Microfabrication and Scaling of Biomedical Devices

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With the advent of integrated circuit technology in the 1960's, there has been a ubiquitous and obvious trend of increasing miniaturization in electronic systems. More recently, with the emergences of micromachined sensors, actuators and multi-component systems (MicroElectroMechanical Systems, or "MEMS") and nanodevices ("NEMS"), the trend has increasingly affected areas of biomedical endeavor. Indeed, reduction in scale can provide many benefits to components and systems, but typically not without significant, inherent trade-offs. With the initial hype having greatly diminished in the MEMS field, successful devices and products designed with clear understanding of these trade-offs are emerging. To those who worked in the field from the early days, this increasing "reality-to-noise ratio" is a welcome development. Nanotechnology, still in the very early phases likely will require longer for these pros and cons to be fully understood. The focus of this paper is to describe both the positive and negative aspects of scaling as they relate to biomedical devices, with a distinct emphasis on present technology and issues for realizing systems where component or overall scaling confers true benefit to the patient population.

MECHANICAL

The original drivers for MEMS development were mechanical, encompassing strain gauges, pressure sensors, accelerometers, resonators and other transducers. In the early years of the field, such devices racked up impressive performance records and later made significant commercial headway in everything from airbag deployment sensors through bathroom scales. The addition of on-chip circuitry, made possible by the use of silicon substrates, has expanded the commercial prospects via signal-conditioned polysilicon-transducer accelerometers and gyros [1], micromechanical projection television systems [2], nascent production of acoustic microphones capable of withstanding modern printed-circuit board assembly methods [3], and emerging single-crystal based devices as replacements for the near-omnipresent quartz-crystal oscillator [4].

Some of the negative aspects of micro-scale mechanisms have manifest as mechanical noise (akin in nature to Johnson noise in electrical resistors) as moving masses scale down, manufacturing issues with stiction (adhesion) between structures and substrate, increased concern over effects of thin-film stresses and stress gradients, and the need for hermetic packaging on- or off-chip. In all of these areas, however, impressive strides have been made in "engineering around" the problems.

It is noteworthy, however, that despite the biomedical origins of many early mechanical MEMS devices [5], they have yet to reach sufficiently small dimensions concomitantly with nano-level power usage to allow production use in some of the most size-sensitive applications - implantable devices such as pacemakers and their intracardiac leads. In contrast, there are many applications such as external pressure sensors for in-hospital

monitoring, where miniaturized silicon pressure sensors [6] have quietly achieved marketplace dominance and (for such disposables) comfortable manufacturing volumes.

More importantly, some significant advantages for mechanical scaling that have proven out over time have been the reproducibility of lithographically fabricated mechanisms, the extreme fatigue-resistance of single-crystal silicon and ultrathin metallic films, and cofabrication of on-chip signal-processing circuitry in some cases, as mentioned above. Perhaps the largest potential advantage for the batch-fabricated micro-scale devices of all types is the economies of scale to be realized if R&D costs (sometimes a combination of federal and private funds) are amortized over high-volume production runs. At the moment, however, it is difficult to know (largely because such information is rarely made public) if, on a true net basis, this benefit has been realized for any but the longest-running device types, such as piezoresistive pressure sensors and strain gauges.

OPTICAL

In a sense, the miniaturization of photonic devices has long been underway independent of the "MEMS" community. Photosensors, LED's and related devices have been in volume production for several decades. By volume, more complex devices are dominated by CMOS imagers (with a few hold-out CCD application areas) due to massive usage as digital imagers in cameras, cell-phones and other devices. Riding the aggressive scaling of commercial CMOS technologies, such imagers have reached truly tiny dimensions and given rise to such things as ingestable intestinal cameras (it is noteworthy that, at present, these are unguided cameras, necessitating the viewing of lengthy and somewhat random footage of colons) [7].

Another very visible, but not biomedical, commercial insertion of MEMS technology has been the Texas Instrruments DLP™ projection television systems [2]. After well over a decade of development and enormous investment, these devices dominate the video projector and rear-projection television market. In the long term, as truly flat screen technologies improve and emerge, it remains to be seen how enduring this success will be. In any case, one cannot dismiss the DLP as a huge success of microengineering ($900M in sales in 2004, which includes sales to 13% of the large-screen TV market [8]).

Other, more complex photonic MEMS devices (planar waveguides, 3D optical devices, amplitude and phase modulators, etc.) have considerable, but as yet unrealized potential for improving the performance of endoscopic surgical instruments, ophthalmologic instruments, and - a potentially huge market - diagnostics.

