FUTURE CREATION LABORATORY

Carbon Nanotube Biosensor for the Assessment of Personal Quality of Life

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1 Olympus Corpration, CREST-JST and NEDO, 2 NEDO, 3 Mitsubishi Kagaku Iatron, 4 Mitsubishi Chemical, 5 AIST, 6 Tsukuba University, 7 NEDO, Osaku University, CREST-JST, and AIST

FUTURE CREATION LABORATORY

Prolegomenon Quotation from our HP

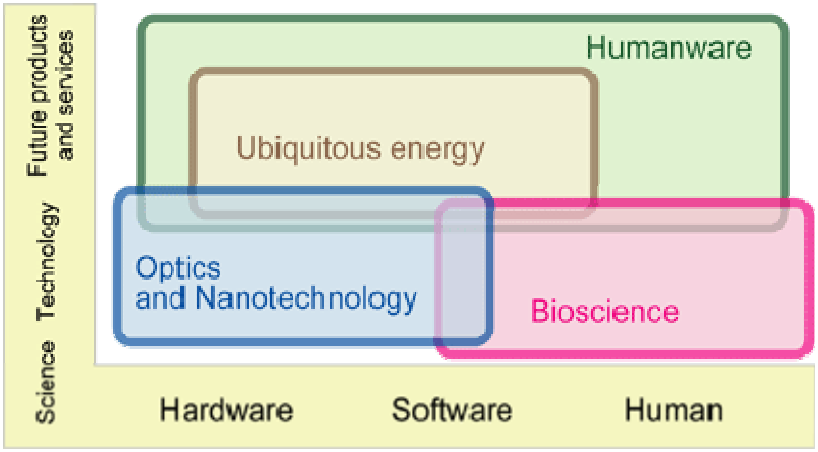
- Future Creation Laboratory of Olympus Corporation
  - Our goal: enhancement quality of life (QOL) on mind and body
  - The Future Creation Laboratory is committed to pursuing a variety of research projects aimed at identifying and creating future values for enriching people's lives.

FUTURE CREATION LABORATORY

Our researches

The Future Creation Laboratory conducts highly original research in "HIKARI"-HI Technology, primarily focusing on four areas:Bioscience, Humanware, Optics and Nanotechnology and Ubiquitous energy. Closely linked, these fields will yield new discoveries and values for the future.

Approaches taken from four research domains

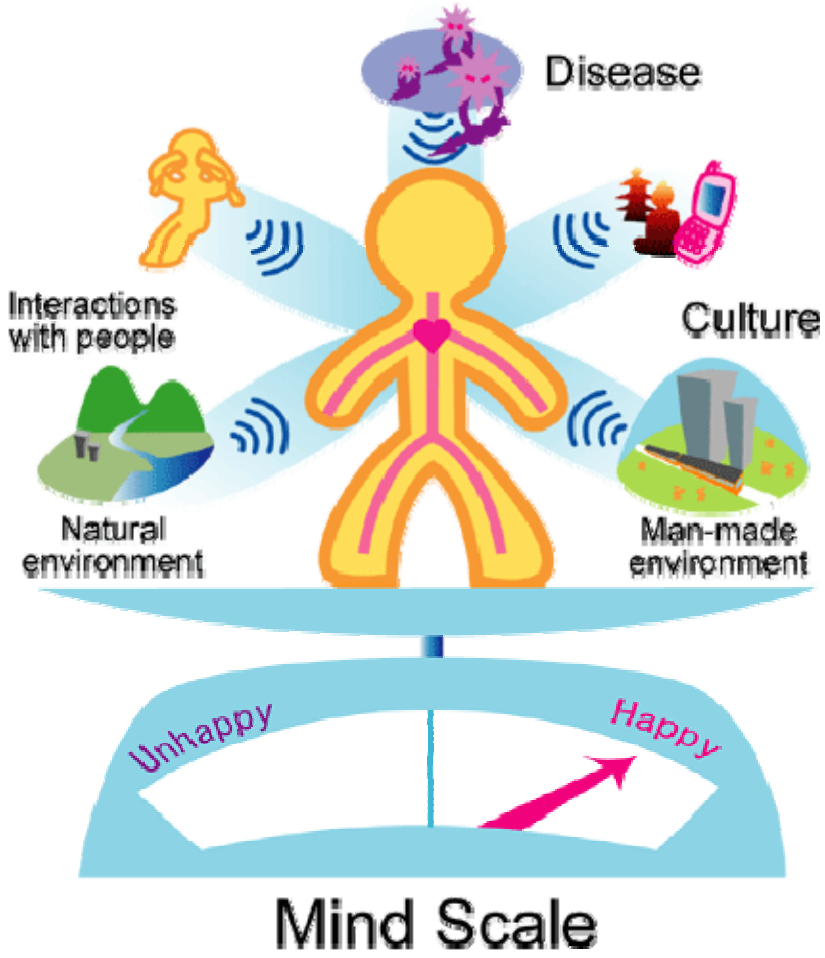


`We explore what future generations want and what universal values will be like in the future.`

FUTURE CREATION LABORATORY

Bioscience domain

-Enhance QOL on mind and body-



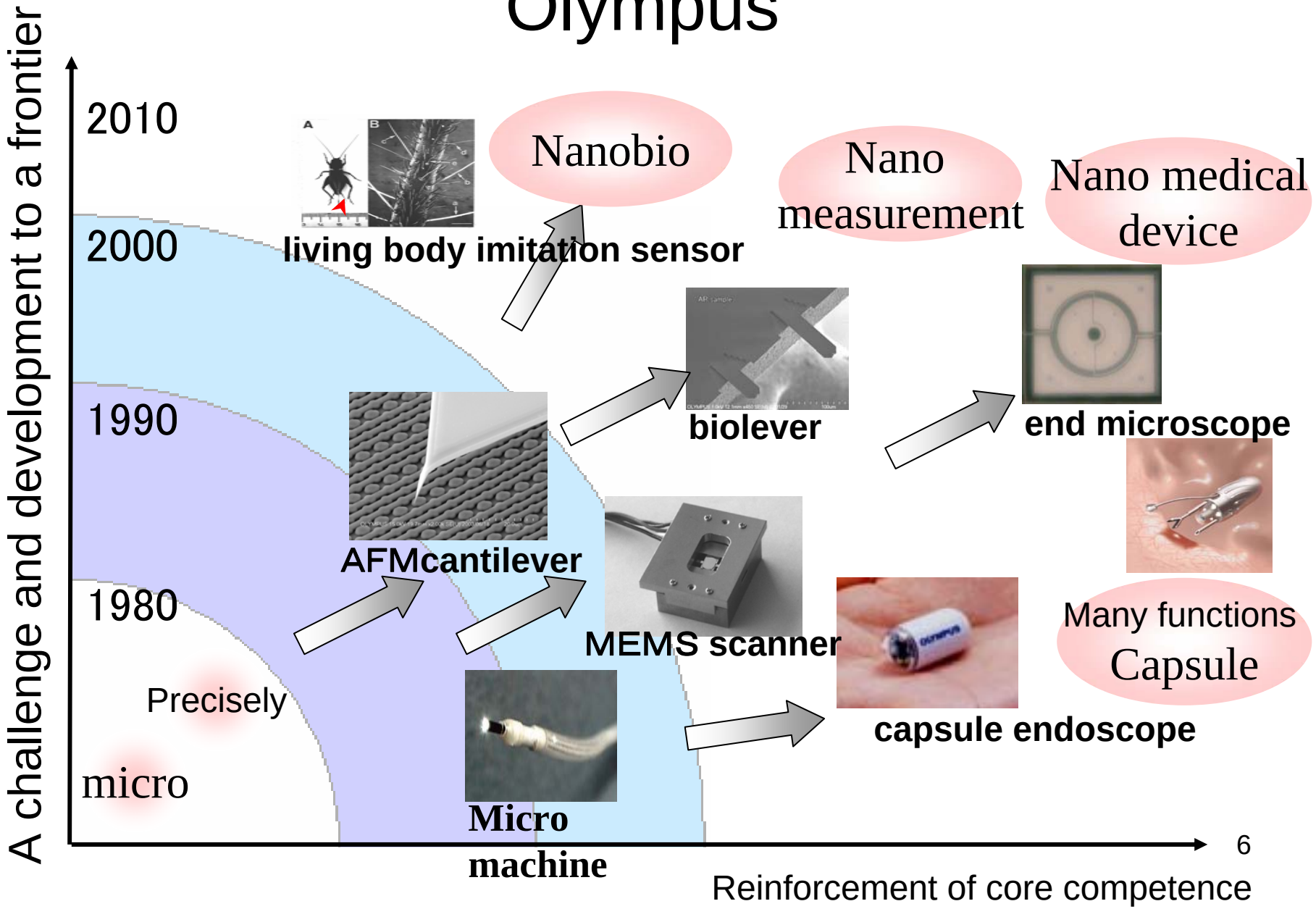
Our future dreams and goal

In the area of carbon nanotube (CNT) biosensors research, we are attempting to establish a technology that allows the ultrasensitive measuring (so called “single molecule detection”) of biomolecules by applying the CNT single electron transistor to biosensors.
This technology will open a new possibility for home physical check-ups and will contribute to preventive medicine and health management during recovery.

Introduction
What is Personal QOL

This project is "**Research and Development of Nanodevices for Practical Utilization of Nanotechnology**" in NEDO

Challenge to nanotechnology of Olympus



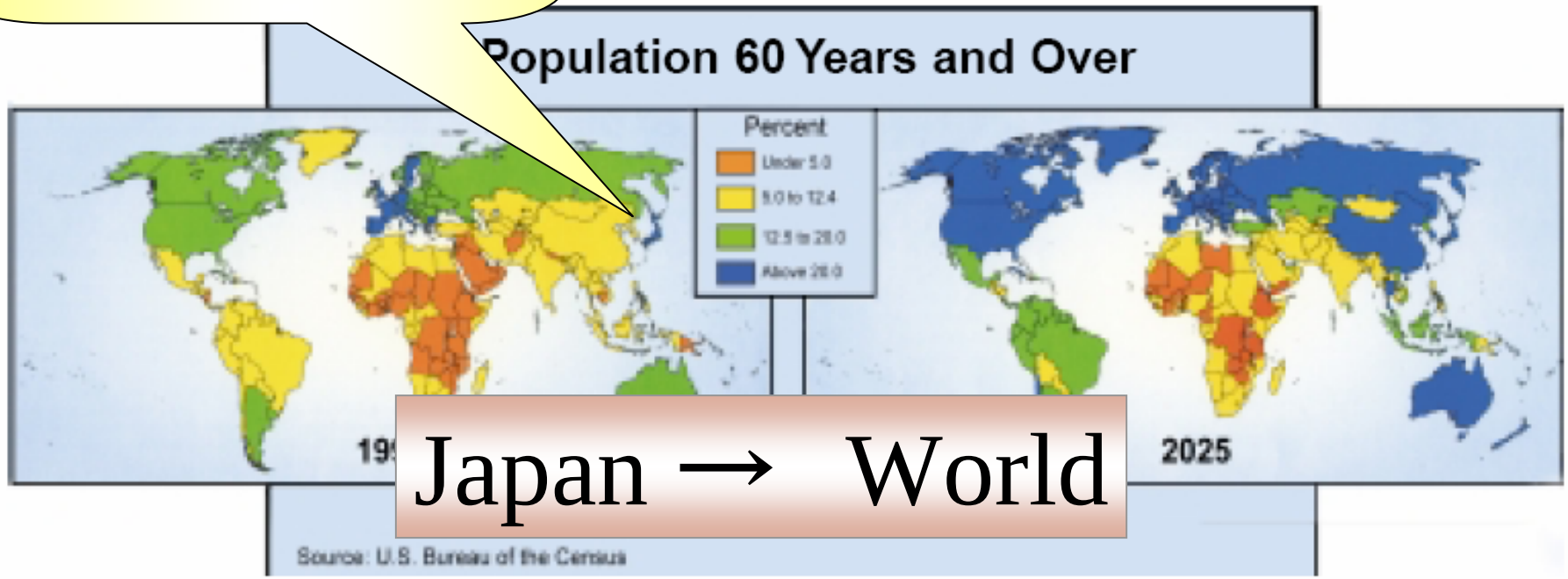
We take the fastest problem of aging speed underhand

