The life sciences revolution

Semiconductor manufacturing technology is enabling the life sciences sector to develop. By **David Boothroyd**.

Semiconductor developments during the last five decades or so have transformed the electronics industry beyond recognition. Now, the amazing techniques developed by semiconductor manufacturers are doing something similar for an entirely different industry: life sciences.

Semiconductor expertise – especially in photolithography, but also elsewhere – is underpinning dramatic advances in 'lab on chip' devices which, in turn, are transforming medical and biological research and commercial applications.

Lab on chip technology, also known as microfluidics, deals with the behaviour, control and manipulation of fluids. Typically this is at the sub-millimetre scale, but increasingly at the nano level. The first application for microfluidics was in the early 1980s, when the technique was used in the inkjet head for Hewlett-Packard printers.

The manufacturing process for microfluidics comes principally from the microelectronics industry. Many chips are glass, although silicon is also used, and the channels that control the flow of the fluids are laid down using photolithography.

A pioneer of semiconductor photolithographic techniques for life science applications is Californian company Affymetrix, which introduced the first commercial DNA microarray in 1994, a 'GeneChip' for analysing HIV.

Microarrays can process large amounts of biological material using high throughput screening methods – effectively doing thousands of experiments in parallel. Affymetrix' technology has helped make discoveries in areas such as Parkinson's disease, diabetes, malaria and cancer.

Another example of the growing ties between the semiconductor industry and life sciences is ATMI, a semiconductor manufacturer which recently announced plans to double its global production capacity of ultraclean, disposable biological processing vessels for life sciences applications through upgrades and modifications to its North American manufacturing facility. Its site currently supplies the ic and flat panel display markets, and ATMI is adding a Grade B clean room for fabricating complex 3d storage, mixing and bioreactor vessels for life sciences customers.

"Beyond the new clean room, the upgraded facility will house a bio test laboratory to analyse and manage sterility levels in the manufacturing environment to capitalise on our proficiency in semiconductor, clean room and ultrapure manufacturing and to leverage that expertise in the life sciences market," said ATMI.

The whole lab on chip market is booming, with new applications appearing regularly. A few examples include: the MESA+ Institute for Nanotechnology, which has developed a tiny electrochemical cell that can mimic the behaviour of medicine inside a human body; Tel Aviv University, where researchers have created a nano sized laboratory, complete with a microscopic workbench, to measure water quality in real time; Johns Hopkins University, where a lab on chip has been designed to mimic the chemical complexities of the brain; and UCLA, where researchers have invented a system that can perform more than 1000 chemical reactions at once on a pc controlled chip, accelerating the identification of potential drug candidates for treating diseases like cancer.

The semiconductor industry's favourite material, silicon, is used as the base for some lab on chip devices and one advantage of this is that intelligent functionality can be integrated directly on the chip. Often, a combination of silicon and a polymer material is used, as Frederic Breussin, Life Sciences Researcher for French market consultancy Yole Developpement, explains.

"Using a polymer means you can produce a low priced base and integrating silicon on it provides an active processing and control capability.

Photo: Eric Millette/BigShotStock

TURNER: "WE ARE USING HIGH PERFORMANCE SILICON BASED PHOTONIC SENSORS ... AND A POWERFUL PARALLEL COMPUTING ARCHITECTURE."

For example, if you wanted heating on the chip, an active silicon area would give you control of that, or you could create a sensor capacity for direct detection of substances."

But beyond helping with the technology itself, Breussin believes the semiconductor industry has an equally important role to play in life sciences – systems integration.

"The semiconductor industry's experience in high levels of integration, at system level packaging and in making devices that are robust and manufacturable, will be crucial. There has been plenty of excellent work done by universities and researchers, but much of it has yet to be developed commercially."

One example of how this is starting to change is STMicroelectronics, which is marketing a DNA detection platform called In-Check. With Veredus Laboratories of Singapore, STM has launched VereFlu, a lab on chip application for rapid detection of all major influenza types at the point of need. VereFlu is the market's first test which has integrated two molecular biological applications in a lab-on-chip. It can identify and differentiate human strains of Influenza A and B viruses, including the Avian Flu strain H5N1, in a single test.

Several other major semiconductor companies are actively involved in the life sciences and their expertise in advanced packaging techniques like stacking and 3d could prove invaluable, given the need to combine different elements, such as microfluidic channels, cmos processing, a power element, and an optical device together on one chip.

