Microtechnology in Medicine: The Emergence of Surgical Microdevices

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New microsurgical techniques that address the small size scales of tissues and individual cells are spurring the advent of a fundamentally new class of miniature devices. Accompanying this technological advance are the necessary means for deploying, actuating, and controlling these microscale tools. The push for this new frontier comes from many directions, including the realization that significant medical advances can be achieved if surgeons can directly and precisely access and treat the small tissues and structures that are specifically affected by disease. Furthermore, unprecedented knowledge of the inner workings of the cell, both in health and in pathology, is opening opportunities for therapeutic interventions at the single cell level. However, although there has already been a trend toward minimally invasive surgery, conventional microsurgical instrumentation that are manufactured by traditional machining and their manual operation by the surgeon are limited to a scale of approximately a millimeter to a few hundred microns. Such instruments do not permit surgery on small tissue structures nor at the cellular level. The emerging generation of microscale surgical tools, constructed using fabrication methods adapted from the microelectronics industry, potentially allows the surgeon to reach further down the length scale with operating elements sized no larger than individual cells.

The earliest of these biomedical microscale devices are providing unprecedented access for manipulation, monitoring, and diagnosis in some of the previously inaccessible reaches of the human body. These tools have been developed to take advantage of the physics of small-length scales to perform mechanical actuation, manipulations, and even drug delivery. Some tools perform monitoring capabilities as miniature sensors measuring temperature, pressure, and other parameters in locations such as small blood vessels, the nervous system, and the digestive tract. This review will discuss the basic physics of the small scale and how they govern the design and operation of these new microdevices. Some representative examples of the microscale devices and their unique capabilities will also be discussed.

0148-703/07/5401-0137

MICROFABRICATION

Borrowing from Microelectronics

The technology of Micro-Electro-Mechanical Systems (MEMS) is the basis for producing the next generation of microsurgical tools. Based on the fabrication process developed during the past 50 years for the miniaturization of electronic devices, MEMS arose in the early 1980s to take advantage of both the electrical and robust mechanical properties of silicon and silicon-based compounds (both electrical conductors and insulators).[19,29] The resulting mechanical structures, actuators, and sensors were integrated with microelectronics to provide reliable means for power and control. The microfabrication process generally involves successive depositions of thin films of various materials on a silicon or glass substrate. These deposited films and indeed the silicon substrate itself can be individually sculpted at micron-level resolution via photolithography and a myriad of versatile material etching techniques to produce virtually any desired microstructure[19,23] (*Fig. 24.1*). The planar microstructures formed by the deposited and sculpted films can then be stacked, folded, or lifted from the planar orientation to form strong, three-dimensional structures. Recent advances in this technology have included the addition of various polymer films and the use of biocompatible materials. Details of microfabrication methods and MEMS in general[19,29] with relevance to biotechnology have previously been discussed in a number of reviews.[1,31,36,41]

Software Tools for Microfabrication

This rapid proliferation of MEMS microfabrication has been made possible by the ready availability of basic engineering tools specially targeted to serve microscale design. The design of MEMS devices typically begins with one of several commercially available computer-modeling tools (ANSYS, COMSOL, and Coventor, among others) that allow the designer to integrate the physics of electromagnetics, mechanics, chemistry, and thermodynamics to accurately model the interactions among these various physical principles and provide predictions of the performance of various device designs. After designs are optimized using these modeling tools, they can then realized with a variety of

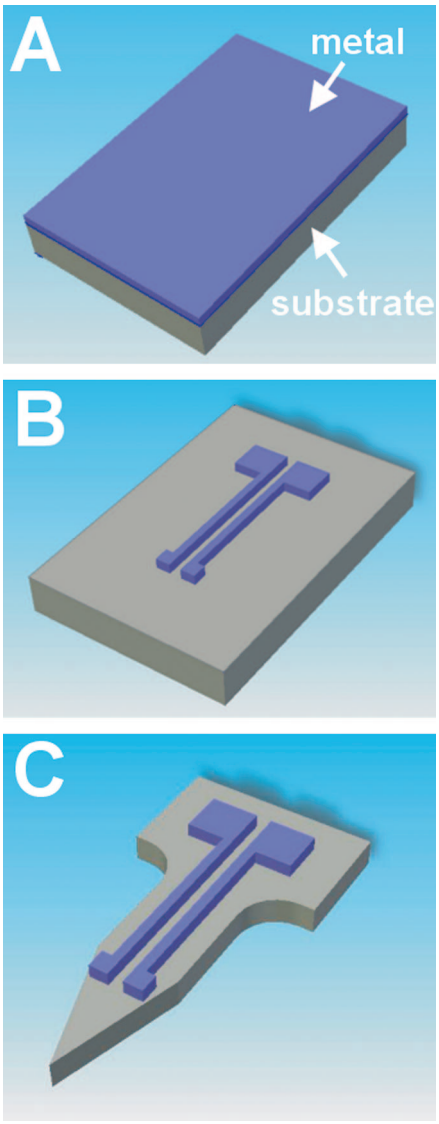

FIGURE 24.1. Adapted from the manufacture of microelectronics, microfabrication processes involve (*A*) depositions of thin films on a substrate (usually silicon or glass); and subsequent etching away of excess material, both in the deposited film (*B*) and substrate itself (*C*) based on two-dimensional templates provided by photolithography. In photolithography, a thin layer of photosensitive material ("photoresist," not shown here) is deposited over the target material and patterned via focused light. The patterned photosensitive resist protects the target material along the desired shape, while the rest of the material is selectively etched away, leaving the desired shape in the target material (*B, C*). In the example shown here, two successive photolithographic steps are performed to produce one shape in the film (metal) and another in the bulk substrate.