NEW WORLD COMING:

ECURITY IN THE 21ST CENTURY

WebPDF file ; 21C US security in the 21st centry

Current Japan is super aged society



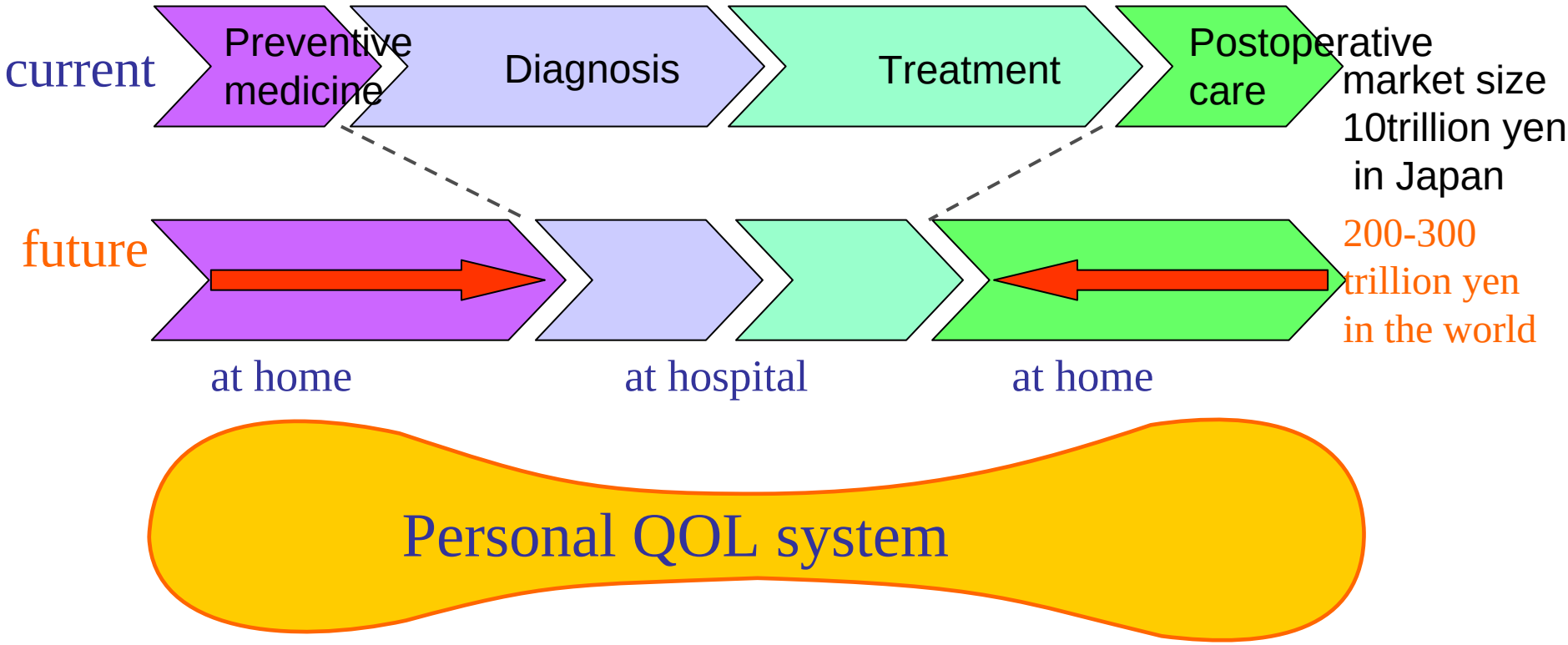
Japan → World

Country of current aged society: about 10

20 years past: about 20

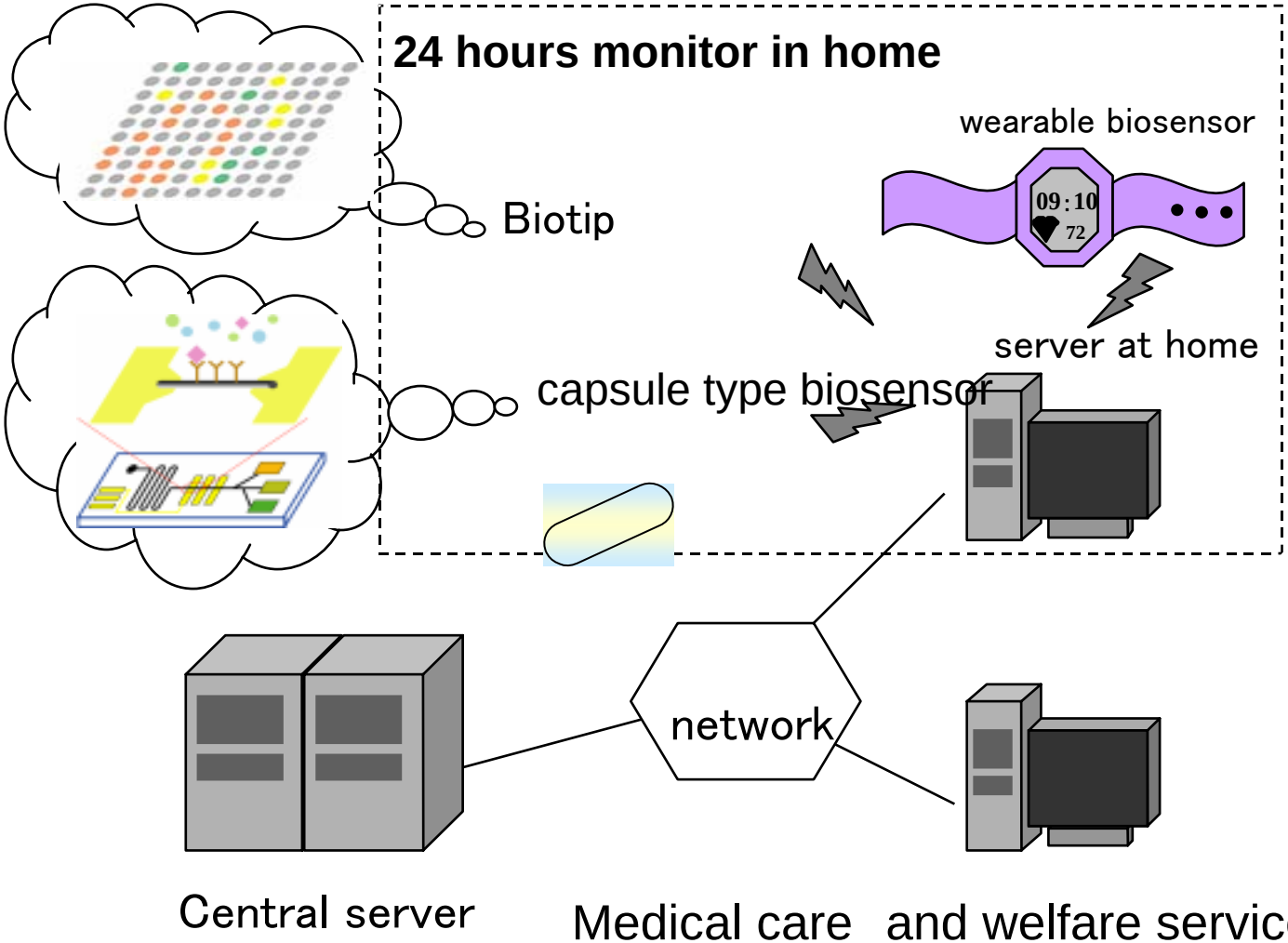
Personal QOL system

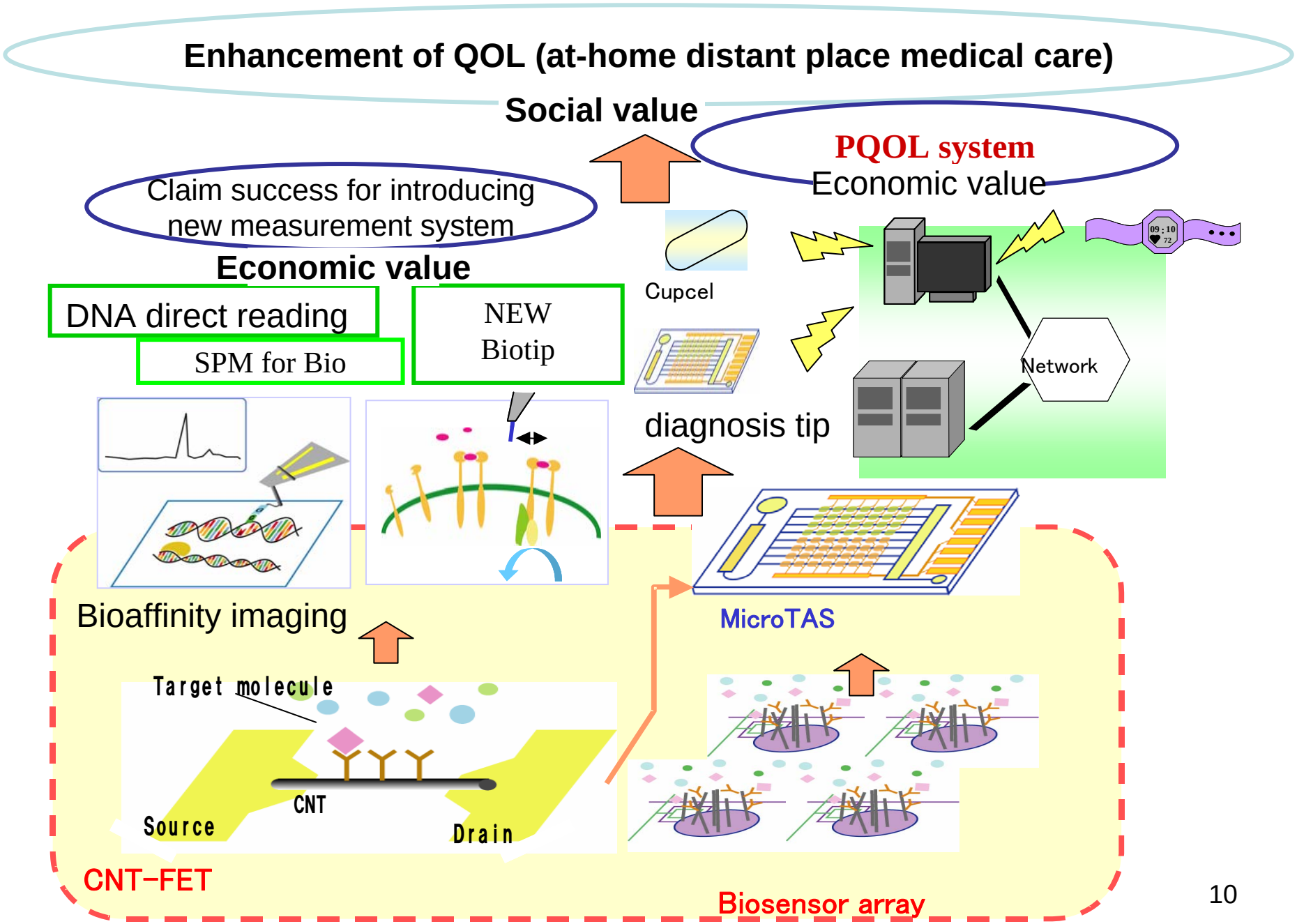
～Aims to reduce medical cost and promote healthy intentions～



