Interoperability of microfluidic components

Henne van Heeren

enablingMNT

henne@enablingMNT.com

Introduction

- Real operability needs standards or at least industry wide supported design rules.
- "Markets make standards, not committees"
- Therefore identify:
  - the barriers and drivers for interoperability and standards,
  - accepted (de facto) standards,
  - technology trends,
  - dominant players and their products.

Barriers & Drivers for standards in microfluidics

Barriers:

- Market position of 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:

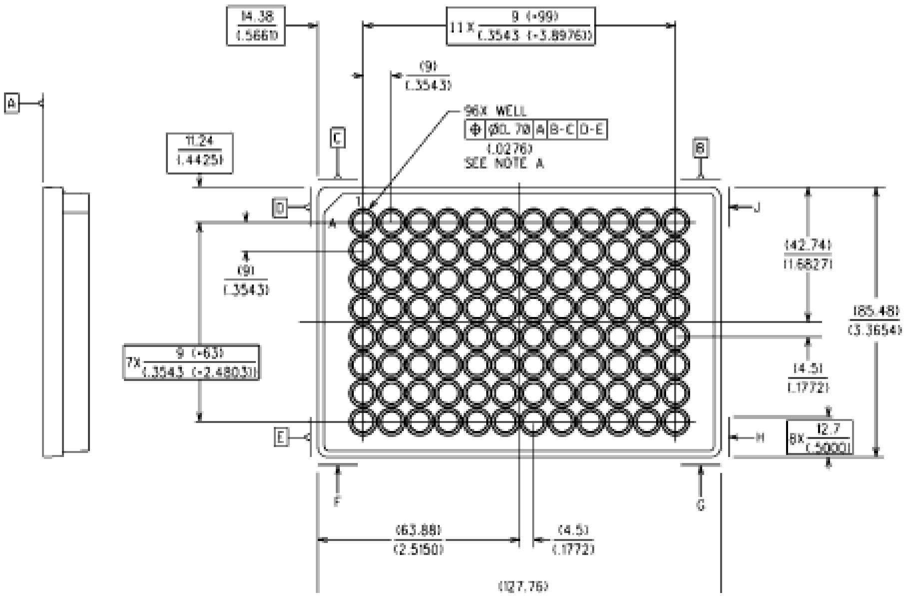
- Health care: to enable diversity in testing, there are hundreds of specific tests needed, but the user wants to limit the number of instruments in the lab.
- Analytical instruments / processing equipment / R&D: to enable the selection of the best components and the ability to compare / qualify those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

Established standards and ongoing discussions

- Established:
  - Microplate Well Positions: ANSI/SBS 4-2004
  - Standard microscope slide: ISO 8037-1:1986 Optics and optical instruments -- Microscopes -- Slides -- Part 1: Dimensions, optical properties and marking
- In discussion:
  - Semi
    - 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:
    - ISO 10991 Micro process engineering - vocabulary
    - Characterization processes for microreactors.
  - Microfluidics Consortium:
    - Multi port interconnects / chipsizes & design manufacturing guide
  - Mfmanufacturing project:
    - European initiative for the standardization and manufacturability of complex micro-fluidic devices

De facto standards for microfluidic designers

<table>
<tr><th>Length
l</th><th>Width
b</th></tr>
<tr><td>$45^{\;0}_{-1}$</td><td rowspan="2">$26^{\;0}_{-1}$</td></tr>
<tr><td>$76^{\;0}_{-1}$</td></tr>
<tr><td>$76^{\;0}_{-1}$</td><td>$39^{\;0}_{-1}$</td></tr>
<tr><td>$76^{\;0}_{-1}$</td><td>$52^{\;0}_{-1}$</td></tr>
</table>

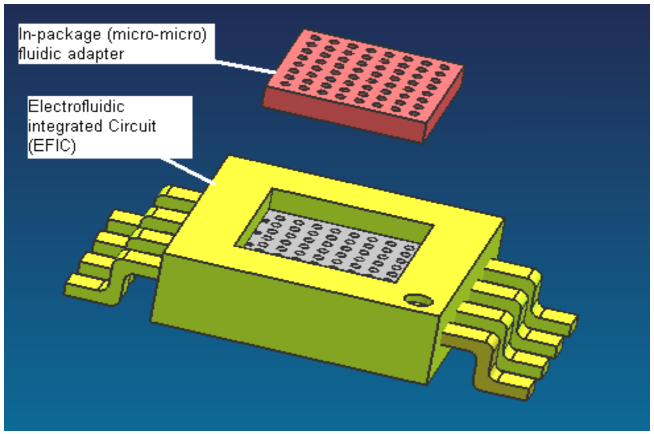


microscopy slide format

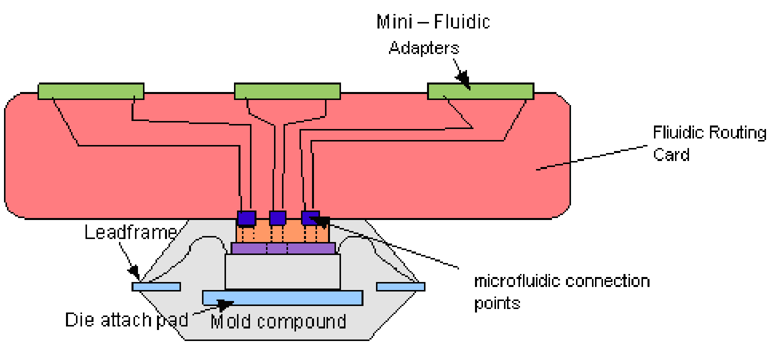
microtiter plate format, layouts with 96, 384 or 1536 wells.

both mostly with miniluer microfluidic interconnections

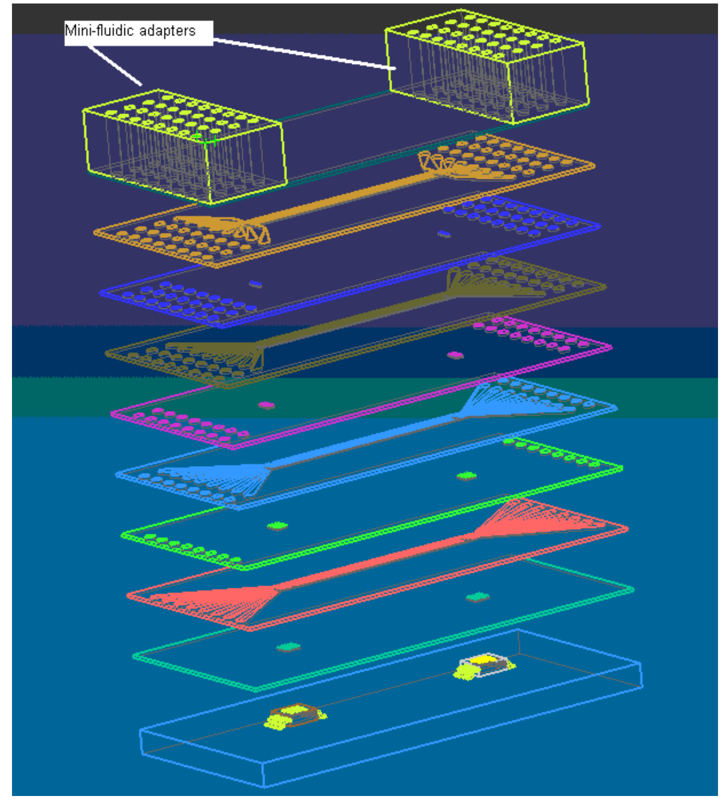
SEMI MS7-0708: Specification for microfluidic interfaces to electronic device packages



