国内のナノテクノロジーの現状と将来

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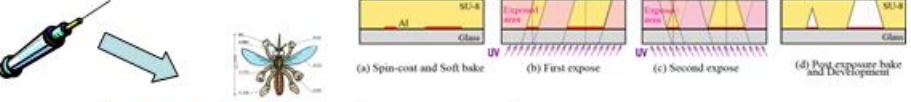
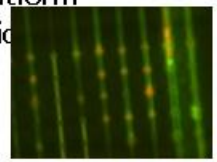
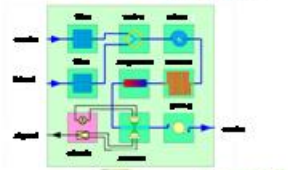
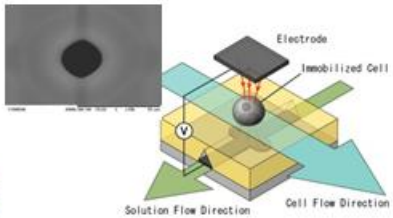
NEDO（New Energy and Industrial Technology Development Organization）

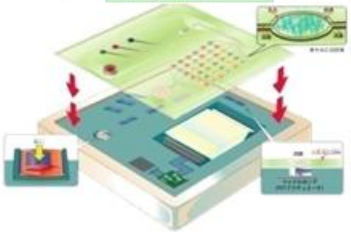


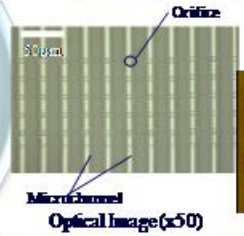
Bio Nano hybrid platform and 3D Fabricatio

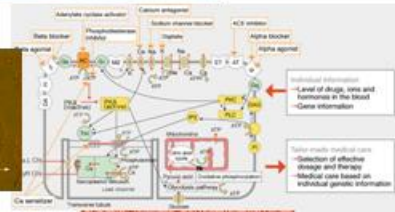












Micro Fluidics/ Micro TAS and SPR

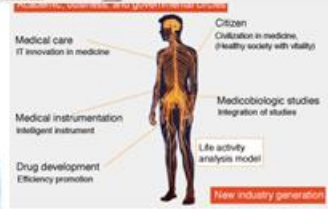
BIOLOGY

CLINICAL LAB. TEST

PHYSIOLOGY

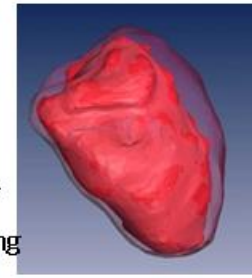
NANO MEDICINE

Education & Fabrication

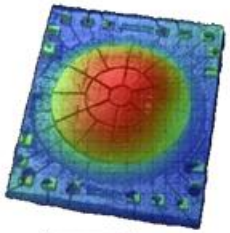


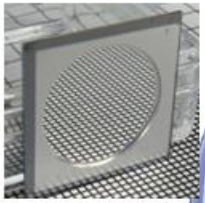
in vitro diagnostic test system

Point of Care



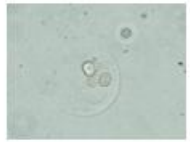
Model and Simulator / Micro TAS for measuring cell performance





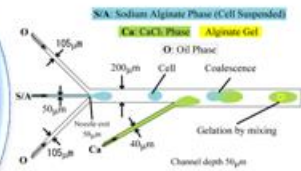
OPTHAL-MOLOGY

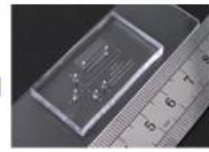
Piezoelectric material & Actuator



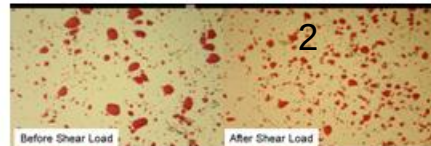
Implantation

DIABETES/ METABOLISM





Bio-Nano Plat form/Micro Fluidic system and micro sensor for single molecule

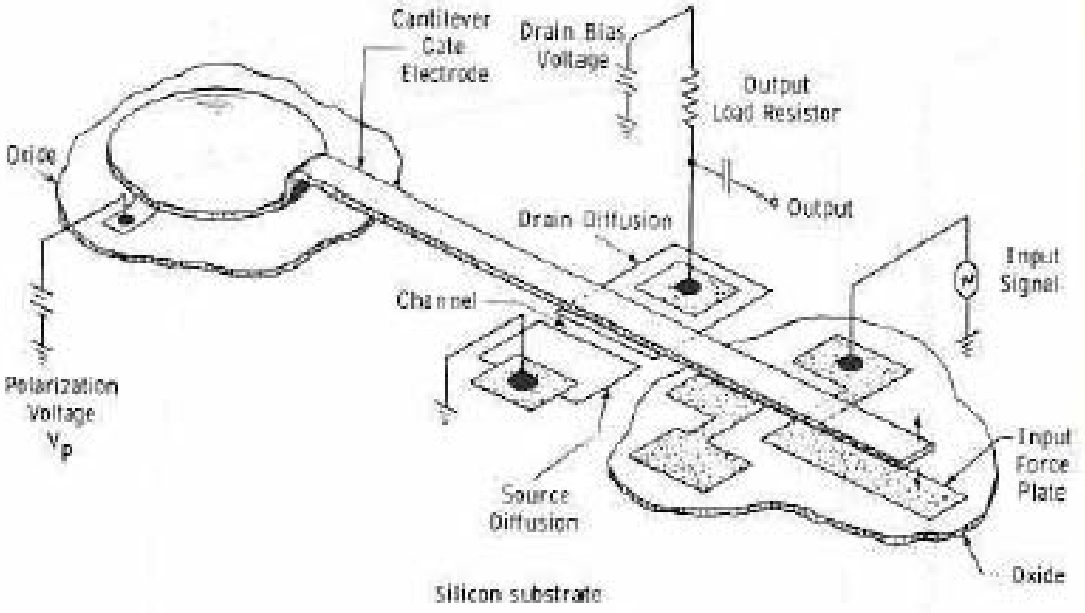


History of MEMS

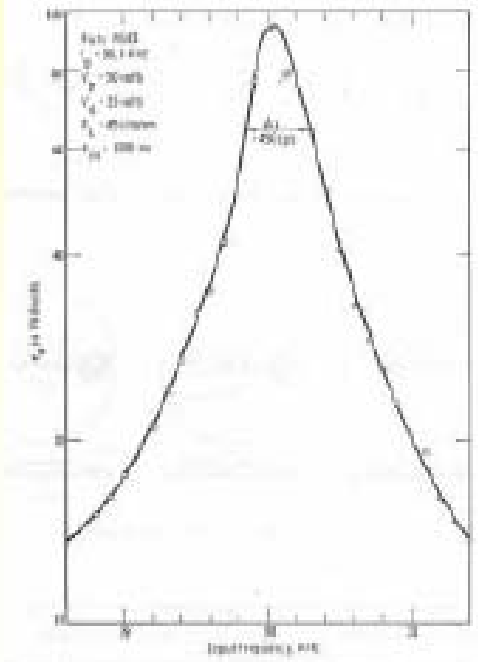
1824 : Discovery of silicon (Berzelius)
1910 : First patent on the MOS transistor concept
1939 : First PN junction (Schottky)
1947 : Fabrication of the first bipolar transistor (Shockley)
1955 : Evidence of piezoresistive effect in Si and Ge (Smith)
1958 : First integrated circuit (Oscillator)
1559 : R. Feynman Famous Talk : 'There is plenty of room at the bottom'
1960 : Fabrication of the first piezoresistive sensor –pressure- (Kulite) –accel. in 1970
1967 : First Surface Micro-machining process (H. Nathanson) : resonant gate transistor
1970 : Silicon-glass bonding
1972 : National Semiconductor : Commercialize a Pressure Sensor
1977 : IBM – HP : Micro-machined Ink Jet Nozzle
1978 : Silicon Bulk Micromachining : K. Bean
1978 : Structure obtained by Micromoulding (LIGA)
1982 : Famous Review paper « Silicon as a Mechanical material » (K. Petersen)
1985 : Assembly of silicon wafers (Si/Si fusion bonding) : Lasky, et al.
1985 : IC-compatible surface micromachining -> Polysilicon comb structures
1988 : Electrostatic micromotor (UC -Berkeley BSAC)
1988 : 1st MEMS conference (1st Transducers conference was held in 1987)
1992 : First MUMPS process (MCNC) (with support of DARPA). Now owned by Memscap
1992 : SCREAM Process (Cornell)
1993 : Analog Devices : Commercialize Multi-axis Accelerometer integrating electronics
1993 : Texas Instrument : Commercialize the Digital Mirror Display (DMD)
1996 : DRIE (Bosch Process)

MEMSの定義：Micro Eelctro-Mechanical Systems

First MEMS Concept is The Resonant Gate Transistor in 1967

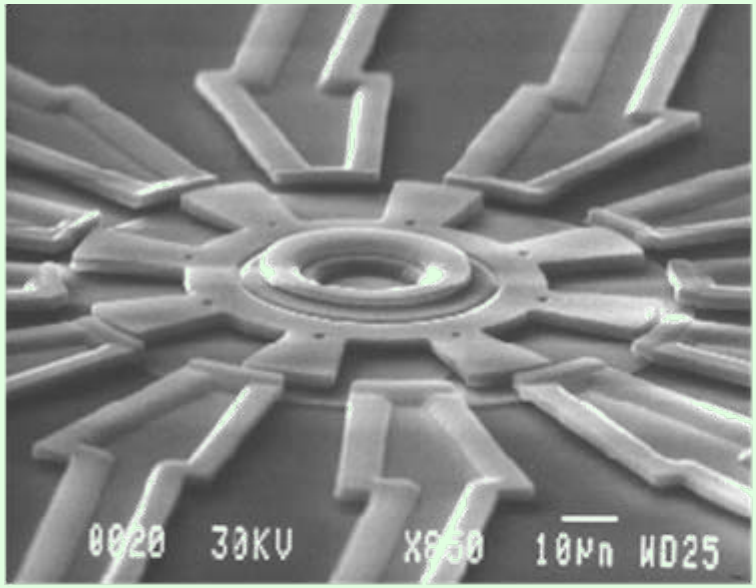


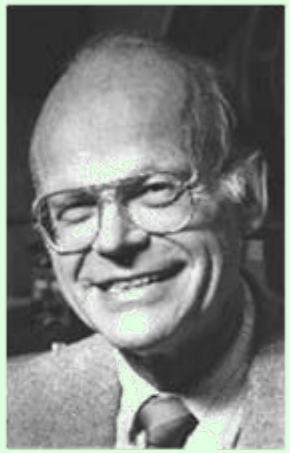
- The gate is a movable Gold cantilever
- Photoresist sacrificial layer
- Drain current modulation by the cantilever motion



Frequency response :
fo ≅ 30khz

references	[H.C. **Nathanson**, *et al*., The Resonant Gate Transistor, IEEE Trans. Electron Devices, March 1967, vol. 14, no. 3, pp 117-133.]





Transducers U.C. Berkeley

Professor Richard S. Muller

references http://www-bsac.eecs.berkeley.edu/project/list_projects_by_director.php?PersonID=703

Bulk Micromachining

▲ Liquid etching; etch rate differences in different crystal directions

<111> etch rate is slowest, <100> and <110> fastest

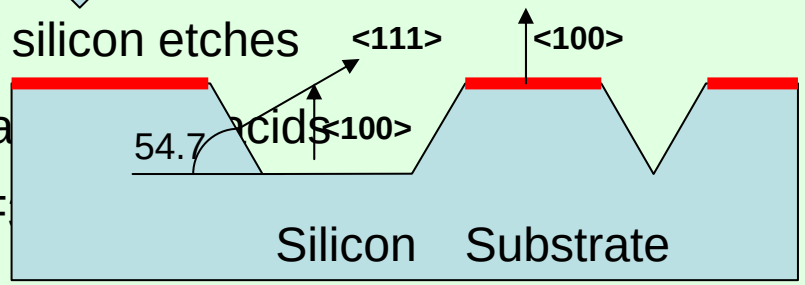
Its rate is more than 400 times

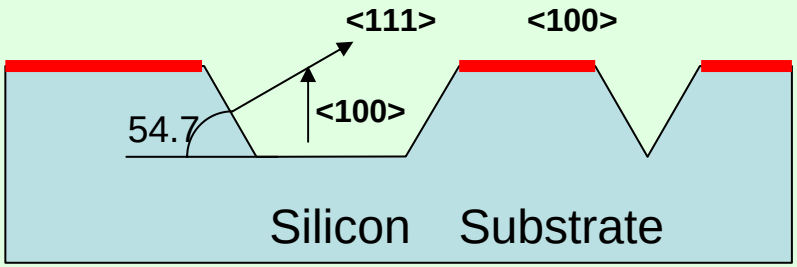
Commonly; anisotropic etches in silicon include KOH, TMAH (Tetramethil Ammonium Hydroxide) and EDP (Ethlene Diamine Pyrocatecol)

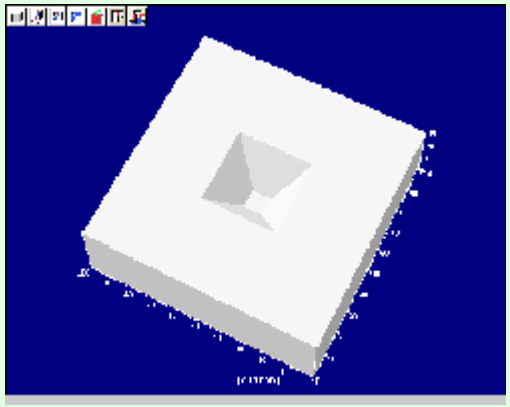
▲Isotropic silicon etches

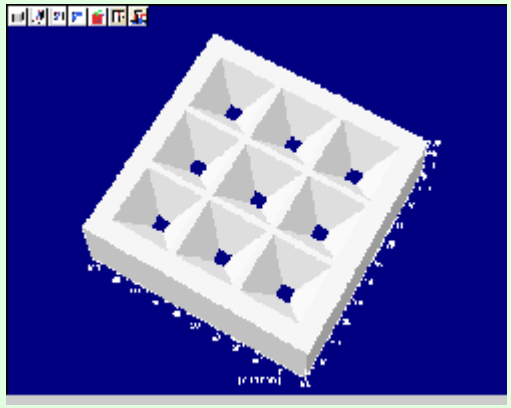
* HF, nitric a acids

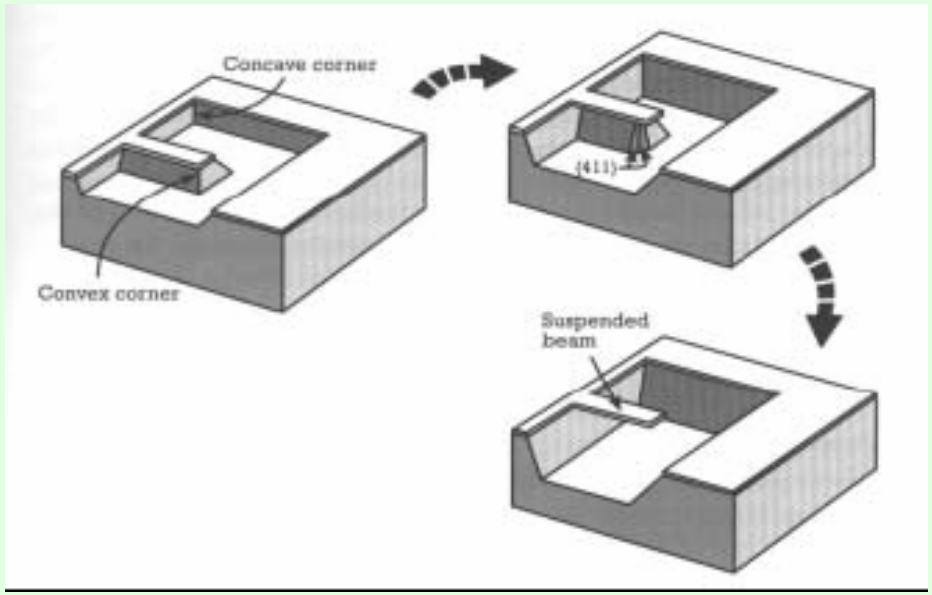
* XeF2BrF







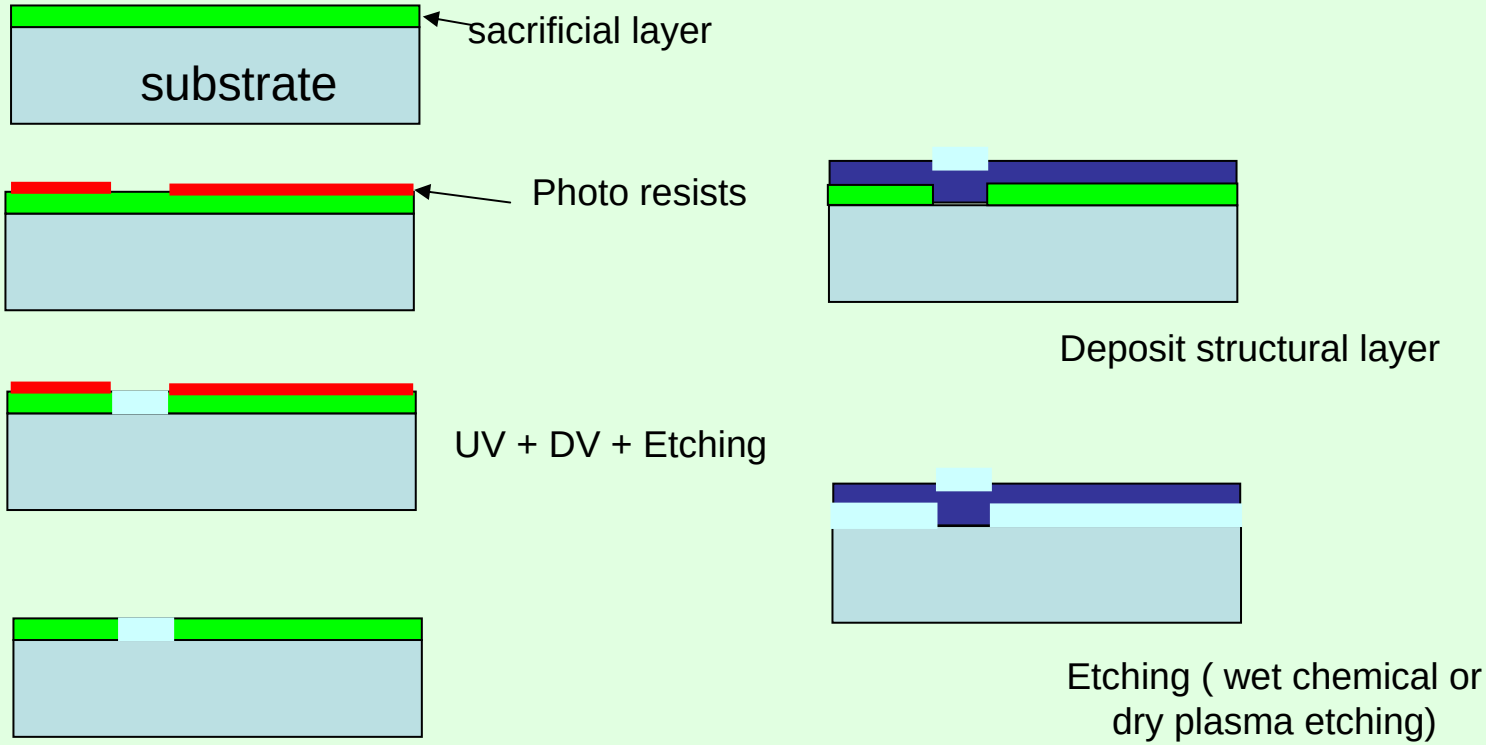


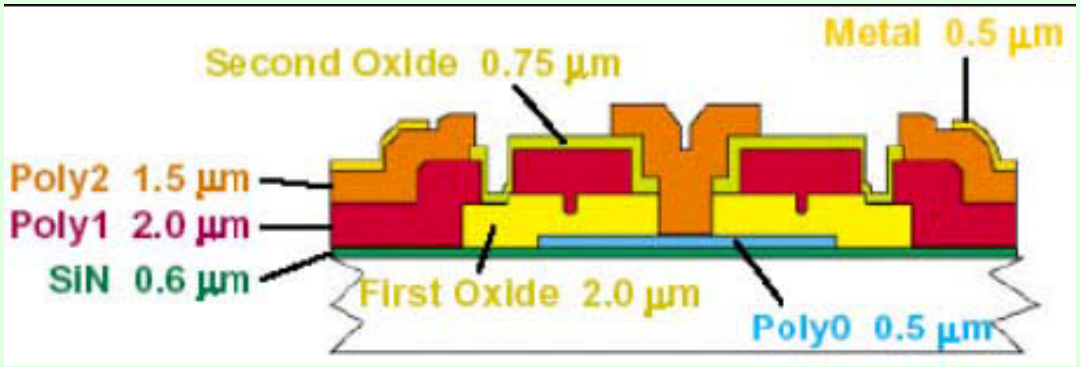


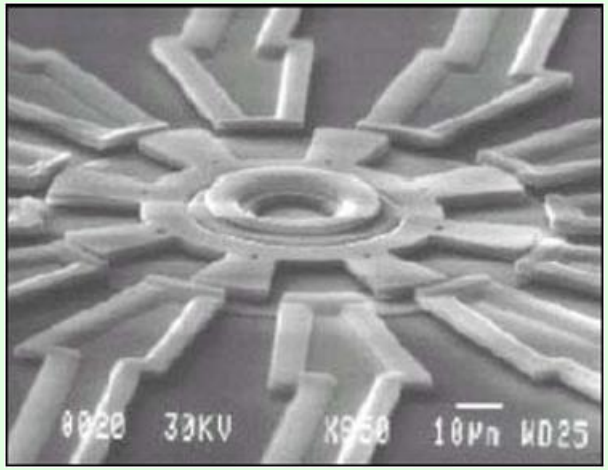
references http://www.mizuho-ir.co.jp/science/microcad/

Surface Micromachining

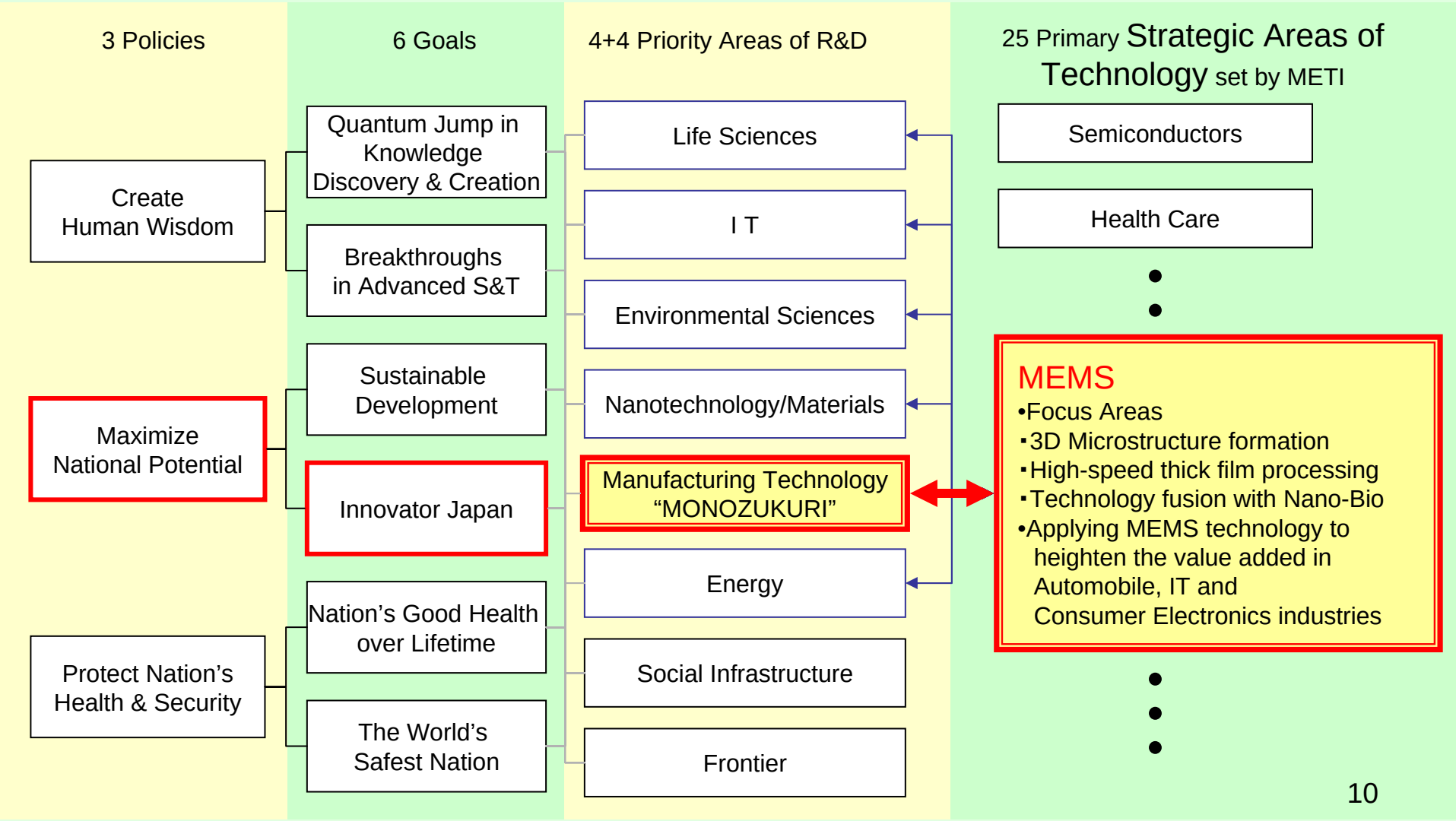
Thin film technology + sacrificial layer



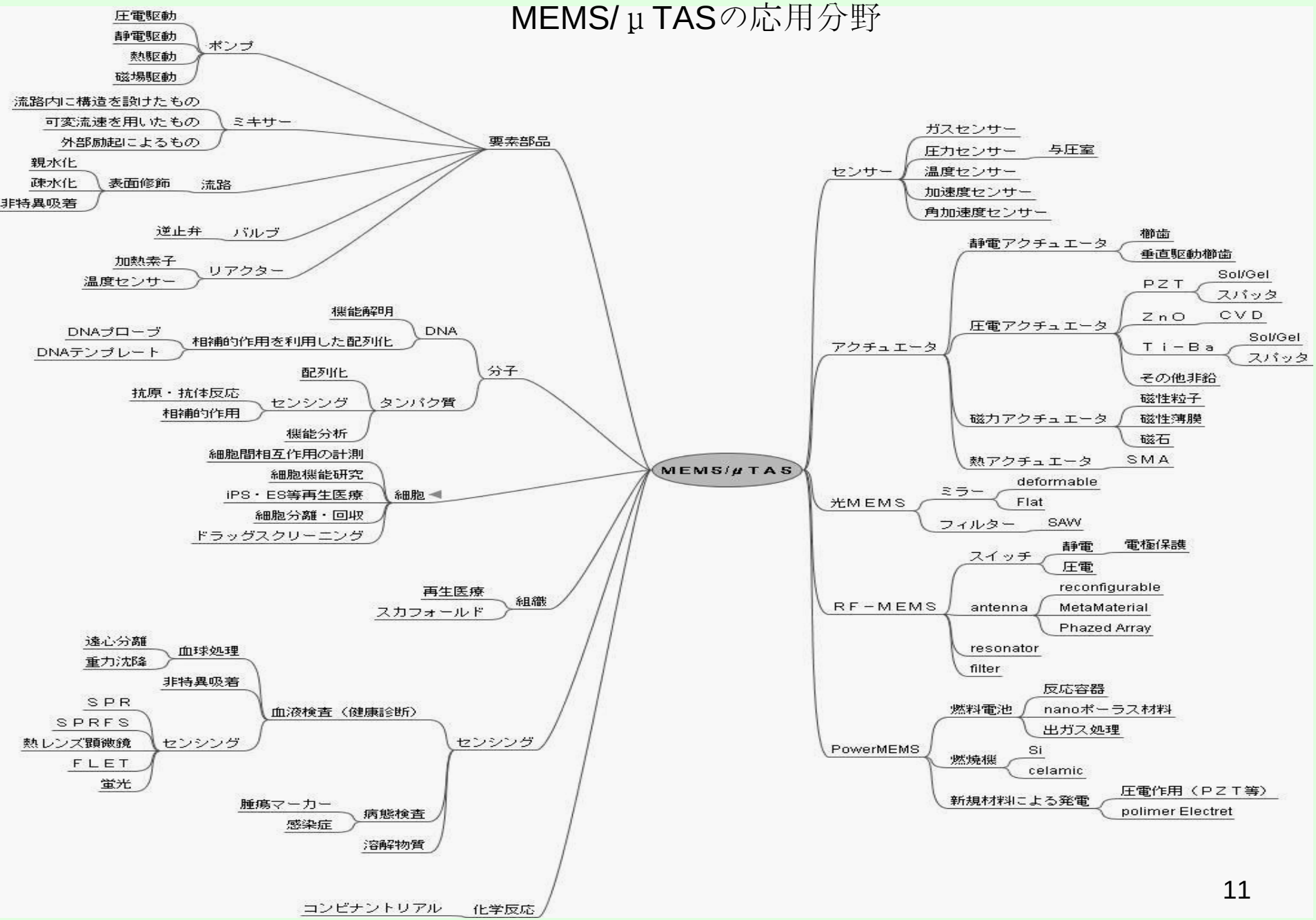

Metal 0.5 µm
Second Oxide 0.75 µm
Poly2 1.5 µm
Poly1 2.0 µm
SiN 0.6 µm
First Oxide 2.0 µm
Poly0 0.5 µm


8020 30KV K950 10µm WD25

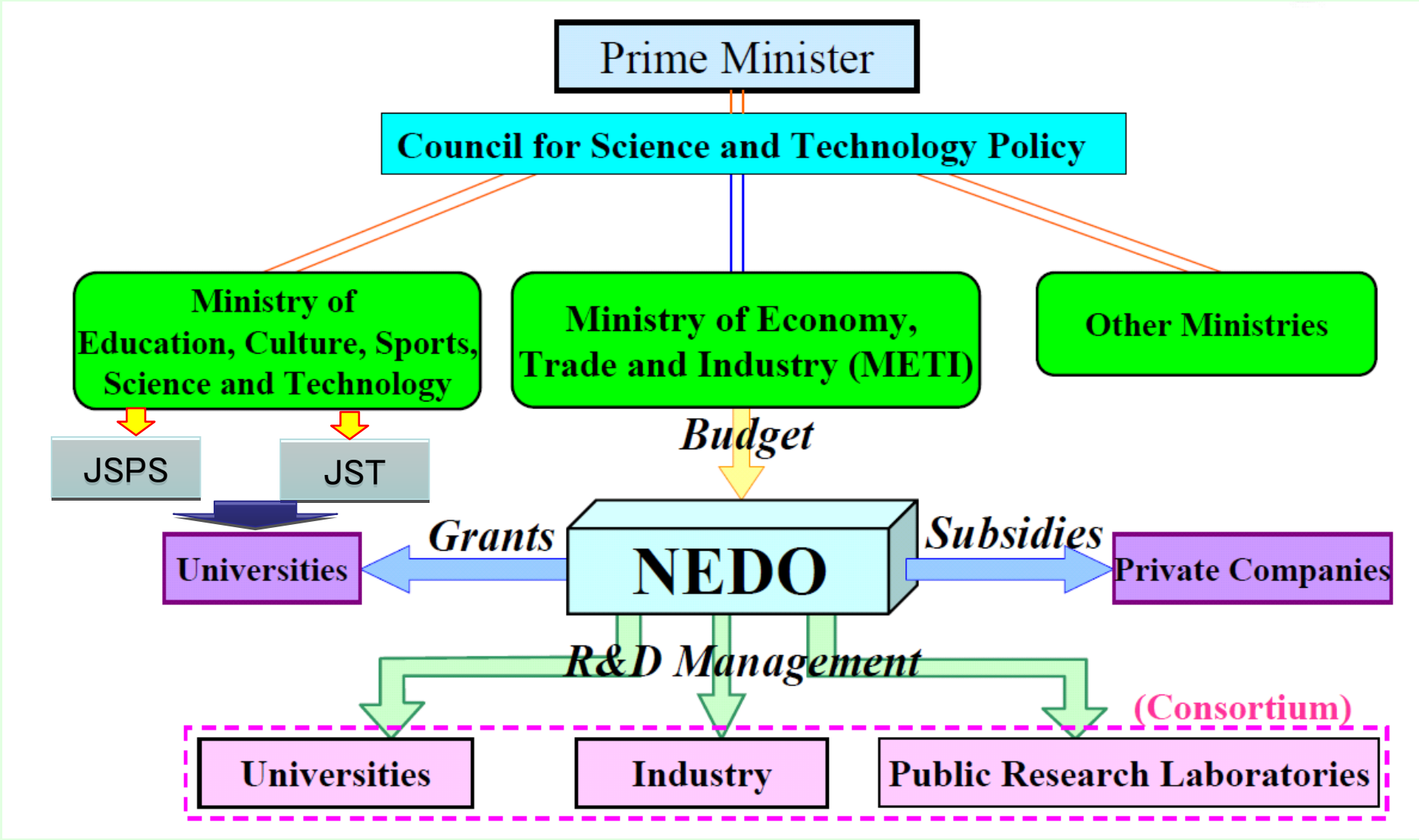
JAPAN's the 3rd Science and Technology Basic Plan & MEMS position (FY2006-2010)



