Update microfluidic standards May 2012

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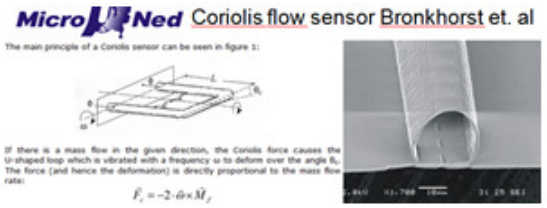
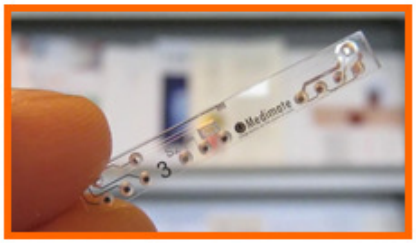
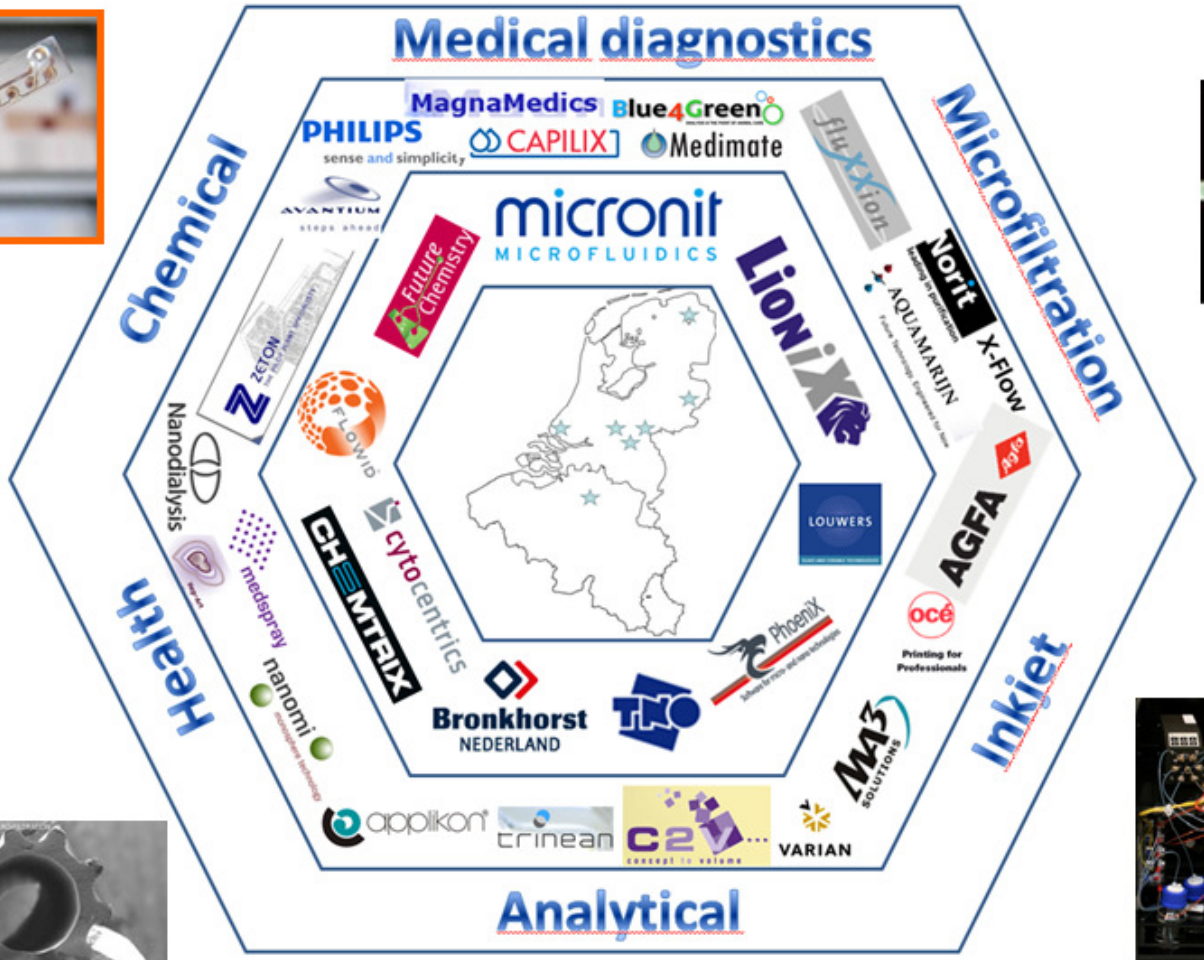
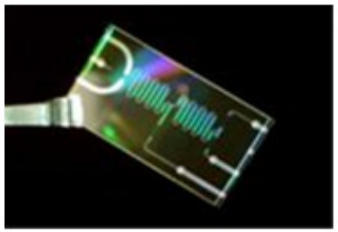
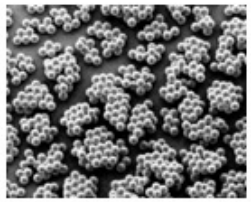
Microfluidics in the Netherlands