Exploded 3-D View of EFIC Package



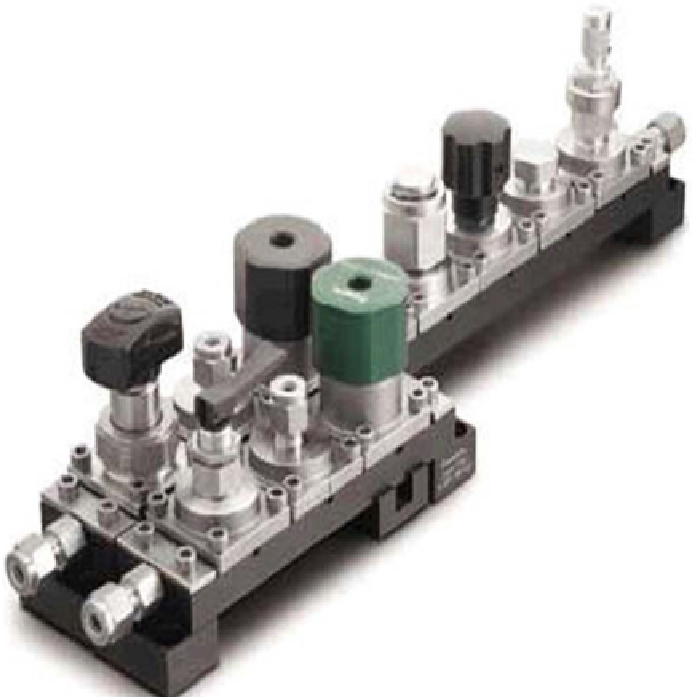
Functional Description of Assembled Parts



EFIC Fluidic Routing Card & Adapters

Republished with permission from Semiconductor Equipment and Materials International (SEMI) 2012

NeSSI™ Modular Sampling Systems



NeSSI generation III systems: microanalytical devices such as lab on chip for process and water control.

- New Sampling/Sensor Initiative
- Surface-mount modular component based gas and fluid handling and conditioning systems
  - ISA SP76 interface specification
  - Elastomeric o-ring seals
- Offer flexibility in design and implementation
- Allows for optimal positioning of analyzers in a process stream

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 Micro ChemTec
- 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

De facto standard in fittings (for instance chromatography)

- Fittings:
  - low pressure fluid transfer: thread ¼-28; flat bottom configuration
  - high pressure fluid transfer: 10-32: coned configuration of port
- Tubing: 1.6 and 3.2 mm

What is not standard?

- “CD format”: different sizes, the only common factor: making use of centrifugal forces.
- “Credit card”: meaning something about the size of a credit card.
- “Platform technology” owned and used by just one company.

TBD: CD-format

- There are international specifications (e.g. ECMA-130) which describe the physical characteristics of a Compact Disc.
  (see http://www.ecma-international.org/publications/files/ECMA-ST/Ecma-130.pdf)

  For the adaption for microfluidic application at least following parameters should be standardized:
  - inner diameter (ECMA-130, 8.2)
  - clamping area (ECMA-130, 8.4)
  - outer diameter (ECMA-130, 8.7)
  - distance of microfluidic structures to the clamping area and to the outer circumference (handling/bonding zone)

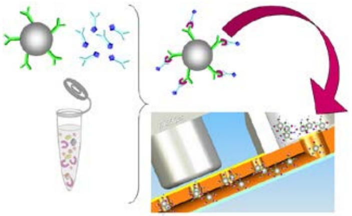
  <u>Proposed characteristics and tolerances:</u>
  - inner diameter: 15.0mm -0, +0.2mm
  - clamping area: between diameter 26mm (max) and 33mm (min)
  - outer diameter: 120mm +-0.5mm
  - thickness: a minimum thickness of 1.2mm is proposed
  - distance of structures to the clamping area >3.5mm
  - distance of structures to the outer circumference >5mm

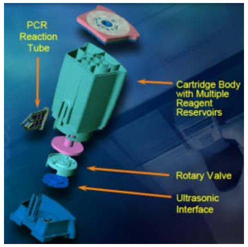
TBD: Creditcard size format

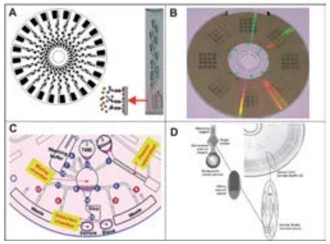
- Outer dimensions of the chip:
  - length: 85.6mm +-0.5mm; width: 54.0mm +-0.5mm
  - a minimum thickness of 1.2mm
  - corner radius: 3.18 mm +-0.03mm (3 corners)
  - bevel: 6mm x 6mm - 45° (1 corner)
- Distance of microfluidic structures to the outer edges at the larger sides >4mm
- Space reserved for interconnections: at the smaller sides a depth of 5.5. mm.
- Port holes following the earlier given positions for clamped interconnections or Luer contacts

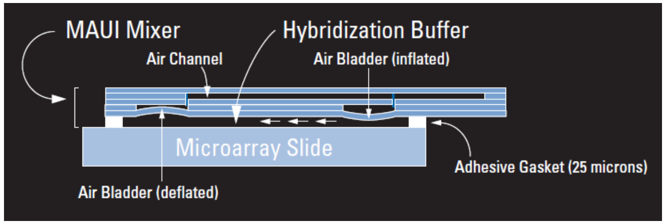
Technology trends?

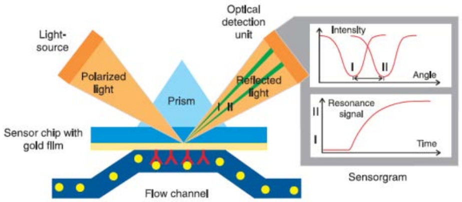
Bewildering number of technologies and concepts