MEMS/μTASの応用分野

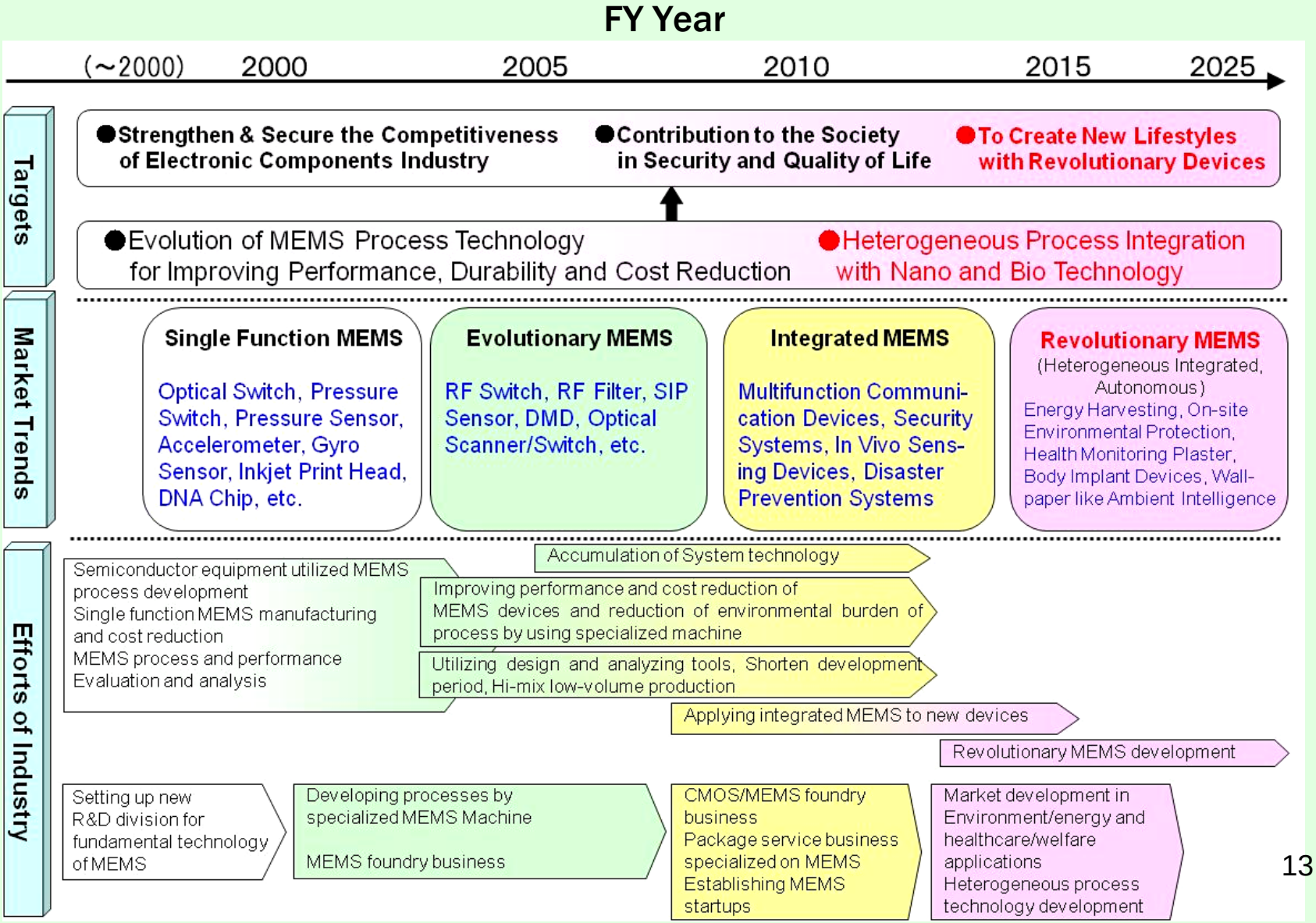


Japan's R&D Promotion Scheme

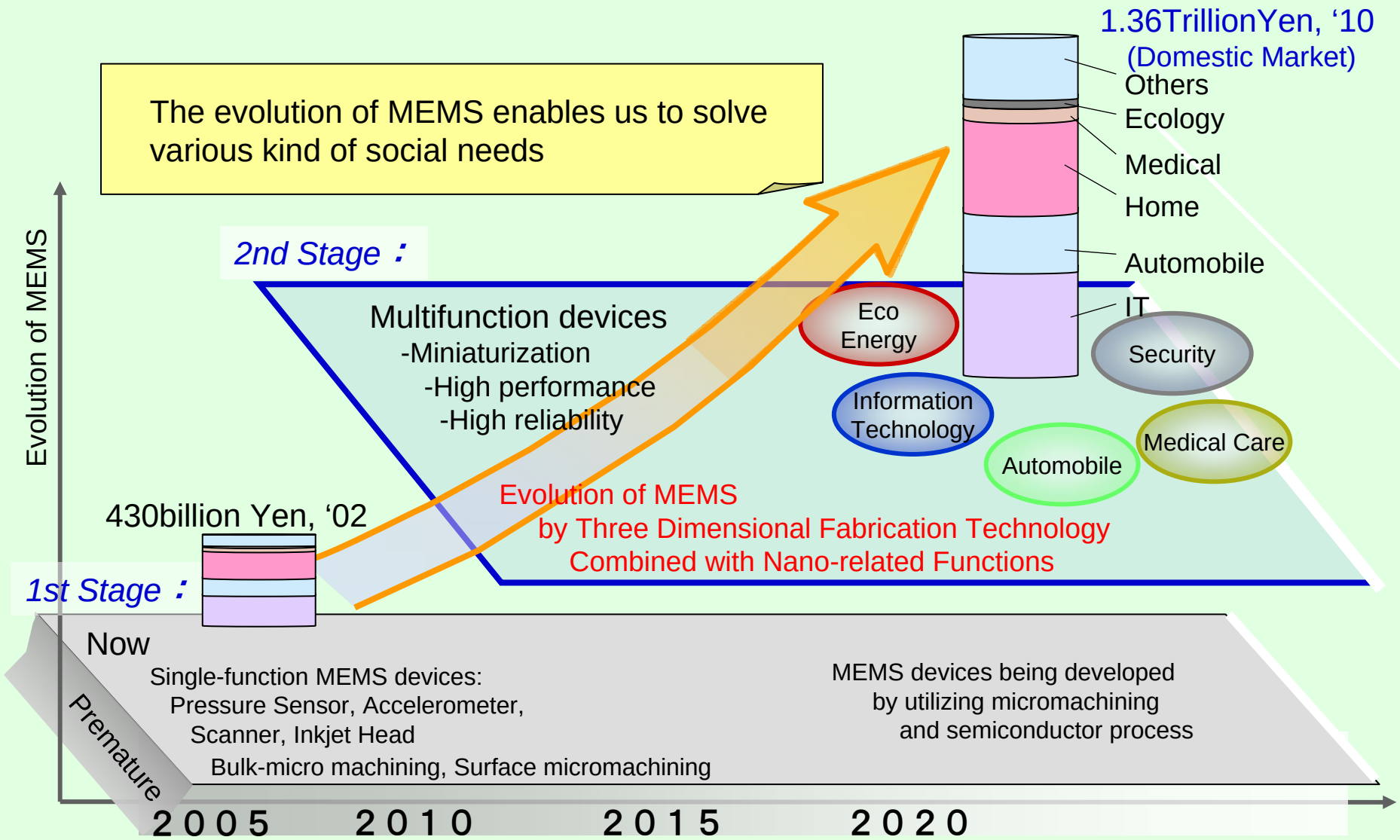


Scenario for Dissemination 1/2

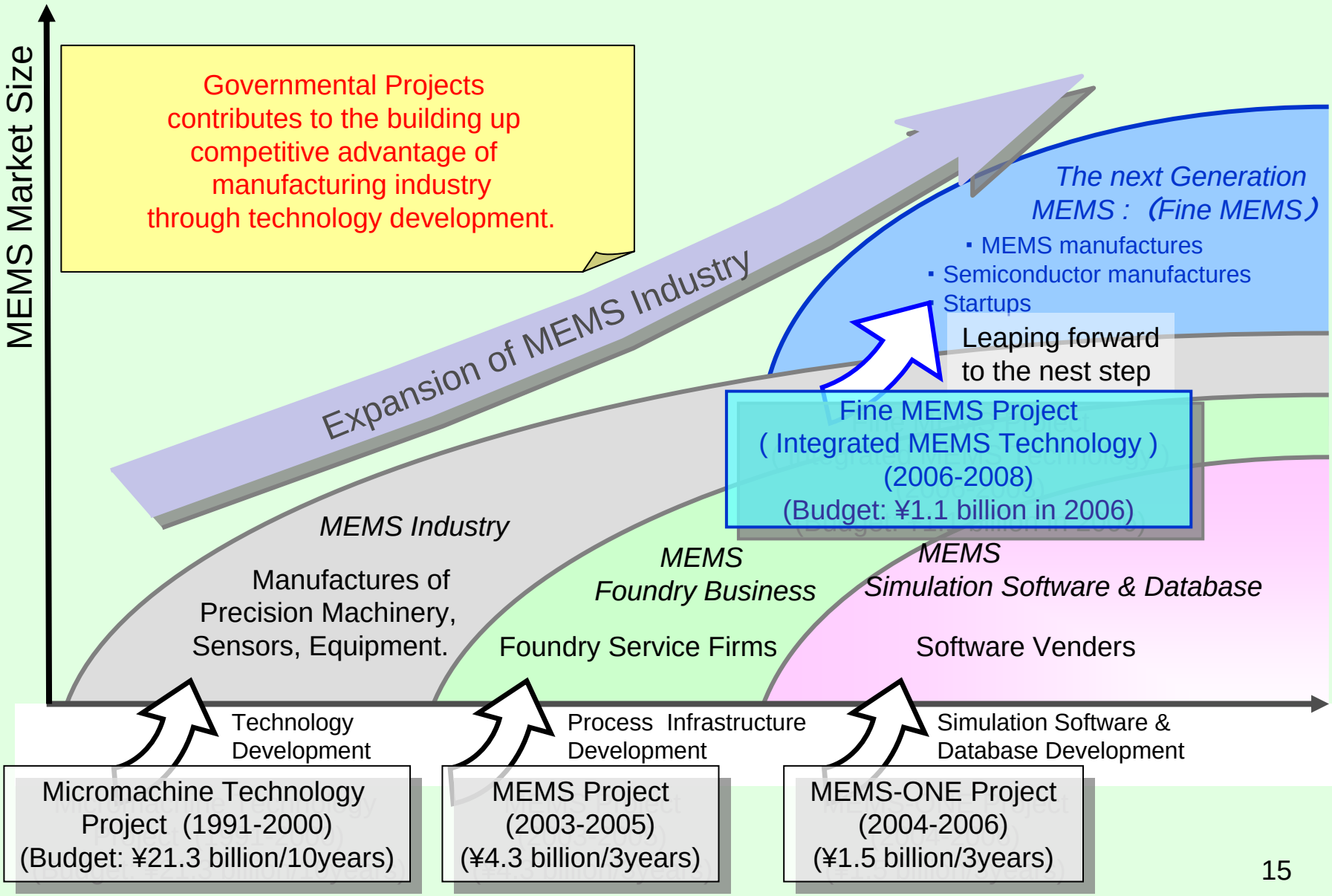
Shows the paths through which R&D outcomes go out into the world as well as relevant measures involved



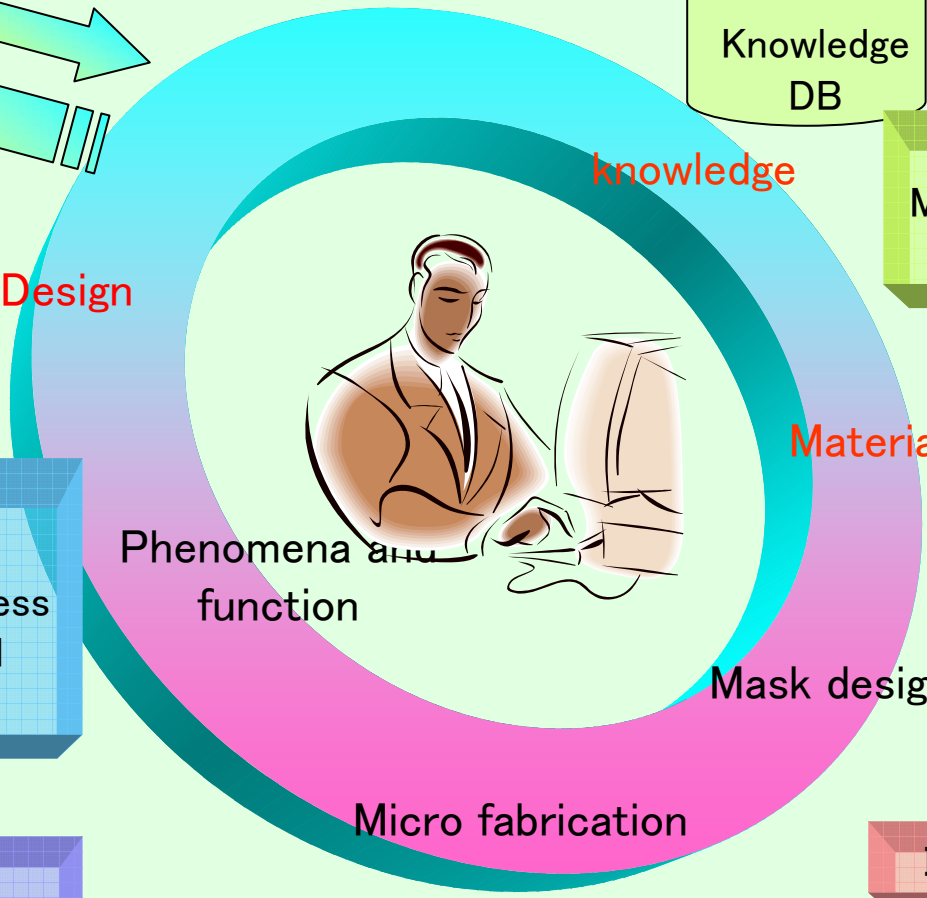
MEMS Industrialization Strategy & Scenario



Technology Development for MEMS Industry Expansion



Technical Concept of *MemsONE*



CAD

Interface for commercial software

High end simulator

Knowledge DB

Knowledge of professional engineer

Knowledge for simulation, MEMS design and fabrication process

Designer system and modeling tools

Material DB

Experimental data

Stress
(Linear & non-linear)
Thermal and thermal stress
Electro-magnetic field
Radio-frequency field

Material properties

Process designer

Tribology analysis

Inverse simulator for mask

Mask layouter

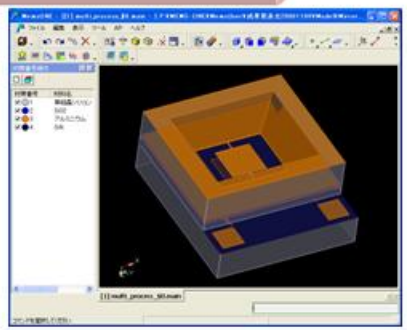
Nano-inprint
(Thermal and photo)

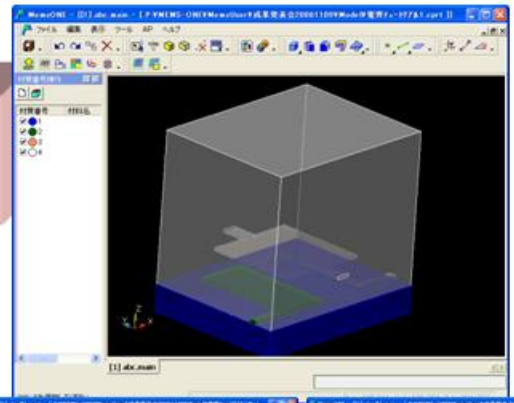
Wet and dry etching

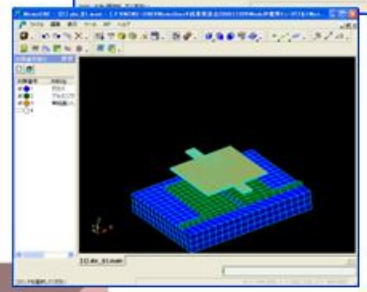
Auto mesh generation

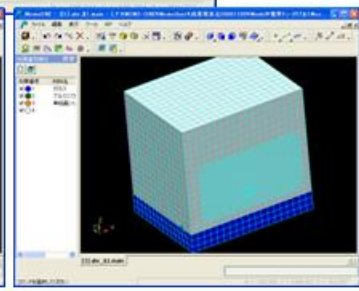
Design system

Mesh Generator





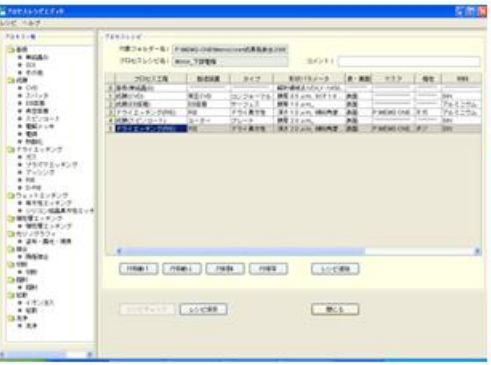


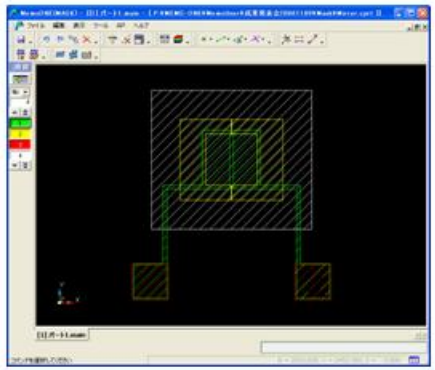


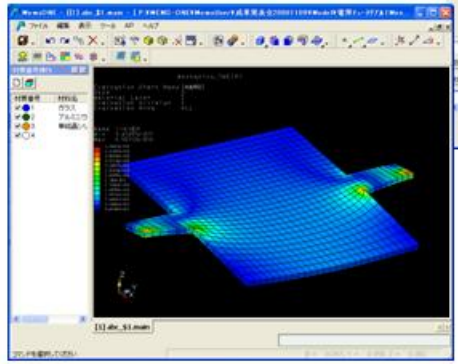
CAD and Solid modeler

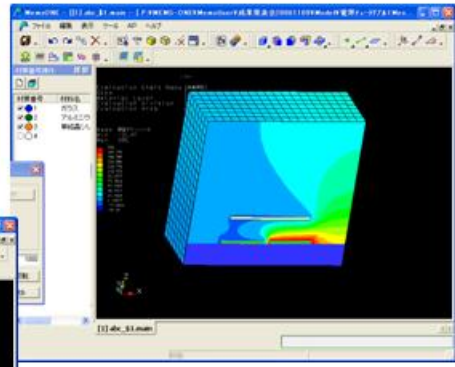
Process recipe

Post-processing







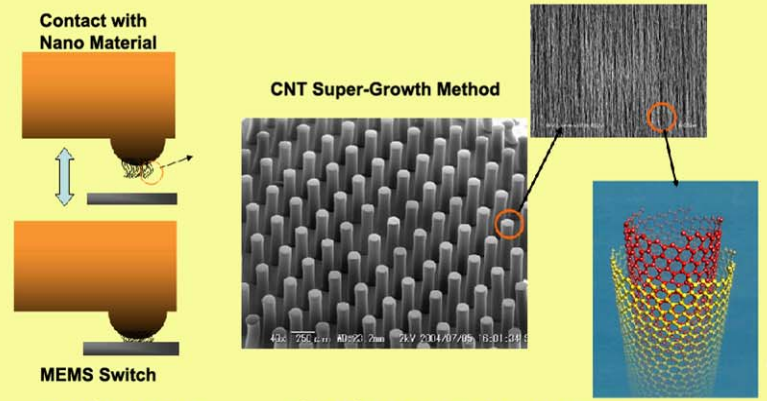


Knowledge database

fine MEMS Project 2006-2008

Target Areas for Technology Development

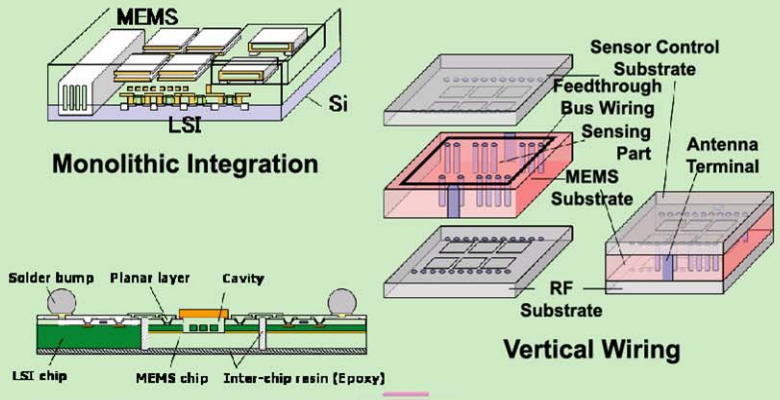
MEMS/Nano-function Combination



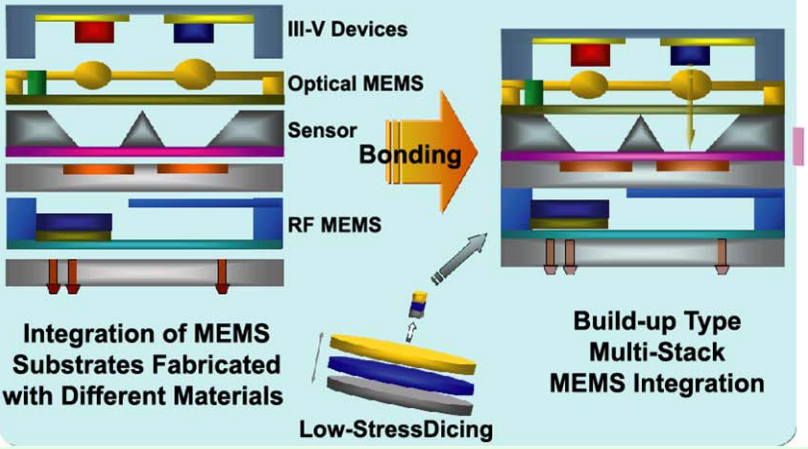
MEMS Devices with Nano Functions

CNT Symthesis Technique on Preferential Areas

MEMS/Semiconductor Integration



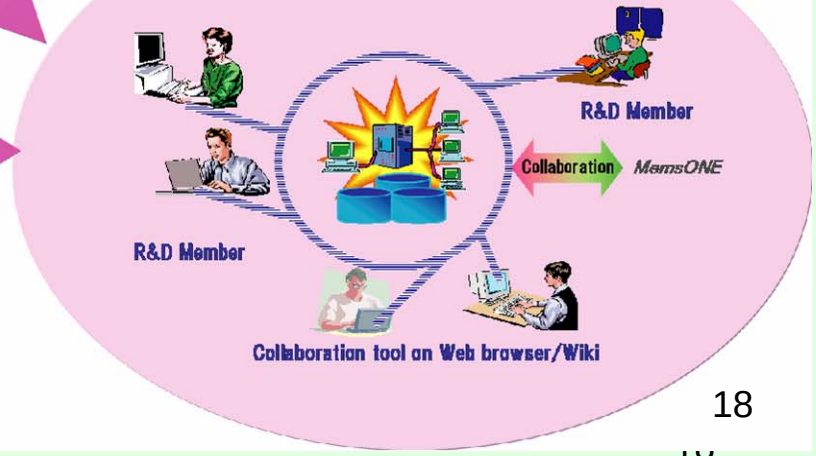
Multiple MEMS Integration



Integration of MEMS Substrates Fabricated with Different Materials

Build-up Type Multi-Stack MEMS Integration

Knowledge Database



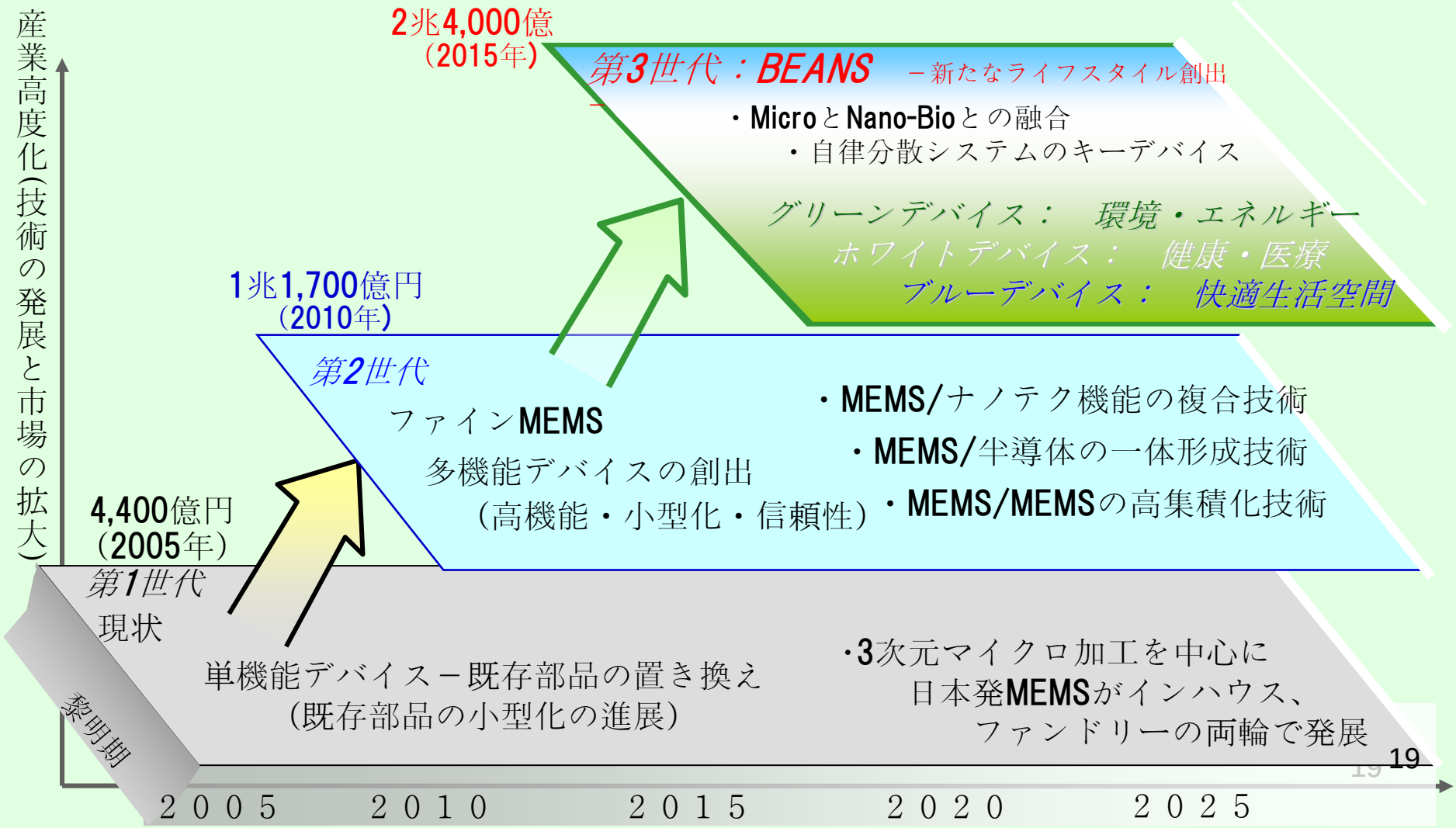
http://www.mmc.or.jp/e/

３－１　MEMS産業・技術ロードマップ

BEANS

Bio **E**lectro-mechanical **A**utonomous **N**ano **S**ystems

ナノ・バイオと電気機械を融合、自律分散で機能するデバイス・システム



3－2　MEMSデバイスの応用例

第3世代MEMS：BEANS
新たなライフスタイルの創生

エネルギー
ハーベスティング

オンサイト
環境浄化デバイス
CO_2固定
水・空気

体内埋込
デバイス
生体機械
ﾊｲﾌﾞﾘｯﾄﾞﾃﾞﾊﾞｲｽ

環境物質
化学物質
五　感
センシング

雰囲気
伝送・再生
デバイス

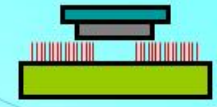
シート型
健康管理
デバイス

壁紙型
アンビエント
インテリジェンス

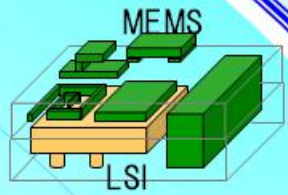
第2世代MEMS
集積化・複合化による
多機能・超小型デバイス

・MEMS/ナノテク機能複合

CNT応用スイッチ



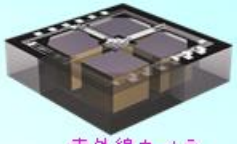
・MEMS/半導体一体形成

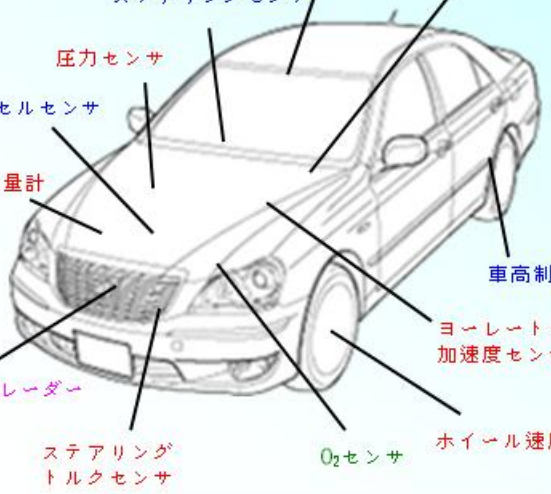


第1世代MEMS

自動車
1,350億円

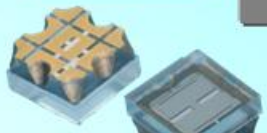
エアバッグ　車両安定制
エンジン制御横転防止





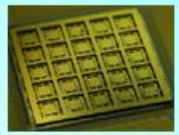
情報通信
1,490億円

RF　MEMS

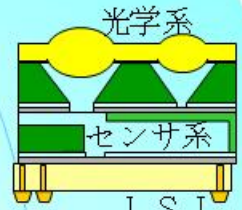


インクジェット
プリン

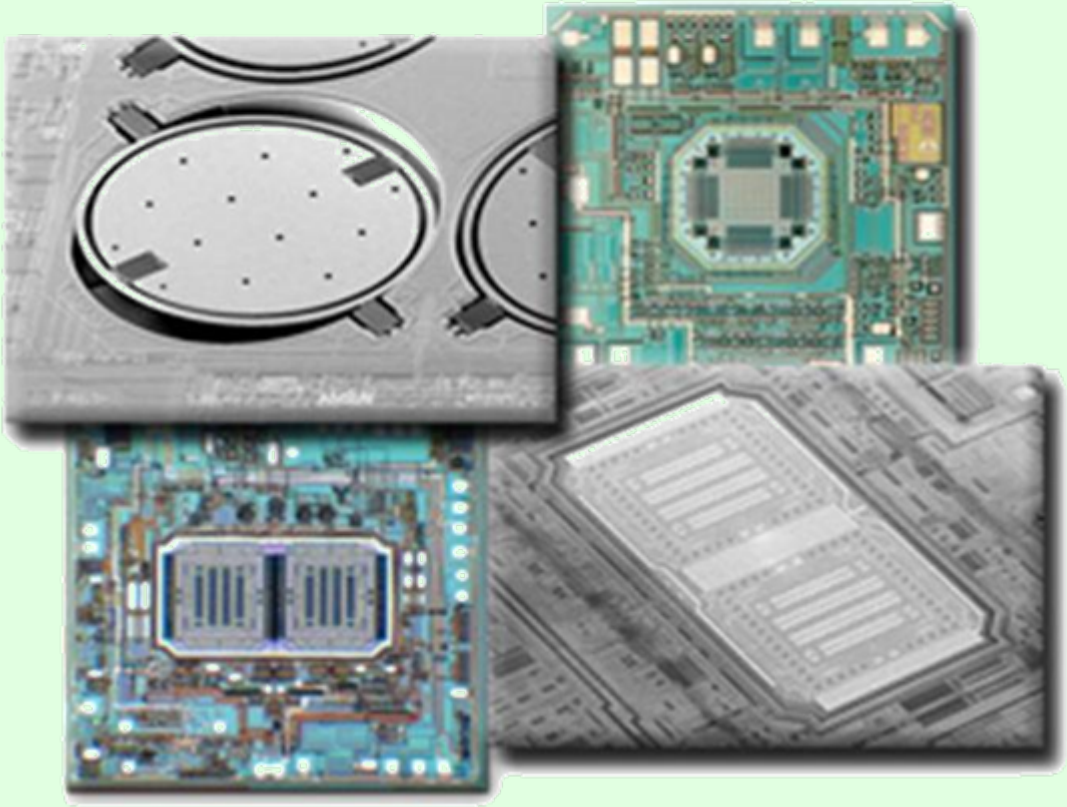
プロジェクター
（ＤＭＤ）



・MEMS/MEMS高集積化

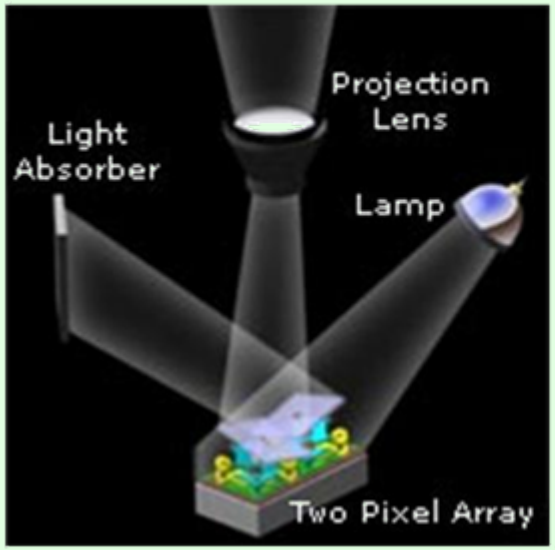


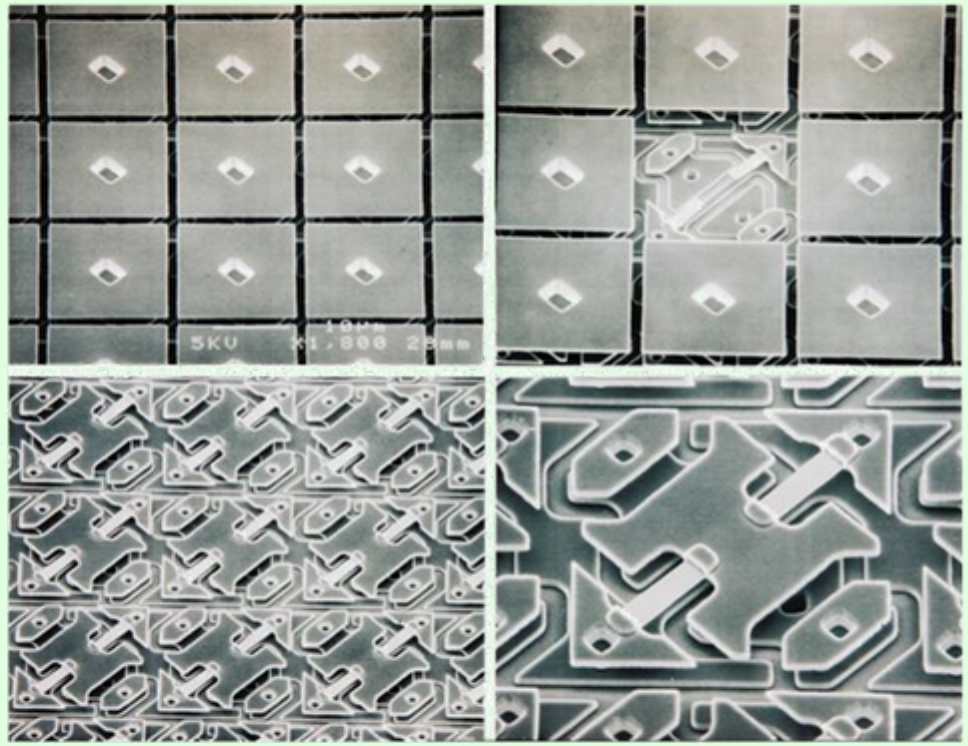
Application of Micro-sensors

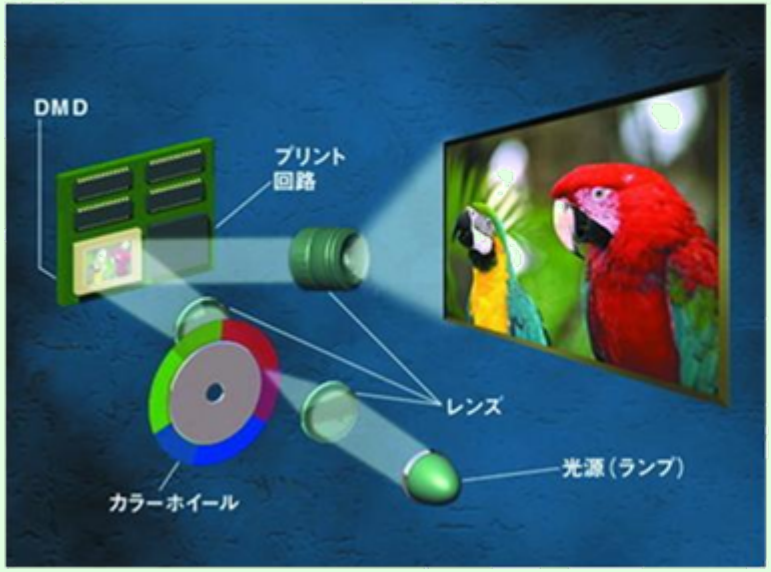


references	http://www.analog.com/jp/cat/0,2878,764,00.html

Digital Mirror Device : TEXAS INSTRUMENTS







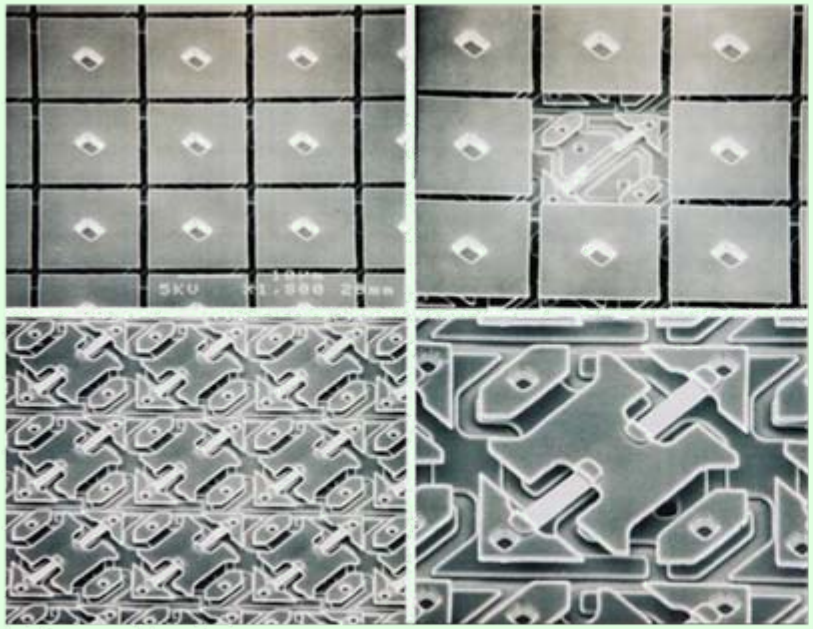
http://plusd.itmedia.co.jp/lifestyle/articles/0409/03/news054_2.html

