Introduction to Bio-inspiration and Lab-On-a-Chip system:

仿生與實驗室晶片導論

An-Bang Wang

王安邦

國立臺灣大學 應用力學研究所

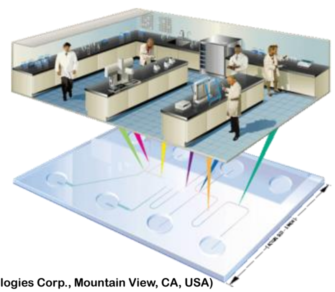
Institute of Applied Mechanics, National Taiwan University

What is Bio-inspiration?

- **Bioinspiration** is the development of new things inspired by observations/solutions in **nature**.
- Bioinspiration vs. biomimicry/biomimetics the latter aims to precisely replicate the designs of biological materials. Bioinspired research is a return to the classical origins of science: it is a field based on observing the remarkable functions that characterize living organisms, and trying to abstract and imitate those functions. (Wikipidia)

What is Lab on a chip ?

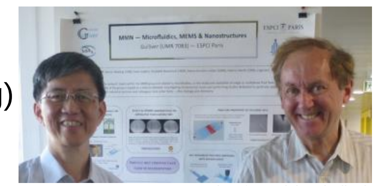
LOAC (or LOC): **combining different operations**, which are originally performed in laboratories, **in a single microdevice**. (Berthier & Silberzan)



(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,* ***LOAC,*** *μ-TAS* (*TAS*: **T**otal **A**nalysis **S**ystems)*, BioMEMS, biochip, nanofluidics, nanoflows… etc.*
- ***μ-fluidic*** is the study of flows, which are circulating in artificial μ-systems. (Prof. **Patrick Tabeling**)



(Prof. Patrick Tabeling)

Lecturers

- 王安邦　臺大應用力學研究所、醫療器材與醫學影像研究所特聘教授
- 林致廷　臺大電機工程學系教授、奈米機電系統研究中心主任
- 林順區　臺大奈米機電系統研究中心辦公室主任
- 侯詠德　臺大生物產業機電工程學系助理教授
- 黃念祖　臺大電機工程學系生醫電資所副教授
- 陳建甫　臺大應用力學研究所副教授
- 楊鏡堂　臺大機械系終身特聘教授
- 蘇剛毅　臺大醫學檢驗暨生物技術學系副教授

Course Organization (I)

實驗室晶片(Lab-on-a-Chip)系統是**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系統上**。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；生化實驗可以減少人因干擾、**避免**人員直接曝露於有害試劑的**危險工作**；另外，實驗室晶片因具有可**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且具表面體積比增大之優點，更可**大幅減少試劑用量、減低操作成本及縮短操作處理時間**。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、電泳分離、聚合脢鏈鎖反應（PCR）、核酸的定序反應分析等等，而拋棄式的塑膠晶片也有漸成設計主流之趨勢。

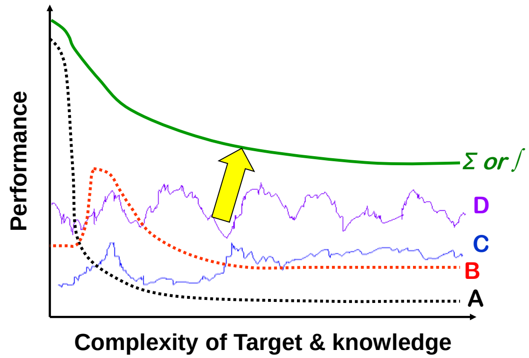
Course Organization (II)

- 從大自然可以領略更多的靈感，所以本課程也將介紹相關**仿生案例**，讓同學可以多體會大自然的奧祕、並觸類旁通，以幫助實驗專題設計與執行。
- 課程設計上，這是一門結合「自然與工程」、「理論與實作」和「研究與應用」六合一的實際動手參與，以完成不同**實驗專題**的應用導向之工程與實作多樣學習課程。
- 第**5**、**10**週將安排在臺大奈米機電系統研究中心無塵室實習；第**16**週將安排在醫學院醫學檢驗暨生物技術學系上課，並參觀臺大基因體中心。

Course Organization (III)

- 在課程中，將讓同學到實驗室動手製做，讓同學們**結合不同專業組成跨領域團隊(每隊1-3人)，以實際動手完成不同的實驗專題**，訓練同學們以**目標為導向**之**團隊合作與邏輯推理能力，同時開啟未來可能之研究方向**。
- Language: Chinese; lecture notes mainly in English
- Lecture Notes on Web: (http://bernoulli.iam.ntu.edu.tw)
- Grading Policy: Class participation (10%); 1st & 2nd Mid-term project presentation (15 + 15%); Final oral & written report of term project (30%+30%)

Why interdisciplinary?



