MEMS' Trends

ISSUE N°9
JANUARY 2012

Magazine on MEMS Technologies & Markets

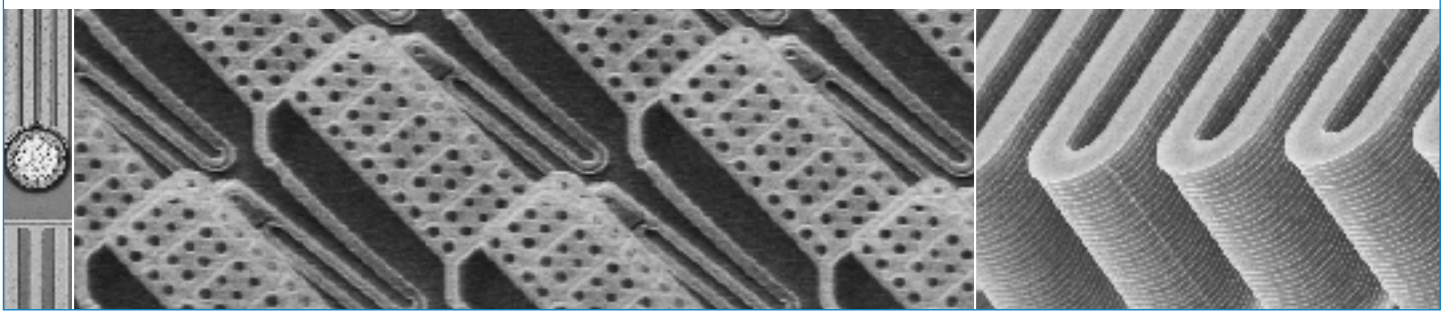
Printed on recycled paper

INDUSTRY REVIEW
Biomedical MEMS move from sensing to treatment

ANALYST CORNER
Microfluidics sector poised for 23% growth...

COMPANY INSIGHT
Pacific Biosciences argues its low cost tools meet the need for more detailed information

YOLE DÉVELOPPEMENT



EDITORIAL

BioMEMS & Microfluidics are poised for growth!

A lot has changed in the bioMEMS & microfluidics businesses since the last issue of *MEMSTrends* dedicated to this topic, just one year ago. That's why we've decided to focus this first *MEMSTrends* issue of 2012 on the microfluidics market and applications.

Indeed, since the first microfluidics acquisition in 2009 (when Beckton Dickinson acquired Handylab), the frequency of acquisitions has increased -- especially toward the end of 2011. The ongoing entry of large diagnostics companies into the field is an encouraging sign for further growth in the near future. Also encouraging is the fact that big companies are not the only ones to invest in microfluidics. In the last three years we've identified over 200 new microfluidics players, and financial investments are today in the multi-million range.

The prevailing technology in microfluidics is still mainly polymer and glass processing, but "traditional" polymer industrial players should be wary of potential competition from higher-skilled players like Sony or Konica. Microfluidics is becoming increasingly smarter – one example of this is electronics and sensors directly integrated below the microfluidics channels (Ion Torrent is one of the most promising new companies in this area and is probably close to a market introduction of their second generation device).

On the applications side, we believe industrial & environmental testing applications will be the sector with the highest growth, followed by microfluidics devices for research in pharmaceuticals and Life Science. One of the main obstacles to the market introduction of microfluidics devices and bioMEMS is the long developments cycles, which are then followed by clinical development and testing cycles. But despite this constraint, we recently identified the use of bioMEMS sensor feedback from inside the body as a better and safer intervention method in the case of implantable devices and minimally invasive procedures. More on this topic can be found in this issue.

Last but not least, we wish you a Happy New Year!

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Dr. Eric Mounier, Project Manager, Yole Développement
Dr. Eric Mounier has a PhD in microelectronics from the INPG in Grenoble. Since 1998 he is a cofounder of Yole Developpement, a market research company based in France. Dr. Eric Mounier is in charge of market analysis for MEMS, equipment and material. He is Chief Editor of Micronews and MEMS'Trends magazines (MEMS Technologies & Markets).

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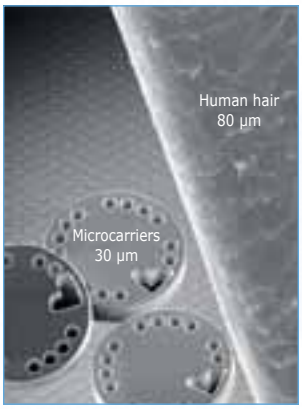

Biocartis is developing a proprietary technology platform designed to further expand the Company's market reach by offering an innovative, integrated, rapid and multiplexed analysis platform. The platform is designed to support a broad range of biological assays from immunoassays to nucleic acid tests. The core of the technology consists of digitally encoded silicon microparticles coated with specific capture molecules in microfluidic channels. One key feature of the platform is the ability to simultaneously detect and quantify a large number of biomarkers from a sample. (Courtesy of Biocartis)

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- **SLAS**
  February 4 to 8, 2012 - San Diego, USA
- **IMRET**
  February 20 to 22, 2012 - Lyon, France
- **Lab-on-a-Chip European Congress**
  March 28 to 29, 2012 - Edimburgh, Scotland

FINANCIAL BUZZ

Valuation of Jyve from Fairchild acquisition reveals strong need for innovative consumer gyroscope technology

Laurent Robin,
Market Analyst, MEMS,
Yole Développement

While Fairchild Semiconductor never issued a press release or made a dedicated announcement, we have finally been able to piece together the information regarding its acquisition of Jyve Inc., a startup founded by Janusz Bryzek (the veteran of several MEMS startups in Silicon Valley) who was also its CEO at the time.

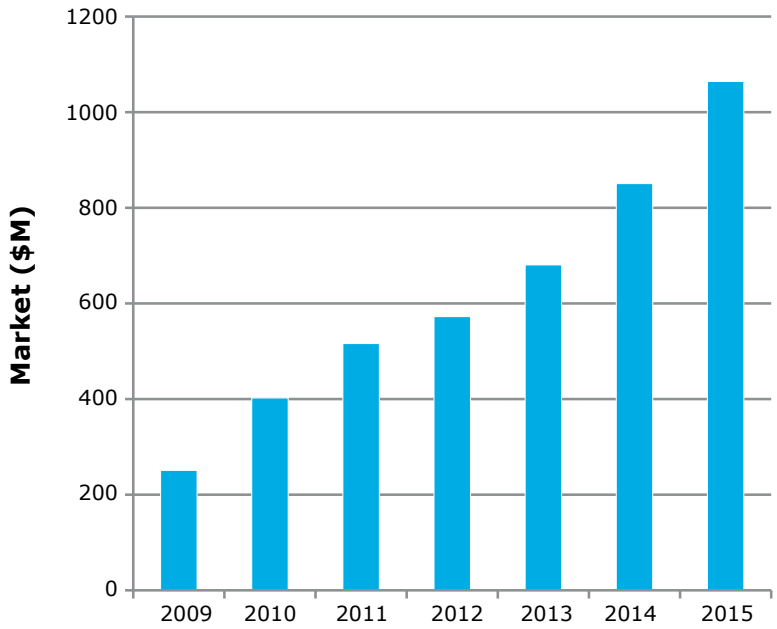
Deep within its Annual Report for 2010 and in the conference call transcript for its Q4:10 and 2010 year-end numbers, Fairchild discussed the acquisition of a MEMS start-up in November of that year. At the same time, Janusz repeatedly revealed in descriptions of his professional experience on several public webpages that his new MEMS venture was acquired by Fairchild in November 2010, where he is now VP Development, MEMS and Sensor Solutions. We can thus deduce from this information and these events that the inertial MEMS start-up mentioned by Fairchild was in fact Jyve, Inc.

Some of the details of the terms and conditions of the acquisition highlighted in the Fairchild 2010 annual report certainly put the deal in the upper quartile valuation range for inertial sensors as tracked by Yole Finance, especially since Jyve was probably a pre-revenue company. The details disclosed in the report indicate that it consisted of an upfront payment of $11.0 million in cash, combined with some contingent consideration (likely stock) to be earned over the next five years (now four) and dependent on the success of the technology. At the time, Jyve was developing inertial MEMS with a very disruptive technology that would significantly lower manufacturing cost and possibly offer higher performance than today's consumer sensors. We expect to learn more in the next few months, including more details on Fairchild's growth plans for this business unit. There are indications in the market that a product introduction is expected in 2012, and so this looks like another success story for Janusz Bryzek and an attractive acquisition for Fairchild.

As motion sensing becomes part of more and more smartphones and tablets, the hype surrounding MEMS gyroscopes companies has never been higher. InvenSense's IPO was very successful: announced mid-November 2011 at $8.25, the shares were priced at $11.30 by the end of November (see the next article, which is dedicated to InvenSense's IPO). Also, two inertial MEMS companies were acquired this year because of the technology's potential in the consumer market: SensorDynamics was acquired by Maxim in July 2011 for $130 million in cash, and VTI was acquired by Murata in October 2011 for $265 million.

As the inertial business on the consumer side becomes more and more competitive, prices for 3-axis gyroscopes are dropping quickly. Most companies are trying to find disruptive design and sensing principles that will reduce manufacturing costs even further, since the traditional comb-drive design has reached its limit in terms of miniaturization and cost reduction. This is why disruptive developments coming from start-ups such as Jyve are raising so much interest.

Market for MEMS gyroscopes in consumer electronics ($M)
(Inertial Combo Sensors for Consumer & Automotive report, Yole Développement, 2011)



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FINANCIAL BUZZ

InvenSense now listed on the stock exchange: what does it mean?