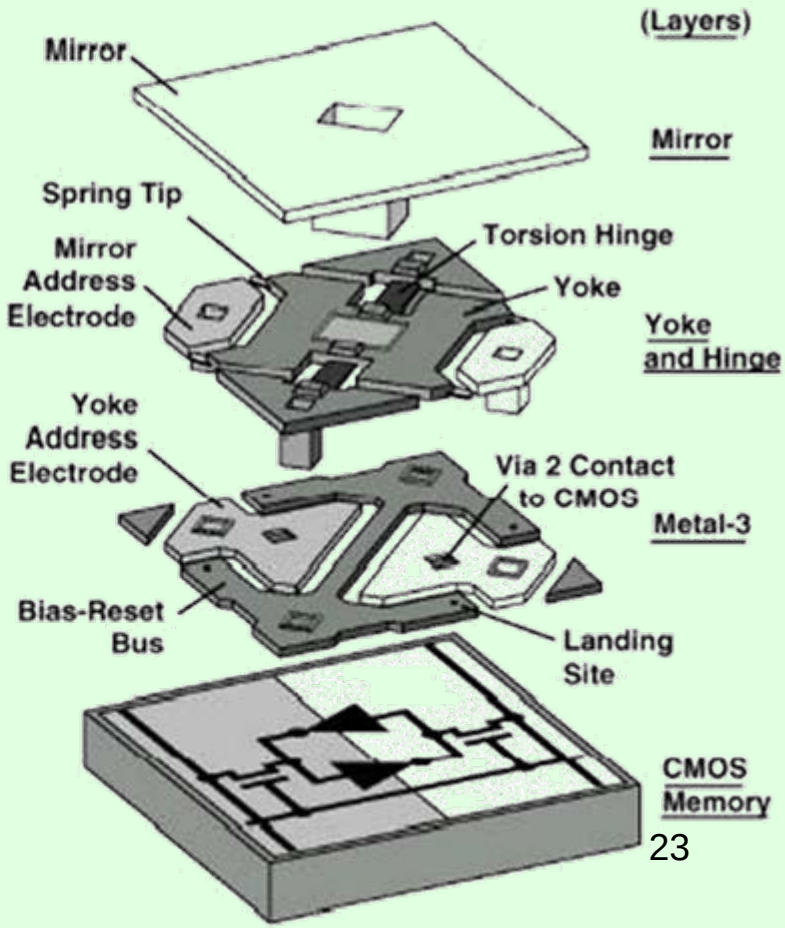
References

http://www.ti.com/sc/docs/products/dlp/index.htm

http://www.dlp.com/about_dlp/about_dlp_images_pixels_micro.asp

Digital Mirror Device : TEXAS INSTRUMENTS



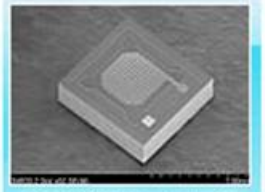


Reference www.ti.com/dlp/resource/library/

P.F. Van Kessel et al., T.I., Proc. IEEE, Vol. 86, p 1687, 1998

モバイルを変える、ミクロの音響革命。

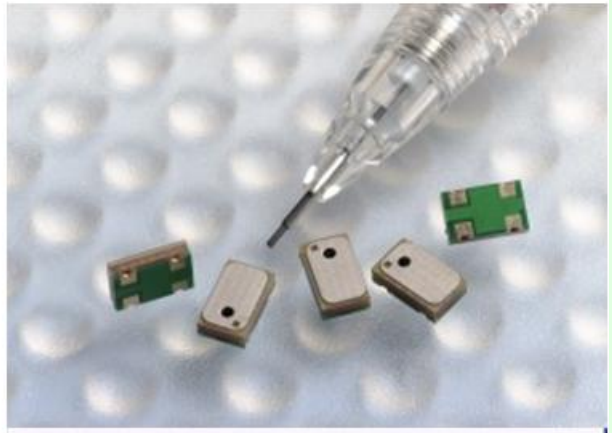
MEMSマイクロフォン

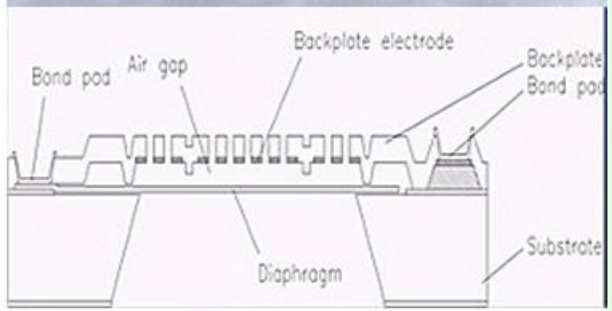


電子顕微鏡による画像

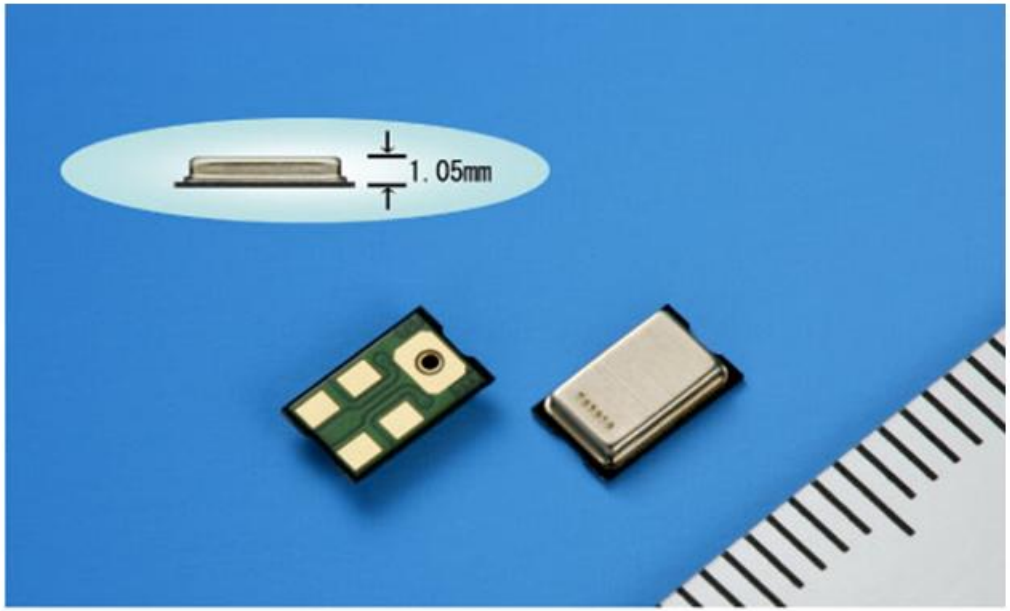
MEMSマイクロフォン
チップの構造

http://www.omron.co.jp/ecb/products/memsmicro/phonechip/





http://www.knowles.com/search/



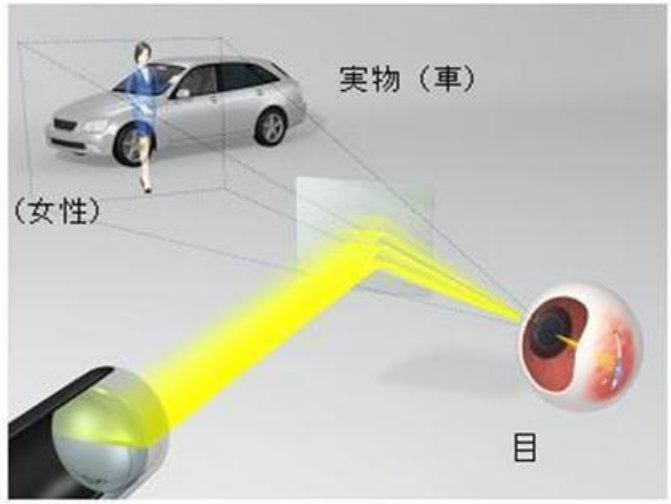
薄型で高耐熱性を有する「MEMSマイクロホン」
（2007年 5月 パナソニック半導体デバイスソリューションズ（株））

http://panasonic.co.jp/corp/news/official.data/data.dir/jn070517-1/jn070517-1.html

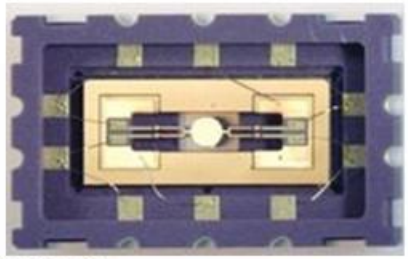
メガネ型網膜走査ディスプレイを開発

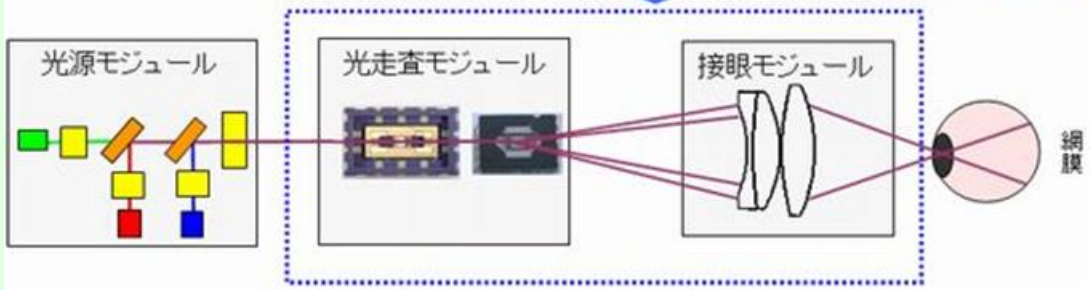
http://www.brother.co.jp/news/2008/rid/index.htm

RIDの画像（女性）



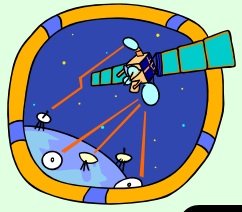
光を発生させる装置



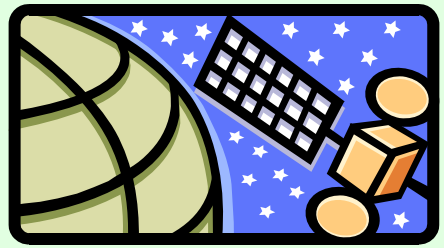


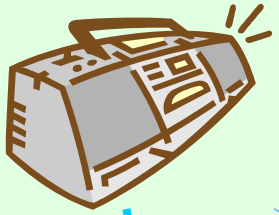
駆動方式
ミラー径
光学振角
周波数
サイズ：圧電方式(ピエゾ方式) 共振駆動
：約φ1 mm
：約20°
：約30KHz
：約 12mm(L)× 8mm(W)× 2mm(T)

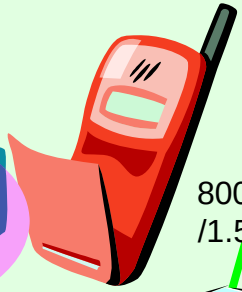
RF-MEMS



GPS:1GHz

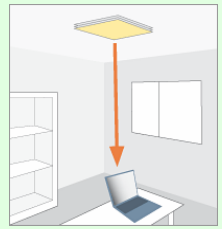


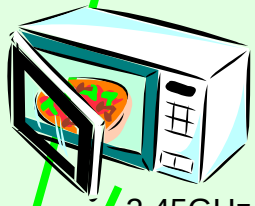




800MHz
/1.5GHz

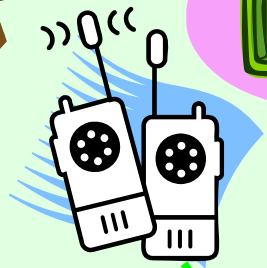
10GHz-
30GHz





100MHz(VHF)-
800MHz(UHF)

2.45GHz



50MHz

100m 1m Wavelength 1cm 1mm 10μm

$3x10^5$ $3x10^6$ $3x10^7$ $3x10^8$ $3x10^9$ $3x10^{10}$ $3x10^{11}$ $3x10^{12}$

Frequency (Hz)

Microwave

light

Application of Wireless Network(1)

Ubiquitous

Seamless Connectivity with FTTH (Fiber To The Home) ; **Last 5m**

Optical network?

Microwave network?

! Quality comparable between wire-line network and wireless network

Entertaiment

Game

Optical Network

Tele-Communication

Video Movie

Visual Interface

Monitor

Food and Heath

House hold articles

HDD

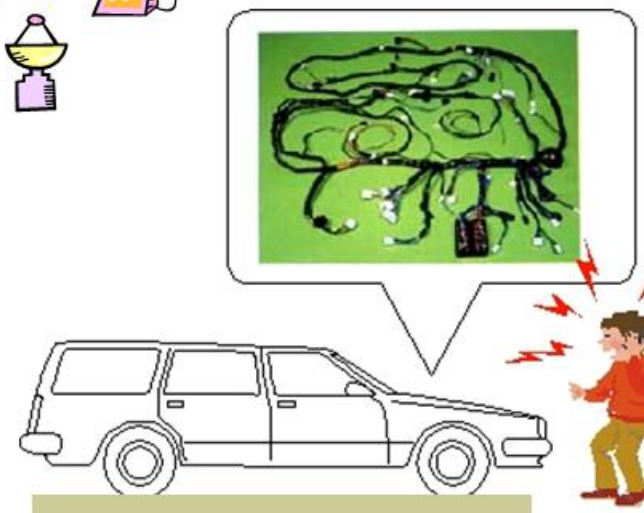
Data Storage

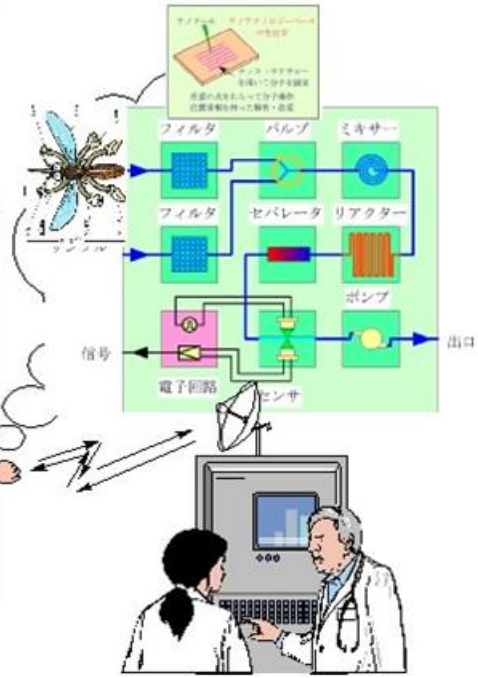
Information Processing

PDA

Energy Management and Control

Application of Wireless Network(2)



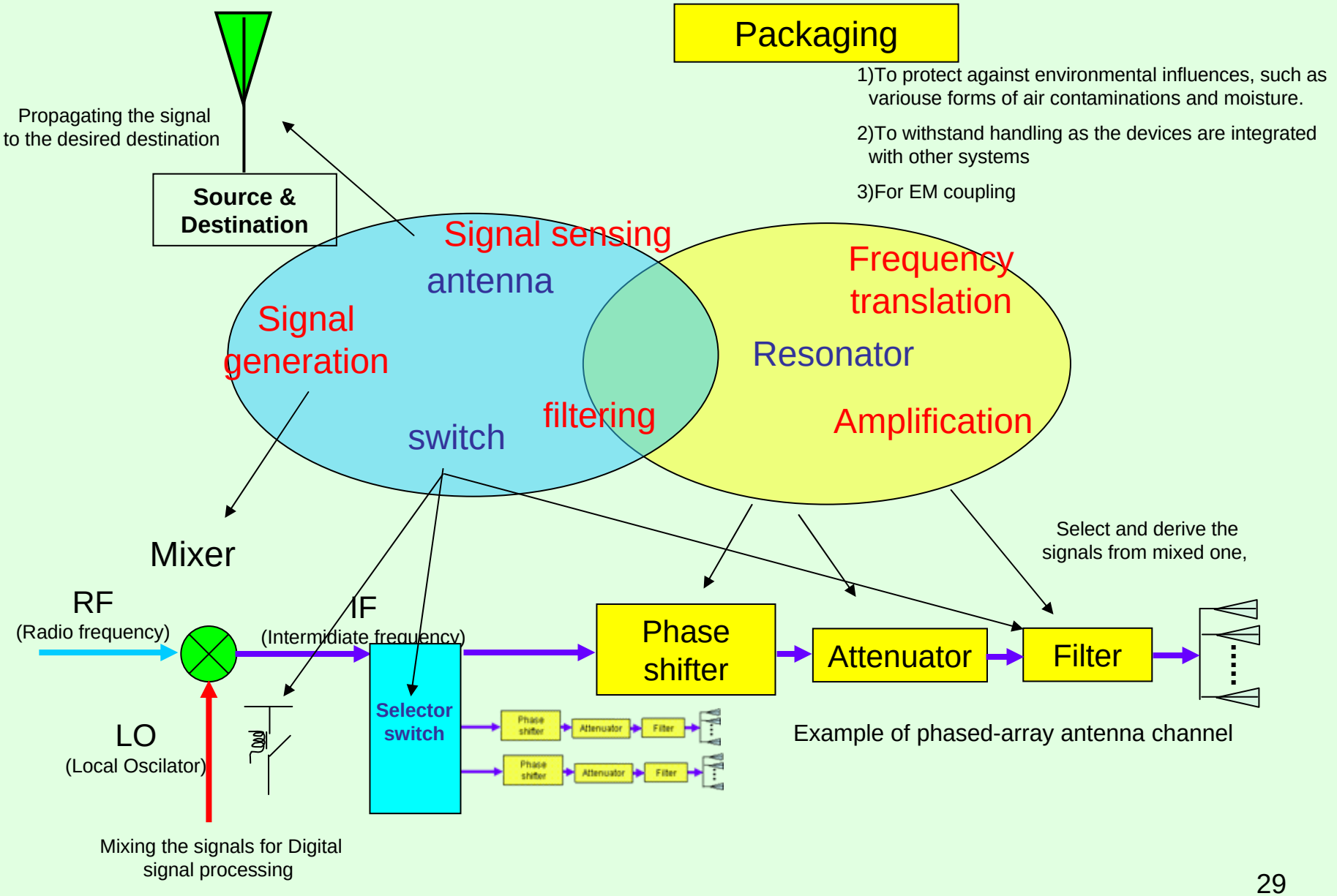


Tele-monitoring

http://www.fujikura.co.jp/mach_elec_mate/carwire/carwire.htm

http://www.is.aist.go.jp/humanoid/hrp-2p/hrp-2p.htm

Components for RF communication

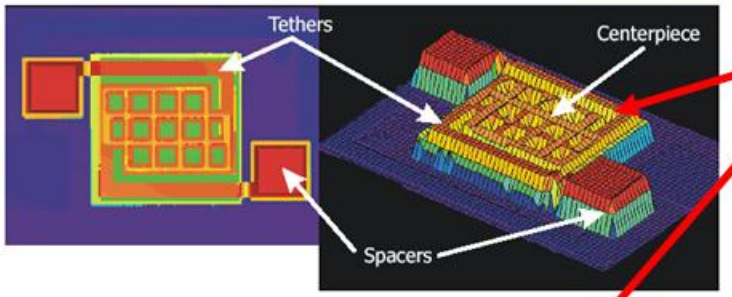


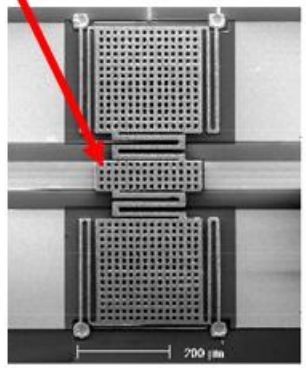
Switching speed relates to the resonant frequency of the switch

$$f = \frac{1}{2\pi}\sqrt{K/M}$$

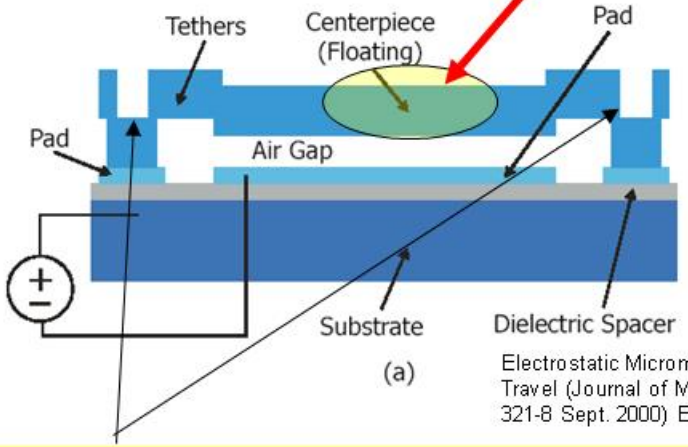
K is equivalent Young's Modulus and M is Mass

There are through holes to reduce the total mass and to decrease the Reynold's stress





University of Michigan MEMS switch



Electrostatic Micromechanical Actuator with Extended Range of Travel (Journal of Microelectromechanical Systems, Vol. 9, No. 3, pp. 321-8 Sept. 2000) Edward Chang and R.Dutton

INTEGRATED FIVE-BIT RF MEMS PHASE SHIFTER FOR SATELLITE BROADCASTING/COMMUNICATION SYSTEMS

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Materials and Devices Laboratory,
LG Electronics Institute of Technology.
16 Woomyeon-Dong, Seocho-Gu, Seoul, 137-724, Korea
Telephone: 82-2-526-4486, Fax: 82-2-3461-3508, E-mail: kojoon@lge.com

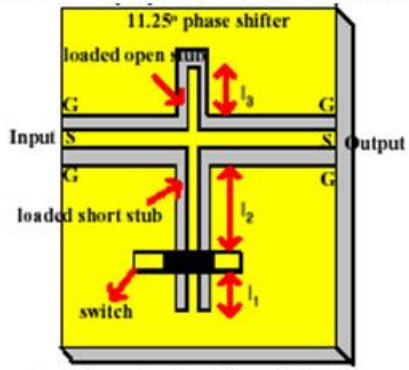


Figure 6. Schematic drawing of the phase shifter with 11.25°-phase bit.

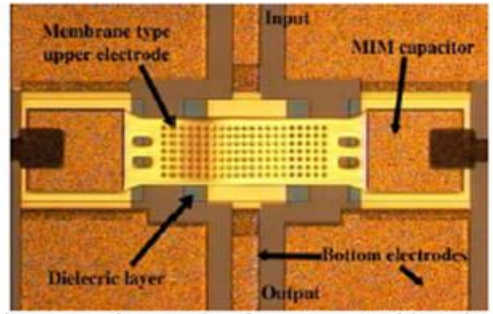


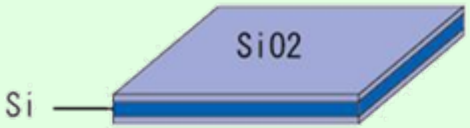
Figure 2. Photograph of MEMS capacitive shunt switch

MEMS2003 pp.144

Reduce **K** to gain the deflection and to reduce the driving voltage

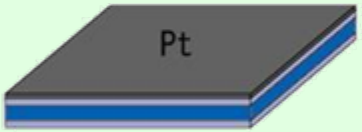
Driving voltage may be 20V up to 50V

Fabrication process of the X-bar type actuator



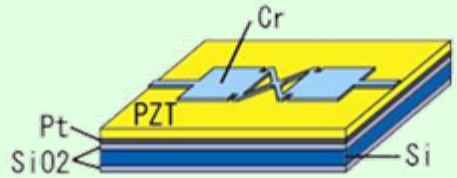
(1) Prepare the thermal-oxidized Si substrate

(2) Ti sputtering

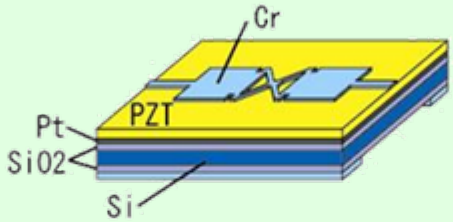


(3) Pt sputtering

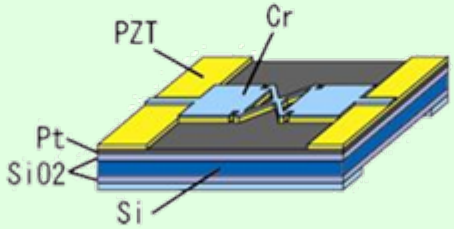
(4) PZT sputtering



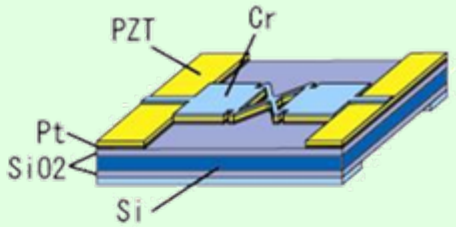
(5) Cr patterning by lift off process (Electrade)



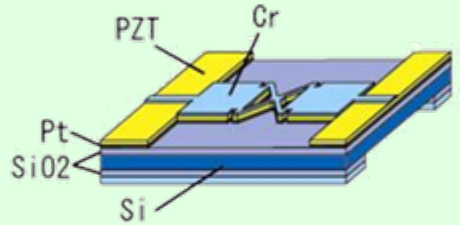
(6) Cr patterning by lift off process (Metal mask)



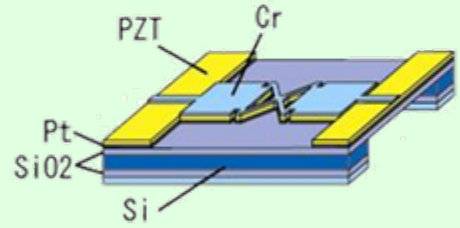
(7) PZT wet etching



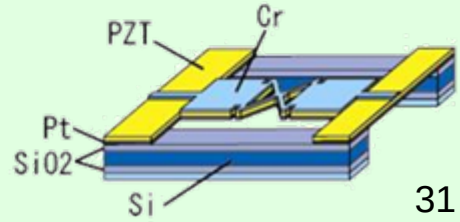
(8) Ti/Pt dry etching (Ar)



(9) SiO2 dry etching (CF4+02)

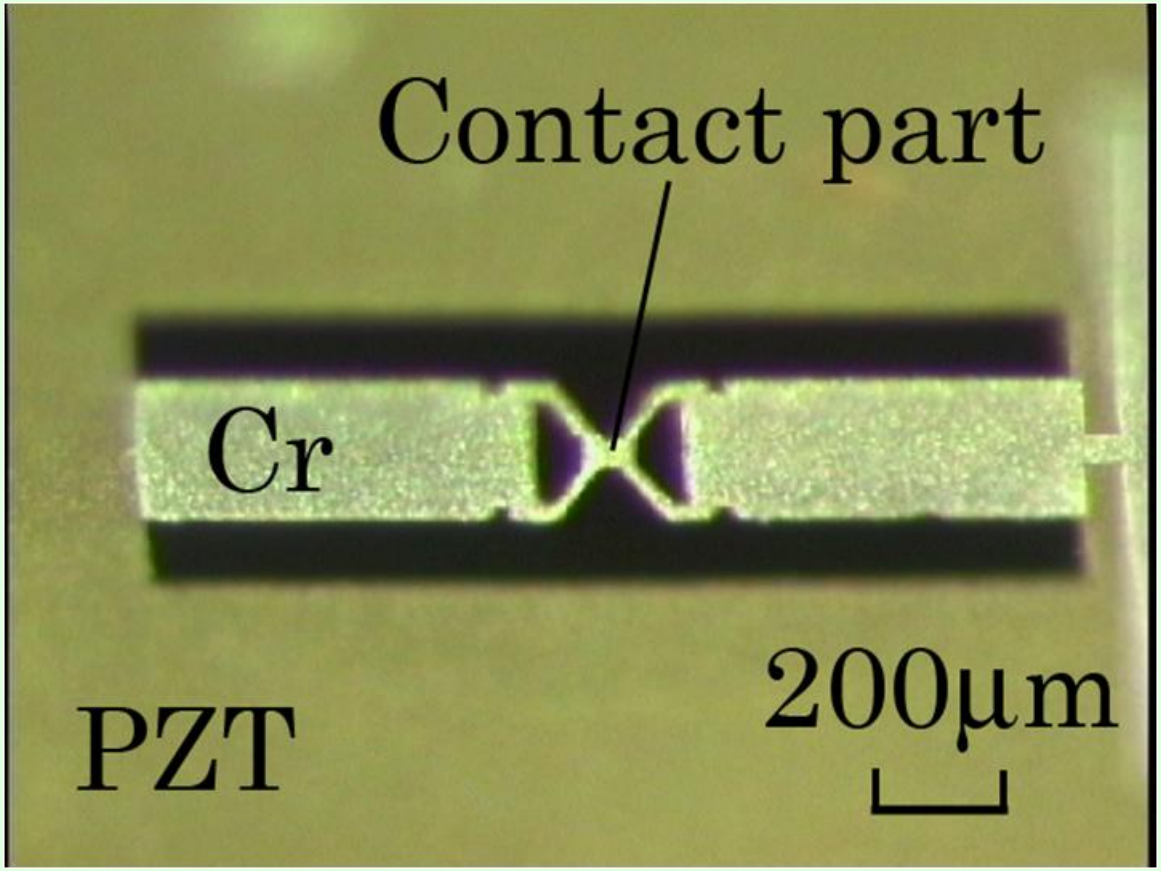


(10) Si dry etching (SF6)



(11) SiO2 dry etching (CF4+02)

Fabricated X-bar actuator



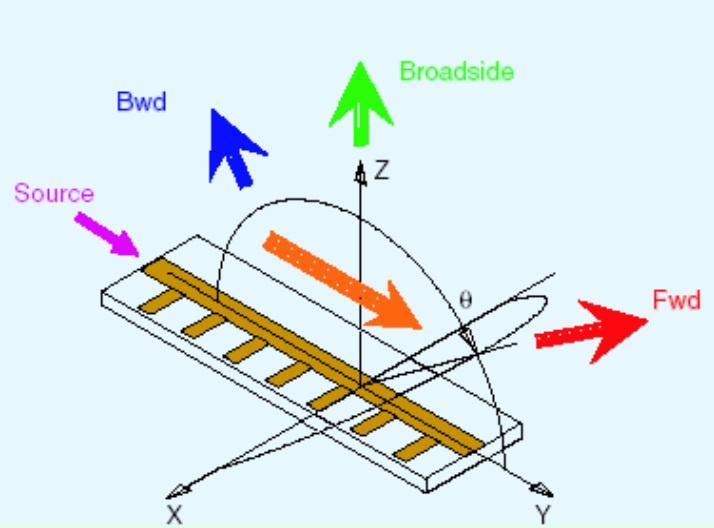
Fabricated X-bar actuator

800μm in length, 200μm in width,
3.4μm in thickness
(Pt:100nm,PZT:2.5μm,Cr:0.8μm)

Composite Right/Left-Handed Metamaterial and Metastructure for designing the reconfigurable Millimeter wave antenna (M^3-project)

Definition: Metamatrial and Metastructure are artificial structures that can be designed to exhibit specific electromagnetic properties not commonly found in nature.

