Microsystems and Nanoscience for Biomedical Applications: A View to the Future

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At present there is an enormous discrepancy between our nanotechnological capabilities (particularly our nanobiotechnologies), our social wisdom, and consensus on how to apply them. To date, cost considerations have greatly constrained our application of nanotechnologies. However, novel advances in microsystem platform technologies are about to greatly diminish that economic constraint while developing new industries. Properly used in a solid legal and ethical framework, within an educated population, these advances will vastly enrich our quality of life without being intrusive. Improperly used, these technologies could lead to a modern-day Luddism, social turmoil, or possibly even to emulating those societies described in the darkest of novels. These technologies must be developed in tandem with the social and legal frameworks needed to ensure that they improve both individuals and our society. To ensure that this occurs, we need to have the ethical, legal, scientific, and engineering experts working together and with the public.

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Nanotechnology is a very rapidly expanding field that generates enormous excitement within specialized scientific communities. However, for the general public it is, at best, largely unknown and is, at worst, the focus of alarmist science fiction. The applications of nanotechnology, particularly in the biomedical arena, involve a postulated trillion-dollar, new economy with otherwise undreamed of benefits for health care, public safety, environmental monitoring, and forensics. For example, nanoscale manipulations may enable tissue regeneration, in vivo medical monitoring by nanoscale robots, precise and convenient drug delivery, novel drug formulations, real-time molecular pathology, affordable testing at diagnosis, and monitoring of a wide variety of diseases and sophisticated health care in remote locations. The development of portable handheld devices implementing nanoscale molecular manipulations is likely to facilitate accurate, sensitive, and fast monitoring of air and water quality in the field to determine environmental safety, identify environmental pollutants, and inform cleanup efforts. Similar devices could rapidly identify potential threats to public safety through sensitive detection and identification of infectious agents. For many of the anticipated benefits of the nanotechnology revolution,

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microsystems will provide essential interfaces between the macro world of human beings and the nano world of molecules. Microsystems implementing microfluidics and nanofluidics to establish molecular connections and disconnections will likely provide the enabling technologies for these nanoscale molecular interactions.

Expected front-line innovations using microsystems are likely to provide demonstrable economic benefits to health care systems in developed and undeveloped countries, benefits to industry, and, perhaps most importantly, improvements in the quality and accessibility of sophisticated health care diagnosis and monitoring. By optimizing medical interventions through more precise and faster medical testing, high-quality health care becomes more affordable, thereby providing significant economic benefits while maintaining social values. Automating technically complex tests using platforms that incorporate microfluidics and molecular manipulations has a high probability of improving health care delivery by lowering the costs of analysis and increasing the availability of testing to enable risk-adapted tailoring of treatment customized for each patient, earlier detection of disease, and the potential for preventive strategies.

Much of the impact of the microelectronics revolution was brought about by virtue of the simple fact that microelectronics became vastly cheaper. Among other things, microelectronics has made computation, data storage, and video surveillance inexpensive, and this in itself has brought about major changes. In concert with other technological changes, our society's concept and practice of privacy has been radically altered. It is becoming feasible to perform surreptitious biometric analyses (e.g., identification on the basis of facial features and walking gait). It is becoming increasingly possible to track our conversations, movements, and personal information, and increasingly difficult to protect that information. Our social awareness and legal and ethical framework have lagged behind our technology as society has drifted into changes that would have seemed unthinkable in the past. Yet these substantial changes were brought about simply because it was cost-effective and convenient to institute them. Present and future microsystems technology will implement nanotechnologies that will offer compelling arguments in favor of their adoption but that could have a significantly greater impact upon our society.

Microsystems

Microfluidic devices are the result of applying microelectronic fabrication technologies to produce, instead of microconductor networks in silicon and metal, microchannel networks in glass. Within these microchannels, reagents can be manipulated by applying electric fields and results detected by optical means. Microsystems provide high-resolution molecular separations and can combine multiple functions on a single chip (e.g., cell selection and extensive genetic analysis). Microsystems lend themselves to the analysis of individual cells, which may lead to a greatly improved understanding of many diseases, particularly cancer, where the cells comprising a tumor mass are often quite heterogeneous.

There is an enormous disconnect between the generation of new biomedical knowledge, particularly genomics and proteomics, and the ability to usefully apply it in the community. Disease profiling offers the promise of more effective treatment, but clinical laboratories lack the required expertise to perform such testing, and health care systems throughout the developed world cannot afford it. In the developing world, these issues are not even being considered. The potential ability of automated chip platforms to carry out many of the tasks normally performed by technologists and/or by multiple large and expensive pieces of equipment is enormous. Microsystems with nanoscale molecular manipulations will enable more specific disease classification based on predicted response to treatment, thereby allowing more directed clinical decision making for appropriate patient management. Cost-effective prescreening strategies that could monitor patients over time would enable identification of high-risk genetic profiles as soon as they arise. The development of a suitable integrated platform that is versatile, reliable, multifunctional, and socially acceptable requires intensive interactions among multiple sectors of the scientific community, the social sciences, government, and the general public.

