Review of the microfluidic landscape

Henne van Heeren
enablingMNT
henne@enablingmnt.com
www.enablingmnt.com

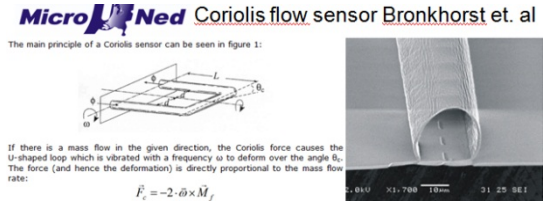
enablingMNT

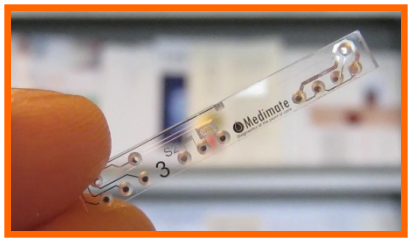
- The **enablingMNT** group provides support to new and established businesses in the Micro & Nano Technology (MNT) and System Integration sectors where the uptake of MNT offers enhanced performance and potential market advantage.
- Its partners each have over 20 years of experience in business development, marketing, and technology related services delivered to both private and public sector customers.
- The group have maintained a leading position in the field through strong participation in European projects in the MNT and System Integration areas and collaboration with international support organisations including MEMS Industry Group, NEXUS, MANCEF, IVAM, etc.