The Russian physicist Veselago presented about theory of metamaterials with simultaneously negative permittivity (ε) and permeability (μ) in 1967, which are commonly referred to as left-handed materials. (V.Veselago," The electrodynamics of substances with simultaneously negative values of ε and μ", Soviet Physics Uspekhi, Vol.10,No.4,pp.509-514,1967)



Lai, A.; Itoh, T.; Caloz, C.,"**Composite right/left-handed transmission line metamaterials",IEEE Microwave magazine,Vol.5,Issue 3.2004** pp. 34- 50

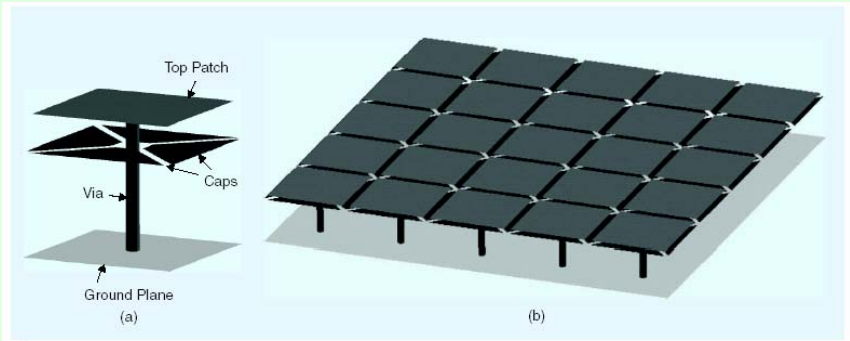
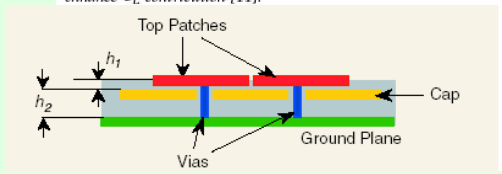
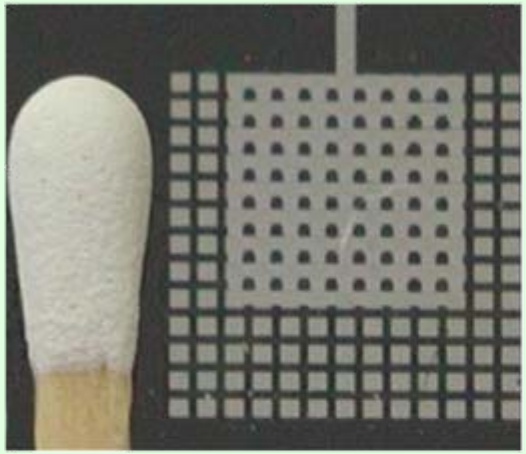


Figure 11. *Open 2-D CRLH mushroom structure. (a) Unit cell [14]. (b) 2-D CRLH structure formed by periodic repetition of the unit cell. The caps are floating (not connected to the vias) patches located at a short distance from the connected patch to enhance C_L contribution [14].*

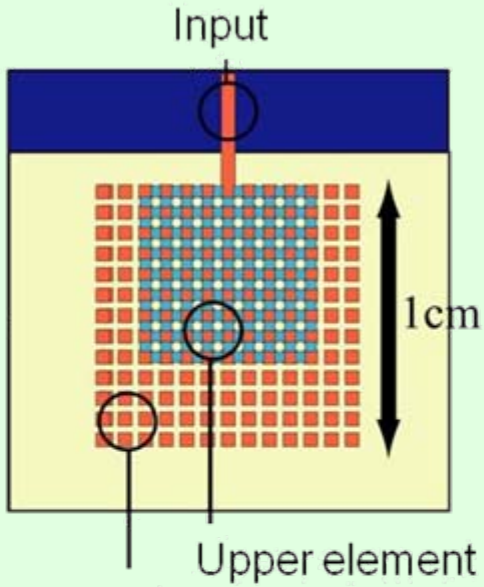


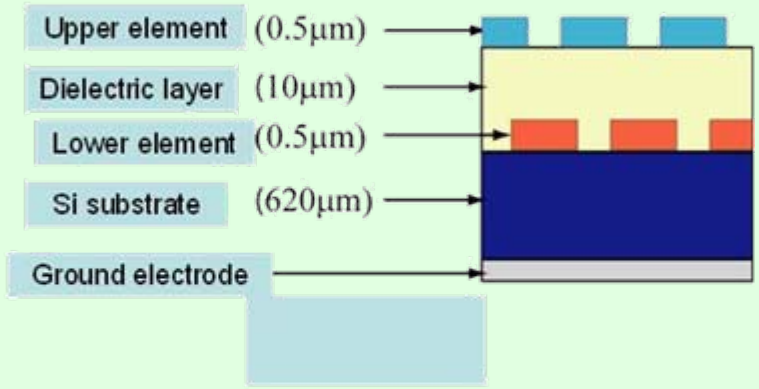
A. Sanada, C. Caloz, and T. Itoh, "Planar distributed structures with negative refractive properties," *IEEE Trans. Microwave Theory Tech.*, vol. 52, pp. 1252–1263, Apr. 2004.

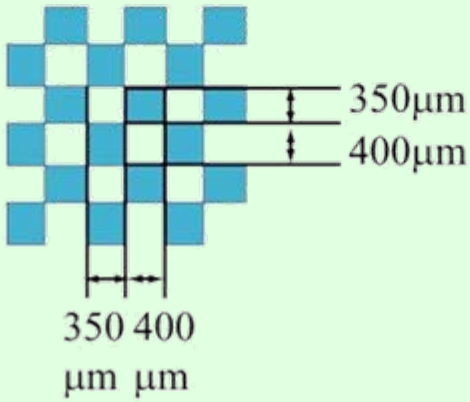
Structure of DLME antenna



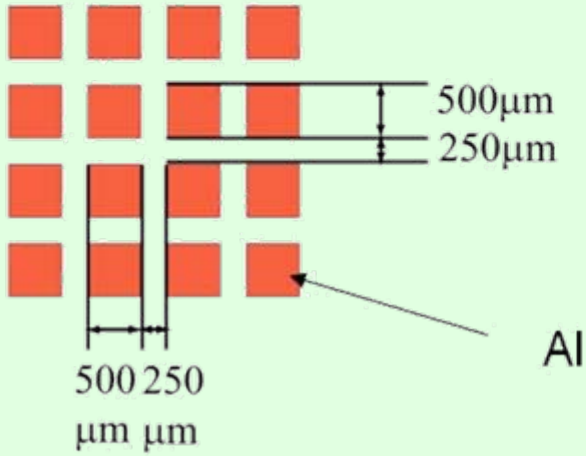
(a) Plane view (Photo)







(d) Upper element



(e) Lower element

Phased array antenna type 1

Horn-array type Millimeter wave antenna

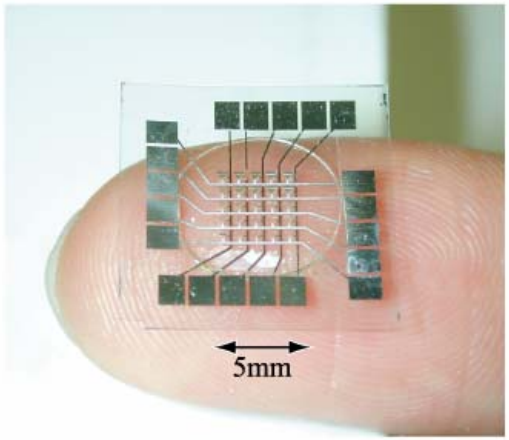
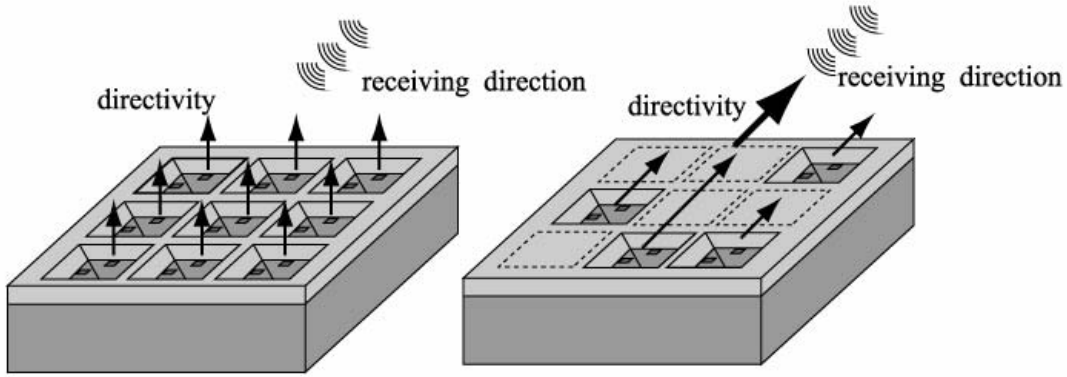


Figure1.Horn array antenna



(a) wating mode (b) active mode (reconfiguration)

Figure3. Reconfigurable directivity by calculated receiving wave strength

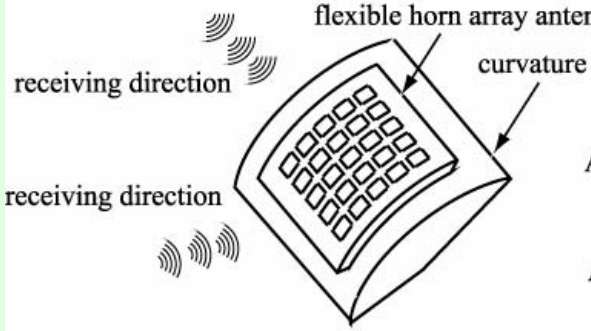
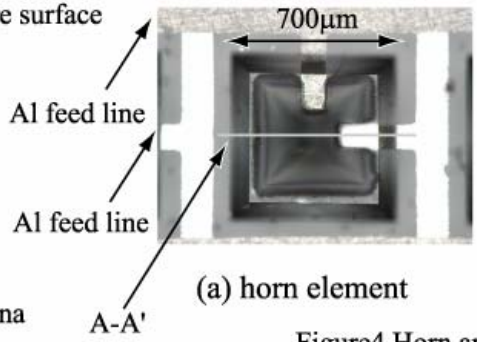
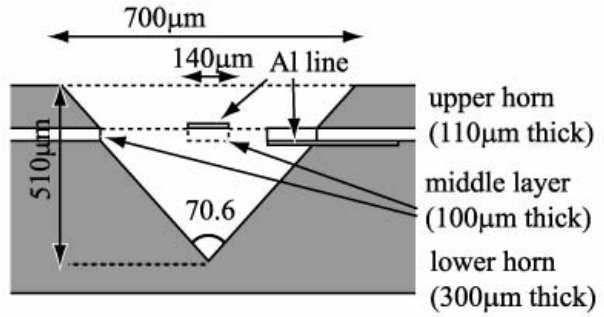


Figure2. Multi-directivity of horn array antenna mounted on the curvature surface



(a) horn element

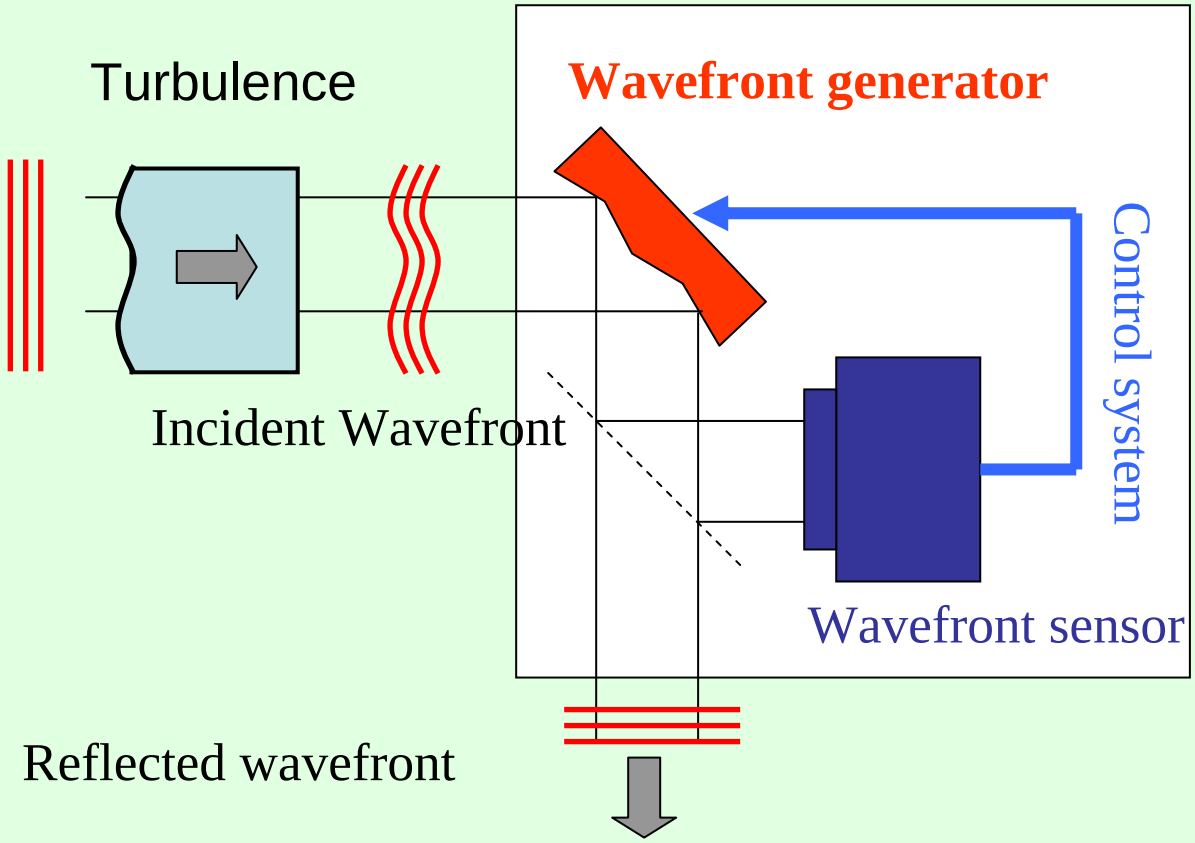


(b) A-A' cross section of horn array antenna

Figure4.Horn array antenna composed of three layers

Adaptive Optics system

Adaptive optics is used for correction of disturbed wave front.
This technology has been developed in astronomy.



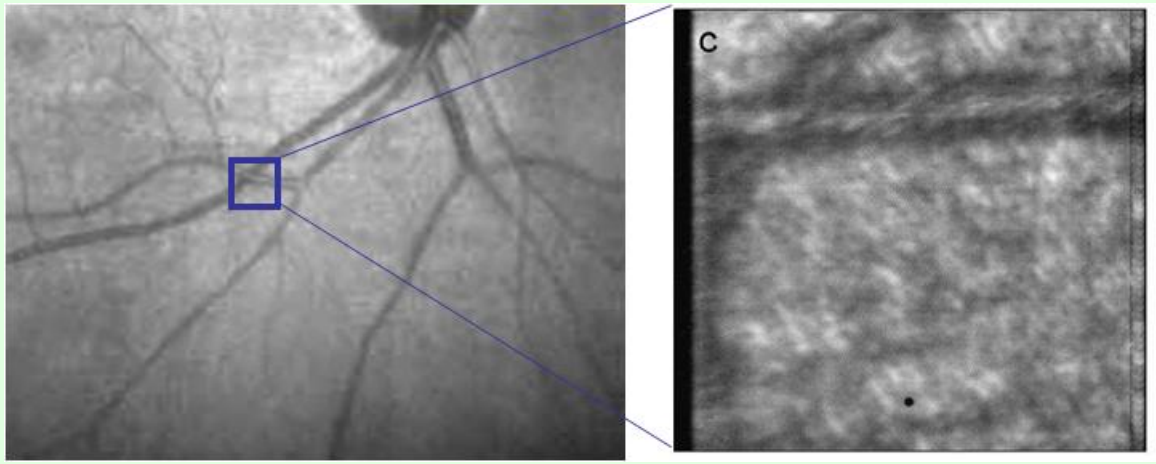
眼底検査

眼底の検査

診断

網膜はく離，緑内障
糖尿病，動脈硬化

眼科だけでなく
内科などの他診療科に
とって基本＆重要



眼底画像（走査型レーザー検眼鏡で撮影）
Daniel X. Hammerら撮影

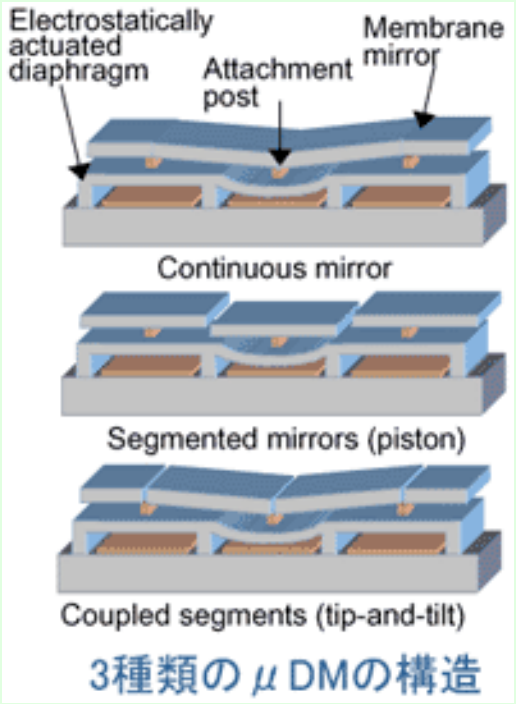
眼球は生体の中でもとりわけ
透明度の高い伝播媒質

しかし

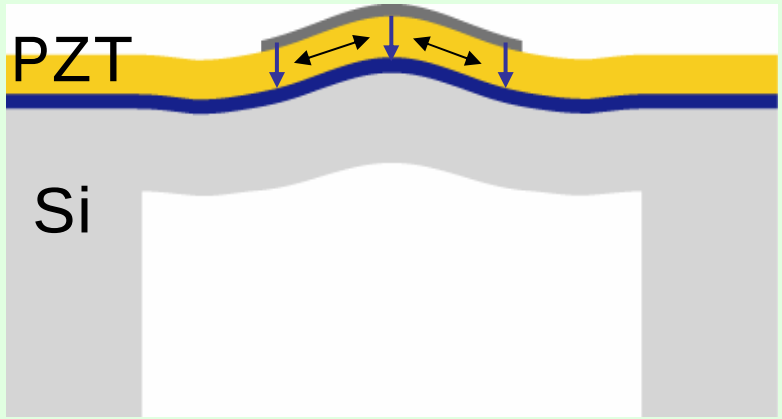
検査光は眼球内部で歪み，
波面収差を持つ

補償光学装置で波面収差を
取り除くことが必要

Structure of Piezoelectric Deformable Mirror



3種類のμDMの構造



Principle & structure

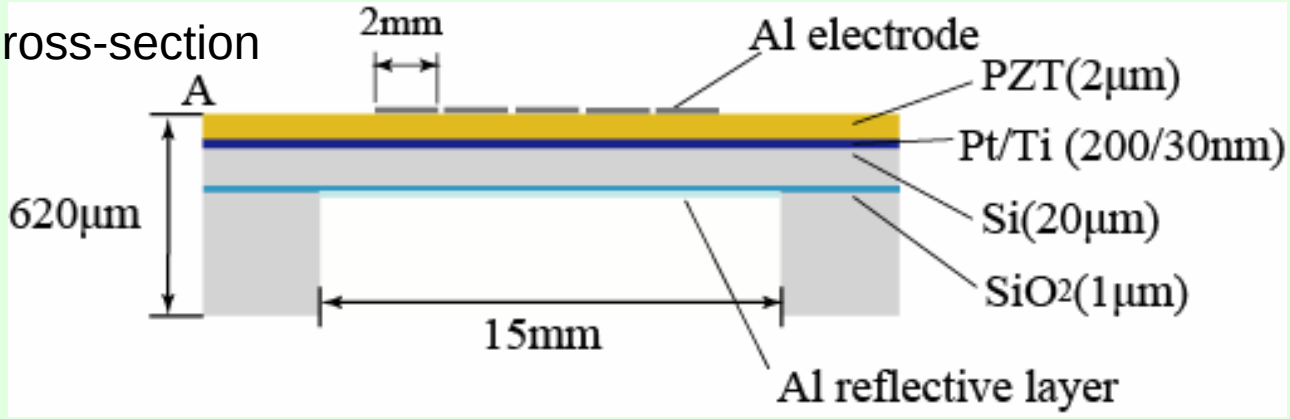
Boston MEMS

Electrostatic Actuator

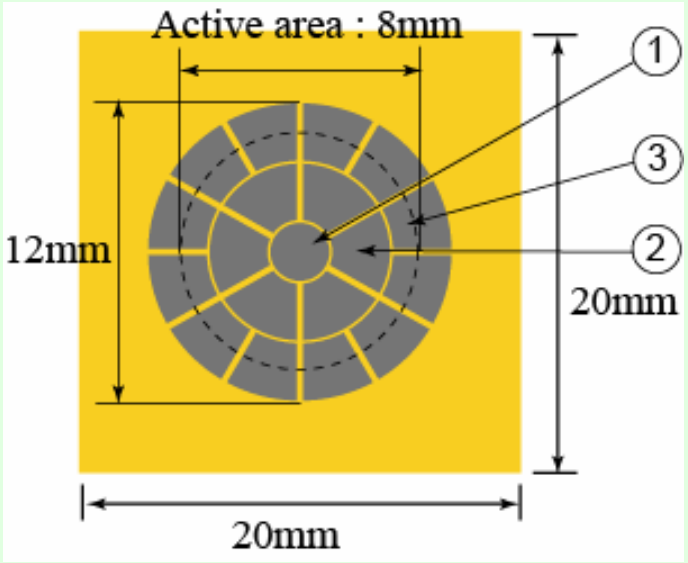
Piezoelectric thin film
➔ ±10V , ＞1KHz, Simple structure

Structure

Cross-section

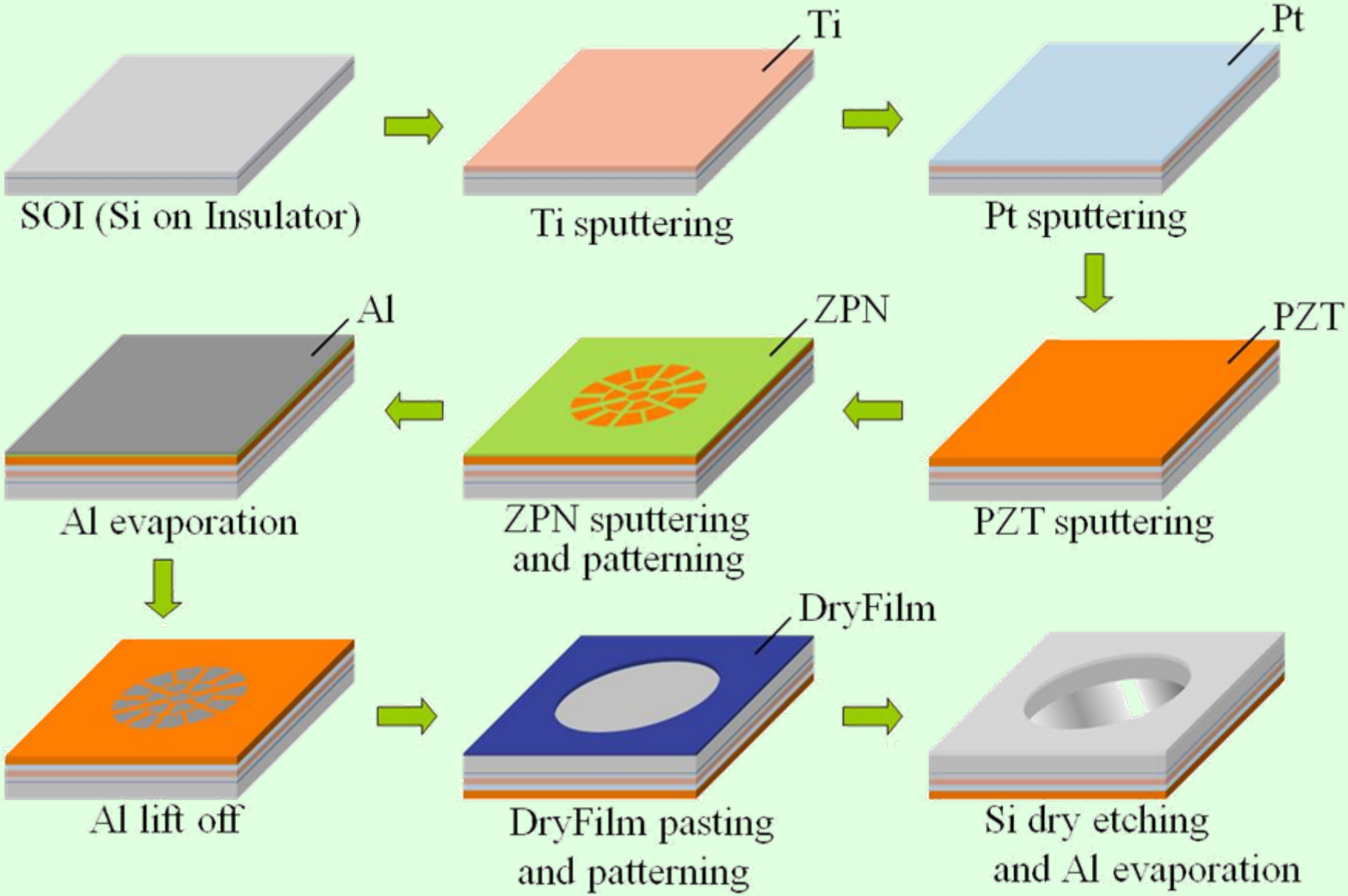


Plane



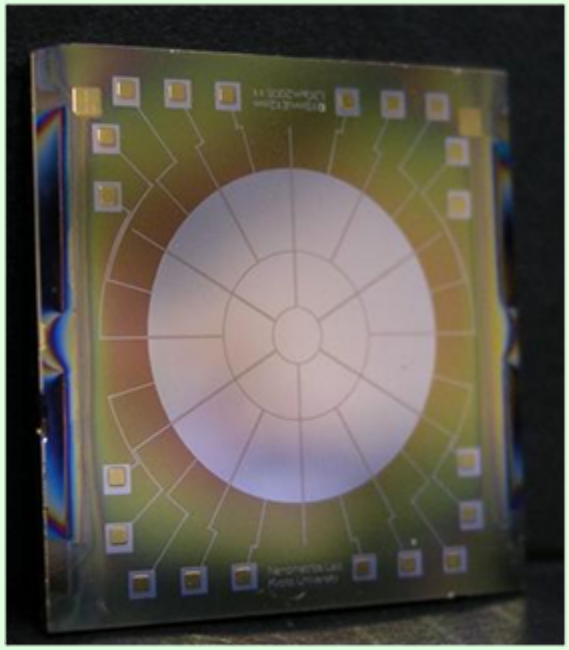
- Unimorph actuator array is composed of PZT films (2 μ m) and Si(20 μ m)
- 19 segmented ring electrode on PZT film
- Al reflective layer on SiO2 in SOI

作製プロセス

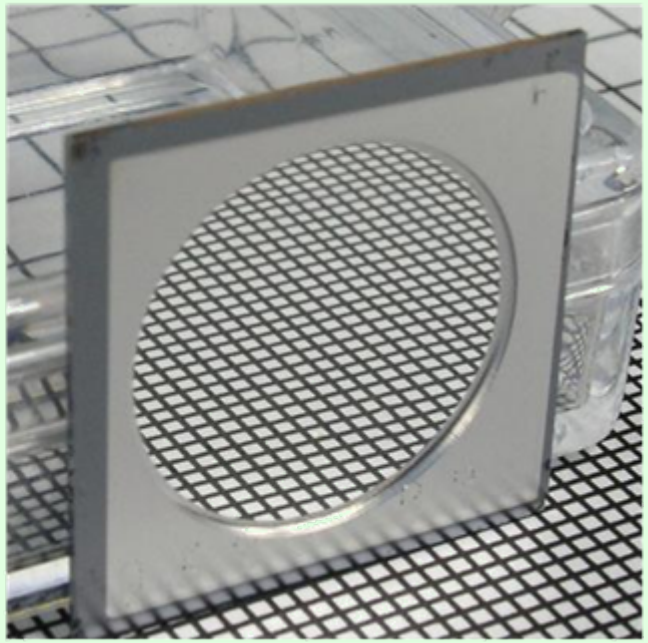

SOI (Si on Insulator)
Ti
Ti sputtering
Pt
Pt sputtering
PZT
PZT sputtering
ZPN
ZPN sputtering
and patterning
Al
Al evaporation
Al lift off
DryFilm
DryFilm pasting
and patterning
Si dry etching
and Al evaporation