- Feature
- 24 hours monitor with a terminal in home
- Biotip, microTAS

PQOL system

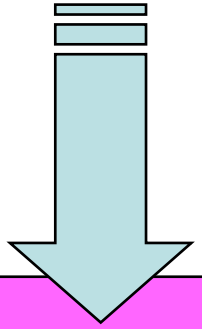

24 hours monitor in home
wearable biosensor
09:10
72
Biotip
server at home
capsule type biosensor
network
Central server
Medical care and welfare service institution


Enhancement of QOL (at-home distant place medical care)
Social value
PQOL system
Economic value
Claim success for introducing new measurement system
Economic value
DNA direct reading
SPM for Bio
NEW Biotip
Cupcel
Network
diagnosis tip
Bioaffinity imaging
MicroTAS
Target molecule
CNT
Source
Drain
CNT-FET
Biosensor array

Positioning of this study

- Fundamental studies of CNT-transistor

CREST-JST project: Olympus, AIST, Mitsubishi Kagaku Iatron, & Osaka Univ.



- **PQOL system using CNT-Biosensor**

NEDO project: Olympus, Osaka Univ. & JAIST

Relationship between JST & NEDO Project

- CREST-JST Project
- Mainly fundamental research
  - CNT-field effect transistor (FET)
  - using CNT-FET in biosensor

- NEDO Project
- Investigation for practical use
  - measure yield, , quantifiability, selectivity, sensitivity, stability, reliability Establishment of micro total analysis system (TAS) by MEMS technology

Position of CNT biosensors in CNT applications

Mass-production method of CNTs must be established

Hydrogen storage

Catalyst

Electrode of Fuel cell

Capacitor

Filed emission

DDS

FET

STM tip

CNTs not required in large quantities

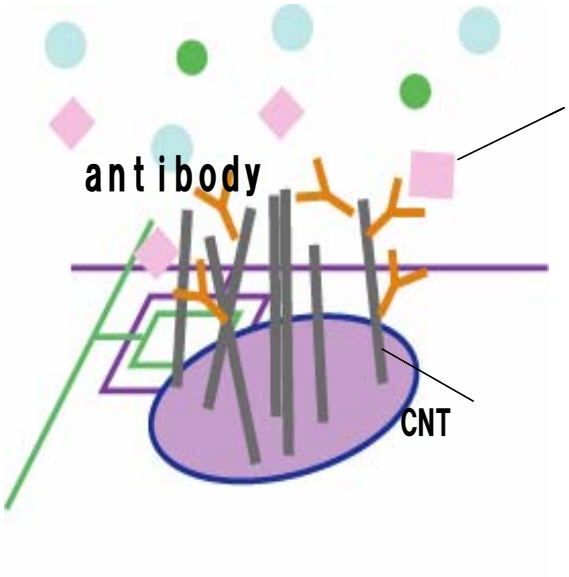
Contents of this presentation

- What is CNT biosensor?
- Problems for practical use and solutions

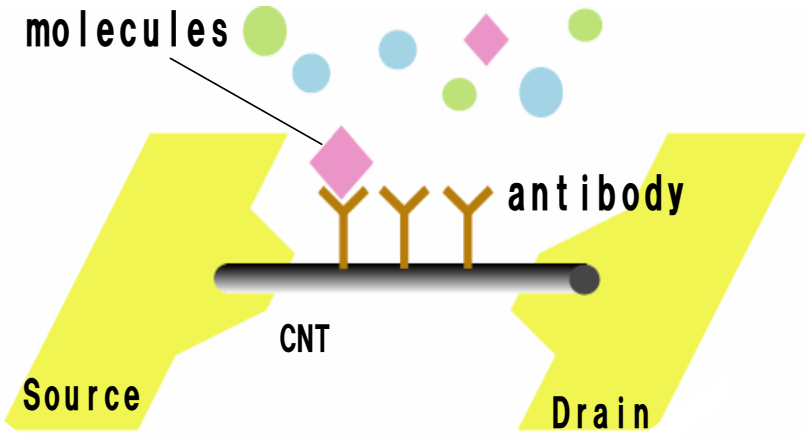
What is CNT-biosensor?

- We studied
  - Amperometry
    - High reliability
  - Potensiometry
    - High Sensitivity

CNT biosensor of Amperometry or Potensiometry



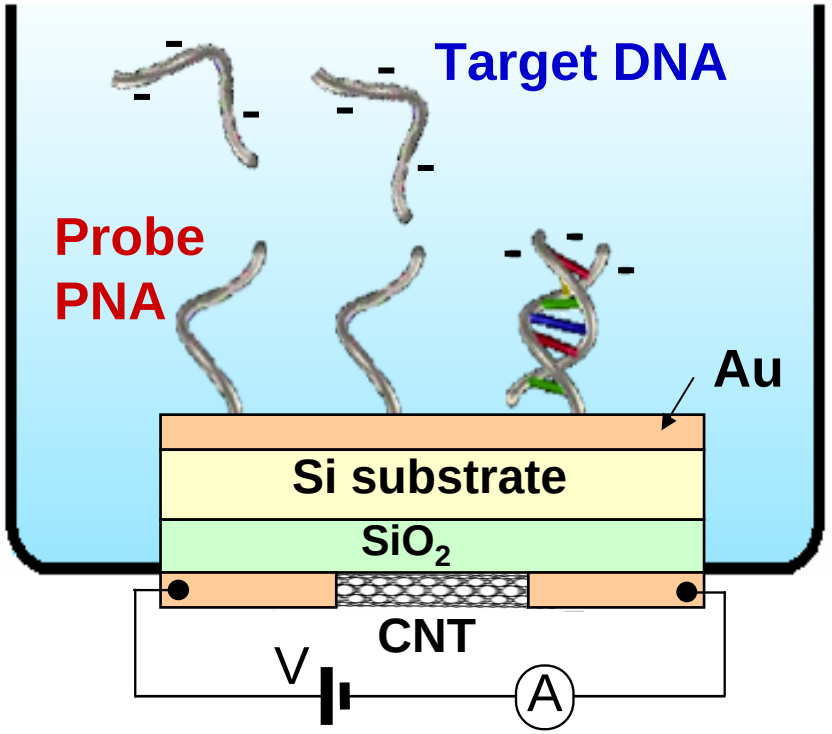
Amperometry
（Large surface area electrode）



Potensiometry
（FET）

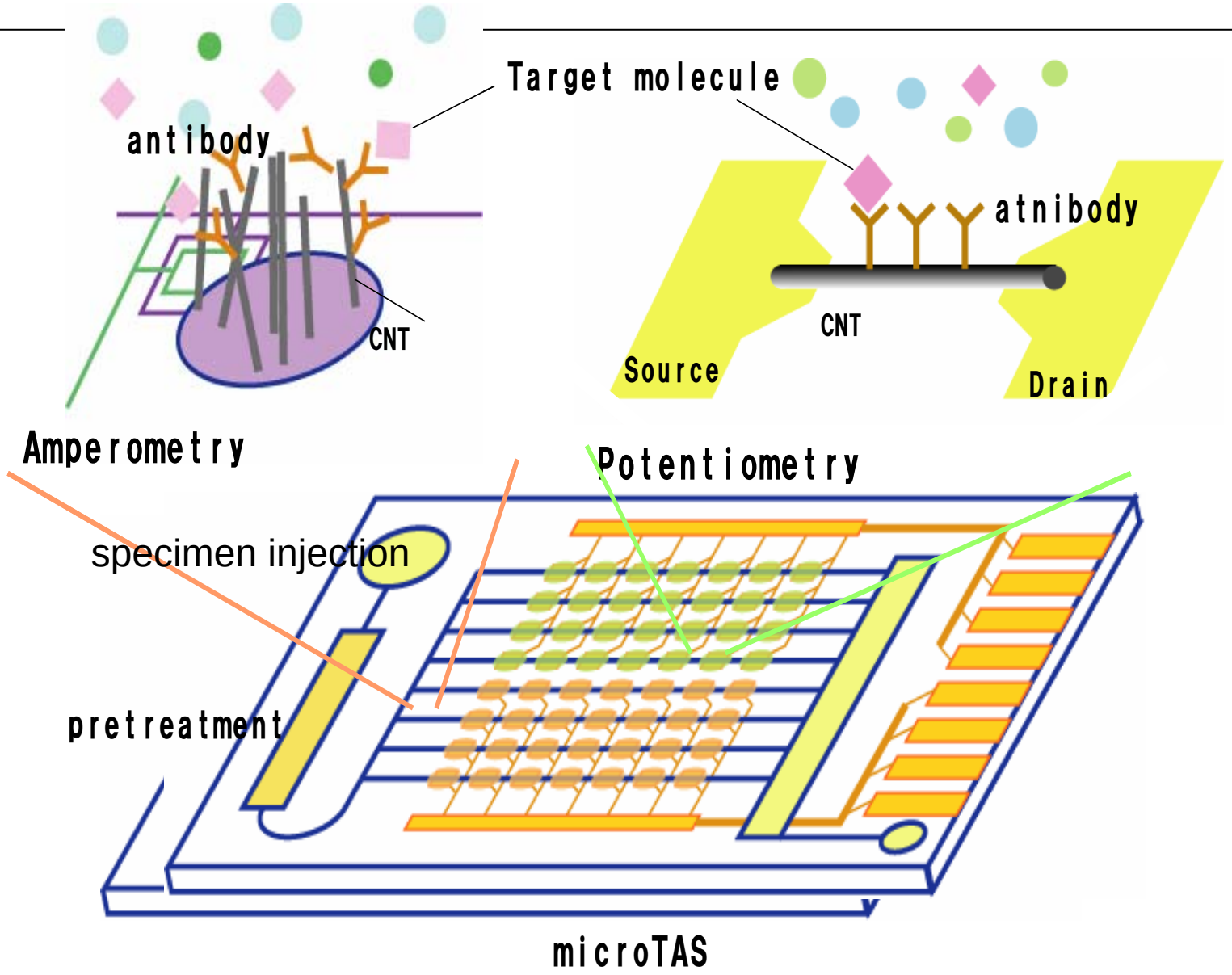
Previous CNT-FET biosensor research

DNA Hybridization



We achieved detection of 6.8 fmol/L of DNA using a CNT-FET biosensor

Biosensor array



Why did we select a CNT biosensor for PQOL system?

