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

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Project DIGINOVA: Biomedical Applications for Digital Fabrication, 6th November 2013, CPI's National Printable Electronics Centre, UK

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

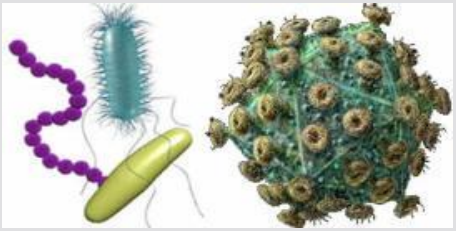
- Typically, pressure, acoustic, electrokinetic, centrifugal
- Acoustic & electrokinetic scale as L^2, where L is the capillary diameter; pressure & centrifugal force scale as L^3
- Pressure
  - External syringe pumps; non-pulsating flow & corrosive liquids not in contact with pump but multiplexing difficult
  - 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

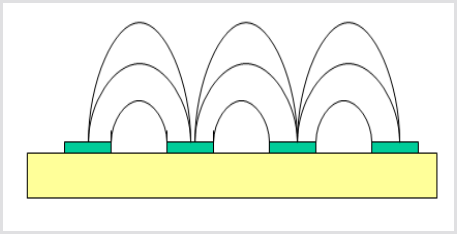
Integrated Transducers

- 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



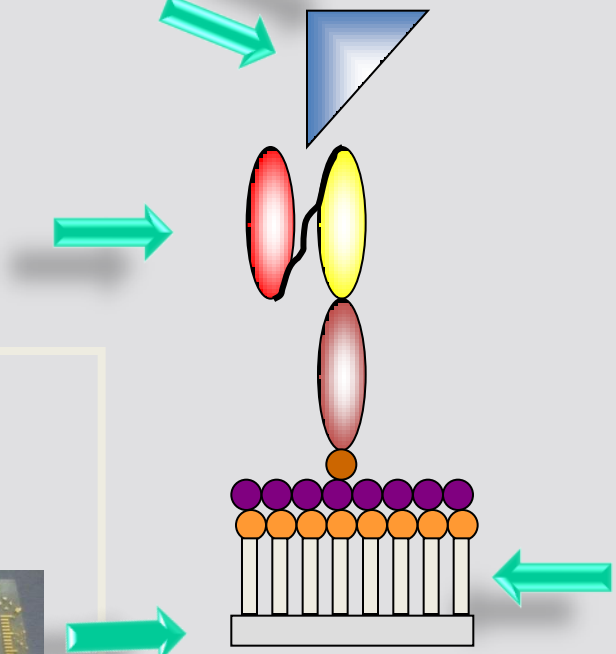


Analytical approach

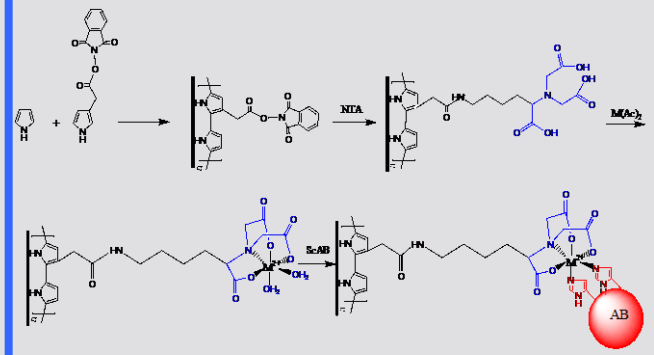
"model" recombinant antibody fragment with His tagged and appropriate antigen

Impedance measurements

Dynamic range of detection of the antigen

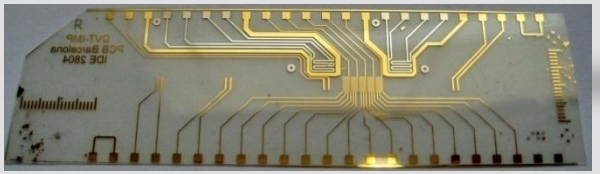


- Conducting polypyrrole with redox probe NTA/Cu
- Immobilisation of Tag antibody on a NTA/Cu as linker