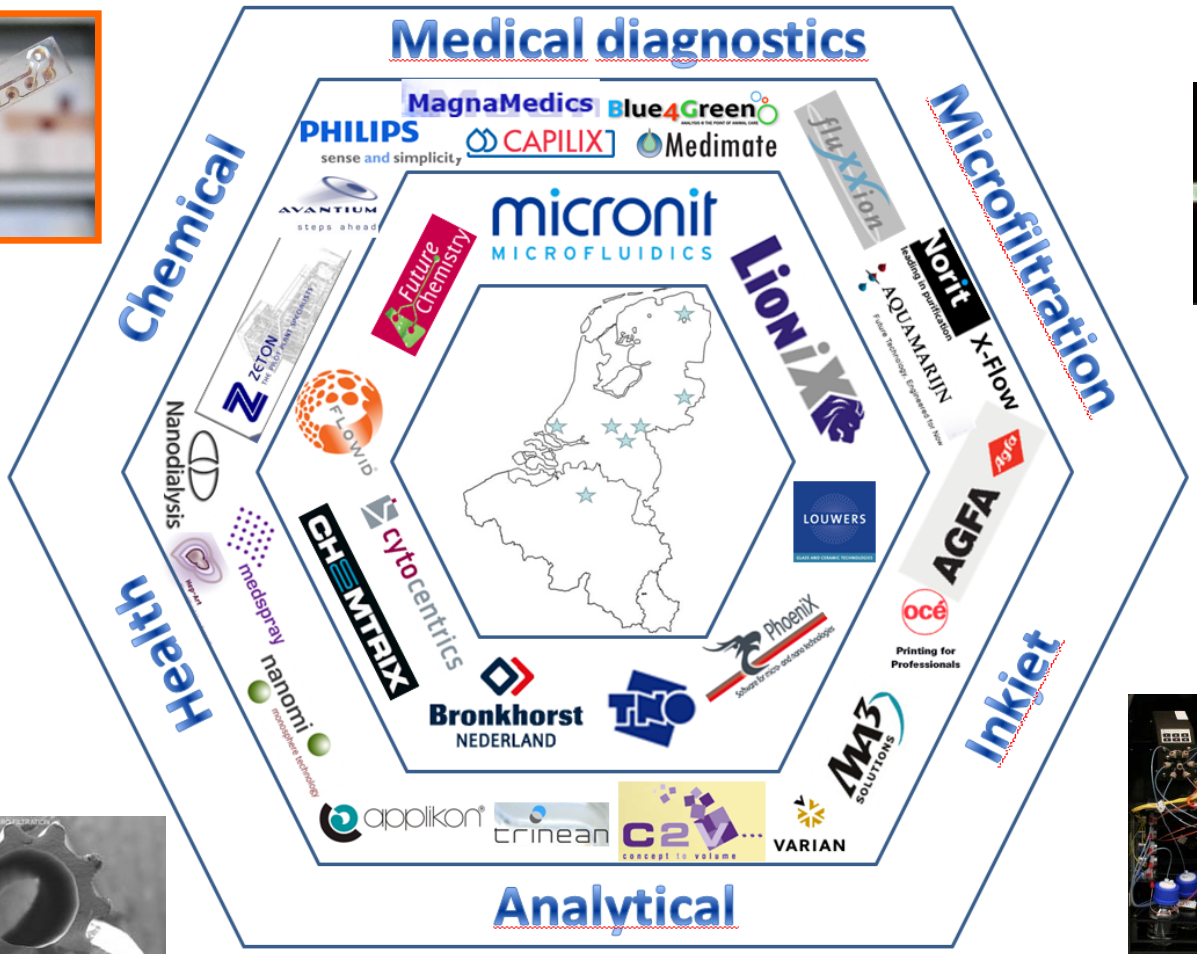
Megafluidics in the Netherlands

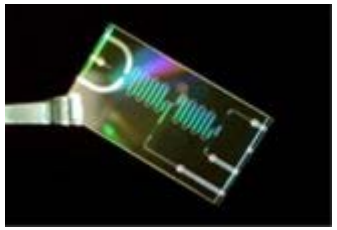
Microfluidics in the Netherlands

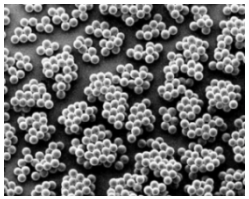
enabling MNT micro nano technology

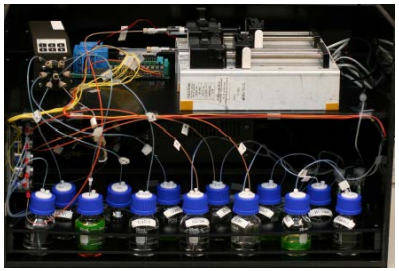






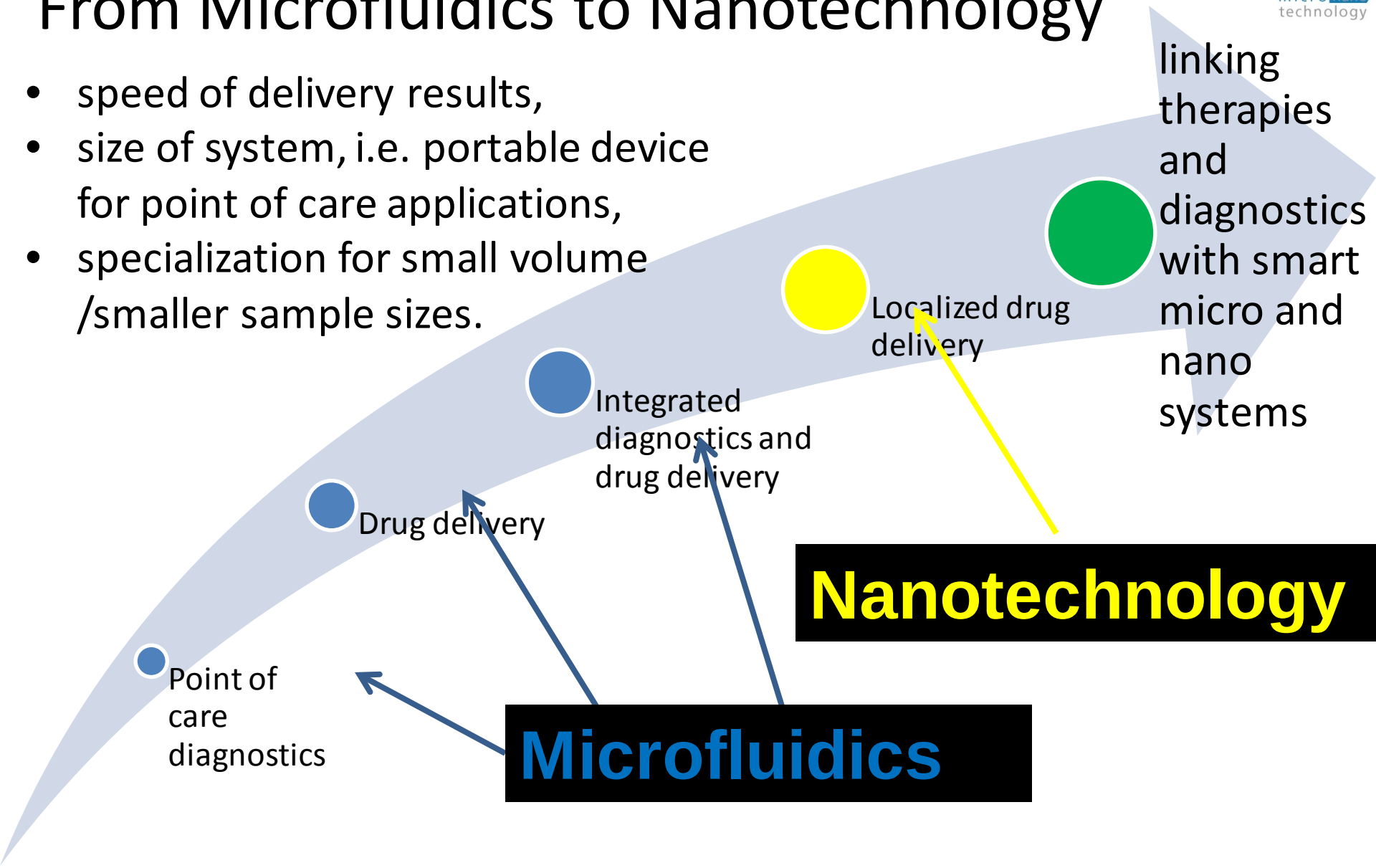




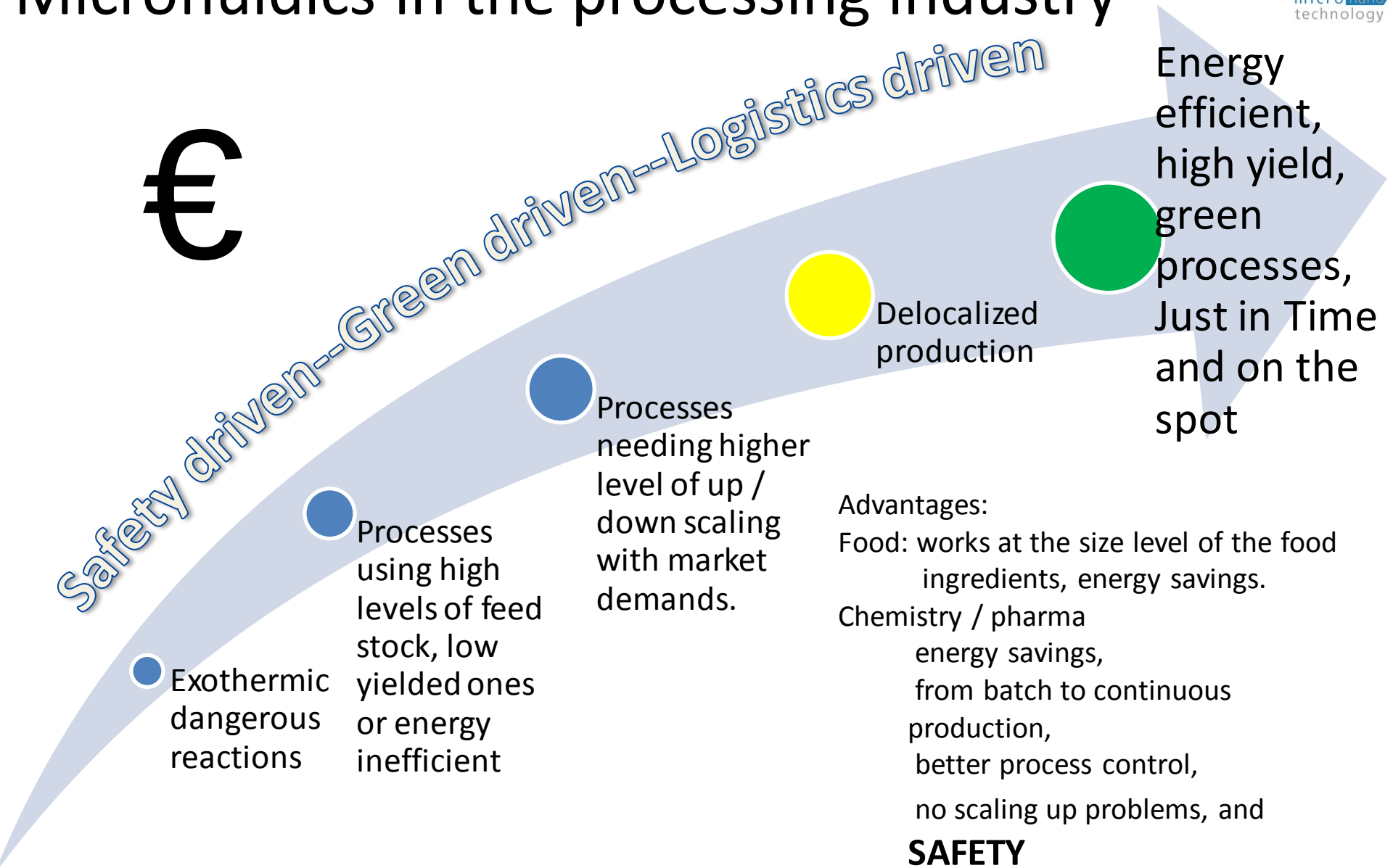


From Microfluidics to Nanotechnology

- speed of delivery results,
- size of system, i.e. portable device for point of care applications,
- specialization for small volume /smaller sample sizes.



Microfluidics in the processing industry



Advantages:

Food: works at the size level of the food ingredients, energy savings.

Chemistry / pharma

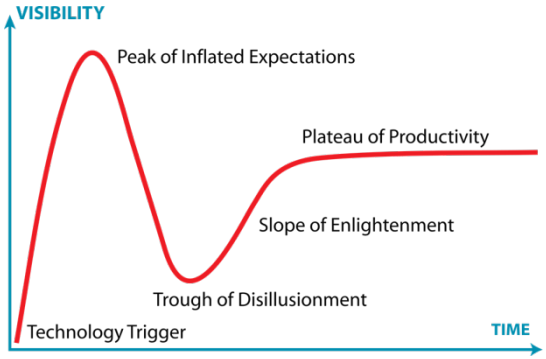
energy savings,

from batch to continuous production,

better process control,

no scaling up problems, and

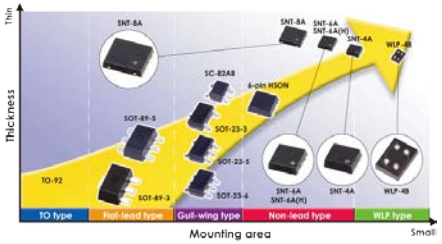
SAFETY



New industries will go through

- Hype
- Trends (agreement about what is important and what not)
- Application roadmaps (agreement about product performance criteria)
- Technology roadmaps (agreement about technology drivers and trends)