computer-aided software tools to lay down the precise configurations of prospective microstructures. These electronic drawings can then be directly transferred to patterned lithographic templates, which in turn is a central component for transferring designs to actual materials during microfabrication.[19,23]

Advantages of Microfabrication

The advantages of the MEMS fabrication processes are many fold. First and foremost, of course, these fabrication processes can create structures with minimum feature sizes of 1 μm or less, whereas conventional machining techniques are limited to tens to hundreds of microns minimum feature sizes. Fabrication typically takes place with multiple copies of the same devices on a single substrate, permitting large batches to be fabricated in parallel and potentially minimizing unit costs. Because of the use of computerized design tools, engineers can systematically vary device features, allowing for rapid prototyping. In addition, because of its origins in microelectronics, these fabrication processes readily permit integration of electronic devices to provide control and power for the mechanical components. Lastly, because the microelectronic industry has flourished for decades and continues to evolve, the infrastructure for microfabrication technology is very robust and constantly provides improvements in miniaturization that benefit the MEMS field.[19,23]

MEMS Microdevices in Daily Use

MEMS technology is responsible for many common products in everyday use (see *Fig. 24.2* for examples). One of the earliest commercialized MEMS product was the miniature accelerometer that is now standard for triggering airbag deployment in automobiles. Based on mechanically strong membranes made by the deposition of thin films during microfabrication, this basic technology has enabled the development of cheap miniature pressure sensors found in various industrial applications. On the consumer side, MEMS fluid driving devices have made their way into our daily lives as ink-jet printer heads. The digital light projection (DLP) video projectors have at their core vast arrays of individually moveable micromirrors manufactured using MEMS technology. In addition, newly developed, robust high-frequency mechanical resonators are promising to supplant purely electronic resonators in a variety of common electronic devices, such as cellular telephones.[30]

From these examples, one can see that, although MEMS devices commonly have operating features that are just microns in size, they have been used in many demanding applications in which they are subjected to extreme speeds of operation (movements at kilohertz to megahertz) and also extreme acceleration and deceleration. Their ability to function reliably under these conditions with high durability, is, as discussed below, directly a result of their inherent small size, which allows them to be used with tolerances proportionally well beyond that of any macroscale counterpart.

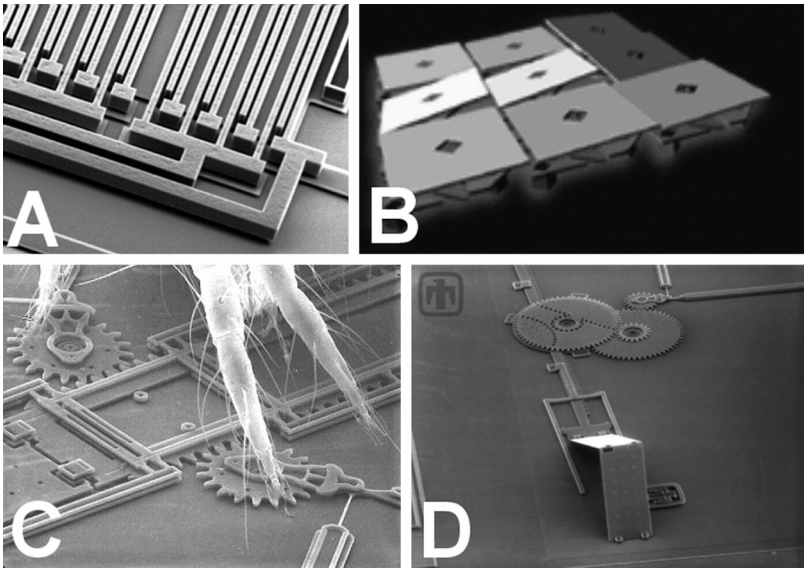

FIGURE 24.2. Examples of MEMS microdevices. *A,* comb-like sensors in a commercially available accelerometer, similar to those used to trigger airbags in cars. Each beam is only a few microns wide (SensorDyanmics AG; http://www.sensordynamics.cc/cms/cms.php?pageId=51). *B,* part of an array of microscale mirrors used in a DLP chip. Each of the mirrors, approximately 10-μm wide and spaced 1-μm apart, is individually mounted and actuated, capable of scanning at high speeds to facilitate projection of a video image. Each projector has up to two million of these little mirrors (Texas Instruments, Inc.; http://www.dlp.com/about dlp/about dlp image library.asp). *C,* a mechanical linkage of microscale gears and sliders compared with the legs of a common mite (Sandia National Laboratories, SUMMiT fabrication process; http://mems.sandia.gov/scripts/images.asp). *D,* these linkages can form microengines to drive the assembly of three-dimensional structures, such as this mirror being raised from the plane of the substrate (Sandia National Laboratories, SUMMiT fabrication process). All photos are press images.

UNFAMILIAR PHYSICS AT SMALL SCALES

In considering microscale devices or instruments, it is necessary to be mindful that as characteristic dimensions shrink into the micron range, various scaling laws result in dramatic differences in the relative importance and relationships among various physical forces and phenomena. These important differences represent a unique challenge to engineers and designers, because they represent a substantial departure from the intuitive comprehension of physics one develops from perception at the macroscale. However, this seemingly "new physics" of the microscale offers some important advantages that have helped to produce devices operating on fundamentally different principles from those commonly used at the macroscale. These advantages include the favorable scaling of material properties as well as unique force generating, actuating, and sensing mechanisms.