THERMAL

It has long been clear that thermal transport and isolation properties can be changed radically using miniaturization technologies. In the former case, heat removal structures comprised of highly conductive materials such as silicon can be designed to have very high surface areas with good fluidic flow properties, allowing for very high thermal

energy fluxes into cooling fluids. There have been several demonstrations of such extreme thermal transport used in cooling of lasers and integrated circuits on an experimental basis. While this scaling feature has yet to significantly impact commercial markets, cooling of microprocessors increasingly suggests a potential role for micro-scale heat exchangers at the chip level.

Thermal isolation possible using ultra-thin membranes or suspension members has been shown repeatedly to allow for relatively high thermal gradients to be maintained at low power or, conversely, for very high temperature changes to be achieved relative to small incident thermal energy fluxes. In the first case, a variety of electronic power sensors have long ago been implemented that while not sold to end-users, enable the sale of high value-added test equipment items such as RF power meters and signal generators. Increasingly, the impact of the second type of isolation benefit is affecting the market in the form of low-cost infrared imagers (useful in biomedical settings), bringing the price points down markedly from the days of exotic compound semiconductor detectors.

Finally, excellent thermal isolation combined with short time-constants has allowed the mass-scale success of ink-jet printers, the disposable print heads of some types representing a very substantial revenue source to their manufacturers. These technologies can also be used to deposit high-resolution patterns of biomolecules, useful in fabricating a variety of diagnostic devices.

CHEMICAL, BIOLOGICAL & FLUIDIC

In recent years, largely following the lead of funding sources such as DARPA (funding U.S. researchers), much effort in system miniaturization has focused on chemical, biological and fluidic microsystems. It is noteworthy that in the excitement of a new and growing field, long extant technologies like precision injection molding have been *de facto* incorporated into the "MEMS/NEMS" communities, to much benefit. Once again, it is proven that claiming preexisting, proven technologies as part of one's own field is a winning strategy.

In these application areas, scaling has a wide variety of impacts, positive and negative. First, fluidic properties change dramatically at small scales, primarily because laminar flow is almost unavoidable at realistic pressures and flow rates. This has advantages in that parallel flows can be set up where solutes exchange on the basis of diffusion, yet without significant bulk mixing (i.e., larger particulates such as cells can be confined to one flow) [9]. On the other hand, achieving effective mixing of multiple fluids where diffusion is not the only driver has proven more difficult and resulted in a great deal of useful research output. Yet other aspects of scaling on fluidics manifest as increased susceptibility to blocking by trapped bubbles or particulates, as well as fouling due to enhanced deposition of solutes (seldom reported in the literature, since test fluids tend to be deionized water with, conveniently, only the desired analytes added). Thankfully, as most of the successful applications have been in disposable devices, these limitations have not seriously impeded progress toward realistic applications, often involving clinical samples (e.g., bodily fluids).

In terms of chemical and biological sensing, one of the most striking trade-offs with down-sizing is one of sensitivity. In simple terms, as one reduces the volume in which to detect an analyte, the sensitivity decreases in proportion. In other words, if one is looking for lower and lower concentrations, the volume one has to look in for enough molecules to register on a given sensor increases. As simple as that appears, there were numerous claims made of doing complex, sensitive molecular assays on nano- or picoliters of blood, for example, without adequate sample size to contain the requisite number of analyte molecules. Thankfully nano-scale fluid samples can still be quite adequate for plentiful clinical analyte species such as alkali ions, dissolved gasses, and glucose. In fact, measurement of the latter represents a still-tempting market entry for micromachined fluidics and sensors as diabetes management bears the commercial earmarks of high volume (billions of units per year) disposable products. In addition, molecular amplification mechanisms such as the polymerase chain reaction (PCR) or various enzymatic gain or second messenger systems have improved the sensitivity of small-sample assays.

More globally, it is becoming recognized that there are not only volume and sensitivity trade-offs, but also some boundaries on the possible (assay time)•(sensitivity) products. Reports of single molecule detection in picoliter sample volumes are fairly common. However, to achieve this sensitivity in, for example, a 1 ml clinical sample would require exchanging and probing the sample volume one billion times. So, in this case, one would have an impressive-sounding molar limit of detection (LOD) of the inverse of Avogadro's number per liter ($\approx 2 \times 10^{-24}$ M/l) yet an unworkable throughput for most diagnostic uses. In cases where the sensor is in a more open volume, mass transport delays often create similar issues (for example, DNA hybridization microarrays require many hours of incubation to allow for diffusional transport).