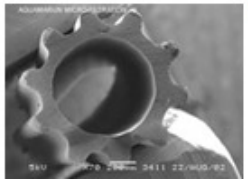


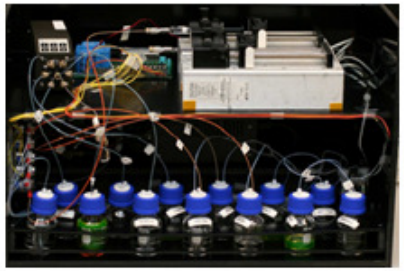








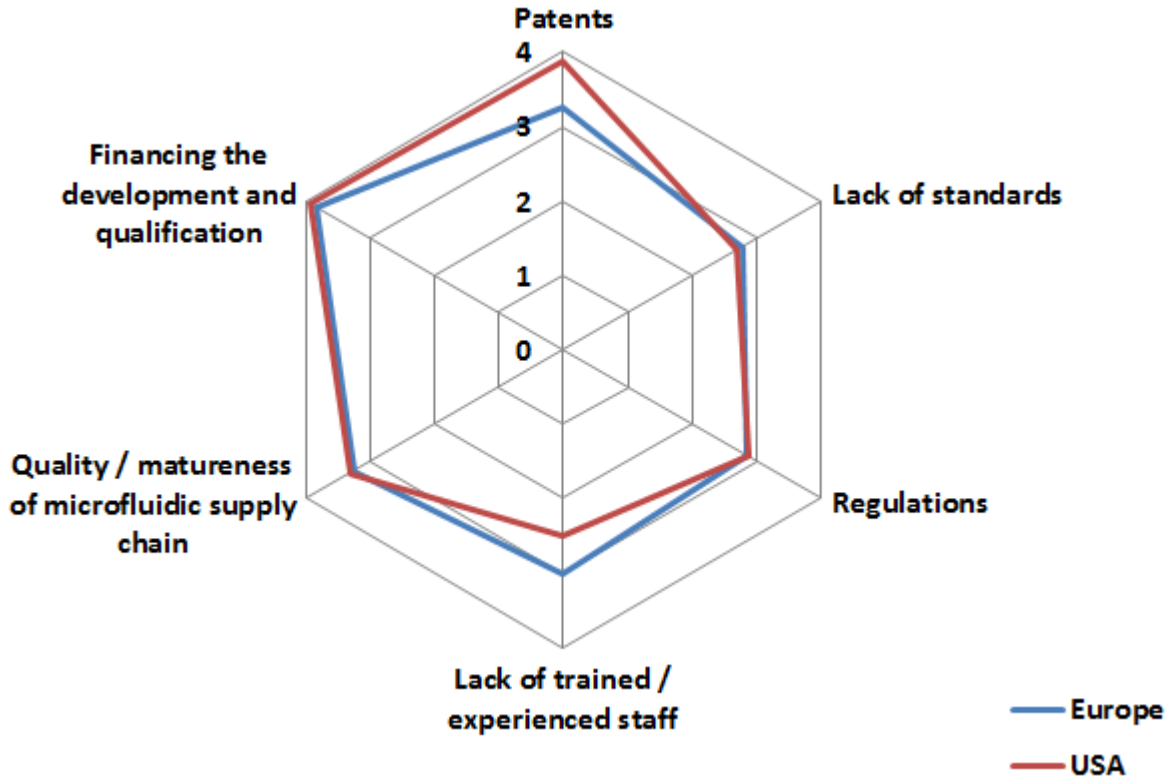




Major conclusion standard discussions 17-18 May 2012

- Things like port layout / spacing are less controversial than actual connector designs, so this will be the way forward.
- R&D connectors are obvious 'low hanging fruit'
- Established (large) fluidic components suppliers are entering the discussion.
- The call for "generic readers" at POC is well worth latching on to.
- A new discussion area might be the low sample volume interconnect problem and/or droplet transfer.

Biggest challenges facing the microfluidic industry



Development priorities per segment:

- Processing industry: integration of microfluidic components
- Analytical equipment suppliers: component development + design and modeling
- Supply chain: test & measurement
- Research community: application development
- ALL: RELIABILITY

Plug and play microfluidics needed

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

Barriers & Drivers for standards in microfluidics

Barriers:

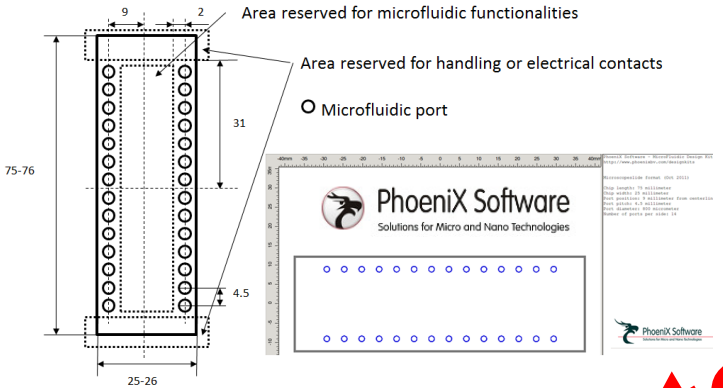
- Market position of the companies dominant in the market or are expecting to achieve such dominance.
- Investment in current products might become worthless.
- Diversity in the existing products already on the market.
- Lack of uniformity in our vocabulary.
- Existing standards in established industries.

Drivers:

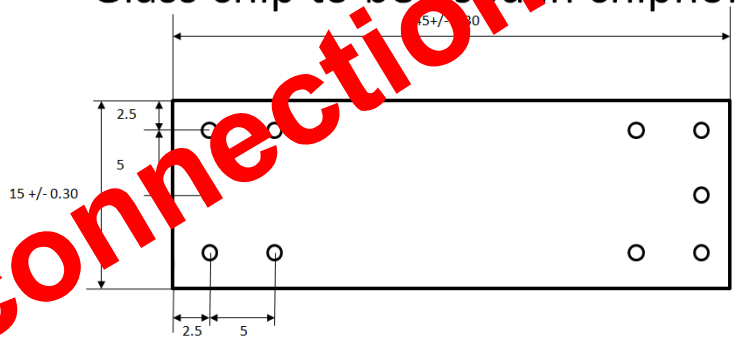
- Health care: to enable diversity in testing, there are hundreds of specific tests needed, but the user wants to limit the number of instruments in the lab.
- Analytical instruments / processing equipment: to enable the selection of the best components and the ability to compare / qualify those components and the systems.