- PQOL system requires
  - wearable biosensor
    - small and light
    - microTAS
  - real time sensing
  - non disposable

CNT biosensor compared with conventional protein sensing methods

	CNT Biosensor	Chromatography	Chemical luminescence
Sensitivity	**c.a. 1 μ mol/l conventional study**	nmol/l order	most high sensitivity
Mobility	yes	yes	no
sensor array	yes	no	yes
Real time sensing	yes	no	no
Not disporsable?	yes	no	no

Problems for practical use of CNT-FET based biosensor

- CREST-JST
  - Fundamental design
  - Stability & reliability

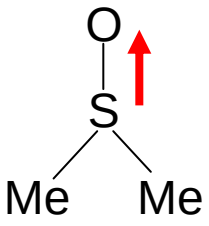
- NEDO
  - Quantifiability
  - Sensitivity
  - Yield
  - Selectivity

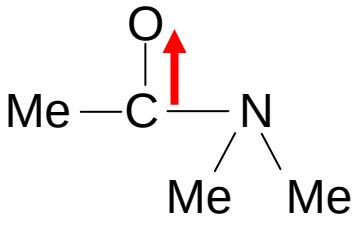
Contamination provides less stability of CNT-FET

Washing CNT using aprotic solvent

What is DMSO & DMAC

- aprotic solvent
  - Dimethylsulfoxide（DMSO)
  - Dimethyl acetamide（DMAC)

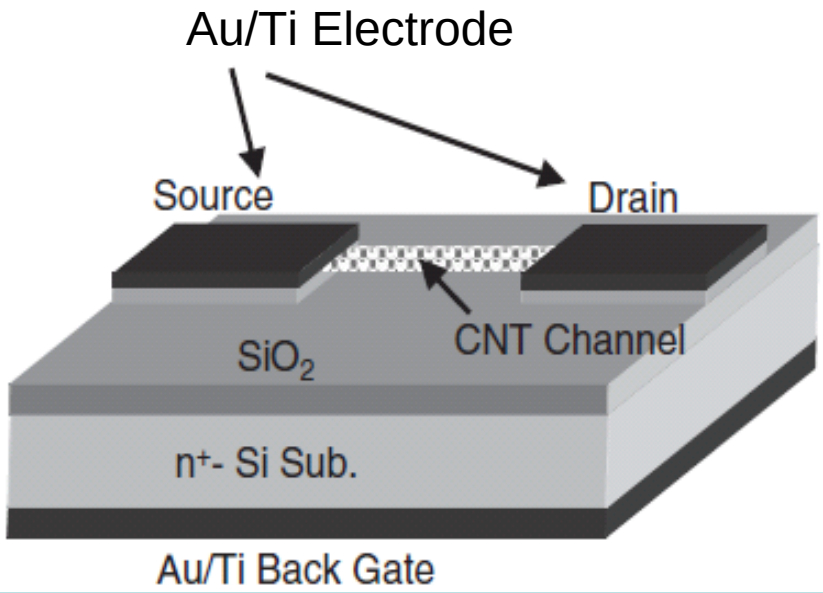




Aprotic solvent features

- hydrophobic
- hydrophilic
  - strong dipole moment
  - strong nucleophilicity（basic）

Experiments and sample preparation



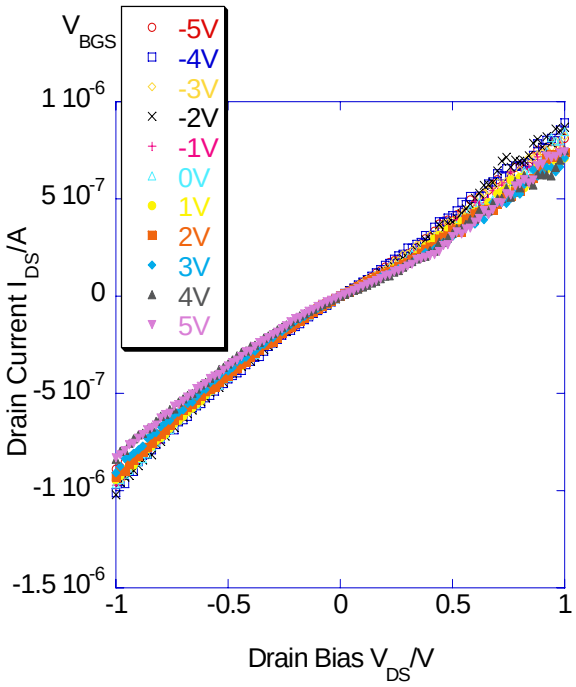
- Photolithography
- CVD
  - EtOH 750sccm
  - H2 500sccm
  - @900℃ 10min.
- Wash by DMAC

CVD process contaminates the CNT with pitch, amorphous carbons and so on

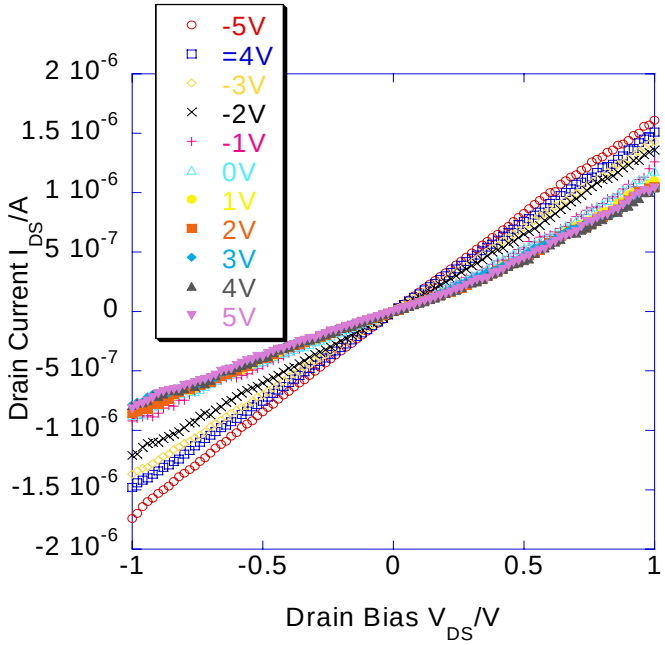
Photolithography process makes lots of photoresist residue.

Vd-Id Characteristic of CNT-FET Before and After Washing

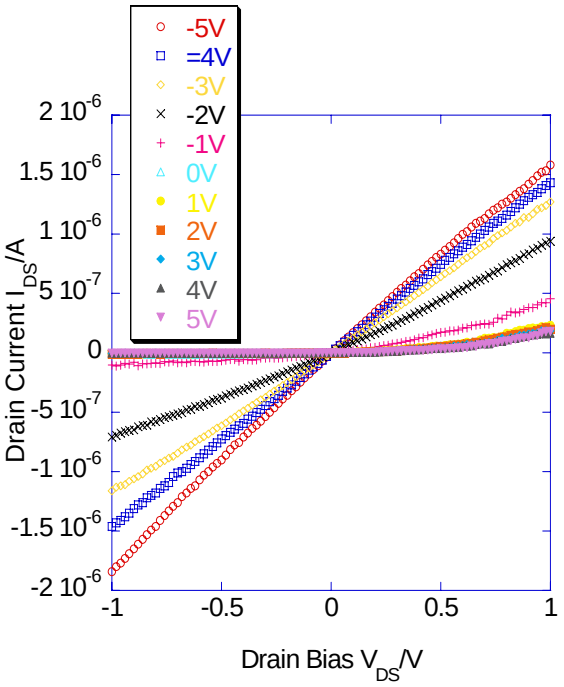
As Prep.



