Getting Started with Microfluidics

James Gwyer et Al (Members of the First European Microfluidics Consortium)*

Introduction:

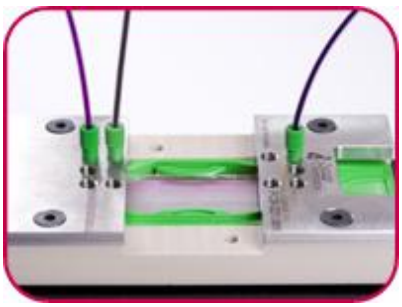
This paper is designed to support people new to the field when they plan and perform their first microfluidic experiments. It has been prepared by James Gwyer of Philips Research and other members of the First European Microfluidics Consortium [Ref 1, box D] drawing on their experience with their first microfluidics experiments. The paper briefly addresses 'What is Microfluidics and Why Should I be interested?' (this theme is covered in more detail by papers published by the consortium on its dedicated website) and then moves on to 'Theoretical Considerations when Working with Microfluidics' and 'Designing your First Experiment' focusing on: 'What are you trying to achieve?',' Choice of Materials', 'Prototyping Options' and subsequently looking at 'Dealing with Technology Providers', 'Accessories and Peripherals' as well as some brief notes on 'Intellectual Property'. We conclude with a discussion of 'where next' and highlight some of the material which the consortium hopes to cover in subsequent White Papers.

What is Microfluidics and Why Should I be Interested?

For the purpose of this paper, Microfluidics is the study of liquids in picolitre, nanolitre or microlitre volumes moving in channels with dimensions measured in micrometres up to a fraction of a millimetre. For experimental purposes a modular approach, quickly assembling individual elements for transport, routing, processing and testing in a desired combination able to use a wide range of fluidics (including body fluids) is convenient for investigating many applications. The small size of the liquid channels leads not only to smaller (portable!) instrument, it also has benefit in terms of faster and more accurate measurements. The ability to perform controlled/reproducible reactions using small volumes of samples + reagents, under temperature and pressure control quickly and with a minimal energy requirement is another benefit of the microfluidic approach. Parallelization and integration of the essential structures in such modular solutions (including sensing) into a production device provide a route for scale up and production/cost engineering.

The great flexibility and potential for automation of this approach has led to device and system development by chemists, biologists and engineers for applications across a wide range such as medical diagnostics, forensic science, chemical synthesis and sensing [Boxes A, B and C]. However the path from R&D to proven commercial devices is not well trodden and there are many traps which await the unsuspecting researcher, leading to waste of time, money and creative energy. This paper is designed to help reduce the risks of the reader falling into these traps!

Box A:



FutureChemistry uses glass microreactors to perform flow chemistry making chemistry safer and more cost –effective. The microeactors with channels and mixing structures proving high levels of accuracy and inertness are manufactured by Micronit Microfluidics.

Theoretical Considerations when working with Microfluidics

As the size of channels in which a liquid flows becomes smaller and smaller, local effects such as surface tension, laminar vs turbulent flow, Reynolds number and surface chemistry play a larger role in the physics and the chemistry of the reactions under investigation. See ref [2]. The maths involved soon reaches a level of complexity beyond that with which the average chemistry/biology researcher is comfortable!

While software 'Microfluidic Modules' for Computational Fluid Dynamic Packages such as [3] exist you should not assume that these are able to deal with every fluid/material/dimensional variant which you might want to use. The modelling discipline is just not developed enough.

In the face of this, some options include:

- Use simple models:
    - such as modelling the branches of a microfluidic device like resistances in an electric network where "Pressure = Resistance x Flow") – but recognise that it will be imperfect
    - conservation of volume/mass
- Consider working with 'droplets' (oil in aqueous or vice versa) whose movement within a microfluidic device are often easier to observe/manage. Box B.
- Consider the trade-off between doing a theoretical calculation and a handful of 'scoping' experiments to empirically prove the dynamic model of your system around its desired operating point.

You should consider some of the factors which might 'spoil' a theoretical result such as: non-homogenous liquids (eg those containing cells or solids); surfaces which are not smooth or chemically inert; places within your device where flow is likely not to be laminar) .

Getting Started

Before starting it is important to think hard about what you are ultimately trying to do (eg develop a portable medical device; design a high volume chemical synthesis process) and what operating conditions will this require (battery power/high pressure/temperature/corrosive resistance?) Will these conditions put any constraints on your final device which need to be considered in your proof of principle experiment?