The microfluidic industry is still in the hype phase, but are there trends? Roadmaps possible?



Microfluidic scene

- >450 companies active in microfluidics
- ~80% less then 50 staff
- >50% selling products
- 336 OEMs or would be OEMs (174 of them from the USA)
- >100 companies offering services and components
- Dominated by many start ups and a few multinationals.

successful

unsuccessful

Very successful

What application?

- Inkjet deposition on paper, PCB, foil, array etc.
- Sample pretreatment for analytical instruments
- Digital microfluidics
- Microreactors / flow chemistry
- Point of care
- Bioreactors
- Lab on chip
- Micro cooling
- Etc.

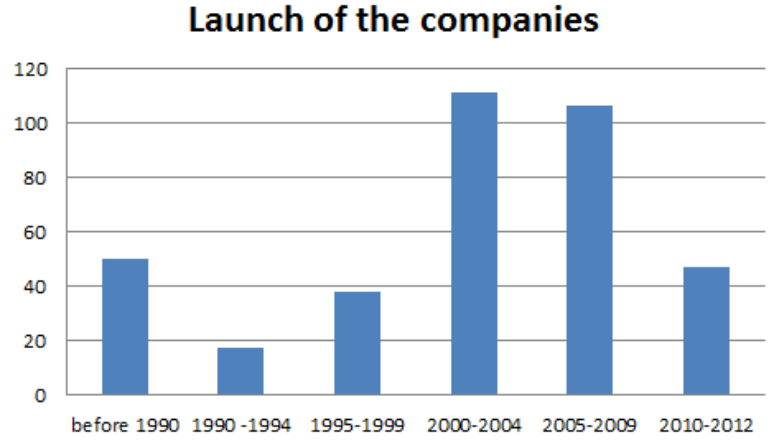
- Pathogen detection
- Drug delivery
- Drug discovery / screening
- Patch clamp
- Veterinary & agricultural
- HPLC, MS, GC
- Emulsification
- Spray drying
- DNA/RNA screening /PCR
- Molecular diagnostics
- Etc.

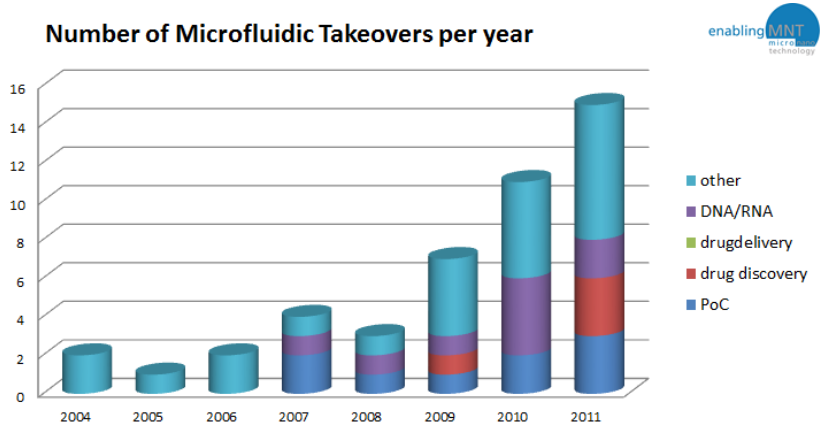
TREND 1: Chips suppliers are becoming component suppliers.
TREND 2: Would be medical diagnostic companies divert into other diagnostic applications.