Wash by DMSO



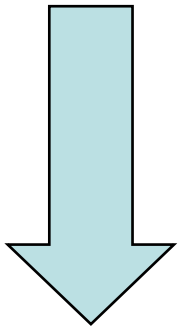
Wash by DMAC



become sensitive to gate voltage

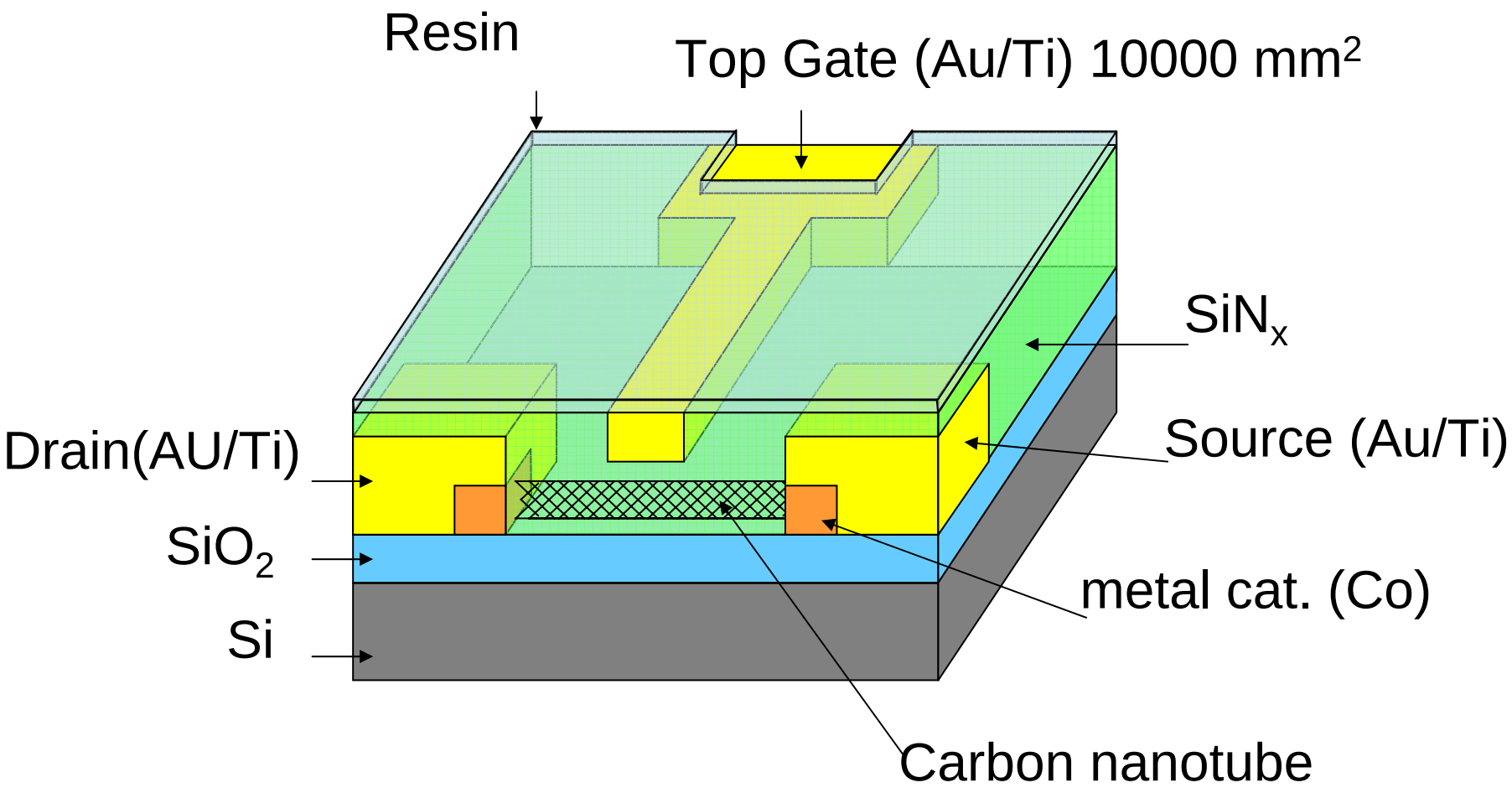
Results: top gate is best structure

- CNT must be kept clean for optimal CNT-FET performance

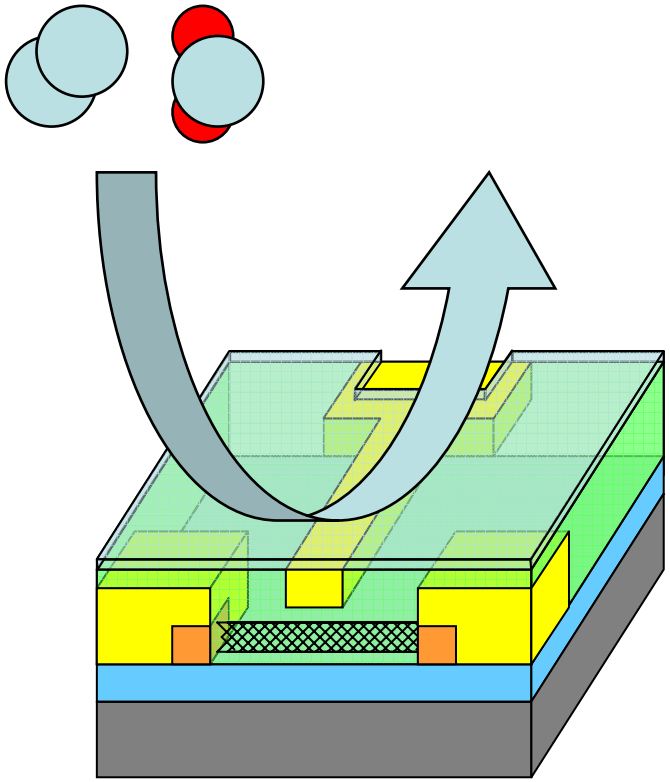


- Top-gate CNT-FET biosensor
  - CNT kept clean because CNT is covered with SiNx.

Top-gate CNT-FET illustration



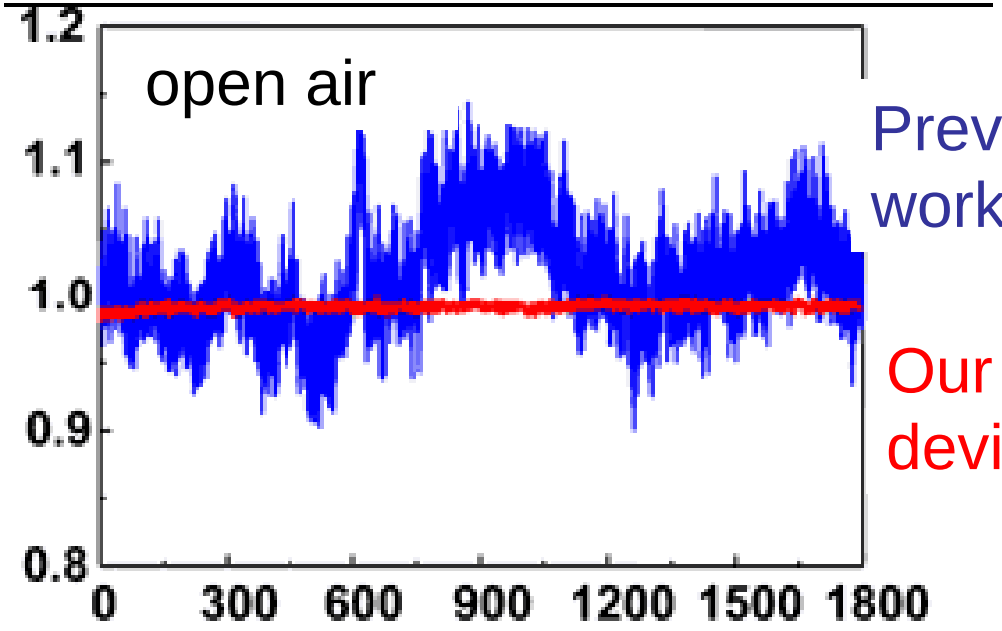
Top-gate structure prevents adsorbing contamination on CNT



Water, oxygen and other contaminates cannot adsorb on CNTs

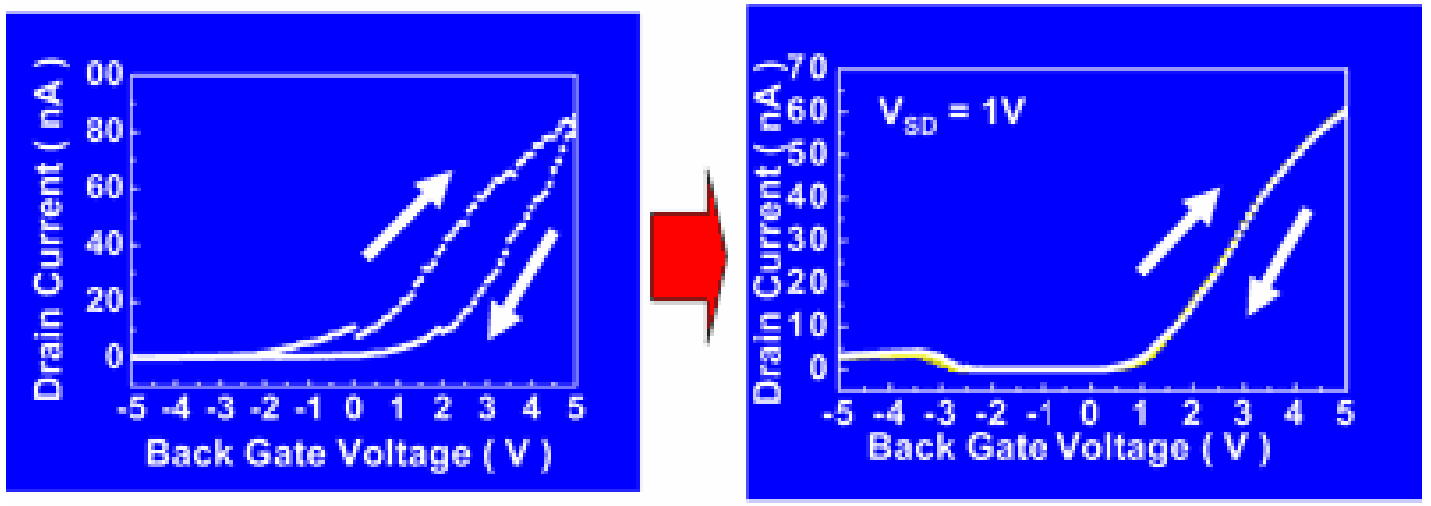
Top-gate CNT-FET has high stability

Little change in drain current

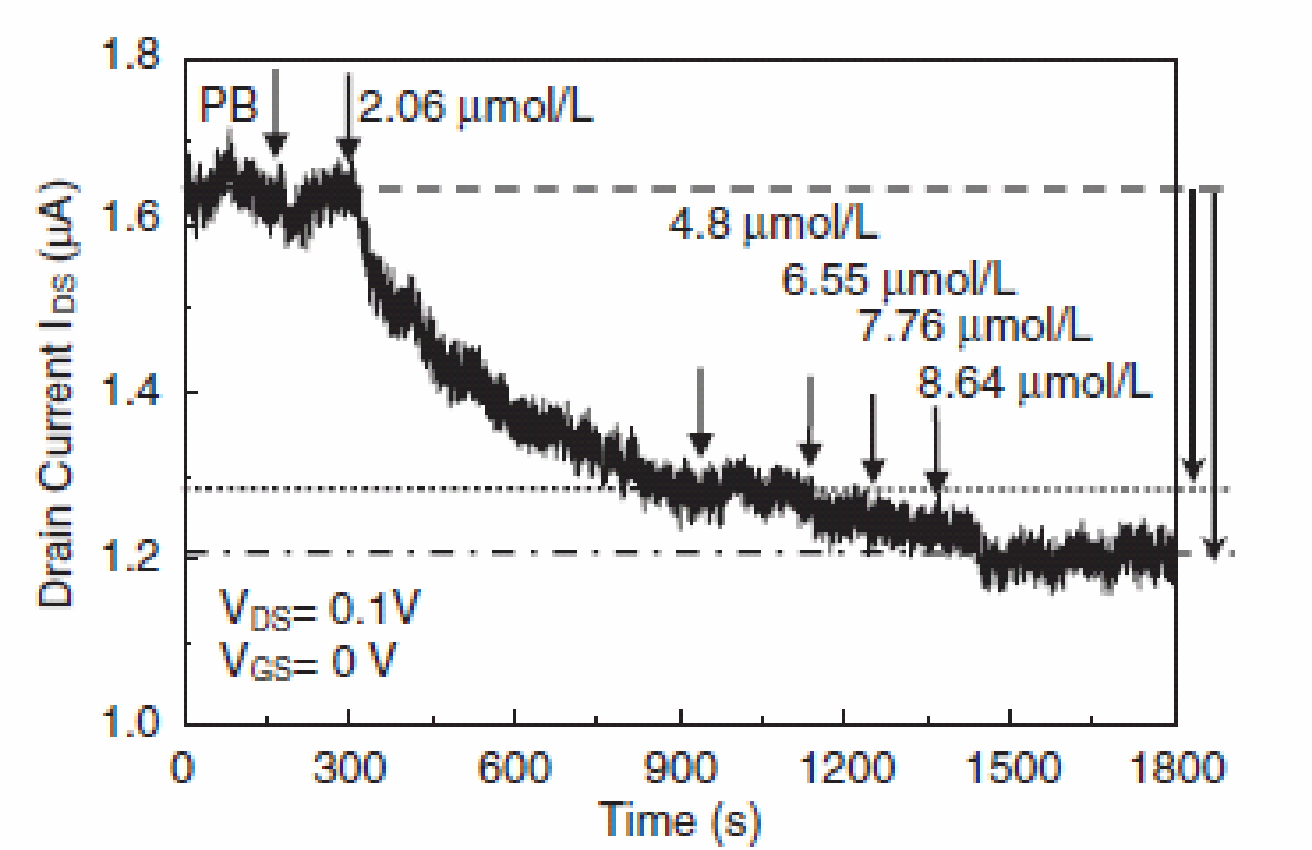


Top-gate CNT-FET produces no hysteresis

Little hysteresis occurred in our top-gate device



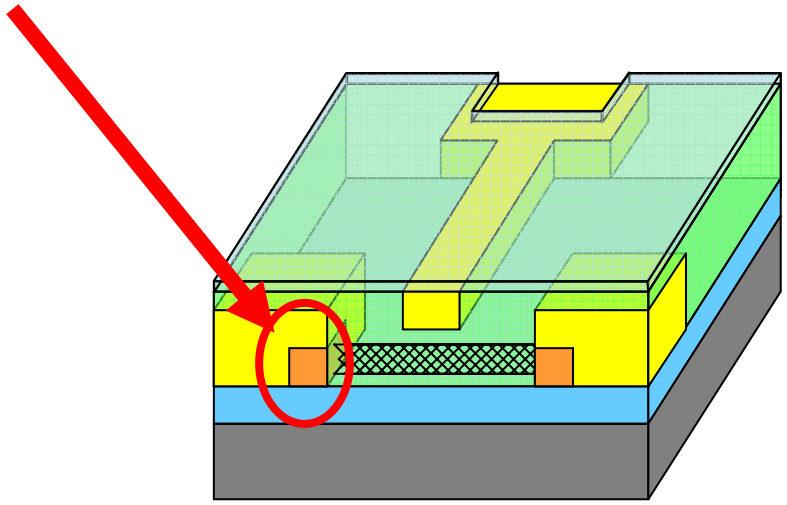
Top-gate CNT biosensor has low sensitivity



Why low sensitivity?