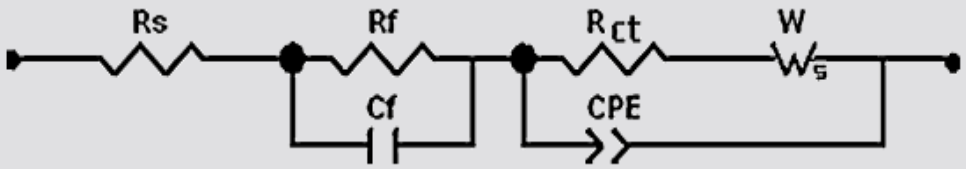


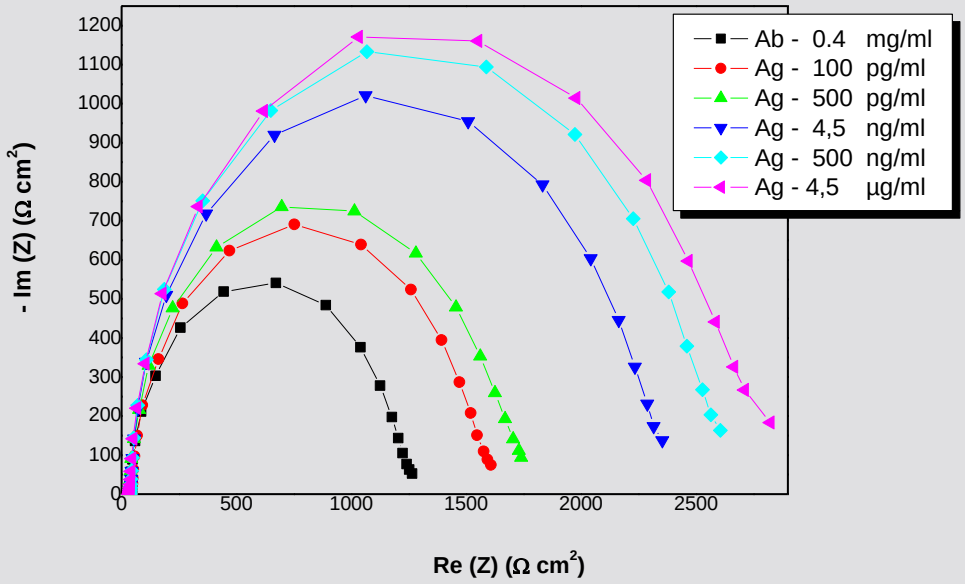
IDE microelectrodes

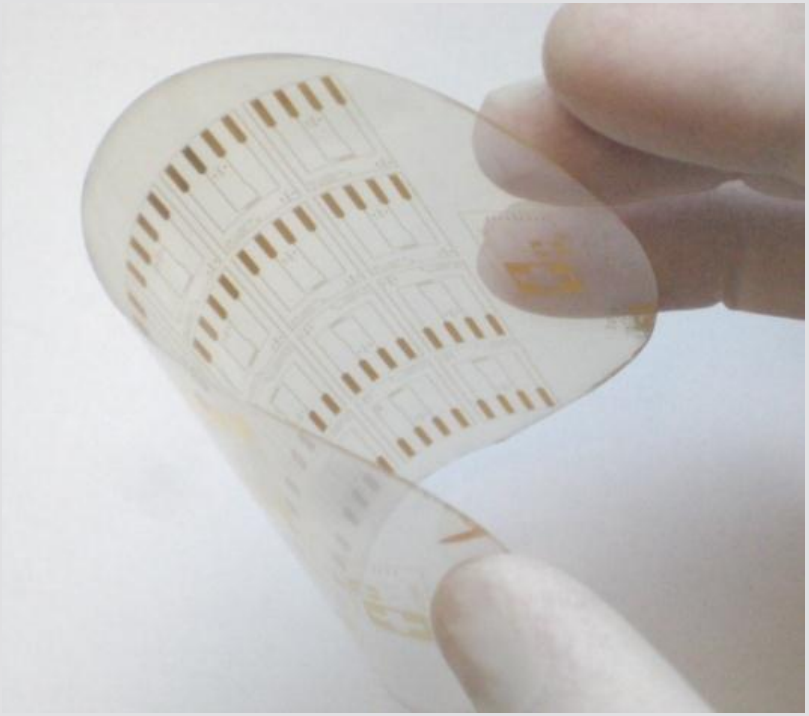
Chips electrodes



Point-of-use Diagnostics







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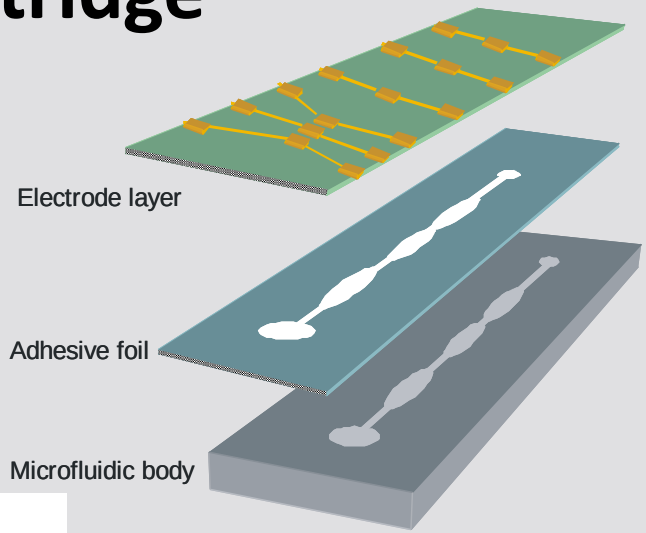