InvenSense is one of the few successful MEMS start-ups, having generated $100 million-plus in annual business in only a couple of years. This success has put InvenSense in a very good position in terms of creating value for its shareholders, and more than likely it has attracted the attention of other potential strategic investors who want to strike while the iron is hot.

What drove InvenSense's IPO?

After Kionix's acquisition for a very nice multiple in late '08, a similar step seemed like an attractive option for InvenSense -- and one that would provide it with the necessary global footprint for future growth. Instead, InvenSense decided to remain an independent company and moved toward an IPO in order to generate the capital necessary to increase its product offering both organically and through acquisitions in the short and medium-term – understanding well that building a global organization and infrastructure to support a growing number of demanding customers requires a significant amount of capital and other important resources. It is worth nothing that most of the proceeds from the IPO went to VCs -- none of the money went to Invensense, as it has $48 million cash in the bank right now. We thus expect it will stage a follow-up offering soon in order to raise more cash. The most important challenge for this U.S. start-up will be to stay ahead of its competition, which is particularly aggressive in the gyroscope market space. ST Microelectronics is InvenSense's primary competitor -- the two companies are today the only two companies in the world that have 3-axis gyroscopes massively integrated into cellphones and tablets. Their competition began in 2009, when ST entered the market with a large, aggressively-priced portfolio of single and dual-axis gyroscopes (more than 30 models released!).

In the consumer accelerometer market, only a few companies are really doing well, while most are struggling to turn a profit. In fact, only ST Microelectronics and Bosch Sensortec are succeeding, while others like Freescale and Kionix try to keep up, and many, such as ADI, have failed to stay competitive. As such, there is a very little room in the consumer gyroscope market and consumer motion sensing business and so InvenSense needs to continue investing in order to maintain its position in the market.

Over the last couple of years, the gyro business has become a hotbed for competition. According to Yole's analysis, InvenSense was number one in the consumer gyroscope business in 2010 with 23.6% market share, finishing ahead of Epson Toyocom and ST Microelectronics. Epson was strong thanks to key contracts in the gaming and high-end DSC market – however, its prospects in the booming mobile phone market are not as bright, since it still relies on single-axis devices. InvenSense's position became very unstable by the end of 2010 because the company was strongly dependent on one customer, Nintendo, which accounted for 85% of InvenSense's business in fiscal year 2010. Also, InvenSense missed out on two key contracts in 2010: first, ST was chosen for the iPhone contract, which was bad news for InvenSense but good news for the gyroscope business in general because it meant that the handset business was about to boom. The second missed opportunity was the iPad: the first generation of the Apple tablet featured an accelerometer and a compass, but it was probably designed to also feature a gyroscope -- indeed, there is an empty slot on the board just beside ST's accelerometer, with a number of pins which fits with InvenSense's 3-axis gyro. So it is likely that InvenSense's 3-axis gyro was very close to being included in the iPad, but at the last minute Apple decided not to integrate it for some reason. It is important to note that the second generation iPad did integrate a gyroscope that enabled users to benefit from applications which had been developed for the iPhone 4 gyroscope, and from brand-new applications as well, but this gyroscope was sourced to ST. Indeed, Apple uses ST's gyroscope in its iPhone, and the two companies have enjoyed a long-term collaboration.

"InvenSense has raised the bar for the next generation of early-stage MEMS device companies," says Laurent Robin, Yole Développement.

Due to its "slow" start in the 3-axis gyro market, InvenSense eventually lost its number one position to ST, but 2011 was a different story. Despite a decrease in Nintendo orders, InvenSense was able to penetrate new markets and diversify its customer base with many design wins related to Android products. InvenSense now supplies Samsung, LG, HTC, RIM, Acer and other large OEMs for smartphone and tablet applications. InvenSense also successfully introduced new products to the

market (including the first 6DOF accelero-gyro combo solution), and developed a significant software offering. They now look like a very solid company which is positioned to play a major role in the booming motion sensing business over the next couple of years.

InvenSense is the opposite of ST in nearly every respect. Contrary to ST, InvenSense is fabless and thus depends on external foundries to produce its sensors. Since optimization of production costs is one of its biggest key success factors, InvenSense will need to work hard with TSMC and other foundry partners in order to really get its costs lower, and produce on 8 inch wafer lines at a reasonable yield. The reverse costing study of InvenSense's 3-axis gyro performed by System Plus Consulting shows a component manufacturing cost ranging from $1.10 to $0.81 according to yield variations. A similar analysis of ST's 3-axis gyro shows a production cost in the same range.

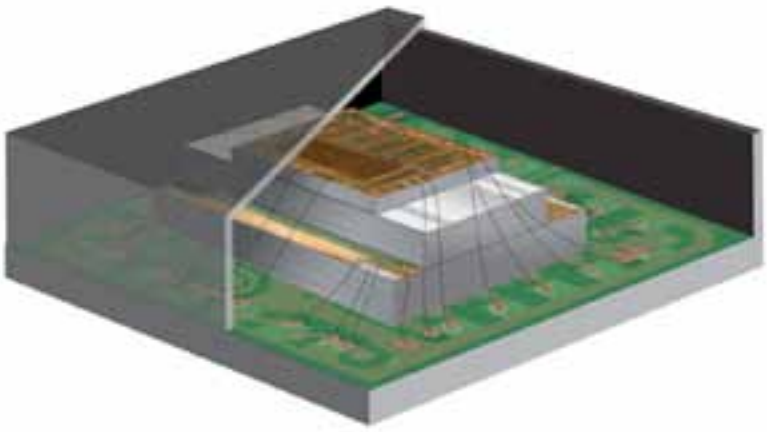
In addition to InvenSense and ST Micro, many other companies are eyeing the gyroscope market, and competition is intensifying as the market becomes increasingly attractive. Established players are pushing hard to introduce 3-axis gyroscopes to more markets, while large accelerometer suppliers such as Kionix are entering the market too. Panasonic recently launched its own 3-axis gyroscope, which it is actively promoting to the gaming and mobile phone industries. Competition will further intensify now that Murata (VTI acquisition), Maxim (SensorDynamics acquisition) and Fairchild (Jyve acquisition – see previous article) have also made the strategic decision to get into the game. In total, Yole Development has screened more than 50 companies involved in motion sensors for mobile applications.

Is the motion sensing business really this hot?

According to Yole's forecasts, the market for MEMS gyroscopes is expected to be one of the most dynamic in the coming years for all motion sensing devices used in consumer and mobile applications. Indeed, an annual growth of 19.8% is expected, versus 9.9% for MEMS accelerometers and 10.9% for magnetometers – in fact, the gyroscope market is expected to grow from $516M in 2011 to $1.27B in 2016! Given that mobile phones, tablets and gaming applications alone will represent more than two-thirds of this market, it's no surprise that competition is so tough!

The MEMS accelerometer market will also offer some very nice business opportunities in the coming years, with a projected growth from $622M in 2011 to $998M in 2016. This market will be especially strategic because many applications are expected to rely on a 3-axis accelerometer + 3-axis gyroscope in a single package: early reports are that the market for such motion sensor combos will reach $659M in 2016, a gigantic leap from a miniscule $5M in 2011. A strong synergy between accelerometer and gyroscope players has developed, and it would not be surprising to see gyroscope companies buy accelerometer technologies if they don't choose to develop their own internally like InvenSense did.

Magnetometers are also positively affected by such market traction. From 2011 to 2016, it is expected that this market will grow from $386M to $646M, and will find growth opportunities outside of the mobile phone area. Already, new functions using low-cost motion sensors are being realized: one example is the successful integration of a compass in Sony's DSC-HX5V, released in 2010. In this product, a GPS receiver associated with a compass is used for advanced geo-tagging, with proprietary Sony software -- the exact position and heading can then be indicated on a map. Social networks are the main driver for this type of function – for example, it lets your Facebook contacts know where you've been.



InvenSense MPU 9150 scratch (Courtesy of InvenSense)

Who'll be the next InvenSense?

InvenSense's success story is clearly unique, and many people are now wondering: "Who's next?" InvenSense has raised the bar for the next generation of early-stage MEMS device companies, and due to market attraction and fierce competition we are now seeing a race to achieve lower-cost versions of inertial sensors. Market leaders are working hard on reducing production costs, and new companies like Baolab in Spain are emerging, with a focus on developing ultra-low cost devices for current markets.

To the question of what the next technology revolution in motion sensing will be, we see a strong demand for more precise and longer-term navigation solutions (tens of minutes with an accuracy of a few meters) in markets such as indoor pedestrian navigation. Such solutions will require the sensor fusion of data from A-GPS (if available), Wi-Fi and of course motion sensors or a combination of motion sensors. However, the required precision is far from what can currently be achieved today – the one exception being the expensive MEMS sensors used in the aerospace and defense industries. Perhaps the next InvenSense will come from one of a handful of promising start-up projects, such as Qualtre, MCube and Jyve -- each of these ventures has developed revolutionary motion sensing technologies by using a different sensing principle or a different way of combining motion sensors, while residing within a low cost production infrastructure. Also, companies like Movea have started to impact the traditional supply chain model by bringing a novel expertise in software and sensor fusion.

The MEMS market is still very fragmented, and motion sensors are just one part of many. We've seen an increase in M&A activity, driven by some large companies that are interested in broadening their portfolio of products and integrating new functions in their existing devices. Recent examples of this are Qualcomm's acquisition of Pixtronix (MEMS displays) and Sony's acquisition of Micronics (point of care diagnostics), both of which occurred in 2011.