Pro/forma microfluidic standards

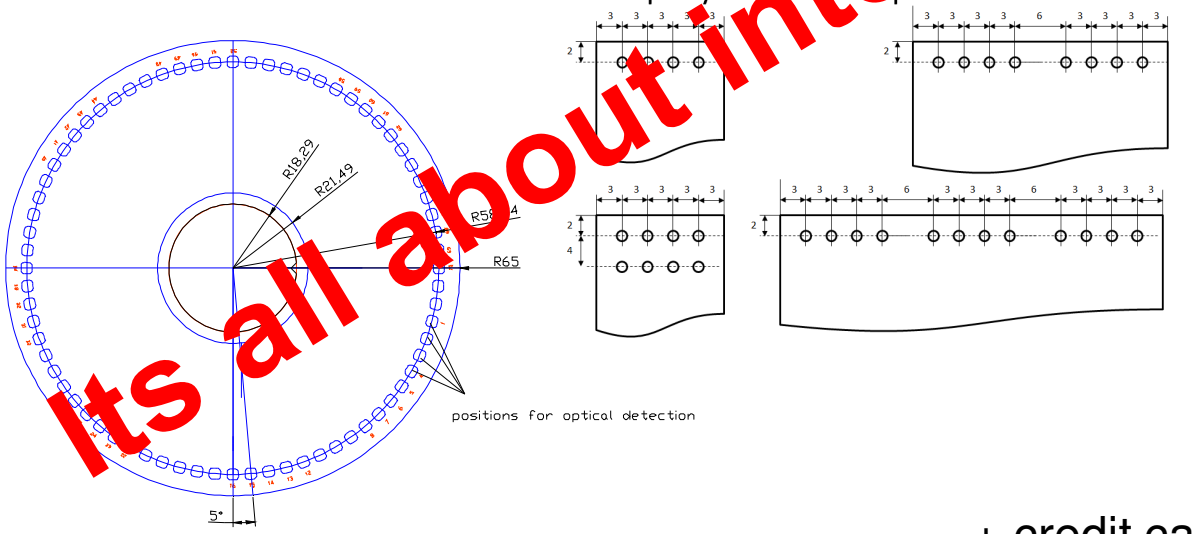
Microscope slide format



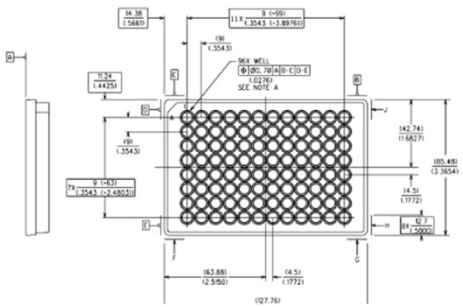
Glass chip to be used in chipholders



Chip layout for clamped interconnects



Microtiterplate format



Position of fluidic interconnects: similar to the positions of the wells

Its all about interconnections!

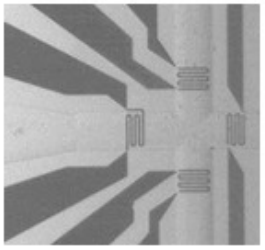
+ credit card format?

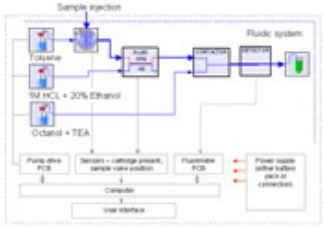
Introduction to Dolomite

Dolomite has 3 primary streams of activity - 65% US, 20% Asia, 15% EU

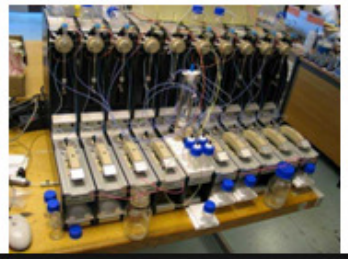
- **Productising Science: Instrument/System Solutions – 60%**
  - Customer describes full problem
  - Dolomite develops Instrument, Software and Devices
  - Dolomite manufactures or sets up manufacture

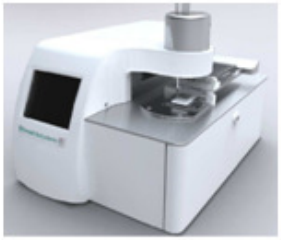
- **Standard products – 35%**
  - Dolomite offers a range of standard devices





- **Device design and Fabrication – 5%**
  - Customer describes device requirements
  - Dolomite designs device and interfaces
  - Dolomite fabricates and supplies devices



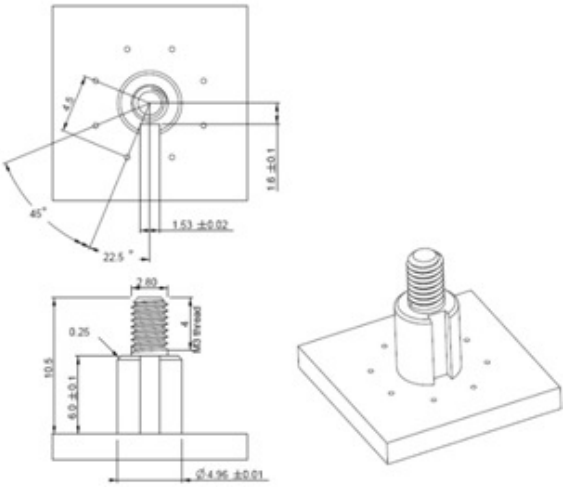


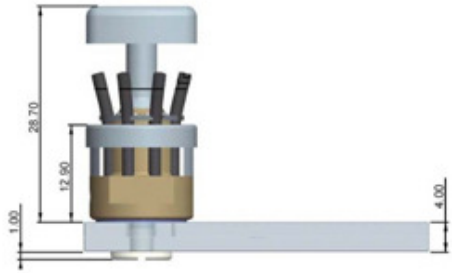
Background to Multiflux

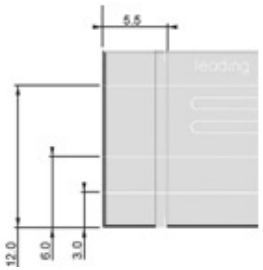
- Fluidic systems for manipulation, analysis and control of small amounts of materials are becoming increasingly sophisticated. In addition, there is an increasing trend for these kind of systems to be designed at smaller and smaller scales into the microfluidic domain.
- At present, most fluidic connectors only allow the connection of one fluid tube at a time. Furthermore, connecting microfluidic devices to macro-scale systems presents many challenges. If these are not addressed well, the benefits of working within the microfluidic regime may be compromised through time consuming assembly and resolving leaks.
- Dolomite had a set of issues with existing connector solutions:
  - In the field of electrical connections we are all used to robust, easy to use, multi-way connectors. Imagine being asked to connect between your laptop and projector with 15 single wires and being expected to get each wire in the correct position otherwise the projector would at best not work, or at worst get damaged. We would all see that as simply unacceptable!
- Multiflux is a multi way fluidic interface standard