Material Properties

In their own right, silicon and many silicon compounds are mechanically strong materials; in fact, single crystal silicon is actually stronger than steel.[29,37] However, perhaps the most important advantage conferred by going toward the microscale is the favorable scaling of material strength and stiffness versus masses. For example, in any given object, the modulus (mechanical stiffness) is an inherent material property and, therefore, independent of length. Similarly, the mechanical strength of a material scales only with the second power of length. However, the object's mass (and, therefore, weight) scales with the third power of length. Thus, for microdevices with inherently very small mass, the importance of mass diminishes much more compared with the other parameters, such as stiffness and strength as size shrinks[29,32] (*Fig. 24.3A*). This beneficial relation in scaling allows various structures to be constructed using just a seemingly precarious assembly of thin films and beams, formed from materials such as silicon or some electrically insulating silicon compound such as silicon dioxide or silicon nitride. From the point of view of a macroscale observer, these thin microstructures seem to be surprisingly robust against proportionally large loads, much as an ant seems surprisingly strong in its ability to lift loads many times its own weight. The resulting advantage is that microdevices can be constructed much more simply and with proportionally less material and less structural reinforcements than would typically be associated with construction of a macroscale object designed to serve an analogous purpose.[19]

Silicon and silicon-based compounds used in microfabrication also have the benefit of exhibiting no plastic deformation, as many conventional metals do. These materials are

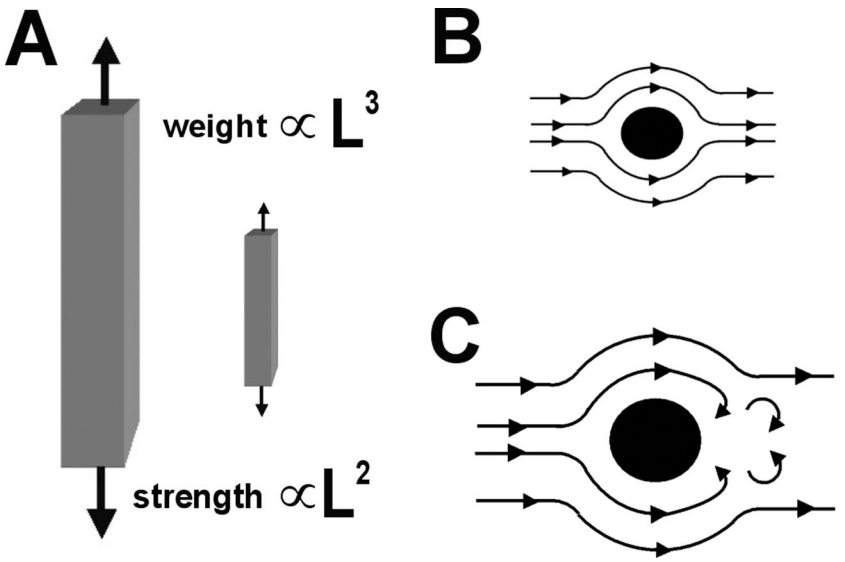

FIGURE 24.3. *A* beams in simple tension. Relative to its weight, the beam's strength is inversely related to length scale (*L*). Thus, the smaller beam is stronger than the larger beam relative to its own weight. *B*, in low Reynolds number regime, fluid flow is always contoured around a solid object, regardless of shape. Viscous forces and friction from the fluid flow against the solid surface become the dominant factors. At small length scales, fluid flows are often associated with low Reynolds numbers. *C*, fluid flow around a solid object at a moderate to high Reynolds number. Fluid momentum is an important factor, and flows inevitably separate behind an object in a manner dependent on the object's shape. In this case, forming a recirculation region at high flow speeds, turbulence (unsteady flow) can form (not shown here).

mostly linearly elastic,[19,23,29] meaning that a component constructed with these materials is not subject to permanent deformation, and the original shape will reliably be restored after the mechanical loading has been removed. Although materials such as silicon used for microfabrication are strong, they will nevertheless fracture if stressed beyond their ultimate strengths. It is, therefore, important to use these devices within the structural limits to prevent material failure.

Fluid Mechanics

Because most surgical tools must operate within a liquid environment and drug delivery often requires direct movement of fluid, it must be recognized that the fluid mechanics of water at the microscale is dominated by viscous forces and surface tension.[33] At these scales, mechanical dissipation caused by viscous losses or friction of fluid flow against a solid surface is highly important, whereas the effect of fluid momentum (inertia) is negligible. In fluid mechanical analysis, this crucial relationship between inertia and viscosity is represented by the Reynolds number.[25] For water at the microscale, a low Reynolds number regime is said to dominate (*Fig. 24.3B*). Furthermore, in addition to the prevalence of low Reynolds numbers, the forces associated with movement of devices through the air-liquid interface must also be carefully considered and accounted for, because this interface can exert as much force as produced when devices contact solid surfaces during operation. The beneficial tradeoff in this fluid mechanical regime is the absence of more complicated (and less predictable) fluid flow patterns (*Fig. 24.3C*), including flow separation turbulence.[33] The steady motion of viscous-dominated flow is much easier to model, and the behavior of fluids and solid structures moving through fluid at the microscale as well as the forces and pressures generated are therefore much easier to predict.