Indeed, Yole Development sees many other potential high-volume device businesses operating outside of the "hot" inertial area: in oscillators (Sand 9, IDT), RF MEMS switches (Wispry, DelfMEMS), microdisplays (Qualcomm MEMS), and MEMS speakers (Audiopixels).

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Tables below are depicting October, November and December latest M&A & new investments in MEMS

Several very important financial transactions in the MEMS & Microfluidics industries: InvenSense IPO and acquisition of QuantaLife, VTI & Pixtronix.

M&A

Company	Type of product	Type of investment	Value of the transaction (USD)	Acquirer	Yole Développement comment
Oct. 2011					
QuantaLife (US)	Digital PCR technology	Acquisition	$162M	Bio-Rad Laboratories	QuantaLife has developed a disruptive PCR technology with a very high sensitivity compared to traditional techniques. Thousands of micro drops can be produced in a few seconds, which can be used to generate ADN or ARN. The corresponding instrumentation was planned to be commercialized in 2011. With this acquisition, BioRad strengthens its position in the PCR market
VTI (FI)	Low g accelerometers, inertial combos, pressure sensors, oscillators & resonators	Acquisition	$265M	Murata	Few months after SensorDynamics acquisition, this is another very large M&A that happens in the MEMS inertial industry. We see several motivations that explain this move from Murata: - Murata is traditionally involved in consumer gyroscopes with piezoceramic technology (tuning forks) but its market shares are decreasing since 2 years. Indeed the silicon technology is now preferred for many applications because of higher integration (3 axis), thin sensors, and now low pricing. Murata get access to a disruptive Silicon technology with VTI: both 3-axis gyros and 3-axis accelerometers, with business expected to start in high end consumer applications such as remote controls - Murata has already a silicon MEMS gyroscope that is sold to the automotive market. This is for navigation. Murata competes with Epson Toyocom and Panasonic in this market, which is declining. With VTI, Murata get access to a strong position in the inertial automotive market. Indeed VTI is leading the low g accelerometer market and has a large success on ESC combo sensor. A significant growth of this business is expected for VTI in 2011. Murata thus gets a larger footprint in the automotive market, in applications which are dynamic and with a competitive technology - Another strong driver for this acquisition is the willingness to remain a key player in the timing market. Murata is traditionally a strong player in ceramic resonators, a segment which is declining. Murata decided to invest in newer technologies. In May Murata announced a cooperation agreement with Tokyo Denpa on quartz resonators. VTI is developing silicon MEMS timing technology which is expected to be disruptive in many market segments: resonators for MCUs, oscillators, and potentially TCXO-grade products within a few years. First products are expected to be released end 2011
Nov. 2011					
InterSense (US)	MEMS-based inertial measurement units	Acquisition	NA	Gentex	With close to 50 employees, InterSense is a specialist of ultra-miniature, low-power motion sensors and flexible software. InterSense recently launched the world smallest high-performance IMU: 6DOF on a chip (in a 24.0 x 13.5 x 9.1mm3 package), based on MEMS technology, which achieve 10°/h bias instability. Gentex is the world's largest supplier of automotive auto-dimming mirror, by far, but also has activities in the aircraft and protection industry. We expect that IntereSense motion tracking technology will be deployed in diverse commercial and military high-performance tracking, navigation, visualization and stabilization applications in the future
Dec. 2011					
Pixtronix (US)	MEMS displays	Acquisition	NA (sources indicate $175M to $200M)	Qualcomm	Pixtronix and Qualcomm are the leading MEMS display companies. Founded in 2005, Pixtronix has raised $59M in total. The technology is focused on MEMS shutters, in order to achieve very low power displays. TFT lines can be used and only 3 mask steps are necessary, resulting in a cheap manufacturing cost. The hype around low-power MEMS display is currently high: Pixtronix recently announced joint development and licensing to Hitachi display and to CMI, while Qualcomm announced in November the high-volume commercialization of its color Mirasol display in Korea (Kyobo e-reader). Purchase of Pixtronix has not been announced officially, thus it is difficult to comment on the motivations behind this transaction. According to some sources, price of the acquisition would be significant: between $175 million and $200 million

New investments (VC rounds, IPOs)

Company	Type of product	Type of investment	Level of new investment (USD)	Investors	Yole Développement Comment
Oct. 2011					
Calient Technologies (US)	Photonic switching products based on internal MEMS mirror technology	13rd round	$19.4M	Cayuga Venture Fund, Intuitive Venture Partners, TeleSoft Partners	The first part of this transaction was announced in the last issue of MEMS trends as a $4.38M transaction was already closed. The demand for high-speed high bandwidth switching systems is currently soaring, driven by data centers and cloud computing networks
Sand 9 (US)	Silicon MEMS timing devices	4th round	$1.3M	NA	Sand 9 is seeking to raise $6.2M in total. Production of MEMS oscillators for RF transceivers and A-GPS is expected to start in 2012. Silicon MEMS timing had continuous market adoption in 2011: SiTime and Discera 2011 revenue was about 2 times more than in 2010
Nov. 2011					
Microvision (US)	Picoprojector based on scaning MEMS mirror	Public offering	$9.8M	NA	This financial operation bring cash to Microvision which had a disapoiting 2011 year as the picoprojector sales are not yet booming and as the company is still making large loss. TI DLP and LCOS solutions still dominate the picoprojector market by far
InvenSense (US)	MEMS gyroscopes, motion sensor combos	IPO	$75M	NA	For many reasons, InvenSense IPO is the most exciting event that happened in the MEMS industry since years! See analysis article

FINANCIAL BUZZ

Microfluidics, a Dynamic Market: Mergers and Acquisitions analysis

Even though Microfluidics has existed since 1980, industrial interest in it only emerged on a large scale in the 90's. Since then, and especially over the last ten years, large diagnostics companies have kept an eye on this promising market, waiting for the right time to enter. For a while though nothing happened, as each company waited for the other to make the first move.

BD Diagnostics was the first to act with the acquisition in 2009 of Handylab, a Michigan-based company that develops and manufactures molecular diagnostic assays and automation platforms. Since then, others players have followed. In 2010, Life Technologies acquired Ion Torrent. In 2011, a large wave of acquisitions occurred: Agilent acquired Biocius and Lab901, Danaher acquired Beckman Coulter, Perkin Elmer acquired Caliper Life Science, Sony acquired Micronics and Bio-Rad acquired QuantaLife.

Amidst this slew of acquisitions, it's important to understand the motives behind them: intellectual properties (Perkin Elmer and Caliper Life Science), desire to enter the diagnostic systems market (Sony and Micronics) and acquisition of a promising technology (Life Technologies and Ion Torrent).

To follow is a table that illustrates Yole Développement's analysis of these activities.

The entry of these major diagnostics companies into the Microfluidic market will provide the basis for strong growth in the coming years. Indeed, these big players have the distribution processes and marketing capabilities necessary to pull and develop the Microfluidic market quickly. Yole Développement estimates that the Microfluidic devices market will grow as a whole with a CAGR of 22%, and will reach $4 billion in 2016.

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Benjamin Roussel, Market & Technology Analyst, Yole Développement

Company Acquired	Purchaser	Date	Turnover	Value of the transaction	Yole Développement Comment
HandyLab	BD Diagnostics	2009	$10M	$275M	First big acquisition in the Microfluidic area.
Ion Torrent	Life Technologies	2010	0	$375M	High value, high risk acquisition because the technology is still under development. Competition already present in this market, which will remain limited to research application for some years
AES Laboratoire	bioMérieux	2011	$107M (2010)	$259M	bioMérieux´s and AES Laboratoire´s product lines are highly complementary. The acquisition is logical because bioMerieux is a world leader in agro food testing. (conversion into dollars was done on 05/20/2011)
BIOCIUS	Agilent	2011	NA	NA	Agilent expands its portfolio of molecular biology solutions.
Lab901	Agilent	2011	NA	NA	A new Microfluidic technology company acquisition for Agilent.
Beckman Coulter	Danaher	2011	$3.7B	$6.8B	Danaher has made many acquisitions, and has recently focused on companies involved in the Life Sciences & Diagnostics segment (AB Sciex, Radiometer).
Caliper Life Sciences	PerkinElmer	2011	$124M (2010)	$600M	The acquisition cost seems quite high (about 5 times higher than Caliper 2010 revenue). But although Caliper's revenue has decreased over the past 3 years, the gross profit has increased thanks to a focus on the most valuable product areas, and the company is now supposed to be profitable.This transaction gives Perkin Elmer access to complementary detection and imaging technologies. The major benefit for Perkin Elmer is the acquisition of a very broad patent portfolio in Microfluidics. Among other products, Perkin Elmer gets access to the well-known "LabChip", a reference electrophoresis chip.
Micronics	Sony	2011	$20M (2010)	NA	This was the second major Microfluidic acquisition in September, coming a few weeks after the Caliper acquisition. Micronics is a technology provider in point-of-care diagnostics and has a broad IP portfolio. This transaction is in line with Sony's strategy to become a leading player in the medical and healthcare fields.
QuantaLife	Bio-Rad Laboratories	2011	0	$162M	QuantaLife has developed a disruptive digital PCR technology with a very high sensitivity compared to traditional techniques. Thousands of micro drops can be produced in a few seconds, which can be used to generate ADN or ARN. The corresponding instrumentation was set for commercialization in 2011.With this acquisition, BioRad strengthens its position in the PCR market.

MEMS IN IN THE WORLD

Medical devices and microfluidics in China

The Chinese medical system is comprised mostly of public hospitals. Analysis, diagnostics and purchase of drugs are handled at these public hospitals, since small, personalized clinics are still uncommon.