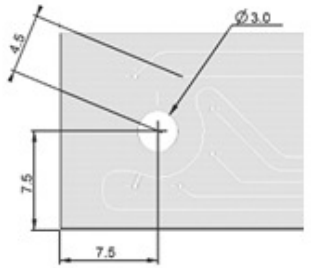
Multiflux now

- Originally Dolomite viewed its connectors as proprietary
- However over the years, more and more customers asked Dolomite to use our connectors with other manufacturers chips
- We therefore in 2009 decide to make our standards open
- We now have a widely growing range of connectors which we have called Multiflux
- There is an online design guide to enable people to use them with their own chips
  - A fast growing range of customers are increasingly using the connectors together with their own chip designs
- Dolomite sells 10x the value in connectors that is does in chips
  - Dolomite has no strategic objective to supply production microfluidic chips and we partner with many fabricators



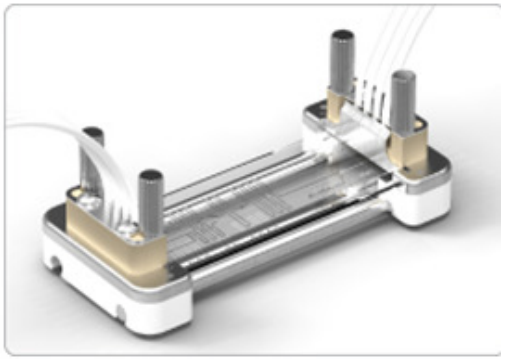






Multiflux is an open standard

- Dolomite has a roadmap of new connectors for:
  - Tubing of 0.8mm OD
  - PDMS devices
  - More connections



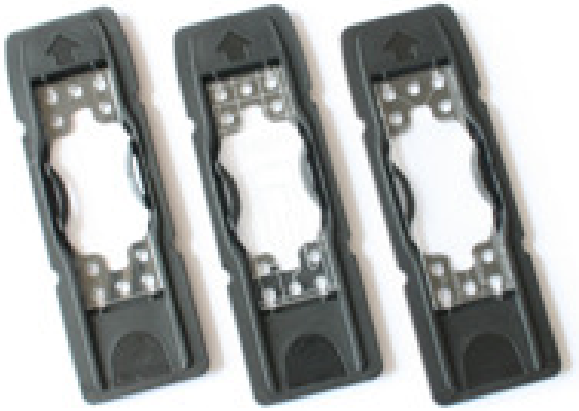
- Dolomite is extremely enthusiastic to collaborate with partners interested in new connections that are not currently satisfied by the existing Multiflux connectors
- Let us know what you need! ☺
- Dolomite is happy to make multiflux connectors to meet any new up and coming standards

MICRONIT MICROFLUIDICS

- Founded in 1999 by Micha Mulder (now CEO) and Ronny van 't Oever (now CTO)
- Around 400 customers in about 40 countries
- About 40 employees
- Highly educated people
- ISO 9001:2008 certified

