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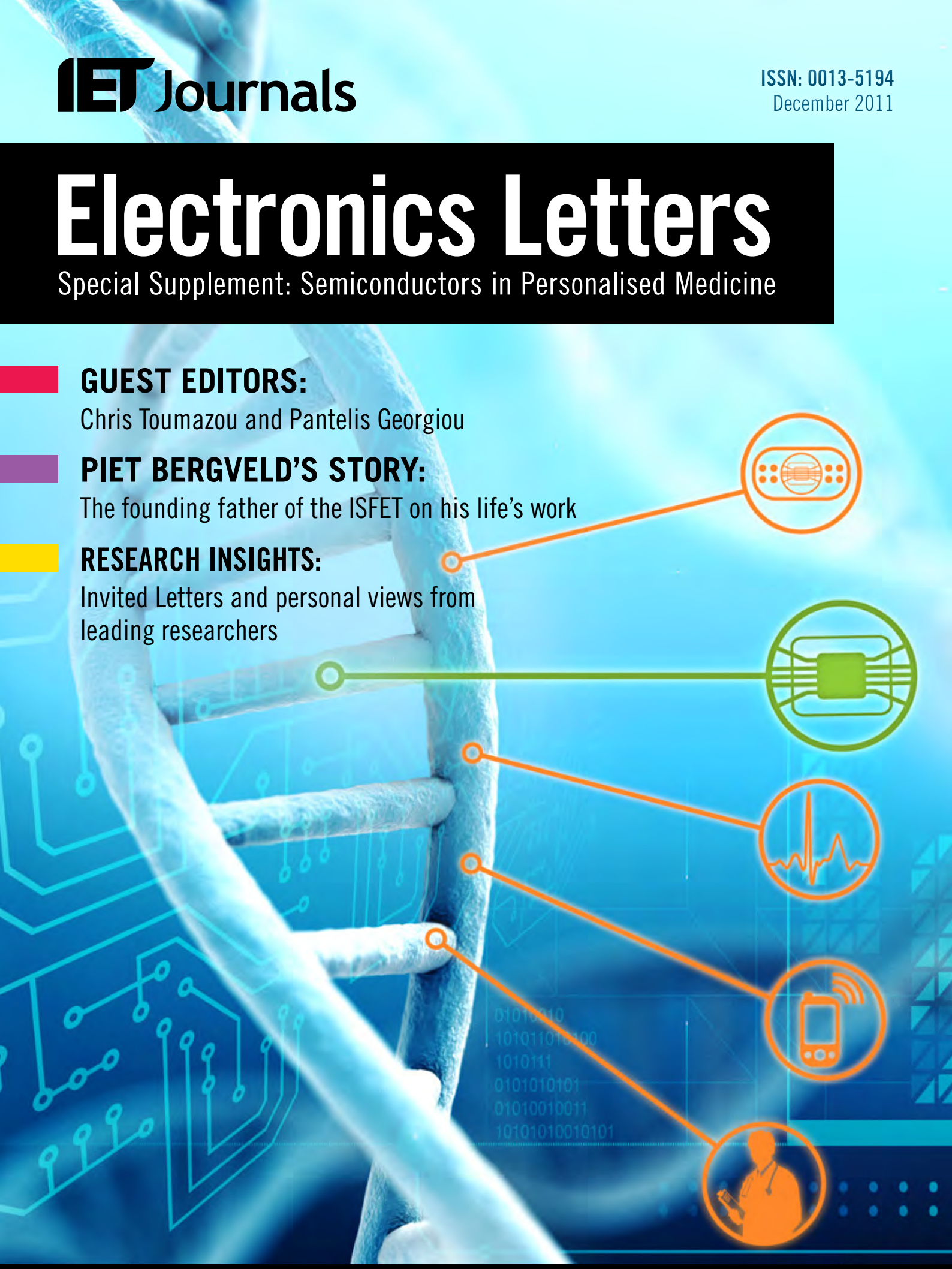

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Semiconductors in Personalised Medicine

