CUSTOMER CASE STUDY

Microscopic barcodes developed with low-cost MEMS/IC design tools drive medical testing

A combination of micro and nanotechnology is helping to speed up medical tests, as Paul Double of EDA Solutions explains.

Nanotechnology is seen as a leading edge technology requiring leading edge tools at leading edge prices, but a UK startup is using a relatively affordable design tool to produce some leading edge micro and nanotech results.

SmartBead Technologies, a spin out of the world-renowned Cavendish Laboratory at the University of Cambridge, aims to use micro-machined components to reduce the time and effort required to perform clinical diagnostic tests. Under the Ultraplex brand, it is using micro and nanotechnology to combine many different existing tests in one new test. This is a substantial improvement on the current situation where each diagnostic test has to be done separately, requiring more time, more reagents and a much larger patient serum sample. UltraPlex brings clear benefits to patients and clinicians alike.

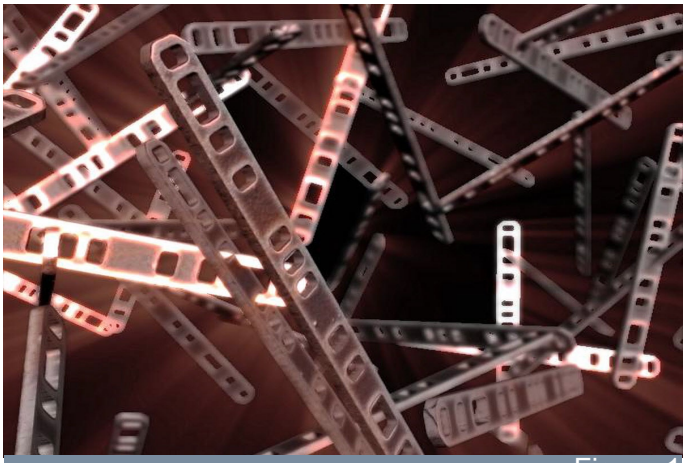

Figure 1

The technology is based around a 'barcoded' microparticle that is just 100um long - the thickness of a human hair, and just 10um wide and 1um thick. These microparticles, shown in Figure 1, have rows of holes and solid areas, with dimensions of a few microns, which act very similarly to supermarket barcodes. They are designed and manufactured using technology from the semiconductor chip-making industry. Whilst most of the process is the same as making a microchip, the wafer carries a "release layer" so that after fabrication, a solvent can be applied to dissolve the layer and release the microparticles.

The barcodes in the microparticles are read using a CCD image sensor and SmartBead's pattern recognition algorithms to identify and decode them. Error checking and correction built into the coding prevent misreads. Commercial barcode technology saves us all time and money, is well proven and reliable, and has been imaginatively implemented on the microparticles.

The current design of microparticle provides over 100,000 different codes. This is more than enough for the initial range of UltraPlex diagnostic tests, which will have between ten and thirty different and simultaneous tests combined for use with one patient sample. There are also UltraPlex patient profiling assays being developed that will use hundreds or thousands of codes.

After release of the micro-particles from the chips, the manufacture of a diagnostic test kit continues by coating sets of microparticles. All micro-particles with the same code number are coated with a specific "capture antigen" (Figure 2-A) which will capture a particular "target antibody" (Figure 2-B) in the human serum sample. The presence of one or more types of the target antibodies in the patient's serum sample can be an indicator of a specific disease condition in the patient.

Kits are then assembled that contain all the permutations of the microparticles and their associated codes and capture antigens. Thus a whole range of tests can be combined in a single test, or assay

The assays are carried out in industry standard 96-well plates, typically measuring 152mm x 102mm, with liquid handling being performed by an UltraPlex robotic system. Each well contains micro-particles coated with the capture antigens and serum from one patient.

The capture antibodies on the surface of the microparticles react with target antibodies in the serum and capture them on the surfaces of the micro-particles. In the final stage of the assay, a fluorescent "reporter antibody" (Figure 2-C) is attached to all the target antibodies that have been captured by the capture antigens on the micro-particles. These "positive" micro-particles then become fluorescent.

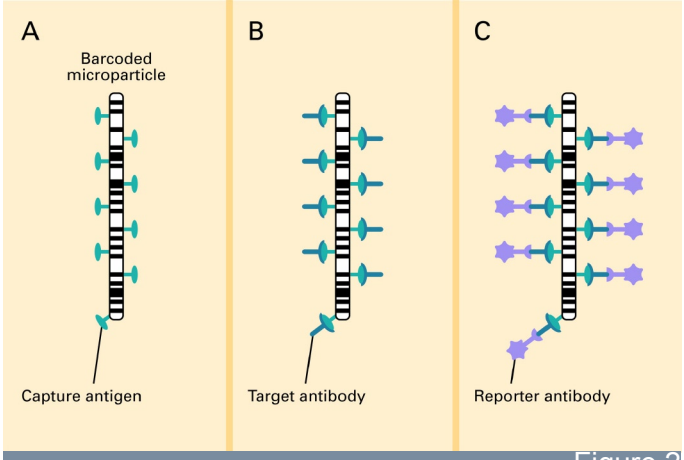

Figure 2

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The assay plate is then transferred to the Ultraplex Reader where the microparticles are decoded and their fluorescence levels measured. The reader then produces the results for each patient showing which target antibodies their samples contain and therefore from what condition they may be suffering.