Actuation and Force Generation

At the microscale, several unique phenomena are often exploited to generate forces to produce various forms of actuation. In many applications, a natural choice is some form of piezoelectric transduction,[19,21,44] in which electrical signal is transduced into small material deformations, which, in turn, can be harnessed into mechanical displacement and force generation. Piezoelectric actuation is also particularly well suited for generating high-frequency motions, which opens the way for creating vibrating devices, applications using ultrasonic actuation, and even for producing fine pumping motion with small volumes of fluids. Another fundamental actuation mechanism takes advantage of the differences in the thermal expansions of dissimilar materials to produce displacement and generate forces[14,39,43] (*Fig. 24.4*, *A* and *B*). This operating principle is harnessed with thermal bimorphs, which are formed by sandwiching films of two different materials, which are then actuated simply by heating and cooling. With careful design and configuration of such bimorphs, thermal-induced deformation can be leveraged to construct a variety of actuators and deforming structures. Although the use of thermal actuation does not enjoy the same benefits of high-frequency motions, because of the small thermal masses of microscale devices, there is negligible lag resulting from the heating and cooling of these thermal actuators during operation.[43]

Both thermal and piezoelectric actuation are well suited for microsurgery, because the actuating elements can either operate within an aqueous environment or be easily encapsulated and isolated from the surrounding environment. Less suitable for aqueous environments is a third popular actuation mechanism, based on electrostatic attraction and repulsion. The limitation with electrostatically based actuators is that

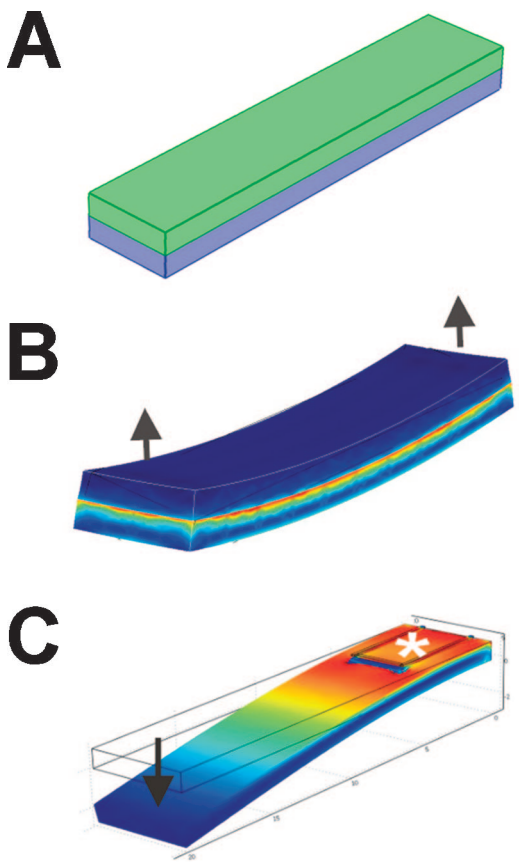

FIGURE 24.4. *A* thermal actuation operates by sandwiching two different materials with different thermal expansion properties. In this example, the lower material has a much higher coefficient of thermal expansion (in other words, expands more when heated). *B*, thus, when this sandwich, or "bimorph," is heated, the assembly will deform, bending in the case of the example shown. Such deformations can be harnessed to actuate displacement or generate force. *Color* denotes stresses in the structure; note that the highest stresses occur at the interface between the two materials. *C*, force sensing is typically accomplished by embedding small strain gauges in deformable structures. These strain gauges typically consist of thin traces of piezoresistive materials, whose electrical resistances change markedly in response to mechanical strain. In the simple example shown, a simple bending beam (caused by load at the *arrow*) results in high strains at the fixed base. Strategically placed strain gauge traces in this area (*) provides the highest sensitivity to the transverse deflection of the beam (*arrow*). *Color* denotes strain in the beam, with the highest strains occurring near the base. The examples in this figure are illustrated by simple models in COMSOL Multiphysics.

they cannot operate in ionic solutions and are difficult to isolate from their environment. For this reason, electrostatically operated devices, which are commonly used in other MEMS applications, are generally not used for "wet" biotechnological applications, including microsurgery. Magnetic actuation may be somewhat more favorable, but the generally weak forces (scaling with the third power of length) generated for small objects have meant that this mechanism has, to date, found little use.

Sensing

In microsurgical tools, sensing needs would generally include the capability to measure force, pressure, and temperature at specific locations. Force sensing follows the same principle of strain gauges,[32,37] which typically involves piezoresistive elements, namely an electrical resistor whose resistance changes because of the mechanical strain of the structure in which it is embedded (*Fig. 24.4C*). Because most MEMS materials are linearly elastic (with no plastic deformation) the strain in the structure in turn is directly proportional to the force incident on it. A similar principle governs the mechanism for measuring pressure, which, like force, produces a strain in some mechanical component (for pressure sensors, usually a thin-film membrane).[29] The high strength of materials relative to relevant forces ensures that the measurement function will not likely exceed the ultimate mechanical limits of the sensors. Thermal measurements operate in a manner similar to thermistors,[19] again using resistive elements, but harnessing the changes in resistance caused by temperature changes. Again, a key advantage at the small scale is the small thermal masses of measuring elements, permitting very rapid thermal equilibrations and small time scales.

EXAMPLES OF MEMS IN MICROSURGERY

A range of MEMS-based instrumentation has been proposed and is being developed for use in various types of microsurgery. Most of these devices are still in the development stage and have yet to become practical instruments in the operating room, although a few have progressed to early stages of commercialization. Each device or system has been constructed using the basic fabrication principles discussed above and has sought to harness some combination of the basic physical principles described in the previous section. It is likely that these devices will be eventually used in conjunction with some macroscale instrument, such as a catheter or endoscope to deliver the microdevice to the intended area of operation.

