Fabrication Challenges for Point-of-care Diagnostics and Organ-on-chip

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Introduction

1. Chemical and biological processing on a chip
2. Fluid manipulation on chip
3. Integration of transducers
4. PoC diagnostic for Deep Vein Thrombosis (DVT)
5. Organ-on-chip for high-throughput screening
6. Merits of digital fabrication for microfluidic devices
Pottery Tableware, Pompeii, ~ AD 79
History

• Microfluidics, Lab-on-a-chip, μTAS
  – Chemical and biological operations in miniaturised and automated manner
  – High reproducibility
  – High level of parallel operations, e.g. in High Throughput Screening
  – Reduce use of reagents and higher efficiency arising from scale
  – Portable and remote use (patient’s bedside, riverwater, ..)
  – Use by non-specialists
Chemical and biological processing on chip

- Requires combination of fluidics, electronics, mechanics, optics, biology, chemistry, ...

- Fluid control
  - Directed (exertion of force), statistical or mixture

- Materials
  - Polymers, glass, Si, paper, hybrid

- Transducer
  - Electrochemical, optical, ....

- Packaging, interface with macro world
  - Inter-connections for fluidics, mechanical, optical and electronic elements
Fluid Moving

• Typically, pressure, acoustic, electrokinetic, centrifugal
• Acoustic & electrokinetic scale as $L^2$, where $L$ is the capillary diameter; pressure & centrifugal force scale as $L^3$
• Pressure
  – External syringe pumps; non-pulsating flow & corrosive liquids not in contact with pump but multiplexing difficult
  – Integrated pumps; precise flow control, fast response, small dead volume but modest flow rate, low pressure, large chip area, pulsating flow
• Electrokinetic
  – Easy to implement but more difficult for polymers & also joule heating
• Centrifugal
  – Wider volume range, easier multiplexing but constrains on device design
Integrated Transducers

• Optical
  – Absorbance, fluorescence, chemiluminescence, evanescent wave, ..
  – Choice of optical elements to be integrated onto chip cost & feasibility
    • Light source, photodetection
    • Lenses, mirrors, filters, waveguides

• Electrochemical detection
  – Potentiometric, voltammetric, impedimetric
  – Good for turbid sample
  – Requirement to pattern electrodes on substrate, easier to implement for on-chip detection

• On-chip electronic processing

• Bioreceptor
  – Methods of integration onto transducer
Impedimetric Detection

- Label-free ligand/receptor binding using immobilised bioreceptor on impedimetric transducer
  - Bacteria
  - Virus
  - Aptamers and DNA/RNA hybridization
- Selection of different targets through altering electric field by changing electrode configuration
  - 100s of Daltons such as atrazine
  - 2-5 microns particles such as bacteria
- Automated washing reduces non specific binding
  - Minimal sample pre-treatment required
Analytical approach

“model” recombinant antibody fragment with His tagged and appropriate antigen

Impedance measurements
Dynamic range of detection of the antigen

- Conducting polypyrrole with redox probe NTA/Cu
- Immobilisation of Tag antibody on a NTA/Cu as linker

IDE microelectrodes
Chips electrodes
Point-of-use Diagnostics

Hafaid, I., et.al., *Biosensors and Bioelectronics*, 2010, 26(2), 736-742
Korri-Youssoufi, H., et.al., *Sensors and Actuators, B:Chemical*, 2010, 144, 323-331
Integrated Microfluidic Cartridge

- Quality of electrode layer: dimensional accuracy, metal adhesion, fabrication efficiency
- Microfluidic body: fine feature replication
- Assembly quality: accuracy, passivation, septum
- Compatibility with mass production: micro-injection moulded microfluidic body, R2R fabrication of electrode layers

Photolithography

Lamination of photoresist

Development

Cu etch

Stripping of photoresist

Cr etch

Laser dicing

Technology prototype realised in copper
Organ-on-chip

- High attrition of drug candidate compounds
- Cell culture increasingly used to predict clinical response to drugs
  - More representative than simple biochemical assays
  - Reducing need for whole animal testing; lengthy, expensive, ethical issues
- Small footprint, low cost device for culturing of multiple cell lines for HTS of chemotherapeutic drugs
- Cytotoxicity assays of pyocyanine on MCF-7 cells and assessed for toxic effect on HepG2 as indicator of liver injury
- Sequential combination of paclitaxel and aspirin drugs on MCF-7 cells
• 4x6 array of microchamber elements addressed by series of row and columnar pneumatically actuated normally closed valves
• Three parts; fluidic, control and membrane layers
Selected fluorescent images of MCF-7 cells after sequential treatment with the drugs paclitaxel and aspirin.
Digital Fabrication

• Complex architecture can be built using layer by layer approach
• Potential for each layer to be of different material and providing different functions
• Additive manufacturing reducing complex processing necessary within subtractive approach and so reducing cost
• Very high volumes not always required; allows more bespoke and functional systems at lower volumes
Thank You & Questions

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