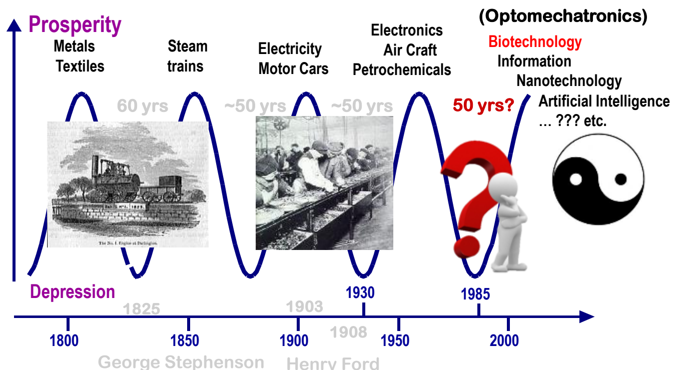
Course Contents (I)

1. Introduction to LOC仿生&實驗室晶片導論及議題設計介紹
2. Introduction to Biomimetics 仿生學簡介 (I)
3. LOC & Term project assignment
   實驗室晶片導論與實驗室晶片議題分配
4. 肝臟與肝臟晶片技術簡介、應用與未來展望
5. General fabrication techniques
   微製程技術簡介 & 實作(I) : MEMS實作篇(A)
6. Introduction to Biomimetics 仿生學簡介 (II)
7. Microfluidics for bio-sample pretreatment
   用於生物樣本前處理之微流道系統
8. Introduction to Optofluidics 光流體系統簡介
9. 1st Mid-term project presentation & lab course
   第一次期中報告與實驗室分組實作

Course Contents (II)

10. Lab course 實驗室晶片設計與實作(II): MEMS實作篇(B)
11. Design of micro-reactors and its application
    微流體混合/反應暨生醫化材應用
12. Polymer-based microfluidic sensors 塑基微流體感測器
13. Paper-based microfluidic sensors 紙基微流體感測器
14. 2nd Mid-term project presentation
    第二次期中討論與報告
15. Electronics-based bio-sensing technologies
    生醫電子感測元件
16. 醫學分子檢驗新技術 (& Lab course)
17. Transport phenomena of droplets and lab-on-a chip
    液珠輸送與檢測晶片
18. Final report 期末報告

Trend of the world



Can the nature guide us the way of change?

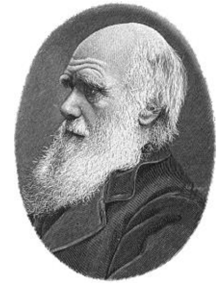
Who can survive in the changing world?

- The one that is the strongest
- The one that is the most intelligent
- The one that is most active
- The one that works very hard
- The one that is most modern
- The one that is most rich
- …

A Simple Answer

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

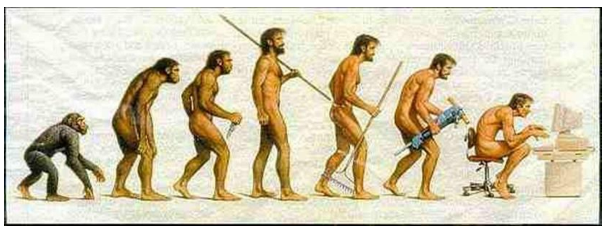
It is the one that is the **most adaptable to change**.



Charles Darwin
(1809~1882)

That's it?

- **Another answer?**
- Converging or diverging trend?
- Related effect: lower/higher entrance barrier?



