An Overview of DNA Analysis and Microfluidic Lab-on-a-Chip for Life Science Applications

The markets for these types of product have taken much longer to evolve than originally anticipated. Although the market for DNA microarrays is now well established, there is still scope for technological innovation of an incremental and disruptive nature. With a few exceptions, microfluidics is at an earlier stage of development for life science applications and, despite the potential, looks set to take a while to really invoke a paradigm shift. A high level roadmap for some of the technologies mentioned in this article is presented in Diagram 1.

DNA Microarrays

The purpose of these technologies is to determine the sequence of subunits that constitute DNA which can be used to identify the proteins that a gene codes for or to determine the degree of similarity between samples.

Typically, an analysis sample of DNA is amplified enzymatically and then broken into short fragments (in a controlled manner) that are fluorescently tagged. These fragments are allowed to bind with their complement DNA fragment (immobilised on a slide as a component of a DNA microarray) as determined by fluorescent detection (with an external reader). Subsequent computational analysis making use of algorithms allows the original sample DNA sequence to be determined. DNA sample preparation has proven to be a bottleneck in the overall process although microfluidic devices have been developed (e.g. ST Microelectronics) to address such problems.

DNA sequencing has many applications including:

- Forensic investigation
- Pathogen identification
- Water quality determination
- Defence
- Determination of single nucleotide polymorphisms (SNP)

The leading company in this area is Affymetrix which provides standard and custom DNA microarrays which it produces using a mixture of photolithography and solid phase combinatorial chemistry techniques. The company is further miniaturising its arrays with the aim of achieving a complete human genome analysis on a single chip. The drive for further improvements in speed and cost is being supplemented by the US government (Advanced Technology Program) which has issued a challenge to reduce the cost of a DNA test by 1 – 2 orders of magnitude and increase speed by a factor of 10. Such progress should open up the market for DNA analysis to a wider range of applications as cost and speed reach acceptable levels for more routine activities (Diagram 2).

New technologies such as dip pen lithography may allow the printing of very high density DNA microarrays and the use of quantum dot based classes of fluorescent tags may improve the sensitivity and scope of detection. Although external detection following hybridisation dominates current data acquisition techniques, there is potential for the use of nanopore sequencing that would circumvent hybridisation and allow sequencing to be translated directly into an electrical signal.

Microfluidic Lab-on-a-chip Devices

The purpose of these devices is to manipulate and process solution based samples and systems by carrying out typical procedures such as mixing, heating and separation. Processed samples may be delivered to some form of detector that subsequently transmits data.

These devices typically consist of a monolithic material that is patterned with microscale channels and features such as mixers, valves, injectors and separators that can assume the role of equivalent macroscopic laboratory equipment. Appropriate connection to the macroscale world for inputs and outputs (not trivial) is required and so the microfluidic device is likely to be part of a system. Typically, materials used are either glass or polymer although some hybrid silicon components may also be used. Microfluidic technology allows the reliable handling of smaller samples and provides greater control over a process with increased safety. True lab-on-a-chip devices would also incorporate some means of detection thus providing a ‘reagents in – data out’ apparatus although the material output of processed reagents may be desired.

Microfluidic devices have a broader range of applications than DNA microarrays as they can be used for applications that include:

- Chemical reactions (e.g. microreactors)
- Biological assays
- Sample preparation
- Sample purification
- Sample analysis
- Diagnostics

There are a number of reasons for the slow progress of microfluidic devices for life science applications. From a users point of view, awareness of the technology requires further effort and microfluidics currently represents a different and novel way of doing things which creates potential difficulty of translating day-to-day activities to these new systems and a poor understanding of the benefits that can be realised. Only by a growing experience of these technologies can the scope and limitations of these technologies be understood and exploited. There is some uncertainty with the choice between standardised products and the use of bespoke devices that are designed specifically for a particular function. Whereas the first are cheaper and more versatile, performance is compramised. Performance is not an issue with the second but bespoke devices would require a good understanding of what is to be achieved (only possible with experience) and will be more expensive and less versatile. Integrating detection into a lab-on-a-chip device may result in the introduction of detection techniques that are not in standard use which may take time to be adopted by users. Some routine analytical techniques cannot be integrated into a lab-on-a-chip device due to technical or cost issues.

From a supply point of view, there continues to be a proliferation of technical solutions and microfluidic components that serve to increase choice (and confuse) but few of which have been proven in real applications or manufacturing environments. Each of these developments is typically a component or part of a required solution and more effort is required to integrate these components into functional devices and move from proof of concept to prototype. With respect to manufacturing, microfluidic devices often use processes that originate from the semiconductor industry which seeks high volume 'killer' applications for cost competitiveness. The desire for a high volume killer application is at odds with the life science microfluidics market which is likely to be typified by a large number of modest volume markets with a limited product lifetime. Only diagnostic applications are likely to achieve the desired high volumes (probably polymer based) and these will only evolve fully once the lower volume applications have resulted in an adequate understanding of biological systems.

The current use of robotic laboratory systems in conjunction with microtitre plates is well established and ongoing incremental developments allow this incumbent paradigm to remain competitive. Only when microfluidics offers a distinct and proven advantage over these solutions can they start to be replaced.