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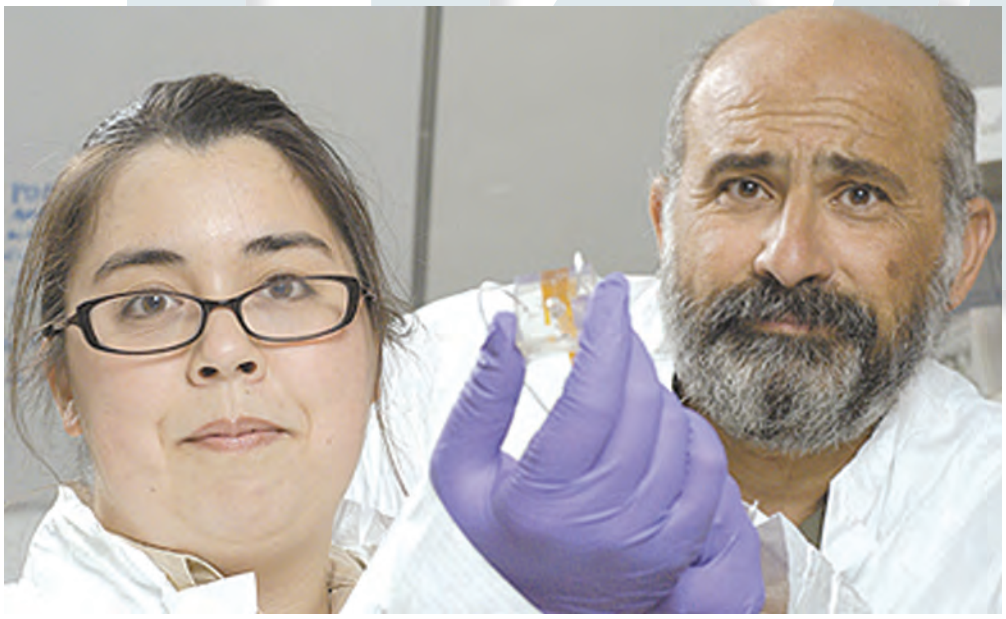
Andreas G. Andreou

Johns Hopkins University



Dr Andreas G. Andreou (right) and past PhD student Jennifer Blain Christen show the chip-scale autonomous silicon/silicone incubator. Jennifer Blain is currently Assistant Professor of Electrical Engineering at Arizona State University. Photograph by Will Kirk

PROF. ANDREAS G. ANDREOU was born in Nicosia, Cyprus. He is the co-founder of the Johns Hopkins University Center for Language and Speech Processing and Director of the Whitaker Institute Microfabrication Laboratory. His research is aimed at brain-inspired microsystems for sensory information, life sciences microsystems and human language processing. Notable microsystems achievements over the last 25 years include a contrast sensitive silicon retina; the first CMOS polarisation sensitive imager; silicon rods in standard foundry CMOS for single photon detection; a large-scale mixed analogue/digital associative processor for character recognition; the first truly autonomous chip-scale hybrid silicon/silicone microsystem for cell culture and incubation; and an ultra-low power CMOS sensor for retinal prosthesis. In 1996 Andreou was elected as an IEEE Fellow 'for his contribution in energy efficient sensory microsystems.'

Q. What inspired you to become a researcher?
A. My father instilled in me the desire to understand how things work and a passion for innovative engineering. My mother, on the other hand, taught me how to do things carefully and the virtues of perseverance. My father, Gregory Andreou, was a radio engineer with the Cyprus Broadcasting Corporation and in the late '50s, the early days of radio and television in Cyprus, he was responsible for much of the early installation and maintenance of remote broadcasting TV stations. I spent summers and often weekends with him on trips to these stations up in the mountains, and I was fascinated by this piece of equipment that 'autonomously monitored and diagnosed' the state of the radio transmitter, radio links etc., and send reports back in the main station. Somehow at that age, the telemetry of the station, which my father called the 'brains' of the station is what impressed me most and certainly had an impact on what I do today!

Q. How did you get started in your academic career?
A. My father did some of his electrical engineering education in Washington D.C. (Capitol Radio Engineering Institute) and he had friends in Baltimore at Johns Hopkins University. When I was applying to graduate school, he suggested that I should look at Johns Hopkins. I started my academic career after finishing my PhD there. I am one of those people that some would call 'lifers'; those that never leave their own institutions! I have been a faculty member at Johns Hopkins since 1989.

Q. When did you start in the biomedical field?
A. While a graduate student at Johns Hopkins I got interested in the work of Moise Goldstein. He is one of the co-founders of the Biomedical Engineering programme at Johns Hopkins University and the Director of the Sensory Aids Laboratory. He studied the auditory system and alternative approaches to providing sound signals to profoundly deaf children. By participating in Moise's group meetings I also got interested in speech processing and the auditory system. Through Moise, I met Terry Sejnowski, then Professor at JHU, who got me further interested in the brain and encouraged me to pursue an academic career in engineering and neural systems. I dedicated a significant amount of my academic life exploring biomimetic computational studies building on the foundation of the work of Carver Mead at Caltech; an endeavour that I still pursue today.

Q. Has the biomedical field developed as you might have expected? What have been the biggest surprises?
A. When you are in a place like Johns Hopkins, you're biased to believe that biomedical engineering will have an impact on the world. What is surprising is the rapid progress that the field has made, partly because of Moore's Law. The computational life sciences (medical imaging, bioinformatics, machine learning etc.,) have grown beyond my expectations.

