery systems such as tablets or injections typically result in a drug-delivery profile that is initially marked by a sharp increase in concentration to a peak above the therapeutic range. Then, there is a relatively rapid decrease in concentration until the drug falls below the therapeutic range. Therefore, the time spent in the optimum concentration range may be short

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(Figure 1 a). Sleeping pills are a good example for illustrating the importance of drug concentration. If the drug concentration is below the therapeutic range, enhancement of sleep is not observed. If the drug concentration is above the therapeutic range, potentially fatal toxicity may be encountered. Therefore, the ideal concentration profile, in some cases, would reside in the therapeutic range and be nearly independent of time (Figure 1 a).

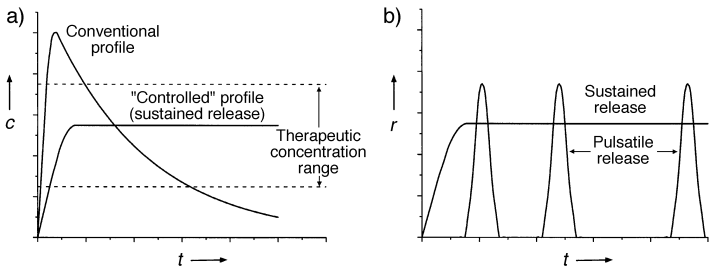

Figure 1. a) Exemplary concentration c vs. time t profiles for conventional and controlled-release drug-delivery devices. The controlled release profile here is characteristic of sustained (or continuous) release. b) Exemplary release rate r vs. time profiles demonstrating the difference between sustained (or continuous) release and pulsatile release.

2.1. Sustained Release

The field of controlled release initially focused on achieving a sustained (or continuous) release of drug over an extended


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Michael J. Cima is the Sumitomo Electric Industries Professor in the Materials Science and Engineering Department at MIT. He earned a BSc in chemistry in 1982 and a PhD in chemical engineering in 1986, both from the University of California at Berkeley. He has written 130 scientific publications and nine patents and has received numerous honors, including the International Award of Materials Engineering for Resources, R&D 100 Award, ALCOA Foundation Science Award, and election as a Fellow of the American Ceramics Society. His research interests include ceramics processing, ink-jet and other printing technologies, and drug delivery.

John T. Santini, Jr. received a BSc from the University of Michigan in 1994 and a PhD from MIT in 1999, both in chemical engineering. His graduate study was supported by a National Science Foundation Fellowship and focused on the design, fabrication, and characterization of microchips for chemical and drug-delivery applications. At present he is continuing his drug-delivery research at MicroCHIPS, Inc. and at MIT as a research affiliate in the Harvard-MIT Division of Health Sciences and Technology.

Amy C. Richards received a BSc in materials science and engineering from MIT in 1997. She is currently a National Science Foundation Fellow and is working toward her PhD in materials science and engineering under the guidance of Professor Langer and Professor Cima. Her doctoral research involves the integration of polymer science, polymer processing, and drug delivery to develop and characterize novel controlled-release devices.

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period of time (Figure 1b) with minimal influence by outside factors such as pH.[4] Much of this work involved polymers that released the drug at a nearly constant rate due to diffusion out of the polymer or by degradation of the polymer over time. These controlled-release systems may be of a macro- or microscopic size and exist in a number of different forms, such as oral tablets, polymer implants (rods, wafers, or pellets), and polymer microspheres. Two examples of commercially available polymeric devices for constant drug release include Gliadel[5] (implantable polyanhydride wafers that release carmustine for the treatment of malignant brain tumors at a nearly constant rate as the polymer degrades) and Lupron Depot[6] (injectable polymer microspheres, for treatment of endometriosis, precocious puberty, or for the nearly constant release of LHRH analogues for prostate cancer therapy).

Transdermal delivery is another method that achieves sustained release of drugs. It has proved successful for small lipophilic drug molecules such as scopolamine (motion sickness), fentanyl (pain), clonidine (hypertension), estradiol (hormone replacement), testosterone (impotence), nicotine (smoking cessation), and nitroglycerin (angina).[2, 7] A major advantage of transdermal delivery is that first-pass metabolism of the administered drug by the liver is reduced.[7b] However, there is typically a lag time between the application to the skin and the establishment of a stable concentration of the drug in the bloodstream, and only a limited number of drugs can penetrate the skin at rates fast enough to reach a therapeutic steady-state concentration in the bloodstream without chemical enhancers or external stimuli such as ultrasound.[8]