Tissue Handling and Microgripping

Perhaps one of the most basic surgical functions is the manipulation and movement of tissue. This fundamental function has been widely explored by MEMS researchers and engineers. Indeed, among the first MEMS devices fabricated were tiny grippers and tweezers. Although the earliest tweezers were operated electrostatically, which renders them unfit for an aqueous environment, newer developments that followed soon after used alternative means of actuation. Keller, Ferrari, and Howe (13–15) (*Fig. 24.5*) have developed a basic

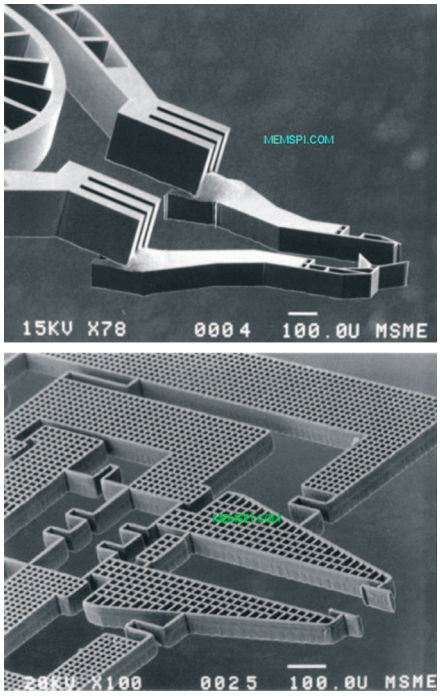

FIGURE 24.5. Microscale tweezer and gripper fabricated from silicon. Capable of grasping objects only a few microns in size, these devices are thermally actuated and include a series of springs for mechanical compliance and fins to facilitate heat dissipation (courtesy of Dr. Christopher Keller and MEMS Precision Instruments).

paradigm for fabricating thermally actuated grippers and tweezers out of high aspect ratio single crystal silicon and polysilicon via the HEXSIL fabrication process. These actuators have been shown to be mechanically strong and are able to effectively grasp objects only a few microns in size. Moreover, these actuators can easily be adapted to any configuration, depending on the intended application. Heat dissipating fins have also been incorporated into designs to maximize heat transfer and, therefore, minimize the response time of the thermal actuators.

A rudimentary surgical application in ophthalmology has been demonstrated with these microscale tweezers and grippers.[2] Adapted as "microforceps," these devices are much smaller than conventional ophthalmic surgical instruments and are well suited for use within the small volume of the eye. These microforceps have been used to perform lensectomy and vitrectomy, both on living animals and in cadaver eyes, demonstrating the performance and mechanical strength of these silicon based grippers. Additionally, the small size and nonreflective surface of these silicon devices readily permitted visualization of the devices during the procedures.

Developments in the design of MEMS microforceps that are more recent include the use of a polymer-metal bimorph that is easily and cheaply fabricated.[7] Made from a sandwich of gold film and SU8, these grippers have been designed specifically to operate in an aqueous environment, and the grasping of a single cell was demonstrated. SU-8 is a biocompatible polymer that is mechanically strong and widely used in simple MEMS devices. The polymer has the added advantage of not being brittle, thus, it would be unlikely that parts would snap off during operation.

Tissue Cutting

Along with tissue handling and manipulation, the critical step in any surgical procedure is cutting. Microdevices used for tissue cutting must be designed to withstand the forces necessary to penetrate the tissue matrix. One strategy is to use a small knife with a rudimentary blade that is reciprocated longitudinally at high frequency using piezoelectric actuation.[21] The principle of such high-speed, low-amplitude motion is to reduce the required penetration force of cutting while focusing mechanical energy at the target location. A number of such microfabricated piezoelectric "horns" have been developed through the years and fitted with a blade for cutting tissue or simply to break up tissue. At an even smaller scale, a similar device has also been used to facilitate the penetration of a microneedle through the membrane of a single cell, where the needle can potentially sample cytoplasm or deliver drugs and other materials.[44]

Recently, a passive manually operated cutting instrument has also been demonstrated (*Fig. 24.6*). Instead of vibratory mechanical motion, this cutting device relies on an ultrasharp, nanoscale cutting edge formed by molding silicon

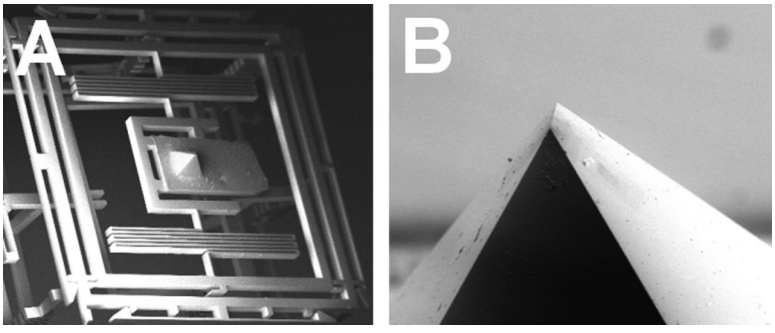

FIGURE 24.6. A passive cutting tool based on an ultrasharp nanoknife. *A,* the knife is a pyramid shaped from silicon nitride and supported at the center of a compliant suspension mechanism. The square-shaped suspension is approximately 1-mm square. *B,* the apex of the pyramid is ultrasharp, sporting a radius of curvature of only 20 nm.

nitride over silicon etched precisely along crystal planes.[5,38] The nanoknife has been used to target and cut subcellular components, such as a single neurite or axon, both in vitro and in vivo. It has also been shown to be able to perform cutting at a larger scale by cutting planar, 10-μm-thick tissue sections. This nanoknife has also recently been demonstrated for neurosurgical use on peripheral nerves in a living animal.[4] In this study, a miniature, custom-built platform was deployed to isolate and mechanically stabilize an intact nerve (*Fig. 24.9B*). The nanoknife was then used to progressively pare down the nerve, while the cutting process was monitored visually and documented by recording the attenuation of the electromyographic signal recorded from the target muscle. During this procedure, it was also possible to identify and cut individual axons. This demonstration showed that microdevices designed specifically as microsurgical instruments may enable a new realm of surgical procedures at unprecedented small length scales.

