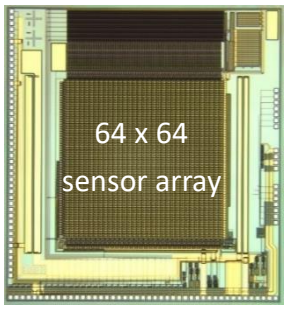
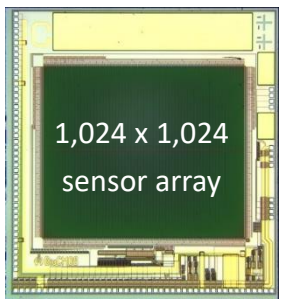
# BioCMOS

## *revolution of analytical instrument and biomedical sensing*

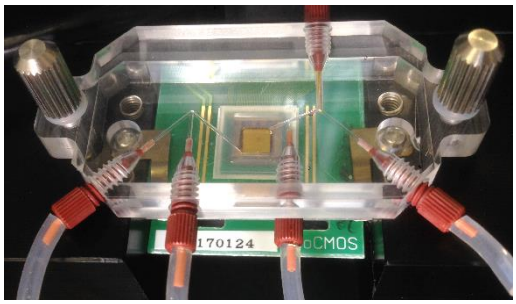
***BioCMOS chip***

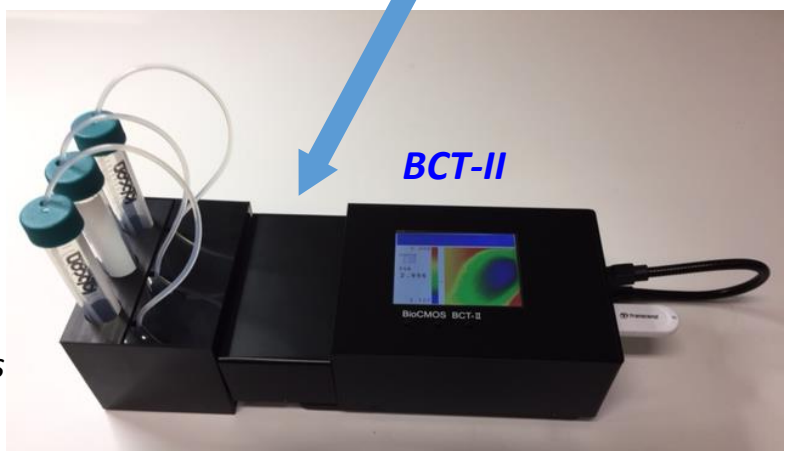



7mm


30mm




*potentiometric*
*amperometric*
*impedimetric*
*photometric*

*4,096 sensors or 1,048,576 sensors on a chip*


general-purpose equipment to test in laboratory

handy equipment specialized for specific application

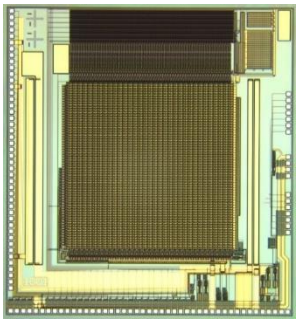
***IoT***
***Big data***

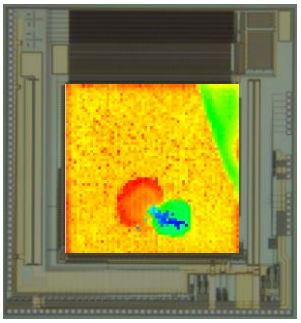
***internet***

**BioCMOS** : biomedical CMOS LSI circuit

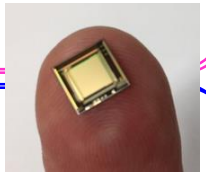
CMOS is an abbreviation for complementary metal-oxide-semiconductor. CMOS is not only image-sensor where “CMOS” is emphasized in order to distinguish it from CCD image-sensor. Present LSI (Large Scale Integrated) circuits are constructed by CMOS, including processor, memory, transmitter, receiver, controller, and (now) *biomedical sensor*.