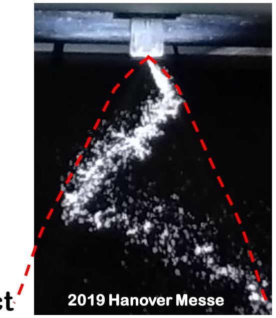
https://evblog.virginiahumanities.org/2012/05/the-kkk-and-evolution-in-virginia/

"Adaptable to change"

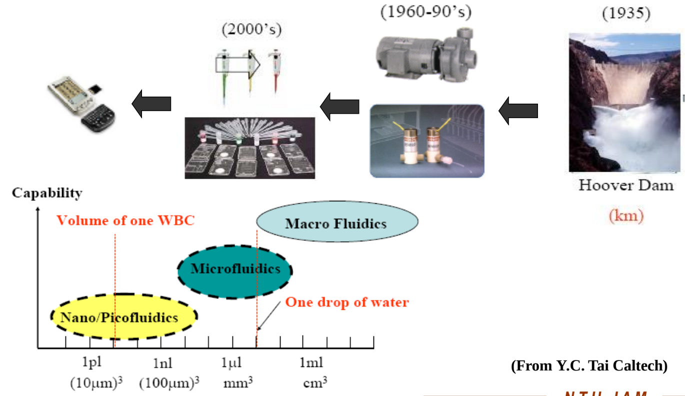
- What can the "**change**" bring (for you)?
  Can you waive the "change"?
- "**Change**" vs. "**Novelty**"
  Keep changing from the same to be different
- What is/are the key parameter(s) of "**adaptable to change**"?
  Learning from the nature (Biomimetic).
- What is/are the key(s) of "change" that related to us (**students / professors**)?

What is Microfluidic technology

- **Fluidic:** manipulating (or control) fluids
- **Microfluidic = “Micro” + “Fluidic”**

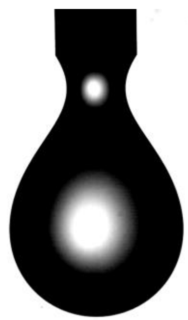


From Fluidic to Microfluidic technology



(From Y.C. Tai Caltech)

Is it a microfluidic device?



1. Yes
2. No

*Microfluidics is **not** so far from our life!*

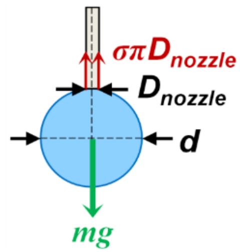
Prediction models for dripping drop sizes (I)

Tate (1864)

$$F_\sigma = F_g$$

$$\sigma\left(\pi D_{nozzle}\right) = mg = \rho\left(\frac{1}{6}\pi d^3\right)g$$

$$\Rightarrow \left(\frac{d}{\lambda}\right) = \left(\frac{6D_{nozzle}}{\lambda}\right)^{1/3}, where\ \lambda \equiv \sqrt{\frac{\sigma}{\rho g}}$$



- σ : Surface tension of liquid
- ρ : Density of liquid drop
- g : Gravitational acceleration
- D_{nozzle} : Diameter of nozzle

$$d^* = 1.82\left(D^*_{nozzle}\right)^{1/3}$$

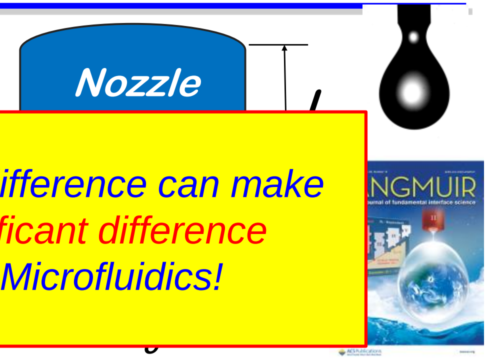
Prediction models for dripping drop sizes (II)

Yildirim, Xu & Basaran (2005)