University spin off hot spots (microfluidics)

- **University of California, Santa Barbara: (**Cynvenio, SpectraFluidics)
- **Stanford University**: (Cooligy, Helicos BioSciences, Orchid Cellmarks)
- **Havard** (Claros, Vista Therapeutics, gnubio, DFA, Nano Terra)
- **MIT** (Bostonms, Firefly BioWorks, Netbio, Pharyx, Biosscale, Hepregen, Microchips)
- **University of California Berkeley** (Cellasic, Nanomix, IntegenX)
- **University of California San Diego** (Celula, Nanosort, Biological Dynamics)
- **University of Texas (**Resonant Sensors, Nanomedical systems, Leonardo Biosystems)
- **Cornell University** (HμREL, Pacific Biosciences, Advion)
- **Caltech** (Labsmith, LeukoDx, Fluidigm)
- **EPFL** (Spinomix, Diagnoswiss, Biocartis, Ayanda, Abionic)
- **Imperial College London** (DNAE, Microsaic, Molecular Vision, Deltadot
- **Cambridge University** (Cambridge Biomagnetics, Sphere Fluidics)
- **A*STAR / National University of Singapore** (Micropoint Technologies, Veredus, Cellsievo, Curiox, Clearbridge, CE Resource)
- **IMM** (Ehrfeld, Mikroglas, ThinXXS)
- **University Twente** (U-needle, Aquamarijn, Ibis Technologies, Kryoz, Medimate, mylife technologies, Medimate, Ostendum, Opisense, Senzair, Tide Microfluidics

Happy ending for university spin offs?



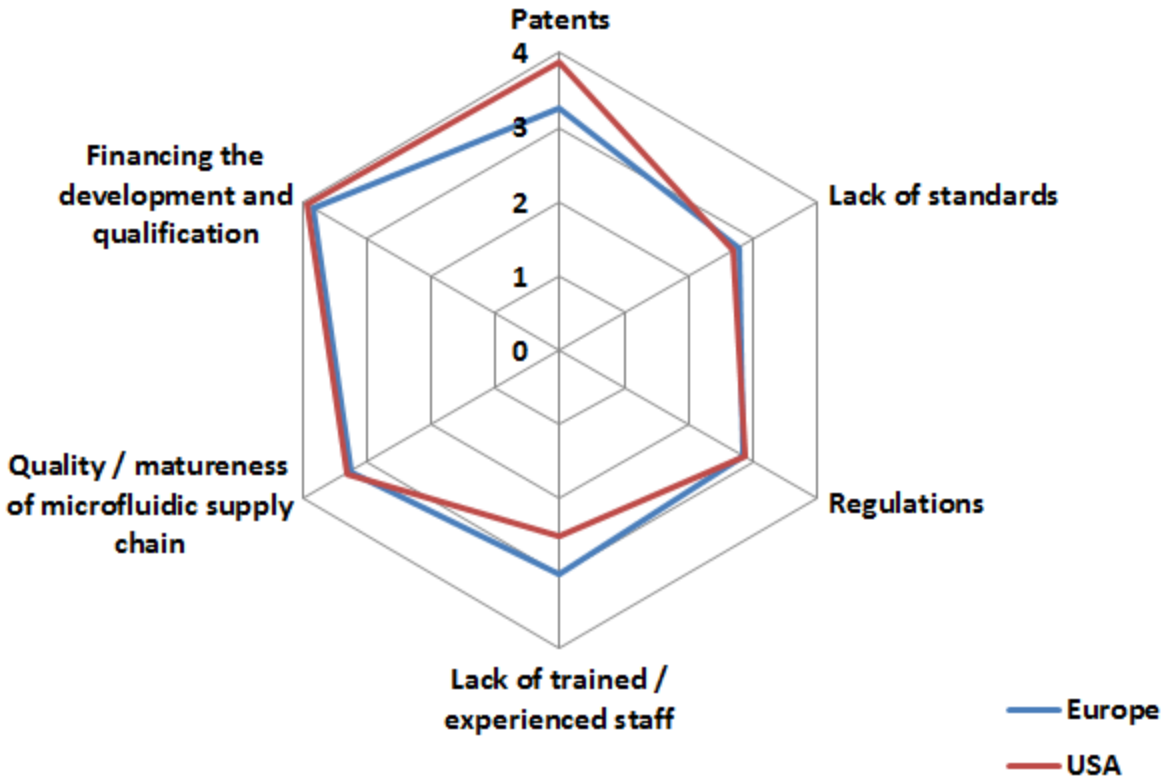


Survival of the fittest	Survival rate
R&D project	200
Start up company	10
Some funding	9
Acquired	8
Market introduction	5
"Big" market success	1-2?

Staying power needed:

- Time to "success": average 9 years
- Time to failure: average 7 years
- Time to market: average >10 years

Biggest challenges facing the microfluidic industry



Buyers

Abott (i-Stat, IBIS)

Agilent (Biotrove, lab901, Biocos)

Beckman Coulter (Advalytix, Blue Ocean Biomedical)

Inverness Medical Innovations (Biosite, Epocal)

Johnson & Johnson (Veridex, Amic)

Life Technologies (Cytonix, StokeBio, Ion Torrent, Biotrove)

Pall (Genesystems, MicroReactor Technologies)

Roche (454, Biomicrosystems, Medingo)

Sony3 (iCyt, Miconic)

PerkinElmer (Caliper, Evotec Technologies)

Bio-Rad (Quantalife, Digital PCR Technology)

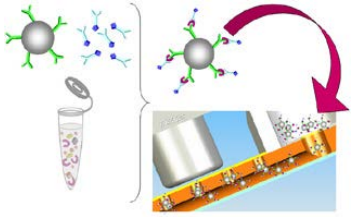
Becton & Dickinson (Handlylab)

GE Healthcare (Biacore)

And many others

TREND 3: Universities are actively generating microfluidic start ups.
TREND 4: Pharma and electronic companies are buying them. (If having a promising product or technology).

Bewildering number of technologies and concepts



Bionas.