2.2. Pulsatile Release

The examples presented in Section 2.1 are designed to release drugs at a nearly constant rate. In numerous cases, however, sustained release is not the optimal method of drug delivery. Instead, delivery of pulses of drug at variable time intervals is the preferred method (Figure 1b) and is commonly referred to as pulsatile release. This delivery method works better in certain cases because it closely mimics the way in which the human body naturally produces some compounds. Insulin is a well-known example of a compound secreted by the body in a pulsatile manner.[9] Another example of compounds produced by the body in a pulsatile or periodic manner are the hormones of the anterior pituitary gland (adenohypophysis), for example gonadotropin and growth hormone, which are important in regulating reproduction and growth, respectively. Many compounds and environmental factors can stimulate or inhibit the production of these hormones. However, compounds secreted by the hypothalamus, called releasing factors or hormones, play a primary role in the regulation of adenohypophysial hormones. For example, women suffering from gonadotropin releasing hormone (GnRH) deficiency may not ovulate normally, making it difficult to conceive a child. Growth hormone releasing hormone (GHRH) deficiency in children may lead to dwarfism. Pulsatile administration of GnRH and GHRH can help reduce the severity of these deficiencies.[10] In fact, continuous adminstration of GnRH results in desensitization of GnRH receptors on the pituitary gland and may actually suppress the release of gonadotropins.[11]

Much previous work on methods of achieving pulsatile release focused on developing polymers that respond to specific stimuli:[12] changes in electric[13] or magnetic[14] fields, exposure to ultrasound,[14b, 15] light,[16] enzymes,[17] changes in pH[18] or temperature,[19] or molecules present in the human body, including antigens.[20] Transdermal delivery, typically a route for sustained delivery, can be modified to produce a more pulsatile release pattern in the presence of ultrasound[8] or voltage pulses (high voltage: electroporation, low voltage: iontophoresis).[21] Pulsatile release systems can be externally regulated (open-loop) or self-regulated (closed-loop).[22] A polymer implant that releases a drug when an oscillating magnetic field is applied is an example of an externally regulated system,[23] while a system that releases drug in response to antigens in the body is an example of self-regulation.[20] An example of oral and implantable polymer devices capable of delivering pulses of drug without the use of an external stimulus are those fabricated by Three Dimensional Printing. They are based on the controlled microstructure of the polymer matrix and release drugs at specified times as determined by the permeability of the polymer and the position of the drug in the device.[24]

An alternative method of pulsatile release involves the use of pumps and catheters. Pumps work well for both sustained and pulsatile release and can be programmed to deliver pulses of drug solutions to a patient through a catheter at different times. In fact, one of the current methods for treating GnRH deficiency in women involves wearing a pump (about the size of an adult fist) on a belt with a subcutaneous or intravenous catheter.[25] The pump delivers a pulse of a solution containing 5 μg of GnRH every 90 min for several weeks to months. However, some external pump and catheter systems can be inconvenient and uncomfortable, can limit the patient's mobility, can be expensive, and may result in irritation or infections at the catheter site. Completely implantable pumps, developed for diabetes, oncology, or analgesia,[26] for example, may improve patient mobility and reduce infections by eliminating transcutaneous catheters, but they may still be hampered by their size, cost, ability to deliver only drugs in solution, and the limited stability of some drugs in solution at 37 °C.

3. Overview of Microfabrication Technology

Microfabrication can be generally defined as the production of microscale features in or on a material by techniques such as deposition, etching, micromolding,[27] along with patterning techniques such as photolithography[27a–c] or microcontact printing.[28] Microfabrication has traditionally been used to produce integrated circuits for microelectronic devices such as computer microprocessors. However, microfabrication has been used increasingly to produce microscale devices whose primary function is mechanical, chemical, or optical in nature. Such devices include microreactors, micro-

pumps, accelerometers, and micromirrors, and are commonly referred to as microelectromechanical systems (MEMS). MEMS are commonly made with silicon and microelectronic processing techniques. However, MEMS can also be made from plastics, glass, metals, or ceramics by processes such as stamping, casting, molding, and laser ablation.

MEMS have found use in a number of fields. Two notable examples are the fabrication of nozzles for ink-jet printers[29] and accelerometers for automotive applications.[30] More recent advances in MEMS include the development of microreactors for the production of chemicals[31] and microturbine engines for aerospace applications.[32] For the purposes of this review, microfabricated devices for biological applications can generally be classified as microfluidic devices and nonmicrofluidic devices.

3.1. Microfluidic Devices

Microfluidics is an area of microfabrication that focuses on the miniaturization of fluid-handling systems such as pumps, valves, and flow channels. The concept of fabricating entire chemical labs-on-a-chip or miniaturized total analysis systems (μTAS) that include pumps, valves, mixers, reactors, and separators has recently generated much interest.[33] The demand for such systems has resulted in the development of numerous microfluidic components such as micropumps and microvalves.[34] Micropumps can be based on moving parts such as diaphragms or piezoelectric components that mechanically pump liquids[35] or they can move ionic fluids by using electric fields (i.e. electroosmotic pumping).[36] Microfabricated valves with pneumatic[37] or thermoelectric[38] actuators can operate reversibly. Irreversible valves based on electrochemical actuation have also been suggested.[39]