(simulation: *We* ≤ 10^{-5} & *Oh* ≤ 1) $We = \frac{16\rho Q^2}{\pi^2 \sigma D_{nozzle}^3}$ $Oh = \frac{\mu_d}{\sqrt{\rho \sigma D_{nozzle}}}$

$$d^* = 1.61\left(D_{nozzle}^*\right)^{0.288}$$

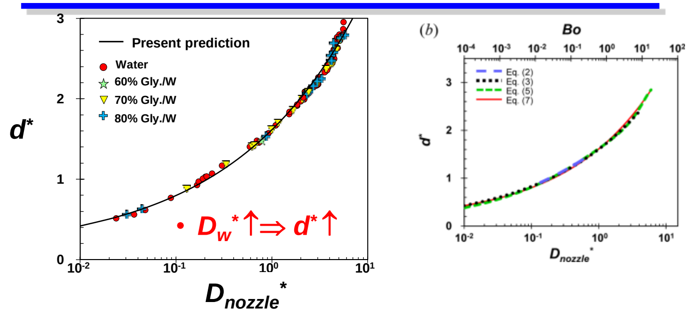
What should be the characteristic length D_{nozzle}?



Subtle difference can make significant difference in Microfluidics!

Tsai & Wang, **Langmuir** (2019), 35, 4763−4775.

Prediction models for dripping drop sizes (III)



- ***All data*** **can be well-predicted by a single parameter** D_w^* **in the whole range by** $d^* = 1.51 D_w^{*1/3} + 0.10$

How to precisely metering in biomedical lab?

What is a microfluidic platform?

- It's a toolbox …
  - containing a reduced number of building blocks
  - for a dedicated set of microfluidic operations
  - that can easily be combined
  - within a well defined (low cost) fabrication technology
- The platform concept is not new …
  - type setting in book printing ("Gutenberg bible")
  - computer industry
  - automotive industry

(Zengerle & Haeberle)

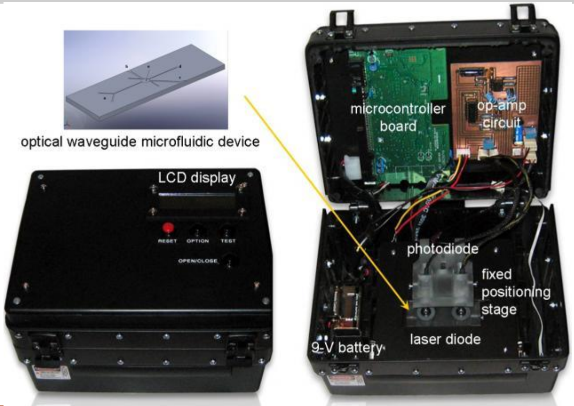
The Trend of Industry

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)

A Lab-on-a-chip system example



Microfludic Platform @ AB WANG's Lab

Microfluidic components

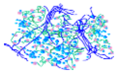
- Microvalve
- Micropump
- Micromixer
- **Microdistributor/ coater**
- Microflowmeter

Integrated microfluidic systems & Applications

- **Micro-squential control system**
- Micro- reactor / emulsion system for novel materials
- Compact Pattern Coating System
- **Compact Desktop Coating System**
- **Micro-liter POCT analysis system**
- Biomedical μm/nm 3D Printing system
- On-line Coating Film Measuring System
- Long-period Drug-delivery & Monitoring System

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

Why liquids?

- About 70% of the Earth is covered with water, and 97% of that is the salty oceans.
- The human body is 72% saline (salt) water.
- A significant fraction of the human body is water. This **body water** is distributed in different compartments in the body. Lean muscle tissue contains about 75% water. Blood contains 83% water, body fat contains 25% water and bone has 22% water (Wikipedia).

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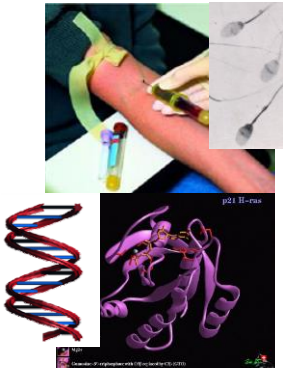
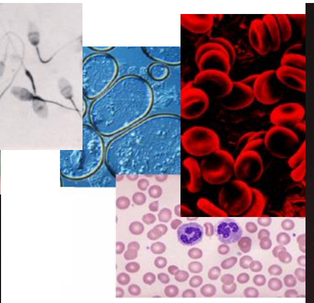
Biological Fluids





1. Cells & Blood
2. Proteins
3. DNA

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Issues in the biomedical applications

- Sample
- Contamination
- Accuracy
- SOP
- Automation
- Timing of Sequence
- Cost
- Space