SENSING AND FEEDBACK

The capabilities of surgical microdevices can be complemented by equally effective sensing elements. Microscale sensing components can be integrated directly with the actuating structures of the device. A number of recent developments in microfabricated surgical tools have emphasized the need for tactile or force feedback components to allow the surgeon to both judge the mechanical properties of target tissue and to monitor the mechanical loads on the device.[8,9,28] Force sensors typically consist of piezoelectric or piezoresistive elements that are embedded at critical locations along the structure of a mechanical device to provide a three-dimensional map of the mechanical deformations in the device.[32] An intriguing alternative mechanism of force sensing uses local, in situ optical measurements to track the multiaxial displacement of moveable and actuating structures but may be more difficult to assemble.[28] In addition to force sensing, feedback of local temperature, hydrostatic pressure, and even electrical impedance can reveal other important information regarding the state and health of surrounding tissue and environments.[10,34]

Verimetra, Inc. has developed a "data knife" (*Fig. 24.7*) that integrates an impressive array of devices and functionalities on to one tapered, microfabricated shaft.[34] This device has been billed as a smart, multifunctional scalpel. At its tip, the microfabricated device is able to perform a cutting function facilitated by piezoelectric actuation. However, this device, designed to be held in a surgeon's hand, also contains several key sensing capabilities, such as strain-sensing elements to provide force feedback to the user. There are also pressure sensors and electrodes to make measurements of the surrounding fluid and tissue environment. The electrodes provide electrical impedance measurement, which provides yet another means of assessing and identifying the nature of the surrounding tissue. Finally, temperature sensors are embedded near the knife edge to ensure that the targeted tissue is not being excessively heated by the cutting process. Thus, this data knife potentially provides an extensive suite of actuation and sensing capabilities in a single surgical tool.

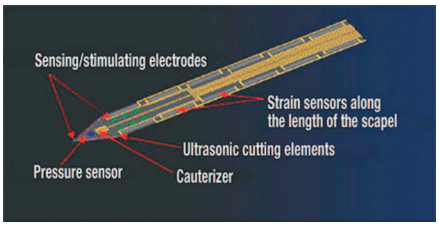

FIGURE 24.7. The multifunctional Data Knife from Verimetra, Inc. (generic press image).

NEURAL INTERFACES

Perhaps the most prominent microfabricated device in neurophysiology is microelectrode arrays designed to perform in vivo recording and stimulation.[6,12,17,42] These devices (*Fig. 24.8*) were originally intended to replace simple metal probes traditionally used for electrophysiological recording and stimulation. Using MEMS processing techniques, precisely sculpted, mechanically strong "neuroprobes" have been fabricated with onboard metal electrode pads positioned at specific locations along the probes. These probes can then be inserted into neural tissues, where the precisely positioned electrodes stimulate or record from local neuronal populations. Since the initial work of Dr. Kensell Wise's group at the University of Michigan,[12] numerous designs and configurations have been conceived, fabricated, and tested for various in vivo applications in live animals. The key advantage of such devices compared with traditional recording probes is the possibility of integrating large numbers of electrodes onto one platform and having them positioned at desired spacings within the tissue. Such devices can also be custom configured to serve specific experimental needs while maintaining the advantage of mass production.

More recent developments in neuroprobe devices have benefited from further innovations in microfabrication techniques developed specifically for biological applications. Several designs in the past few years have added a network of buried microfluidic channels on the neuroprobes to deliver neurotransmitters and other drugs directly to the tissue in conjunction with the recording and stimulation functions.[6,17] The introduction of new polymers, such as polyimide, has permitted the fabrication of flexible and possibly more biocompatible probes, which are potentially more suitable for long-term implantation.[24] These new devices have opened the possibility for extending the capabilities of the "neuroprobe" from merely a research device to those of integrated "neural interfaces," which may serve therapeutic functions by helping

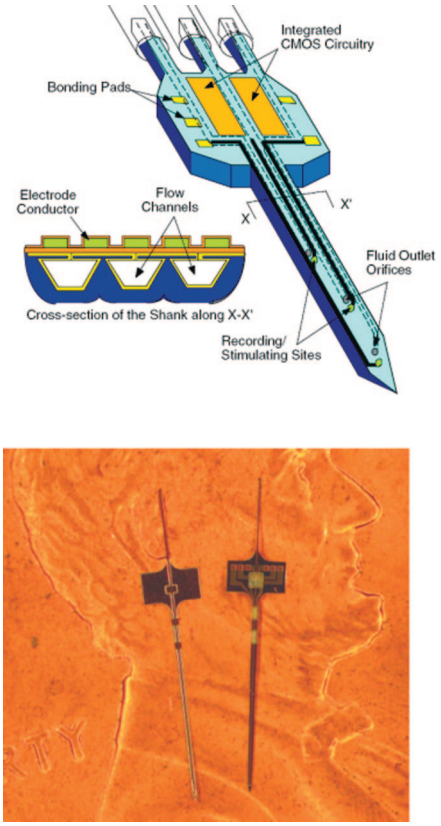

FIGURE 24.8. Neuroprobes fabricated from silicon. *A,* an illustration of a probe shaped and etched from bulk silicon, including conductive metal traces for electrical recording and buried microfluidic channels to deliver small volumes of chemicals at the recording sites. CMOS, complementary metal oxide semiconductor. *B,* actual fabricated devices with metal traces and buried channels (not seen) placed against a Lincoln penny (courtesy of Dr. Kensell D. Wise, University of Michigan).