Wenbin Ding,
Market & Technology Analyst,
Yole Développement

"And for the past five years, start-up biotechnology companies have started to appear in the Chinese market -- there are now more than 50 biochip companies in China" says Wenbin Ding, Yole Développement.

Some hospitals practice the western medical treatment system, while others practice Traditional Chinese medicine (TCM). Increasingly, a large percentage of hospitals have begun practicing a mixture of western and TCM. Like many other countries, before any new drug, technology or instrument enters a public hospital in China, it has to be approved – in China's case, approval is granted by the SFDA (State Food and Drug Administration).

For various reasons, Chinese scientists were slow to begin development of high-tech biologic devices. When the Chinese Academy of Sciences, the nation's leading scientific research center, took notice of this global trend in the late 90's, it started to become more engaged in the field. Since then, several R&D institutes have joined the Academy of Sciences in order to accelerate development. Despite the government's and the R&D centers' efforts, high-tech products such as biochips and microfluidic devices are still at an early stage of production, and quality still needs improvement – hence the reason why most biochips and microfluidic devices used in hospitals are mainly imported from Europe and the USA. The downside to this is that, though here is a huge need for such products in China, imported devices are usually too expensive for Chinese patients to afford. To counter this problem, the government has increased its support of local R&D institutes and companies.

DICP (Dalian Institute of Chemical Physics), SIMIT (Shanghai Institute of Microsystem and Information Technology) and IMAS (Institute of MicroAnalytical Systems) are the most important Chinese R&D institutes in biochips and microfluidics for drug delivery and diagnosis, and have achieved some success. And for the past five years, start-up biotechnology companies have started to appear in the Chinese market -- there are now more than 50 biochip companies in China. However, production is still limited because the technology is not yet mature, and so most of these companies supply only the Chinese market. Some have their own products, but most still import European or American products, and provide analysis services. Products from large international companies such as Affymetrix, Phadia and Biomérieux are widely used in China.

The local Chinese biochip market is complicated since some of the companies are not listed, but key players are: CapitalBio, Shanghai BioChip, Health-Digit, United Gene, Yulong, and BaiO. For Microfluidic analysis services, there are two big Chinese companies: Shanghai BioChip and CapitalBio. Other small companies have a few market shares as well. Shanghai BioChip and CapitalBio are working very hard on the development of their own products, and CapitalBio has started to export its products to Europe and the USA.

Another medical device with high demand in China is the pacemaker. The development of pacemakers in China is still immature and there are barely any brands on the market, even locally. About 1.14 million Chinese people died from heart attacks in 2008, and since only 10,000 people get pacemakers or similar devices implanted every year, the need is huge. Most pacemakers used in China are imported from Europe. These represent about 80.46% of the market, which equates to around $55.6 million. The biggest Chinese company starting to produce pacemakers is QinMing Medical. Other Chinese labs and universities are accelerating development of their own pacemakers as well, but it will take some time.

Pacemakers from Qinming Medical (Courtesy of Qinming Medical)

With regard to medium or low-end medical devices such as electronic blood pressure monitors, basic diagnostic equipment and electronic wheelchairs, the local industry is quite mature. The leaders in these fields are Golden Elephant of Xinxiang and Yuyue Medical Equipment.

In conclusion, the Chinese high-end medical device and microfluidic product industries are in the early stages of development, and so the Chinese market still depends a lot on imported products from Europe and the USA. However, this huge market offers a vast amount of opportunities, and though Chinese R&D institutes and companies have a long way to go before they catch up, they could be promising in 3-5 years' time.

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Biomedical MEMS move from sensing to treatment

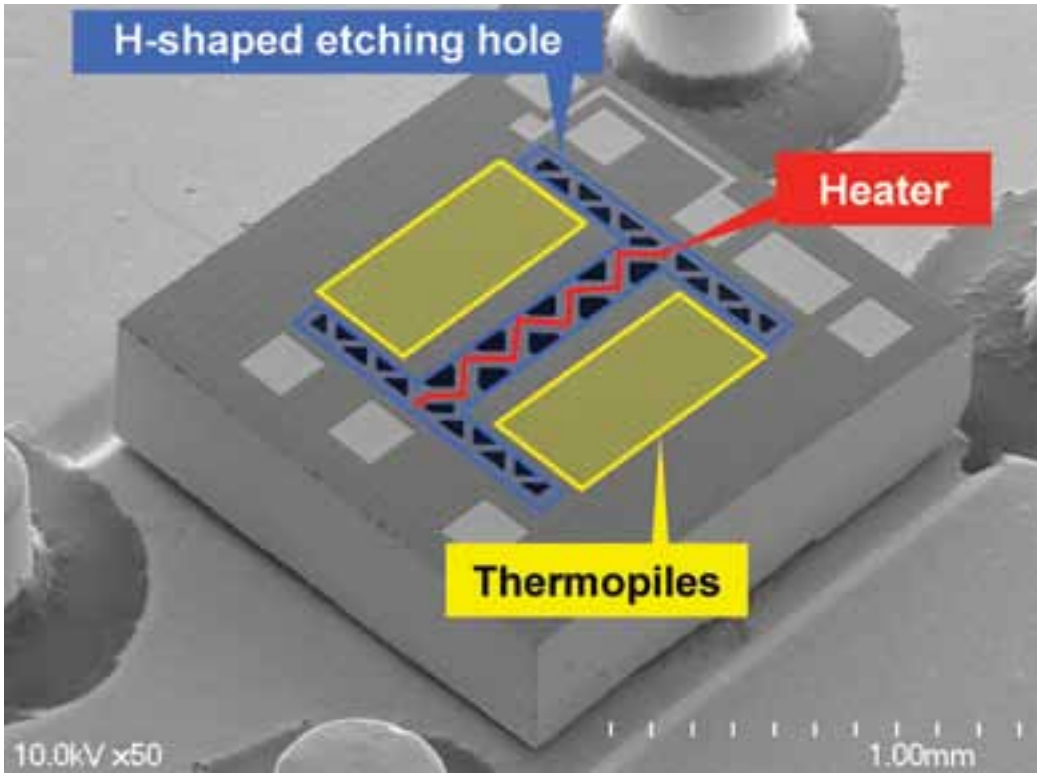
Longer biomedical development times mean it has taken a little longer for the recent advances in MEMS technology to show up in biomedical devices, but products using sensor feedback to control interventions inside the body are starting come to market.

MEMS have long been used in biomedical sensing applications around the patient, for monitoring things like blood pressure or activity levels in people or flow rates in bedside equipment. But now products based on the major progress in MEMS technology of the last few years are starting to make it through the long biomedical development process to the market, applying that sensing information to intervene inside the body, in smarter implants and better minimally invasive procedures.

Inertial sensors help control chronic pain

Medtronic's neurostimulator implant to treat chronic pain, approved for use in the US in November, uses a MEMS accelerometer to help maintain stable pain control as the patient moves around. Development of the product started back when consumer motion sensors in the Wii and the iPhone first attracted attention to the progress in accelerometers, and Medtronic researchers saw an opportunity to put these devices to use. But the sensors then used as much energy as the stimulation therapy did, so researchers adapted a robust commercial consumer 3-axis accelerometer to the more demanding medical application, customizing the ASIC and the algorithms to drastically reduce power usage and to offset drift to assure stability for the extended lifetime of the device. By 2007 they'd designed the interface signal chain and algorithms with techniques like correlated double sampling to cut energy consumption to 100x what was available at the time, down to 100nanoamps per axis. Also challenging was finding the balance of robustness vs resolution vs energy use. The device has to survive in the unique biologic environment, which has relatively stable temperatures and limited sensitivity range, but it also had to survive things like high- g drops on to stainless steel trays, in case the surgeon dropped it before implantation, and possible extreme temperatures during transport and storage. "There's the hardware development cycle, and then there's the clinical development cycle, and then you have to loop back to complete the engineering work, and it's all serial," notes Tim Denison, director of neuroengineering and technical fellow. "Medical devices just take a long time."

"There's the hardware development cycle, and then there's the clinical development cycle, and then you have to loop back to complete the engineering work, and it's all serial" notes Tim Denison, Medtronic.



Omron Electronic Components' thermopile flow sensor (Courtesy of Omron)

The implant treats pain from nerve damage in the back and legs by inhibiting and modifying pain signals from selected nerve fibers in the spinal cord by stimulation with an electrical field. Conveniently the leads from the implanted stimulator can stimulate the target nerve fibers by this field from outside the blood/brain barrier surrounding the spinal cord. Inconveniently the target fibers move in and out of the stimulation field as the patient bends and moves around, explains Mark Lent, Senior Director of Technology, Medtronic. Earlier generation implants had to be continually adjusted by the patient. Now the MEMS sensor enables automatic adjustments to the pain-blocking field to keep the target fibers continually activated, once the patient trains and calibrates the device.

Neuromodulation and chronic pain are big business. Medtronic saw $1.6 billion in revenues from neuromodulation in fiscal 2011, including both neurostimulation and implantable drug delivery systems for specific sites to treat a variety of disorders. The company cites studies that report some 116 million adults in the US suffer chronic pain, with low back pain from nerve damage among the most common and hardest to manage types. Some 200,000 people around the world have used Medtronic neurostimulation for chronic pain to date, and some 80%-90% of the patients in the recent clinical trial of the MEMS position sensing version reported less pain, more convenience or clinical benefit.

The motion sensor also tracks and records patient activity in onboard memory, giving the patient and the doctor good data to track the effects of activity on pain, to help identify issues such as disrupted sleep or too much or too little rehabilitation exercise that impact pain. "Our hope is that quantifiable information will lead to better treatment," says Denison.