Q. Tell us about your current research activities.
A. Throughout my career, my research has had two sides. On the more applied physics side, work in my group explores experimentally fundamental engineering questions at the interface of biology, physics and chemistry, and the design of microsystems for the life sciences. These include CMOS imagers and silicon retinas for retinal prosthesis, as well as multi-core architectures for the computational life sciences. The algorithmic aspects of our research focuses on statistical pattern recognition algorithms and cognitive machines for audition and vision. I am also interested in the fundamental link between information and energy and the limits of computation.

Q. Within your area, what are the key challenges?
A. In an era of exponential growth in knowledge, extracting information from the vast data is the biggest challenge. Unless we are able develop machine learning algorithms to augment human cognition, progress in all scientific communities and, as a consequence, technologies will be limited.

Q. It has often been said that CMOS is an enabling technology for novel healthcare applications – do you agree?
A. Absolutely. CMOS is here and will be the foundation for future and emerging technologies. CMOS will create the world beyond Moore and that world will include emerging organic semiconductor and non-CMOS nanotechnologies that will be pervasive in healthcare.

Q. What do you see as the prospects for exploiting semiconductors for use in personalised medicine, and what are the key barriers?
A. The prospects of exploiting semiconductors in personalised medicine are high. The key barriers at this point are regulatory and cultural rather than technological.

Q. What one key thing would transform the healthcare field?
A. Sustained funding for the biomedical field at the global scale is a crucial step in transforming the healthcare field.

Q. What are the potential applications that you find the most exciting?
A. The most exciting application is what I will call 'closed loop personalised medicine'. That is, healthcare delivered 24–7 using patient monitor services and chip-level implantable instrumentation. Wireless, electronically programmed chips control delivery of drugs in a timely and precise fashion based on algorithms that monitor the individual daily function and behaviour.

Johns Hopkins on the chip: microsystems and cognitive machines for sustainable, affordable, personalised medicine and healthcare

A.G. Andreou

Semiconductor technology is contributing to the advancement of biotechnology, medicine and healthcare delivery in ways that it was never envisioned – from chip micro-arrays, to scientific grade CMOS imagers and ion sensing arrays to implantable prosthesis. This exponential growth of sensory microsystems has led to an exponential growth of data. Cognitive machines, i.e. advanced computer architectures and algorithms, are carefully co-designed to extract knowledge from such health data making rational decisions and recommendations for therapies. Nano, micro and macro robotics driven by sophisticated algorithms interface to the human body at different levels and scales, from nano-scale molecules to micron-scale cells to networks and all the way to the scale of organisms. The present era is one where semiconductor technology and the 'chip' is the foundation of sustainable and affordable personalised medicine and healthcare delivery.

The state of the art: Since the invention of the integrated circuit – the 'chip' in short – in the 1950s, the microelectronics industry has seen a remarkable evolution from the centimetre-scale devices created by Jack Kilby [1] to millimetre-scale integrated circuits fabricated by Robert Noyce to today's 8nm feature size MOS transistors [2]. During this time, not only have exponential improvements been made in the size and complexity of the devices [3], but the Computer Aided Design software and workstation technologies have advanced at a similar pace, enabling the design of complete truly complex systems on a chip (SOC). The advances in the microelectronics industry have also enabled the proliferation of computational fields for bio-informatics, systems biology [4], imaging and multi-scale multi-domain modelling [5].

Medical imaging has witnessed revolutionary progress on device technologies grounded on clear understanding of human physiology and anatomy. The stunning convergence of semiconductor technology and life science research is transforming the landscape of the pharmaceutical, biotechnology, and healthcare industries, signalling the arrival of personalised and molecular imaging diagnosis and treatment, speeding up the pace of scientific discovery, and changing the practice and delivery of patient care [6].

Thanks again to Moore's law, with the increased resolution and sampling speed of CMOS (complementary metal-oxide semiconductor) based imagers, a huge amount of 3D/4D data are now collected from spatial and temporal sequences of life science events at all different scales from whole organisms to organs to cellular networks to molecules. Using advanced CMOS-based fluorescence imaging technology today one can measure optically intra-cellular calcium concentration as well as voltage levels with high spatial resolution and 1ms temporal resolution, sufficient to visualise voltage and calcium action potential propagation in myocyte cell tissue [7]. Capitalising on the dramatic advances in the scaling of the MOS transistor, analogue CMOS imagers are being replaced by all digital architectures. Sophisticated digital arrays, read-out integrated circuits and computational sensors are currently being developed to extract and quantify the subtle and intricate information from the huge amount of data so that eventually one can better capture the cell and tissue behaviours in visible and infrared wavelengths [8]. Future systems will allow ultrafast-based time resolved single photon spectroscopy using silicon photomultiplier detectors [9]. The development of innovative bio-engineering devices and tools enables better visualisation and understanding of human anatomy, metabolism, and organ function for diagnostic purposes.