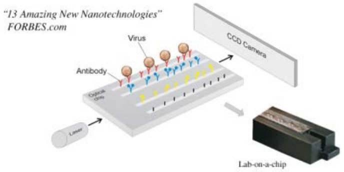


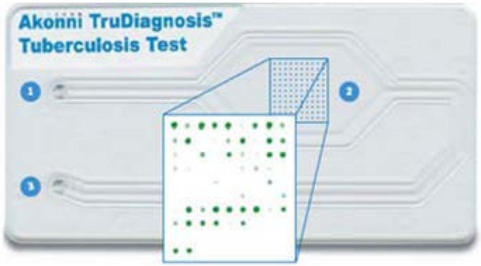


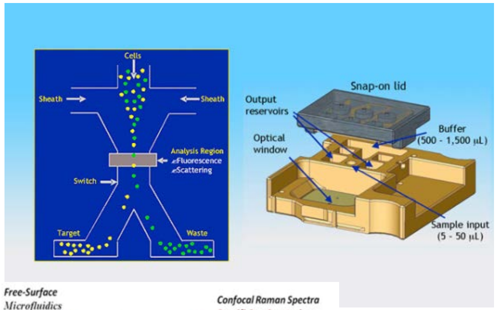


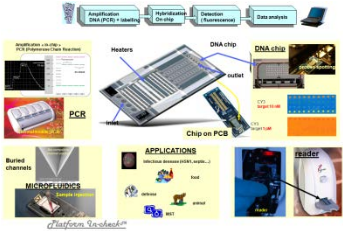


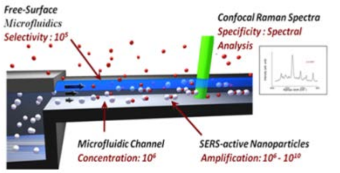


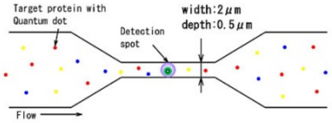


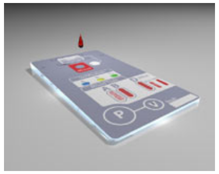


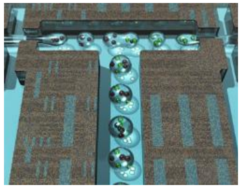








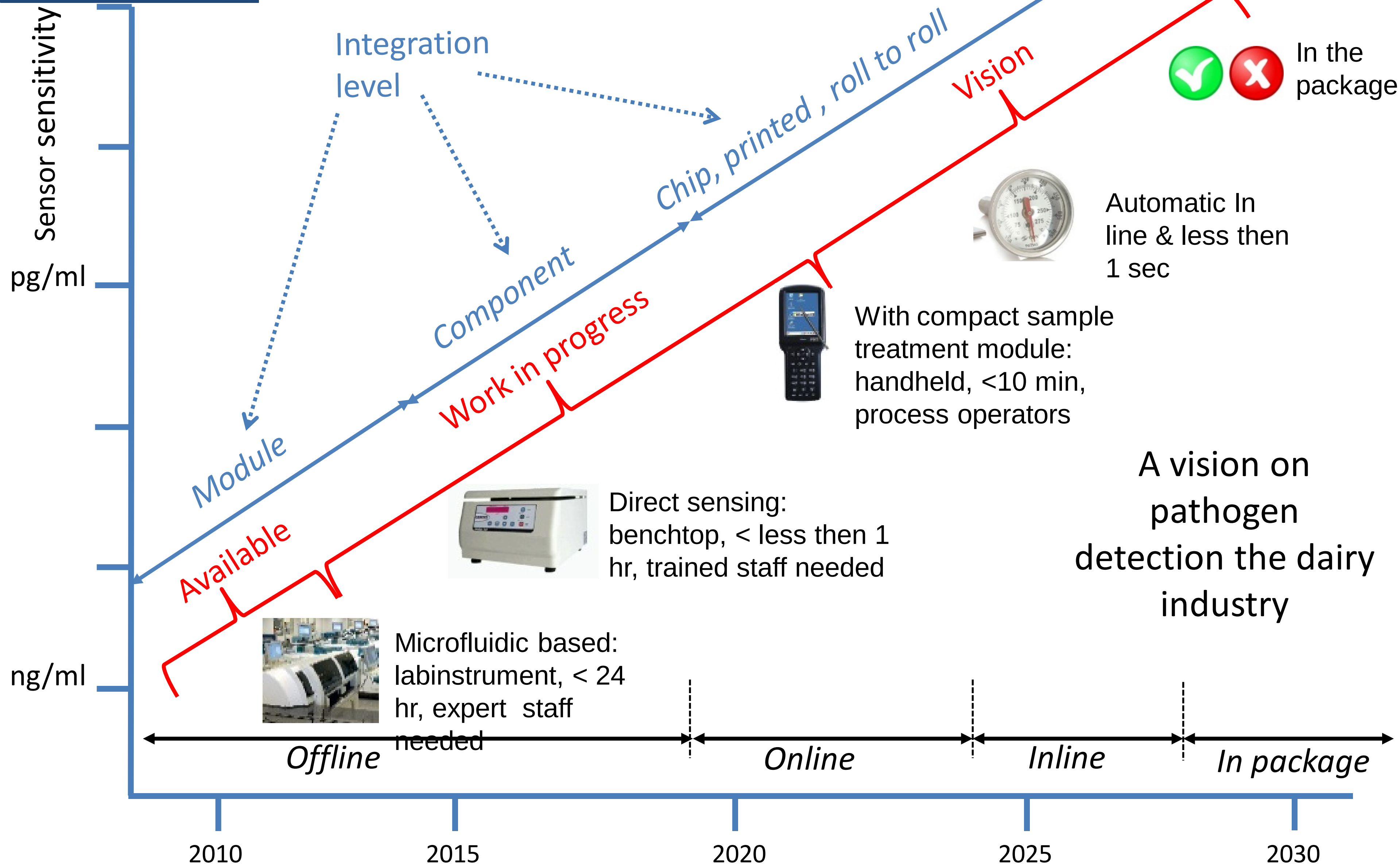




No consensus about methodology let alone technology (example HIV diagnostics)

	Technology	Status
BD FACScount	Flow cytometer, microbeads, fluorescence, Calibration needed; need of additional chemicals	available
Partec Cyflow	Flow cytometer, Simple sample pretreatment needed; dry stored chemicals, 6 months shelf life	Near market?
Alera Pima analyser	Fluorescence, image analyzing, Dried reagents on board	Released 2009
Chembio	Immuno assay	Launched 2013
BCR	Elisa, Fluorescence, nanodetectors	Near market?
Visitect	Measures CD4 protein; immobilized with antibodies, visual readout, Chemicals do not need cold storage	Near market
Zyomyx	Bonded to heavy particles, separated by density; magnetic beads used to remove monocyte contamination	close to launch,
Daktari CD4 counter	No labeling, no optics. On board chemicals Microfluidic cell, cartridge, lysate impedance spectroscopy, chromatography	Field test ongoing
Wave 80	Cartridge, integrated sample preparation, microarray? On board chemicals	Prototype
Diagnostic chips	Electrical readout, electro kinetic pumping	Prototype
Mbio	Cartridge, optical waveguide, Fluorescence	In development
LeukoDX	Cartridge, Fluorescence	In development
QuantumDX	Nanowire based FET, PCR, microfluidic cartridge	Expected in 2015
Oj-Bio	SAW with antibodies, mobile phone based	Concept only
DFA	Paper based	Concept only

Roadmap for food diagnostics



Integration: a key driver for smaller and faster diagnostic devices.

- Drivers:
  - Need for small sample sizes.
  - Ease of use / robustness.
  - Need for low cost disposables.
  - Short time to measurement result.
- Challenges:
  - Microfluidics doesn’t scale as easy as electronics (or even as mechanics) & electrons are electrons, but in microfluidics…………..!
  - Combining electronic, mechanical, fluidic and optical components or structures.
  - Technology and business environment are immature.

Always integrate microfluidics?

	PoC third world	PoC (home)	PoC (other)	Central Lab	Research
Acceptable time to result	Seconds to minutes	Seconds to minutes	< 6 minutes	Up till half an hour	Up till several hours
Cost of instruments	Up to a few 100's of $	Up to a few k$	Up to a few k$	Up to 100's of k$	Up to a few M$
Staff	Untrained	Untrained	Semi trained	Trained	Highly specialized
Cost of disposables	< 0.5 $	Preferable < 1 $	Preferable <3 $	Up to 10's of $	Less relevant
Number of tests running in parallel	1	1	1-10	Typical 10 -20	Less relevant, but flexibility needed
Level of integration to be expected	Very high	Very high	High	low	Very low

Identified integration concepts:

- The whole process from input sample to result (detected electrically or optically):
  - Chip: all microfluidic functions in one chip.
    - on the market: glass, polymer, silicon chip.
    - In development: paper, roll to roll manufactures films etc..
  - "CD": centrifugal driven microfluidic flow
  - 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 a plane or in a 3D configuration.
  - Not integrated: connections by tubing and wires.