This first instance of building an artificial reflexive response system into the body does take advantage of the unique spinal case, where stimulation works on nerve fibers from outside the blood brain barrier. "There's a reason the RestoreSensor is our first product," jokes Denison. "Most MEMS is integrated with hardware, but ours is integrated with the body, so integration is much harder."

TheFreedom® portable driver is CE approved for use in Europe & undergoing an FDA- approved Investigational Device Exemption (IDE) clinical study in the U.S. Caution: The Freedom driver is an investigational device, limited by United States law to investigational use. (Courtesy of Syncardia)

The next challenge for MEMS as a field, he suggests, is how to make more intimate contact with the nervous system, developing micromachined electrodes with long term biocompatibility at the cellular level.

"MEMS is also helping bring down the size of some medical support systems to small enough to be portable" notes Donna Sandfox, Omron.

Smaller sensors enable portable support for artificial heart

MEMS is also helping bring down the size of some medical support systems to small enough to be portable. SynCardia's implanted artificial heart has been used for some years as a bridge to transplant for patients waiting for a heart transplant, but all the electronics and controls and vacuum pump and high pressure air tanks required a 400 pound external console, keeping the patient tethered to the machine in the hospital. The next generation electronics and pneumatics, now approved in Europe and under clinical trials in the US, use MEMS among other technologies to reduce the external unit to under 14 pounds, so it can be carried around in a backpack or a shoulder bag, allowing patients to return home and be mobile while waiting for a donor.

One of the enablers allowing this more compact unit to power the Total Artificial Heart is a flow sensor from Omron Electronic Components.The thermopile technology, where the gas flowing across a thermopile creates a temperature differential to measure the flow, helps reduce power consumption down to 15mA to help allow battery operation of the unit. Etching the cavity under the thermopile from the top so the opening on top is larger increases the sensitivity of the device, says Donna Sandfox, Omron product manager, new business development. Tweaking the electronics reduced response time down to under 5ms for the artificial heart application. Omronis now starting to integrate the ASIC and the connector with the flow sensor to further reduce size and cost.

Sensors and actuators start to enhance minimally invasive, robotic-assisted surgery

More sensors are also starting to be used in minimally invasive or robotic surgery, especially to give the surgeon the tactile sense or force feedback that's missing when operating through a laparascope or robotic console. Besides its technology for touch screens, haptics supplier Immersion Corp. has also licensed technology and designed custom systems and software for biomedical applications, to translate sensor input into tactile effects with actuators that provide vibration or resistance or a physical stop. "We're expecting there will be a lot of opportunity over the coming years as people see more applications for sensors," says Cheryl Shimek, Immersion director of product marketing, medical.

"We're expecting there will be a lot of opportunity over the coming years as people see more applications for sensors," says Cheryl Shimek, Immersion Corporation.

Mako Surgical is one user, adding tactile feedback to its robotic-assisted surgery system for more accurate knee surgery. A map based on a CT scan of the knee is used to determine exactly how much bone to cut away, and that line is programmed into the robotic arm. When the surgeon then uses the robotic arm to assist the surgery, it gives push back at the line to prevent going too far. The technology is also licensed to SOFAR for its new ALF-X robotic surgery system, developed in conjunction with the European Commission Joint Research Center. A SOFAR brochure out this fall advertises that the yet-to-be-released system will provide natural perception through haptic feedback of the consistency of soft tissues and of the forces exerted by the surgical instruments. Shimek notes that haptics added to current surgery tools that doctors are already used to using is typically limited to providing feedback for new information, often as a physical stop or vibration as an alarm or alert mechanism.

Minimally invasive or robotic surgery is also creating a market for MEMS devices that control the flow of gas through the laparoscope for argon beam cauterization, to seal the blood vessels to stop bleeding while cutting, or to remove irregular cells, in robotic or minimally invasive procedures. Omron is working with multiple medical customers on using its flow sensors to control the argon to do these procedures, reports Sandfox, though the flow sensor and controls remain outside of the patient in the robotic support system.

Haptics bring reality to medical simulators

Haptics are already well established in for giving physicians realistic force feedback as they learn to do minimally invasive laproscopy, endoscopy and catheter procedures on virtual reality simulators for the procedures, where the systems haven't had to go through the longer approval process required of clinical equipment. CAE HealthCare in Canada acquired Immersion's simulator business in early 2010, one of a round of acquisitions related to its $275 million investment in building up its medical simulation business. The company uses the haptics technology to give the realistic resistance of inserting a catheter in a person, or that mimics the feel of the endoscope bumping into the esophagus or intestinal wall, while the user views the procedure on a screen that's like looking through the endoscope.

Paula Doe for Yole Développement

Cheryl Shimek
Director, Product Management, Medical for Immersion Corporation
Cheryl Shimek is responsible for development of haptic user interface licensing partnerships in the medical marketplace for Immersion Corporation. Prior to joining the company in 2009, Shimek served in product management & marketing leadership positions at several medical device companies. She also spent over 10 years as a cardiac critical care nurse. In addition to her healthcare degree, Ms. Shimek has an MBA from Simmons School of Management.

Tim Denison, Ph.D.
Director of Neuroengineering and Medtronic Technical Fellow
He received his Ph.D. in electrical engineering from MIT in 2000.

Mark Lent
Senior Director of Technology for Medtronic's Neuromodulation business
Mark has a Master of Science in Management of Technology and a Bachelor of Science in Mechanical Engineering with high distinction from the University of Minnesota.

Donna Sandfox
Product Manage for Sensors and MEMS Products for Omron Electronic Components LLC.
Her primary area of expertise is in MEMS Mass Flow Sensors. She also supports Omron's pressure, thermal IR, tilt/vibration and optical (photomicrosensors) sensors, as well as their RF MEMS Switch products. Donna received her bachelor's degree in mechanical engineering from Southern Illinois University and an MBA from Roosevelt University.

ANALYST CORNER

Microfluidics sector poised for 23% growth

Frédéric Breussin, Business Unit Manager Microfluidics & Medical Technologies, Yole Développement

Heavy recent investment by big players and significant new technologies now poised for introduction are accelerating the growth of the microfluidics market, pushing it towards $4 billion by 2016.

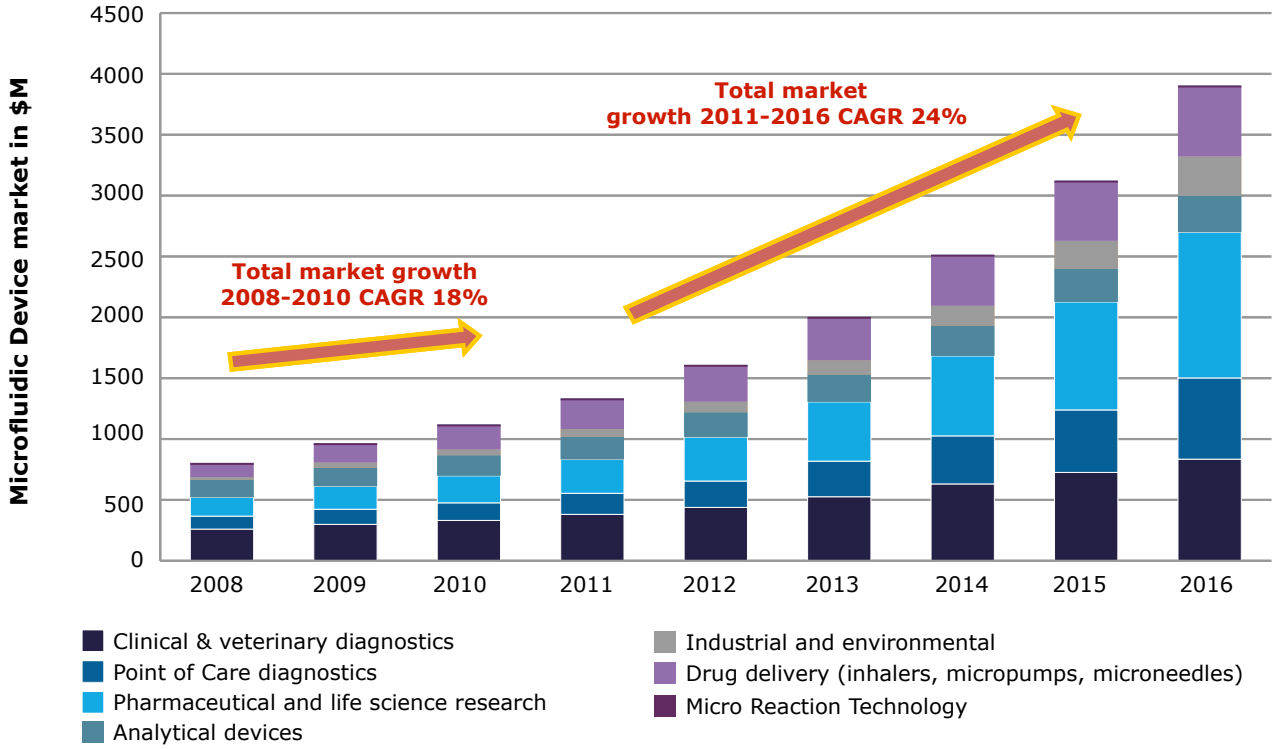
We estimate sales of microfluidic devices were up a healthy 19% in 2011, reaching roughly $1.3 billion, outpacing the 18% growth the sector saw from 2008 to 2010. We expect growth to pick up further over the next few years, with sales of fab-level microfluidics devices (not including chemistry) to average 23% annual compound growth through 2016, pushing the sector to almost $4 billion.