Recent interest in microfluidics for biological applications has focused largely on developing microsystems for chemical[33c, 40] or DNA[33b,d, 41] analysis. Other areas where microfluidic devices have been utilized include combinatorial chemistry,[33b] bioassays,[42] and capillary electrophoresis systems. For example, various methods of capillary electrophoresis on polydimethylsiloxane and fused silica microdevices have been used to separate DNA fragments,[43] oligonucleotides,[44] polymerase chain reaction (PCR) products,[45, 46] single DNA molecules,[43a, 47] and single-[41e] and double-stranded[48] DNA. Capillary electrophoresis on microdevices has also been used for DNA genotyping[49] and the separation of neurotransmitters,[45] amino acids,[50] peptides,[43a] insulin, and lysozyme.[43b]

3.2. Nonmicrofluidic Devices

Nonmicrofluidic devices for biological applications do not involve the pumping or controlled movement of fluids and include many biosensors and some "DNA chips". Biosensors can be manufactured from silicon by using semiconductor processes, but their fabrication often involves at least one unconventional step to produce surface features or coat the sensor with a biologically or chemically active compound.[51] Similarly, DNA chips use immobilized materials on the device surface to identify genetic material or other chemicals.[52] Over the last several years, DNA chips have become popular with pharmaceutical companies for high-throughput drug screening and combinatorial chemistry.

The use of microfabrication technology in biological applications has grown tremendously in recent years. However, microfabrication has found limited use in the fields of controlled release and drug delivery. One could envision using microfluidic devices to achieve drug release, but the potential limitations of delivering only liquid drug formulations, the instability of certain drugs in solution, the complexity of some fabrication schemes, and the presence of moving parts that are subject to breakdown may present obstacles to their clinical and commercial use. As a result, the field of controlled release has yet to take full advantage of microfabrication technology.

4. Controlled Release Microchips

The ultimate goal of our work was to develop a microfabricated device with the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving parts.

4.1. Theory of Operation

Figure 2 shows a model embodiment of a controlled-release microchip consisting of an array of reservoirs that extend through an electrolyte-impermeable substrate. Each reservoir is sealed at one end by a thin membrane of material that

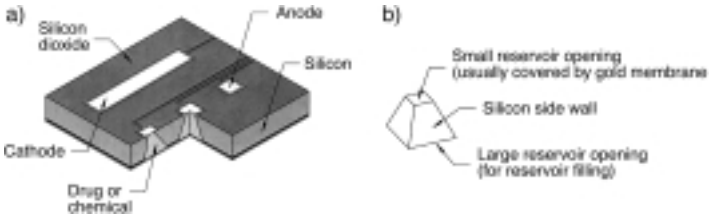

Figure 2. A schematic of a typical controlled-release microchip. a) Cut away section showing anodes, cathodes, and reservoirs, b) shape of an individual reservoir (see Section 4.2 for typical dimensions).

serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an electrolyte. There must be at least one other electrode on the device surface to serve as a cathode in the electrochemical reaction. The cathode can be made of any conductive material but is usually made of the same material as the anodes to simplify fabrication procedures. In addition, any number of cathodes can be included on a microchip, and they can be of any shape or size to suit the electrode design desired for a particular application. The reservoirs are filled through the open end with the chemical to be released. The open ends of the reservoirs are then sealed with a waterproof material.

The device is submerged in an electrolyte containing ions that form a soluble complex with the anode material in its ionic form. An electric potential is applied to an anode membrane when release from its corresponding reservoir is desired. This causes oxidation of the anode material and formation of the soluble complex with the electrolyte ions. The complex then dissolves in the electrolyte, and the membrane disappears. Figure 3 shows the principle of operation schematically. The chemical in the newly opened reservoir is now exposed to the surrounding electrolyte and is free to dissolve in the electrolyte and diffuse out of the reservoir.

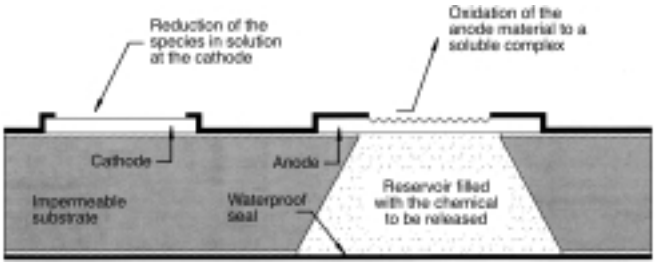

Figure 3. A cross section of a typical controlled-release microchip illustrating the principle of the electrochemical reservoir opening mechanism. The materials used in prototype microchips are described in Section 4.2.