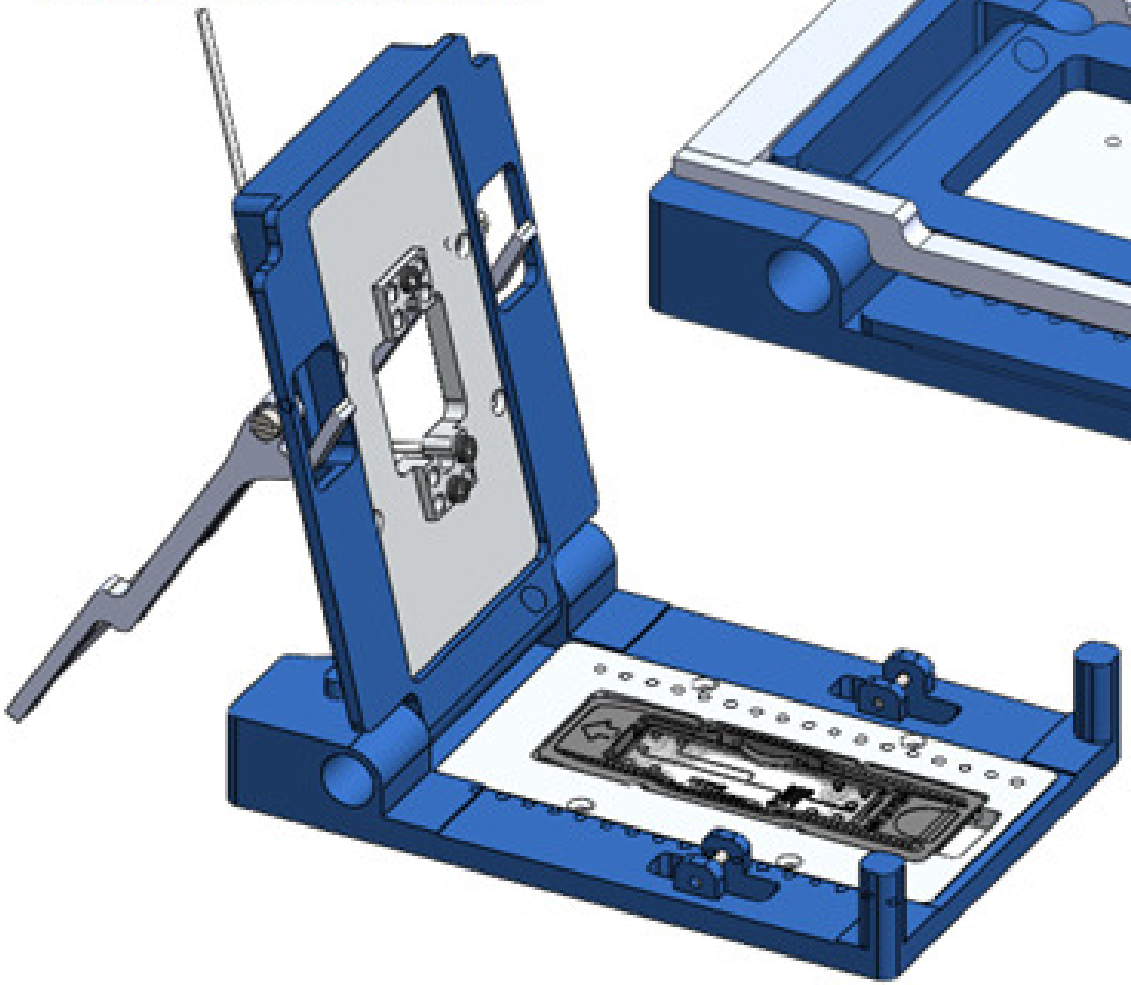
MICRONIT MICROFLUIDICS

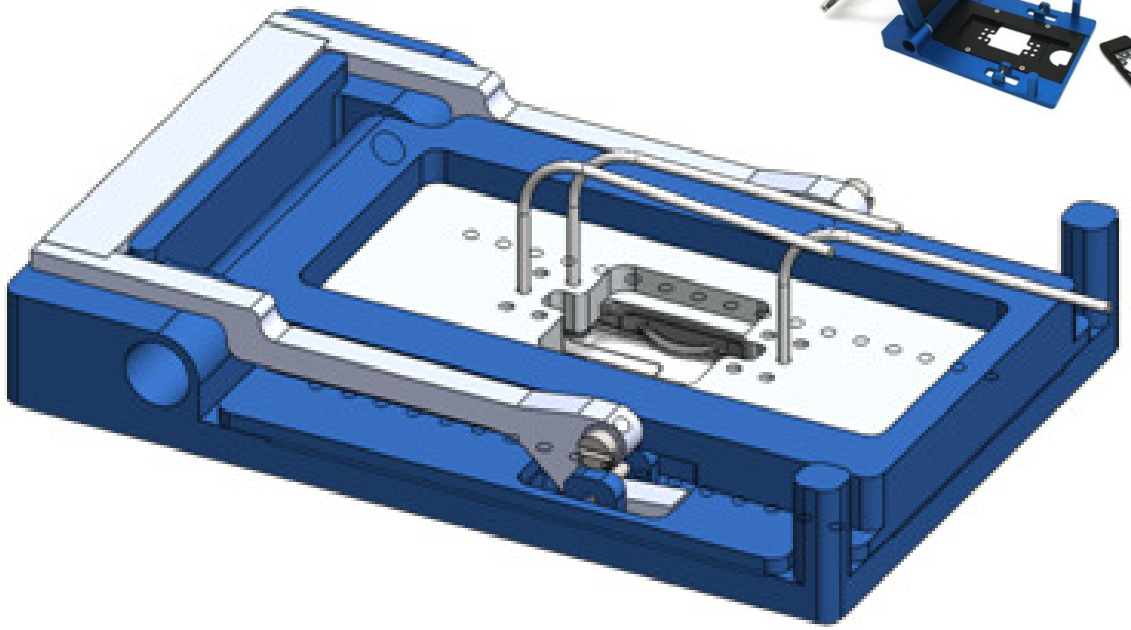
- Developing, prototyping and manufacturing of (custom) lab-on-a-chip products
- Microfluidic solutions for life sciences and chemistry
- Unique combination of microfluidics know-how and micromachining capabilities
- Market innovator through R&D department, cleanroom facilities and intellectual property

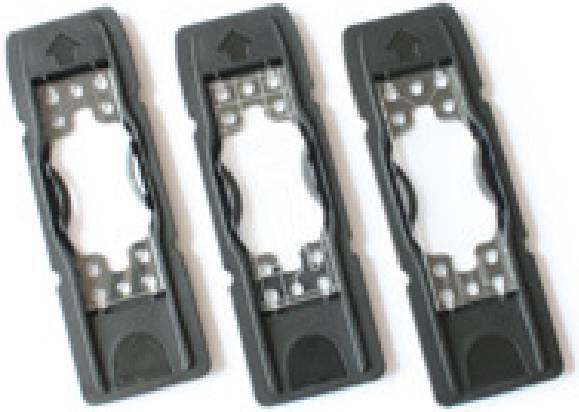


Fluidic Connect Pro with standard Micronit chip

Fluidic Slide compatible setup



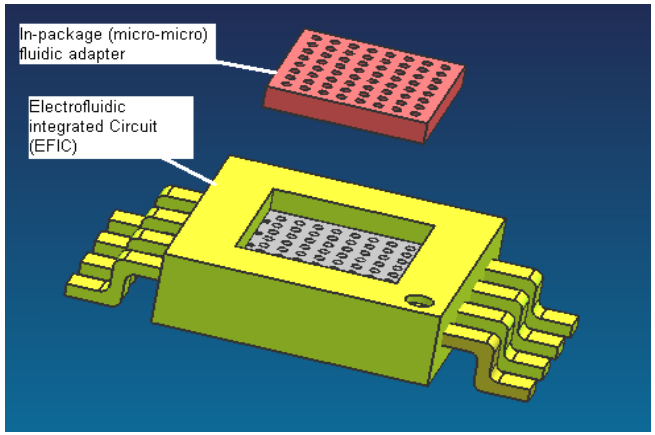




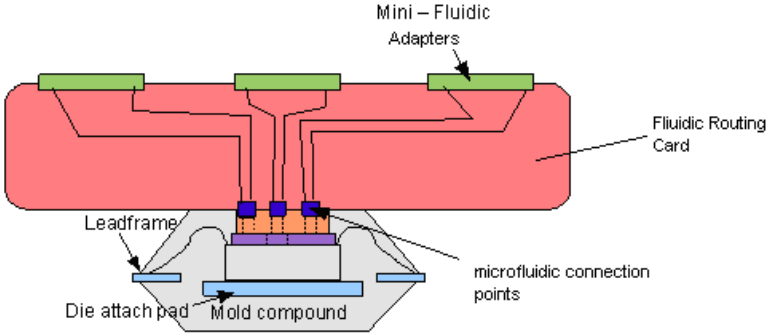
Ongoing standard discussions:

- Semi: proposal for multi port interconnect in discussion. (8 parallel fluidic tubes with a center to center spacing of 0.500 mm and an ID of 0.250 mm)
  - SEMI Draft Document 4691, New standard: specification for high density permanent connections between microfluidic devices
  - SEMI MS7-0708 - Specification for Microfluidic Interfaces to Electronic Device Packages
  - SEMI MS6-0308 - Guide for design and materials for interfacing microfluidic Systems
- Nessi: mainly about sampling for process control.
  - ISA-SP76, Composition Analyzers?
- DIN standardization group on microreaction technology: Also working on characterization processes for microreactors.
  - ISO 10991 Micro process engineering - vocabulary
- MF3 (Microfluidics Consortium): multi port interconnects.