Cancer Detection and Treatment

Cancer is a highly diverse family of diseases. A significant clinical problem is that the characteristics of one form of cancer may be radically different from those of another form or even of another phase of development of the same cancer. A noninvasive, inexpensive, and multifunctional characterization tool would enable widespread prescreening to provide better diagnosis and more effective monitoring. With the large volume of genetic information so far accumulated, it becomes increasingly important to consider the logistics of performing these tests.

Microsystems are capable of testing cell populations from blood, bone marrow, or other tissues for indications of cancer-related anomalies and of performing large numbers of tests for genetic sequences of interest. The end result would be to assemble a detailed cancer signature for each patient. Microsystems hosting nanoscience molecular manipulations to detect cancer signatures could enable noninvasive early detection of rare aggressive variants, detection of residual tumor cells, or metastatic cells at distant sites following the removal and treatment of an existing tumor. They will facilitate targeted intervention delivery and monitoring of intervention as well as analysis of tumor heterogeneity with the possibility for real-time assessment and tailoring of therapy for each patient.

Polygenics, Pharmacogenomics, and Data Banks

With few exceptions, most diseases are polygenic, that is, they involve far more than one gene. As such, we know how to test for only the relatively few known, simpler diseases such as haemochromatosis and cystic fibrosis—diseases that are associated with mutations in a few known regions of the genome. Haemochromatosis is a common disease that can lead to organ failure and death. Yet this is a disease that can be cured by information; once the condition is known, lifestyle changes can prevent damage. Perhaps if we knew more, we would find many more examples that could be cured with knowledge alone. To understand the more complex, polygenic diseases, we will likely need vastly more data. Public participation will, for example, require protection for participating individuals against being denied insurance by virtue of having been discovered to be at high risk for some potential future medical condition.

Similarly, many drugs have a therapeutic effect on a large portion of the population, but a relatively small proportion of the population suffers unacceptable side effects. In the future, much of our health care may be individually tailored. This may provide us with more options in terms of drugs but will require that our health care providers know much about our individual genomes. In an age in which medical information is being collected in databases that are increasingly accessible to any health care provider, this will present a dangerous situation in which very sensitive information is widely available while being very valuable to insurance companies and others. Large databases of personal information are likely to be accumulated in the future. Who will mind the store?

Microsystems, Social Values, and Public Trust

Because the availability of fast, accurate, and sensitive genetic analysis has significant potential for misuse, an extensive public consultation process is needed to educate and then consult with end users, the medical community, governmental regulators, and the general public to determine societal priorities and the level of risk—in terms of the social impact of fast, accurate genetic testing—that is considered to be an acceptable tradeoff to gain the benefits of on-chip analysis in the clinic.

In general, literature on the social implications of the revolution in genomics is growing rapidly and is demonstrating the value of taking a multidisciplinary approach. Scholars in medicine, law, and the social sciences have examined genetic privacy, counseling, and intellectual property rights (Lemmens & Austin, 2001). The convergence of genomics, information technology, and microfluidics has created a need for broader and deeper multidisciplinary analysis. The development and use of microfluidic platform technologies for genetic analysis will pose unique challenges and opportunities for medical practitioners, engineers and scientists, governments, courts of law, patient advocacy groups, and the private sector.

By its very nature, genetic testing is a double-edged sword. On one hand, the identification of genetic markers has revolutionized our understanding of human genetic variation. For instance, the Human Genome Project has helped coordinate international efforts to identify specific genetic mutations by mapping and sequencing the human genome opening the door to earlier and more accurate diagnosis, susceptibility testing, carrier testing, and pharmacogenomics. On the other hand, genetic testing raises concerns about privacy (Nissenbaum, 1998) and ownership of our genome; the ascendancy of genetic determinism as an ideology and practice that may narrow our understanding of the parameters of health (Keller, 2001; Morange, 2001); and the widening of gaps in health care by increasing medicalization in public health spending, defined as a process whereby a condition comes to be defined and understood as an illness and is thereby moved into the sphere of the medical profession.

Although a comprehensive analysis and critique of the many social concerns associated with genetic technologies is beyond the scope of this article, it is worth noting that there is a rich literature that is highly relevant in this context (e.g., Buchanan, Brock, Daniels, & Wikler, 2000; Tri-Council, 1998). Because microsystems will allow for fast, accurate, and sensitive genetic analysis, they have the potential to intensify many of the issues that have been identified with, for example, the introduction of genetic testing technologies.

Currently, many clinical practitioners lack the appropriate knowledge base to advise patients on the use of genetic services (Hunter, Wright, Cappelli, Kasaboski, & Surh, 1998). Obtaining meaningful consent thus becomes difficult and may intensify the possibility of genetic malpractice law suits, particularly given the complex, risk-based nature of much of the relevant information (Caulfield, 1999). In addition, the speed of microsystem testing will amplify many of the challenges associated with genetic counseling. Which tests require formal counseling? Who will provide the information? Will the speed and ease of the test increase pressure to get tested?