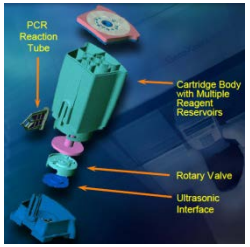
Simultaneous measurements of:

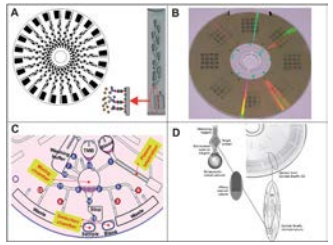
-pH

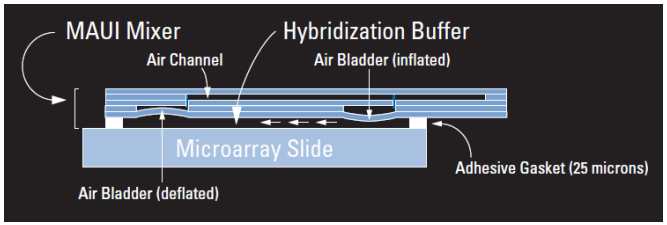
-O_2 consumption

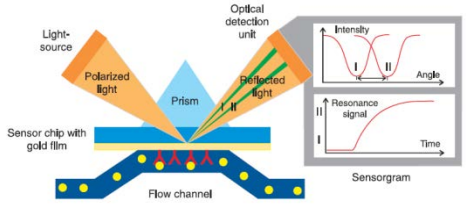
-Adhesion/confluency

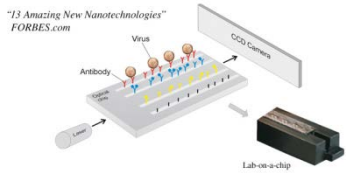
Online/real time measurements.

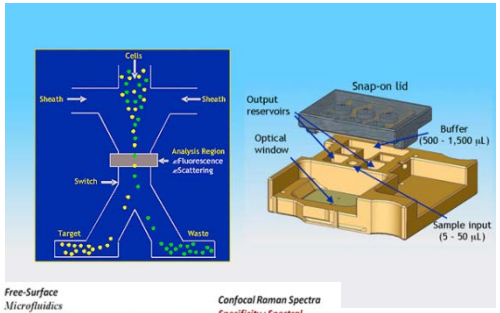


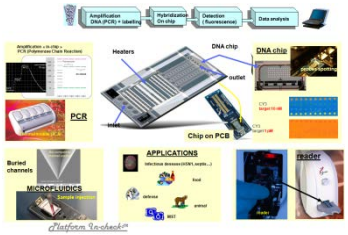


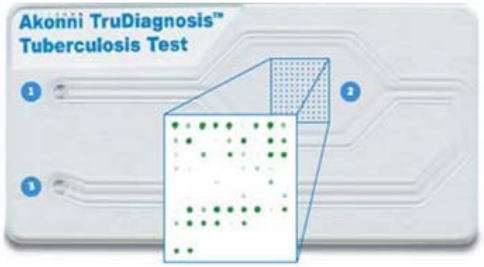


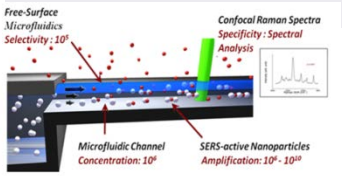


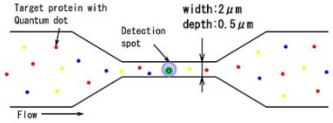


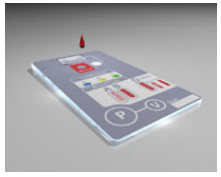


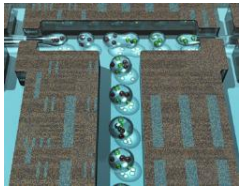




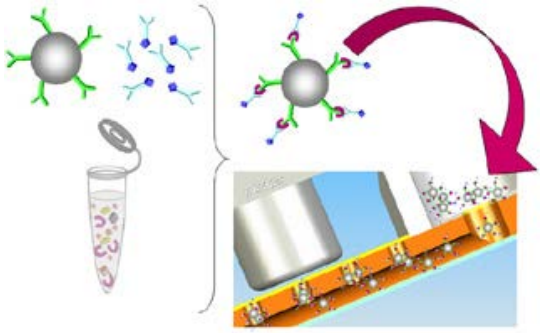








Magnetic beads

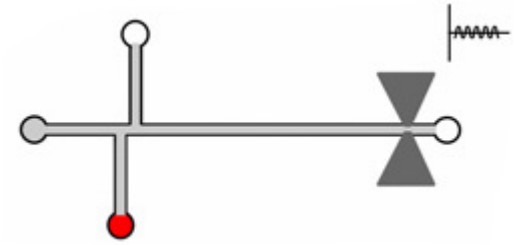


- The most efficient way to separate the target material from the sample.

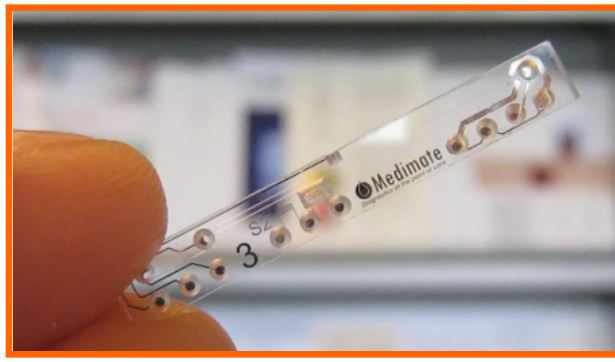
Fluorescence based immunoassay

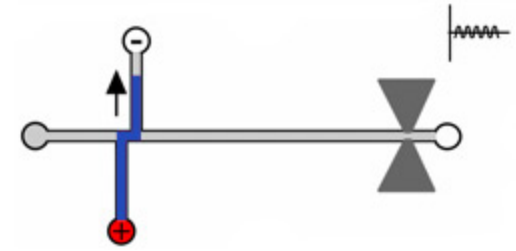
- Workhorse of microfluidic based detection. Well known and reliable, but add complexity and needs large amounts of target material

Capillary electrophorese (Courtesy Medimate)

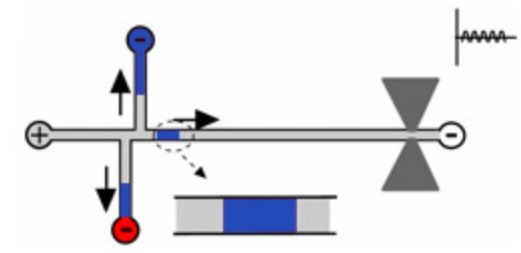


One drop of blood is placed on the sample reservoir at the end of the sample channel.