4.2. Experimental Prototype Specifications

Four-inch-diameter silicon wafers were used as the initial model substrate material for the prototype controlled-release microchips. The prototype was a 17×17 mm square silicon device containing thirty-four reservoirs that extended completely through the silicon. The reservoirs were square pyramidal in shape (see Figure 2b) due to the potassium hydroxide etching method used to fabricate them. The small reservoir opening was approximately 50×50 μm, and the large opening approximately 480×480 μm. The thickness of the silicon substrate varied between 295 and 315 μm, so that each reservoir had a volume of approximately 25 nL. Each reservoir was sealed at the small end by a 0.2–0.3-μm gold membrane that served as an anode in an electrochemical reaction. Three thin-film gold cathodes were placed at different intervals across the surface of the device. Some portions of the gold anodes and cathodes were covered by a 0.4–0.6-μm silicon dioxide film to prevent corrosion in those areas during the application of an electric potential. The prototype microchip shown in Figure 4 had only three cathodes for thirty-four anodes. Twenty-one such prototype microchips can be fabricated on one four-inch silicon wafer.

The size of the prototype device was selected strictly for ease of handling during release experiments and compatibility with commercially available device packaging. However, devices are not restricted to that size and could be made much larger or smaller (< 2 mm), depending on the particular application. A device of the size used in these studies (17×17 mm) can accommodate over 1000 reservoirs.

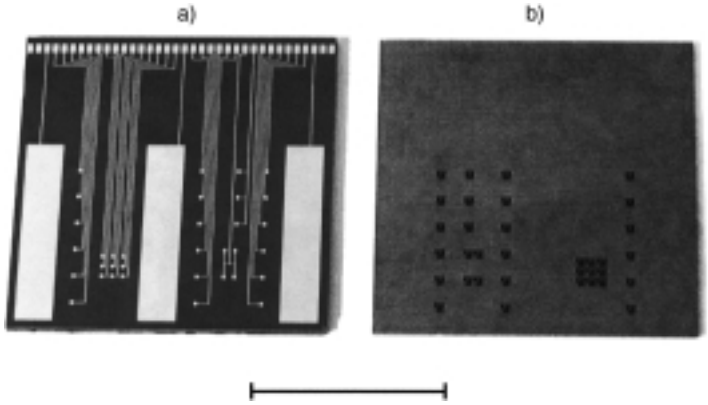

Figure 4. Photographs of a prototype microchip. a) The electrode-containing front side, b) the back side with the openings for filling the reservoirs. (Scale bar: 10 mm; photographs by Paul Horwitz.)

4.3. Selection of the Membrane Material

Selection of the proper membrane material is critical for the reliable operation of controlled-release microchips. A key requirement for the membrane material is that it should remain stable in the solution in the absence of an applied electric potential to prevent premature release of the chemical from the microchip. The membrane material must also be able to dissolve quickly and selectively when a specific electric potential is applied to it. However, selecting a material possessing both of these qualities is difficult because biological fluids contain a small amount of dissolved oxygen and chloride ions, which cause many metals to corrode spontaneously.

Gold was selected as the initial model membrane and electrode material primarily due to its unique electrochemical properties. Gold has long been considered a noble metal. It is easily deposited and patterned, has a low reactivity with other substances, and resists spontaneous corrosion in most aqueous solutions over the entire pH range. The fact that the gold surface remains clean (i.e., the native oxide layer on a gold surface, if present, is very thin) and does not corrode in most environments led to its widespread use in jewelry, currency, medical implants, and microelectronic devices. Pourbaix diagrams indicate the thermodynamically stable species in a solution at any combination of applied potential and solution pH. A computer-generated[53] Pourbaix diagram for gold in aqueous solutions free from complexing substances is shown in Figure 5. The diagram indicates that gold, when no electric potential is applied, is immune to corrosion over the entire domain of water stability (the area between the dotted lines). The species in areas delineated by solid lines are the thermodynamically stable, solid species at each combination of applied potential and solution pH.

The presence of a small amount of chloride ions in solution creates an electric potential/pH region that thermodynamically favors the formation of water-soluble chlorogold complexes.[54] The presence of a complexing substance such as chloride can change the Pourbaix diagram for gold in aqueous solutions (Figure 6a). However, thermodynamics does not tell the whole story. It is also important to look at the kinetics of

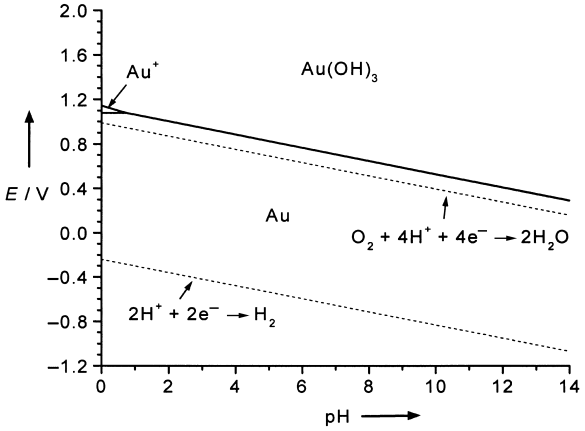

Figure 5. A Pourbaix diagram for the gold–water system in the absence of complexing substances such as chloride ions (applied potential E relative to SCE).