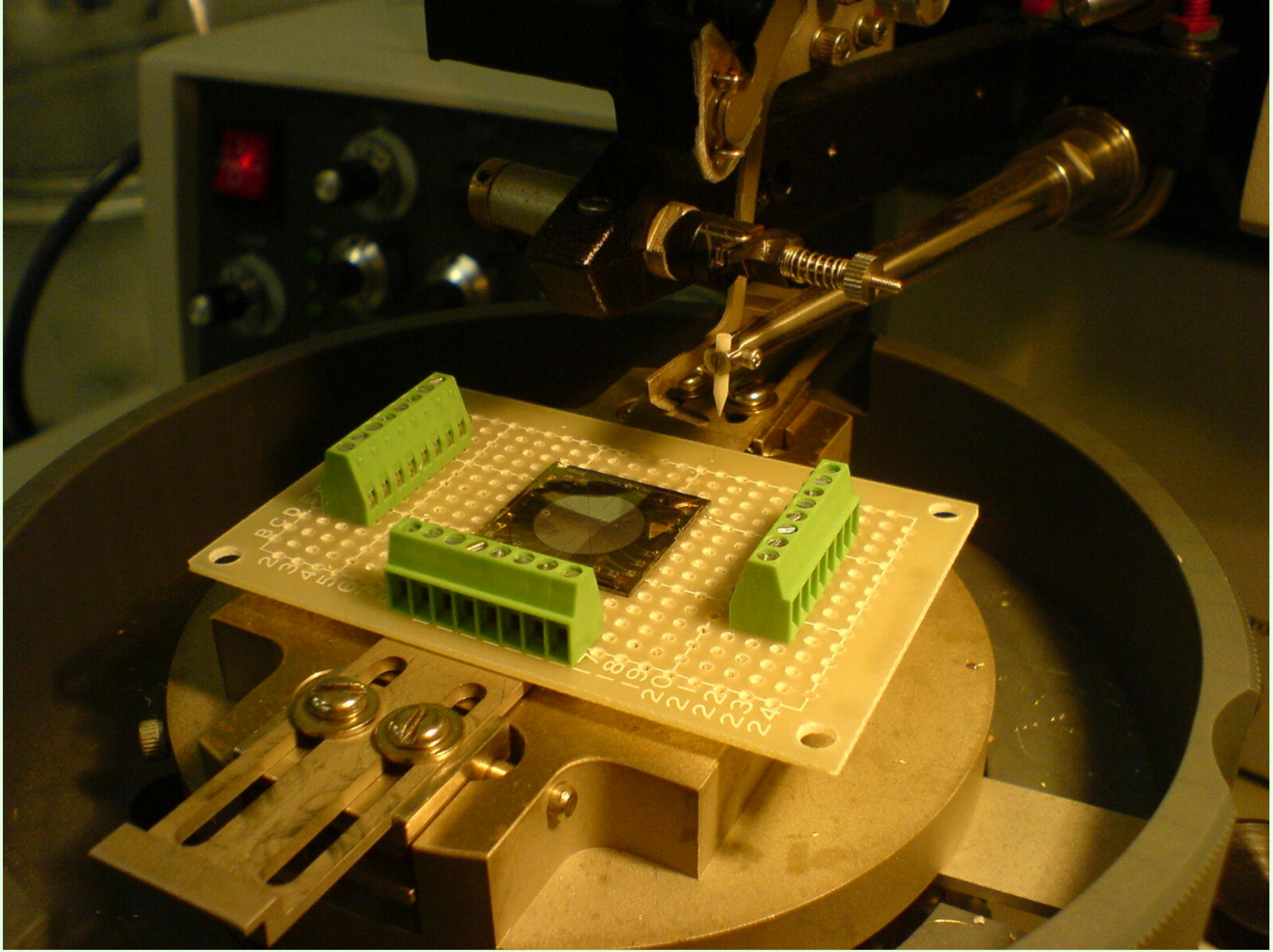
Photographs of mirror

Actuator side



Mirror side

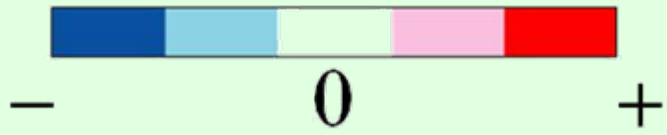


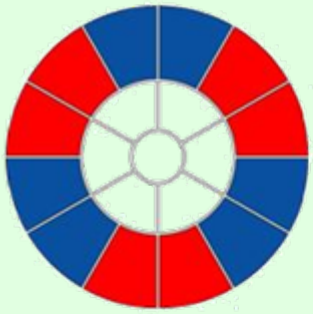


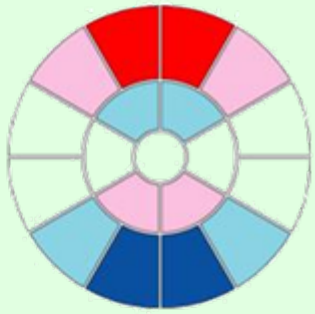
上部電極の設計

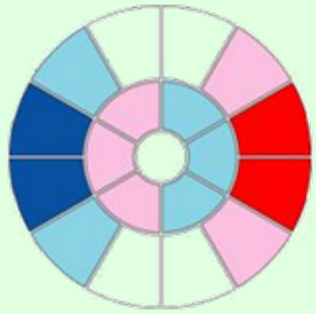
ゼルニケ形状3次の再現を考え設計

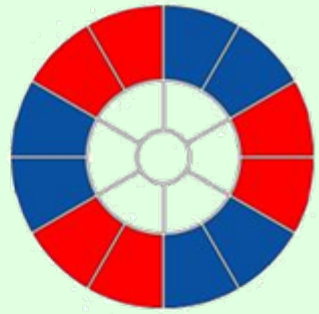
上部電極の印加電圧

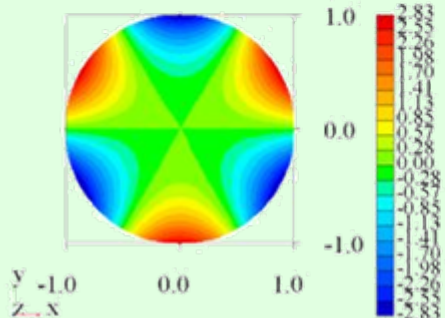


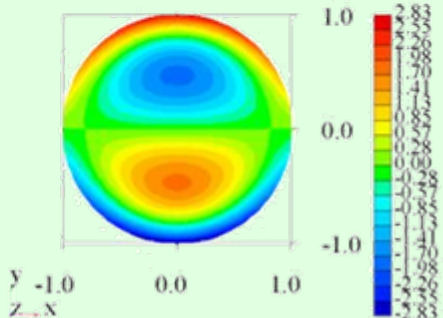


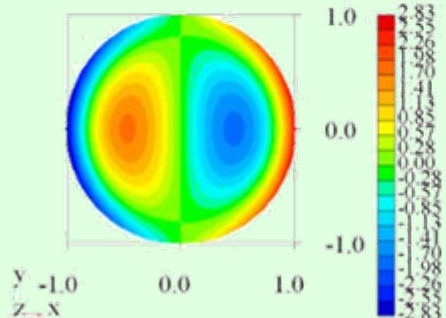


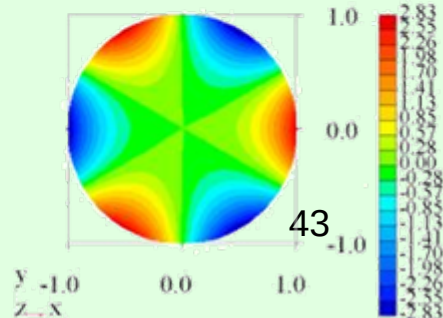




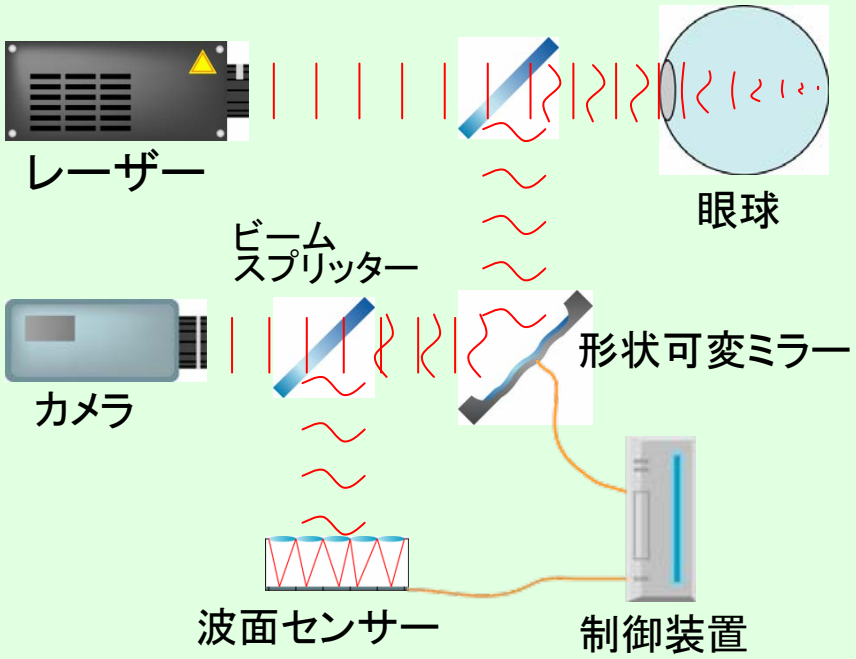








波面補償光学装置



システム図

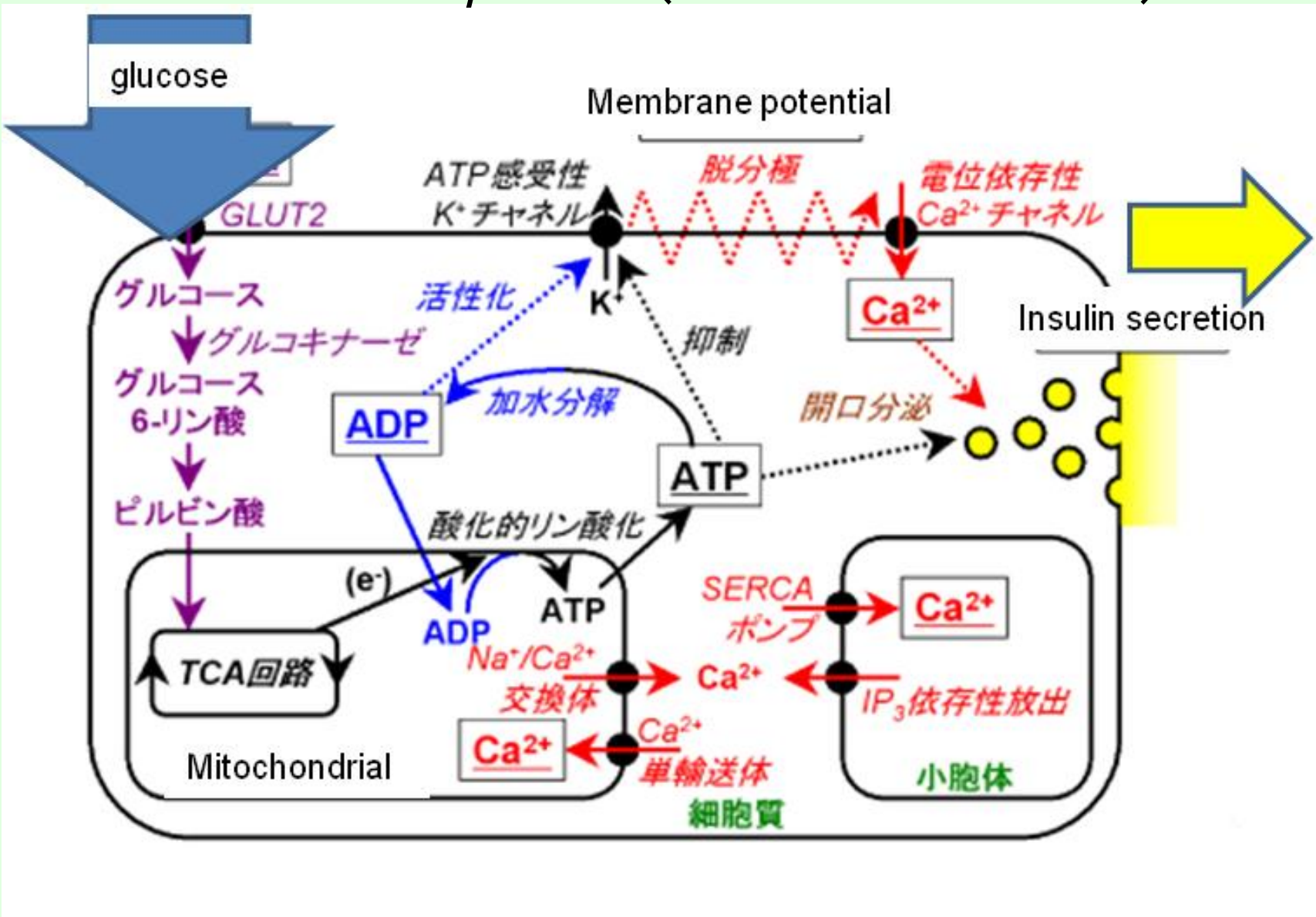
①眼底からの反射光を
波面センサーによって測定

②波面収差を打ち消すように
光路中に置いた形状可変
ミラーを変形させる

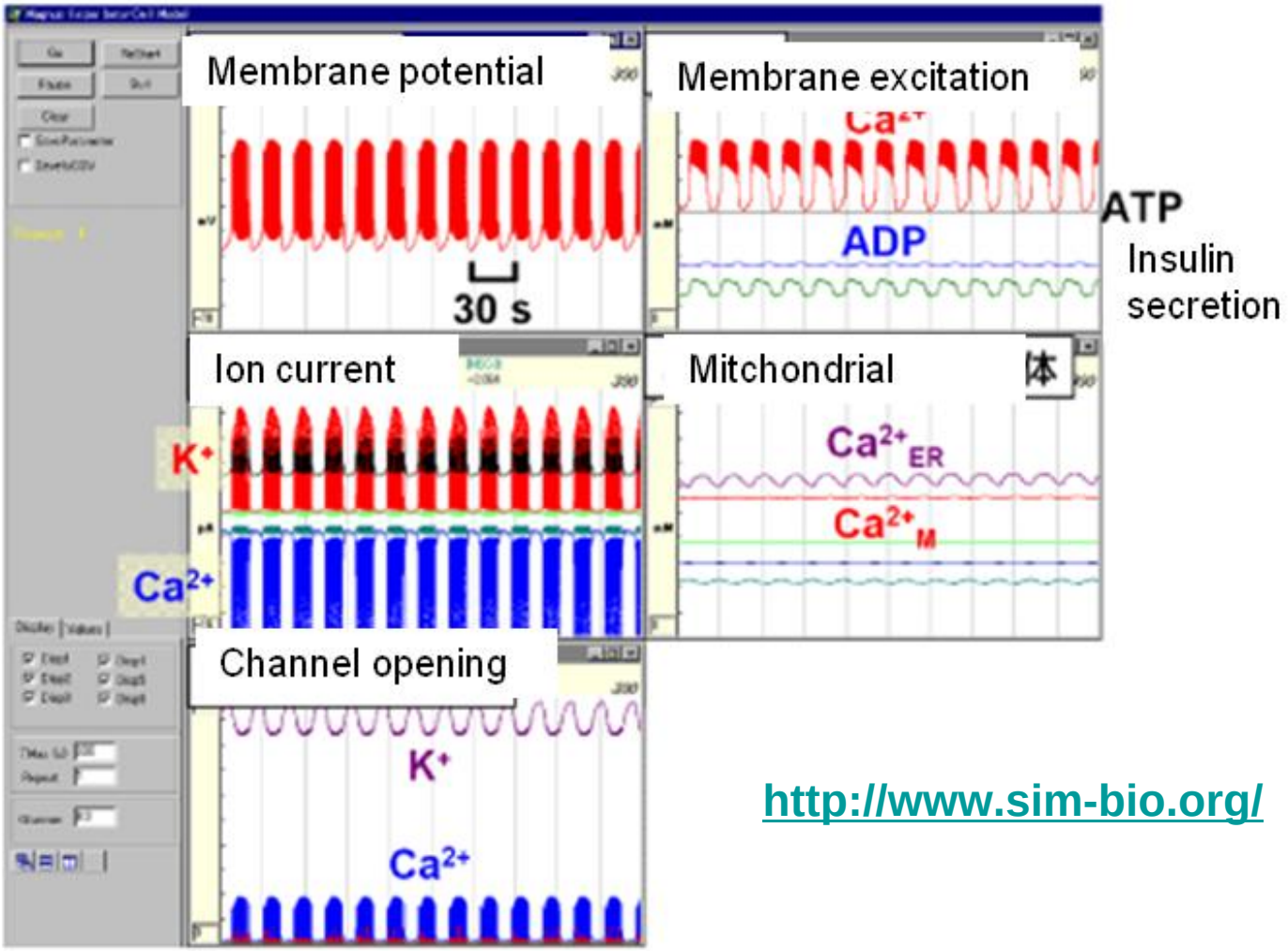
③反射光は波面収差を
補正される

Measuring Cell-Cell Communication and Regeneration of tissue

Pancreas β cell (insulin secretion)



Bio Simulator



http://www.sim-bio.org/

Pancreas β cell (insulin secretion): Type 2 Diabetes

Normal glucose

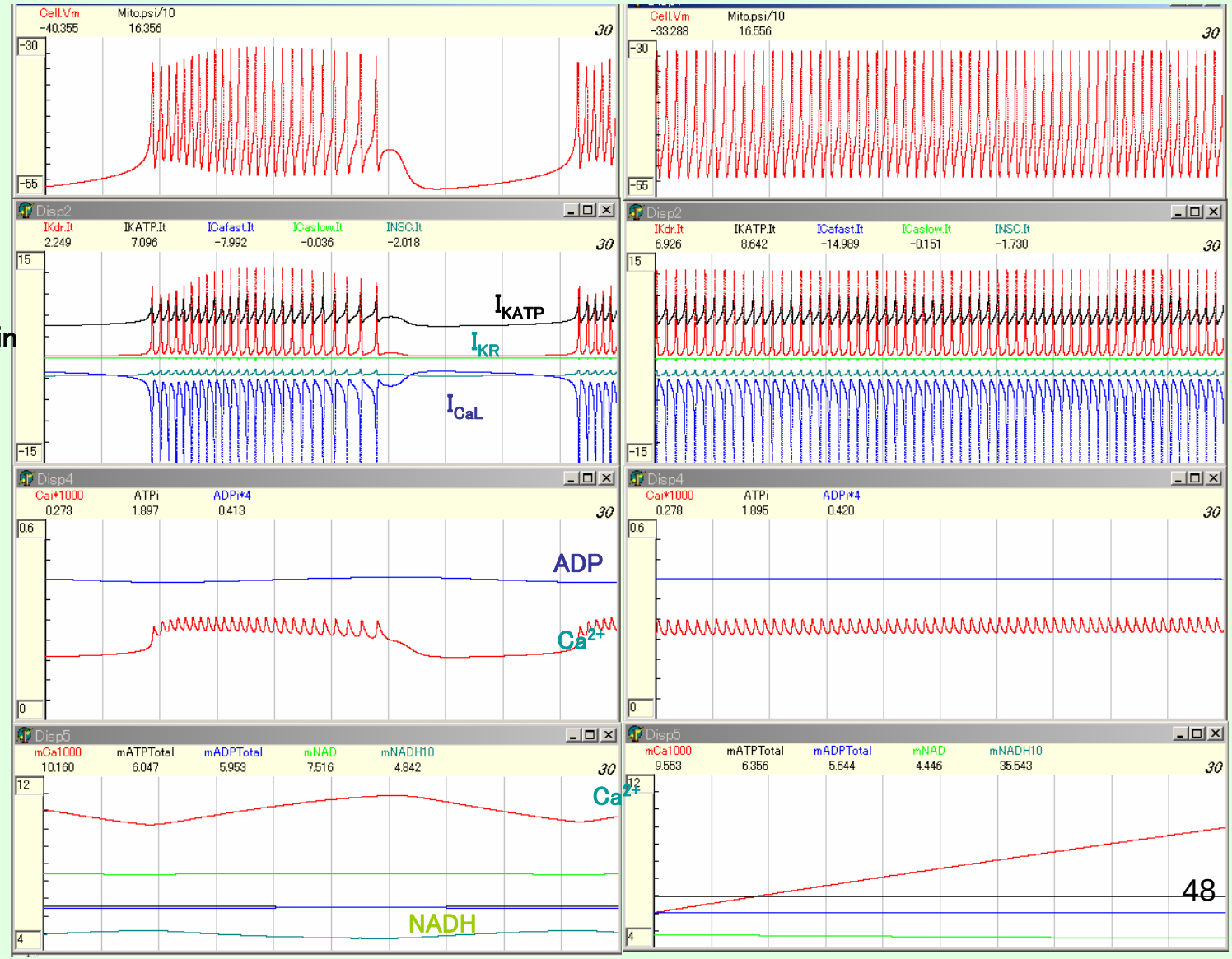
High glucose

Membrane potential

Channel protein actuation

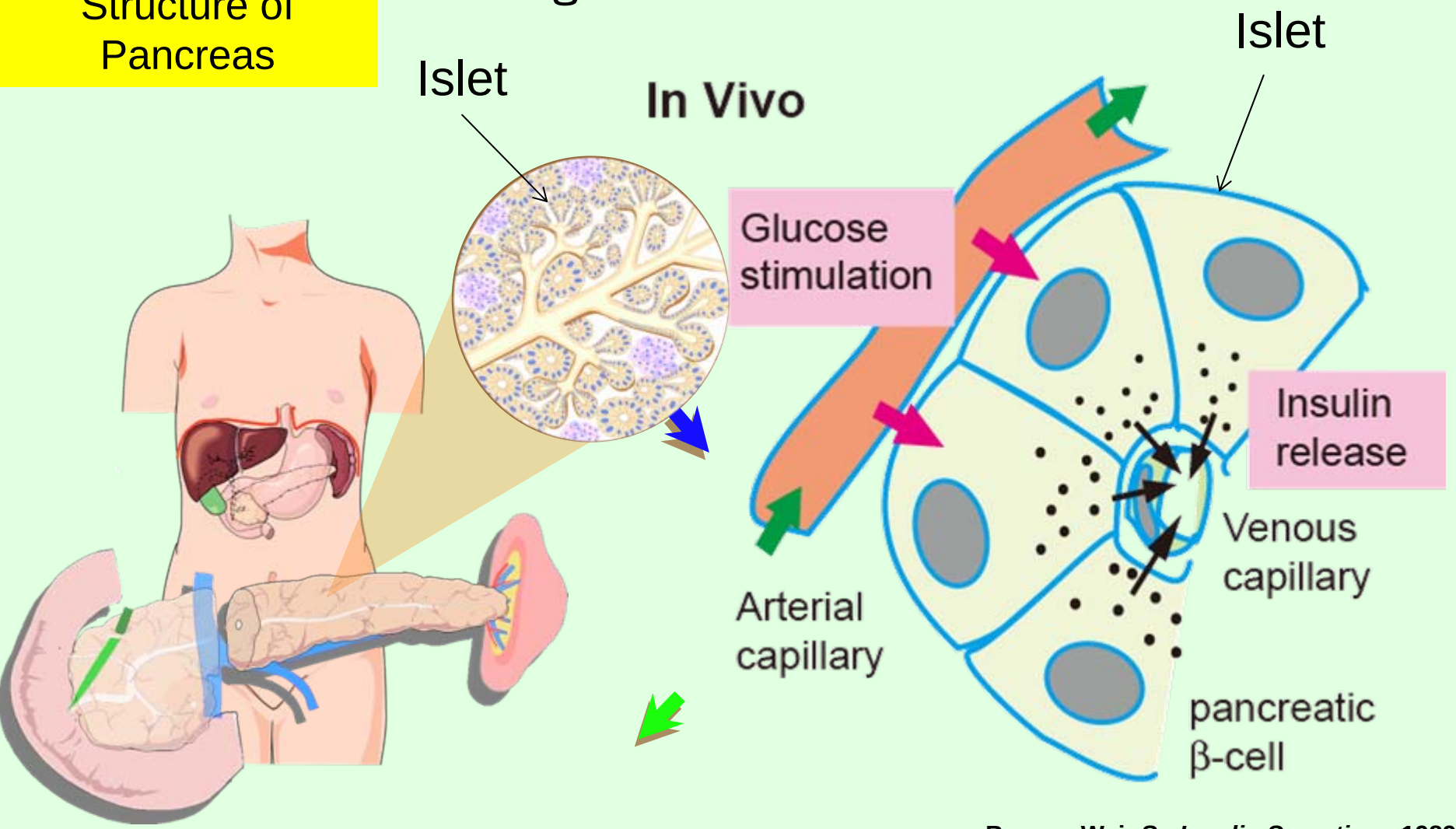
Ionic reaction inside the cell

Ionic reaction in mitochondrial



Measuring Cell–Cell Communication and Regeneration of tissue

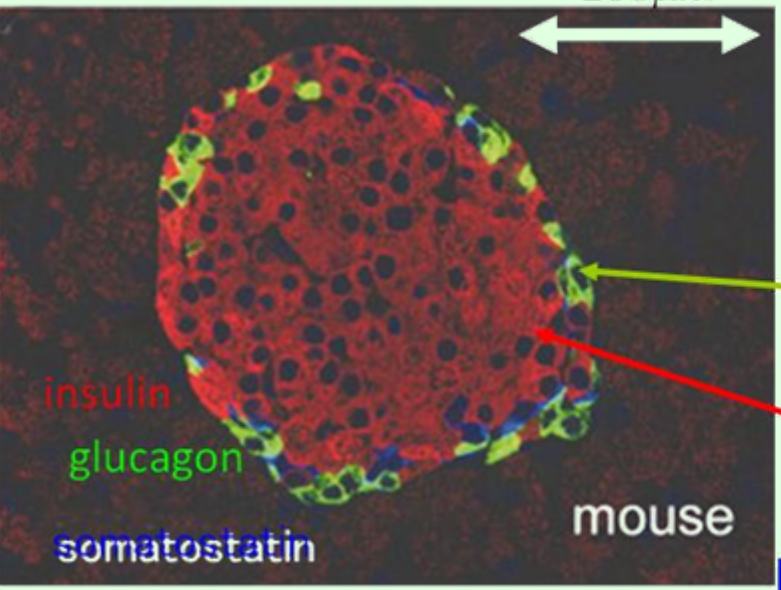
Structure of Pancreas



Bonner-Weir S, *Insulin Secretion*, 1989

Q: How the cell response for the Glucose stimulation?

Structure of ISLET （Mouse）



- Aggregating Cells with Different Functions
- 3D-Construction to Function Effectively
- Secrete hormones to regulate blood glucose

α-Cells：Glucagon （Blood glucose↑）

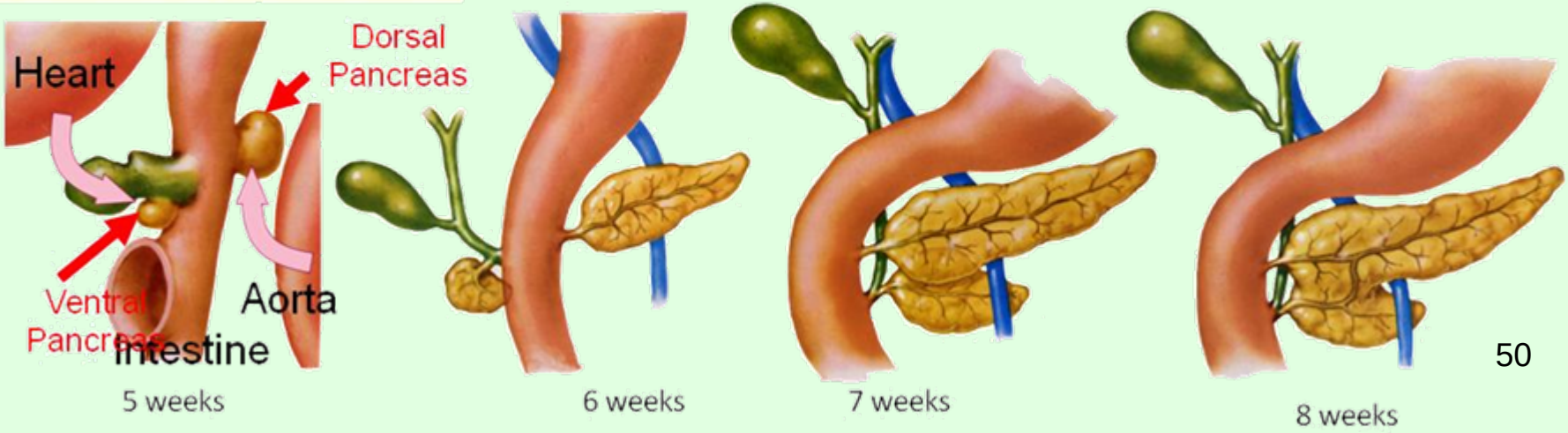
Cell–Cell interaction:
Glucagon Secretion from α–cells inhibits Insulin secretion from β–cells

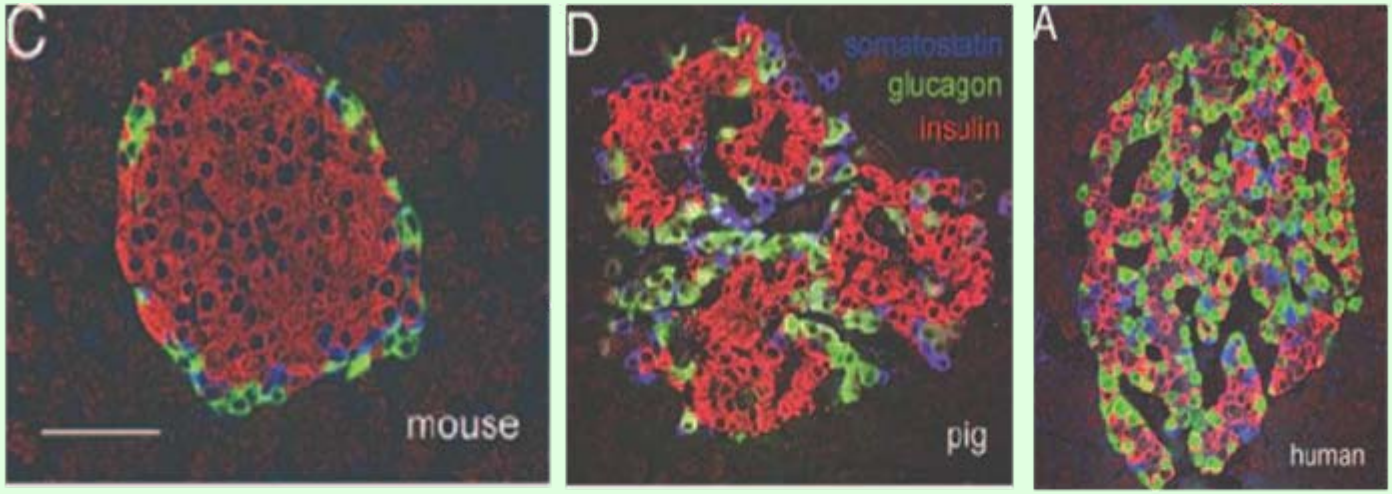
β-Cells： Insulin （Blood glucose↓）

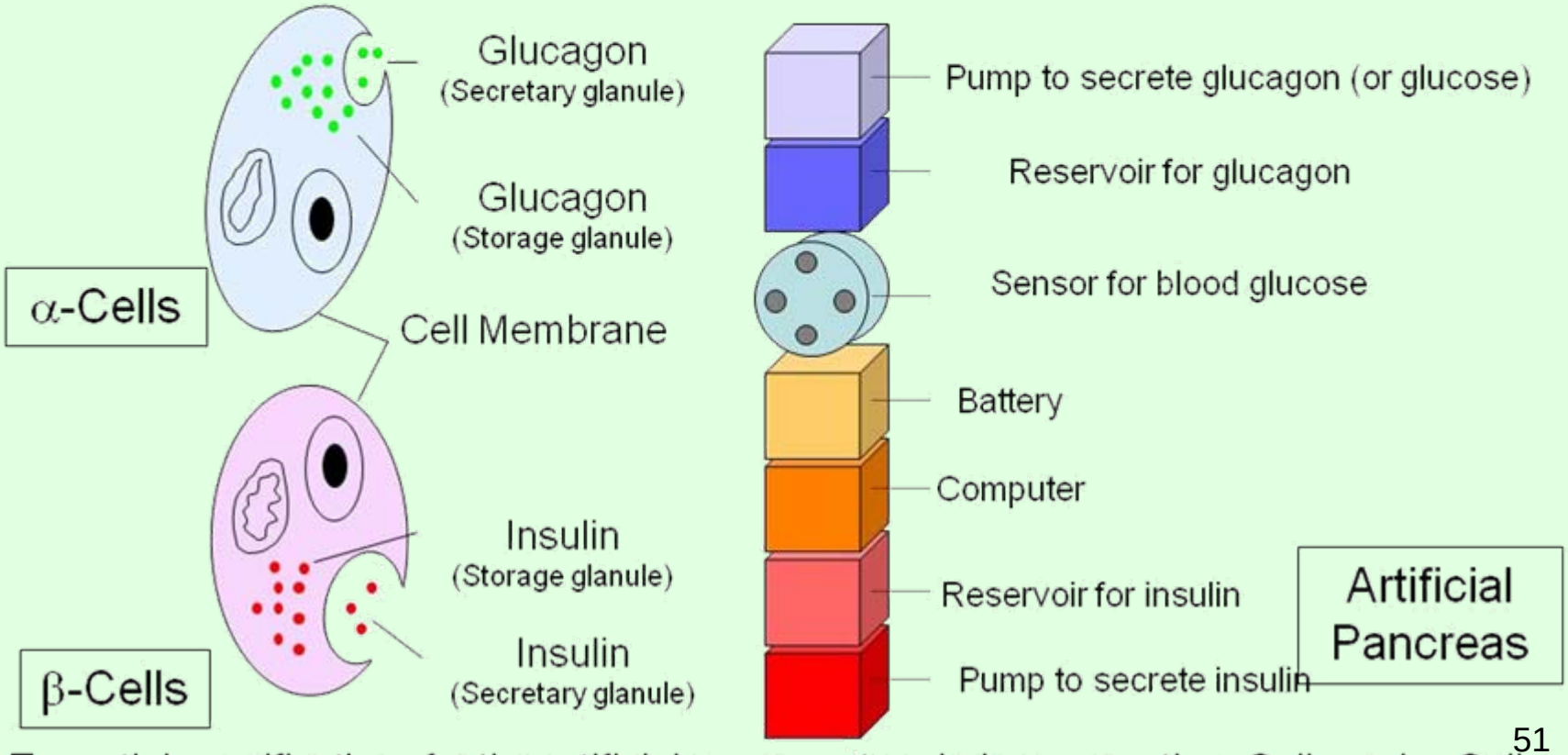
Aggregating β-Cells secrete more dose of insulin than that in total from the same number of isolated β-Cells.
➔ Cell-Cell Interaction

Patient Number of Diabetes：
Type 1: 50000
Type 2: 1 00000000

Development of Pancreas



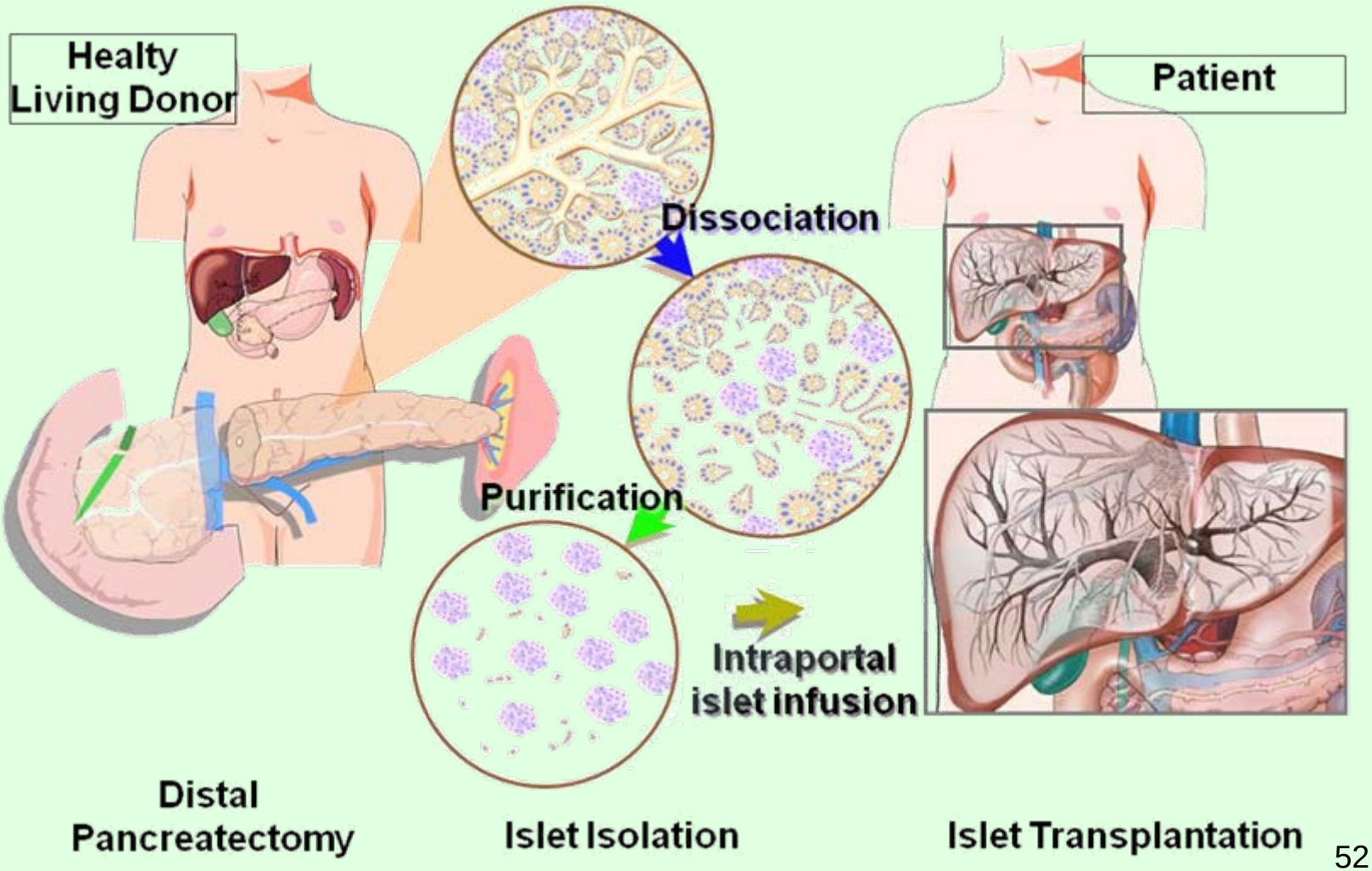




Essential specifications for the artificial pancreas to mimic pancreatic β-Cells and α-Cells

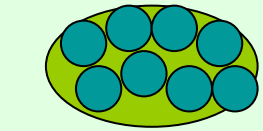
Clinical Application of Regenerative Medicine