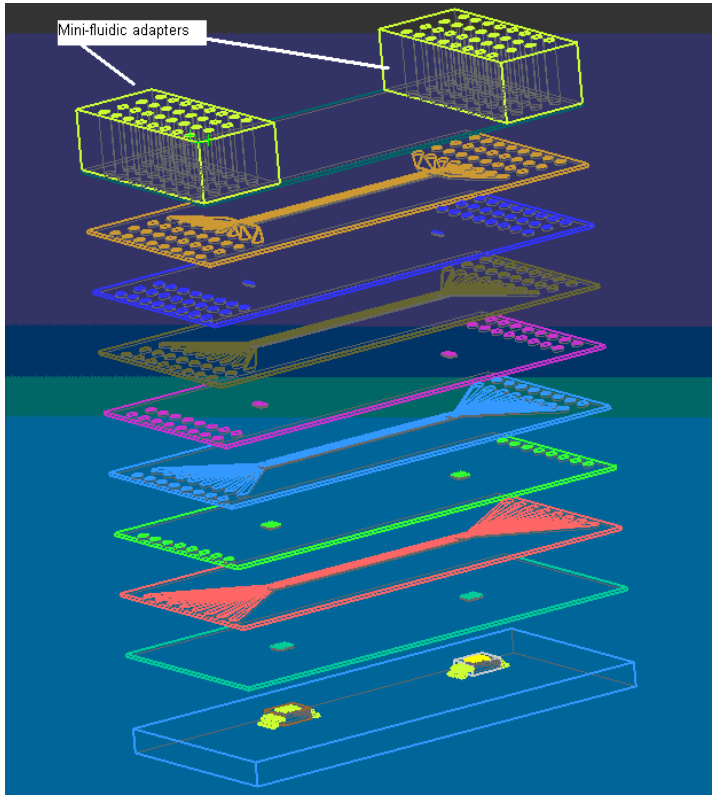
SEMI MS7-0708: Specification for microfluidic interfaces to electronic device packages



Exploded 3-D View of EFIC Package



Functional Description of Assembled Parts



EFIC Fluidic Routing Card & Adapters

invenios

bonding your future

The Invenios Group:

- Invenios, Inc. Santa Barbara, California, USA
- mikroglas Chemtech GmbH, Mainz, Germany

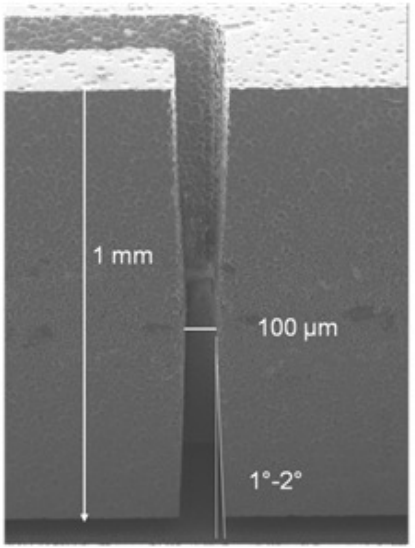
mikroglas

The Invenios Group designs, engineers and manufactures custom micro-fluidics chips for gene sequencing, digital PCR, sample control, micro-reaction technology, drug discovery and pathogen research and -discovery.

➢ Room Temperature Bonding

➢ FOTURAN ®

Photo-Structurable Glass-Ceramic



Standardization activities in Germany

working on standardization for micro fluidic components:

- DECHEMA Fachgruppe Mikroverfahrenstechnik

  Board Members: Dietrich (mikroglas), Stenger (Evonik), Dittmeyer (KIT)

- DIN Arbeitsausschuss Mikroverfahrenstechnik

  Chairman: Dietrich (mikroglas)

activities:

- standard of fluidic interfaces proposed by

- terminology norm ISO 10991 already in place

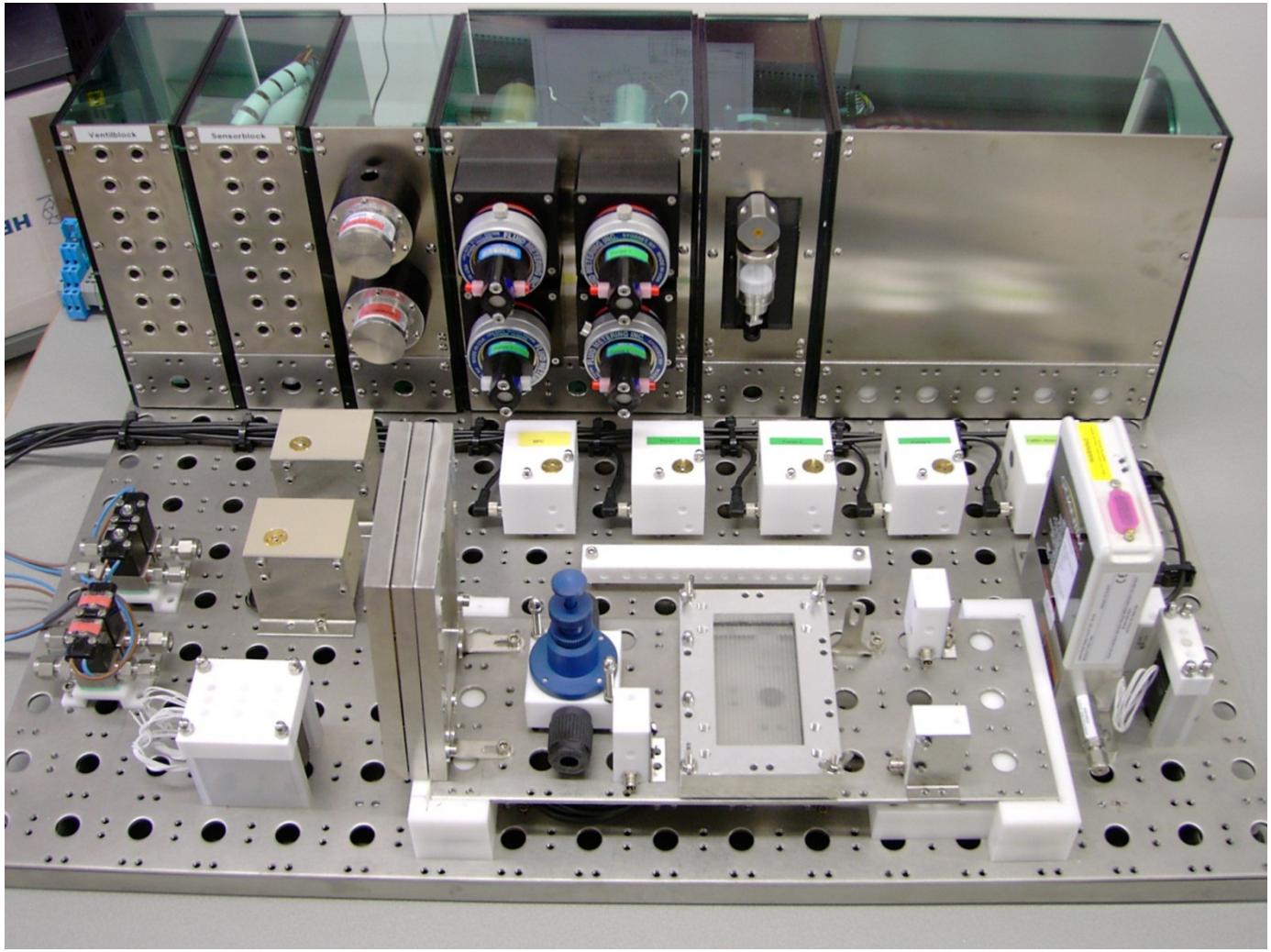
- DIN norm on explosion protection with micro fluidic components in preparation