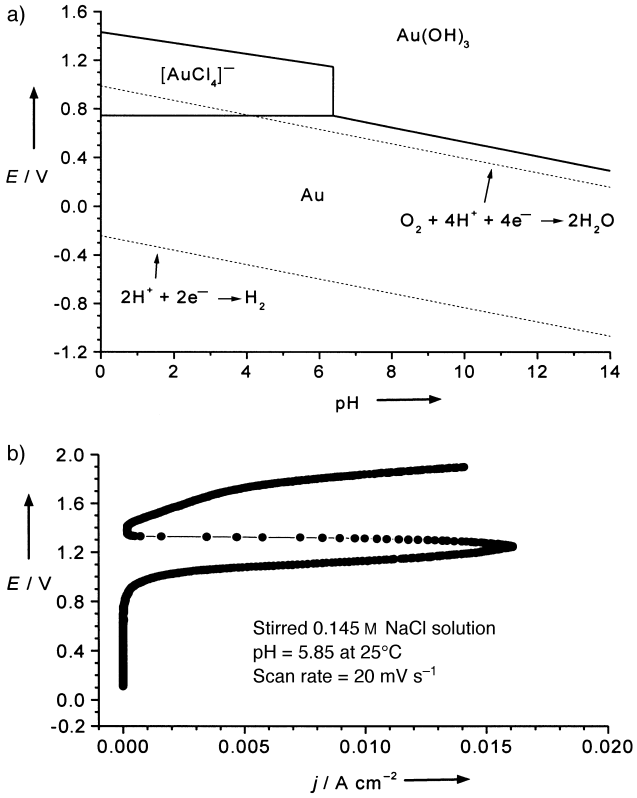

Figure 6. a) A Pourbaix diagram for the gold–chloride–water system containing 0.145 M chloride ion. b) An Evans diagram for the same gold–chloride–water system obtained potentiodynamically. This diagram represents the kinetics of the gold corrosion reaction in chloride-containing solutions.

the formation of chlorogold complexes. Evans diagrams represent the kinetics of corrosion and indicate how the corrosion rate (shown as current density) changes with applied potential. A potentiodynamic Evans diagram for gold in 0.145 M sodium chloride solution (Figure 6b) begins to show a rise in current density corresponding to the formation of tetrachloroaurate(III) at an applied potential slightly above its thermodynamic barrier potential of approximately +0.75 V relative to a saturated calomel electrode (SCE). Gold corrosion by the formation of water-soluble chlorogold(III) complexes is thermodynamically and kinetically favored and occurs at appreciable rates at potentials slightly above +1.0 V versus SCE. Corrosion of gold membranes occurs rapidly (typically 10–30 s for a 0.1–0.3 μm thick membrane at +1.04 V vs. SCE) and is clearly evident in the scanning electron micrographs of Figure 7.

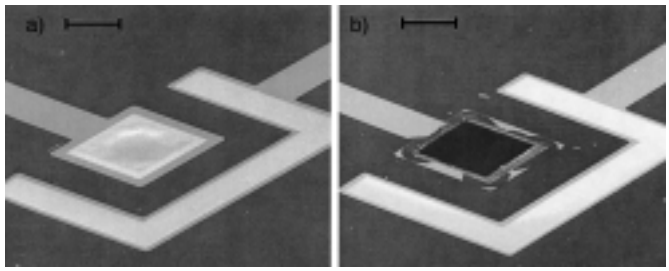

Figure 7. Scanning electron micrographs of a gold anode membrane covering a reservoir a) before and b) after the application of +1.04 V vs. SCE for several seconds in phosphate-buffered saline (PBS). (Scale bar: 50 μm.)

In addition to its favorable electrochemical properties, gold was selected as the initial model membrane material for proof-of-concept experiments due to its biocompatibility. Gold and its ionic compounds have been studied for many years due to their extensive use in dental materials, transdermal gene delivery, and drugs for treating rheumatoid arthritis.[55] Typical cumulative doses of Au^{I} salts used for treatment of rheumatoid arthritis can range from milligrams to grams, and the most common adverse side effects (various forms of dermatitis) are rarely seen in patients with a cumulative dosage of less than 250 mg.[55] The local effects of Au^{III} compounds have been less extensively studied. Some data have been reported for Au^{III} compounds in vitro,[56] but few studies have examined the local effect of Au^{III} in vivo. The quantity of Au^{III} that is locally released due to the opening of one reservoir is small (ca. 2–6 ng), and the diffusion and clearance kinetics of Au^{III}, which affect its local concentration, are dependent on the implantation site.