The microparticles are designed using the well-established Microsoft Windows-based tool, L-edit, developed by Tanner EDA and supplied by EDA Solutions in Southampton. This tool is more often used for designing integrated circuits but the ability to handle different angles and design rule checking has lead it to be used for designing Micro-Electro-Mechanical Systems (MEMS) around the world, including the design of advanced polymers at Cambridge Display Technology for plastic displays.

As designers create more system-on-chip configurations requiring the incorporation of electrical and mechanical devices on the same chip, the design methodologies for the two are starting to converge. They therefore need tools specifically made to handle MEMS and IC design simultaneously.

L-Edit MEMS Design, the company's Microsoft Windows-based MEMS design platform, now includes all-angle design rule checking (DRC) capabilities. With online design rule checking (DRC), users can now find out instantly if their design violates rules for standard or custom fabrication processes.

All-angle DRC means that, for example, a designer can check for minimum spacing between any type of polygonal object on various layers. Any violations are highlighted the instant they are made. Also, the user can easily create customized DRC rules to meet proprietary MEMS fabrication processes. Development and maintenance of technology files is easily manageable through a series of Design Setup dialogue boxes. This is very important in design environments where the process is rapidly evolving and the designer is also responsible for maintaining a technology files database.

So far, SmartBead only require a few dozen different codes, so each permutation of micro-particle is designed by hand on L-Edit. Figure 3 shows a typical microparticle design created by the tool. A key advantage, for the future, is that L-Edit allows macros, known as T-cells, to be defined. As the number of tests and therefore the number of codes required grows, the ability to use the T cell macros to quickly and automatically design the hundreds or thousands of coded micro-particles will be essential.

L-Edit also has the added advantage of having the ability to produce a design in a format called GDSII that is used to make the masks for chip manufacture.

Both these factors are important in ensuring a smooth, rapid progression from the design of a micro-particle set through to manufacture of the particles on silicon wafers at the Scottish Microelectronics Centre in Edinburgh.

L-edit is easy to use for both the production microparticles and also for experimental versions with different shapes, different dimensions and different coding systems. Some

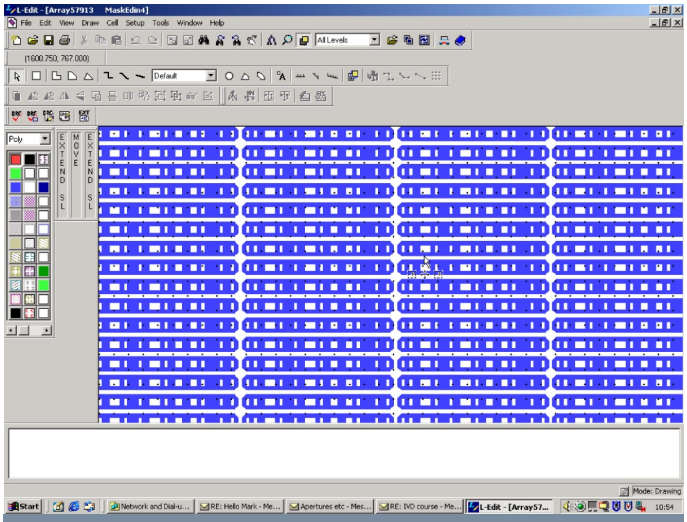

Figure 3

of these micro-particles will be even smaller than at present, allowing a greater number of micro-particles, codes and therefore capture antibodies in each assay. Smaller particles also mean more per wafer in fabrication, thus making each assay even cheaper.

The first commercial Ultraplex system using these microparticles is being used in Broomfield Hospital in Chelmsford, Essex, with ten different capture antigens in each assay for connective tissue auto-immune disorders.

But the auto-immune testing is just the first niche that Smartbead Technologies has made its own. The technology can be applied to any range of tests, as long as there is an appropriate capture antigen and reporter antibody for the target antibody that indicates a patient's condition.

Using chip-making design technology such as L-edit provides an established, reliable way of designing the microparticles themselves, the layers needed to make them and the barcodes that are at the heart of the Smartbead Technology. It is also allowing new versions of the microparticle to be developed that will increase the range and sensitivity of the tests and also reduce the cost of testing and the test time even further.