Perhaps an even more stunning example of where semiconductor technology scaling and high level integration has lead to phenomenal advances in biotechnology aimed at personalised medicine is the development of ion-based, genome sequencing technology [10]. Sequencing that was once only available in major centres is now routinely found in core biotechnology labs. Just as mainframes gave way to personal computers, there may be a shift towards delocalised sequencing at a hospital or clinic near you. This distributed sequencing capability is creating an unprecedented data deluge. By way of example consider a centralised sequencing installation with 100 first-generation Sanger technology sequencers yielding about 2 Giga-bases per week. Moving to the second-generation technology (e.g. [11] HiSeq 2000) 10 second-generation machines can yield over 2 Tera-bases per week, a 10000-fold throughput. Assuming raw storage of data and 320 bytes/base the 10 machines will produce approximately 10^{15} bytes (1 Petabyte) every week. In comparison, Eric Schmidt – the CEO of Google – estimated that all the information available in the world wide web is roughly 5 Petabytes. Using ion-based sequencing technology, the cost of sequencing an individual human genome is today down to approximately $10 000, and there is no reason to believe that this cost cannot be decreased by a factor of 10! Whether through tissue and organ imaging, labs-on-chip or genome sequences, biotechnology and modern medical diagnostics are generating a staggering amount of data that needs to be 'consumed', i.e. processed intelligently to extract the relevant information.

Parallel to the advances in CMOS semiconductor technology, in the last decade we have witnessed a revolution in microfluidics for biotechnology and the life sciences. Borrowing ideas from silicon semiconductor manufacturing, soft lithography [12] has emerged as a new way of patterning soft materials. Using soft lithography, it has been possible to design and fabricate silicone 'chips' [13], fluidic analogs of integrated circuits that include storage, channels, valves and fluidic decoders made of poly(dimethylsiloxane) (PDMS) a soft organic material widely used in the manufacturing of disposable contact lenses. PDMS has become the mainstay of soft lithography for applications in the life sciences. The low cost (approximately fifty times cheaper than silicon), biocompatibility and its ability to be readily adapted to micro-fabrication techniques are among the numerous reasons PDMS has become immensely popular. A start-up company focused on micro-reactors for high throughput protein crystallisation. PDMS based microfluidic systems, or labs-on-chip as they are often called, are transforming microfluidics into laboratory automation [14]. Alas! These microfluidic 'integrated circuits' must be coupled to expensive macro-scale laboratory equipment to achieve the functionality necessary for real world healthcare applications. These labs-on-chip are the equivalent to human-scale bioanalytical laboratories with all the plumbing and glassware but without microscopes, optical detectors, cameras or computers! More recently a new paradigm has emerged for the life sciences and biotechnology microsystem design and fabrication, aimed at instrumenting lab-on-chips. The essence of the approach is the integration and embedding of CMOS electronics into PDMS microfluidics, and the approach was demonstrated through a specific system central to life science research and biotechnologies: the cell incubator [15]. In the latter work, disposable microfluidic structures were fabricated to control and manipulate liquids and gases, and were integrated with reusable functional CMOS silicon blocks. The latter approach is aimed at simple, inexpensive fabrication methods for components with elementary fluidic functions for use in tandem with more expensive, highly functional CMOS components that can be created once and reused many times in the same or other systems.

Fast forward to the future: Going forward to the future the path may be well marked but certainly not without obstacles. Every endeavour that relies on an exponential growth of knowledge and technology and rapidly advancing multi-disciplinary fields is inevitably going to offer challenges, but at the same time opportunities. These challenges often go beyond the traditional scientific and technological issues and into regulatory, financial and policy matters that often transcend single nations and individual societies. The limited available space does not allow us to address patients' safety, privacy concerns and ethical issues which are of course of paramount importance. In the following Sections we will focus on two such challenges and point to opportunities for future technological advances: (i) computing in the era of exponential data growth; and (ii) the sustainable manufacturing of future bio-electrofluidic chips.

Computing in an era of exponential data growth: Alex Szalay, a physicist and computer scientist in the Physics department at Johns Hopkins University argues that the successive generation of inexpensive sensors is creating an exponential growth of data [16]. While his observation is made based on his experience with astronomy data, this observation holds true for the field of biotechnology. Extracting knowledge from this exponential growth in data generation has become a serious issue. The biggest engineering and technological challenges in advancing personalised medicine are related to the integration, analysis, and interpretation of the massive quantities of heterogeneous biological, chemical, imaging, clinical and cognitive data available as a result of the rapid advances in data collection during the past few decades. Never before has the merger between engineering, computer science

and biomedicine been so strong and there needs to be an ever stronger effort to bridge and increase productivity at the interface between these two disciplines.