4.4. Fabrication

Controlled-release microchips are fabricated by standard microelectronic processing techniques such as chemical vapor deposition, photolithography, and plasma etching. The details of the stepwise process of making the prototype controlled release microchips can be found in the literature.[57]

4.5. Proof-of-Principle Release Studies

Proof-of-principle release studies were designed to determine whether chemicals could be stored in a microchip and released on demand. The model chemicals used were selected primarily according to two criteria. The first criterion was the minimum concentration that could be reliably detected (i.e. detection limit). We wanted to be able to detect concentrations as low as 1.0 nM. The second criterion was the ease of

using a particular detection method. We preferred to use a method that would allow us to analyze our release samples with minimal sample preparation. This makes the release studies easier to conduct and reduces the opportunities for introduction of errors by complicated sample preparation. The two chemicals selected were the fluorescent dye sodium fluorescein and radioactive calcium chloride $^{45}CaCl_2$.

Ink-jet printing or microinjection was used to fill the reservoirs from the backside of the microchip with a liquid or gel containing the chemicals to be released. Each reservoir of a given microchip is typically filled with the same volume of liquid or gel. For in vitro experiments, the open ends of the filled reservoirs were covered with a thin film of plastic and then sealed with materials such as water- and solvent-resistant epoxy resins. A more detailed description of the fabrication and preparation of the prototype microchips can be found in the literature.[57]

Microchips filled with one or both of the model chemicals were sealed, packaged, and inserted into 100 mL of saline solution, with or without phosphate buffer. A saturated calomel reference electrode was placed in the solution near the microchip to allow the anode to be held at a particular potential. An electric potential of +1.04 V versus SCE was applied for up to 30 s to an anode when release was desired from the corresponding reservoir. Release of the chemical from the microchip was detected within a few minutes of applying the electric potential to the anode, and typically 70% of the chemical was released within 30 min. However, complete release could take a few hours under these experimental conditions. The rate of release of the chemical may be affected by factors such as the dissolution rate of the chemicals inside the reservoir and the diffusion rate of the chemical out of the reservoir. Figure 8 proves that a single chemical can be stored in and released from a microchip on demand.

It was desired to release several chemicals from a single device in a similar fashion. Figure 9 shows the result for a prototype microchip filled with both model chemicals. This is the first demonstration that several chemicals can be stored in and released independently from a microchip on demand. These results provide proof-of-principle for microchips as chemical delivery devices.

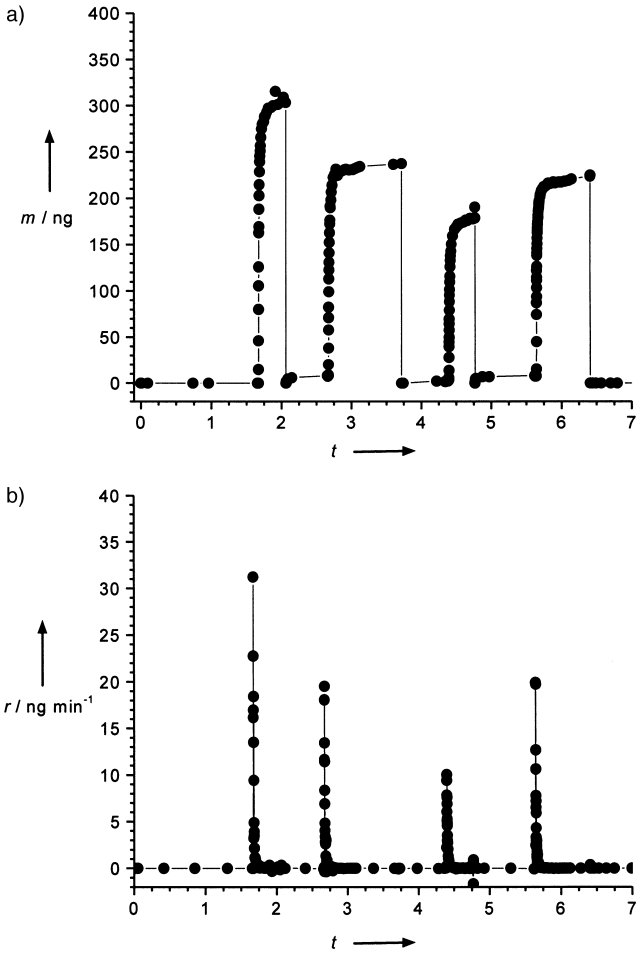

Figure 8. Pulsatile release of a single substance (sodium fluorescein) into PBS from four identically loaded reservoirs of a prototype controlled release microchip. a) Mass m released vs. time t (in days) and b) release rate r vs. time t (in days). In plot (a), m is returned to zero by replacing the release medium with fresh solution between release events.