Prospects appear very promising in this sector, as researchers and corporations embrace the simple formula descended from the earliest disposables: razor blades. Quite simply, if one designs chemical or biological assay instruments such that the essential core is disposable, one can optimize profit margins and dodge thorny issues such as device cleaning and some aspects of repeatability. Microfabricated genomic arrays, electrophoretic separation chips, and multi-analyte clinical diagnostics are all becoming commonplace in the market and progressing toward the long-promised "point-of-care" use (and, with luck, widespread profitability).

ELECTRONIC

Clearly, one of the most overarching impacts of scaling, and its foremost driver, has been the thus far relentless reduction of dimensions of CMOS integrated circuit elements. Not only have mainstream CMOS processes transitioned to the "deep submicron" level, but several levels of interconnect have been added to allow unprecedented system complexity (via the apparent demise of the so-called "tyranny of interconnects" that had prevented significant down-sizing of mainframe computers). With the advent of such tiny transistors, the potential functionality of a given piece of silicon real estate has increased dramatically. This can make it harder to justify going to the trouble of co-fabricating electronics on microtransducer substrates, which requires the often troubled marriage of somewhat incompatible fabrication processes.

Another important issue is the increasing complexity of achievable electronic circuitry and the potential for unplanned operating modes (referred to both as "bugs" and "features" in some engineering sectors). Further, the greatly reduced transistor scales can, in some cases, increase vulnerability of circuits to upsets from impinging radiation, either from external sources (e.g., cosmic rays) or from other components of the packaged systems. As device scaling progresses, designs must include mitigation measures to prevent such problems.

NANOTECHNOLOGY

One could not prepare a manuscript on scaling without some reference to "nanotechnology," despite the fact that much of the demonstrations to date might more properly be classified as "chemistry" or "materials science." Nonetheless, there is more than a glimmer of hope for breakthroughs at this next physical frontier that go beyond nanotubes, buckyballs, and stain-repellent fabrics. As with the success of atomic force microscopy, there is significant benefit to be obtained at the convergence of scales, i.e., the "MEMS-to-NEMS" or "nano-to-tissue" interfaces. In addition, at the truly molecular end, we have the ultimate existence proof that nanotechnology can work: life itself.

This latter example represents what is referred to as "bottom-up" nanotechnology, in other words assembly of molecules and atoms, versus "top-down" nanotechnology which is continued miniaturization of fabrication processes which may be related to those used for MEMS. It is likely that both approaches will be important and convergent in practice.

Time will tell how much impact the nanotechnology efforts will have. However, it is very clear that there is no shortage of interesting avenues to pursue, including developing materials that are nanostructured, yet ordered over much greater sizes (as already evidenced by essentially "single crystal" macro-scale components of such high-performance mechanical systems as jet engines). In addition, it is clear that there are many problems to be solved at the level of molecular, cellular and tissue-level interactions with micro-scale sensors, actuators and systems.

CONCLUSIONS: SYSTEMS IMPACT

At present, the system designer is faced with an enormous number of options for miniaturization, ranging from precision plastic and metal fabrication approaches to micro- and nano-scale features and devices. It is clear to most of them that smaller scales often require exponentially increasing R&D expenditures to achieve if commercial components are not available. Thus, one needs to carefully consider net benefits of any scaling. This includes amortization of R&D costs over product life, a balanced consideration of the pros and cons of scaling (mass, volume, power, environmental compatibility, interface requirements, etc.), and more complex matters such as tying products to sometimes single-sourced or potentially short-life third-party technologies. That latter point may be of more importance in biomedical applications than in consumer markets due to the added time burden of the unavoidable regulatory processes.

In terms of biomedical applications, it appears that a wide variety of miniaturized clinical devices (therapeutic, analytical, etc.) will be appearing on the markets in the near term. With growing volumes of interventions and chronic-care patients, and the impending move toward matching pharmaceuticals to patient genomes, there is every incentive imaginable driving creative efforts in these areas. It is hoped that not only will well-conceived scaling efforts have major impact on externally used biomedical devices, but also on implantables and other durable goods. It thus seems clear that biomedical devices are steadily progressing toward decreased volume and mass, increased functionality, and improved clinical and financial performance.

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