Choice of materials for making your microfluidic device is also important. Consider the rough guidance below

	Chemical Resistance	Optical Readout Properties	Temperature / Pressure Etc Stability	Cost of Prototype Device	Cost of Mass Produced Device
Polymers (also suited for prototyping)	Very Low	Good	Poor	Low	High
Hard Polymers	Low	Good	Medium	Medium	Low
Glass	High	Excellent	Good	High	Medium
Metal	High	None!	Very Good	Medium	Medium
Silicon	High	None!	Good	Very High	Medium

Remember that while Prototyping Polymers (where thermo set like PDMS or thermoplasts like PMMA) are convenient for rapid prototype creation, they are relatively soft and will be attacked by a whole range of chemicals including most alcohols! Besides, a product made with a certain material might have very different properties when created from another material and/or other production process.

Also when choosing materials, consider lead time for producing your next device/prototype/experiment.

	Do it yourself fabrication – or support from your local university? (Only days to set up)	Purchase of 'standard' Modules from a partner (needs weeks to set up)	Custom design of Modules (Several months needed)	Custom design of integrated solutions (many months only with a partner)
PDMS	Yes	Yes	Easy	N/A
Polymer	No	Yes	Hard	Hard
Glass	No	Yes	Hard	Hard
Metal	No	No	V Hard	Hard
Silicon				

The use of the term 'modularity' above is also to be treated with caution:

- At present interfaces between modules will often consist of time-consuming tubing and glue.
- While some suppliers have catalogues of mutually compatible components, do not assume that modules from different suppliers will easily interface to each other

When selecting and working with a module supplier for the first time, think about:

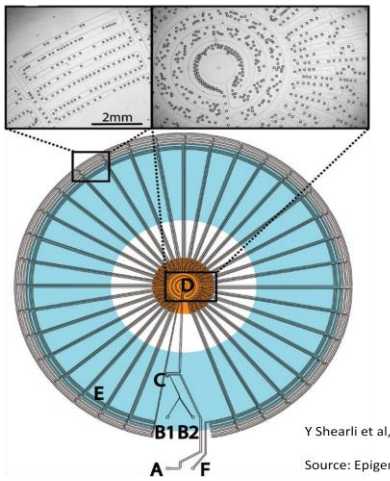
- the possible need for a second source to reduce risk as your device gets closer to market (what happens if your supplier is acquired by a competitor or goes out of business?)

- the possible need to migrate from one material to another as you contemplate scale up

- the attractiveness of (open – ie where the drawings etc are in the public domain or available on a free licence basis) standard interfaces (eg click fit) to equipment from other suppliers. (The European Microfluidics Consortium Ref 1, Box D is seeking to promote such Open Standards).

Box B

Case history: Cambridge, Imperial Univ.s
DNA PCR in microfluidic microdroplets



Y Shearli et al, Anal. Chem. Web site

Source: Epigem © 2010

- PCR in water-in-oil droplets
- 34 PCR cycle in 17 min using static temperature zones on circular design
- amplification from a single molecule of DNA per droplet
- Key component for microfluidic tool kit

When designing your microfluidic structure, ask yourself what property you are trying to demonstrate with a prototype. Examples might be:

- Ability to synthesise chemical 'x'
- Ability to separate out 'y'
- Ability to test for presence of 'z'

.. to a given level of accuracy, yield or with a particular sample condition.

An important class of readout is optical. If your device is acting as a 'wave guide', remember to consider the optical properties of the materials you are using (eg clarity, refractive index, flatness) and include these in your consideration of 'reproducability' (see 'where next')

Working together with a Technology Supplier

Few applications focussed organisations will be able to handle device design/realisation in anything other than prototyping polymer. However, there are a large number of technology suppliers and design partners who can handle this for you and your early experiments and modelling experience, if encouraging, should give you a good idea what you want from such a technology supplier.

In dealing with such suppliers (Several are in the European Microfluidics Consortium Ref [1] Box D and others can be found in the articles published at www.microfluidicinfo.com) you might want to address:

- Detailed technical designs from your 'Powerpoint Concept';
- An agreed number of prototypes which meet your dimensional specification (you can ask for functional specification but the supplier might not be able to understand/deal with this);
- Right to use Intellectual Property filed by the supplier (see below) or other specialist skills.