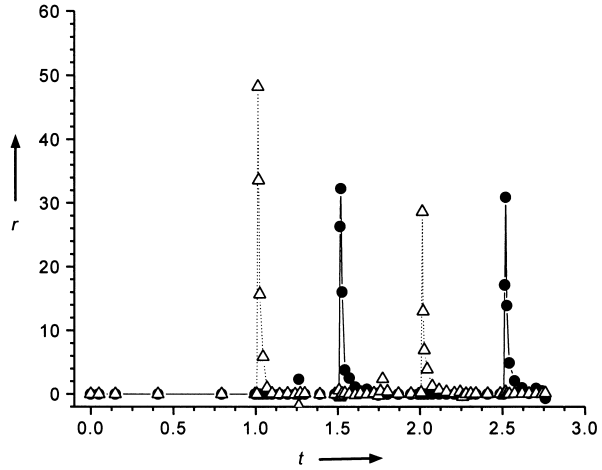

Figure 9. Pulsatile release of multiple substances (sodium fluorescein and $^{45}Ca^{2+}$) from a prototype controlled-release microchip into 0.145 M sodium chloride solution. The release rate r of sodium fluorescein (●) is given in units of ng min^{-1}, and that of $^{45}Ca^{2+}$ (△) in units of 5 nCi min^{-1}. t in days.

4.6. Potential Advantages

The controlled-release microchip has a number of potential advantages, some unique to its design and some stemming from characteristics common to most microdevices (i.e., small size). These are described in the following sections.

4.6.1. Chemicals to be Released

Multiple chemicals can be stored inside and released from the microchip. Each reservoir can be filled with a different chemical or combination of chemicals. Chemicals in any form (solid, liquid, or gel) can be delivered by the microchip. Microfluidic devices such as pumps are limited to delivering liquids. The controlled-release microchip consists of a reservoir covered by a thin membrane of material that can be dissolved on demand. The form of the chemical or drug in the reservoir and the presence or absence of other materials such

as polymer matrices or excipients have little or no effect on the electrochemical behavior of the membrane. Therefore, controlled-release microchips have the potential for a high degree of flexibility in the types of chemicals they can store and release.

4.6.2. Simplicity of Release Mechanism

The microchip has no moving parts. A thin barrier membrane covers each reservoir filled with one or more chemicals. The release of chemicals from the microchip is initiated by the disintegration of the membrane. The membrane is removed by the application of an electric potential, which causes the membrane to dissolve by a simple electrochemical reaction. The absence of moving parts potentially increases device reliability by decreasing the possibility of mechanical breakdown.

4.6.3. Accuracy

A variety of highly potent drugs can potentially be delivered from the microchip in a safe manner. It is important that the amount of drug delivered to a patient matches the amount prescribed, especially for highly potent compounds. It is difficult to accurately measure small quantities of drug for incorporation into conventional drug-delivery vehicles such as pressed tablets. This may lead to large uncertainties in the total amount of drug in the tablet. However, each reservoir of a microchip can be accurately filled with a small amount of the drug by using microinjection or ink-jet-printing techniques. In fact, this dosing approach has been demonstrated in the manufacture of delivery devices by Three Dimensional Printing.[58] The amount of drug administered from a microchip filled by these printing methods can be tightly controlled, and accidental overdose is unlikely because release from active devices can only occur when an electric potential is applied to an anode. Larger doses can be administered by simply opening several reservoirs simultaneously.

4.6.4. Complex Release Patterns

Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchip. Any complex chemical or drug release pattern can be broken down into a combination of two parameters: release time and release rate. A unique feature of the controlled-release microchip is the potential to control both of these parameters.

The time at which release begins from any reservoir is determined by the time at which the anode membrane covering that reservoir is removed. Spontaneous release from a reservoir will not occur if the anode membrane material is stable in the electrolyte solution. Therefore, an anode membrane material is selected that will not dissolve and open until the correct electric potential is applied. Demultiplexing enables each anode membrane covering a reservoir to have its own conducting path to the power source. This makes each reservoir (or group of reservoirs) "independently addressable," so that electric potential can be applied to any combination of reservoirs at any given time. Incorporation of preprogrammed microprocessors, remote control units, or biosensors may potentially allow tight control over the time at which the membranes are removed and release of chemicals begins.

The rate of release from a reservoir is a function of the dissolution rate of the materials in the reservoir, the diffusion rate of these materials out of the reservoir, or both. Therefore, the release rate from an individual reservoir can be tailored to a particular application by the proper selection of the materials placed inside the reservoir (e.g., pure drug(s), drug(s) with polymers, etc.). For example, pulsatile release can be achieved by using materials that quickly dissolve when the reservoir is opened. Sustained release can be achieved by using materials that dissolve slowly after the reservoir opening, or that do not dissolve but allow the drug to diffuse out at a known rate.