"There is no doubt that improvements in photolithography and nanoscale technology in general are enhancing the potential of microfluidics because it makes it possible to use much smaller samples and that makes the process more sensitive, faster and cheaper – all very important factors for the diagnostics and pharmaceutical industries," Breussin says.

In at least one specific area, dramatic advances look to be around the corner: analysing genes, or DNA, using the polymerase chain reaction. A potentially revolutionary new such system is due to be launched commercially next year by Pacific Biosciences (PacBio), a company founded by researchers at Cornell University in the late 1990s.

PacBio is set to launch a radically new kind of chip based DNA sequencing tool, called the Single Molecule Real Time (SMRT) Sequencing System. Ultimately, it could radically transform the process of DNA sequencing, making it possible to perform the hugely complex job of sequencing the entire genome of a person in an hour or less at a cost of a few hundred dollars. The current industry standard technique, Sanger sequencing, took around 13 years and cost $3billion to complete the Human Genome Project!

All organisms use enzymes called DNA polymerases to replicate their DNA. Polymerases work by moving along a strand of DNA, building a complementary copy as they go, base by base. SMRT works by effectively 'spying' on this process, as Steve Turner, PacBio's chief technology officer, explains.

"It watches at the single molecule level as the process happens and attaches reporter labels (fluorescence) to each of the four building blocks used to create DNA – adenine, guanine, cytosine and thymine. By watching the sequence build the complementary strand, you know what the sequence of the original template was."

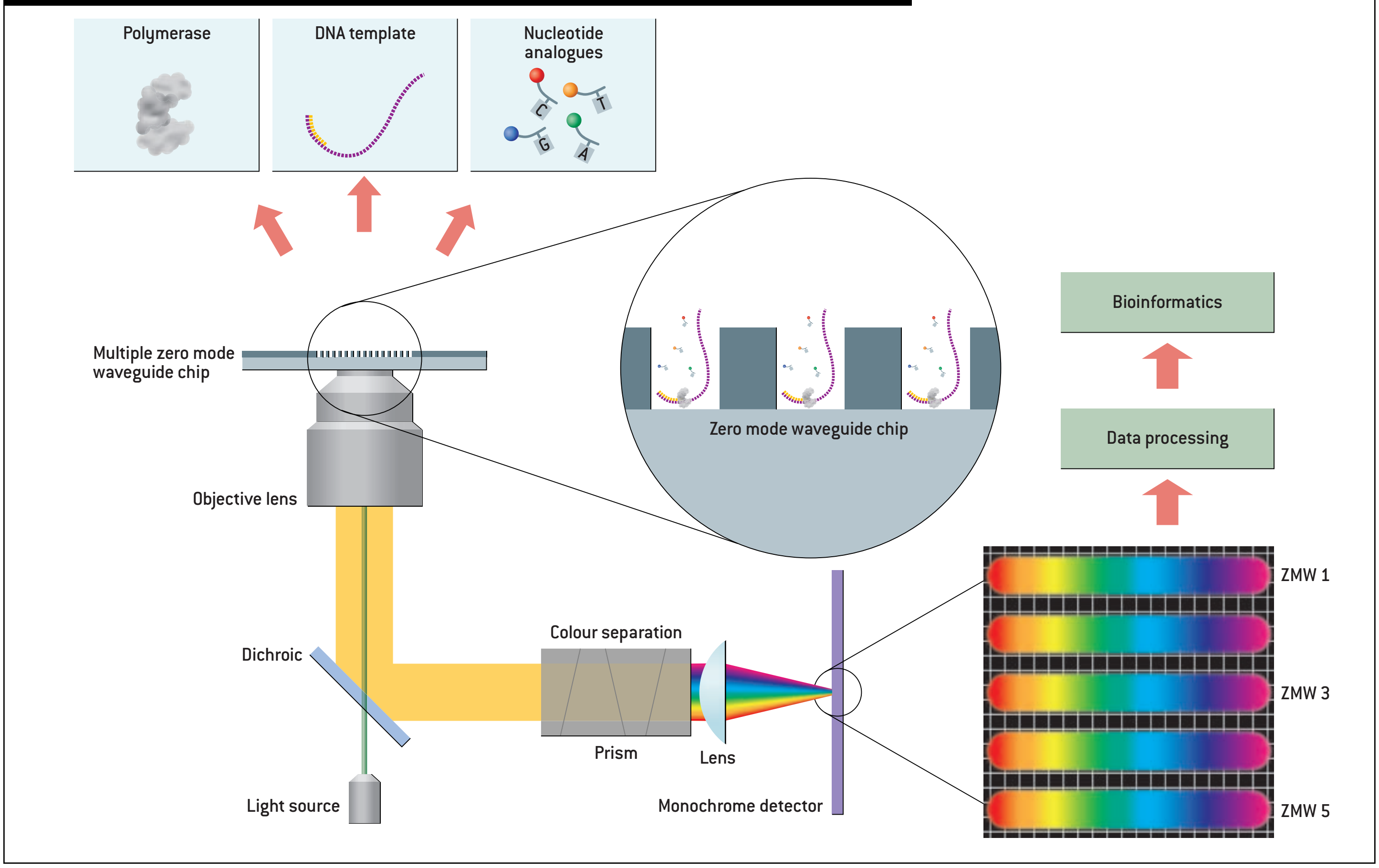
The SMRT sequencer will offer major benefits. Polymerisation is a rapid process, so the SMRT has to work extreme quickly, tens of bases per second. Because the on chip elements that perform the sequencing – zero mode waveguides (ZMWs) – are so small, potentially millions can be put on a standard chip. Current prototype SMRT chips contain thousands of ZMWs.