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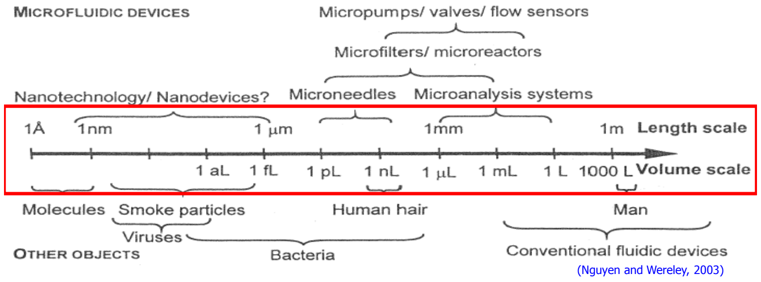
Length scale & Volume scale

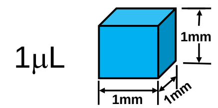
◆ ***Feeling is important***

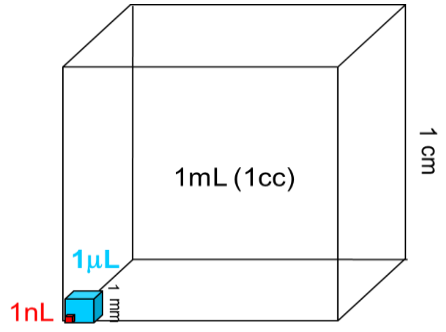


How big is a drop size from a eyedropper?

1. 5000
2. 500
3. 50
4. 5
5. 0.5

(unit: μL)





Why microfluidic technology?

Issues in Biomedical Industry:

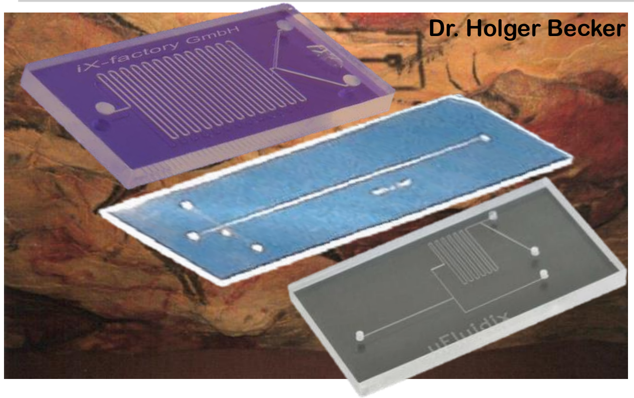
- Constant need of novelty and cost down
  - ⇒ New challenges in manufacturing technology

Advantages of microfluidic technology:

◆ Short diffusion time ($t_D \propto L^2$)
◆ High Surface/Volume ratio ($\propto 1/L$)
 ⇒ better mass & heat transfer
◆ Less samples and fluid consumptions
◆ Short operation time
◆ Well-controlled micro-environment
 ⇒ Parallel operation ⇒ Easy scale up
◆ Automation & Portability

} **Reduce overall costs**

Microfluidic has been around for a long time?



Introduction to Surface Tension

Surface tension is the force applied along the interface of two immiscible fluids per unit length.

Surface tension is the tendency of liquid surfaces to shrink into the minimum surface area possible. (From Wikipedia)

Surface tension is the energy required to increase the interface of two immiscible fluids by an unit area.

http://itsforyourlife.com/

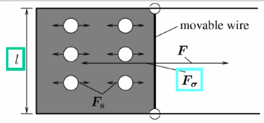
http://www.liv.ac.uk/

http://fphoto.photoshelter.com/

http://www.natoco.co.jp/

Surface Tension & Surface Energy

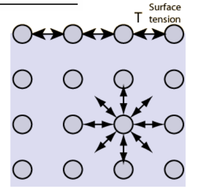
- Definition $\sigma = \frac{F_\sigma}{l}$



Surface tension: Force per unit length [N/m]

- The term „tension" is bad choice (Commonly referred to as force per **area)**
- Microscopical Phenomenon relates to
  - Energy required to **transport molecule** from **bulk** to **surface** region
- More physical definition of surface tension:

Surface Energy: Energy needed to extend surface



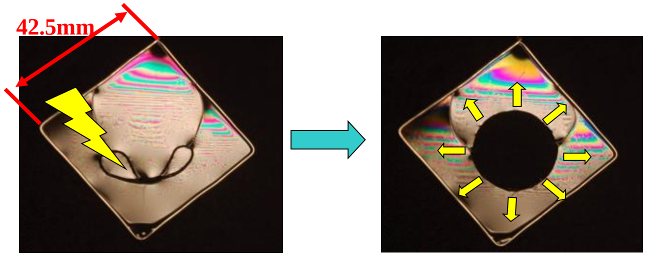
hyperphysics.phy-astr.gsu.edu/hbase/surten.html

$$W = F_\sigma dx = 2\sigma l \, dx$$

- **Systems always search to minimize Energy = minimize Surface/Interface (with highest Energy)**

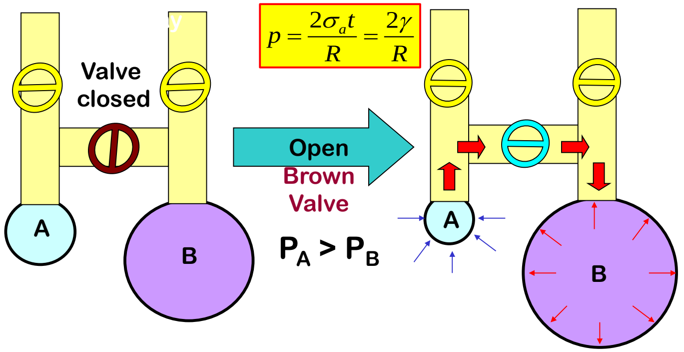
(Ducrée and Zengerle)

A experiment of Surface tension: Soap-film



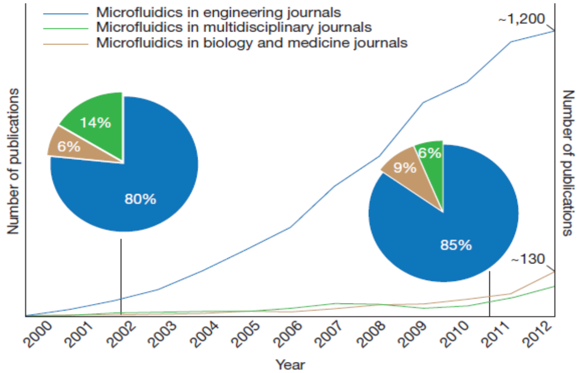
- Circle has **maximum surface** for a **given periphery**
- Surface tension reduces surface energy to be minimum
- Try to think about the liquid shape of different drop sizes

Surface tension vs. Pressure Soap-film Mechanics



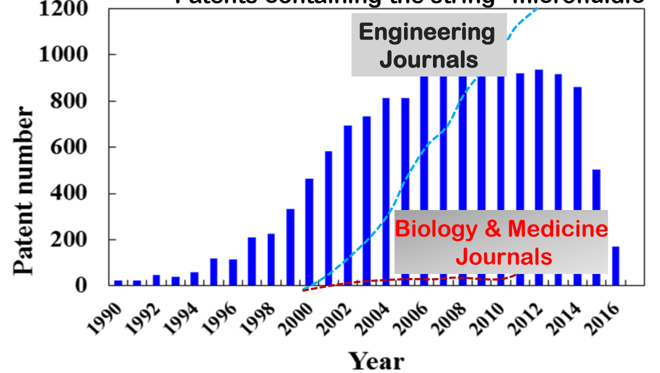
Microfluidics related Journal Papers

Sackmann et al. 2014 Nature



Annual granted microfluidic patents

Patents containing the string "microfluidic*"



Challenges & Strategy

Challenges:

- Proof-of-concept ≠ final product (Sackmann et al., 2014)
- Cool technology ≠ simple & cheap (Whitesides, 2013)
- Long path from Lab and producer to the end users
- Resistance due to "inertia" of experienced users (especially) in biomedical field

Strategy:

- ◆ Papers (for academy)? or Patents (for users/money)?
- ◆ Pioneer? or Better performance?
- ◆ Innovation design? or New system integration?
- ◆ Specific component/System or General method/device?

References

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