to restore critical neurological functions or to mitigate disease conditions. The basic concept of the neuroprobe is not necessarily limited to neural tissues and can also be applied to other electrically active tissues. For example, similar implantable probes, including not only electrical but also temperature and other sensors on the probe shaft, have been used to monitor the health of heart tissue during cardiovascular procedures when the heart is stopped and electrocardiographic monitoring is not possible.[10]

AUTOMATION AND CONTROL

The small scale of MEMS devices and the tiny and sometimes contorted volumes in which they operate means that direct handling and operation by a surgeon is impractical. Even under the best circumstances, human hand tremor has an amplitude of approximately 50 μm. The deployment and operation of MEMS surgical tools, therefore, requires some level of automation and robotic control (*Fig. 24.9A*). Obviously, the type of automation and control depends on the nature of the microsurgical procedure. However, an important goal of any control scheme is to proportionately shrink macroscale human motion to the microscale movements of the device and to filter out human factors such as hand tremble. Probably the simplest implementation of such transduction of movement is with an X-Y-Z micromanipulator, which is a standard tool in many research laboratories. For example, such a device was used to successfully operate a passive nanoknife on an intact nerve and individual axons in vivo[4,5] (*Fig. 24.9B*). Force measurements from devices embedded within the microdevices can provide nearly instant feedback, which can be directed back to prompt the operator as part of the control scheme. An operator actuates a joystick or set of knobs to command corresponding translational or

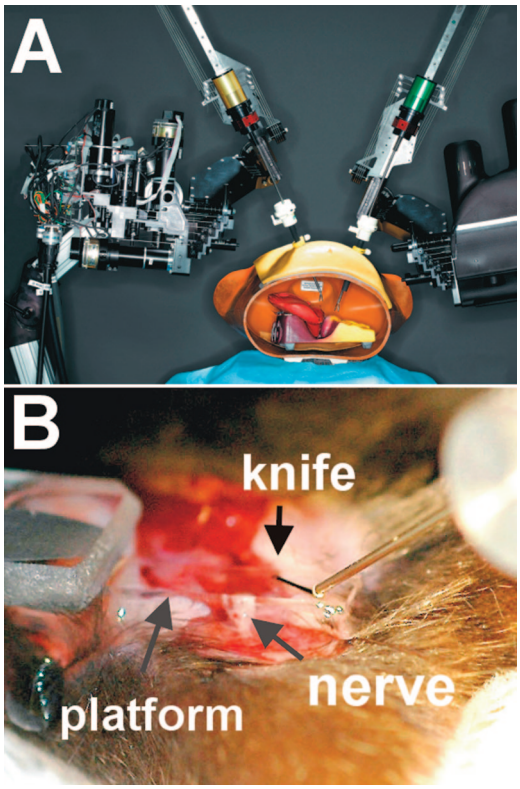

FIGURE 24.9. Use of microdevices in vivo will require specially designed platforms and automated control and handling. *A,* a robotic surgery setting in which the tools are positioned and operated robotically. The human surgeon controls these devices indirectly via a computer interface; the robotic manipulators do the actual surgery on the patient. Such an interface system will likely be implemented to control and operate microdevices in surgery (courtesy of Blake Hannaford and Jacob Rosen, Biorobotics Laboratory, University of Washington). *B,* a custom-assembled platform allows a peripheral nerve to be lifted and stably held outside of an animal while a nanoknife is brought in and manipulated by an X-Y-Z micromanipulator (off the frame).

rotational motions and, in the meantime, sense forces that are proportional to forces incident on the device. As the complexity of surgical devices increase, it will be appropriate to implement some human interface technologies similar to those developed for robotic surgery, such as "virtual reality" or "telepresence," in which more of the dexterity and motions of the human hand are harnessed and translated to the positioning, motioning, and functions of operating devices.[26,34,35] The purpose of automated control schemes is also to provide safety margins for the operation of the device. For example, it may be necessary to set discrete limits on the forces exerted by actuating devices or to prevent structural elements within the device from being stressed to the breaking point. Such safety margins may also be necessary to protect the target tissues from inadvertent injury or heating.

BIOCOMPATIBILITY

For any new devices intended for use in vivo, it is important to consider the suitability of the constituent materials for the target tissue.[18,20,34,40] Biocompatibility can be evaluated at several different levels. A first level is to identify any acute toxins that may have an immediate, detrimental effect on the host tissue. However, longer-term responses of the host tissue caused by the prolonged presence of the materials must, of course, also be considered. Of interest is whether such materials when in contact with tissues can, for example, promote excessive coagulation or elicit undesirable immunological responses and become isolated via scar tissue encapsulation. For many silicon-based materials, biocompatibility has been demonstrated both in vitro with tissue slices and in vivo with long-term implantation. Most studies indicate that these materials do not seem to eliciting adverse responses from host tissues.[18,20] One study explicitly evaluated a variety of commonly used materials in microfabrication, such as silicon, silicon dioxide, silicon nitride, and others against a battery of standard biocompatibility tests.[18] The results did not identify any materials as harmful and concluded that microfabricated materials were generally suitable for use in vivo. In applications in which the biocompatibility needs of these materials are inadequate, MEMS tools can potentially be coated with alternative polymers or even with molecular monolayers to render them less offensive to host tissues.