The billions of dollars of investment pouring into the sector in recent years are starting to have an impact. Big diagnostics companies and other investors have put more money into the microfluidics sector in the last two years than over the last ten. Since BD Diagnostics acquired HandyLab in 2009, big players have invested more than $8.5 billion in acquisitions involving Microfuidics. In this conservative sector new technologies typically come from startups who take the risk of innovation, then are acquired by larger companies who can supply the marketing muscle and distribution network to push the product out into the fragmented global market. Over the last three years we've also identified 200 more players in the market, both startups and established companies in other areas getting into the field.

Some major manufacturers from other large volume polymer industrial markets are looking at turning their injection molding production skills to the microfluidics market. The small microfluidics volumes to date have made it difficult to get full industrial- volume controlled- process quality production –and such efficiencies are needed to spread the mold costs for injection molding over sufficient units to bring costs for disposable polymer microfluidics cartridges down to the necessary levels of $1-$2. But new players like Sony with its video disk experience and Konica with its microlens production skills will bring more sophisticated polymer volume manufacturing technology to the microfluidics sector.

Microfluidic device market - Value and forecast

(Emerging Markets for Microfluidic Applications report, Yole Développement, 2011)



The microfluidic device market will reach $4 Billion in 2016

Big muscle behind new technologies

New lower cost technologies for more useful point-of-care diagnostics are also about to hit the market. Growth in that potentially large market has been slower than expected, as suppliers have struggled to find compelling enough applications at low enough costs. But several elegant solutions for low cost tests for conditions where fast response really matters are poised for commercial introduction. We look for major players like Philips, BioCartis and Samsung to introduce new platforms for low cost polymer microfluidic diagnostic tests for cardiac states, bacterial infections and blood gases this year and next. Samsung Electronics will likely soon get international approvals for the bench- top automated blood analyzer it's now selling to small clinics and hospitals in Korea. The system tests for 19 clinical analytes, including cholesterol, glucose, and indicators of heart, liver and kidney disease, all in about 12 minutes, thanks to a clever cassette design. The approach uses different spinning profiles of centrifugal force to move and mix the fluids for different steps, and laser heating to melt seals on various pre-loaded reagent wells as needed. Royal Philips Electronics and bioMérieux have integrated bioMérieux's assay technology for heart attack markers on to Philips' rapid diagnostics testing platform and are now engineering a commercial disposable cartridge and setting up manufacturing for product launch in 2013, aiming to match lab test accuracy with faster speed and lower cost.

Some of the technology acquisitions are also starting to show the results from the wider reach of their new big-company parents. BD Diagnostics aims to make the automated bench-top molecular test station technology it acquired with startup HandyLab into the laboratory equivalent of the smart phone, partnering with other infectious disease assay suppliers to port more tests to the platform. Beyond the current screening tests for MRSA infections and C.difficile diarrhea in hospital patients and B streptococcus in pregnant women, it's working with Diagenode in Belgium to develop molecular diagnostic assays for respiratory and gastrointestional infections and meningitis, Biodiversity in Italy to port its molecular diagnostics for infections in immunocompromised and transplant patients, and Lab21 in the United Kingdom to add its Aspergillus fungus test to the automated test platform. Similarly, testing giant bioMérieux is porting assays for immunocompromised patients from its acquisition Argene to the automated test cartridges its developing with its part-owned partner Biocartis.

Strong growth for environmental testing and biomedical research

Such biologic diagnostic and medical screening tests, and environmental and industrial uses -- worth some $910 million overall in 2010 -- comprise the majority of the microfluidics market. The major applications are clinical and veterinary laboratory tests, to identify bacterial strains or to track response to cancer treatments. Typically these systems save time and money in the lab by using polymer microfluidics with relatively simple structures to automate testing, to reduce costs and speed turnaround time. Tests range across chemical detection for blood analysis; immunoassays for identifying bacteria and viruses; molecular detection for identifying and quantifying pathogens; and cytometry for blood counts and detection and analysis of cells.

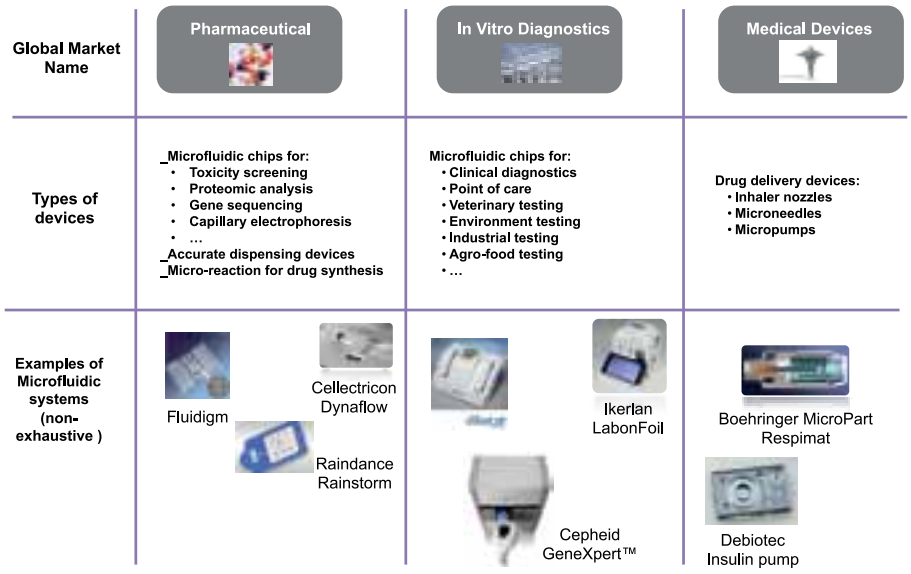
Industrial and environmental testing applications will be the hot growth sector, with 38% CAGR through 2016, driven by the rollout of technology now available that can meet the increasing regulatory requirements and consumer demand for assuring food and water quality, with test for bacteria like e-coli as well as pesticides and other contaminants. Though sending the sample to the lab and inspecting what grows in the petri dish under a microscope a week later remains the standard reference for accuracy, companies are increasingly also using the faster microfluidics tests in house for more immediate feedback, and for ongoing monitoring and optimizing of their control and treatment processes.

Bringing these diagnostic and screening tests out of the lab and directly to the point of care, and expecting analysis in minutes instead of hours has proved rather more demanding, as the risk-adverse medical world still puts more trust in the accuracy of the traditional lab culture, and there are not so many applications where the faster results seem worth the still significantly higher cost—or worth revamping the whole established

"Big diagnostics companies and other investors have put more money into the microfluidics sector in the last two years than over the last ten"
says Frédéric Breussin, Yole Développement.

Example of microfluidic devices by application

(Emerging Markets for Microfluidic Applications report, Yole Développement, 2011)



lab test system with its entrenched interests. But point of care diagnostics now appear to be poised for growth. We project 31% CAGR through 2011-2016. These diagnostics are starting to make inroads in emergency rooms, particularly for diagnosing cardiac events and identifying the bacteria causing severe infections, where saving time saves lives and cost is not an issue. Hospitals are also finding cases, such as kidney dialysis, where avoiding sending the sample to the lab and back streamlines operations enough to save cost, while allowing immediate adjustment of treatment. But the multiplicity of human diseases still means relatively small markets for most types of tests.

Demand for microfluidics devices for research in pharmaceuticals and life sciences is also poised for strong 34% compound average annual growth, to pass the $1 billion mark by 2016, as research moves to more complex biological analysis on more complex devices. Traditionally the pharmaceutical industry has used microfluidics for accurate dispensing of chemicals into well plates for high throughput robotic processing to screen many reactions at once. But it's getting harder to develop major new medications that way. Instead the next generation of new drugs will increasingly require not just more automated screening of chemicals, but biologic testing to understand the underlying processes and the genomes and proteins involved, and the body response on the cellular level, to develop new molecules. That requires genomic and proteomic analyses to quickly screen for different populations or for effective responses. And that needs more complex high density chips with thousands of reaction chambers and high precision structures that have to be etched in glass or silicon, not on polymer. Genomics will continue to be the largest segment, but both proteomics and other miniaturized cell-based assays will see somewhat faster growth opportunities, though will remain relatively small in total unit sales.

Demand for microfluidics for drug delivery systems, primarily asthma inhalers and micropumps, will slow a bit to 20% CAGR for the period.

www.yole.fr

Frédéric Breussin is expert in Microfluidics for diagnostics and life sciences. He has supported many companies in their innovation and product development strategy in making the bridge between micro systems technologies and their applications in Life sciences, diagnostics and medical device industries. He holds an Engineering diploma from INSA Rouen and a DEA in fluid mechanics from University of Rouen.

EUROPEAN PROJECT

A new report and guideline to optimize smart systems penetration into the diagnostics and food/ beverage markets

With the emergence of molecular biology, POC solutions and an increase in demand for industrial testing, diagnostics is a dynamic field. With their uniqueness to provide an increase in intelligence and autonomous solutions, smart systems technologies are well-positioned to bring breakthrough innovation to the field and reinforce European competitiveness.

The more attractive the opportunity, the greater the challenges and barriers are for innovative solutions to enter the diagnostics field. The high market concentration and tight regulation explain why there has been a low penetration rate of smart systems technology in the field.