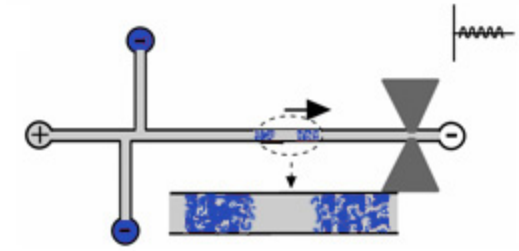




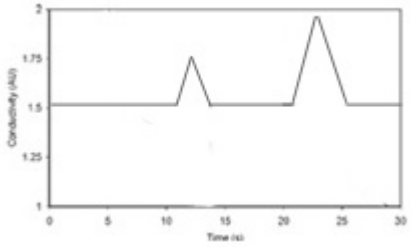
An electric field over the sample channel. causes the positive particles in the blood to migrate to the other end of the sample channel.



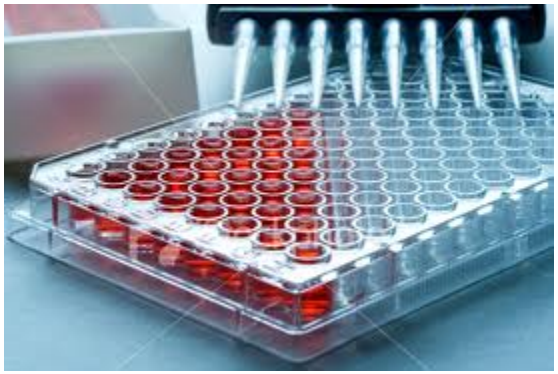
An electric field over the separation channel causes the positive ions at the intersection of the two channels to migrate to the end of the separation channel.



In a long channel the ions are completely separated by the different speeds of migration.



Microplate array

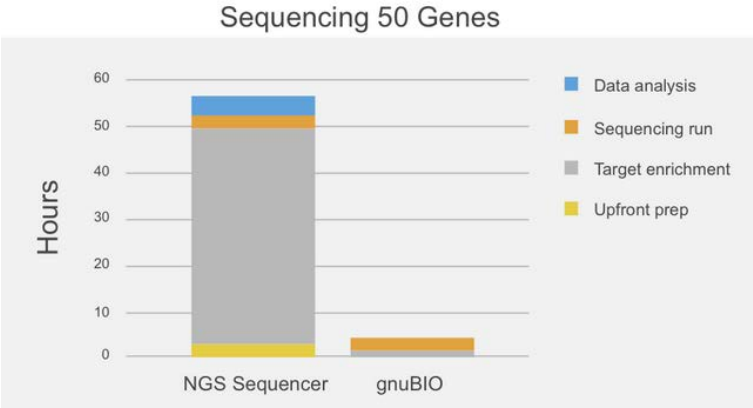


- Well array technology: the most used technology in diagnostic testing, but difficult to automate and miniaturize further; typical laboratory technology

TREND 5: Digital microfluidics is seen as a way to miniaturize well array testing further.
TREND 6: Well array testing is developing into more complex testing more akin to real life situations.

PCR

- Workhorse of sequencing, but time and chemicals consuming.



- How much do we gain by microfluidic PCR?
- Can we do direct sequencing?
  - Digital microfluidics: Gnubio, Raindance, Gigagen.
  - Nanopore/channel: Pacific Bioscience, Stratos Genomics, Nabsys, Nanopore.
  - Micro well and direct detection of H^+ release: Ion Torrent.

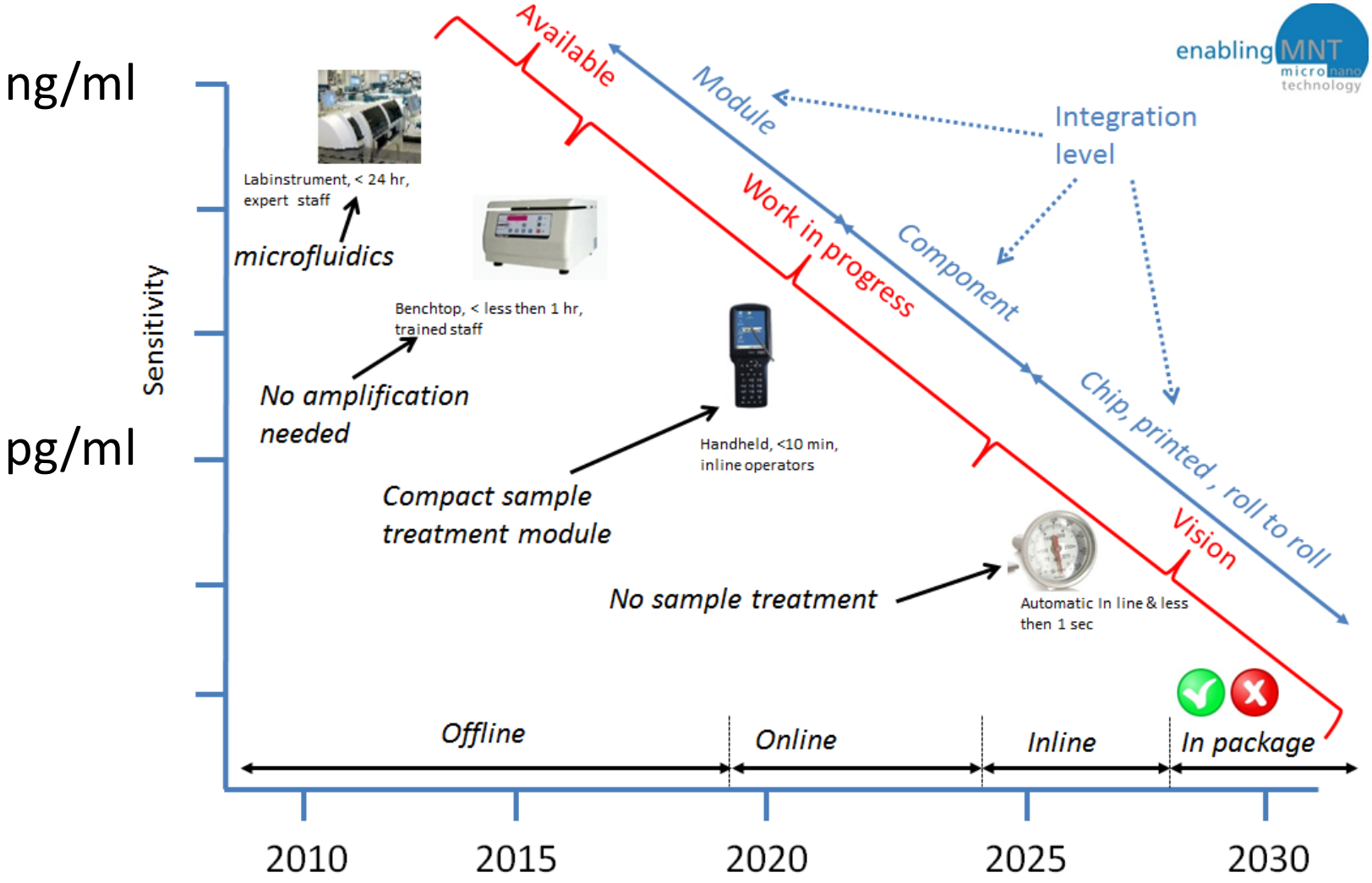
Goals PCR based microfluidic systems:

- A small device with a disposable microfluidic chip that integrates:
  - sample preparation,
  - amplification reaction,
  - concentration,
  - detection
- This device can be used at home, the doctor's office, as well as the field for applications from food safety to pathogen detection.
- Performance:
  - Price (<1 $) per disposable,
  - time to results < 7 minutes,
  - Multiple tests in parallel per disposable.

TREND 7: The industry is looking for technologies that don't need labeling, i.e. biomarker specific sensors.

TREND 8: The industry is looking for technologies that don't need time consuming PCR, i.e. hyper sensitive sensors.

A vision on the future of pathogen detection in the Dairy industry



Integration levels:

- the whole process from input sample to result (detected electrically or optically) is in a:
  - chip: glass, polymer, silicon chip (paper, roll to roll manufactures films etc.)
  - CD,
  - card: microfluidic plate with additional components like a biochip mounted on top of the plate, the fluidic does not leave the microfluidic plate,
  - cartridge: the fluid is transferred from one component to another in plane or in 3D,
  - not integrated.

Towards integration

	Interconnection needed	Main applications	Complexity processing and tests	Typical time to result	Weakness	Comments
Not integrated	Fluidic interconnects to instruments	High volume medical testing or for R&D	High	Several hours	Labor intensive	Fitting to the standard array based workflow
Cartridge level integrated	Not for PoC, sometimes for lab applications	All	High	15-30 minutes	Difficult to achieve price targets	Far out the most popular approach, (but costly?)
Card level integration	Only electrical or free field optical	Professional, Point of Care	Limited	15-60 minutes		More complex tests and pre-processing possible
CD level integration	Only free field optical	Sample treatment	medium	10-15 minutes	right application niche?	Excellent for multiple sample or multiple target testing
Chip level integration	Only electrical or optical	Point of Care	Low	few minutes	Only limited pre-processing possible	Mostly for detection of small ions

Business strategy

Organic growth

- Formulatrix (protein crystallization automation solutions) started in 2002 with 2 people; they managed to survive the first two years with services and introduced their first product during the second year. After 8 year they had 204 employees and an installed base of 237 pieces of equipment at 17 sites.

VC backed

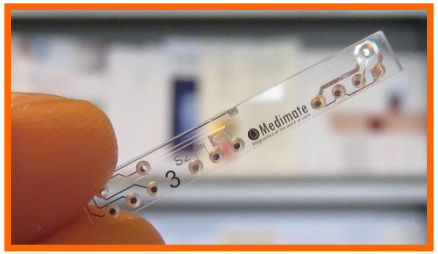
- Oxford Nanopore founded in 2005, secured over 100 M$ for the direct, electronic analysis of single molecules. Intends to commercialize DNA strand sequencing products, directly to customers within 2012.

Not always a straightforward business case

- Tools like implantable pumps or microneedles reduce side effects / optimize the working of a drug (and extend the patent protection period). But they are also making the microfluidic instrument part of the drug sales. Those coupled sales will result in an intertwining of markets and companies.
- Several chronic diseases, the (sometimes costly) measurement can show a substantial added value in another part of the health care chain.
- There are about 10 high volume diagnostic opportunities, like for instance diabetes, TB, HIV, etc., but also hundreds of tests were the volumes are less, often substantial less than 1 million tests per year.
- A recent discussion with the dairy industry resulted in more than 25 applications.

TREND 9: platform technology is seen as a solution for the many niche markets.

Examples of complex business cases



- Medspray inhaler:
  - The big money is in the drug, the microfluidic component is an enabler.
  - Launching customer is paying the development bill; each device is developed in relation to a certain drug.
- Medimate:
  - Big saving is related to the patient's risk of side effects of the drugs
  - the insurance company benefit financially when the products becomes a success.
  - Guess who is investing in the company and who is launching customer?

Examples of new products and products coming soon (1)

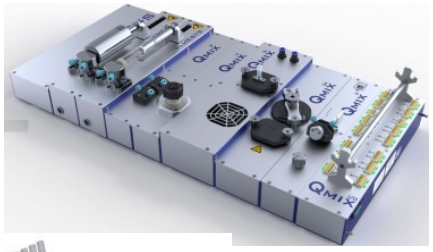
Point of Care instruments

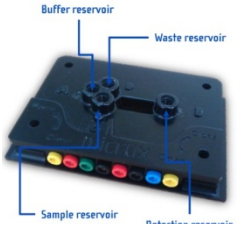
- Epocal FDA clearance for its Point of Care Lactate test, now being sold by Alere
- Lingvitae: low cost generic diagnostic test platform, launched 2011
- Samsung 19 different blood tests in just 12 minutes
- Medimate hopes to also see commercial turnover in 2012 with its lithium home test for patients suffering from Bipolar Disorder.
- Microvisk is gearing up for market introduction in 2012 with its device to monitor the blood clotting.

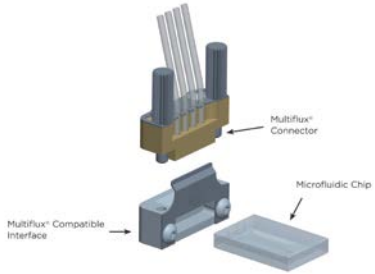
Examples of new products and products coming soon (2)

Industrial equipment:

- Sono-Tek ultrasonic coating device,
- Cetoni & Corning microreactors,
- Microfluidic interconnects by Dolomite,
- Micrux chipholder and the “plug and play” chipholder from Micronit ,
- Advanced MicroLabs: online process analyzer based on CE.