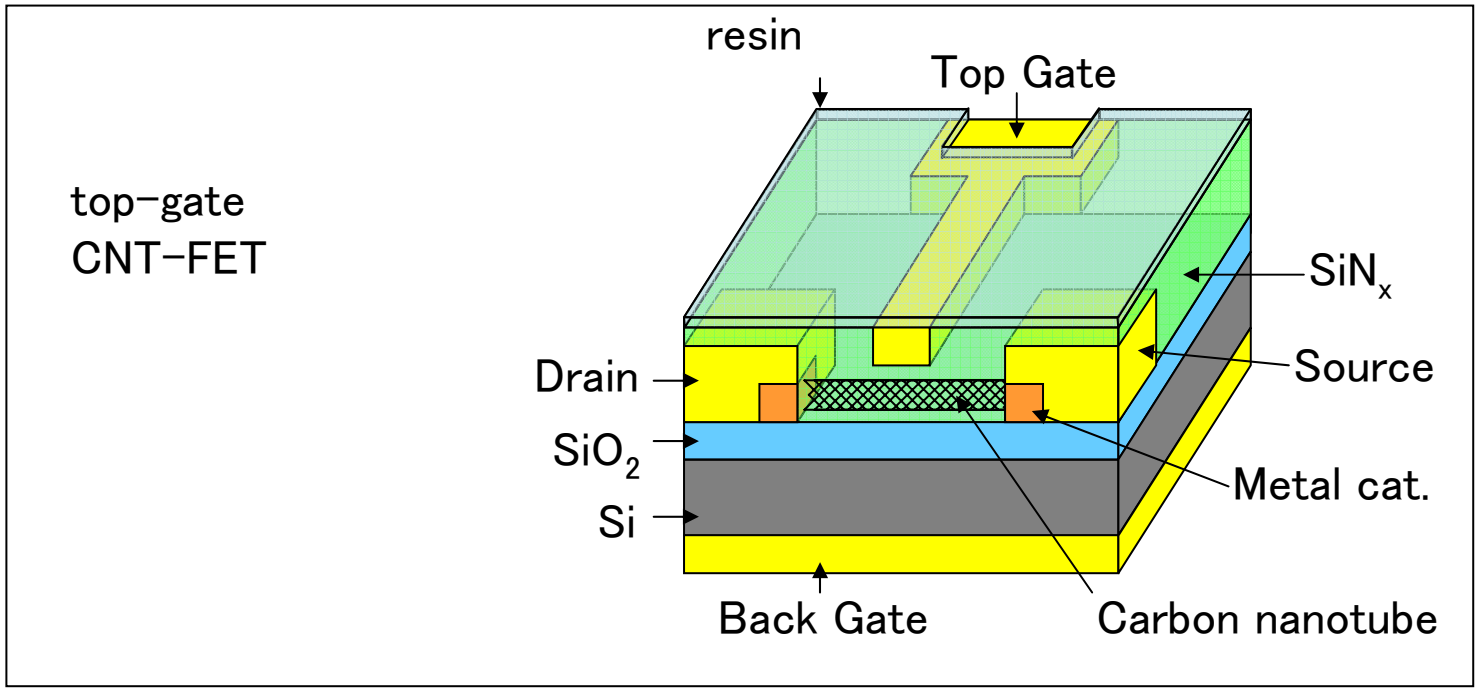
- No modulation by schottky barrier

Schottky barrier



Top-gate FET was modulated by only channel part, back gate FET was modulated by schottky barrier and channel part.

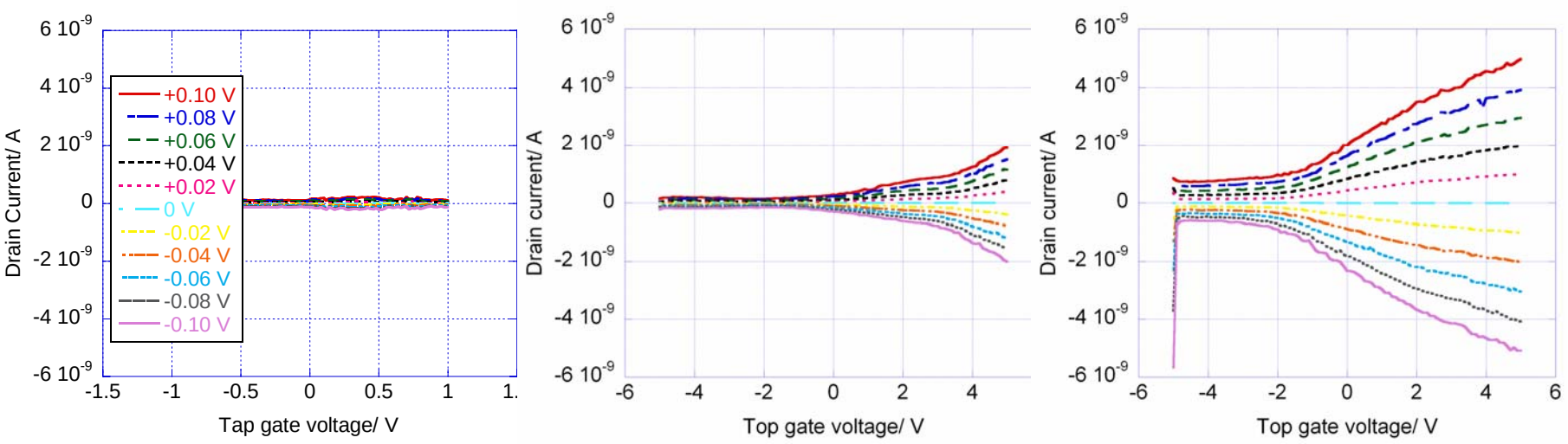
Double gate structure enhances CNT-FET sensitivity



Double gate enhances sensitivity

Back gate voltage

-5 V 0 V 5 V



High sensitivity

Biosensing

CNT-FET can sense proteins based on antigen-antibody reaction

Experimental fixation of protein

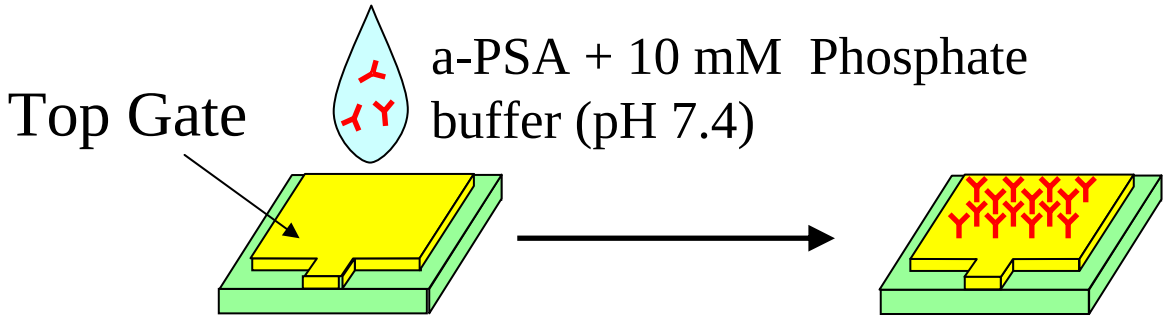
Proteins

Pig Serum Albumin (PSA)
anti-Pig serum albumin (a-PSA)

a-PSA was immobilized on CNT-FET,
and PSA in solution was sensed.

Immobilizing PSA on Top-gate

Phosphate buffer, including a-PSA, was dropped on a top gate of CNT-FET.
a-PSA was physically adsorbed on top-gate.