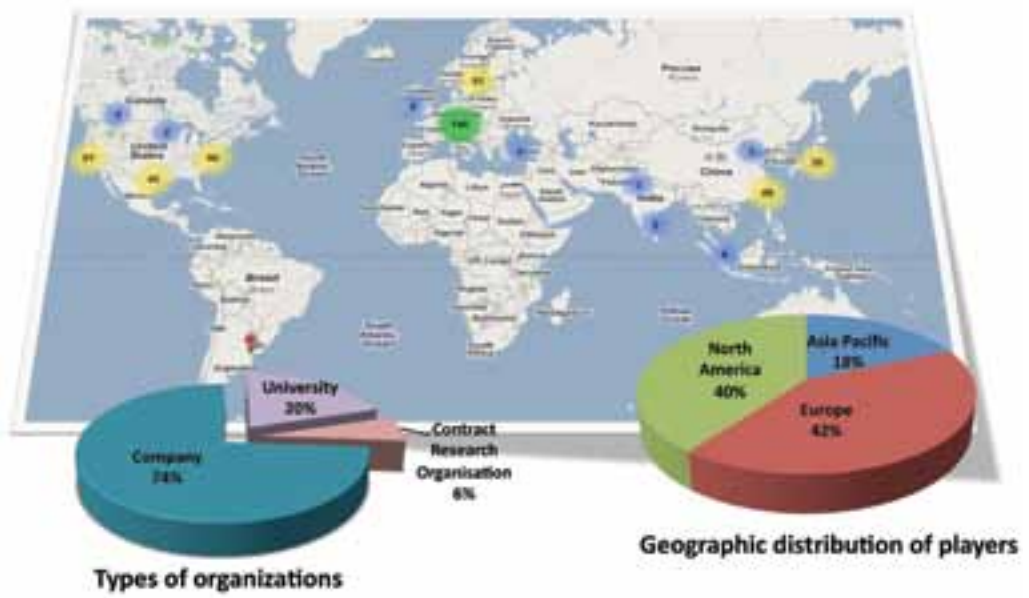
However, over the last three years the situation has evolved. With the acquisition of smart systems-based companies like I-Stat and Biosite by leading diagnostics companies, new products are now entering the market that offer innovative new tests and cutting-edge solutions for better patient diagnoses and management. For example, the "Tear Lab solution" enables the accurate and rapid measurement of biomarkers in tears at the POC, which has never been done before. Also, in the food and water quality control and testing field, Pall Genesystem's Genedisc is growing in popularity and further demonstrates the added-value and market-readiness of microfluidics technologies. This is only the first step -- smart systems are poised to bring widespread innovation to the diagnostic field, with intelligence and autonomous functions that will generate new applications and business.

The European Commission is willing to support Europe's competitiveness in this field, as evidenced by the recent EC FP7 call in which a portion was dedicated to micro and nanotechnologies bio convergence systems. Indeed, as illustrated in Figure 1, Europe benefits from the emergence of many activities in the microfluidics and smart systems fields -- which only adds to an already broad range of competitive European clusters in the Life Sciences field.

On this subject, the European Commission is supporting COWIN, an action dedicated to optimization of smart systems value creation through the better exploitation of research projects results. Through its strong actions, COWIN encourages collaboration between the smart systems community and the players who are active at the applications level -- this is a first step towards bridging the gap between technologies

Geographic distribution of microfluidic players (researchers, suppliers,...)

(Emerging Markets for Microfluidic Applications report, Yole Développement, 2011)



Strong growth, from 420 players identified in 2009 to 620 in 2011.

Géraldine Andrieux-Gustin, COWIN coordinator, Yole Développement

"Smart systems are poised to bring widespread innovation to the diagnostic field, with intelligence and autonomous functions that will generate new applications and business," says Gérandine Andrieux-Gustin, COWIN coordinator.

and market. COWIN also works hand-in-hand with researchers and companies active in the smart systems field to support their diagnostics market penetration by helping them find the right process, partners and resources.

One example of this support is COWIN's forthcoming launch of a new report that presents the main challenges and barriers to bringing miniaturized smart systems to IVD and Food/Beverage markets. This report, created by Yole Développement (which coordinates COWIN's actions), contains added-value information for researchers and companies who want to better understand the diagnostic field's trends and needs. The diagnostic field is very fragmented, and a sound analysis of the right applications to address is required. The report also highlights common beliefs and reinforces the tangible benefit that smart systems offers to different diagnostic markets. Also provided are examples of specifications to better address the food and water quality market, in order to better support smart systems' penetration in this emerging and growing market. Regulatory constraints are also addressed in the report, and a solution is proposed to consider regulation as a driver and not just a barrier.

The report can be used as a guideline to drive R&D projects, and also for building a concrete business plan to ensure that technologies and solutions developed will fit a real market need.

The report is available on COWIN's website: www.cowin4u.eu. If you wish to optimize the commercial exploitation of your research project results in the field of smart systems, do not hesitate to COme to WIN!!!

Register at www.cowin4u.eu and gain access to:

- The report and the key information it contains.
- COWIN customized matchmaking events where you'll have the opportunity to meet key partners that COWIN will identify for you.
- A host of other resources to help drive your R&D projects efficiently.

www.cowin4u.eu

About COWIN

COWIN is a support action launched in 2010 under the 7th Framework Program of the European Commission in order to strengthen European competitiveness in Miniaturised Smart Systems. COWIN is dedicated to the commercial exploitation of advanced technologies developed within the framework of European collaborative research projects.

COMPANY INSIGHT

Oxford Nanopore aims at microfluidics detection platform

Look for the DNA sequencing market to next be disrupted by developments in nanopore technologies that collect direct electrical signals from the real time sequencing of single molecules—possibly on a hardware platform that handles a variety of chemistries.

Dr Gordon Sanghera, Chief Executive Officer, Nanopore Technologies

Though founded to capitalize on a unique biologic technology for creating nanopores, Oxford Nanopore Technologies' most significant contribution may be its platform approach for modular, scalable, nanopore analysis hardware that can be used with a variety of different chemistries.

Feeding a DNA strand through a small- enough hole in a thin-enough membrane generates distinctive electrical signals from each of the four different bases as they pass through, gaining Pacific Biosciences' advantage of reading long strands directly without need for any lengthy amplification process first, while also gaining Ion Torrent's advantage of reading electrical signals directly without need for optical markers. Initial work has used various biologic membranes and pores, but Oxford Nanopore is also working on solid state films and micromanufactured holes.

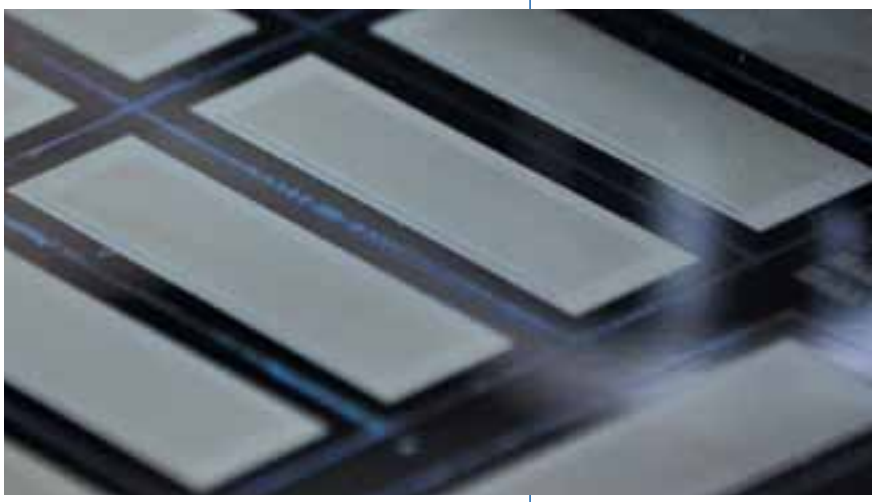
Building a platform for multiple chemistries

But what's speeding up the research progress and allowing collaboration with researchers at multiple leading university programs is the modular microfluidics and sensing hardware, which works with different chemistries and at different scales. The instruments have onboard computing power for real time analysis, and can be used alone or in a clustered series for faster parallel processing or larger analyses. "We're reached the stage where the bottleneck is no longer getting the DNA sequence, but the entire workflow: sample to sequence to the answer to the biological question," says Gordon Sanghera, CEO of Oxford Nanopore. "We're focusing on a simpler way to get to that answer."

The system uses a disposable microfluidic cartridge containing two key chips. A silicon microarray sensor chip contains wells tens of microns in diameter. Each well is topped with a polymer membrane into which nanopores are introduced, and then the sample. Each well is a separate channel with its own electrode to sense individual nanopore experiments as they happen. The sensor chip is accompanied by a high speed ASIC that Oxford Nanopore developed with a partner. Chambers of consumables are contained within the microfluidics cartridge, and all the components are flowed in to assemble the desired system: a polymer to form the membrane, a solution of pore-making proteins distributed about one to a well, an enzyme to control the passage of a DNA strand through the pore, and then the DNA sample or other reagents. The system is designed to determine which wells are populated with a single nanopore, and records the pico-amp signals from the distinctive disruption in the ionic current flow as the DNA passes through the pore. The system samples at tens of kHz per pore for analysis of many bases per second. By changing the type of nanopore machinery present, and adapting some other elements of the machine such as software and analysis methods, the same platform can be adjusted to analyse other target single molecules from proteins to small molecules.

Oxford readies protein pores in lipid membrane

Oxford Nanopore's approach uses a hollow protein made by bacteria that naturally punctures a ~10nm pore in a lipid membrane. Since spun out of the University of Oxford in 2005 by Professor Hagan Bayley to develop the biologic nanopore technology, the company has raised some $115 million, including regular contributions from sequencing market leader Illumina, which is a minority shareholder. The company is cagey about details of the progress of its instrument, but some expect an update at the forthcoming



Sensor chip (Courtesy of Oxford Nanopore)

Dr Gordon Sanghera,
Chief Executive Officer,
Nanopore Technologies

Gordon Sanghera was co-founder of Oxford Nanopore, together with Hagan Bayley and IP Group. He was appointed CEO in June 2005 having acted as a consultant since February 2005 whilst the Company was established. He brings over 15 years experience in the design, development and global launch of novel point-of-care biosensor devices. At Abbott Laboratories, Dr Sanghera held both UK and US Director level positions, including Research Director and Manufacturing Process Development Director. Before its acquisition by Abbott, Gordon led the R&D of Medisense Inc. where he was instrumental in the launch of several generations of blood glucose biosensor systems for the consumer and medical markets. He has also developed and validated market production processes to meet with the regulatory requirements for USA and Europe. Gordon has a DPhil in biosensor technology and a degree in Chemistry.

