Introduction to Lab-On-a-Chip:

實驗室晶片導論

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Course Organization (I)

- **Related courses @ NTU-IAM:**
  543 M6950 實驗室晶片導論 (Introduction to Microfludics in Lab-On-a-Chip) 3 credits

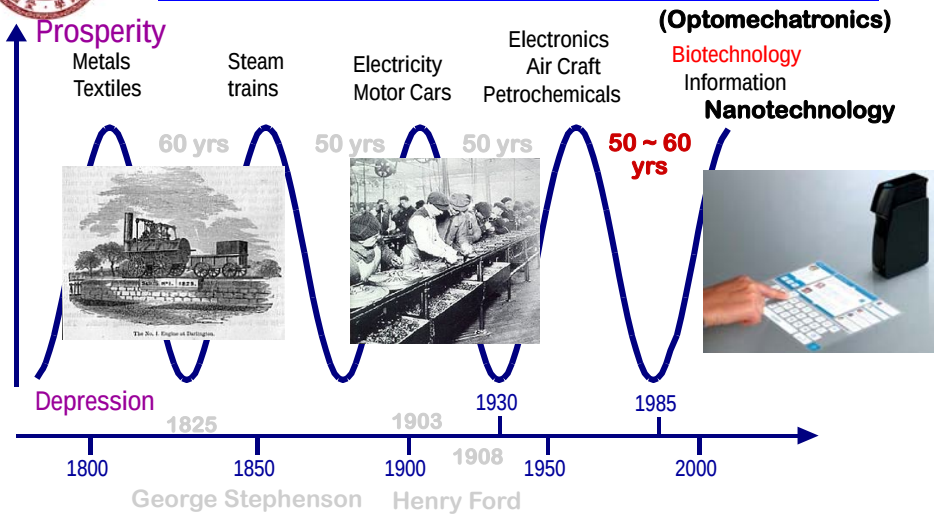
  543M6830 現代熱流量測技術 (*Modern Measuring Techniques of Thermal Fluid Mechanics*) 3 credits

- **Language: Chinese; lecture notes in English**
- **Lecture Notes on Web:**
  (http://bernoulli.iam.ntu.edu.tw/tw/index.htm)
- **Grading Policy: Term project report 80% and final 20%, Q&A 10%**

Course Organization (II)

實驗室晶片(Lab-on-a-Chip)是將原本在實驗室不同階段之操作流程整合並微小化在一片晶片上。利用這種技術，醫生在幾分鐘的問診過程中可同時快速診斷出病人的疾病，並對症下藥；生化實驗人員可以避免直接曝露於有害試劑的危險下工作；另外，實驗室晶片具有可自動化與平行化操作處理的特色，所以可用於快速篩選或合成新藥與產品，並增加實驗的可信賴度；而由於在晶片上僅需極少量的試劑，更可減少試劑用量、縮短操作處理時間及減低操作成本。目前已有越來越多的實驗改在實驗室晶片上進行，例如血液分離、電泳（electrophoresis）分離、聚合酶鏈鎖反應（Polymerase Chain Reaction, PCR）、核酸的定序反應分析等等，而拋棄式的塑膠晶片則有漸成設計主流之趨勢。本課程將提供對此一深具未來性之科技有興趣的同學們(大學部及研究所)，一個**結合「理論與實作」和「研究與應用」四合一**的試煉機會。在課程中，除講授實驗室晶片所需的基礎知識、實驗設計與量測方法外，也將邀請不同應用領域的傑出專家，透過其所提出該領域裡的實務問題需求及方向輔導與討論，讓同學們結合不同專業**組成跨領域團隊(每隊最多3人)**，以實際動手完成不同的實驗室晶片專題，來訓練同學們以目標為導向之團隊合作能力，同時開啟未來可能之研究方向。

Trend of the world



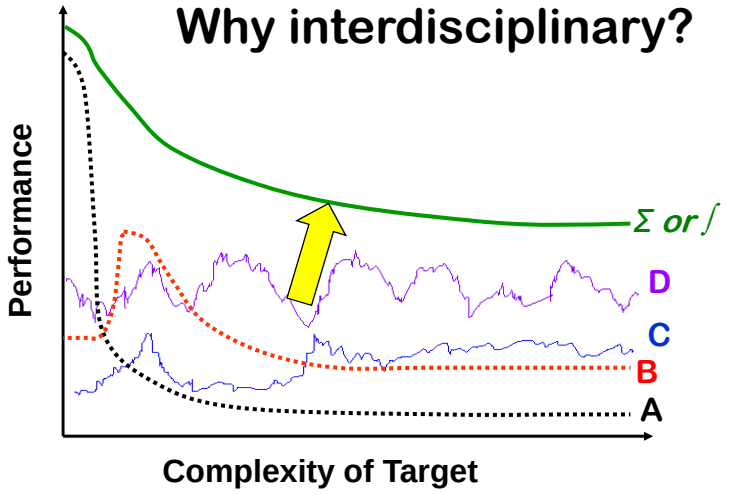
The Trend of Industry

The trend of industry development depends on the trend of human needs.