Technology trends in microfluidics

1. Chips suppliers are becoming component suppliers.
2. Well array testing is developing into more complex testing more akin to real life situations.
3. Digital microfluidics is seen as a way to miniaturize well array testing further.
4. More efficient and faster sample preparation units (PCR in a few minutes).
5. The industry is looking for technologies that don’t need labeling, i.e. biomarker specific sensors.
6. The industry is looking for technologies that don’t need time consuming PCR, i.e. hyper sensitive sensors.
7. Plug and play microfluidic instruments, cartridges, chip holders, connectors etc. are emerging.

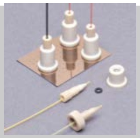
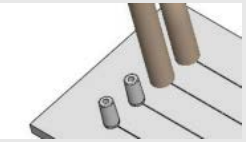
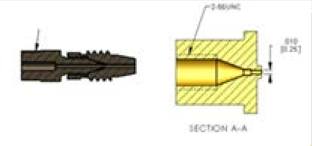
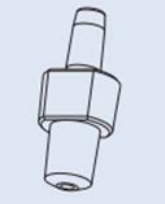
Plug and play microfluidics

Off the shelf Microfluidics

- Main application: R&D and analytical testing
- Dominant players: Dolomite, MFCS, Micronit, thinXXs, others?
- Important resellers: Labsmith (MFCS), Cole Palmer (thinXXS, Micronit), etc.

- Standards for interconnection of components / subsystems would help the market.

Chip to tube connectors

	Temperature	Pressure	Ease of connect	Supported by	
Nanoport		<69 bar	-	IDEX	
Tube over an olive		<3 bar	+		
Captite			-	Labsmith, MFCS	
(Mini) Luer	<80 C	<2 bar	++	ThinXXS, MFCS, Translume, IBID etc.	

Useful, generally accepted but not very practical

Types of Seal

Ratings – 5= good, 1= poor. Although cost is an important criteria it's not provided as it depends on which complementary components are used to allow the seal to operate.

			Ratings							
Type	Description	Application	Solvent resistance	Pressure rating	Re-use	Usability	Dead volume	Cost	Comments	Example
Adhesive	Bonding a length of tubing to a port on the microfluidic device with epoxy or other suitable adhesive	A	1	2	1	2	2			
Flared/ flanged	the flattened surface of a tube is pressed against the flat surface of a chip	A	5	2	5	4	3			Diba
Interference fitting	Two components (ferrule and port, or connector/port) are screw or press-fit together	A	3	2	4	5	1		Resistance depends on material used. High stress loads on chip (connector/interface designed to withstand)	Luer
Push in	Tube is pushed into recess to create interference fit	A	5	1	2	4	3			Uni Cal.
Nipple/Barb	Soft wall tubing is stretched over a conical or cylindrical shaped device	A	4	2	2	3	1			Value Plastics
Needle through membrane	A needle is pushed through a typically elastomeric membrane	A	3	3	3	5	4		limited pressure range,	Cytocentrics
Gasket	Mechanical (typically Elastomer) seal compressed between two components to prevent fluid leakage. May or may not grip and seal onto a tube.	B	4	4	5	4	5		Complicated and expensive connector design	Dolomite
Ferrule	A metal or polymer ring, tube or cap, placed at or fastened to the end of a tube	B	5	4	5	3	5		Complicated to design for multiconnects. Only one component to change in the event of a seal failure	Omnifit
O-ring	An elastomer ring of circular cross-section compressed between two components to prevent fluid leakage. May or may not grip and seal onto a tube.	A	4	4	5	4	1			Generic
Free path	Introducing liquids into an open port on the microfluidic device with the use of an external delivery system such as a pipette	A	5	1	5	3	5		Possibility of leaks and spills, contamination. Discrete delivery. Lack of overpressure restricts the applicability of the microfluidic device.	?

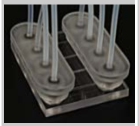
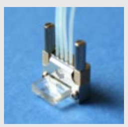
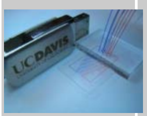
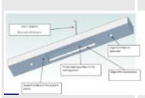
Classes of application

A: up to 2 bar (14, 3 psig or 29 psi) to include practically all PoC, Loc like instruments for instance for biochemical testing.
B: Up to 100 bar (1450 psi) we find here many gasflow sensors etc.
C: The last are the connectors for analytical instruments like GC: up to 1000 or even 3000 bar.

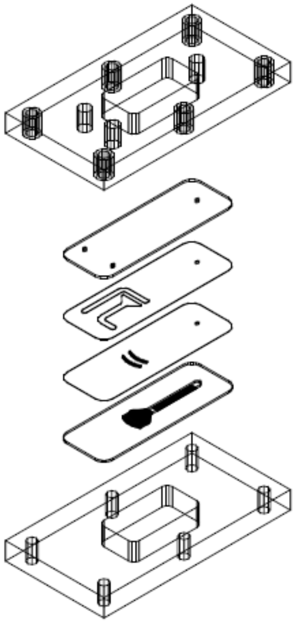
Distinctive factors

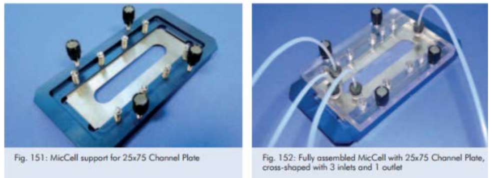
- multiple interconnections
- a small area
- leak tight
- easy to assemble
- chemically resistant
- Smooth fluidic transitions, the ideal interconnect design is one that has the least possible effect on fluid flow.
- low dead volume
- low cost to assemble, and be amenable to automated assembly
- Reversibility; (Cost of servicing and flexibility of system)
- Leak rate; (Loss of fluid and entrance of bubbles)
- Maximum pressure; (High pressures need robust design of the connector)
- Change of cross-section; (influences degassing due to sudden pressure drops and carryover)
- Maximum temperature; (Choice of materials for connector/device)
- Compatibility of materials. (Influences reliability of sample and carryover)

Multi port interconnects

		Temperature	Pressure (bar)	Ease of connect	Supported by	Status	
Quick connect		Room temperature ?	<6.9	++ (magnets)	SFC	Commercial available	
Dolomite		-15 to <150 C	<30	+ (clamped)	Dolomite,	Commercial available	Top and edge connectors, 4,8,12 channels, tubing OD 1.6mm; wetted: PTFE, perfluorelastomer
University of California		?	<3.4	+?	-	In development	
Semi USA		Room temperature ?	Low pressures?	+?	Diagnostic Biosensors	In discussion	
Micro-plumbers		Room temperature ?	Low pressures?	+ (clamped)	Micro-plumbers		
Navel Research Lab					-	Patented, license possible	