However there are dark clouds gathering on the horizon. CMOS computing technology has roughly doubled in performance every 18 months since the first digital computers, a trend popularly known as Moore's law. If we were to extrapolate this trend, we could expect the Exaflop machine (10^{18} Flops = 1 Exaflop) in seven years' time. However, continued miniaturisation of CMOS technology is reaching the physical limit at which further increase in performance will lead to an exponential increase in energy consumption from leakage currents. Fundamental physics (Boltzmann's law) does not allow the physical implementation of a MOS transistor that could behave as a perfect switch, i.e. with zero current flowing when in the off state. Transistors must always conduct tiny amounts of current in their off state. With modern digital integrated circuits having billions of transistors on them, these tiny currents add up to be a significant power dissipation problem. Optimising devices for higher speed has the unfortunate consequence of increasing these leakage currents. What is even more surprising is that none of the advances in non-silicon nano-technologies adequately address the fundamental challenges at the sunset of silicon CMOS technology.

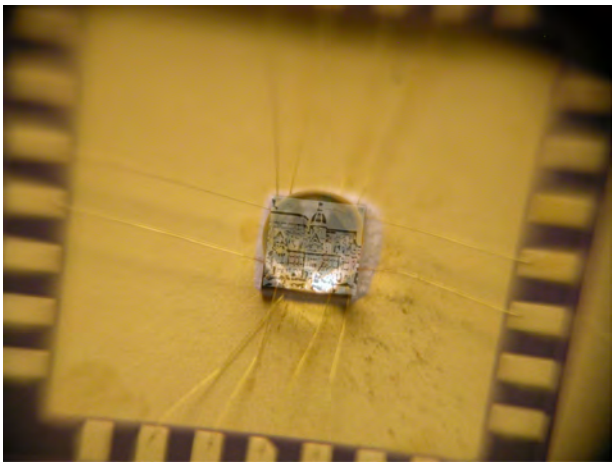


Fig. 1 *Magnetic trap chip designed to manipulate micro- and nano-scale functionalised particles and rods*

All manipulations performed in drop of water that maintains its shape through the hydrophilic/hydrophobic properties of the metal and dielectric structures that are designed on the surface of the chip. What used to be complicated analysis processes involving samples carried by humans from one room to another can now be accomplished in a single drop of water and chip-scale instrumentation [17]

Clock frequency therefore stagnated in 2005, and today the industry is trending towards massive parallelism, i.e. increasing the number of processors per chip and with the processors operating at slower speeds. The performance of the TOP500 supercomputers, the workhorses in the pharmaceutical industry, has continued to increase by a factor of 1.8 per year on average between 1994 and 2010. However, in 2010 the factor dropped to its all-time minimum of 1.4.

Much like mining and heavy industrial manufacturing, pervasive computing at the Exascale 10^{18} and beyond comes at an environmental cost. Today one Petaflop (10^{15} floating operations per second) requires approximately 10MW of power at a cost of approximately 1 million US dollars a year. Seven years from now an Exaflop machine will necessitate approximately 120MW. In 2007 the collective carbon footprint was comparable to that of the global aviation industry (830 million tons of CO_2) and is expected to increase to 1.4 billion tons of CO_2 by 2020, amounting to 4% of the total carbon emissions. Computing centres alone are responsible for 150 millions tons of CO_2 per year (corresponding to 30 million cars). The projected trend of increased computational performance is not sustainable from the point of view of energy consumption, energy cost, and environmental impact [18].

To meet the scientific demand for Exascale computing, we urgently need new energy efficient or 'green' computing technologies [19]. Today's high-performance computing architectures have not been designed or optimised for data intensive computing. The need for exploring alternative architectures is imminent and minimising energy consumption is central to further progress, especially in this era of exponential data growth. Advances in computer architecture aimed at data intensive computing exploit heterogeneous storage technologies to achieve high IO throughput [20], as well as systematic methodologies to design chip-multi-processor systems [21].

One of the most exciting developments in technology is the emergence of 3D CMOS, which allows stacking multiple wafers on top of each other thus allowing the placement of main memory in close proximity to the processor. By doing so one can see big savings, a factor of 100 or more in the energy expended to access main memory. This is a big deal! In essence we see computing technology coming closer to the organisation of the brain that has a layered laminar structure where neurons communicate both laterally within the layer and vertically between layers [22]. Inference engines and bioinspired cognitive machines in 3D CMOS technology have the potential of breaking through the exponential data explosion bottleneck. To accelerate progress, however, it is necessary to forge a coordinated effort between computer scientists, engineers, and scientists in specific domain disciplines (e.g. supra-molecular chemistry or neuroscience). The Human Brain project [23] spearheaded by Professor Henry Markram at EPFL is an excellent example of the coordination between academia and industry in a global international setting that provides fertile ground to tackle the grand challenge problem of linking human cognitive behaviour to molecules in the brain, bringing us one step closer to personalised treatment of neurological diseases.