- ***Providing Ubiquitous Total solution***
- ***Integration of functionality***
- ***Built in precision / inspection / automation***
- ***Reduce time to certification / mass production / market / profit***

(程一麟)

Preface (I)



Preface (II)

[Charles Darwin]

It is not the *strongest* of the species that survives, nor the most intelligent that survives.

It is the one that is the most adaptable to change.

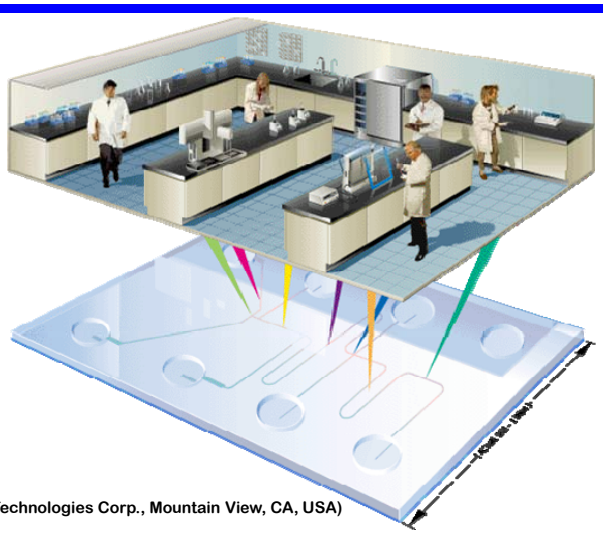
Preface (III)

- 態度決定高度
  - ✓ 科技本乎人性
  - ✓ 團隊優於個人
  - ✓ 細節決定品質
  - ✓ 毅力決定成敗

Course Contents

- **Introduction to LOC & term project assignment** (2/19)
- Specificity of enzyme catalytic mechanism **&** Antibody technology **(2/26,3/05)**
- Micromixers, microreactors, Droplet-based biomicrofluidics and Lab-on-a-chip **(3/12, 3/19)**
- Behavior Genetics: What we have learned from *Drosophila*. **(3/26,4/02)**
- **Mid-term report of Selected topic** (4/09)
- Cantilever-sensor for biosensing & bead-based microfluidics **(4/16,4/23)**
- Electro-Microfluidics **(4/30,5/07)**
- Stem cell and translational medicine **(5/14,5/21)**
- Bioenergetics & Plasma membrane (**5/28,6/04)**
- **Final report of Selected topic (6/21)**

What is Lab on a chip ?



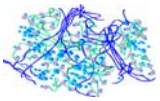
(From: Caliper Technologies Corp., Mountain View, CA, USA)

What are *LOAC & μ-fluidics*?

- ***There are different names used in the literature: μ-fluidic, MEMS-fluidics, μ-TAS, BioMEMS, biochip, LOAC, nanofluidics, nanoflows… etc.***
- ***μ-fluidic*** is the study of flows, which are circulating in artificial *μ*-systems. (Patrick Tabeling)
- ***μ-TAS***: ***M***icro **T**otal **A**nalysis **S**ystems
- ***LOAC (or LOC):*** combining different operations, which are originally performed in laboratories, in a single microdevice. (Berthier & Silberzan)

What are Fluids?

- **Fluid** is a substance tending to flow or conform to the outline of its container (*Merriam-Webster's Collegiate Dictionary,* Static aspect)
  Fluids are the substance that **could not resist deformation,** move and deform continuously under the application of a shear (tangential) stress, no matter how small the shear stress may be. (*F. White,* Dynamic aspect)
- **Fluids include**
  - **Liquid**: a state of matter in which the molecules are relatively free to change the positions w.r.t. each other but restricted by cohesive forces so as to maintain a relatively fixed volume.
  - **Gas**: a state of matter in which the molecules are practically unrestricted of cohesive forces and has neither definite shape nor volume.
- **Some systems contain complex phenomena, like a group of solid that shows the ability to flow and polymers resist deformation etc.**