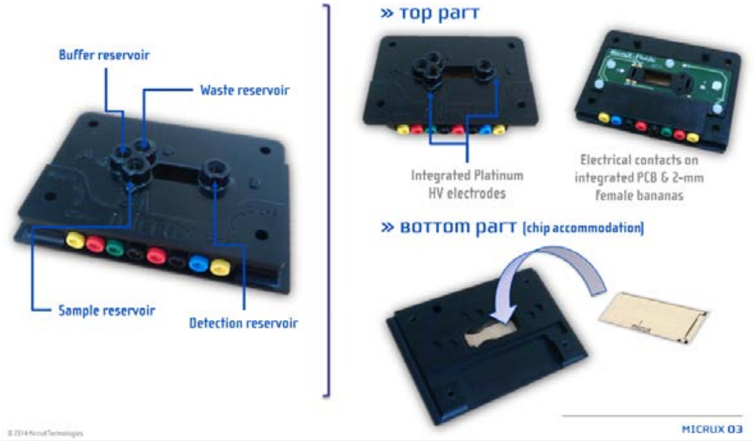
Chipholders /microfluidic adapters



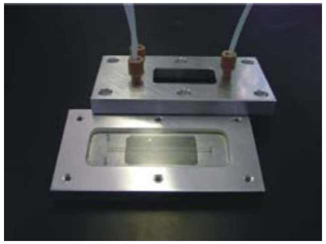


Micell

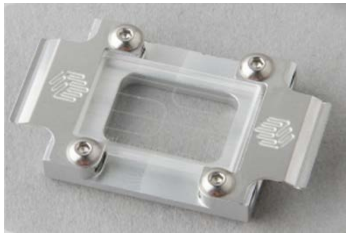
microLIQUID



micrux



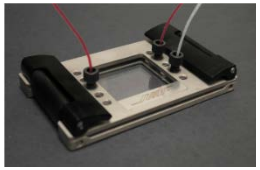
Invenios



Dolomite

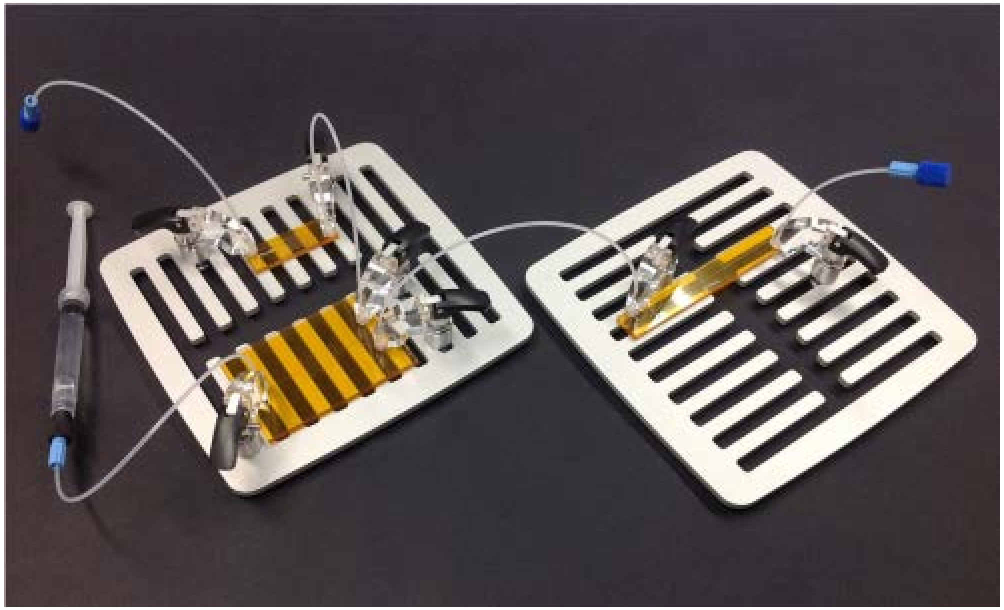
Micronit

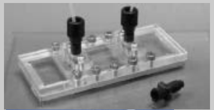
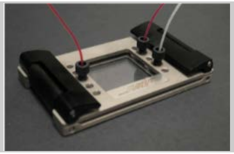
Eksigent



SIMtech

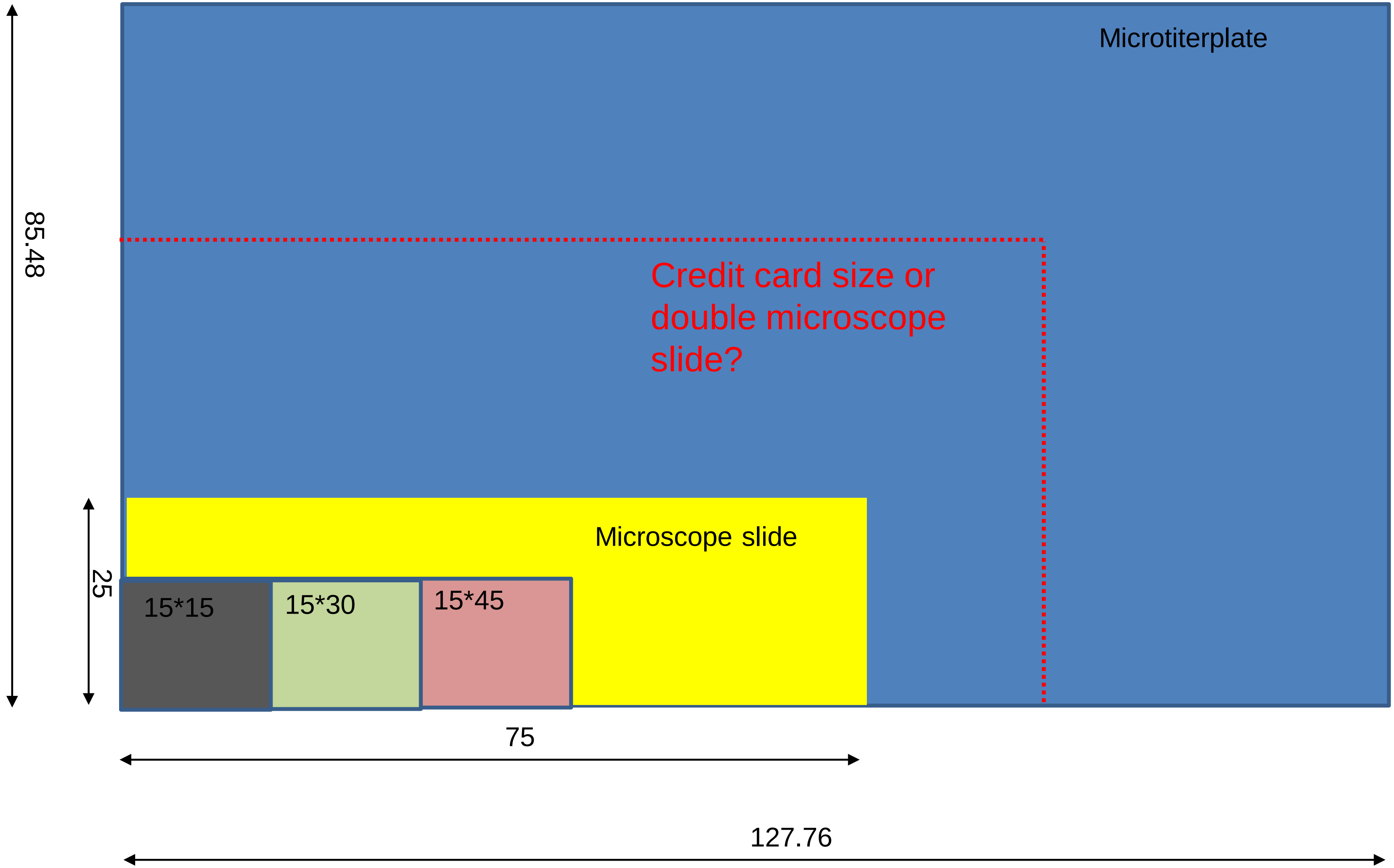
Universal Microfluidic Chipholder (SIMtech)



Company	Product		Fluidic ports	Chip layout	Specs	
Micronit	Fluidic Connect 4515	Inserted chip, 10 ports (also electrical contacts)	To 1.6 mm tube	15*45 mm family & 25 x 75	Up to 100 bar / 80 C	
microLIQUID		Up to 6 fluidic and 16 electrical ports	Luer	10*10 / 30*20/ 45*15 mm		
Dolomite	Mitos Chip Holder H	Used in connection with one or two clamped 4 port interconnects	To 1.6 mm tube	22.5*15.0*4.0 mm	30 bar, -15 to 150 C	
	Mitos Chip Holder C	Used in connection with one clamped 4 port interconnect	To 1.6 mm tube	7*15.0*4 mm	30 bar, -15 to 150 C	
Invenios/ Mikroglass	Several holders		1/4" UNF thread	118 x 28 mm / 118 x 73 mm		
Micrux	ENC-SUB-801	Integrated contacts on PCB and integrated wells, no fluidic ports	1/4" UNF thread	38*13 *0,75 mm		
UCL Micrux	(R&D activity)	2 ports		25*75 mm ?		
MFCS/ Gesim	MicCell	4 ports		25*75 mm or 22*22 mm	<6 bar; <100 C?	
SIMtech	AHQ 010	10 ports	M6 Nut	25*75 & 50*75 mm	10 bar @25 C; 3 bar @80 C.	