Technology suppliers will have built up knowledge from their previous supply contracts and it is important for you to maximize the opportunity to leverage on this. You should ask about:

- Whether they have made devices like yours before
- What the lead times/ costs were? Ask for references and follow them up!
- Whether it is possible to get extra devices to specifications close to yours (from previous runs) quickly and at low cost. These could provide useful reference points.
- What type of data should be used to describe the devices to be produced .. this might range from 'back of a cigarette packet' through to an agreed version of a sophisticated CAD package (like AutoCAD).
- What their views are on simulating the performance of their part of the process before a new module is realised. (The European Microfluidics Consortium is seeking to promote simulations with libraries which can cover modules from a range of suppliers).
- Whether their solutions infringe Intellectual Property belonging to third parties and what the situation on grating a licence to use them will be if such infringement subsequently comes to light (see below)

Box D: The First European Microfluidics Consortium has the objective to grow the market for microfluidic based solutions.

It has worked on:

- Stimulating Standards
- Finding Economies of Scale across Application Boundaries
- Learning together in a spirit of 'Open Innovation' seeking 'Collaborative Advantage'

Members of the consortium: Aquamarijn, BASF, Boehringer Ingleheim, Cyclofluidic, Dolomite, Eppendorf, Epigem, Forensic Science Service, IMT, Imperial College, Micronit, Laboratory of the Government Chemist, Lionix, Dutch Forensic Science Laboratory, Philips Research, SonyDADC, University College, Wellcome Trust, University of Cambridge

The Consortium is managed by 'Centre for Business Innovation Limited' www.cfbi.co.uk

While the work of the consortium is confidential and designed to support the needs of its members, it has chosen to put some of its findings into the public domain at www.microfluidicsinfo.com

- What route they would envisage if your devices are ever to be made in large volumes. Have they done this before? With whom and can they give references?

Accessories / Peripherals

Over and above the design and realisation of the microfluidic devices themselves you should also ask about:

- Pumps – what are the flowrates (and in particular the accuracy of flow rate) that you need? Low flow rates can be a particular challenge. How do you envisage achieving this in (say) a battery driven point-of-care device?
- The connectors they propose using (for example Omnifit or Upchurch standard lab fittings) and the implications for dead volume/flushing which these bring with them.
- The coatings they propose using (as a way to improve chemical resistance or to impart hydrophilic/phobic properties for, say, droplet management) and the detail of the chemical, optical and physical properties of these.
- Valves – these are a particular area to watch out for Intellectual Property (see below)
- Optical Readout devices.

Intellectual Property

There is a very large amount of intellectual property covering:

- physical realisations of devices and features (such as valves/switches)
- Sensing of reaction outcomes
- Solutions to specific application needs

using microfluidics. While many of the original patents in the area will lapse in the early 2010s a significant set of secondary patents have been filed and granted .. particularly to larger American and Japanese companies. Beware of 'Trolls' – ie patents granted to a third party who will wait until you have invested in a factory to build your new device and started to generate significant revenues before they come out of cover demanding back dated licence fees for your infringement!

While there is no easy (or cheap!) solution here, we would recommend:

- Not ignoring this potential problem
- Filing your own IP .. so that you at least have something to trade if a patent battle ensues.
- Commissioning a patent agent to investigate the key aspects of your development
- Budgeting in your business plan to pay licence fees.
- Having deep pockets – or a partner who has them!

When I am happy with my prototype - where next?

This depends on your application and at this stage of the process one solution will not suit all users however things to consider are:-

- Cost per device. How are you going to cost engineer your product to the target price? Options might include:
    - Replacing a modular approach with an integrated approach
    - Changing the materials used and the manufacturing technology
    - Stripping out the things which are not essential
- Reproducibility. How can you guarantee your target levels of accuracy when you move to higher volume production?

    - How reproducibly can devices be made using your chosen manufacturing route. Consider for example tolerances on: injection moulding; milling as well as 'creep' in some materials
    - If there is variability in your device – how can your design allow for this?
- Strategic Issues. How can you insulate yourselves from the unexpected? Eg Business failure of a key supplier? Appearance of a 'Troll' patent? Change in supply materials/components prices or currency fluctuations?
    - Consider 'second sources' for key components
    - Have a continuously evolving 'technology road map' so you know how your current preferred solution will be overtaken as new technology emerges – and you have the option to accelerate development here.

The list of 'where next' topics above is not exhaustive. The European Microfluidics Consortium plans to add new White Papers to address some of these issues as the insight and demand emerges.

We hope that this contribution has helped you en route to developing successful microfluidic based solutions to address today's market needs – and wish you 'Good Luck!'

References

[1] First European Microfluidics Consortium: Organised by Centre for Business Innovation Limited. www.cfbi.co.uk/index_files/microfluidics.htm

[2] Stone et al., Annu. Rev. Fluid Mech. 2004. 36:381–411

[3] http://www.esi-group.com/products/Fluid-Dynamics/cfd-ace/applications-1/microfluidics/?searchterm=microfluidics

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