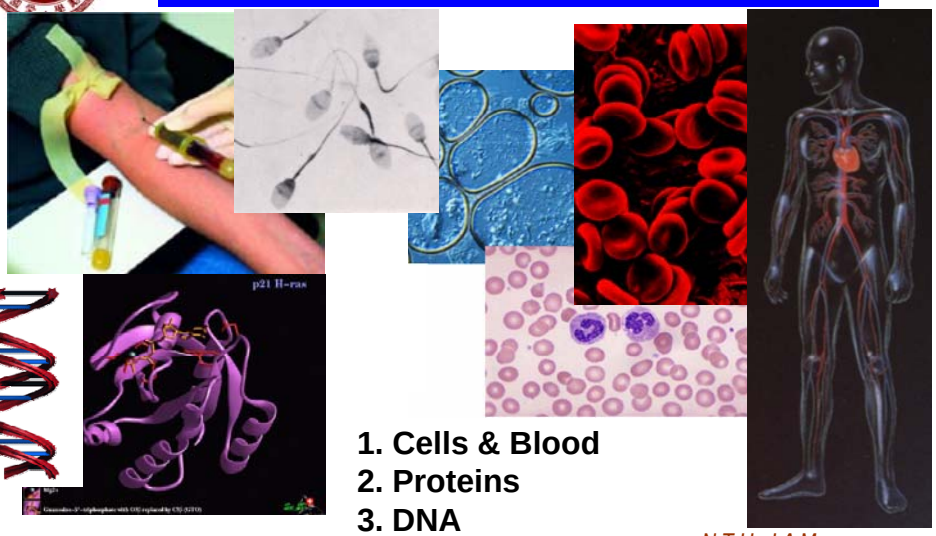


www.chemistry.helsinki.fi

Polymers as frozen liquid

sand as a liquid

Biological Fluids



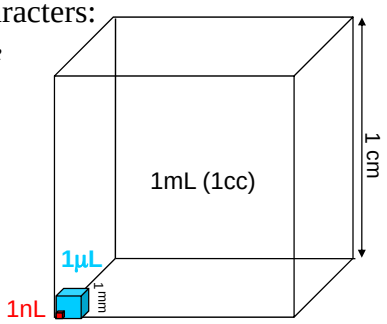
1. **Cells & Blood**
2. **Proteins**
3. **DNA**

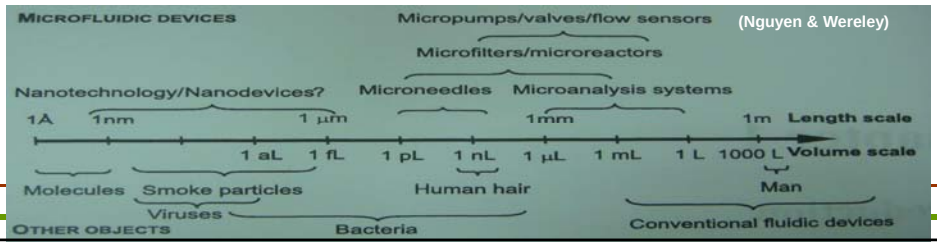
What is Microfluidics (LOAC)?

◆ ***Micro*** is the ***key*** and has at least one of the characters:

- small size (not the ***overall size*** but the ***length scale*** that determine the flow behavior)
- **small volumes (μL; nL; pL; fL (femto-); aL (atto-))**
- low energy consumption
- effects in the micro-domain...

• 1 L = $(10\ cm)^3$
• **1 cc = $(1\ cm)^3$** = 1 mL = 10^{-3} L
• 1 fL or 1aL is still far away from molecular level





Topics of Term projects

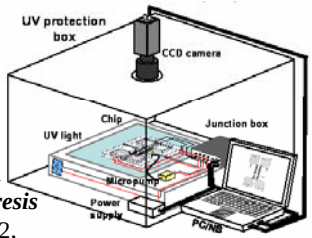
- **Integrative Microfluidic Chip for DNA Recombination**
  DNA重組晶片(2008, 2009, 2010, 2011上, 2011下, 2012上, 2013上)
- **POCTC for CKD** (Point of Care Test Chip for Chronic Kidney Disease)
  腎臟病篩選晶片(2009, 2010, 2011下, 2012上, 2013上)
- **Fly Automatic Sorting and Identification Chip**
  果蠅自動篩選辨識晶片(2012上, 2013上)
- **High throughput Stem Cell Incubation & Test Chip**
  幹細胞高效培養與測試晶片(2011下, 2012上, 2013上)
- **Two-dimensional Electrophoresis Chip**
  二次元電泳晶片(2009, 2010, 2011上, 2011下)
- **C^2MC** (Cell Counter & Measurement Chip)
  細胞計數及量測晶片(2010, 2011下, 2012上)
- **Neuron Development & Test platform on Chip**
  神經細胞發展測試平台晶片(2011下)