# Applications

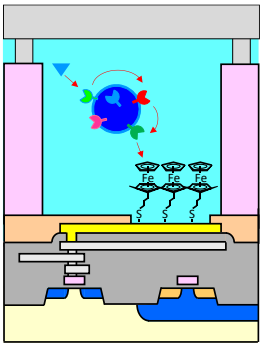


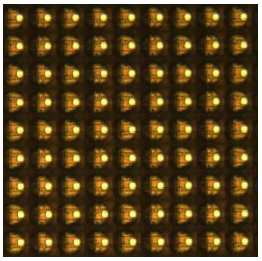


*Real-time 2-dimensional image of chemical reaction*

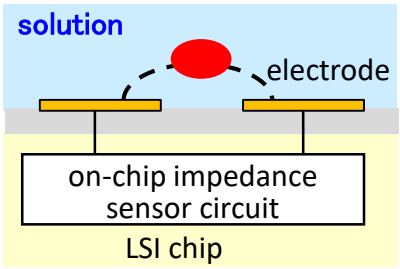


*Parallel detection of different kinds of biomolecules*

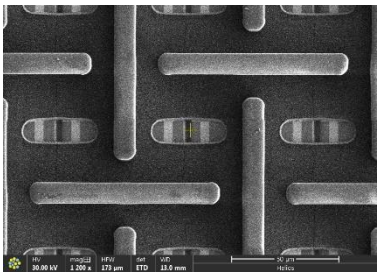


***Detection of single biomolecule***




60μm



**medical database**

network

**hospital**

network

**Home Healthcare & Telemedicine**

**Tailor-made Medicine**

**traceability**

network

**Food Security**

***Portable Diagnostic Inspection System***

**Drug discovery**

network