- Islet Transplantation -



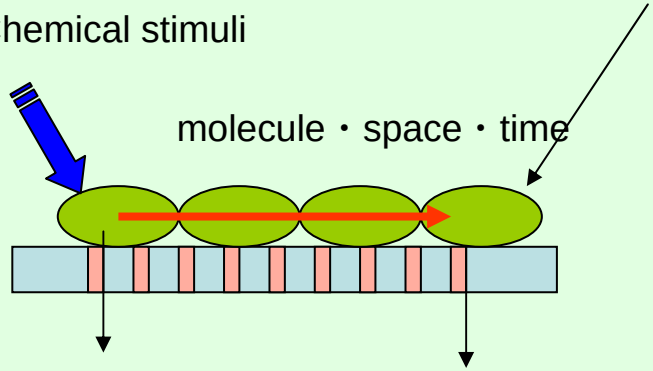
Micro/Nano devices for measuring the cell-cell communication and regenerate islet

islet

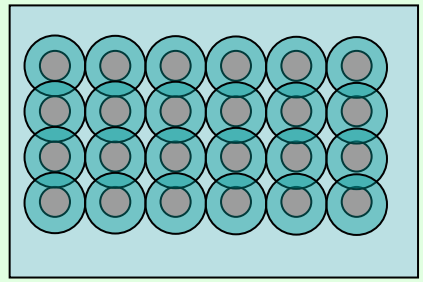


Physical stimuli

Chemical stimuli

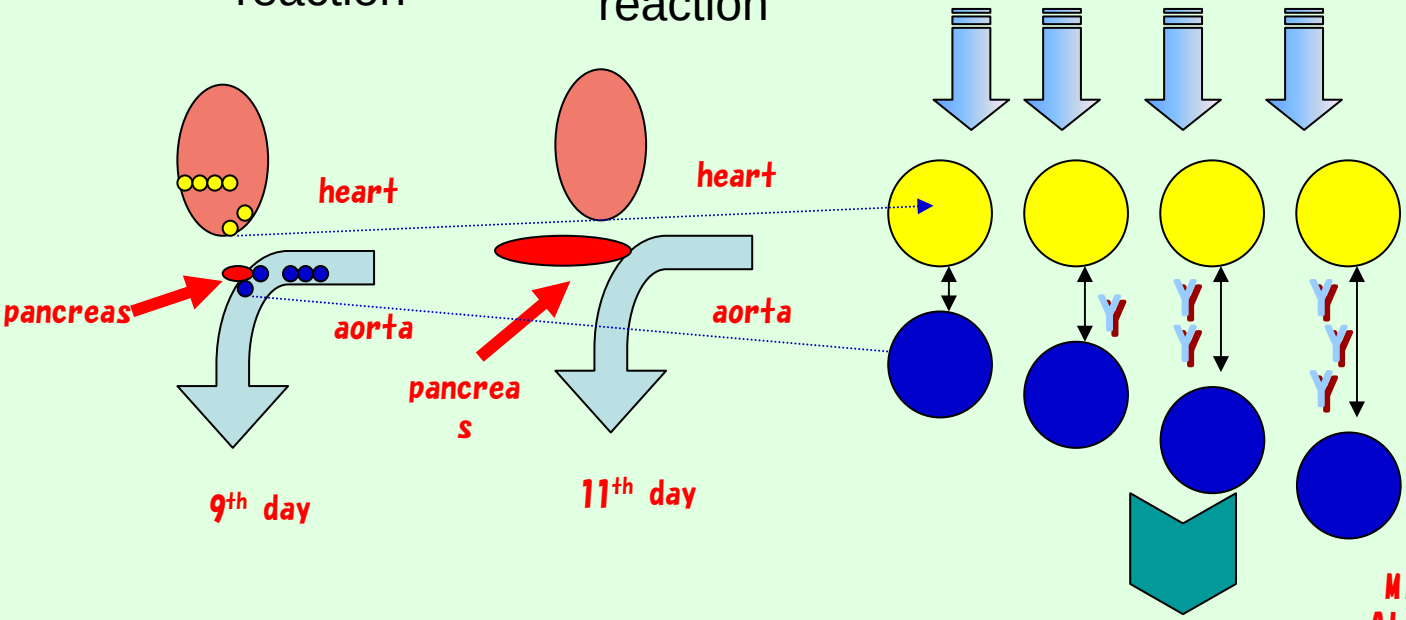


Make clear the phenomenon



psuedo-islet

Micro flow



Sensing the molecules and/or protein

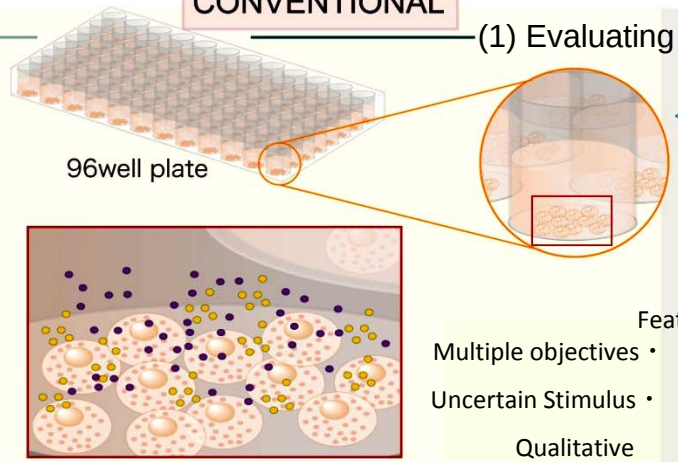
Monitoring

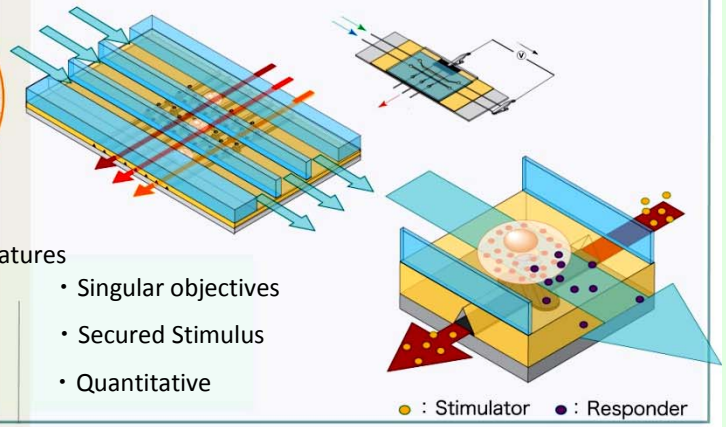
Micro flow and flow control・
Alignment of cells (1D, 2D, 3D)
On site monitoring the protein and/or molecules

CONVENTIONAL

μTAS

(1) Evaluating single cells

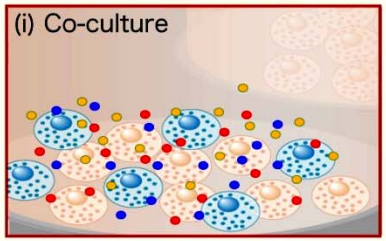


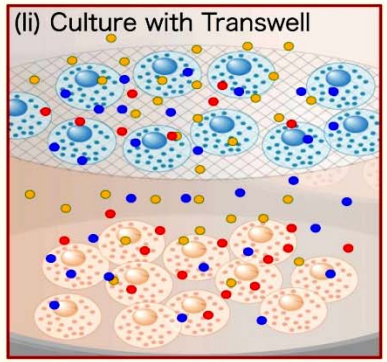


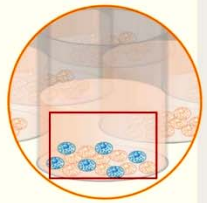
Features	
Multiple objectives ・	・ Singular objectives
Uncertain Stimulus ・	・ Secured Stimulus
Qualitative	・ Quantitative

: Stimulator : Responder

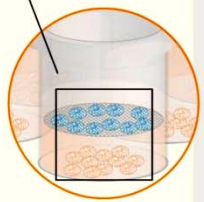
(2) Evaluating multiple cells

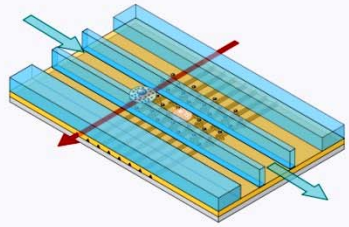


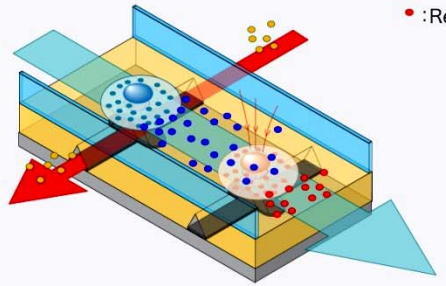




Transwell

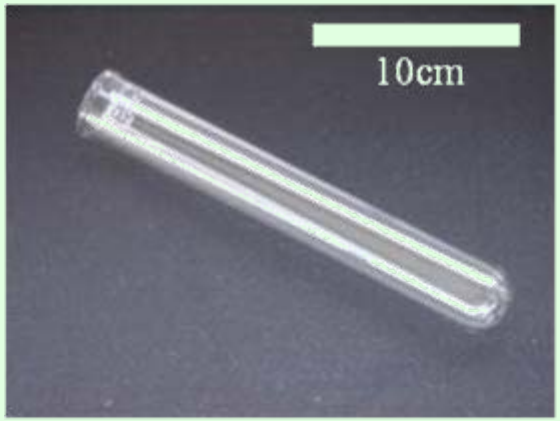






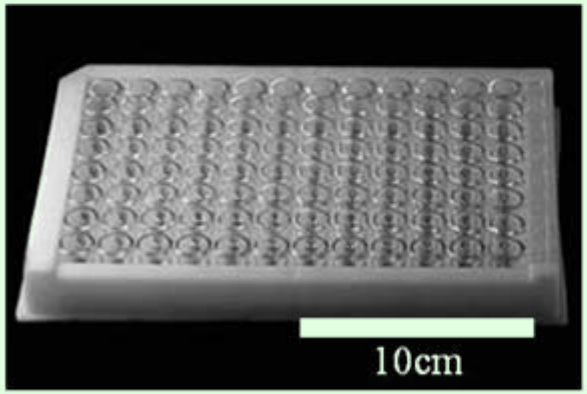
:Cell A
:Cell B
:Stimulator to Cell A
:Responder from Cell A
:Responder from Cell B

Features	
Undirected cell-cell communication ・	・ Directed cell-cell communication
Unspecific objectives to stimulate ・	・ Specific objectives to stimulate
No real-time evaluation ・	・ Real-time evaluation
Qualitative ・	・ Quantitative

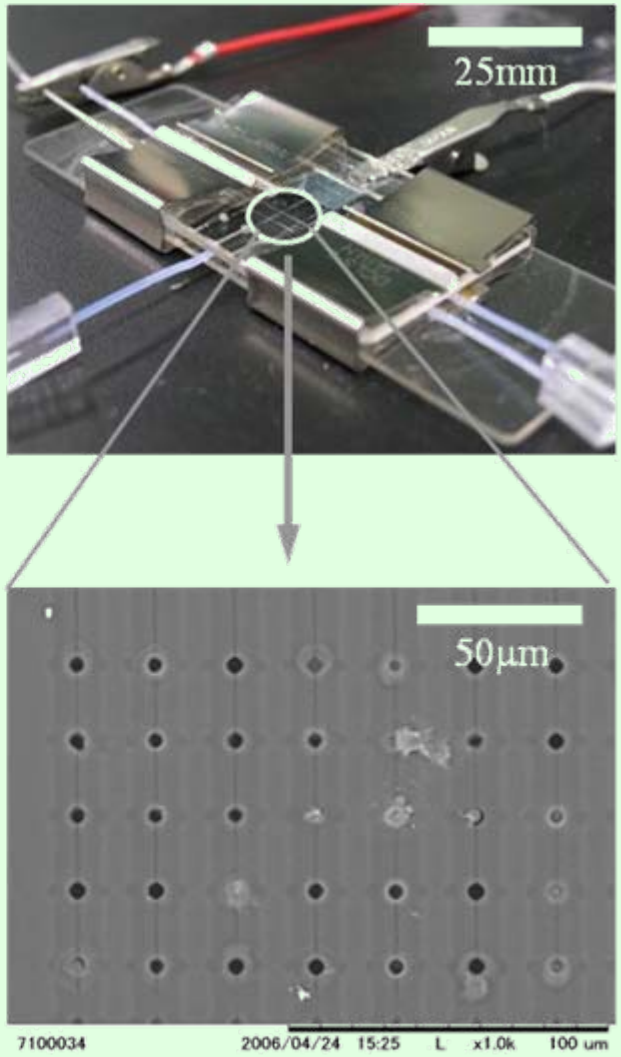


boiling tube

minitualize



Multi –well Plate

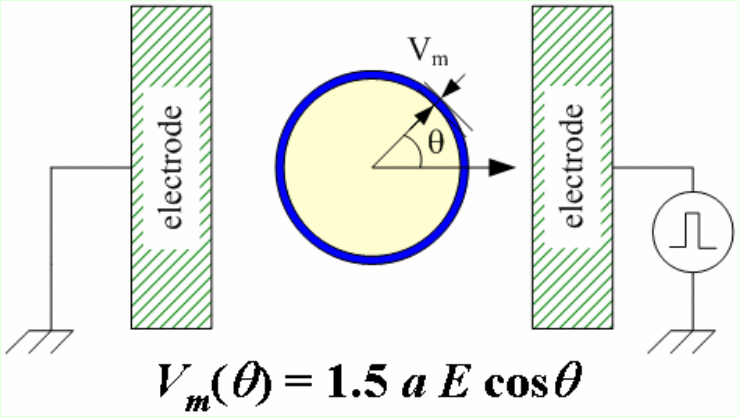


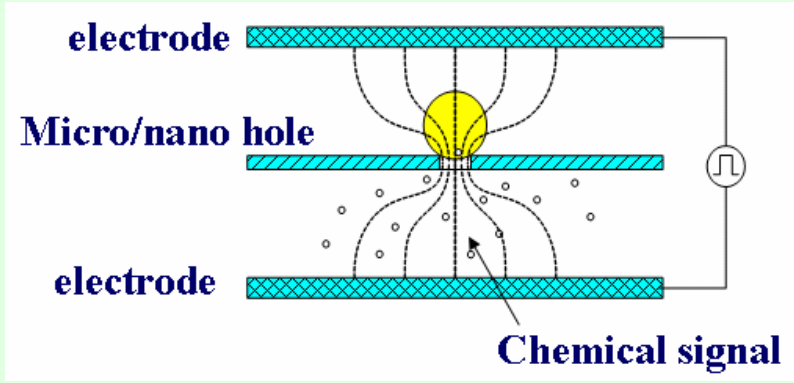
Bio nano Platform

Insert the chemical stimulus by Micro electroporation

Hold the cell at micro hole (～2μmf) insert the chemical signal by electropolation

＊Measuring electric signal





conventional

1) a = 10 μm → E = 10^5 V/m (1000V/cm)

2)Keep the cell membrane?

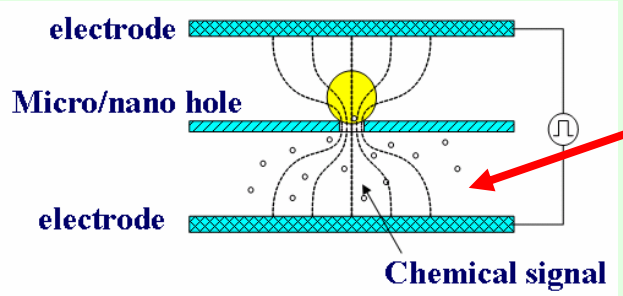
Micro-TAS

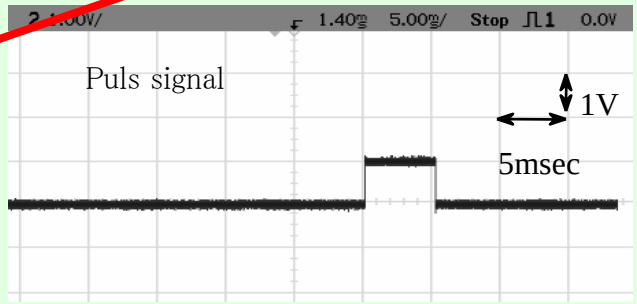
1) Low voltage 1-6V

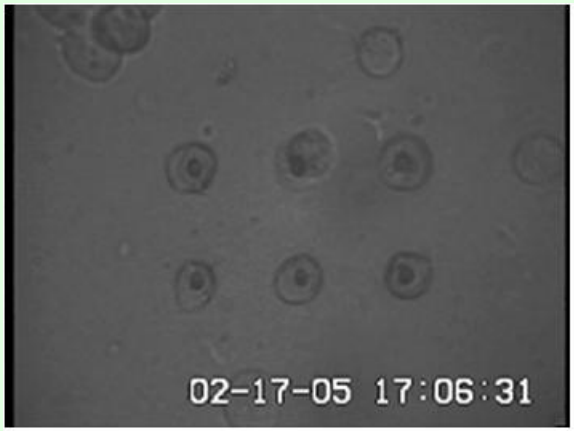
2) Electrode + micro hole + micro channel

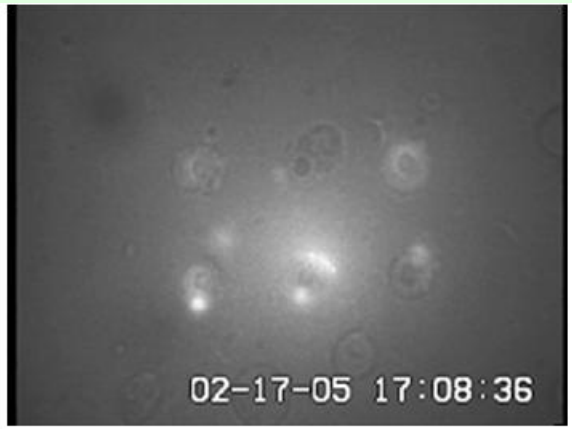
3) Holding mechanizm

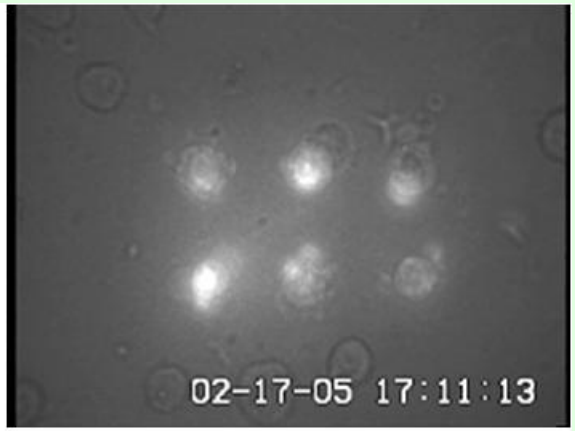
Cell U937 :
Cell suspension : RPMI medium
buffer solution : RPMI medium +10 mM YO-PRO-1





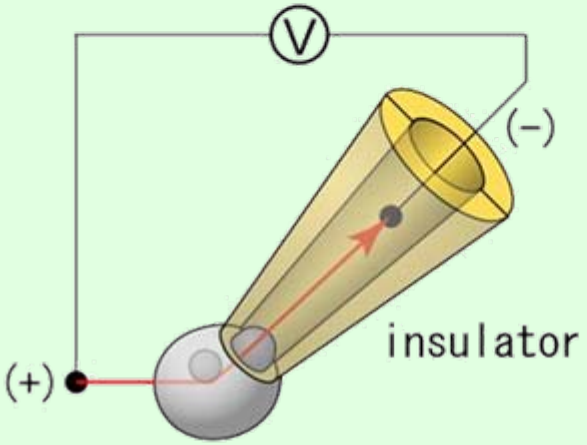




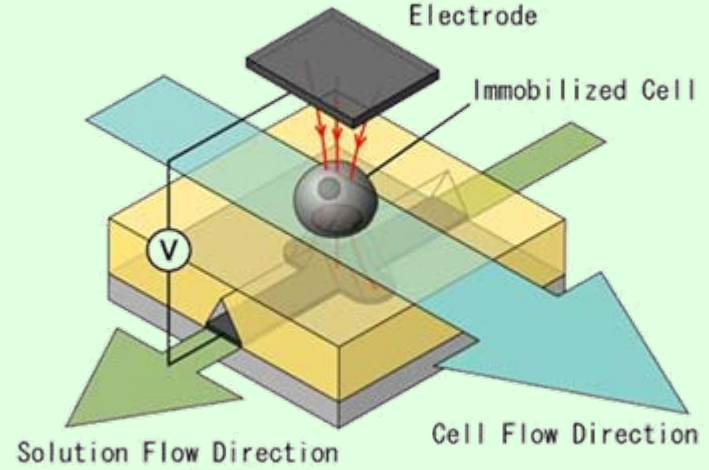


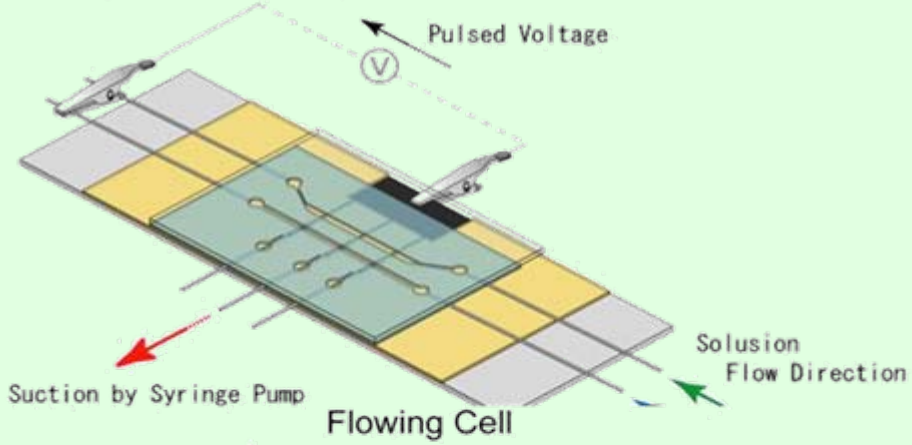
Initial 1V x 30 times 2V x 20 times

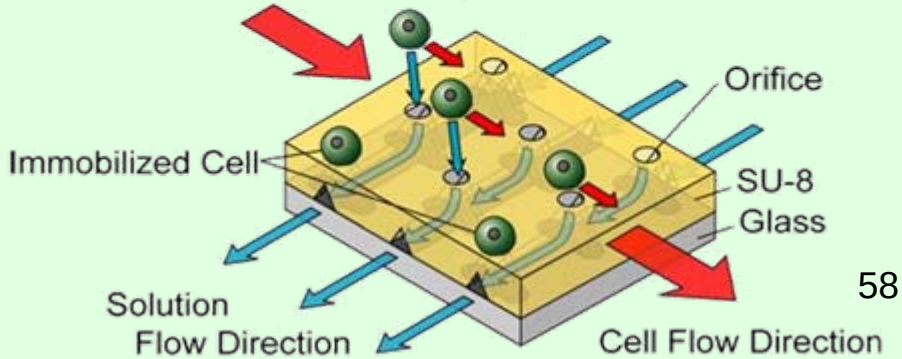
conventional ⟶ μ-TAS



• micro pipette

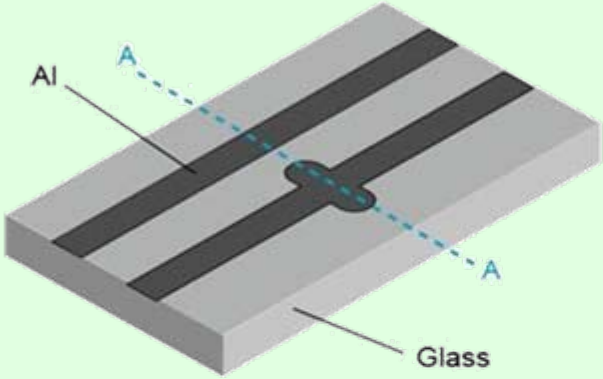


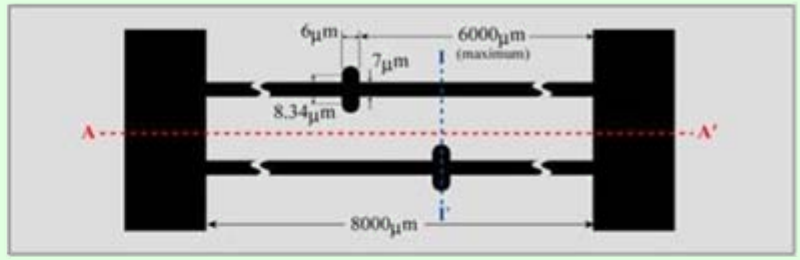




Single-mask inclined UV lithography

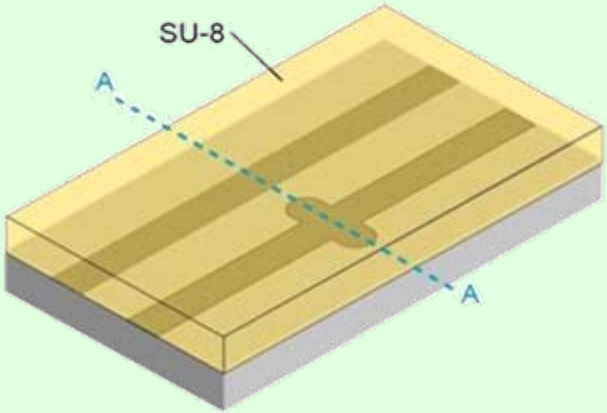
1) Pattern Al on glass substrate





- Evaporating Al on a glass substrate
- Spin coating ZEP (EB resist)
- Exposure with electron beam
- Wet etching Al with phosphoric acid

2) Spin Coat & Soft bake SU-8



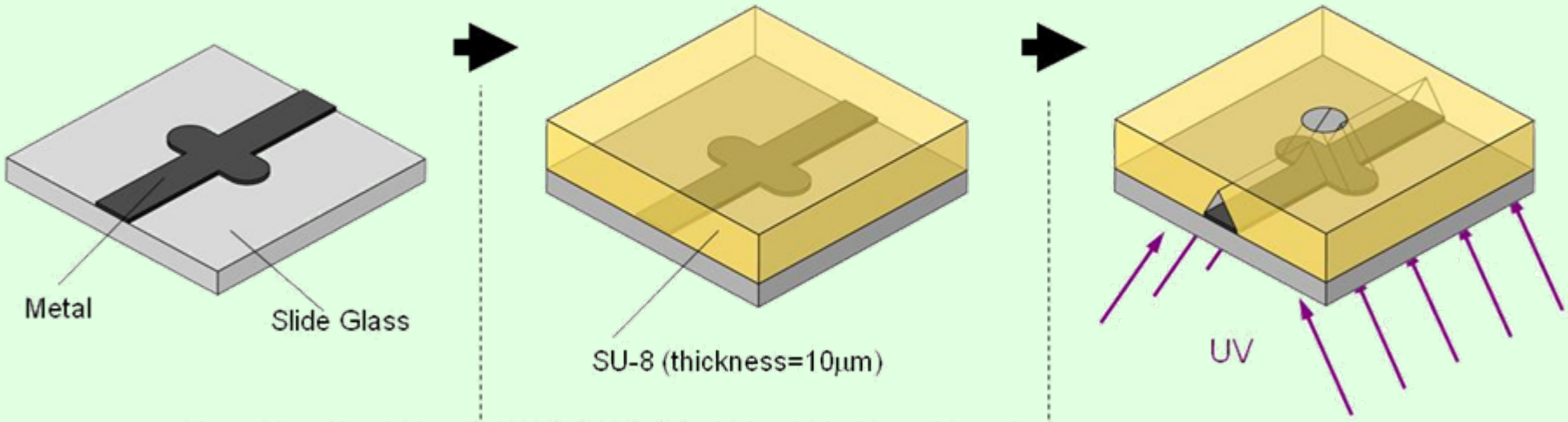
- Spin coating negative photoresist SU-8 (MICRO CHEM Corp.)
- Thickness of photoresist: 10–100 μm
- Soft bake

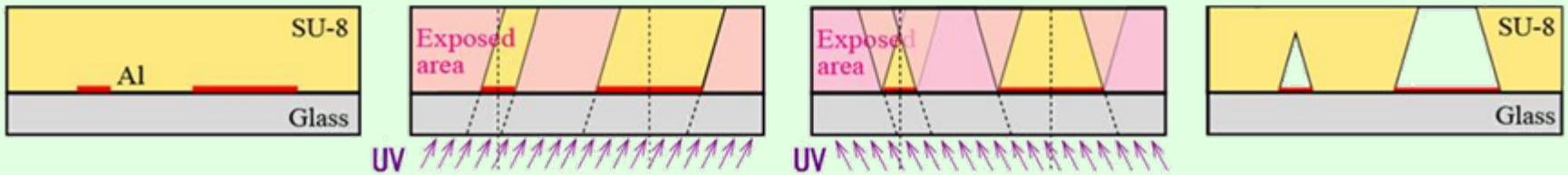
Single-Mask Inclined UV-Lithography

① Metal mask is pattered on glass

② SU-8

③ Inclined exposure by UV light

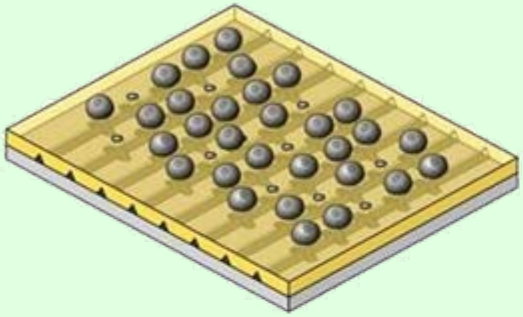




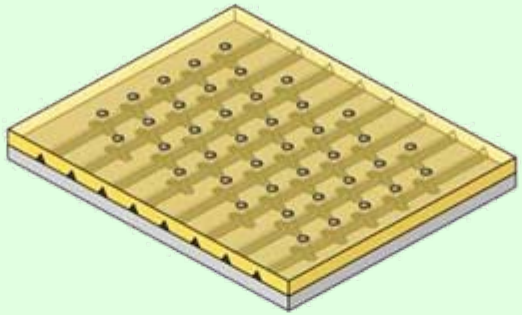
(a) Spin-coat and Soft bake (b) First expose (c) Second expose (d) Post exposure bake and Development

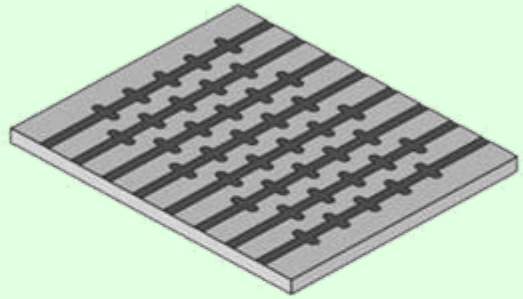
Electroporation chip

Micro channel. Orifice and electrode is fabricated simultaneously

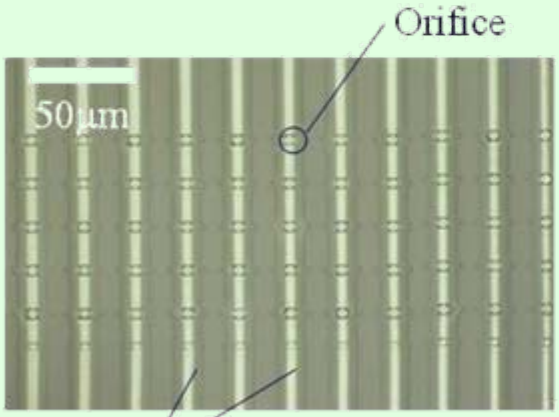


Cell array

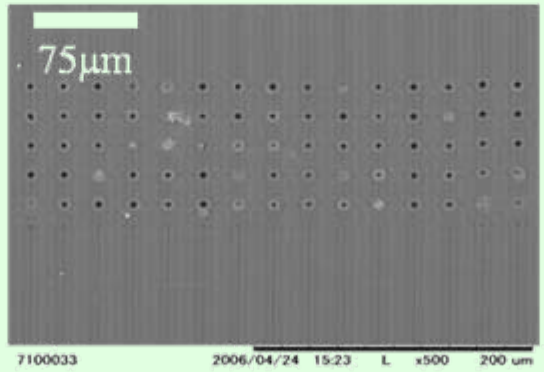


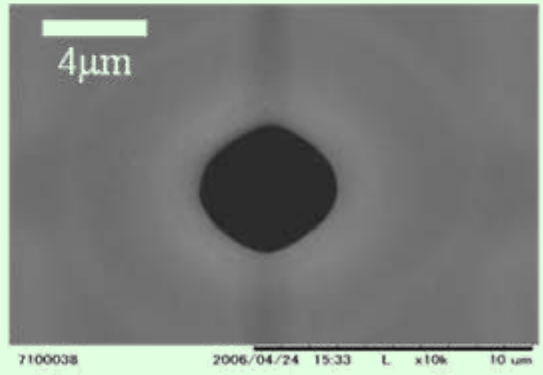


Mask Pattern on Slide Glass

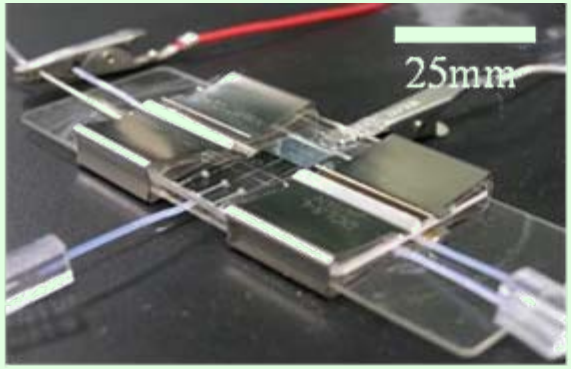


Optical Image (x50)



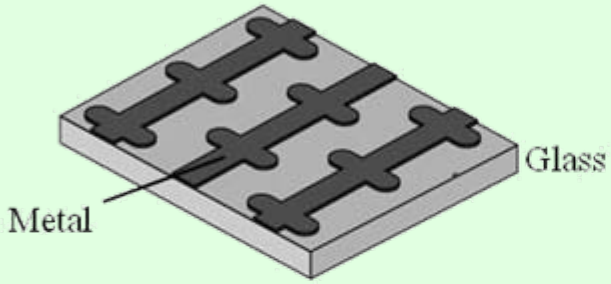


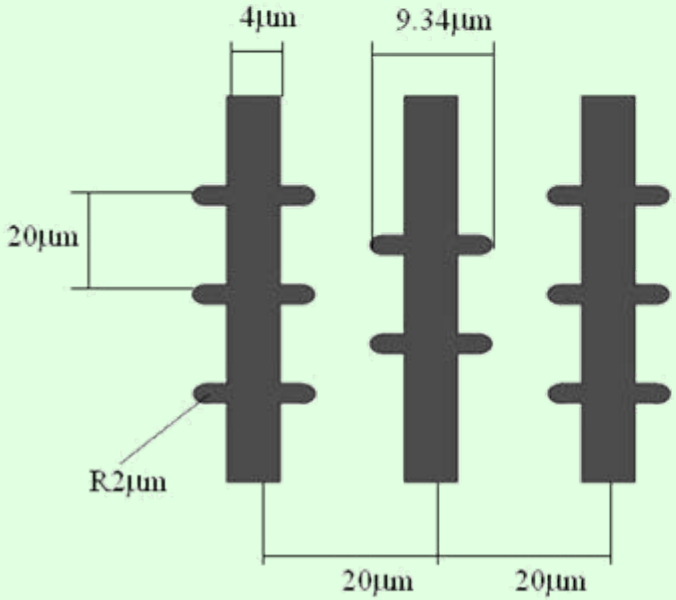
SEM Images

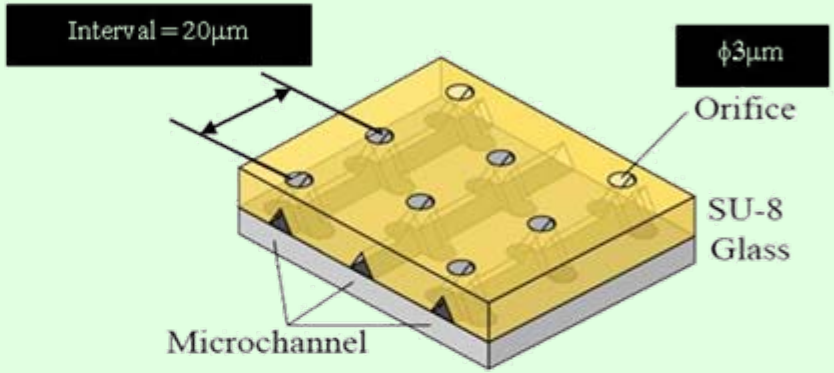


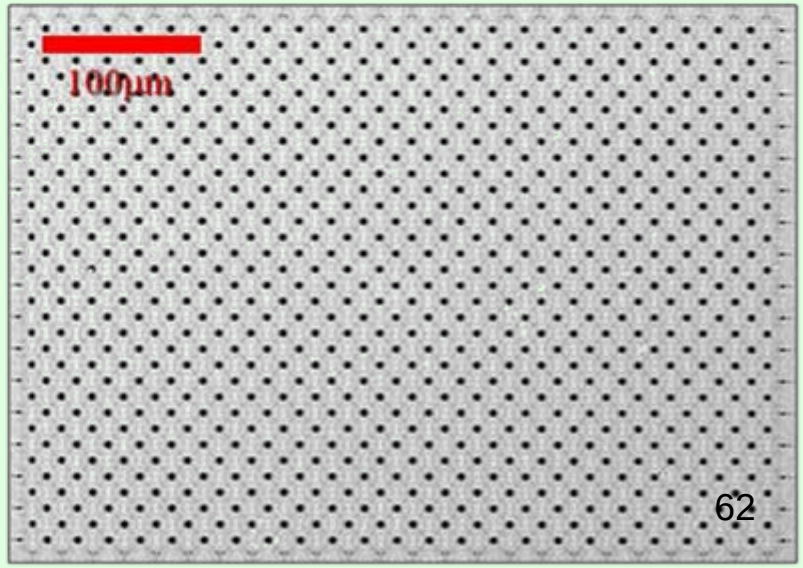
More than ten thousands of cells are measured parallel on one chip