Results of 2008 - 2012 Projects

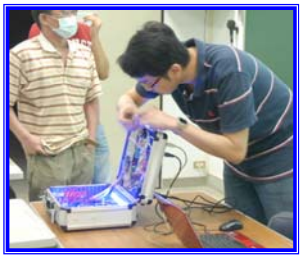
- 1 US & 2 Taiwan Patent pending
- "DNA 重組流程晶片化之研究," Proceedings of 2008年生物醫學工程科技研討會(獲學生口頭論文競賽特優獎)。
- "應用機器視覺影像辨識於DNA 重組流程晶片"，2008年第七屆虛擬儀控研討會，(獲美商國家儀器學術組佳作獎)。
- "Automatic Total Processing of DNA Recombination Chip" 17th Symposium on Recent Advanced in Cellular and Molecular Biology, Taiwan, 2009
- 1 SCI-Journal paper has been published in *"Electrophoresis"* in 2011 (Impact Factor: 3.077)
- "毛細-重力閥門在整合式尿液肌酸酐檢測晶片之研究與應用"，2011年生物醫學工程科技研討會.(學生口頭論文競賽特優獎)。
- …

Examples of Term Projects

In preparation for ***Lab on a Chip***



published in ***Electrophoresis*** 2011, Vol. 32, p.423-430.