NANOTECHNOLOGY AND NANOMEDICINE

Even as microtechnology has flourished and is beginning to yield diverse families of devices for biomedical applications, the even newer realm of nanotechnology is seeking to build even smaller tools and machines beyond the lower limits of traditional microtechnology—typically less than 1 μm. In this new realm of nanotechnology, materials can no longer be treated as continua, and construction must be performed by designing, arranging, and assembling individual atoms and molecules. The rise of nanomedicine, therefore, seeks to take over where microtechnology leaves off and focuses on developing molecular structures and machines to provide access not only to individual cells but also into specific molecular machineries within cells.

Nano Drug Delivery

Many of the recent developments in nanomedicine have focused on new molecular constructs for drug delivery.[22] These constructs include nanoparticles consisting of degradable polymer coated shells, micelles, and even liposomes, in which small quantities of drugs are sequestered, only to be released under specific conditions and at specific locations. Because of their small size, drug delivery devices based on nanoparticles are specifically designed to cross the various membrane barriers within the body and even to target specific cells. On the outer surface of these nanoparticles, it is possible, in many cases, to include specific ligands or signaling molecules to aid in the uptake and localization of the particles to desired targets. The potential advantages of these drug delivery mechanisms include increased efficacy, because the drugs can be released in a controlled manner and then concentrated at desired locations. However, the nanoparticles are also intended to simultaneously overcome physiological barriers, metabolic degradation, and any unfavorable hydrodynamic forces among different organs and tissues. The resulting increased effectiveness in targeting potentially results in lower dosage requirements and fewer side effects. These combined benefits highlight the value of molecular design and may herald a new era in the way drugs are used and administered to treat human illnesses.

Nanoscale Manipulation

In addition to drug delivery, nanomedicine is also beginning to yield tools that can perform manipulations on the molecular scale. A simple tool that is based on the functionality of the atomic force microscope is the nanoneedle.[27] At 200 to 300 nanometers in diameter, it is designed be inserted through the cell membrane and even continue through the nuclear membrane while minimally disturbing the integrity of the cell. It is thought that such a device could someday be used to present or place ultrasmall quantities of molecules at a precise location within a cell. Manipulations within cells that are more elaborate may also be performed by nanotweezers made from a pair of single carbon nanotubes, which have been demonstrated to grasp a cluster of nanoparticles.[16] Using noncontact methods, focused lasers can also be used for nanomanipulations as optical "tweezers"[11] to hold and transport individual molecules or even to perform the nanocutting of single molecules, such as a microtubule.[3]

With ever more impressive developments in both the microtechnological and nanotechnological fields, there are tremendous opportunities for these two realms to interact

synergistically by mutually augmenting the functionalities and capabilities of the other. For many applications, the deployment and transportation of the latest nanotechnology will invariably have to be provided by some microscale tools that are able to generate relatively large forces and provide motion spanning the micron scale. For example, drug-encapsulated nanoparticles may have to be delivered or implanted by devices of a larger scale. Even the nanoscale manipulation tools themselves have to be brought to the site of operation by larger instruments, including devices that have the desired microscale precision. Conversely, the capabilities and functionalities of these nanotools are often analogous to the functions of microdevices and can, therefore, be thought of as extension of microdevice capability to smaller scales. Such analogous devices can naturally be deployed and work together to achieve common purposes.

SUMMARY

With the emergence of technologies to fabricate and mass-produce microscale tools and micromachines, microsurgery stands to potentially benefit through the development of a fundamentally new class of instruments. These new instruments may provide the surgeon with access to the smallest reaches of the body and perform operations that are currently not possible with manually operated tools. These new devices can be variably constructed and configured based on a wide range of design possibilities and can be built to serve many different fundamental surgical functions requiring the manipulation and handling of small tissues and structures, including grasping, cutting, and monitoring. With these functionalities also comes a high degree of integration, allowing tools and space to be used efficiently. Adapted from the techniques of the microelectronics industry, the fabrication methods and materials produce structures that are mechanically strong and easy to reproduce on a large scale. Well-developed design and physical modeling tools mean that the process of instrument development and validation can be streamlined.

Along with these new instruments comes the need to provide automated interfaces to effectively translate human operator intentions into the appropriate actuation and motion of these devices. These interfaces must include the capability to scale down human motions to the range of microns. Most likely, the operation of these new microsurgical devices will resemble the control schemes developed for robotic surgery. The control schemes will provide accurate motions while minimizing the chances of damaging tools or unnecessarily injuring tissues.

Naturally, these new tools and surgical schemes will require a transition from the conventional paradigm. However, with new surgical capabilities that may allow direct intervention into the inner workings of a cell, MEMS and nanotechnology-based tools may become a crucial part of the arsenal for the next generation of surgeons. Invariably, future developments of this new class of instruments will depend in large part on needs identified by the surgeon and an understanding of the enabling properties of microtechnology and nanotechnology. Thus, recognition of the vast potentials of this new technology among clinicians will greatly help to accelerate the development and integration of new microdevices and novel procedures that address disease and injury with unprecedented precision.

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