Single-MASK Inclined UV Lithography

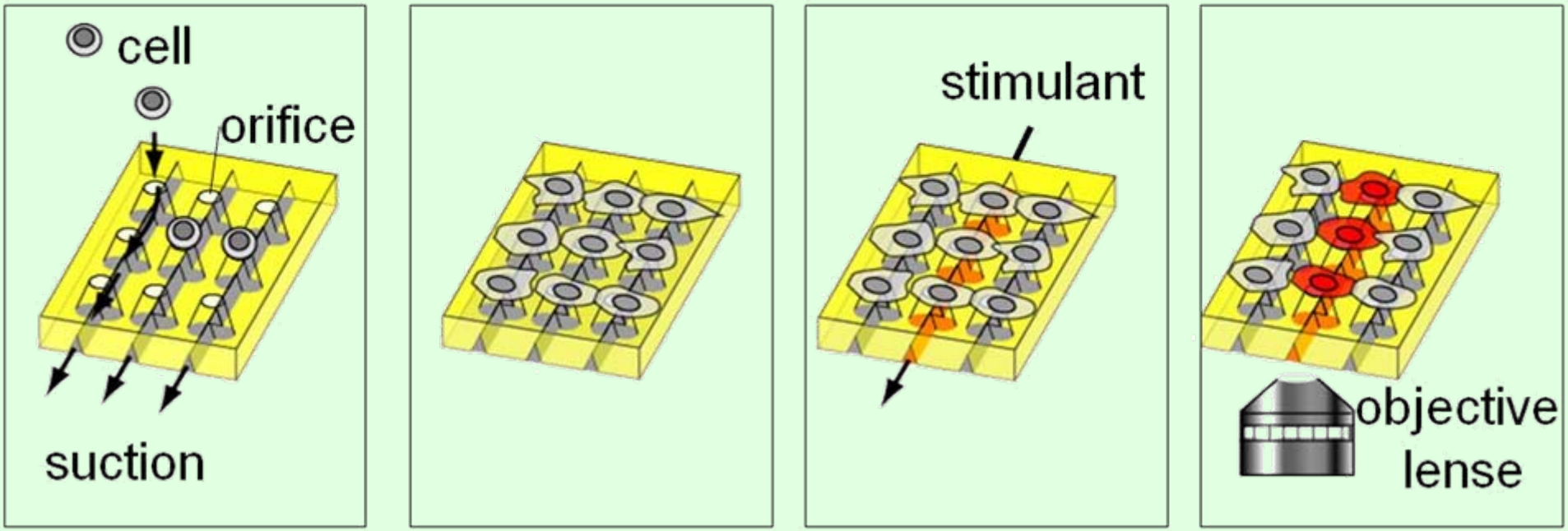


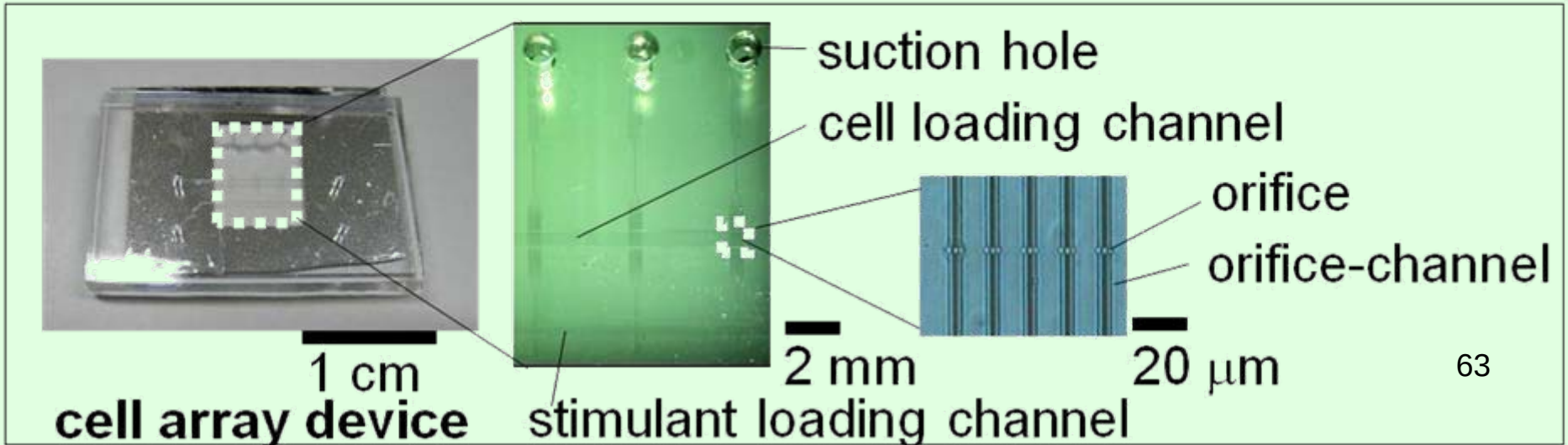




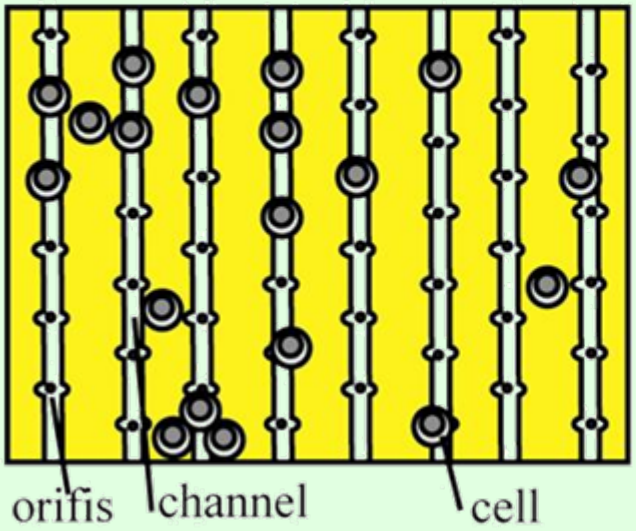


β –Cell (Min 6 m9) humoral transmission

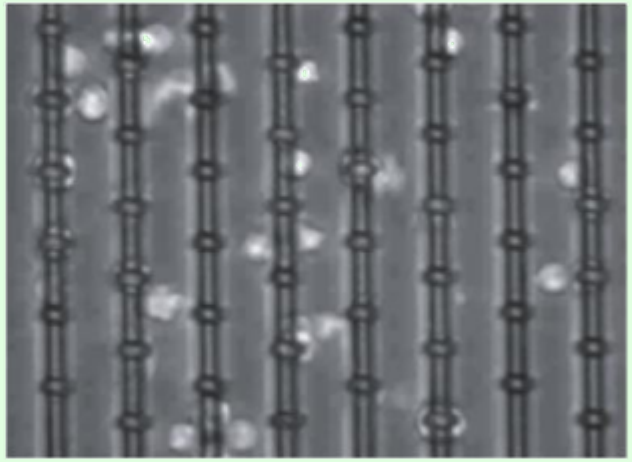




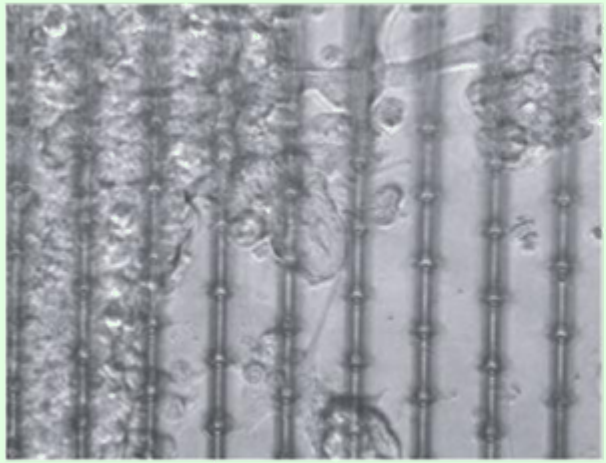
Cell trapping & Culturing



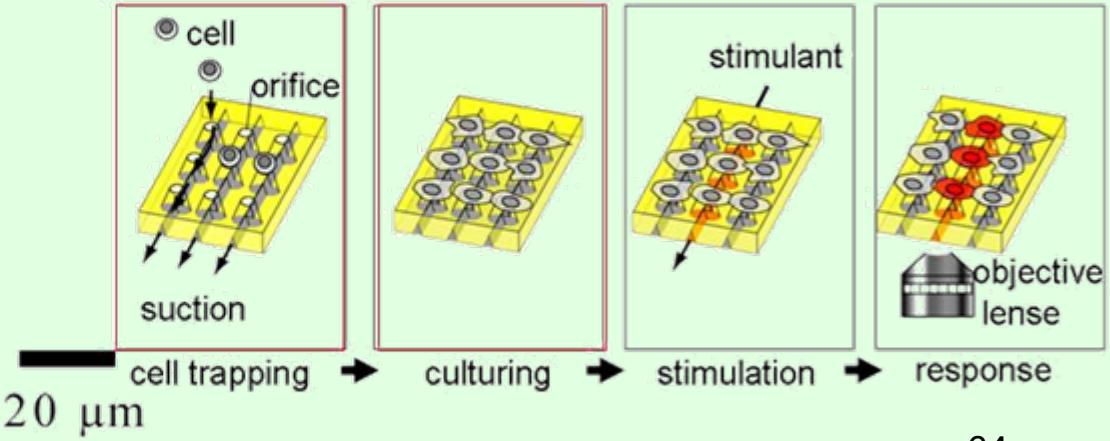
(a) schematic of cell trapping



(b) phase contrast image of cell trapping

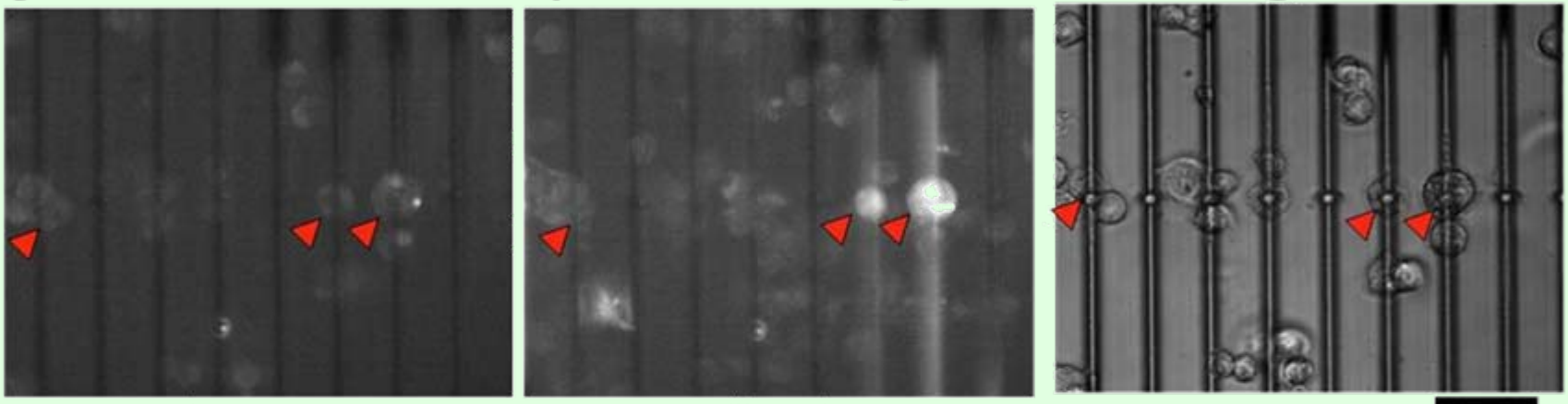


(c) culturing of trapped MIN-m9 cells for 3days

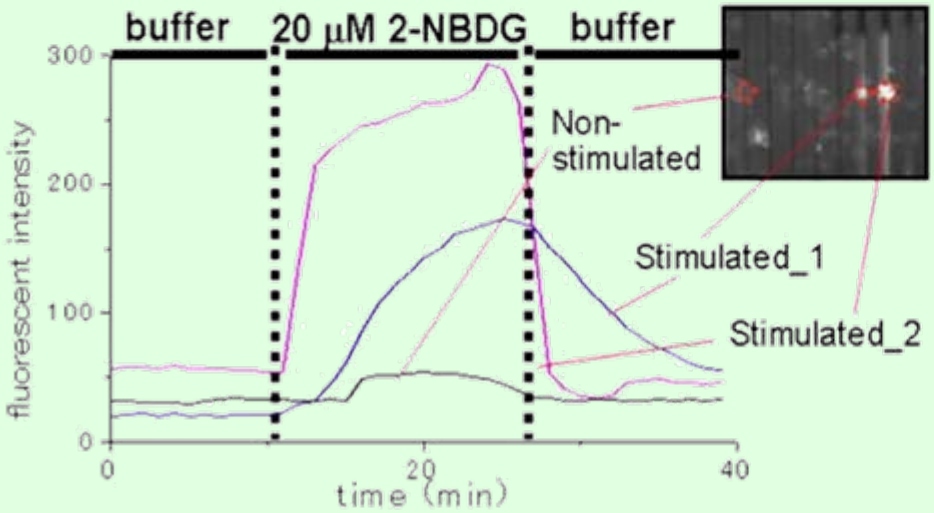


Stimulation

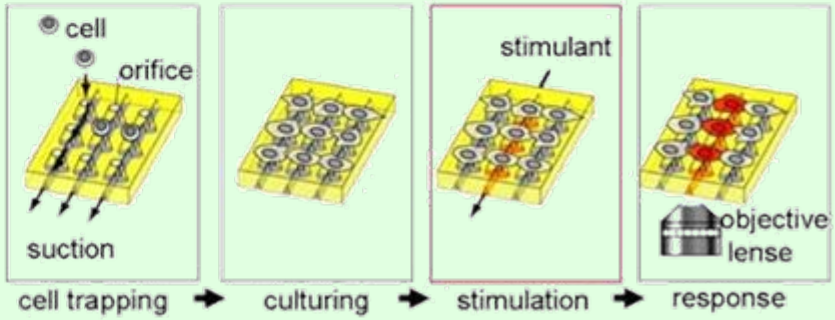
Uptake of a stimulus (fluorescent glucose analogue: 2-NBDG)



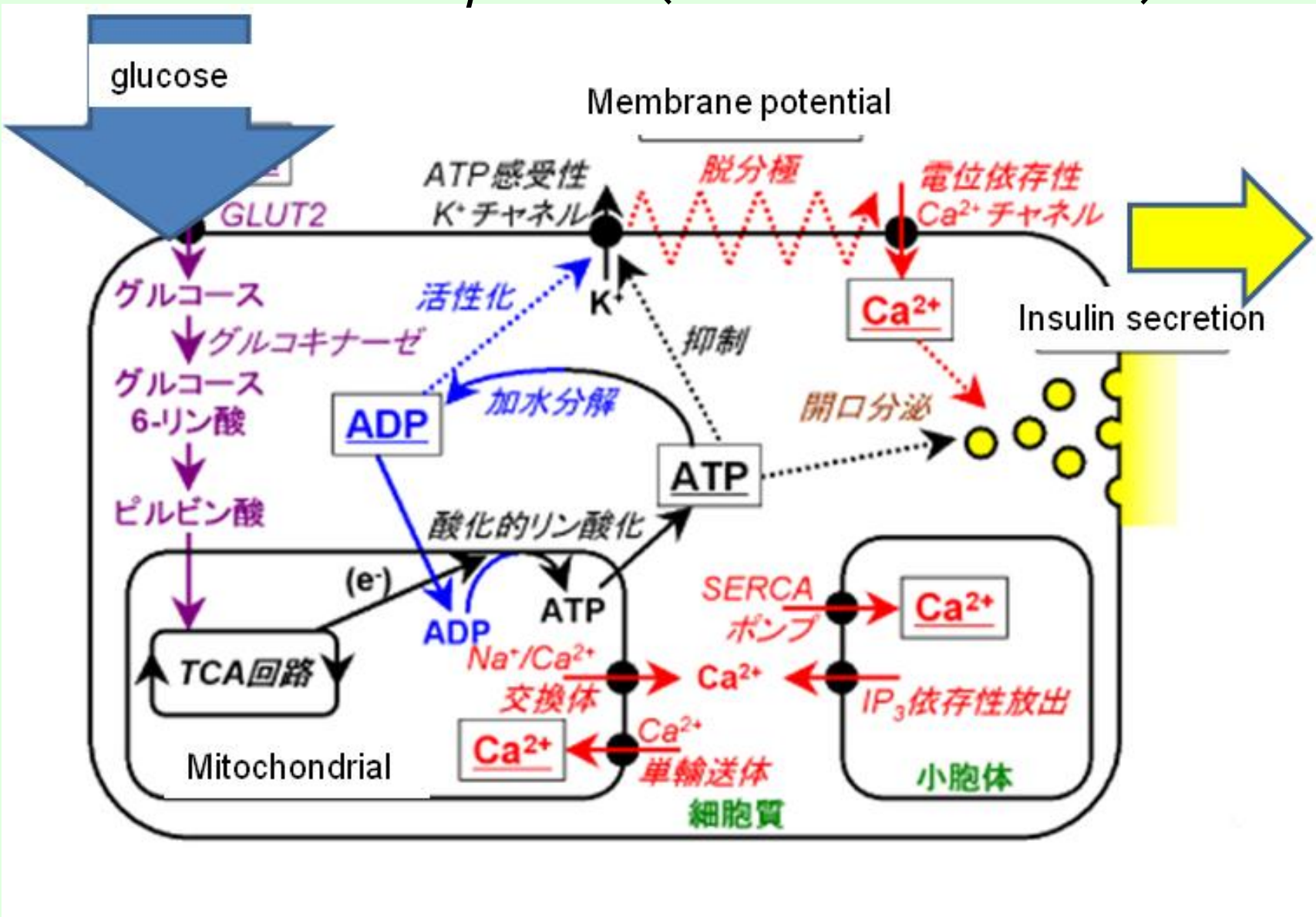
Time course of the uptake of 2-NBDG



Experimental procedure

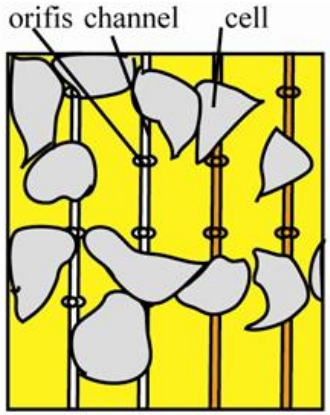


Pancreas β cell (insulin secretion)

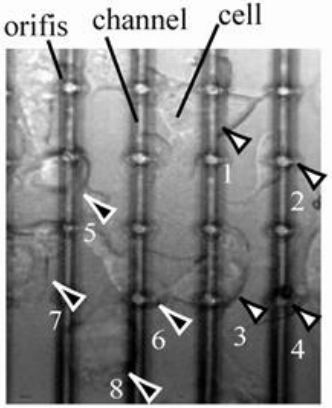


Responsive reaction

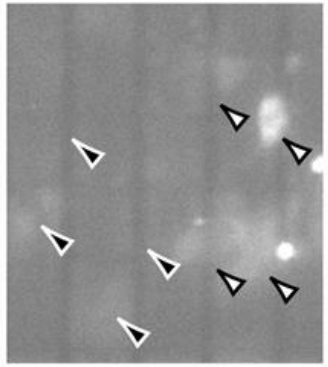
glucose-induced rise in cytosolic Ca^{2+} concentration



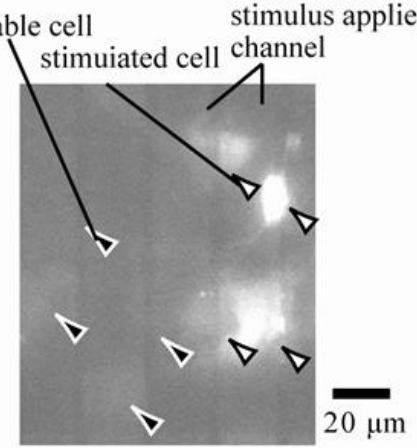
(a)schematic of cells on a chip



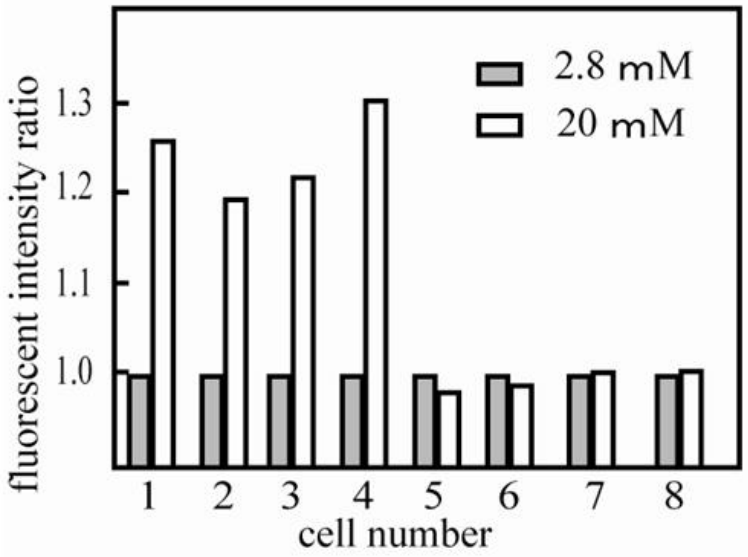
(b) phase contrast image of cells



(c) stable cells in 2.8 mM glucose

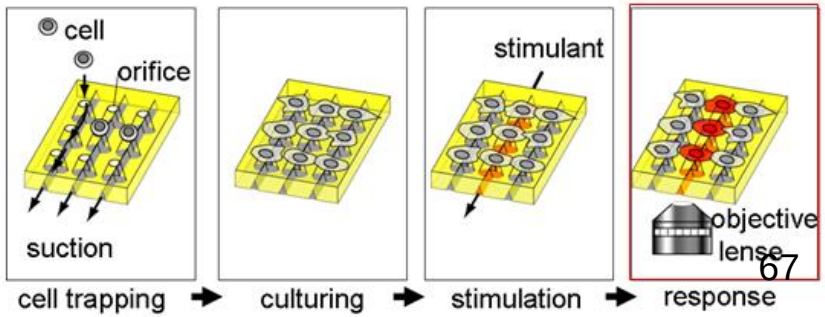


(c) stimulaed cells with in 20 mM glucose

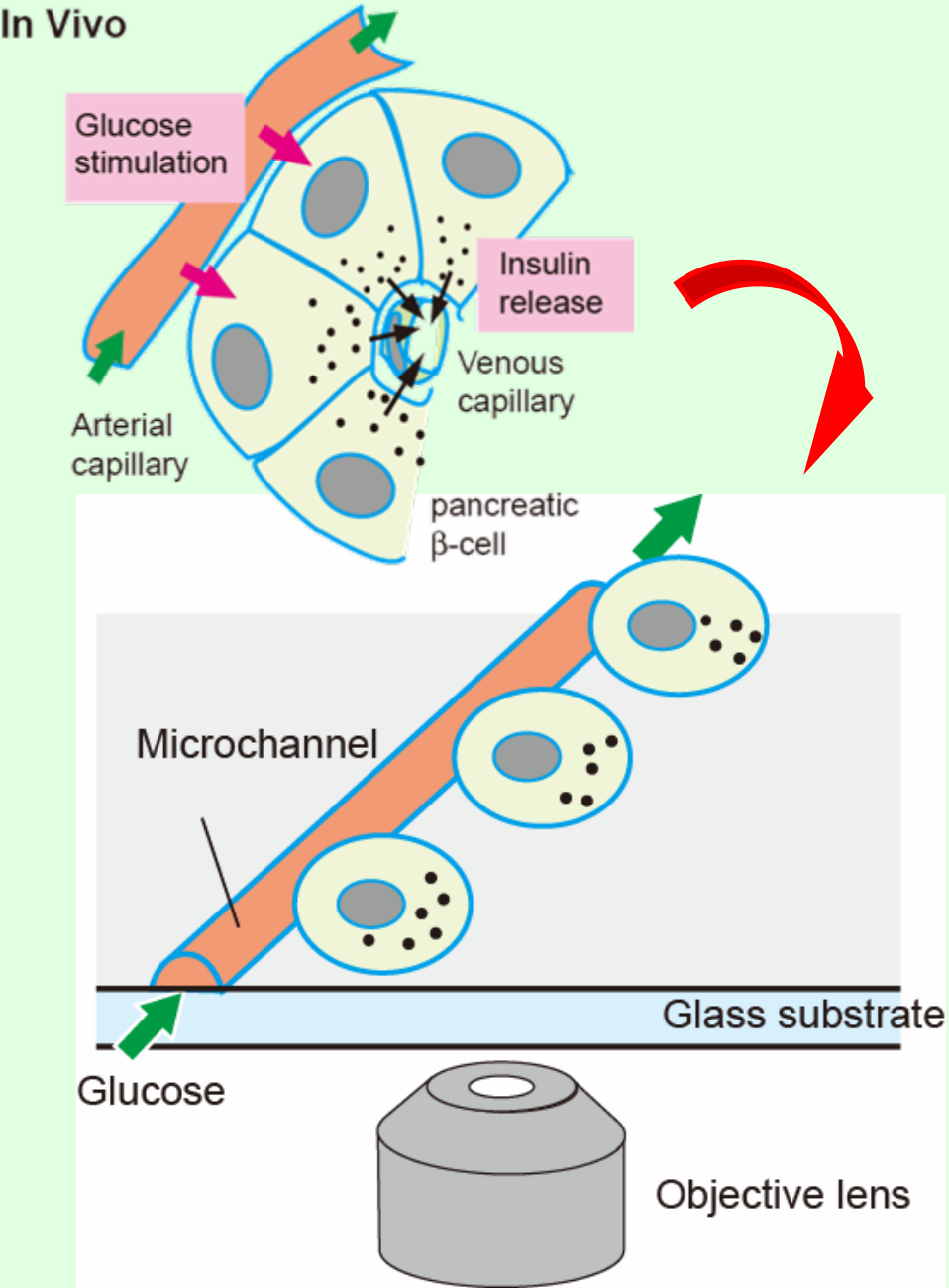


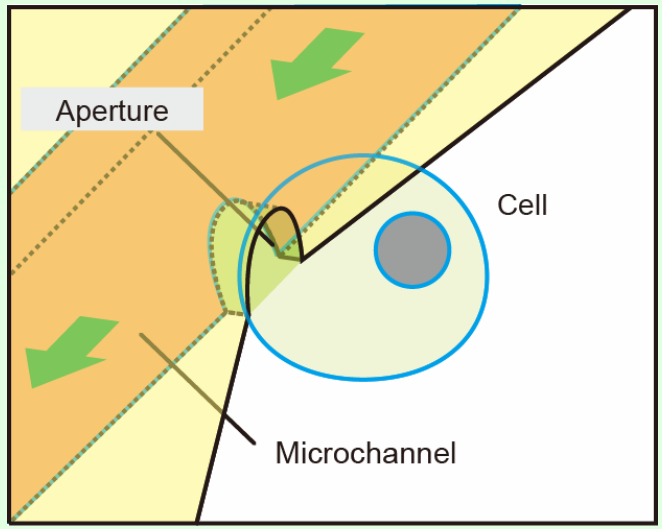
(e) the fluorescence intensity change in response to glucose stimulation

Experimental procedure



Mimicked Tissue Micro-environment





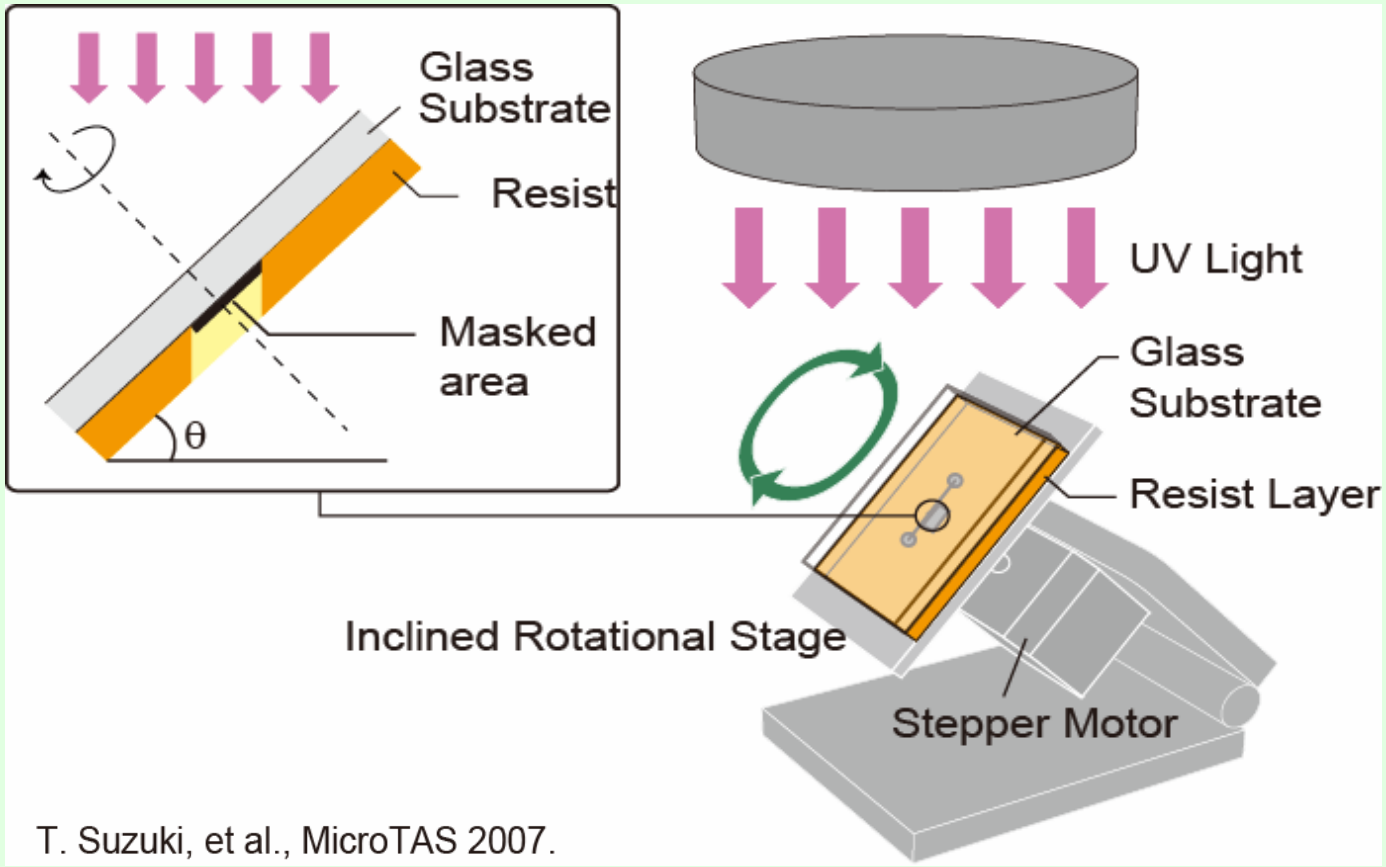
Localization and control mechanism of secreting direction

1. Apply localized stimuli
Stimulate through
“Pseudo-arterial capillary”

2. Measure intracellular response
4D imaging (x,y,z and time)

Fabrication

Multi-Directional UV Lithography.