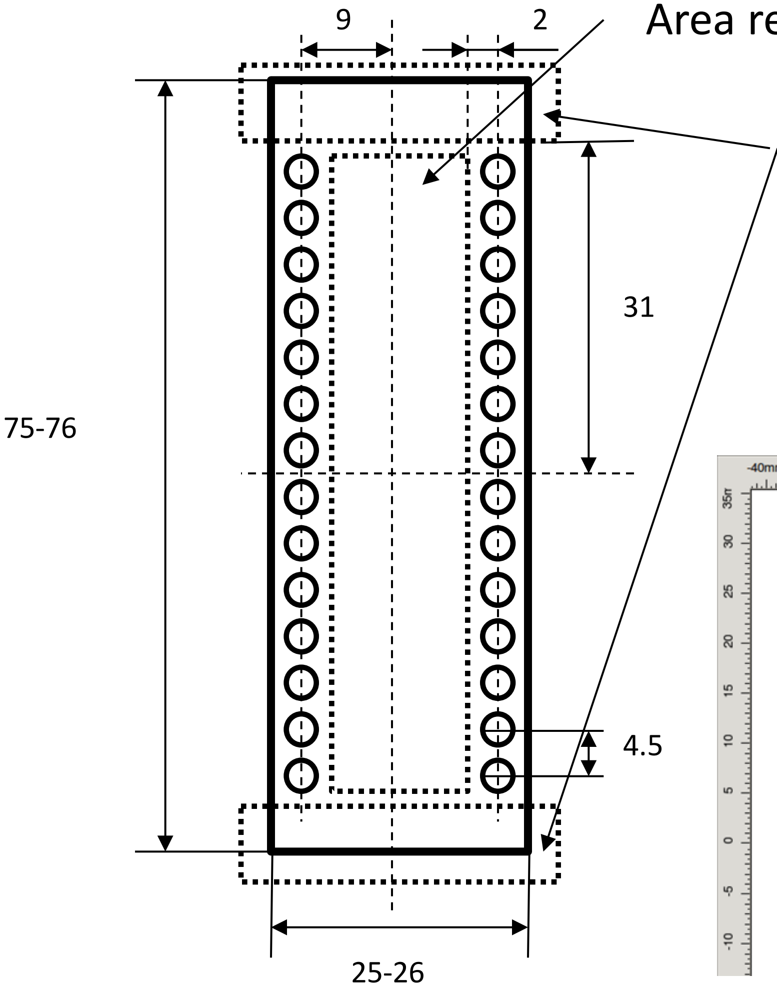
AGREED SPECIFICATIONS (MICROFLUIDIC CONSORTIUM)

The following sheets give the preferred formats for chip sizes and position of microfluidic ports. All dimensions in mm.



Microtiterplate
Credit card size or double microscope slide?
Microscope slide
15*15
15*30
15*45
85.48
25
75
127.76