  will be published in approx. 2 months

- research project on standardization of residence time measurement approved

  will start in July 2012 for 1 year --> standard equipment and measurement procedure

Modular Equipment Approach



Diba

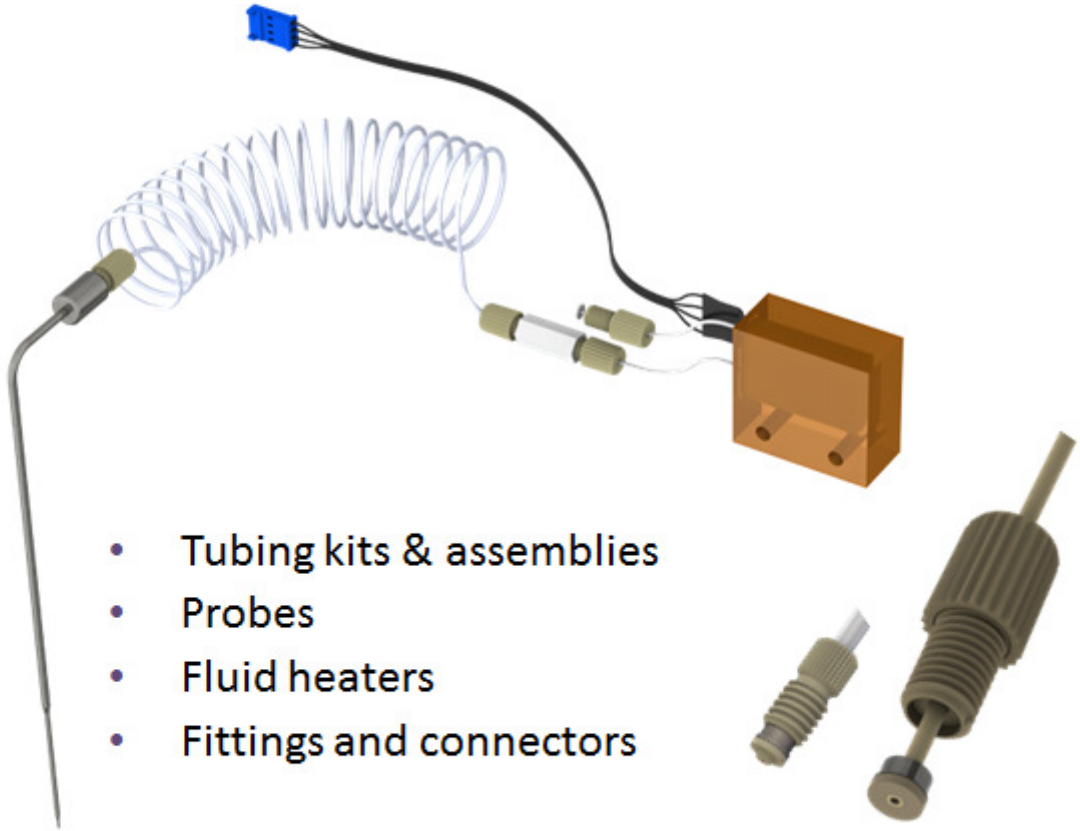
Perfecting Fluidics

Diba Industries

A HALMA COMPANY

Company Overview

- Founded in 1973, 1985
- Located in Cambridge, UK and Danbury, USA
- Part of the Halma Group of companies
- ~120 employees



- Tubing kits & assemblies
- Probes
- Fluid heaters
- Fittings and connectors

Markets

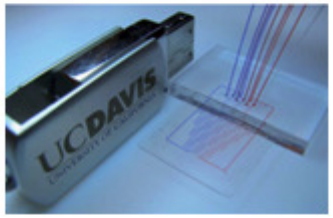
- IVD
- Clinical diagnostics
- Scientific analysis

- Solvent safety bottle caps
- LC columns

Classes of interconnection

A: Upto 2 bar (14,3 psig or 29 psi), temperature: -20 to 100 C?
To include practically all PoC, LoC like instruments for instance for biochemical testing.

Type	Benefits	Challenges
•O-rings •Press-in elastomer	•Tight pitch •Simple fitment •Low cost	•Dead volume •Not secure
•Flares	•Secure •Low dead volume •Interchangeable	•Larger pitch



B: Up to 100 bar (1450 psi), temperature : -20 to 200 C?
Gasflow sensors, microreactors etc.

Type	Benefits	Challenges
•Polymer ferrules •Elastomer ferrules	•Less dead-volume •Secure •Interchangeable	•Larger pitch •More components •More complex

C: Upto 1000 or even 3000 bar, temperature: -20 to 200 C?
Analytical instruments like GC, MS.