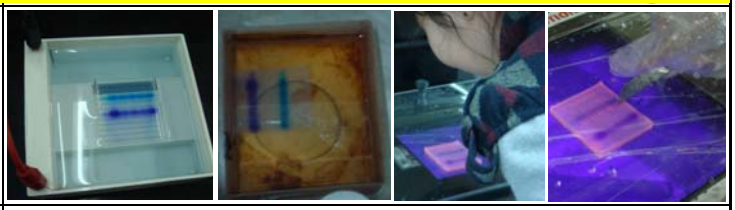


傳統實驗室DNA重組流程

減少操作時間？降低人力需求？

3. 膠體電泳
Electrophoresi

~ 1天



4. 核酸萃取
DNA Extractior
montreal-biotech

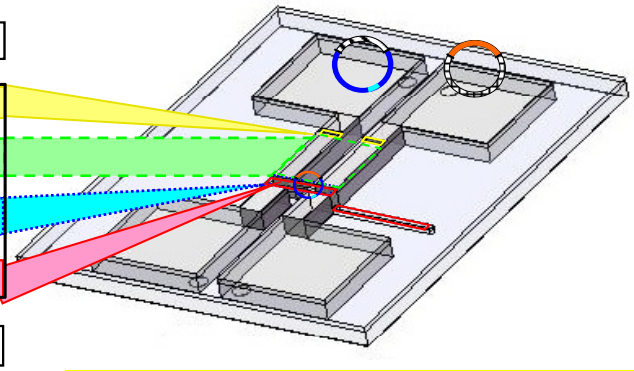
避免暴露於致癌物及紫外光環境？

Concept of DNA重組晶片

By 鄭佳瑋&林怡君&路非遙&陳彥志&潘柏廷&林義暐&管振淇&吳奕鴻&Tetuko

DNA重組流程

1.核酸製備
2.限制酶切割
3. 膠體電泳
4. 核酸萃取
5. 核酸接合
6. 質體轉化
7. 細胞培養與篩選

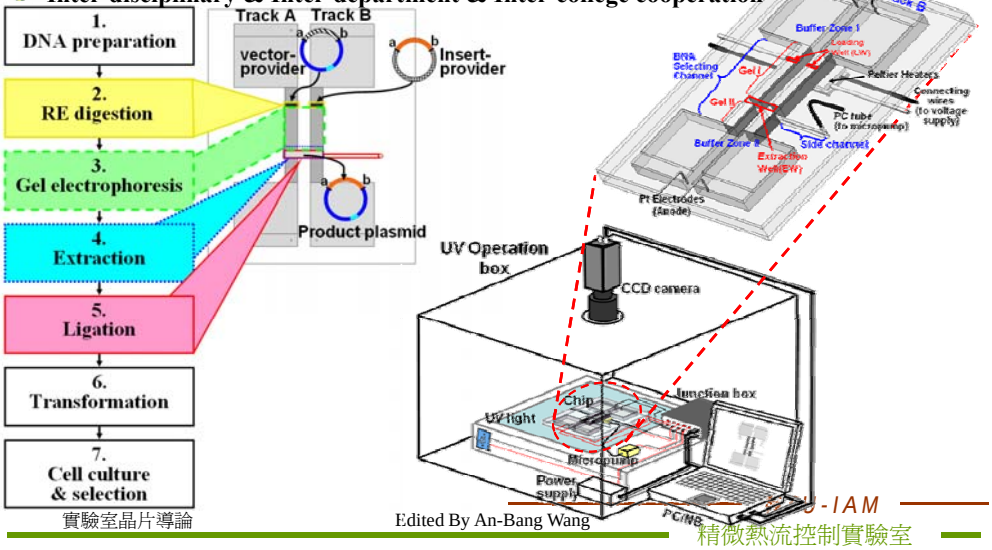


後步驟：使用者由晶片取出重組質體

多步驟DNA重組流程整合至微流體晶片

DNA重組晶片

- Inter-disciplinary & Inter-department & Inter-college cooperation

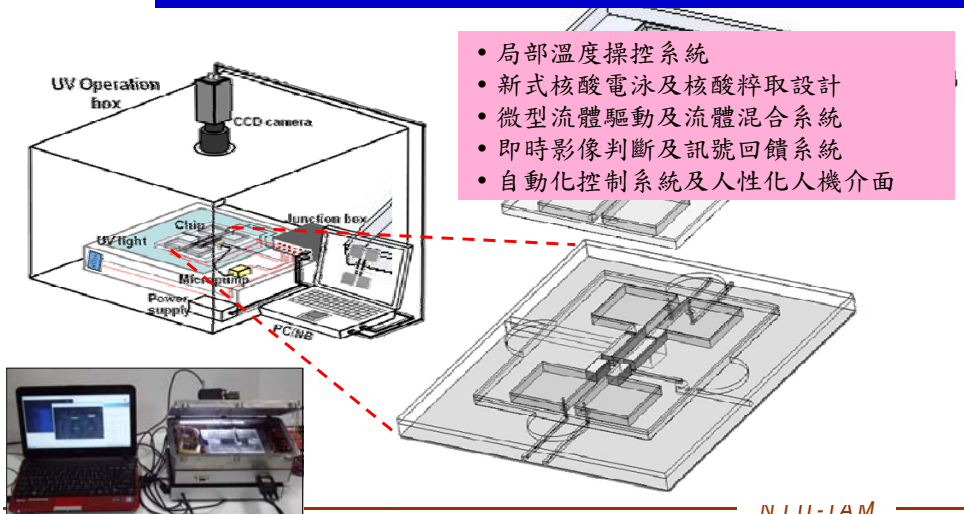


高效能DNA重組晶片系統

By 陳仕昇&林怡君&吳奕鴻

DNA重組微流體晶片整合至自動化控制系統

- 局部溫度操控系統
- 新式核酸電泳及核酸粹取設計
- 微型流體驅動及流體混合系統
- 即時影像判斷及訊號回饋系統
- 自動化控制系統及人性化人機介面



Comparisons of in-lab and on-chip DNA recombination process

	In-lab	On-chip
Time consuming	3–24 h	<1 h
Manual checkpoints during operation	Many	0
Gel cut	Necessary	Unnecessary
Operator exposure to UV	~1 min/sample	0
Gel extraction kit	Necessary	Unnecessary
Minimum DNA sample needed	3–5 μg	0.5–1 μg
Parallel operation	Possible with more manpower	Possible with full automation
Large DNA fragment separation and selection	Difficult	Possible (success at least for DNA up to 4–5 kb)

References

- ***Lab-on-a-Chip, Miniaturized System for (Bio) Chemical Analysis and Synthesis, E. Oosterbroek and A. Van den Berg (Editor), Elsevier, 2003.***
- ***Introduction to microfluidics, Patrick Tabeling, Oxford University Press, 2005***
- ***Fundamentals and applications of microfluidics, Nam-Trung Nguyen, Steven T. Wereley, Artech House, 2006***
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- ***Microfludic, J. Ducree and R. Zengerle, Classnote of IMETK, Albert-Ludwigs-Universityt Freiburg, Germany.***
- ***Process Engineering in Biotechnology, A.T. Jackson, Prentice-Hall Inc., 1991***
- **Journal, conference papers, seminars and information from Webs.**