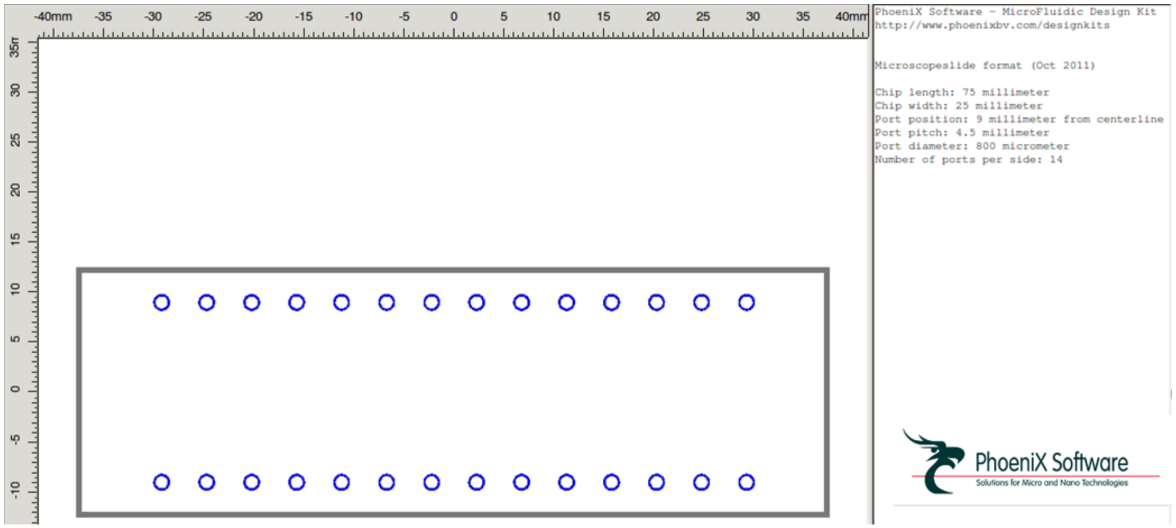
Microscope slide format



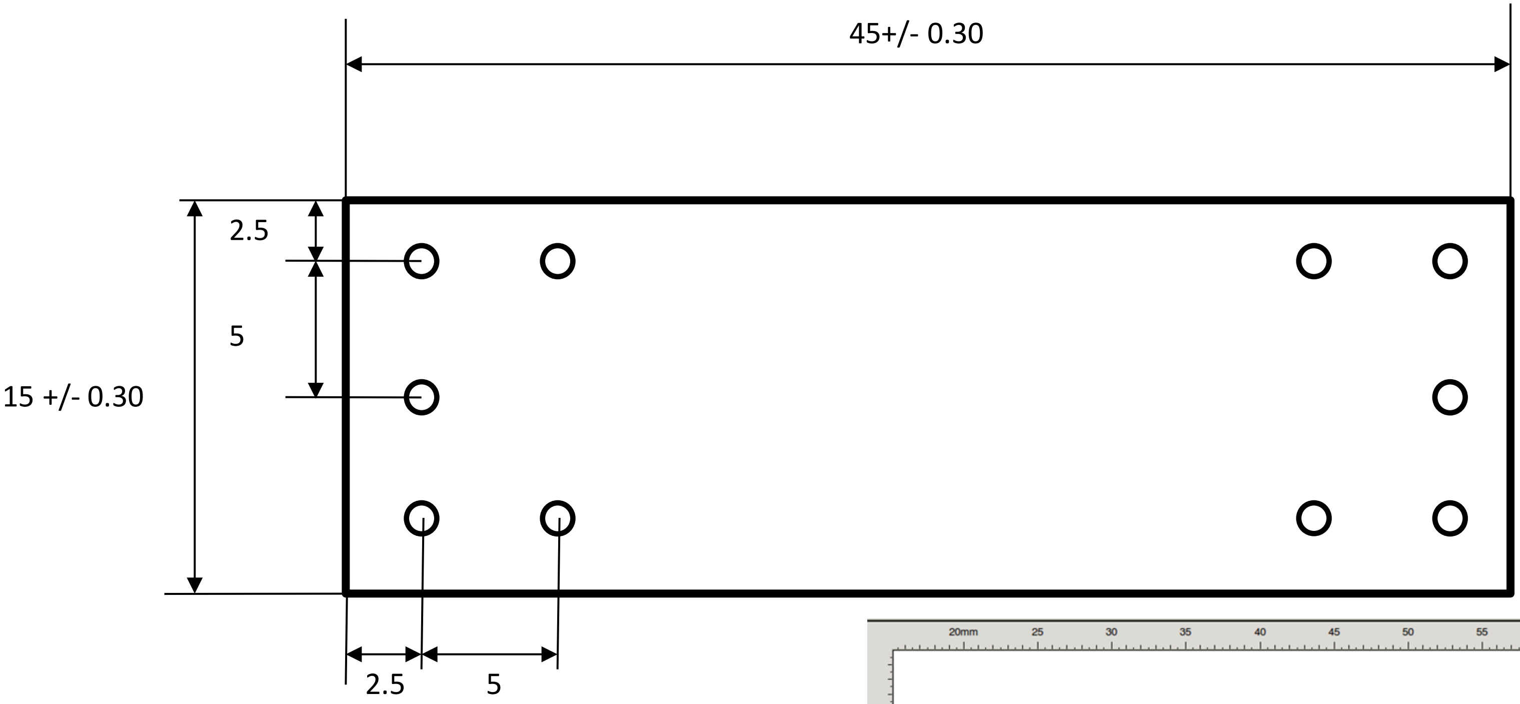
Area reserved for microfluidic functionalities