Type	Benefits	Challenges
•HPLC	•Simple	•Sometimes tooling required •Material compatibility

Creditcard format

- There is an international specification ISO/IEC 7810 which defines the physical characteristics for identification cards. The ID-1 format specifies a size of 85.60 × 53.98 mm (3.370 × 2.125 in). (see http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=31432)

  For the adaption for microfluidic application at least following parameter's should be standardized:
  - length and width
  - shape of corners; a bevel as an orientation mark is proposed
  - distance of microfluidic structures to the outer edges (handling/bonding zone)

  Proposed characteristics and tolerances:
  - length: 85.6mm +-0.5mm
  - width: 54.0mm +-0.5mm
  - thickness: a minimum thickness of 1.2mm is proposed
  - corner radius: 3mm +-0.25mm (3 corners)
  - bevel: 6mm x 6mm - 45° (1 corner)
  - distance of microfluidic structures to the outer edges >4mm

  Medion?

Companies using a CC format:
- Akonni
- Claros (Opko Health)
- Diagnostic Biosensors
- Epocal
- Medion
- Mycrolab

What to standard (from the users perspective)?

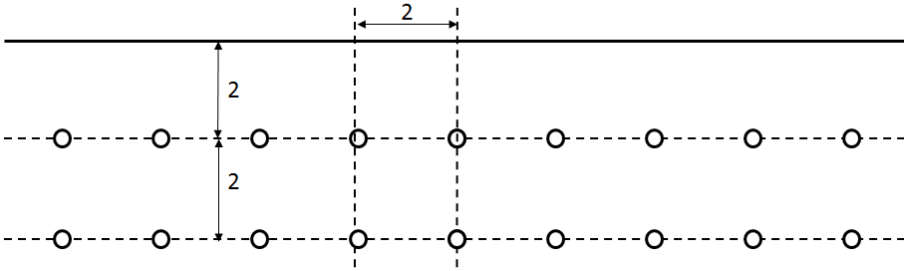
- There is certainly a need for a wide range of microfluidic PoC tests, but:
  - Is there space for the same amount of instruments in the GP's office?
  - Can a few persons master all the different Instruments?
- Taking this into account, shouldn't we look at the format of cartridges????
- Plug and test slot?
- A universal "plug and test" slot?
- Or even discuss shared instrument platforms?

Considerations for a general layout scheme for port layout

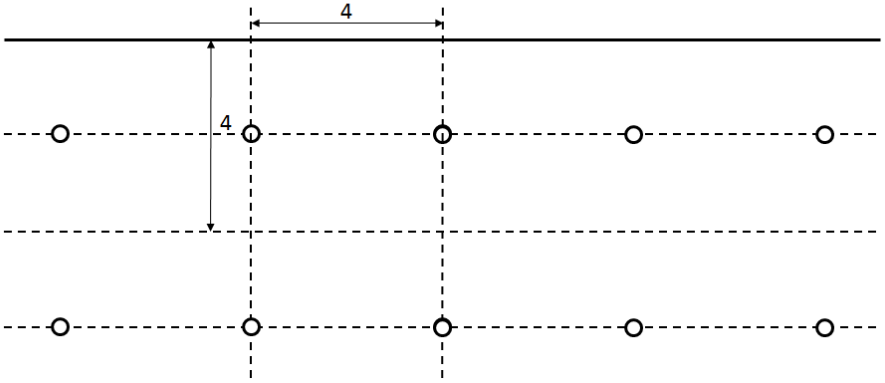
- Once the theoretical grid/pitch of hole positions is defined, the designer can choose to position a port at any of those theoretical positions. It's very similar to electrical connectors which also work to similar standards. The pitch is fixed and the designer can decide which to use, in the example below we take out some pins and don't use them, but we could use them if we wanted.
- The essential distance is between ports. It will be determinate by a) the size of the connector in case of individual connectors like Luers. b) leak tightness in the case of clamped interfaces.
- If a second row is needed, interleaved position gives the highest density of ports. It also makes the layout of the channels easier, a straight line for the port to the center part of the chip is then possible.
- The only thing left to describe is the distance between the first row of chips and the side of the chip. I would propose to take 2mm. To make it all as easy as possible.
- One port on the first row will always be positioned symmetrical on the chip.
- If needed it can be expanded to a super high density concepts (straight or interleaved) by using the 1 mm grid points in between)

General concept port layout

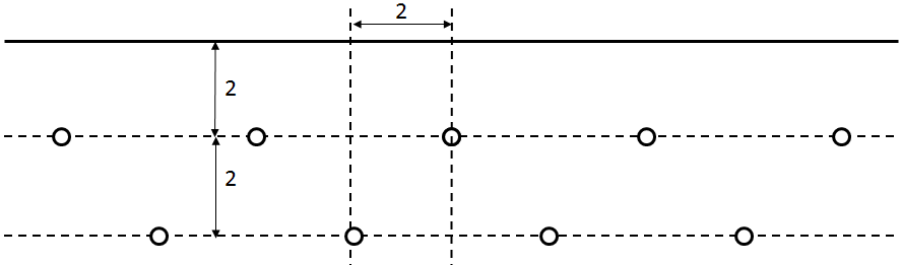
high density straight variation



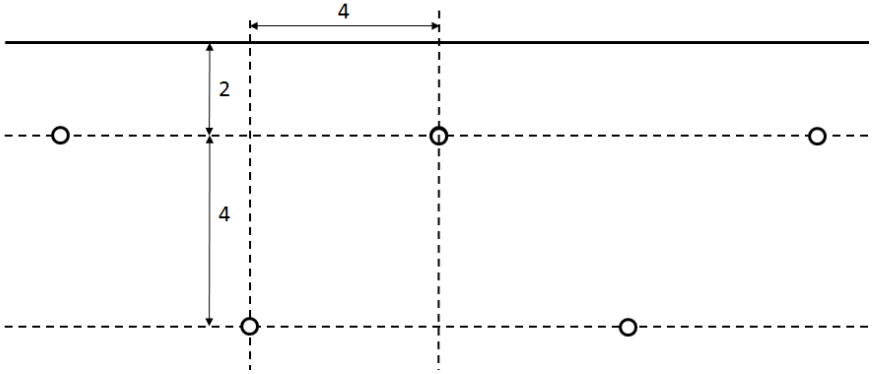
Low density straight variation



High density interleaved variation



Low density interleaved concept



Low cost fluidic interconnects

- TBD

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