AGBT conference. The company is developing two methods of DNA sequencing: exonuclease sequencing (for which it has a commercialisation agreement with Illumina) and strand sequencing (for which the Company has not announced any commercialization partner). For the exonuclease method, an enzyme cleaves off individual bases to send through the nanopore. This assures that each reading is limited to a single base, but does mean some possibility of error from bases going astray. For the strand method, an enzyme controls the passage of a DNA strand through the nanopore. Oxford Nanopore collaborators at the University of California Santa Cruz have reported using a polymerase to push the strand through the pore as it replicates each base. This approach can reportedly rachet the strands through at around 20 milliseconds per base, or about 50 bases per second, apparently a reasonable speed at which to read the changes in the ionic current as each base passes through the pore. Both systems should theoretically allow relatively long reads. The company now has about 110 employees, including some new hires in business development, and is expanding its facilities for commercial production. Though first customers will be R&D labs, the company like other sequencing suppliers ultimately targets the much bigger and more resilient market for clinical diagnostics.

Solid state structures coming next

Ultimately even Oxford Nanopore biologists figure that micromanufactured solid-state membranes and pores will eventually provide better cost and performance than the biologic ones now used, with graphene a particularly promising option. Biologic nanopores can now be designed and fabricated surprisingly efficiently, thanks to sophisticated molecular modeling technology that allows control of impossibly fine details - at an Angstrom level - on the nanopore. The company says it design and produce new structures for the pore-making proteins in as little as two weeks, by infecting the bacteria that excrete the proteins with an appropriate vector of programmed DNA.

But inorganic materials could well be more dependably produced in volume. Oxford Nanopore is working with scientists at Harvard on using graphene, as the single-atom thin material, with its excellent properties of resistance and strength, may enable better signal acquisition at lower cost. Separately, IBM's alternative approach under development uses 2nm holes in a 10nm membrane of titanium nitride layered with silicon, which controls the DNA movement by fast flipping the polarity of the layer. "We anticipate solid state will be cheaper and faster in high volume," says Sanghera. "But there's still a lot of work to do."

www.nanoporetech.com

COMPANY INSIGHT

In increasingly competitive DNA sequencing market, Pacific Biosciences argues its low cost tools meet the need for more detailed information

Adoption of new micromanufacturing technologies is bringing dizzying change to the DNA sequencing business. The first of this new generation of high speed, low cost systems hit the market in 2011, only to be followed already in early 2012 by announcements of still faster, cheaper models. Pacific Biosciences now faces more competition, but stresses it offers fast turnaround of more detailed information for practical applications.

Shrinking government budgets for funding basic research—and the daunting difficulty of finding actionable information in the vast complexity of interrelated genetic data--have slowed the market for high volume DNA sequencing tools. Suppliers are instead starting to target the emerging market for clinical applications, where the lower cost tools enabled by micromanufacturing innovations can offer faster results, at least for smaller volumes of data from small genomes or select parts of genomes.

Sales of the new breed of microsystems-based sequencers started to shake up the market in 2011. Pacific Biosciences says it's sold 55 of its MEMS-based units to date, since introducing its commercial product in April, taking in revenues of ~$21 million for the six months through September at last report .

But the competition is heating up. Ion Torrent has made a bigger splash since launching its semiconductor-based product at the end of 2010, reporting sales of some $41 million for the nine months through September 2011. Its technology cuts costs by electrically sensing hydrogen ions given off by distinctive base reactions, eliminating the need for optical markers, and the company has shown it can scale the semiconductor technology to more sensors per chip to increase throughput, moving from 1 million to 12 million sensors per chip in the second generation last year, and then recently announcing plans for165 million sensors in the second half of this year, and 660 million by 2013. The company's claim that it can sequence the full human genome in a day for $1000 on a $150,000 tool has been met with considerable skepticism, but it's clearly making progress. And it now plans to submit its smaller first generation tool for approval for clinical diagnostics. Market leader Illumina also announced its own new genome-in-a-day sequencer for later this year, albeit at closer to $700,000.

More detail from direct observation of single molecules in real time

Pacific Biosciences says it's not playing the same high volume data game. The company's MEMS-enabled solution for ultra high resolution microscopy can see the DNA replication one molecule at a time in real time. This eliminates the time consuming step of amplifying the DNA first, and allows reading of a longer segment of a strand at one time for faster results and simpler assembly of the analyzed segments into a connected whole genome sequence afterwards. The low cost tool gives fast and detailed information but for relatively small genomes, like those of bacteria and viruses or targeted parts of human genome. "It's not the high throughput workhorse for repeat sequencing," notes CTO Steve Turner. "It's more expensive for the cost per base, but gives higher level information that they can't get any other way, and complementary with the second generation machines." In contrast, the mainstream high volume, high throughput sequencers are more efficient in sequencing the whole 3 billion bases of the full human genome, by looking instead at many nominally identical amplified molecules at once, one reaction step at a time, with pauses between steps to wash away one reactant and introduce the next.

Turner says they stumbled upon the unusual nanoscale behavior that enables 1000x higher resolution imaging of the polymerases scooting along the DNA strand when looking into using nano-aperature near field scanning microscopy. His research group discovered that a metal film with tiny holes got stronger axial confinement of observation inside the bore of the hole, than outside it-- the conventional (and intended) mode of using them. Inside, the light is attenuated in as little as 10-20nm, keeping the light from propagating upwards, allowing

SMRT Cell 8Pac (Courtesy of Pacific Biosciences)

Dr. Turner founder and scientific and technical director, Pacific Biosciences

He was awarded a Ph.D. in Physics by Cornell University in 2000, where he worked with Prof. Harold Craighead to study the behavior of biomolecules in nano-fabricated structures. His work contributed to the establishment of the Nanotechnology Center at Cornell. Dr. Turner's undergraduate work was at the University of Wisconsin, Madison, where he received a Bachelor of Science in Applied Mathematics, Electrical Engineering and Physics. He is listed as the inventor on nine U.S. patents and more than 20 published patent applications.

imaging down to the zeptoliter (10 -21 l) range allowing operation up into the micromolar region, high enough resolution to see the polymerase replicating each base, and about half of the enzymes in nature, most of which can't be seen at the single molecule level by other methods.

MEMS houses helped develop the initial manufacturing technology on standard tools. Improvements to optical lithography over the years allowed researchers to move from e-beam writing of holes in a metalized glass plate, to optical lithography with improved performance and higher throughput. An optical MEMS paraboloid reflector below each tiny hole –a gumdrop-like structure in the glass with a reflective inner surface—folds the light into a lower angle to reduce losses.

Counting on more information in targeted areas

Looking at the continuous process across many steps of replication of one strand of DNA also provides information on the time of response of the chemistry, which turns out to be very useful in distinguishing other, epigenetic, base variations like methylation that turn genes on or off and significantly impact traits, for changes not explained by just the paradigm of mutations in in the genome. "We see from the different tempo and rhythm that some Cs are changed into something else," says Turner, noting that these and other epigenetic traits essentially create an alphabet with more than 20 different bases that explains things the 4 main bases alone cannot, from how poor diet in pregnancy changes the epigenome of the next generation, to what changes make bacterial strains become more virulent. "Researchers have looked hard, but haven't been able to find many common individual letter changes that can usefully inform healthcare," he notes. "It's to a huge degree determined by evolution that the paradigm of common single-letter changes didn't give us the gains we hoped for."

Beyond the first lab users doing sequencing and genomic assembly, Turner says the company is now seeing interest particularly from the microbiology field who want a genome, but at the lower cost per run of the company's smaller runs. It's also seeing adoption for validation of cancer research, for checking the accuracy of results. Though some critics say Pacific Biosciences' tool is less accurate than others, Turner argues that its longer read lengths simplify matching sequence patterns to assembly the complete genome from the longer parts, and its errors within or between runs are random, so repeat runs on the same strand quickly produce very accurate consensus data, while errors from the high throughput sequencers are more likely to be systematic and thus repeated.

The company got to show off the advantage of its fast detailed analysis of short bacterial genomes with the cholera outbreak in Haiti. Turner says it completed all the sequencing in five hours, but was already able to see after just 45 minutes by comparing deletions in the genome to those of others that the strain had originated in SouthEast Asia. With the German e-coli outbreak, Ion Torrent sequenced the bacteria first, but Pacific Bioscience followed up by quickly sequencing that and 11 other e-coli examples, and then using its longer read lengths to identify patterns indicating areas where exchanges with other bacteria apparently created more virulent toxins and antibiotic resistance.

www.pacificbiosciences.com

About Yole Développement

Beginning in 1998 with Yole Développement, we have grown to become a group of companies providing market research, technology analysis, strategy consulting, media in addition to fi nance services. With a solid focus on emerging applications using silicon and/or micro manufacturing Yole Développement group has expanded to include more than 40 associates worldwide covering MEMS, MedTech, Advanced Packaging, Compound Semiconductors, Power Electronics, LED, and Photovoltaics. The group supports companies, investors and R&D organizations worldwide to help them understand markets and follow technology trends to develop their business.

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