Area reserved for handling or electrical contacts

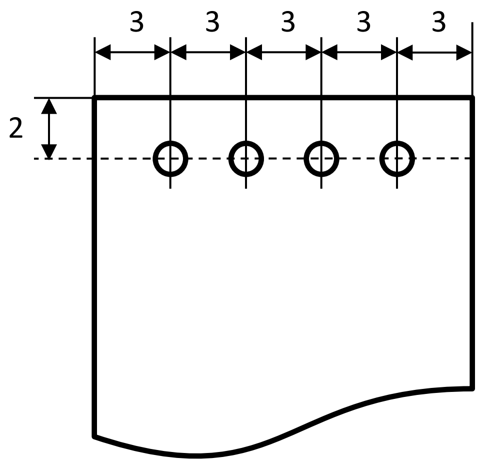
O Microfluidic port

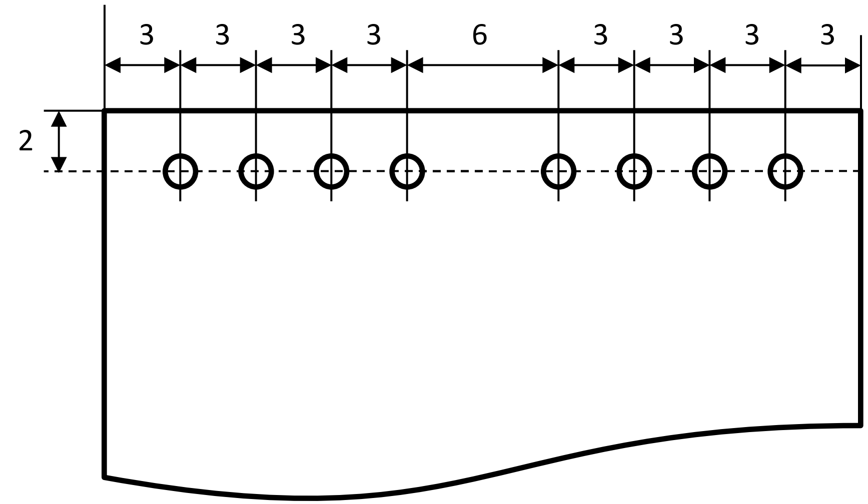


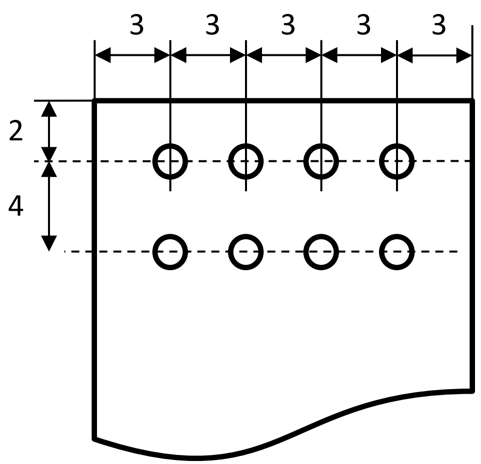
Glass chip to be used in chipholders

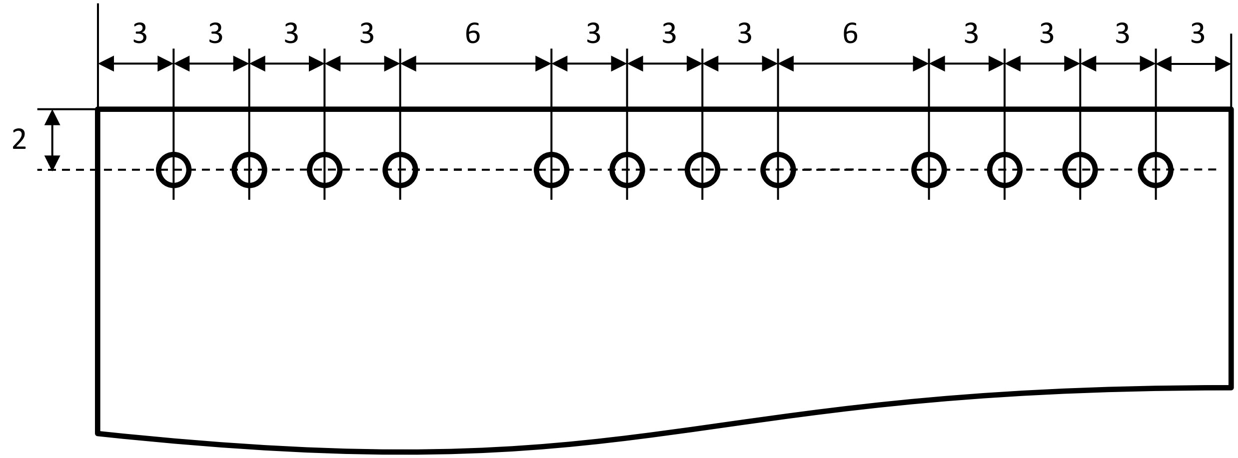


Chip layout for clamped interconnects

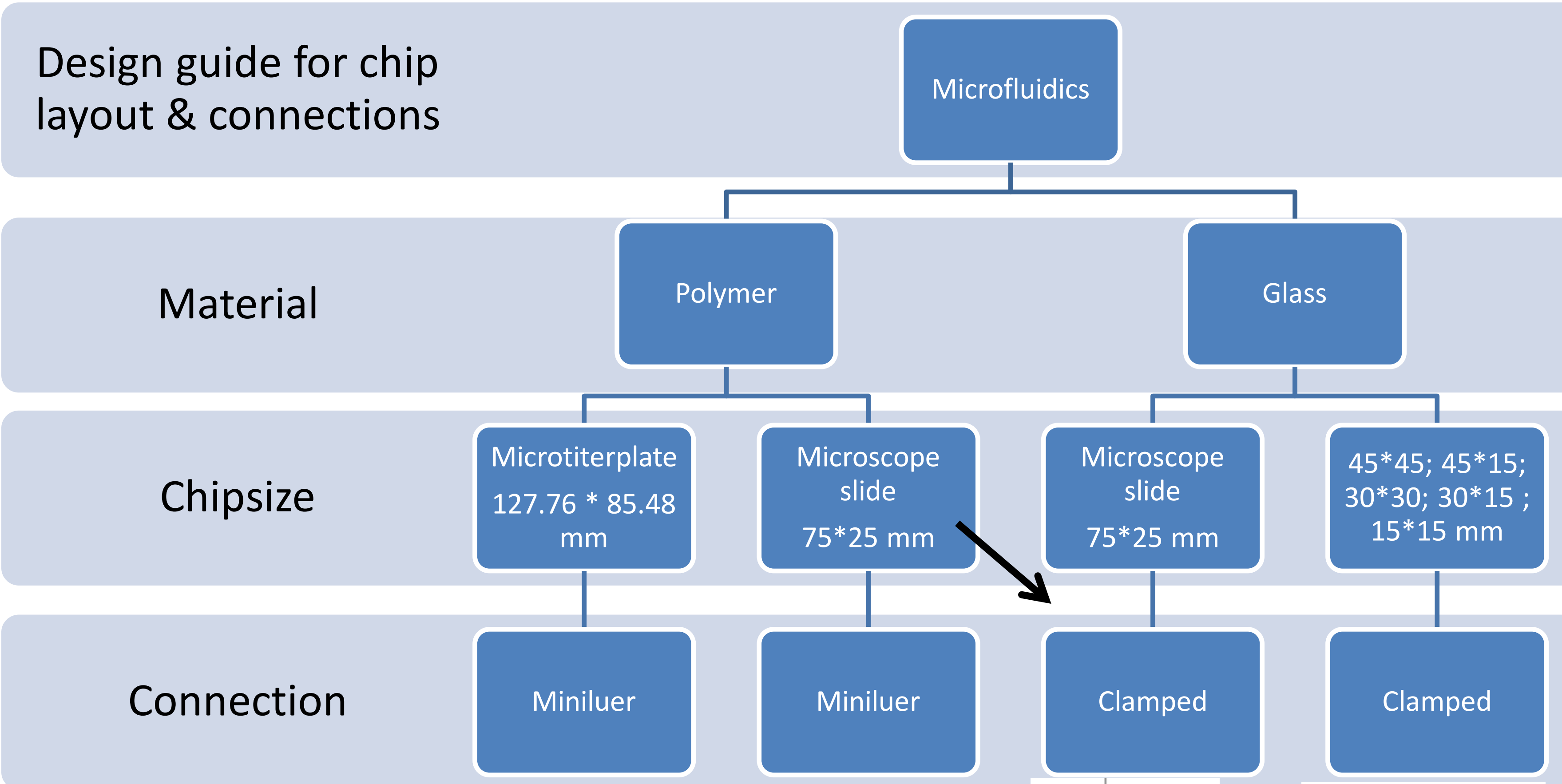


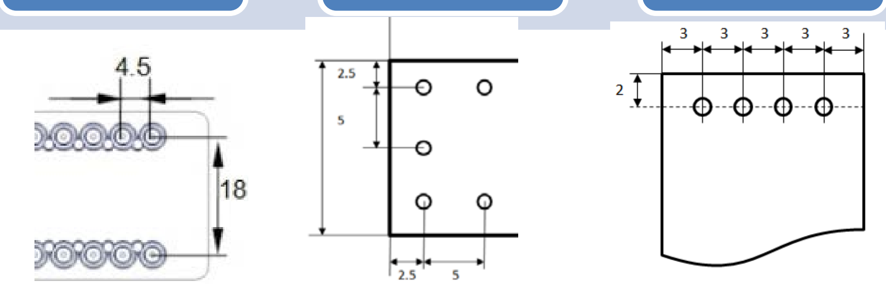






From MF5 design guide for microfluidics





Still to define

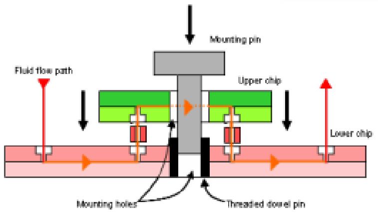
- Area reserved for clamping
- Tolerances dimension holes
- Tolerances all other dimensions including thickness chip
- Chemical inertness
- Tube dimensions
- intended sealing method, port size (inside diameter), port spacing, port location, number of ports in a row or array, any physical alignment features, and the material composition of the flow path.
- Classes of applications?
- CD and CC formats

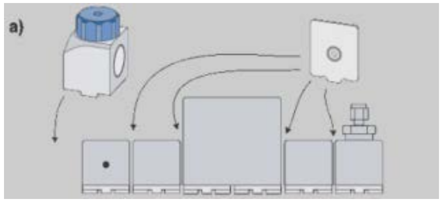
Classes of application

- A: up to 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.
- B: Up to 100 bar (1450 psi), temperature : -20 to 200 C?
  - gasflow sensors, microreactors etc.
- C: up to 1000 or even 3000 bar, temperature: -20 to 200 C?
  - Analytical instruments like GC, MS.

Microfluidic motherboard concepts

- Chip to chip
  - Epigem
- Component to component horizontally using gaskets
  - Ehrfeld
- Component to component horizontally using tubes
  - Labsmith
- Chip to board (chips placed vertical)
  - Not yet tried, but enabled by new developments





Work to do / discussion points

- Taxonomy
- Credit card size definition
- Low cost microfluidic interconnections?
- Pumping / fluidic control standards
- Sample volumes / flows
- Qualifications / measurement materials/dimensions
- Standard Autofluoresence Test Method
- Mobile phone platform?

Low cost disposable interconnects?

- Those interconnects should:
  - Have the simplicity of Luer interfaces,
  - be multi connect,
  - be self aligned,
  - having no dead volume, and
  - be low cost (<< 1 $)
- The temperature regime however is room temperature and the pressure can be < 1bar or even negative pressure.

Acknowledgements

- Ali Tinzali, Gottfried Reiter, Harald Kraushaar (Sony DADC)
- Ronny van 't Oever, Harmen Lelivelt, Marno Blom (Micronit)
- Mark Giligan, Andrew Lovatt (Dolomite)
- Marco Bianchessi, Roberto Brioschi (ST Microelectronics)
- Peter Hewkins (CfBI)
- Mark Tondra (Diagnostics Biosensors)
- Holger Becker (MFCS)
- Richard Bijlard (Ivenios)
- Thomas Dietrich (IVAM)
- Twan Korthorst (PhoeniX)
- Paul Wright (DIBA)
- Thomas Henkel (IPHT)
- Joost Lotters (Bronkhorst)
- Gerald Kreindl (EV Group)
- Mark Crockett (Memsmart)
- Nicolas Szita (University College London)
- Peter van Stiphout (Cytocentrics)
- Ray Filteau (CMC Microsystems)
- Vincent Spiering (Qmicro)
- Alexios Tzannis (IMTag)
- Gary Ng Sum Huan (SIMTech Microfluidics Foundry)
- Daniel Mark (IMTEK)
- Juan G. Santiago (Stanford University)
- And many others