Sustainability in biotechnology growth: In an era where bio-devices will be pervasive and disposable, the hidden environmental and energy costs of their production must be taken into account. It is surprising to many yet true that manufacturing silicon chips outweighs the costs of using them through their lifetime. The environmental impact of the semiconductor industry was first explored in a paper, in which the authors follow the lifetime of a DRAM microchip from its fabrication to its utilisation by consumers by analysing the material and energy that needs to be expended in order to create one chip [24]. The information in this paper came from several resources, including a United Nations Environment Programme, (UNEP) and United Nations Industrial Development Organisation (UNIDO) joint publication and a study published by the Microelectronics and Computer Technology Corporation (MCC). Overall, several forms of chemicals including deposition/dopant gases, etchants, acids and bases, and photolithographic chemicals are needed. It is estimated that 45.2 grams of chemicals are necessary for the production of 1 square centimetre of semiconductor. The largest composition comes from elemental gases of which the largest contributor is nitrogen gas. Aggregate chemical usage information widely differs from source to source, anywhere from 1.2 grams of water per square centimetre of fabricated wafer (national level study conducted by the Toxic Release Inventory) to 610 g/per sq cm (UNEP/UNIDO), with a baseline of 45 g/ per sq cm from the firm. Approximately 18 to 27 litres of water is necessary to manufacture 1 square centimetre of wafer. Energy consumption is separated primarily into two divisions – purifying silicon material into silicon wafers and the processing of the wafer into a chip. The first process that takes quartz (sand) and turns it into a silicon wafer totals nearly 3000 kWh per kilogram of fabricated silicon wafer. It takes about 1.5 kWh to process 1 square centimetre of silicon. On a per-chip basis, including consumer use, in its lifetime, it will use up approximately 56 MJ of energy. Every chip manufactured today must be used for about two years to accumulate energy consumption during operation needed to outweigh the energy cost of manufacturing. Going forward we need a new paradigm for system integration and fabrication of semiconductor-based systems-on-chip for biotechnology, especially those that will have a very short lifetime (use and dispose). We believe: it's time to reinvent the 'chip'! In an era where the semiconductor industry will perhaps be fuelled by applications in healthcare and biotechnology, where devices are 'consumed' very quickly, the 'chip' must be produced in a more efficient, environmentally sound and sustainable manufacturing process. Our vision of a 'chip' begins with organic materials that form the foundation for electronic, photonic and fluidic structures.

From a system perspective, organic semiconductor-based integrated circuit technologies [25] offer attractive solutions where electronics must be spread over a large surface area and can be manufactured with low-cost methods, such as printing [26]. We believe bio-electrofluidics will provide the nexus to large area sensors and actuators, and

photovoltaics for energy harvesting that will further replace traditional silicon technologies in medical and biotechnologies. The question is: how? In all of these applications, a complete, integrated solution is required. Organic integrated structures of centimetre dimensions must be created for containing and transporting fluids, gases and matter. Complementary to these are organic integrated electronic and photonic structures of lower complexity, such as optical waveguides, couplers, photo-batteries for energy harvesting and super-capacitors for energy storage. Much more complex but with smaller dimensions (in the hundreds of microns) are silicon CMOS blocks to provide the necessary ultra-low power digital computations to extract information at the point where inanimate meets the animate world. The essence of the approach goes one step beyond the chip-scale incubator [15] through the inclusion of organic centimetre size active, organic multifunctional substrates. Embedded CMOS super-blocks will continue to provide *in situ* the ultra-low-power information processing that we enjoy today in our entertainment and communication devices. By incorporating parallel processing at the lab-on-chip level, we are assured that our exponential data growth [16] is matched with a distributed parallel growth of computing resources. The components for this 'lab-on-chip-Lego' system will come in parts: a roll of organic multifunctional optofluidic and electrofluidic substrate and a box of CMOS blocks that can be attached to the substrates. Our ultimate goal is the design and synthesis of flexible structures, networks at multiple physical scales in hybrid animate/inanimate technologies that can transduce, adapt, compute, learn and operate under a closed loop for bio-environments. To achieve our goal we must address fundamental questions at the interface of biological and physical systems as we strive to engineer new forms of complex informed matter and three dimensional computational substrates.

Conclusions: As we begin to make small strides in the twenty-first century we are witnessing the birth of an integrative discipline that goes beyond individual domains and is aimed at the automation of the processes and systems that that will enable sophisticated real-time prediction as well as closed loop diagnosis and disease treatment. More importantly, the same technologies will help individual behaviour modification and help encourage a healthier lifestyle.