The problems associated with genetic discrimination will also need to be considered. This is particularly so given that the development and use of portable, rapid, low-cost, easy-to-use microfluidic platform technologies for genetic analysis creates the potential for a wide range of nonclinical uses by insurance companies, employers, and even by individual consumers. Although not all commentators agree that genetic information is significantly different from other forms of health information (Wertz, 1997), the idea of genetic discrimination continues to be a policy concern (Lemmens & Austin, 2001). In fact, rightly or not, survey research has consistently shown that the public views genetic information as fundamentally special and the rules governing access should be more strict than for other forms of personal information. Moreover, when combined with information technology, this revolution in genetic analysis will provide the ability to shift information from its original context to a different context and may open up new avenues for monitoring individuals (Mehta, 2002). This seems likely to create an impetus for stronger and more uniform privacy laws and for improvements in genetic counseling and informed consent processes.

Commercialization pressures may also create unique social issues (Caulfield & Williams-Jones, 1999). First, there are those who believe that the marketing of genetic technologies will lead to their overuse. For example, Biesecker and Marteau (1999) noted, “In a milieu in which marketing materials promote testing and providers have incentives to encourage patients to undergo testing, non-coercive, personal decision-making about genetic testing may well be compromised” (p. 133). Second, commercialization pressure may skew the social definition of disease and normalcy. For example, some are concerned that genetic testing may pathologize a wide range of conditions that may have only a weak genetic link and could fuel social Darwinism by refashioning what is thought of as “normal” and “pathological” (Vandelac & Lippman, 1992). This may put additional resource pressures on an already strained health care system.

Given the wide range of uses for microsystem testing, the concerns about marketing and implementation seem particularly relevant. Indeed, to reap the benefits of this emerging technology, government will need to devise strategies, including the development of appropriate regulatory safeguards, to mitigate the social concerns. As suggested by Francis Collins and Alan Guttmacher (2001), “Before moving such diagnostic tests into mainstream medicine, it is critical to collect data about their clinical validity and utility. Premature introduction of predictive tests, before the value of the information has been established, actually could be quite harmful” (p. 2322). Finally, policy makers will need to develop frameworks for deciding which new technologies should be covered by health care systems (Kristoffersson, 2000). In addition, it is essential that the public be consulted in the assessment of the benefits and risks prior to the introduction of such technologies. To most effectively gain public confidence and respect for the benefits of microsystem interfaces and emerging nanotechologies, this public consultation process must occur up front as the technologies develop.

Multiple studies suggest that trust in science and technology has been on the decline for several decades. Notable technological failures such as Chernobyl, Seveso, and Bhopal illustrate how complex interactions of technology and human error can sometimes lead to catastrophe and erode public trust. More recently, public concerns have focused on the risks posed by tainted blood and genetically engineered foods. To build/rebuild trust and to assess the social acceptability of new technologies, many countries are seeking to improve their consultation with the public. In Europe, consensus conferencing is becoming common. In Canada, public consultation has been done on nuclear waste disposal, xenotransplantation, and genetically modified foods. With advances in nanoscience and the upcoming availability of microsystems that enable widespread applications of modern molecular biological testing, public consultation becomes even more critical. Because science produces technological applications that affect human health and the environment, greater effort must be made to negotiate these impacts with the public at the onset. Microsystem-based platforms will likely be the first of a new wave of health-related technologies that incorporate nanointerfaces and nanosciences to reach the general public. As such, the new diagnostic/therapeutic tools have the potential to intensify existing legal and ethical dilemmas and create new social concerns. For example, the speed and precision of microsystem-based nanotechnologies will make the development of thoughtful genetic information policies all the more essential. As policy makers continue to struggle with defining the clinical utility of existing genetic profiling procedures, nanotechnologies will likely allow for the collecting, storing, and sharing of even more information more quickly. Issues will include acceptable use of information, clinical and social utility, use/distribution of genetic risk information, and identification of needed consent, privacy, research, and health information policies. In addition, basic legal concepts such as the notion of property will be challenged by both the potential dynamic and adaptive nature of nanodevices and the possible melding of living and nonliving things onto microsystems and their nanointerfaces. Further, nanotechnology may strain existing principles of intellectual property—an area of inquiry that will become all the more essential as researchers seek to commercialize nanoinventions.

Overall, if development of prototypes and commercialization are carried out within the context of public perceptions and social values, the benefits of microsystem applications are likely to greatly outweigh the potential disadvantages. They could significantly contribute to alleviating heath care crises in the developing world by providing affordable, automated devices that yield standardized outputs even when wielded by unskilled operators. In the developed world, homebound patients and the elderly would have access to sophisticated diagnosis, monitoring, and drug delivery through microsystems technology within their own homes, facilitated by Web-based transmission of medical parameters to distant health care professionals. Individuals in remote wilderness locations could carry microsystems-based emergency health care kits. Microsystems-based early warning devices would alert the world to emerging infectious agents or toxic pollutants. Finally, in a future that holds travel through space, microsystems coupled to advanced information systems technology may enable the same high standard of medical care in the distant reaches of space as in the most highly skilled, Earth-based research hospitals.

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