TREND 10: Plug and play microfluidic instruments, cartridges, chip holders, connectors etc. are emerging.

Standards, or no standards?

- The general answer can be best described as “perhaps”.
- The likelihood is rated highest for suppliers of analytical instruments and chemical reactors followed, surprisingly, by PoC instrumentation.
- But opinions are divided: over 25% will not participate in any standard discussion.

Why are standards needed?

- Select for the best available.
- Second sourcing.
- Ease of use.
- Limit the number of instruments in labs.

Specification for Industry to develop integrated Point of Care tests to support pathways of care
(NHS East of England Planned Care Clinical Programme Board)

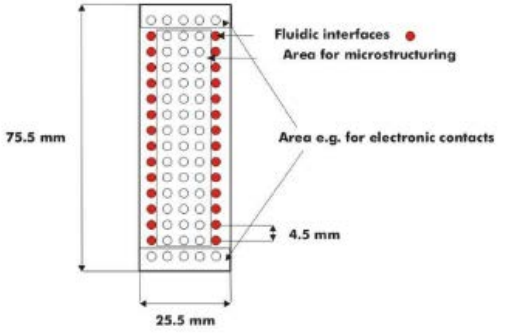
The POC unit must provide assays for

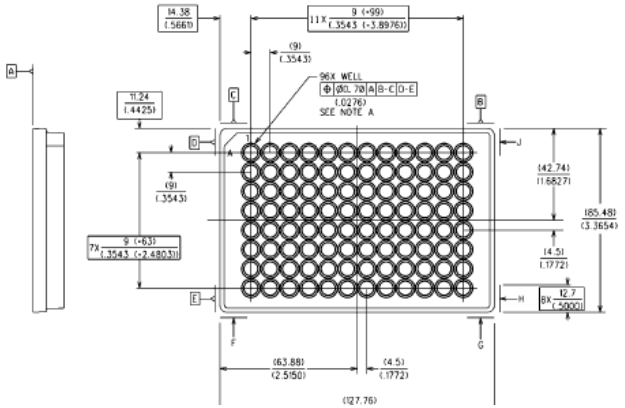
Assay	Diabetes	Hypertension	Chronic Kidney Disease
HcA1C	✓	✗	✗
Creatinine	✓	✓	✓
Thyroid function	✗	✓	✗
Total Cholesterol & HDL	✓	✓	✓
LDL	✓/✗	✓/✗	✓/✗
Triglycerides	✓/✗	✓/✗	✓/✗
Electrolytes (Na+ & K+)	✗	✓/✗	✓/✗
AST	✓/✗	✓/✗	✓/✗
Hb	✗	✗	✓
Ferritin	✗	✗	✓/✗

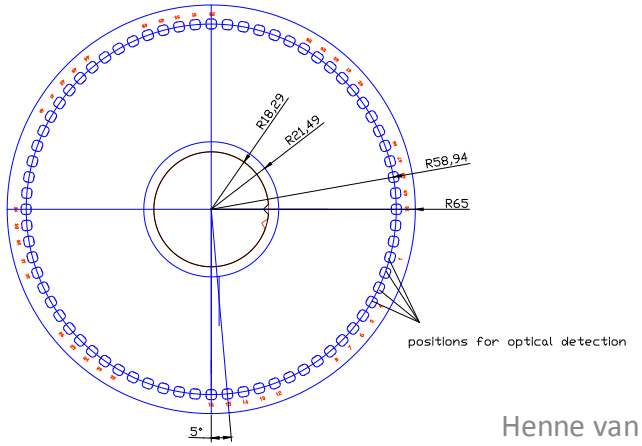
Key: ✓ Required
✓/✗ Desirable
✗ Not Required

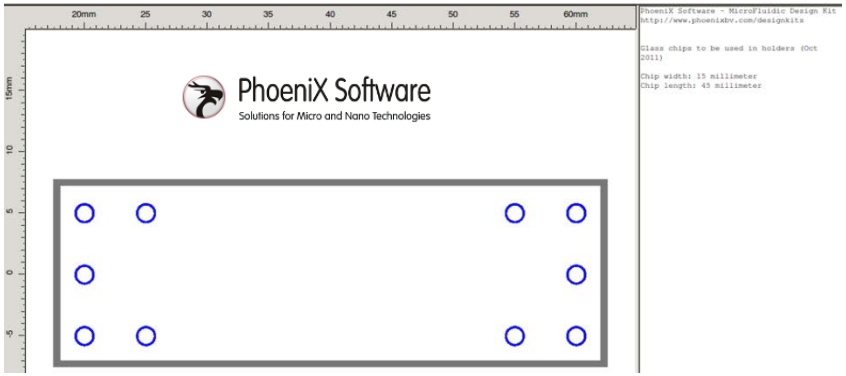
Pro/forma microfluidic standards

- Microscope slide
- Microtiterplate:
- 45*15 mm glass chip
- Optical disk









Trends summarized:

1. Chips suppliers are becoming component suppliers.
2. Would be medical diagnostic companies divert into other diagnostic applications.
3. Universities are actively generating microfluidic start ups.
4. Electronic and pharmaceutical companies are buying them. (If having a promising product or technology).
5. Digital microfluidics is seen as a way to miniaturize well array testing further.
6. Well array testing is developing into more complex testing more akin to real life situations.
7. The industry is looking for technologies that don't need labeling, i.e. biomarker specific sensors.
8. The industry is looking for technologies that don't need time consuming PCR, i.e. hyper sensitive sensors.
9. Platform technology is seen as a solution for the many niche markets.
10. Plug and play microfluidic instruments, cartridges, chip holders, connectors etc. are emerging.

General observations

- The products are there, but are not reliable enough, too expensive and the quality of the components is not good enough. Giving more attention to standards might help.
- The community worries very much about how to finance the development and how to survive the IP situation.
- We see signs of matureness
  - Consolidations
  - License deals
  - Better formulated business proposals
  - Standard discussions
  - Availability of training / easy to use tools etc.
  - Microfluidic Industry Consortiums: MinacNed, FMMC, MF3

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