Today electrical interfaces to the organs of the human body are routinely used to yield information on aggregate behaviour and the state of the system, for example EEG or EKG. Imaging technologies have advanced to the point that soon one will be able to measure the distribution of a specific molecule within the three dimensional structure of a single cell or a patch of myocytes of the human heart while the person is going about their daily exercise routine. However, the subtle yet so important molecular signalling pathways within a cell and in the tissue that have predictive power in the diagnosis of system malfunction can only be interrogated using imaging technologies that are able to sense and measure localised changes in ion concentrations, concentration of a particular chemical and perhaps even key reaction rate constants, as a function of time and space in the tissue. Once this basic capability is achieved one would see a proliferation of implantable devices that would monitor the internal state of the human body, performing diagnosis and therapy such as drug delivery in a timely and effective way. The technologies to accomplish this may not be readily available today but are within our grasp in the decades ahead.

With ever more accelerating technological and scientific progress in the life sciences, 50 years from now, we envision that many of the world's premier medicine and healthcare institutions such as Johns Hopkins will be turned into historical museums. Visitors will be able to get a glimpse of how top tier medical care was taught and research was carried out in the twentieth century. Visitors in Baltimore will be taking a tour of the Inner Harbor, Fells Point and up the hill to Johns Hopkins Hospital museum, much like we today would visit Asklepieion on the island of Kos in Greece. For two thousand years, since the ancient times of Hippocratic medicine, patients had to visit the place called a hospital or a clinic where then could get treatment. This two thousand year old practice will end. Healthcare will be delivered at home using patient monitor services and chip-level implantable instrumentation. Wireless, electronically programmed chips will control delivery of drugs in a timely and precise fashion based on algorithms that monitor the individual daily function and behaviour. This will be the age of medicine without borders. The profession of a physician will also see a radical transformation and the last doctor of medicine (MD) degree – as it is known today – will be awarded in 2043, exactly 150 years from the time the Hopkins School of Medicine opened its doors!

50 years from now, a century would have passed from the invention of the first microchip and Moore's law will be no more. However we will be living in an era where the 'chip' – short for the microchip – in its different forms from imagers to ion sequencers to labs-on-chip and cognitive processor units (CogPUs) will provide the underpinnings and the foundation for affordable, state-of-the-art, global personalised medicine and healthcare delivery.

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One or more of the Figures in this Letter are available in colour online.

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References

1 Kilby, J.S.: 'Turning potential into realities: the invention of the integrated circuit -Nobel Lecture-', *http://nobelprize.org/physics/laureates/2000/kilby-lecture.pdf*, December 2000, pp. 474–485
2 SIA, 'International technolology roadmap for semiconductors (2009 edition)', *ITRS*, *(http://www.itrs.net)* 2009
3 Moore, G.: 'Cramming more components onto integrated circuits', *Electronics*, 1965, **38**, (4), pp. 114–117
4 Kitano, H.: 'Computational systems biology', *Nature*, 2002, **420**, (6912), pp. 206–210
5 Chen, J., Dougherty, E., Demir, S., Friedman, C., Li, C.S., and Wong, S.: 'Grand challenges for multimodal bio-medical systems', *IEEE Circuits and Systems Magazine*, 2005, **5**, (2), pp. 46–52
6 Auflray, C., Charron, D., and Hood, L.: 'Predictive, preventive, personalized and participatory medicine: back to the future', *Genome medicine*, 2010, **2**, (8), p. 57
7 Andreou, A.G., Zhang, Z., Ozgun, R., Choi, E., Kalayjian, Z.K., Marwick, M.A., Christen, J.B., and Tung, L.: 'Contactless fluorescence imaging with a CMOS image sensor', 2011 IEEE Int. Symp. Circuits and Systems (ISCAS 2011), Rio de Janeiro, Brazil, May 2011, pp. 2341–2344
8 Lin, J.H., Pouliquen, P.O., Goldberg, A.C., Rizk, C.G., and Andreou, A.G.: 'A bio-inspired event- driven digital readout architecture with pixel-level A/D conversion and non-uniformity correction', 45th Annual Conf. on Information Sciences and Systems (CISS 2011), Baltimore, MD, USA, March 2011, pp. 1–6
9 Marwick, M., and Andreou, A.G.: 'Single photon avalanche photodetector with integrated quenching fabricated in TSMC 0.18um 1.8V CMOS process', *Electronics Letters*, 2008, **44**, (10), pp. 643–644
10 Rothberg, J.M., Hinz, W., Rearick, T.M., Schultz, J., Mileski, W., Davey, M., Leamon, J.H., Johnson, K., Milgrew, M.J., Edwards, M., Hoon, J., Simons, J.F., Marran, D., Myers, J.W., Davidson, J.F., Branting, A., Nobile, J.R., Puc, B.P., Light, D., Clark, T.A., Huber, M., Branciforte, J.T., Stoner, I.B., Cawley, S.E., Lyons, M., Fu, Y., Homer, N., Sedova, M., Miao, X., Reed, B., Sabina, J., Feierstein, E., Schorn, M., Alanjary, M., Dimalanta, E., Dressman, D., Kasinskas, R., Sokolsky, T., Fidanza, J.A., Namsaraev, E., McKernan, K.J., Williams, A., Roth, G.T., and Bustillo, J.: 'An integrated semiconductor device enabling non-optical genome sequencing', *Nature*, 2011, **475**, (7356), pp. 348–352
11 Davics, K.: 'Illumina's HiSeq 2000 Hits $10,000 Genome Mark', *http://www.bio-itworld.com/issues/2010/mar-apr/hiseq.html*, March 2010
12 Xia, Y., and Whitesides, G.M.: 'Soft Lithography', *Annual Review of Materials Research*, 1998, **28**, pp. 153–184
13 Thorsen, T., Maerkl, S.J., and Quake, S.R.: 'Microfluidic large-scale integration', *Science (New York, NY)*, 2002, **298**, (5593), pp. 580–584
14 Wang, T.-H., and Wong, P.K.: 'Transforming Microfluidics into Laboratory Automation', *J. Assoc. Lab. Autom.*, 2010, **15**, (3), pp. A15–A16
15 Christen, J.B., and Andreou, A.G.: 'Design, Fabrication, and Testing of a Hybrid CMOS/PDMS Microsystem for Cell Culture and Incubation', *IEEE Transactions on Biomedical Circuits and Systems*, 2007, **1**, (1), pp. 3–18
16 Szalay, A., and Gray, J.: '2020 computing: science in an exponential world', *Nature*, 2006, **440**, (7083), pp. 413–414