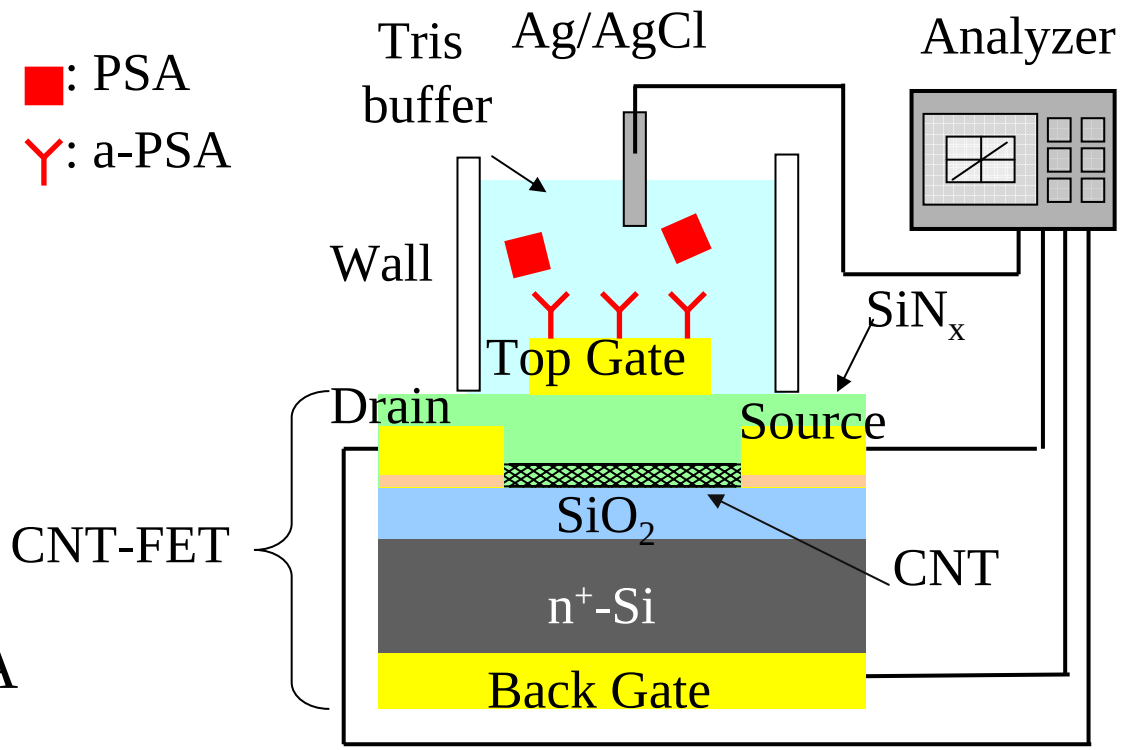


Experimental Sensing

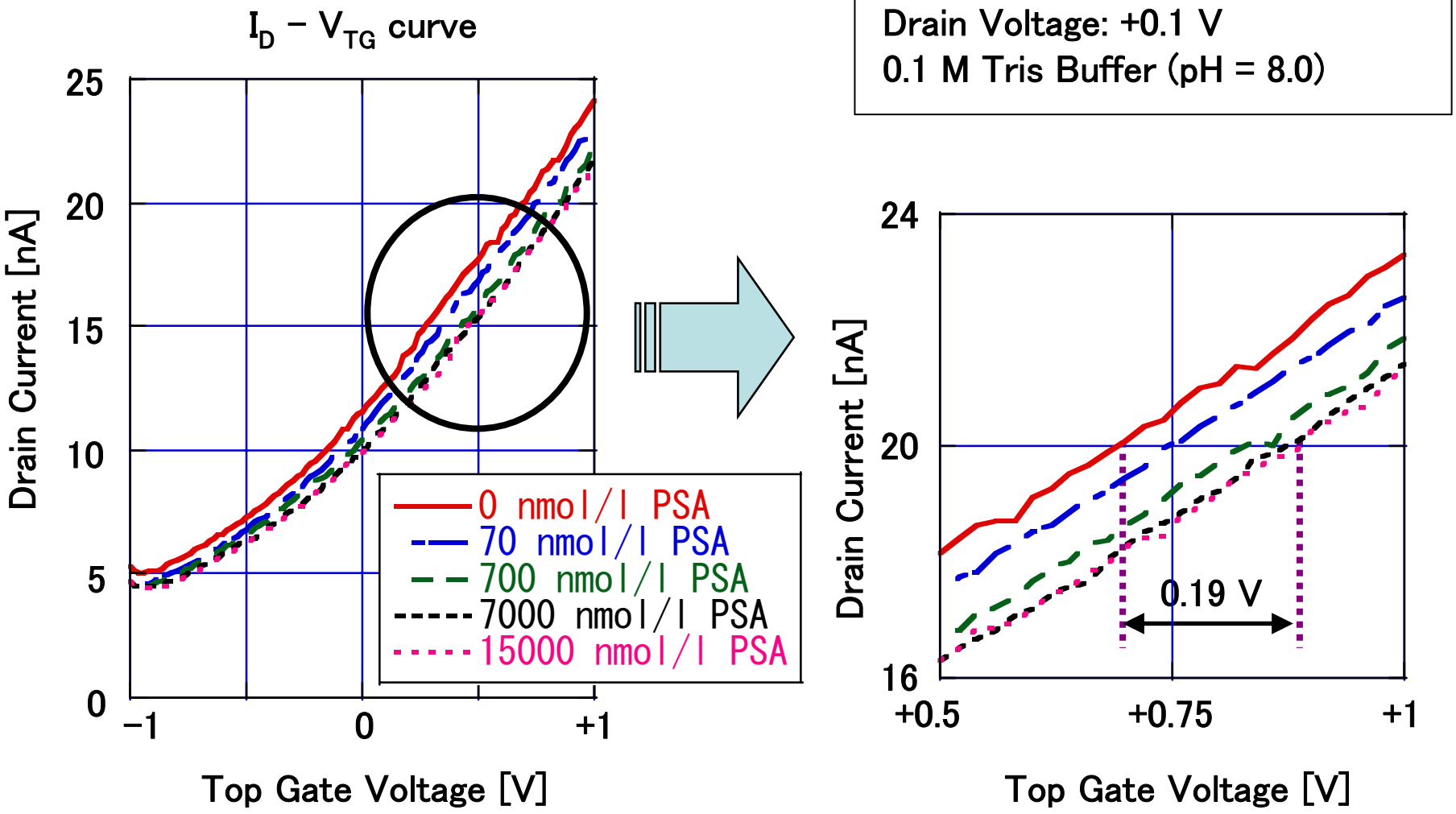
- Silicone rubber wall surrounded top-gate.

- Test solutions added into pool on top-gate, PSA was trapped by a-PSA on top-gate.

- FET characterizations were measured, and PSA concentration represented a decrease in drain current.



Biosensing

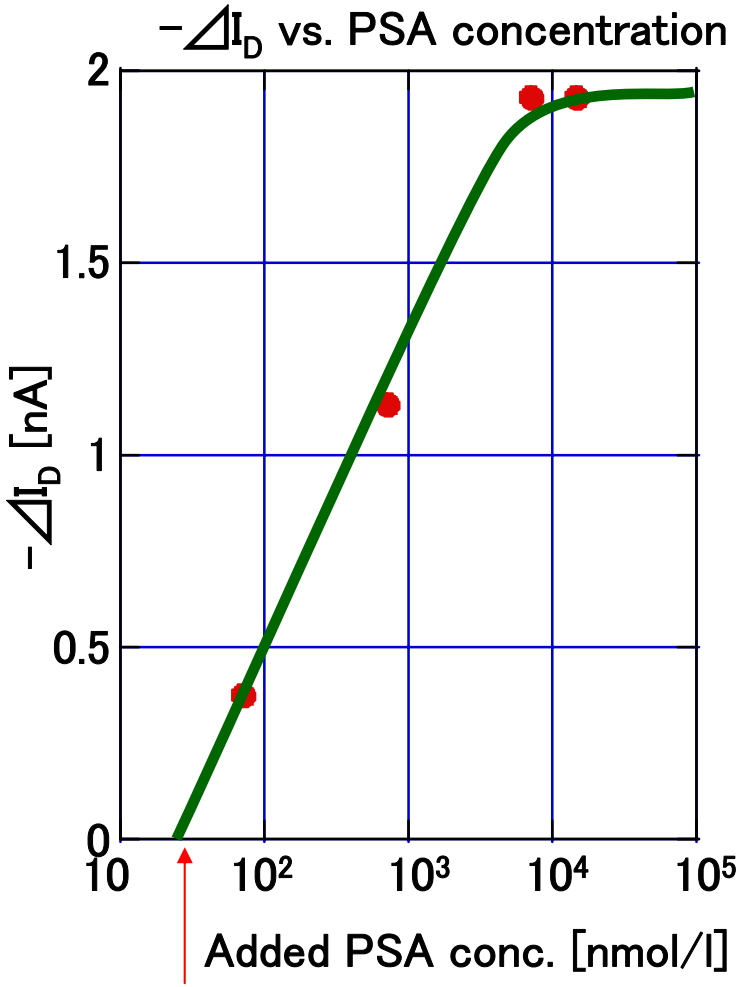

$I_D - V_{TG}$ curve
Drain Current [nA]
25
20
15
10
5
0
−1
0
+1
Top Gate Voltage [V]
0 nmol/l PSA
70 nmol/l PSA
700 nmol/l PSA
7000 nmol/l PSA
15000 nmol/l PSA
Back Gate Voltage: +5 V
Drain Voltage: +0.1 V
0.1 M Tris Buffer (pH = 8.0)
Drain Current [nA]
24
20
16
+0.5
+0.75
+1
0.19 V
Top Gate Voltage [V]

Relationship between drain current change and PSA concentration

Drain Voltage: +0.1 V	Back Gate Voltage: +5 V
Top Gate Voltage: +1 V	0.1 M Tris Buffer (pH = 8.0)

It is the highest sensitivity of the kinds type CNT biosensor.

Sensitivity is possibility to improve with amount of added PSA or top-gate electrode area.

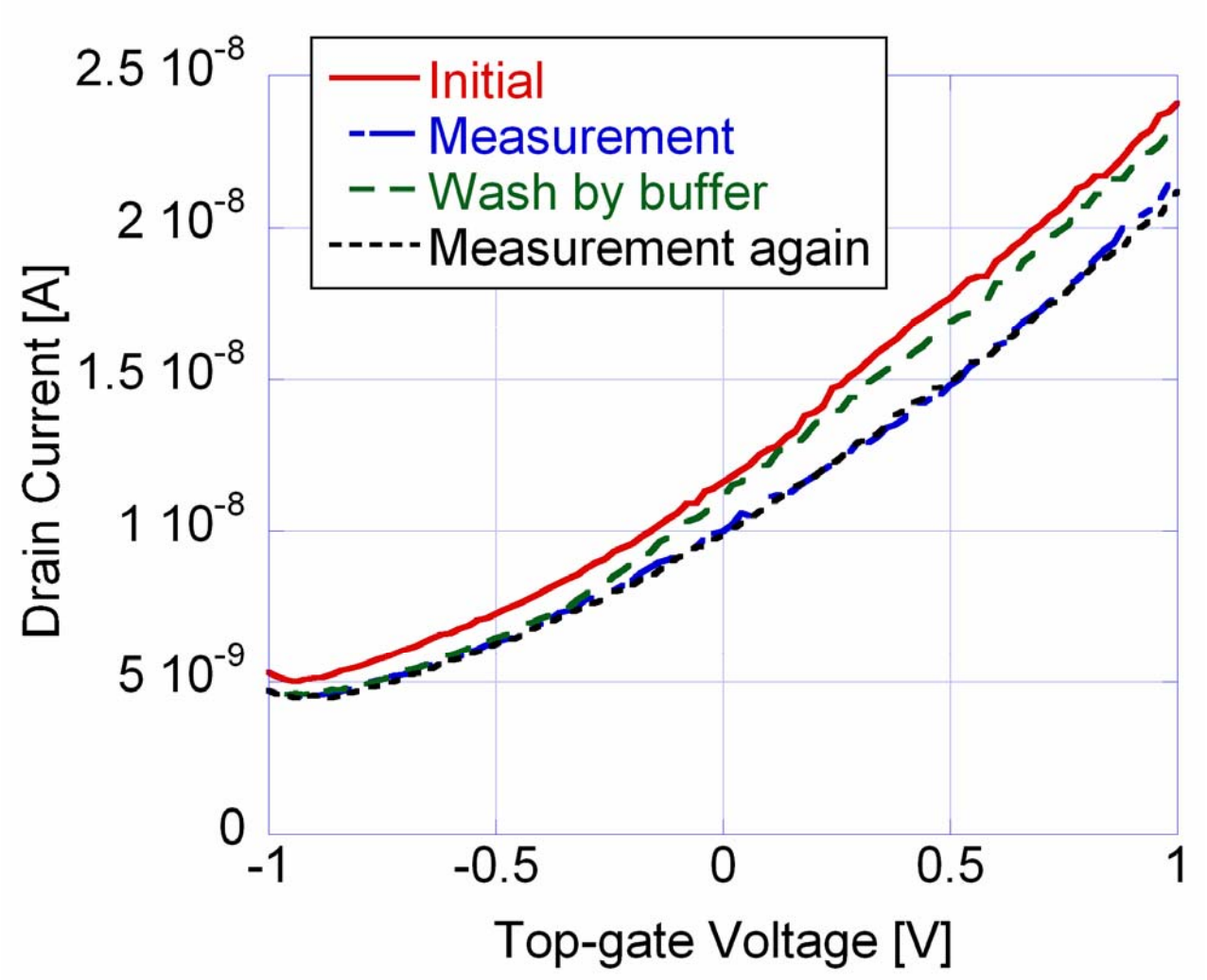


sensitivity limit: 20 nmol/l

Our CNT biosensor obtained high sensitivity

- at least 20 nmol/L of sensitivity limit
- In the case of top-gate area 10000mm^2 and 10 micro L of test solution added.
- Sensitivity limit is changed by above situations.