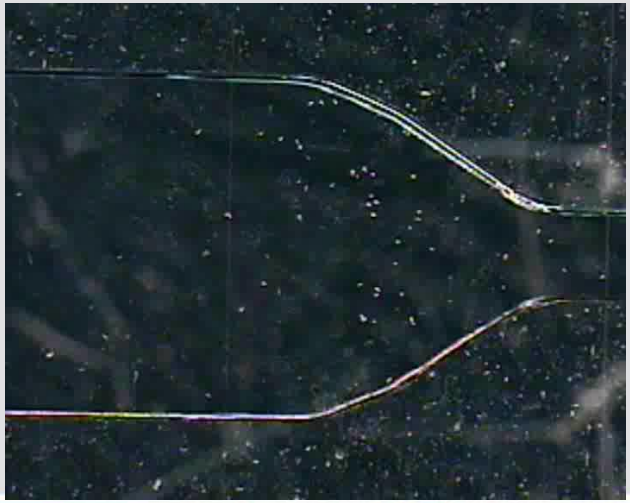
Integrated Microfluidic Cartridge

- 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





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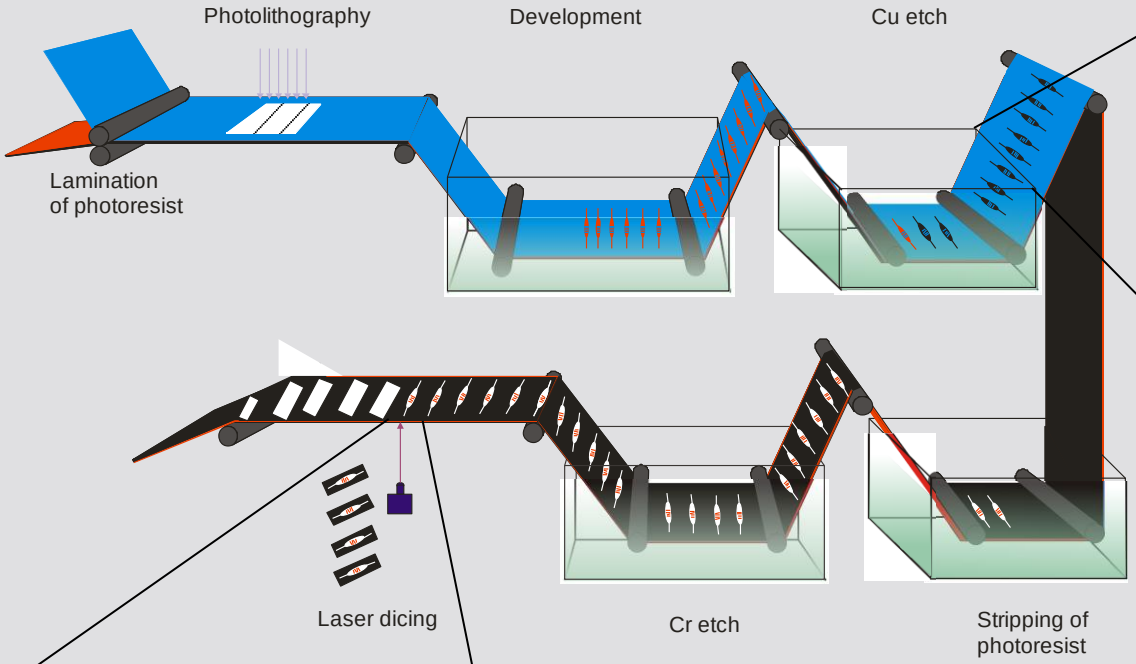
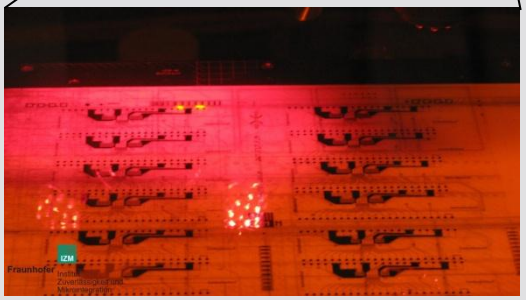
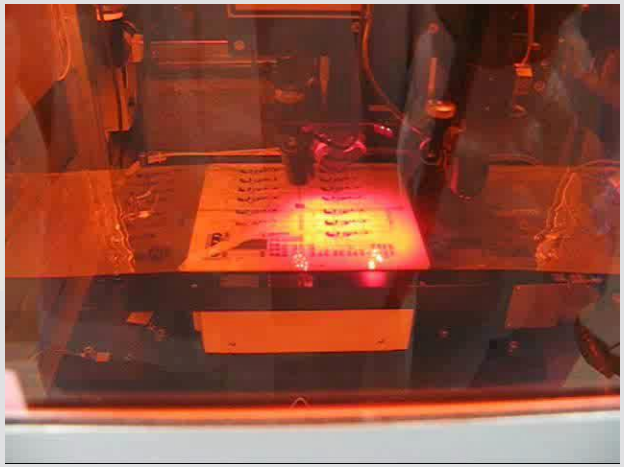
R2R