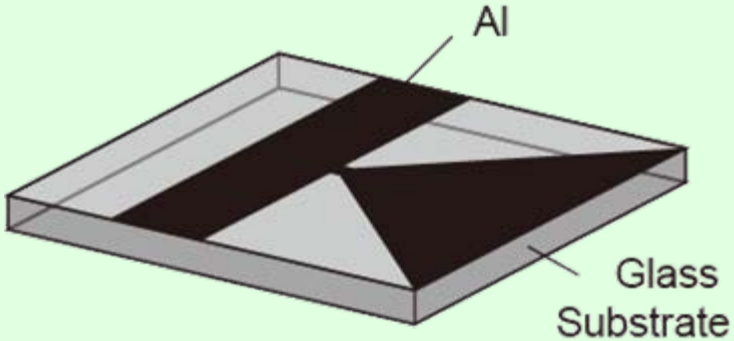


T. Suzuki, et al., MicroTAS 2007.

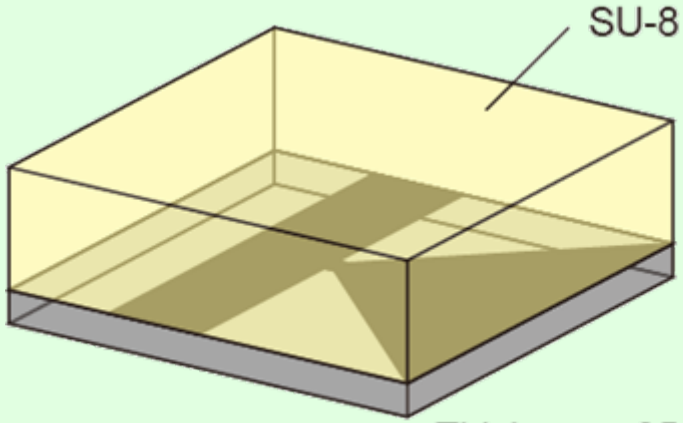
- **Complex micro channel from *Single* photo mask**
- ***No* mask alignment process**

Fabrication

1. Al Patterning

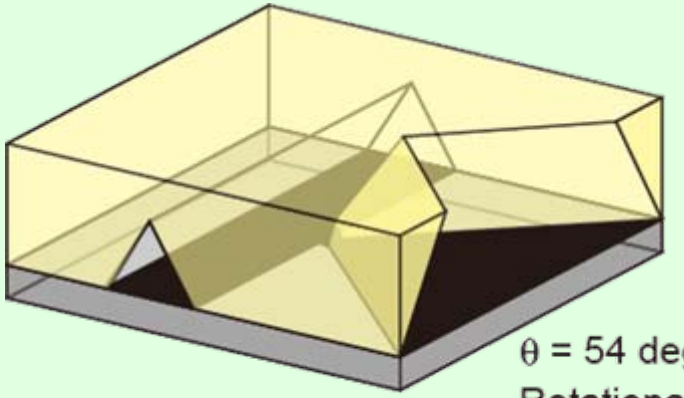


2. Spincoat SU-8



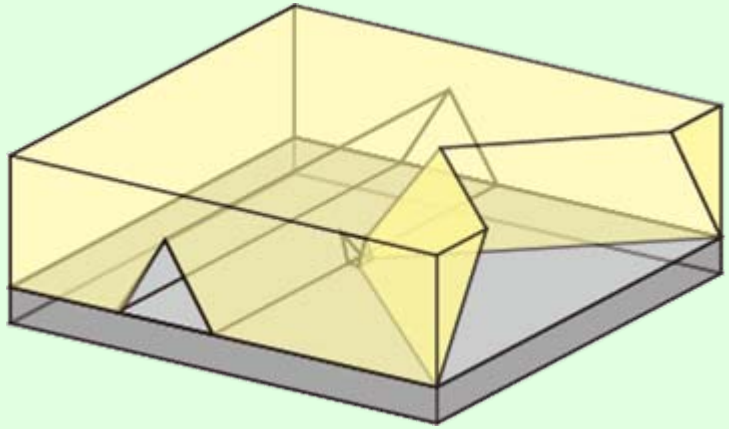
Thickness: 35 µm

3. Multidirectional Lithography

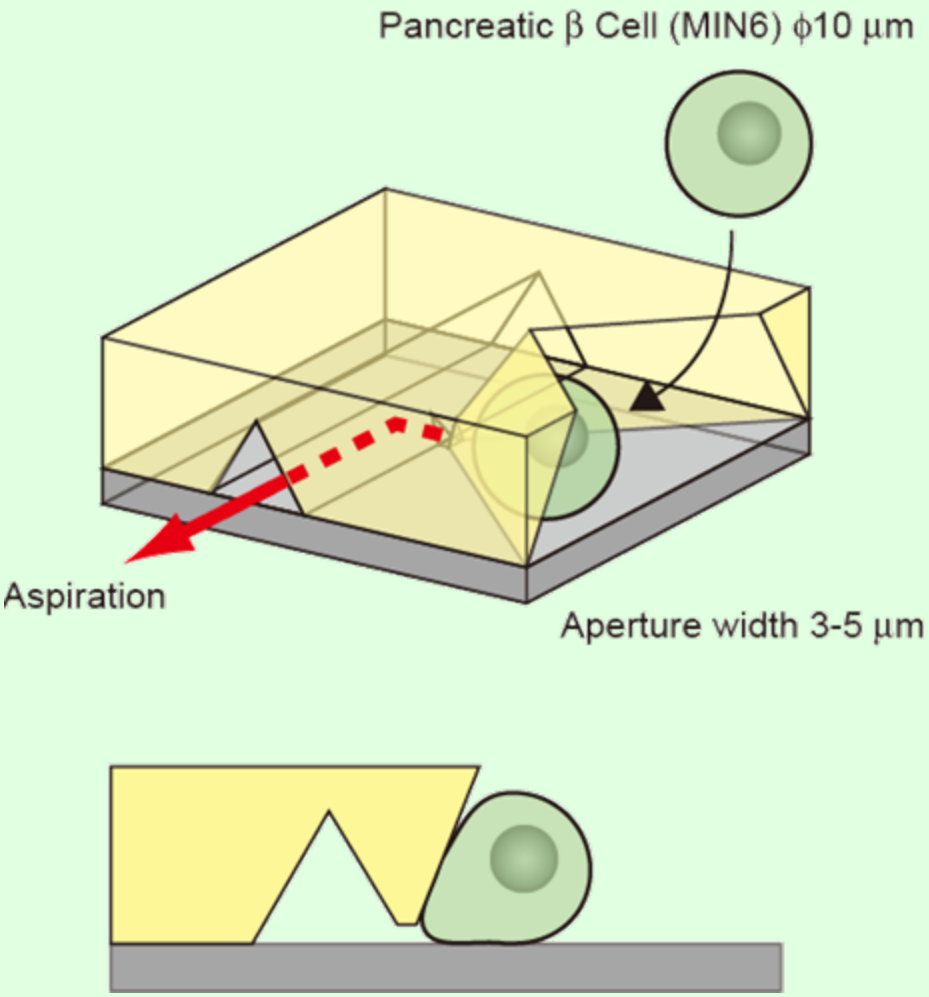


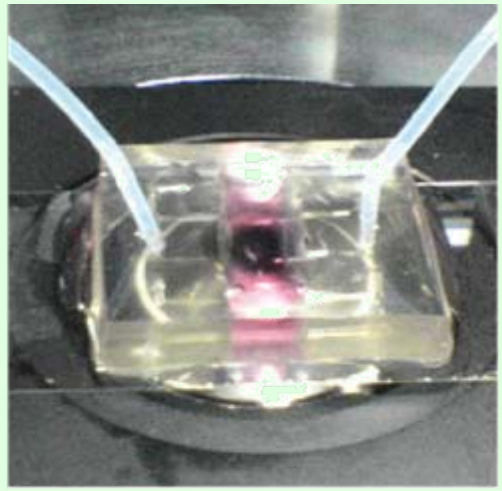
θ = 54 deg.
Rotational Speed: 5 Hz
Dose: 200 - 400 mJ/cm^2

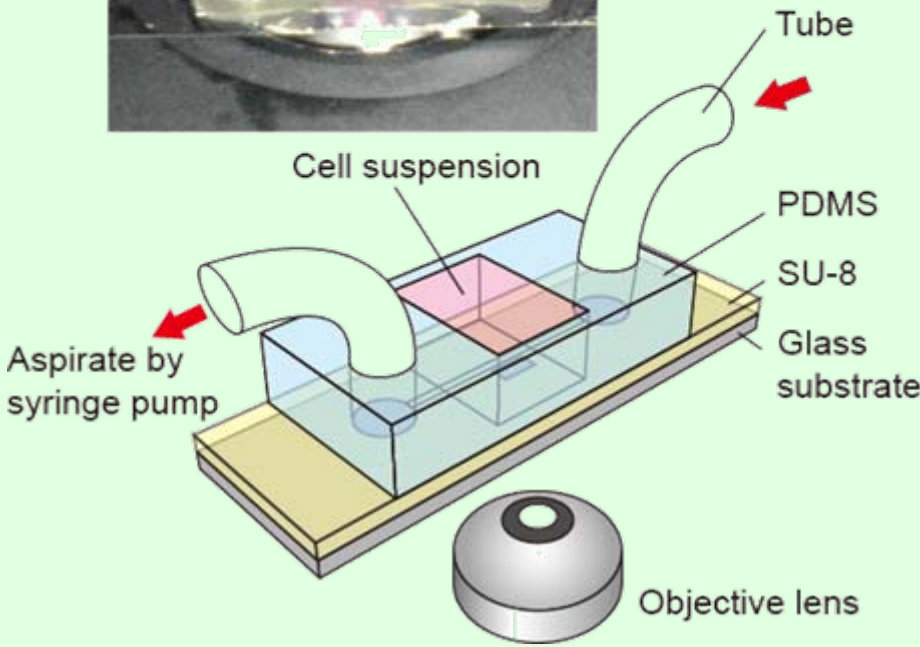
4. Al Etching



Positioning of single cell

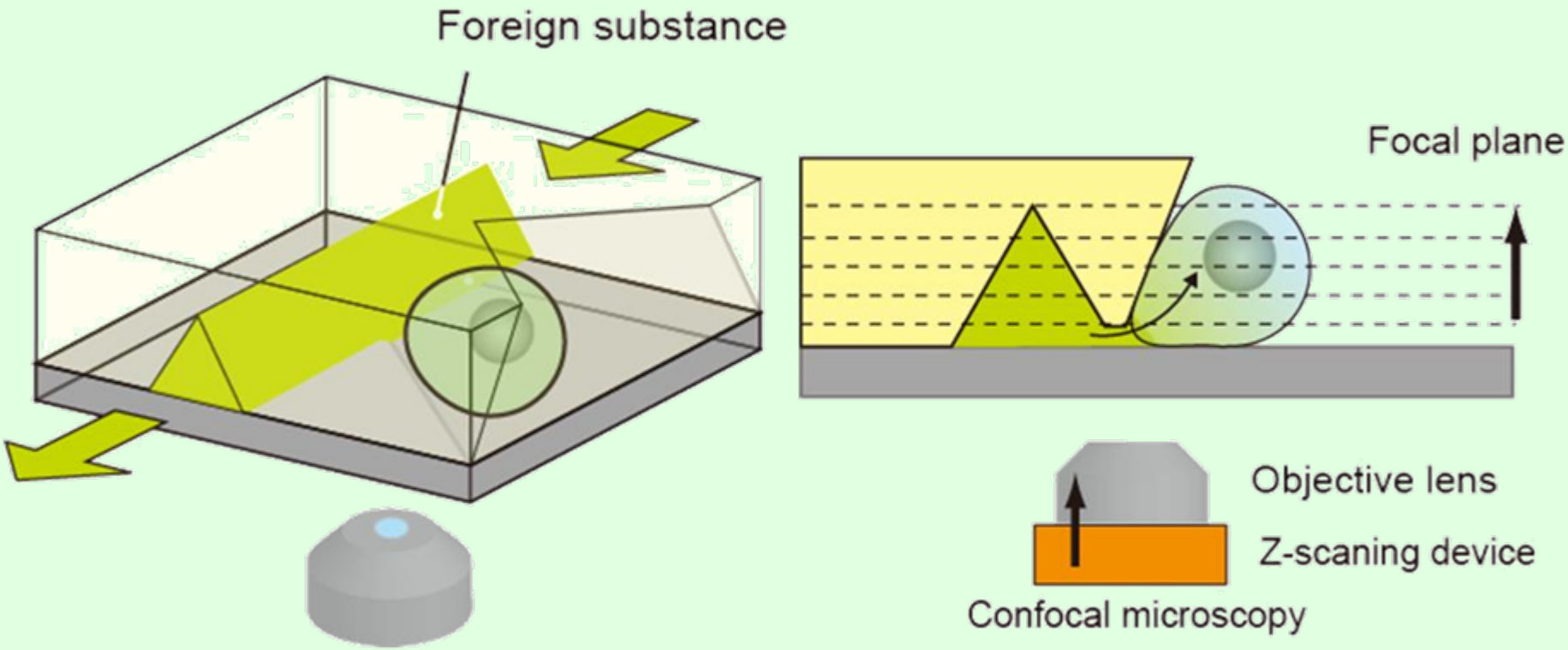






Trap single cell by aspiration through micro channel.

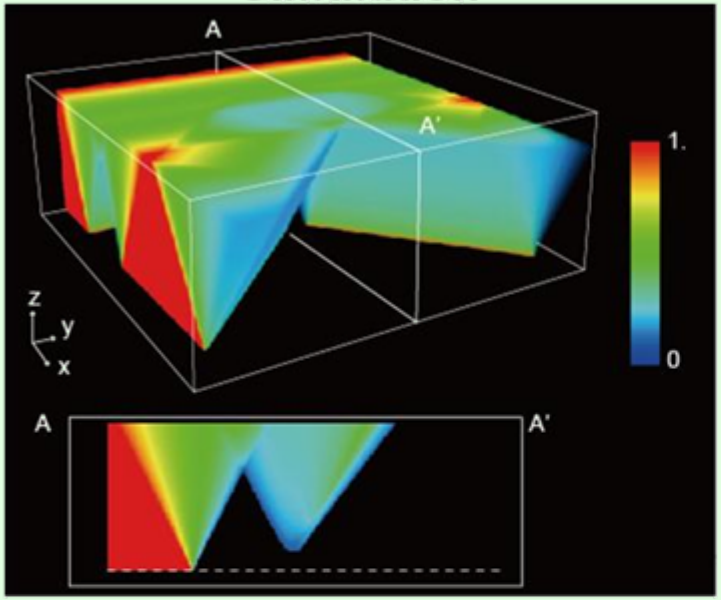
Setup for measuring localization and secretion



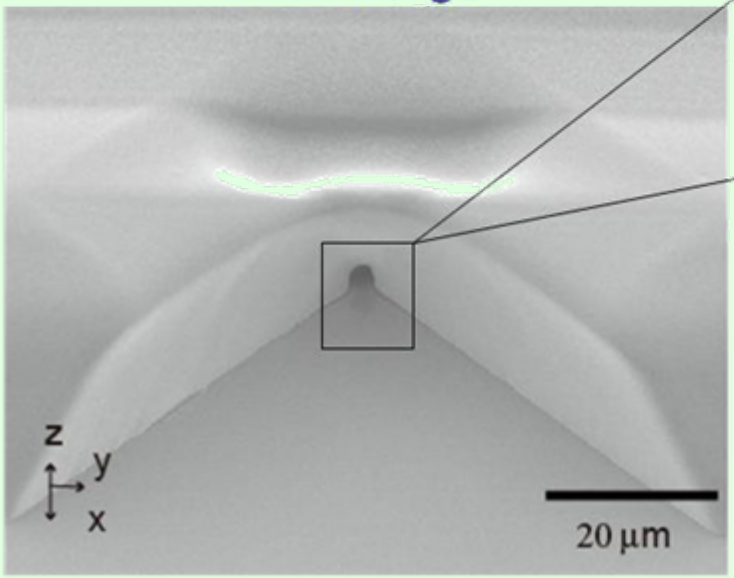
- **Localized stimuli introduction into trapped cell**
- **4D imaging of its uptake and intracellular responses**

Micro channel and hole

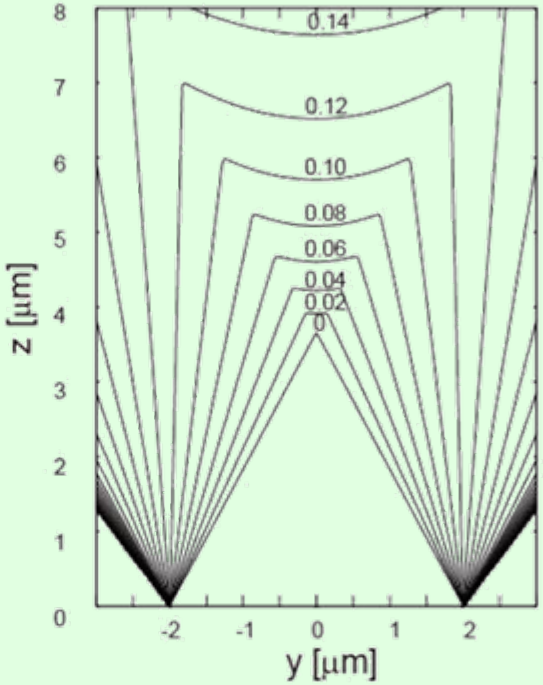
Simulation



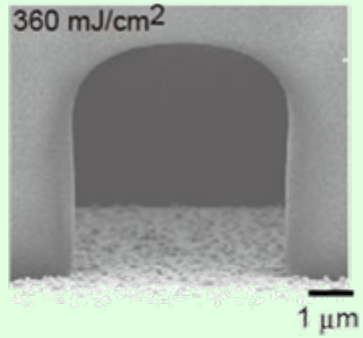
SEM image

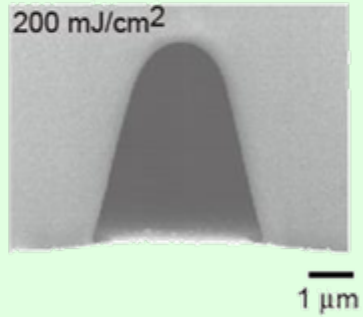


Simulation



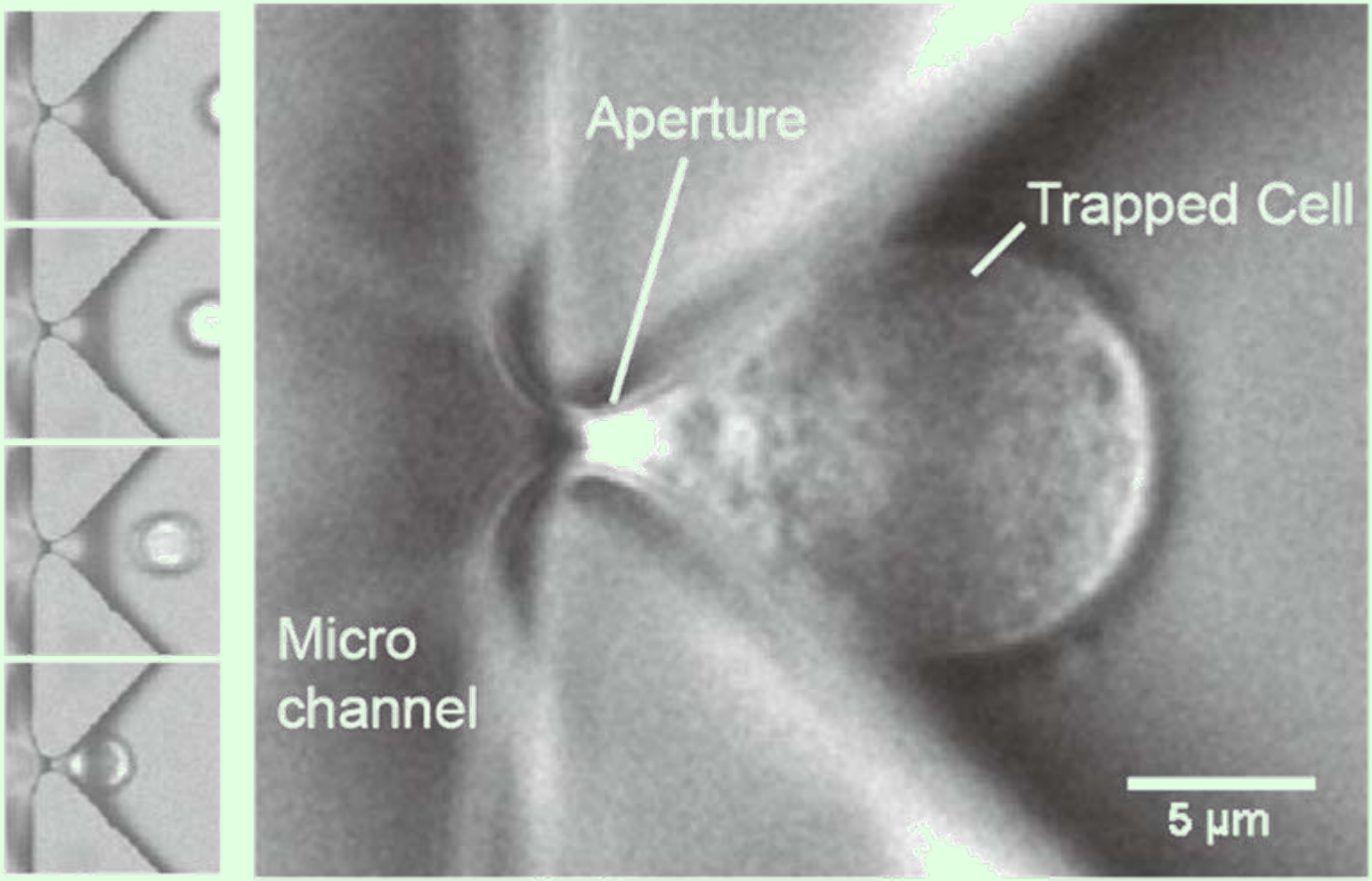
SEM image





- **Aperture-size/shape control by exposure dose**

Cell positioning

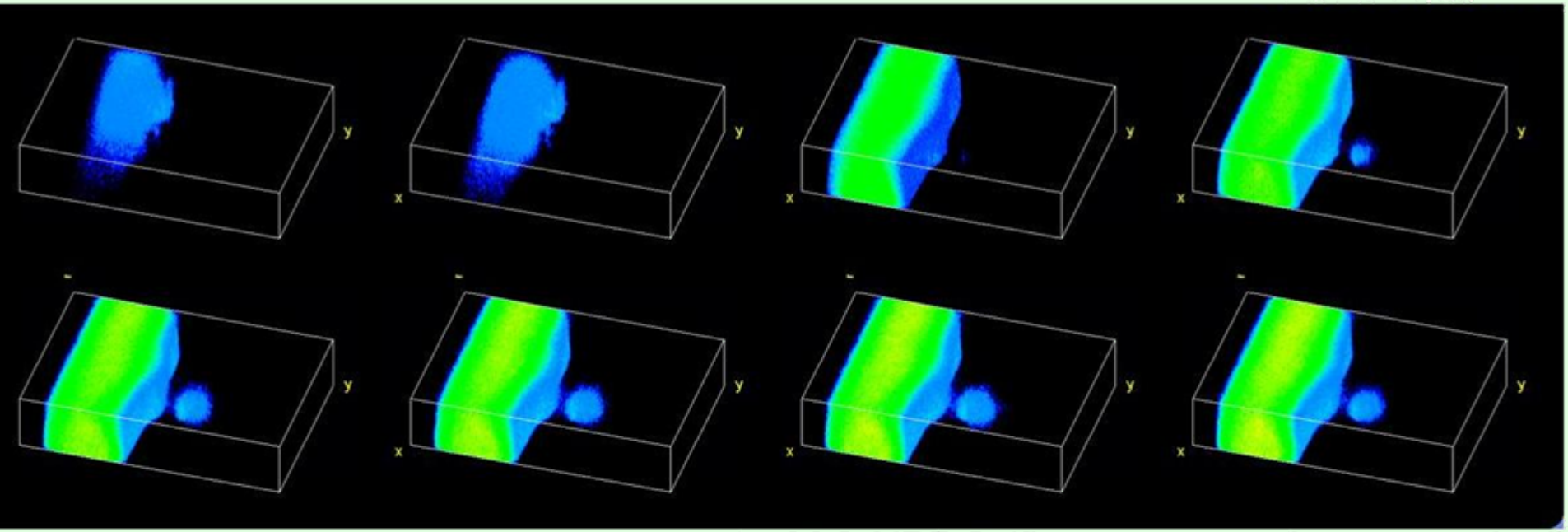


160 ms/frame

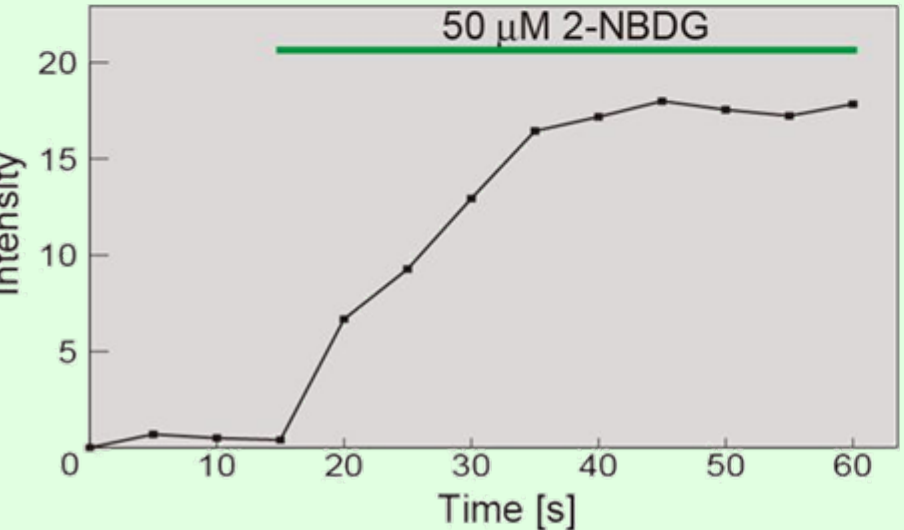
Single cell is positioned at an aperture.

Glucose instability and localization inside cell

10 sec / frame

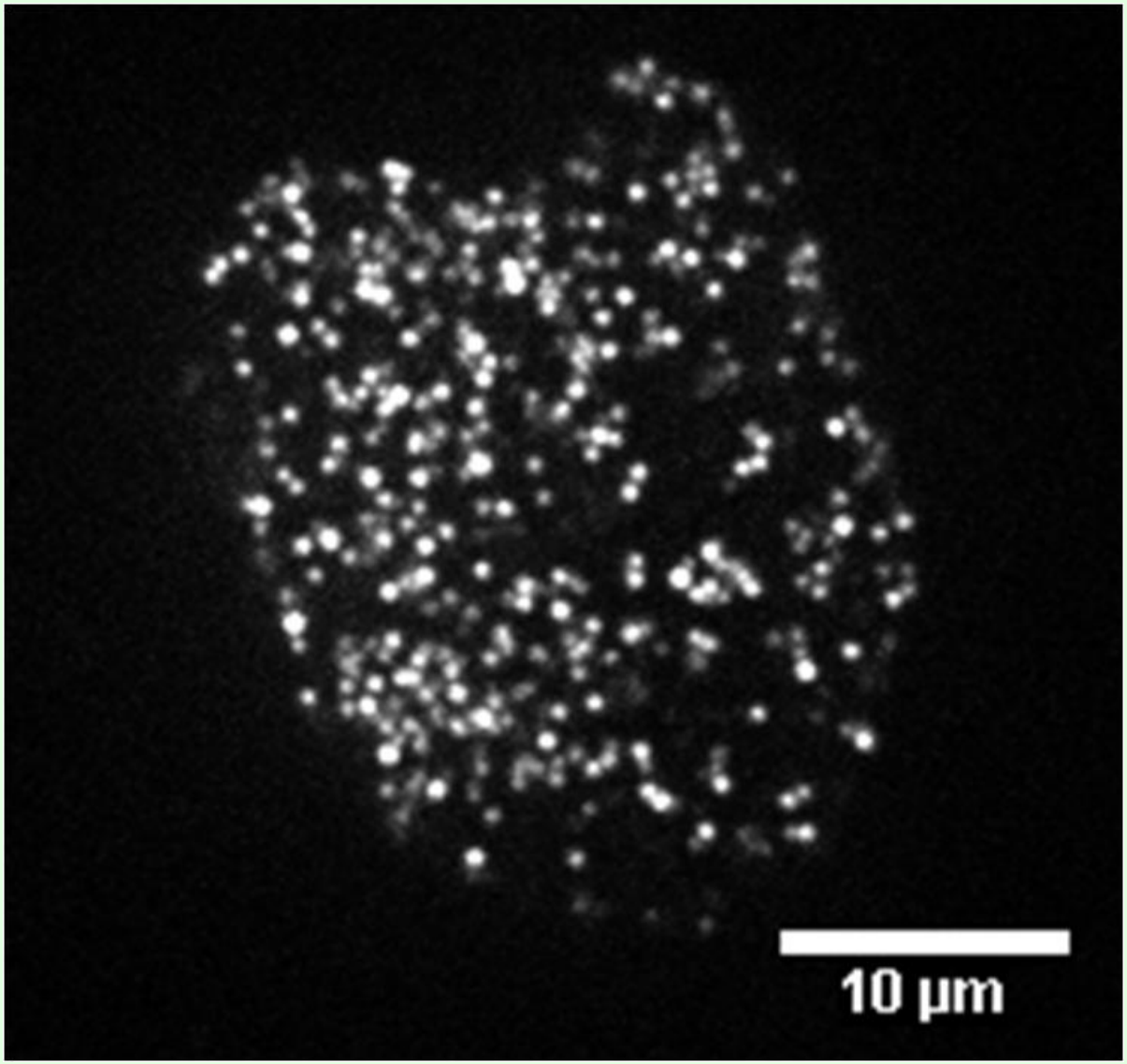


50 μM 2-NBDG (fluorescence glucose analog)



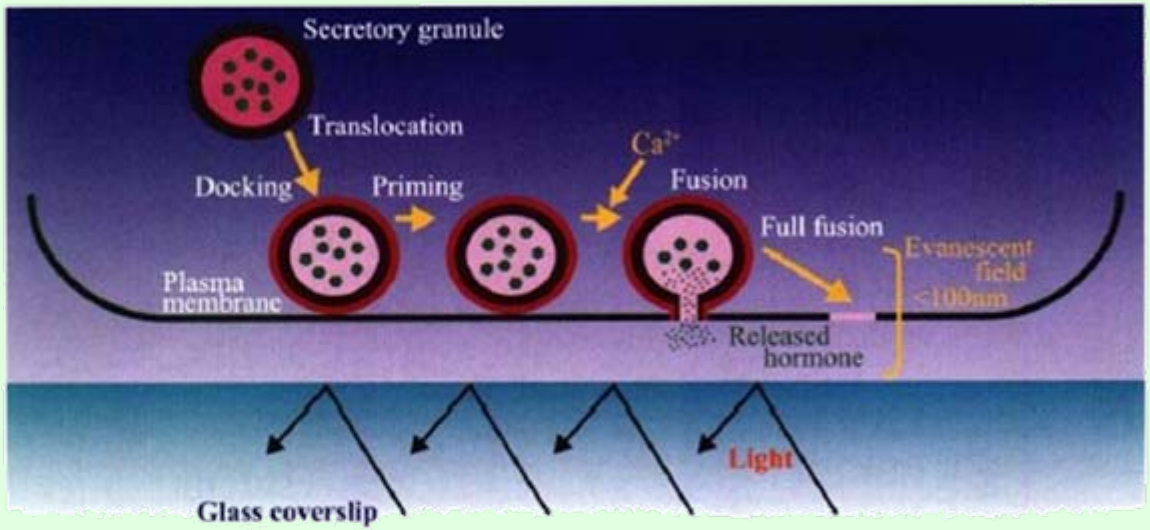
- **External substances is introduced**
- **Glucose uptake is visualized with 4D (x,y,z and time) resolution.**

Insulin GFP is introduce and imaged in β cell

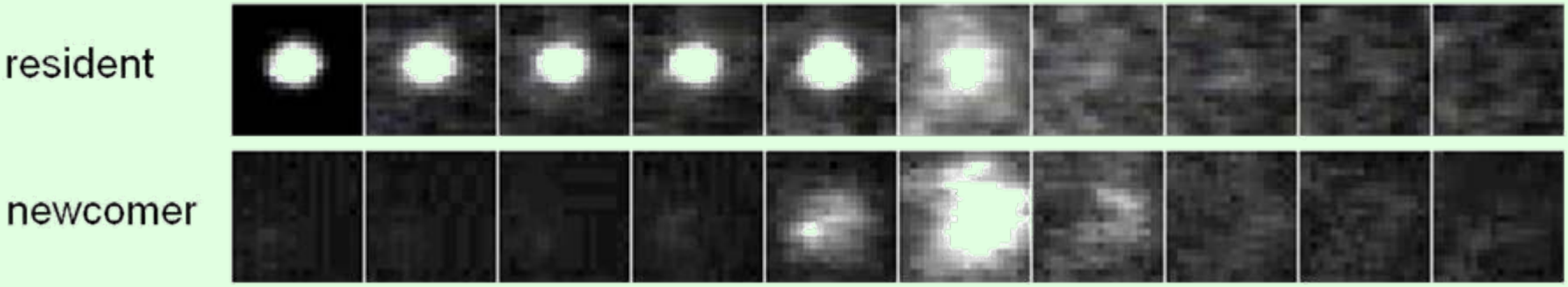


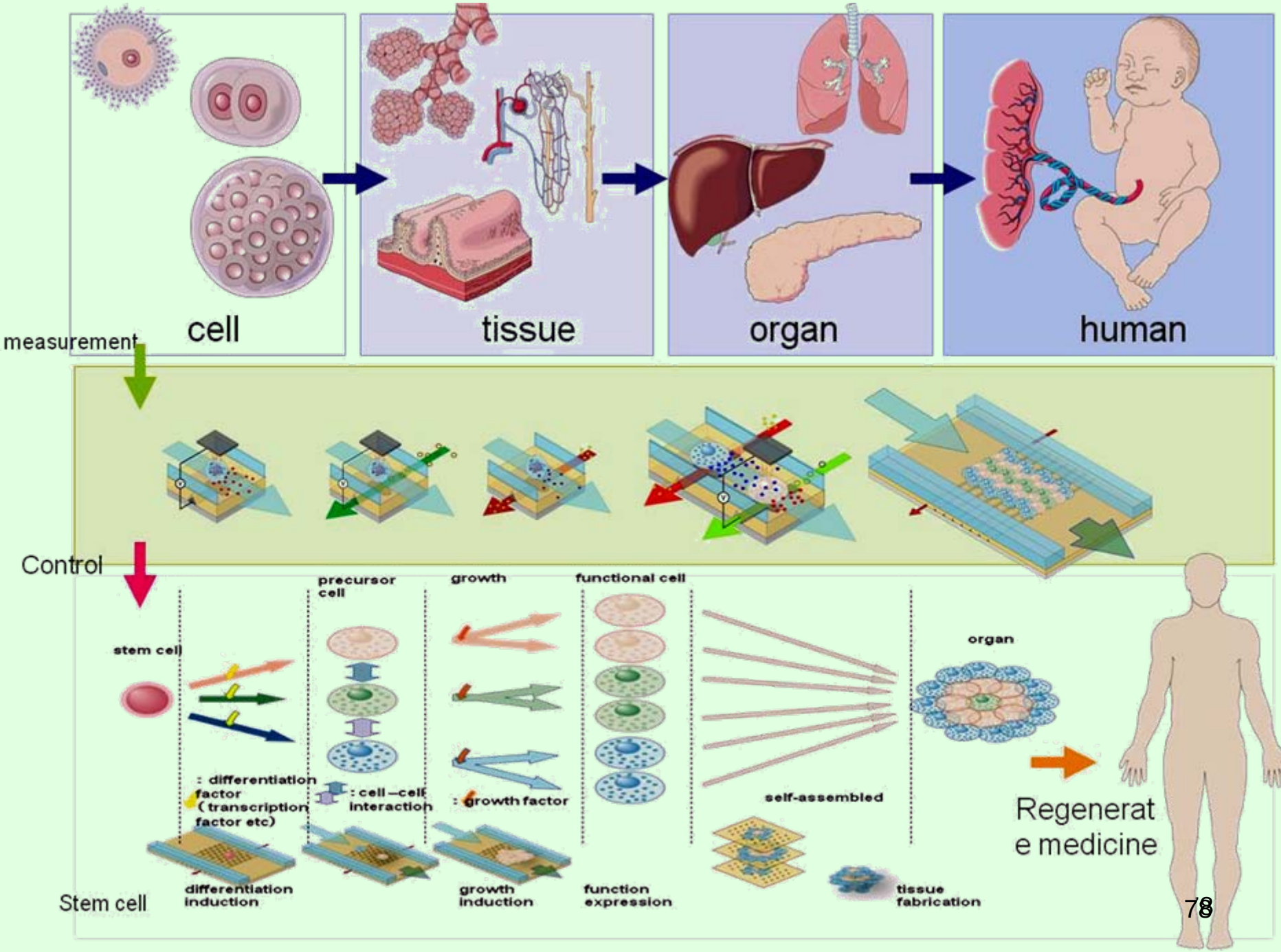
Insulin-eGFP / MIN6 cell

Insulin Secretion



Insulin-eGFP / MIN6 cell




cell
tissue
organ
human
measurement
Control
stem cell
precursor cell
growth
functional cell
: differentiation factor (transcription factor etc)
: cell–cell interaction
: growth factor
self-assembled
organ
Regenerative medicine
Stem cell
differentiation induction
growth induction
function expression
tissue fabrication

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