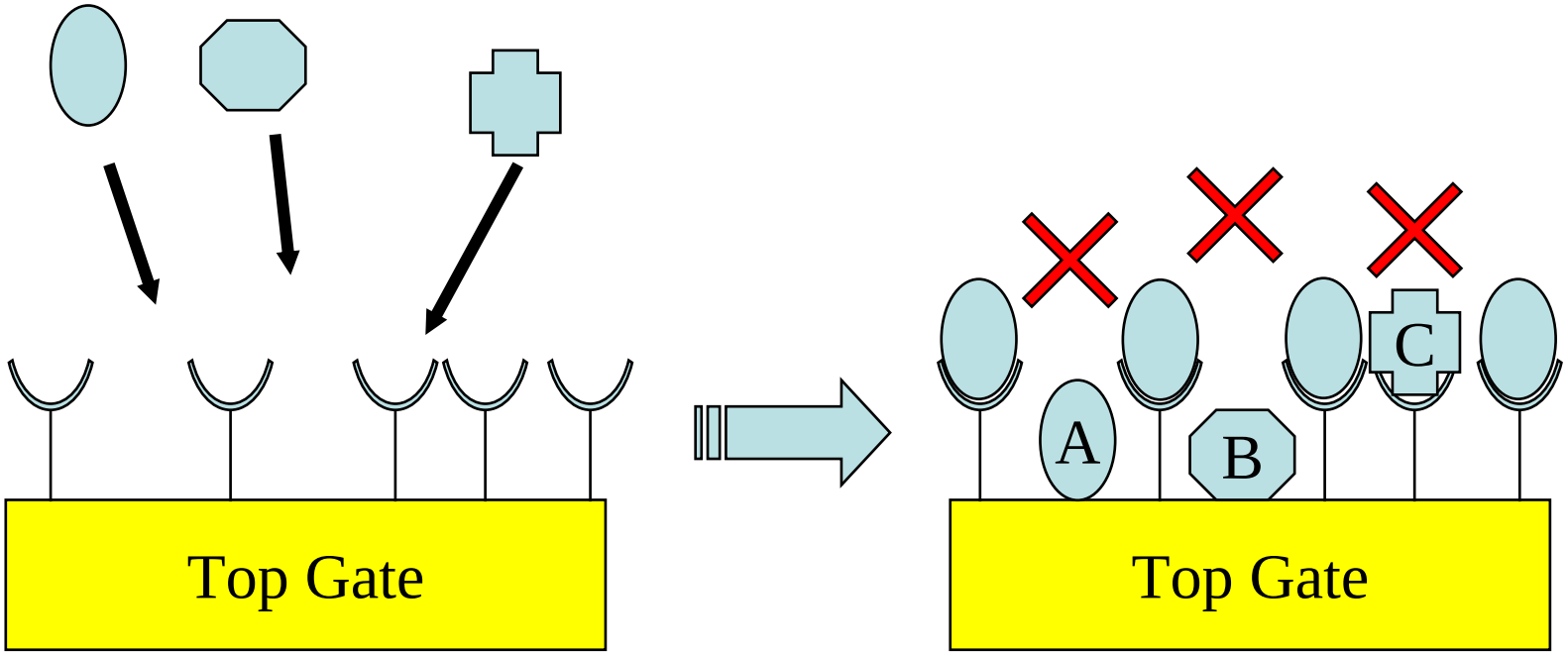
Our device can be used consecutively after washing process



Selective protein sensing for CNT biosensor

First reported study of selective protein sensing

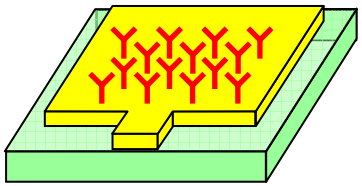
CNT-FET Biosensor Problems
Do we really observe antigen-antibody reaction?



If protein selectivity is not confirmed, we cannot be sure of sensing by non-specific adsorption

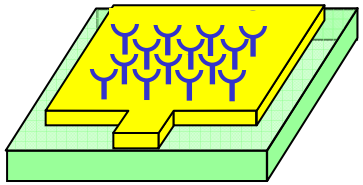
Selective protein detection

Biosensors



a-PSA

CNT-FET immobilized a-PSA
(PSA biosensor)



a-MIgG

CNT-FET immobilized a-MIgG
(MIgG biosensor)
（MIgG：Mouse immunoglobulin G）

Selective detection of protein

- Test solution (shown below) was poured on top-gate of PSA biosensor or MIgG biosensor.

- FET drain current measured, and PSA or MIgG concentration represented a decrease in drain current. .

Test solutions:

Tris buffer without antigens
Tris buffer containing PSA
Tris buffer containing MIgG
Tris buffer containing both PSA and MIgG

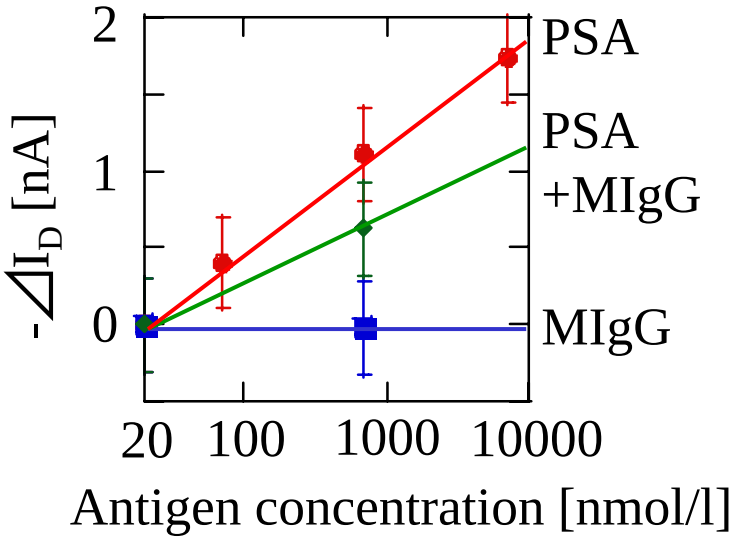
Drain current decrease at PSA biosensor

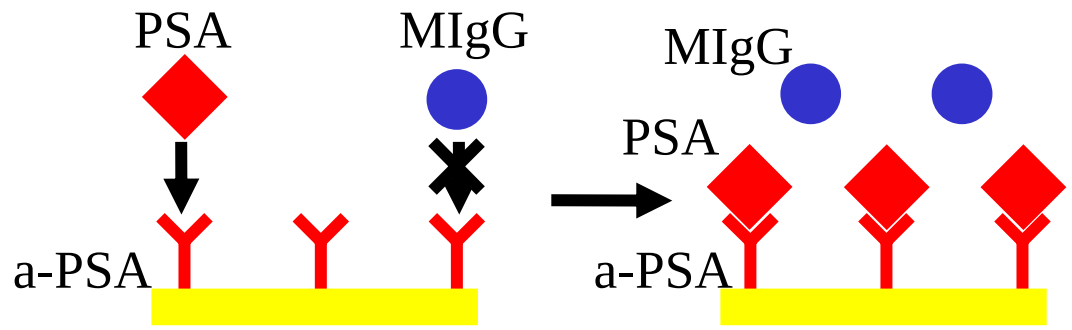
Drain Voltage: +0.1 V	Top Gate Voltage: +1 V
Back Gate Voltage: +5 V	Solution : 0.1 M Tris Buffer (pH = 8.0)

Table. Drain current of PSA biosensor which antigen solution was poured.

PSA [nmol/l]	MIgG [nmol/l]	Drain current [nA]
0	0	23.84
0	700	23.85
70	0	23.47
700	0	22.72
700	700	22.97
7000	0	21.92

$-\Delta I_D$ - PSA concentration curve





At PSA biosensor
Only PSA detected
MIgG was not detected

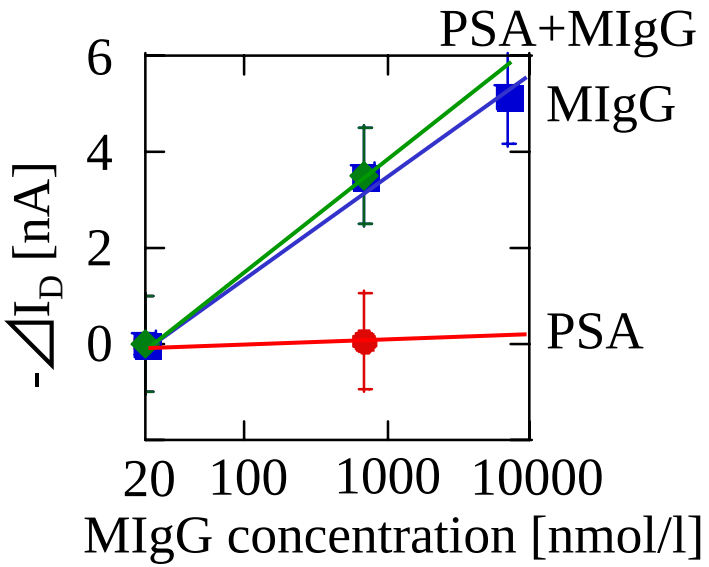
Drain current decrease at MIgG biosensor

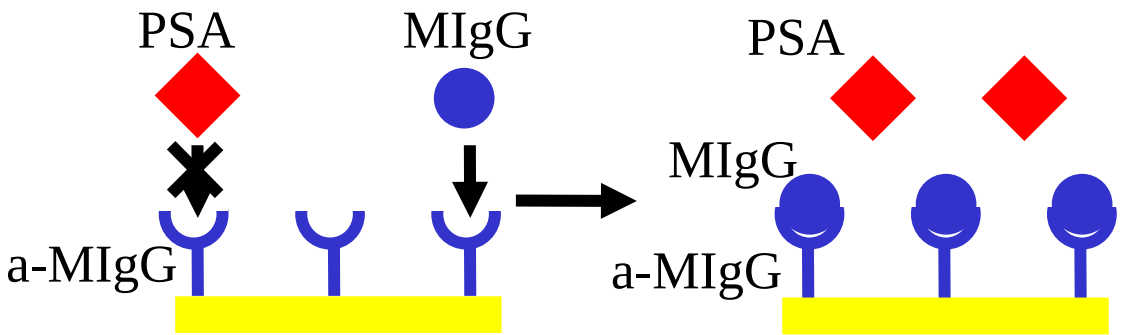
Drain Voltage: +0.1 V	Top Gate Voltage: +1 V
Back Gate Voltage: +5 V	Solution : 0.1 M Tris Buffer(pH = 8.0)

Table. Drain current of PSA biosensor which antigen solution was poured.

PSA [nmol/l]	MIgG [nmol/l]	Drain current [nA]
0	0	106.59
0	700	103.08
0	7000	101.43
700	0	106.54
700	700	103.10

$-\Delta I_D$ - MIgG concentration curve





At MIgG biosensor
Only MIgG was detected
PSA was not detected.

Conclusion

- We successfully achieved real-time sensing and selective detection of proteins using top-gate CNT-FET.

- Our CNT biosensor demonstrated high sensitivity, high stability, and selectivity.

- CNT biosensors have potential uses as industrial product.