Using the latest semiconductor manufacturing technology, a ZMW is a hole tens of nanometers in diameter, fabricated in a 100nm metal film deposited on a silicon dioxide substrate. Each ZMW becomes a nanophotonic visualisation chamber, providing a detection volume of just 20 zeptolitres (10^{-21} litres). At this volume, the technology can detect the activity of a single molecule among a background of thousands of others.

"In order to detect fluorescence at the single molecule level, you need a method of confinement so that you are looking at a small enough volume of fluid so there are not too many of the labelled building blocks in view at the same time," Turner says. "This cannot be achieved using conventional microscopy, which is why we invented the ZMW."

Semiconductor manufacturing techniques have been crucial for building the ZMW chips, as he explains. "Originally, we used electron beam lithography but we have switched recently to high performance photolithography because that has reached a good enough level to provide the fine features we need. We use a photolithographic positive tone process in a metal etch, similar to one that might be used in flash memory. Then we continue down

Fig 1: When a flash of light is separated into a spatial array, the ZMW can identify the incorporated base



the manufacturing process – dicing, cleaning and so on – and the devices are then mounted and packaged much like a conventional semiconductor chip, using a pick and place tool. Surface coatings have to be applied, not unlike some of the coatings you might see in electronic devices."

PacBio's main manufacturing challenge is ensuring the materials it uses are compatible with cmos. But Turner is adamant the impact of the SMRT will be considerable. "Initially, we will be on par with other technologies in terms of sequencing throughput. But we will offer several advantages, like longer read length, the ability to work with single molecules, faster turnaround time, lower systematic error rates and cheaper unit costs. That is just the beginning. By 2013, we will produce a device that can look at 1million ZMWs at once, and that will enable us to sequence an entire human genome in less than an hour."

Electronics is playing a crucial role for other aspects of the SMRT system, for example sensor technology. "We are using high performance, silicon based photonic sensors (currently a single photon sensitive ccd array, but cmos sensors are being considered), and then a powerful, parallel computing architecture," Turner says.

Some of this has been developed by PacBio, other elements have been brought in. For example, the parallel processing system draws on graphics coprocessing technology, providing extremely high performance at relatively low cost. Indeed, Turner believes sensor technology will be the dominant factor in advancing the SMRT system over the next few years.

"Today, our multiplexing capability is limited by the number of pixels in the sensor. If we had a 200Mpixel sensor, we could make a multimillion ZMW device quite straightforwardly. Such sensors are appearing, but they generally have relatively low frame rates and do not yet have single photon sensitivity."

There are plenty of other life science areas where electronics is important, like mass spectrometry, nuclear magnetic resonance and electrochemical sensors like chemFETs. In the latter approach, field effect transistors act as a chemical sensors, where the charge on the gate electrode is applied by a chemical process, used to detect atoms, molecules and ions in liquids and gases.

Turner says: "These are devices where electronics is used not only as you would expect it to operate – to process information that is created from measurements – but also where the electronics is fundamental to how the measurement is done."

Other areas where Turner believes dramatic advances are possible are biological/medical implants. Here, a combination of miniaturisation, advances in packaging, lower power consumption and wireless communication could lead to major developments. Beneficiaries could include devices like enhanced cochlear implants, pacemakers, implantable defibrillators and neuronal stimulation devices, and retinal implants.

Life, and its sciences, will never be the same again.