Technology prototype realised in copper

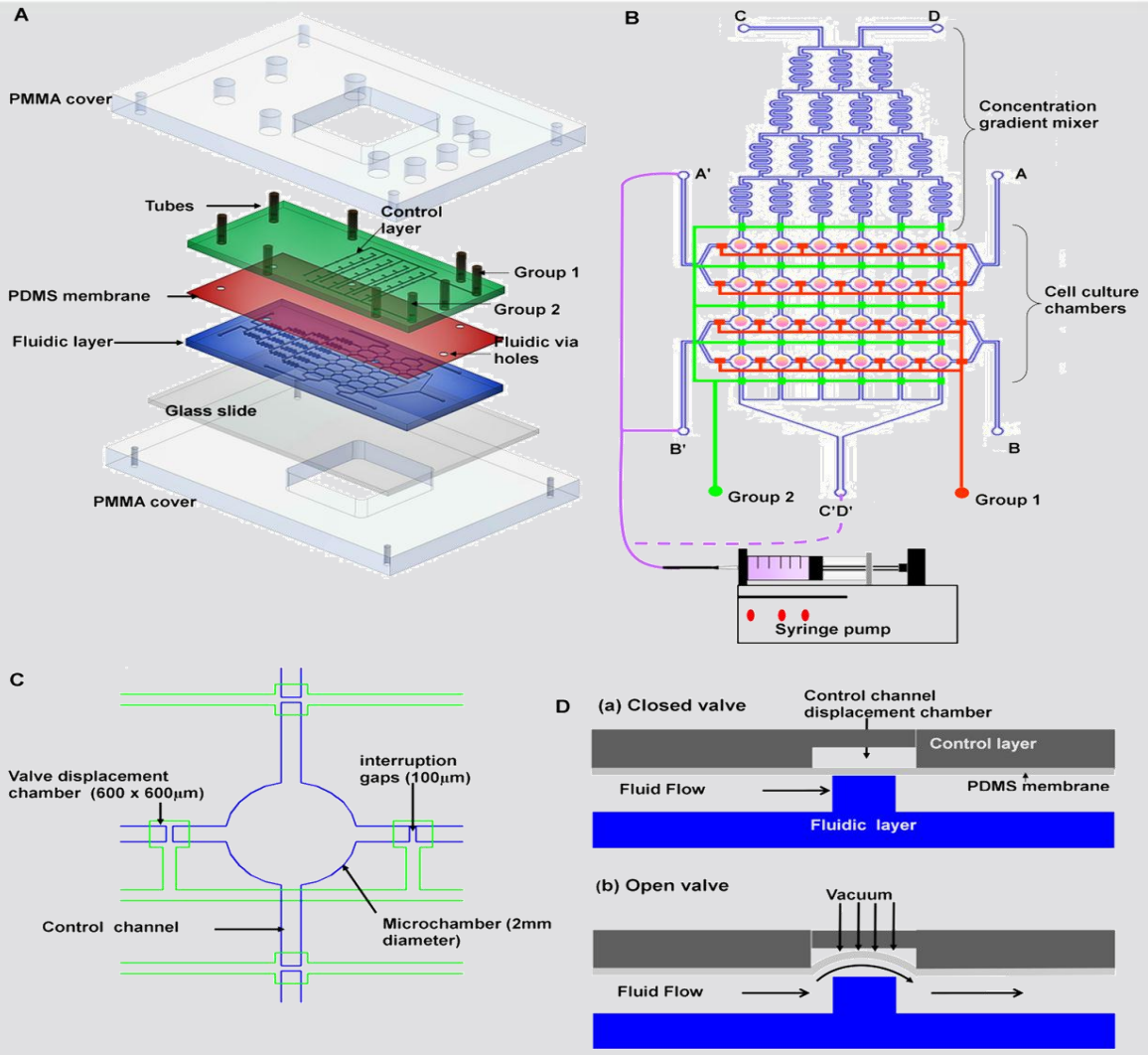


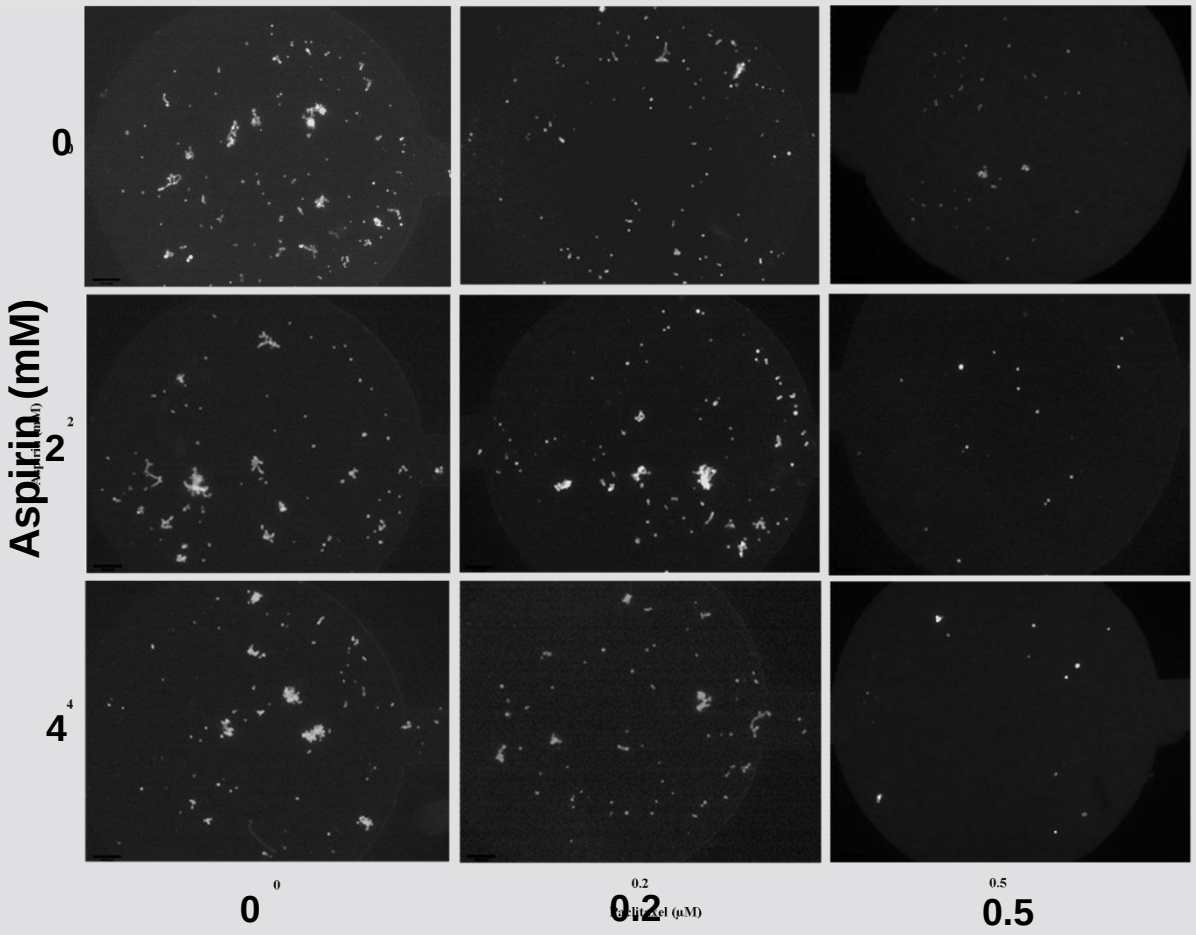
Organ-on-chip

- 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

Organ-on-chip

- 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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