17 Choi, E., Gu, Z., Gracias, D., and Andreou, A.G.: 'Chip-scale magnetic sensing and control of nanoparticlcs and nanorods', *2006 IEEE International Symposium on Circuits and Systems (ISCAS 2006)*, 2006, Island of Kos, Greece, pp. 1319–1322
18 Kogge, P., Bergman, K., Borkar, S., Campbell, D., Carson, W., Dally, W., Denncau, M., Franzon, P., Harrod, W., Hill, K., Hillcr, J., Karp, S., Keckler, S., Klein, D., Lucas, R., Richards, M., Scarpelli, A., Scott, S., Snavely, A., Sterling, T., Williams, R.S., and Yelick, K.: 'ExaScale computing study: technology challenges in achieving exascale systems', *DARPA IPTO Report*, September 2008
19 Andreou, A.G., Dally, W.J., Sejnowski, T., and Abel, T.: 'The future of computing, from extreme to green', *http://www.kavlifoundation.org/science-spotlights/future-computing-extrcme-green*, August 2010
20 Szalay, A., and Bell, G.: 'GrayWulf: scalable clustered architecture for data intensive computing', System Sciences, 2009. HICSS '09. 42nd Hawaii International Conference, Honolulu, HI, USA, 2009, pp. 1–10
21 Cassidy, A.S., and Andreou, A.G.: 'Beyond Amdahl's law: An objective function that links multiprocessor performance gains to delay and energy', *IEEE Transactions on Computers*, 2011, accepted for publication
22 Marwick, M.A., and Andreou, A.G.: 'Retinomorphic system design in three dimensional SOI-CMOS', 2006 IEEE International Symposium on Circuits and Systems (ISCAS 2006), 2006, Island of Kos, Greece, pp. 1655–1658
23 Markram, H.: 'Human Brain Project', *http://www.humanbrainproject.eu/*, October 2011
24 Williams, E., Ayres, R., and Heller, M.: 'The 1.7 kilogram microchip: Energy and material use in the production of semiconductor devices', *Environmental Science & Technology*, 2002, **36**, (24), pp. 5504–5510
25 Crone, B., Dodabalapur, A., Lin, Y., Filas, R., Bao, Z., LaDuca, A., Sarpeshkar, R., Katz, H., and Li, W.: 'Large-scale complementary integrated circuits based on organic transistors', *Nature*, 2000, **403**, (6769), pp. 521–523
26 Gundlach, D.J.: 'Organic electronics. Low power, high impact', *Nature Materials*, 2007, **6**, (3), pp. 173–174
27 Lin, J., Ozgun, R., Pouliquen, P.O., Andreou, C.M., Georgiou, J., and Andreou, A.G.: 'A 3-pin 1V 115 uW 176 × 144 autonomous active pixel image sensor in 0.18 um CMOS', 2011 IEEE International Symposium on Circuits and Systems (ISCAS 2011), May 2011, pp. 1568–1571