Future Directions

Routine processing of samples and microreactors for selected chemical reactions are likely to represent some of the earlier applications of microfluidic devices to allow speed, control and reduced cost compared to incumbent solutions. Although the advances in genomics (in which DNA microarrays have played a key role) have been crucial and will continue to play a vital role they only represent part of the life science puzzle. Proteomics is emerging as the next grand challenge as illustrated by the human proteomics initiative that is now underway. Here, the protein shape is central to understanding its activity and function which is in contrast to the importance of sub-unit sequencing for DNA. Although protein purification, analysis and arrays will be of importance, the effect of immobilisation, their delicacy and the importance of protein-protein interaction are likely to result in a requirement for a more diverse and advanced range of technologies to gain a more complete picture of the life sciences.

This article is a summary of one of the chapters in the available 2005 Microsystems and Nanotechnology in the Medical and Biomedical Market Report prepared by TFI.

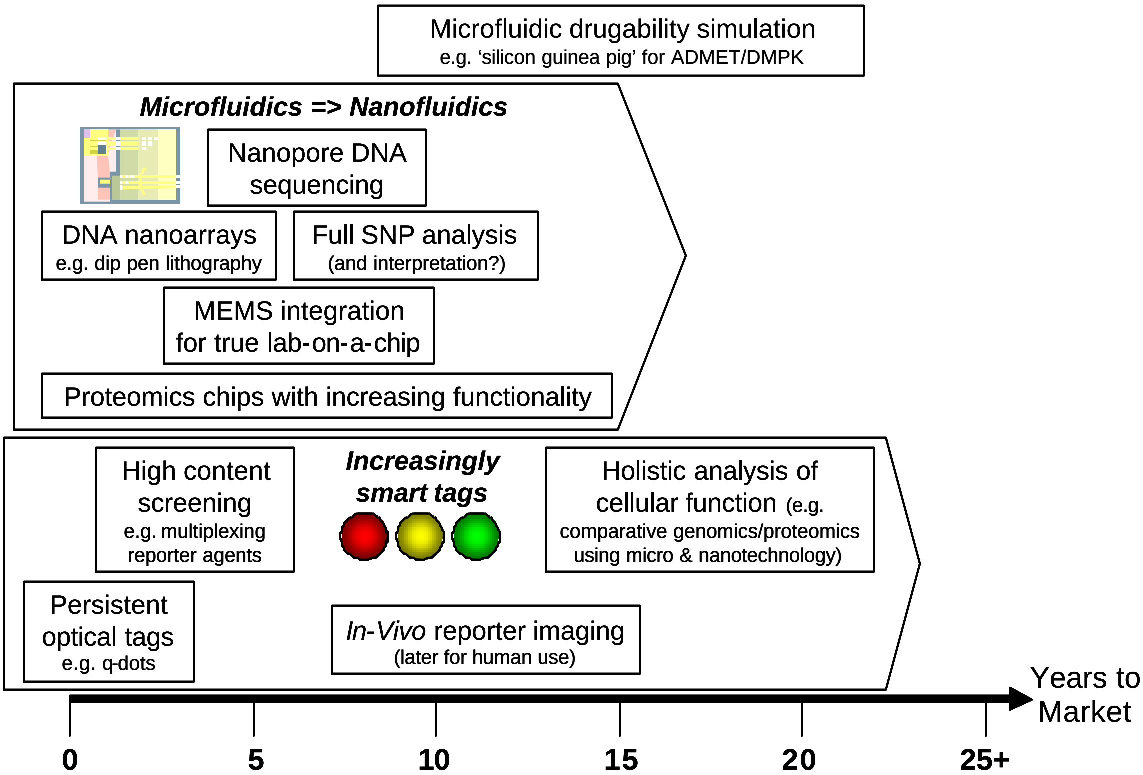

Diagram 1: A High Level Roadmap for Microfluidic and Related Technologies

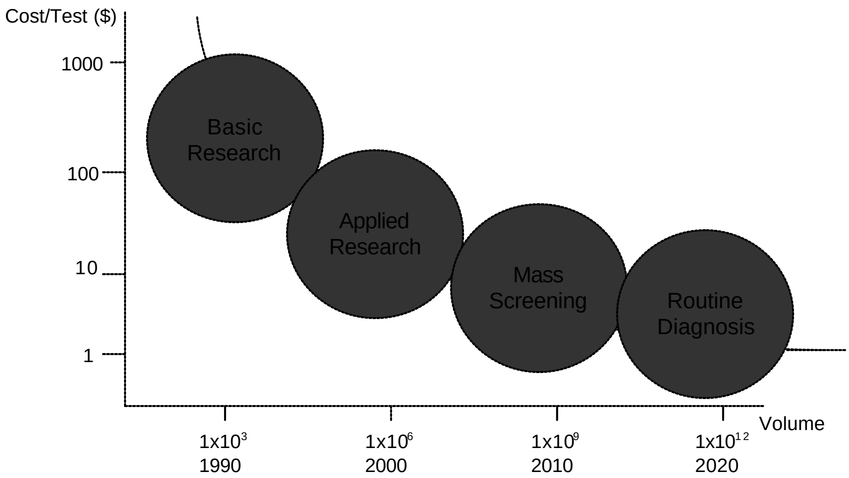

Diagram 2: The Relationship between Test Cost and Application