4.6.5. Potential for Local Delivery

The microchip can be made small enough to make local chemical delivery possible. An advantage of local drug delivery is that high concentrations of drug can be achieved at the site where it is needed, while keeping the systemic concentration of the drug at a low level. This technique is particularly useful if the drug has adverse side effects if administered systemically in high doses. For example, BCNU (carmustine) is used extensively in the treatment of malignant brain tumors.[59] Large amounts of BCNU must be administered to a patient systemically to achieve its minimum acceptable concentration at the tumor site in the brain. This is largely due to the impermeability of the blood–brain barrier to most drugs. The resulting large systemic concentration of BCNU causes many extreme side effects in the liver, kidneys, and spleen. Implantation of polymer wafers containing BCNU at the site of the tumor after its removal allows the local concentration of BCNU at the tumor site to be 1000 times higher than that possible with systemic delivery. However, the systemic concentration of BCNU is kept quite low, and this greatly reduces the side effects normally associated with BCNU therapy. This therapy significantly extends life and greatly improves the quality of life of the patient during treatment and is a good illustration of the benefits of local drug delivery.

4.6.6. Stability Enhancement

Some new protein-based drugs have limited stability (i.e., shelf life). Water penetration into these protein drug formulations is one of the most frequent causes of their instability.[60] The membrane covering the filled reservoirs of a microchip will prevent penetration of water into these reservoirs. Thus, the stability of protein drugs is theoretically enhanced first, because the drugs can be isolated from the outside environment (hermetically sealed) and second, because they can be stored in the microchip in their most stable form (solid, liquid, or gel).

5. Summary and Outlook

There is a direct analogy between computer and chemical microchips. Computer microchips break down any complex operation into a series of simple binary symbols, either 0s or 1s. Chemical microchips are analogous in that any complex chemical release pattern can be broken down into a series of small, simple subunits. The small subunit here is a single reservoir that is closed (0) or open (1). Any complex release profile (continuous, pulsatile, or both) can be approximated by the precisely timed emptying of a series of single reservoirs. Figure 10a shows the release profile that can be obtained with

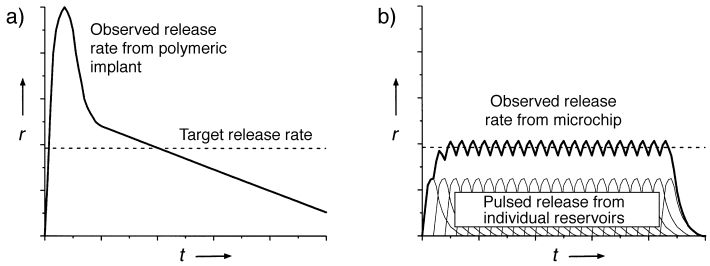

Figure 10. a) A sustained-release profile from a typical controlled-release polymer. b) An example of how a sustained-release profile may be approximated by the precisely timed release of pulses of chemical from a microchip.

a conventional polymer drug-delivery implant from which a sustained, nearly constant release rate is desired. A typical profile is characterized by an initial "burst" release of drug from the device with a slow decrease in the release rate over time as the device is depleted of drug. Microchips cannot only be used for pulsatile release, such as that demonstrated in Figures 8 and 9; Figure 10b shows an example of how a sustained-release rate profile might be approximated by a series of precisely timed pulses of chemical from a microchip. We have termed this the "digitization" of chemical release.

The first demonstration of the storage and release of multiple chemical substances from a microchip,[57] reviewed here, provides the proof-of-principle for the digitization of chemical delivery. Application of this new concept to controlled drug delivery could represent, with further study, a substantial step forward in the development of a "pharmacy-on-a-chip" or other "smart" drug delivery systems. Areas outside of drug delivery where this technology may also find use include medical diagnostics, analytical chemistry, chemical detection, industrial process monitoring and control, combinatorial chemistry, microbiology, and fragrance delivery.

The next step in the development of controlled-release microchips is the integration of active components into the microchip. A battery, a clock, and possibly a reference electrode need to be combined with the microchip into a single package for implantation. Many of the necessary technologies already exist in other areas. For example, cardiac pacemaking is a highly developed field with power and control capabilities that could be applied to microchip drug-delivery devices. Other active components could include a signal receiver for remote control of drug delivery or a biosensor for autonomous, closed-loop operation.

A logical extension of the controlled-release microchip work is the development of a passive, polymer microchip. The term "passive microchip" refers to devices that contain no electronics, power sources, or microprocessors. The passive microchip is similar to the controlled-release microchip discussed in this review in that the substrate contains numerous reservoirs that are filled with the drug(s) to be released or with a matrix material that typically consists of a polymer and the drug. Each reservoir is covered by a layer or "cap" of a degradable material, a cap of a nondegradable material with a known permeability for the drug, or is left uncapped. The time and rate of release from a reservoir is dictated by the degradation rate of the caps or matrix material or the diffusion of the drug through the caps or out of the matrix material. Both parameters can be controlled by varying the composition or thickness of the caps or the formulation of the drug or matrix material within the reservoirs. This type of microchip device could have the additional advantage of being completely biodegradable, so passive microchip implants for drug delivery applications would not have to be removed.

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