**police station**

**Block of Infectious Disease at immigration**

network

**infection route**

**Evidence-based Care**

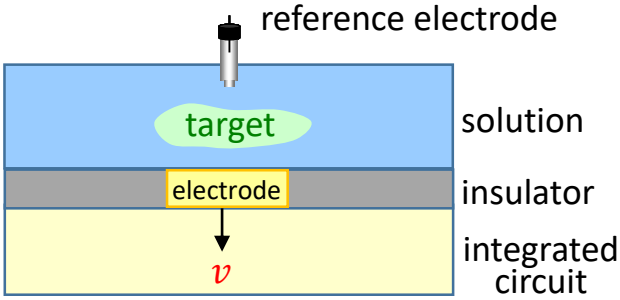
network

**customer database**

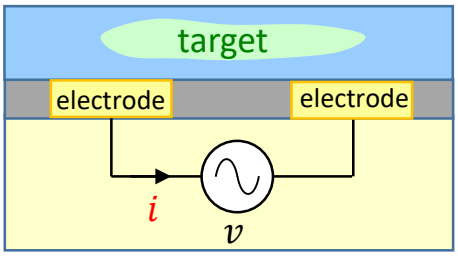
# *stamp-size analytical instrument*


4,096 sensors
on a chip

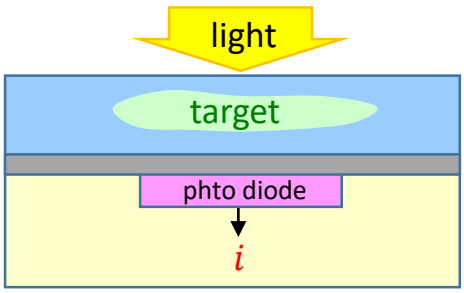
potentiometric sensor



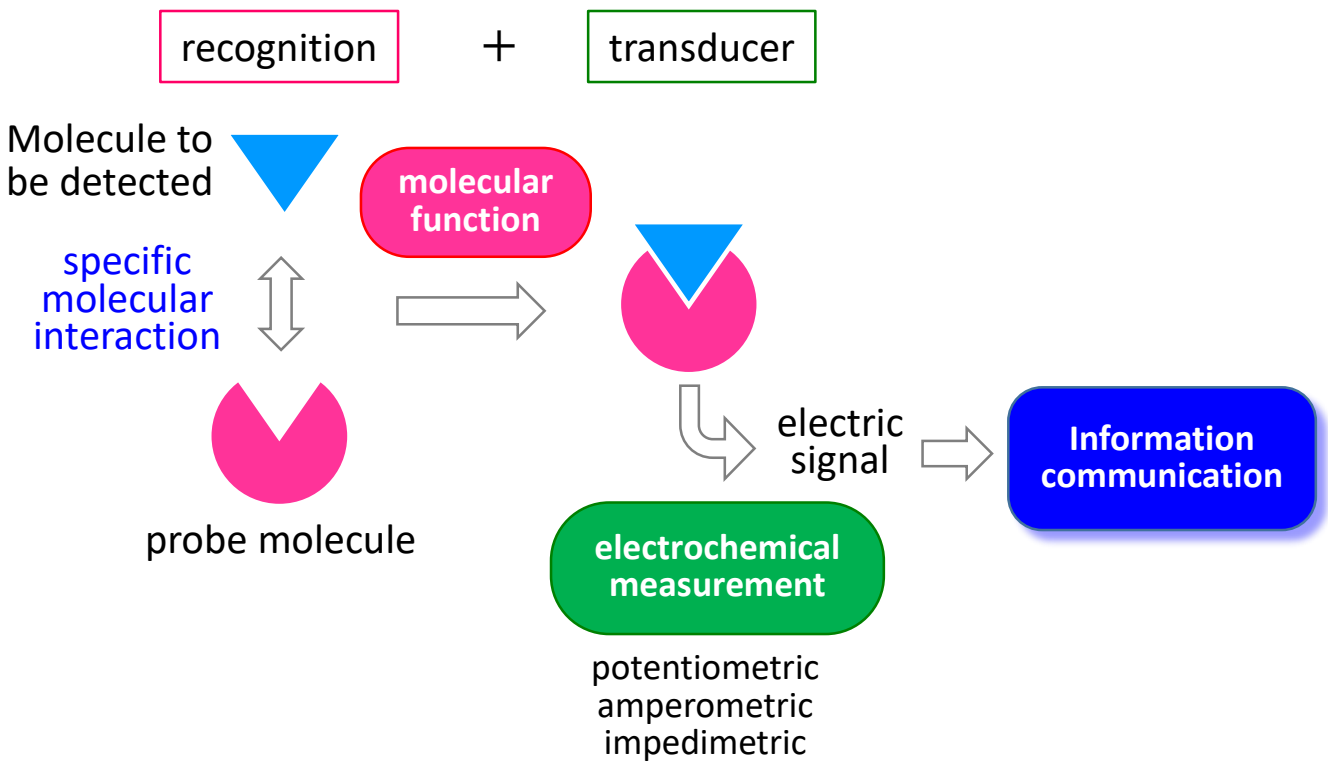

amperometric impedimetric sensor




photometric sensor

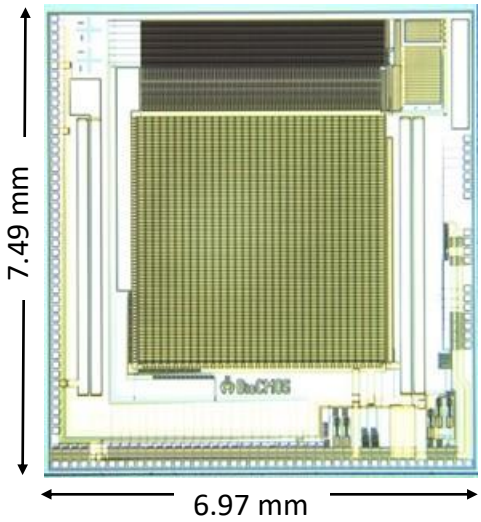



# *electrochemical biosensor*

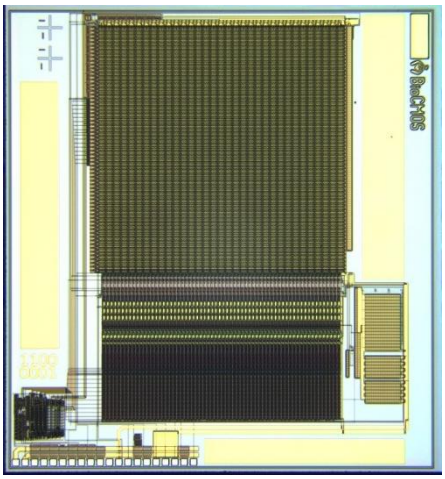


# *BioCMOS chips*

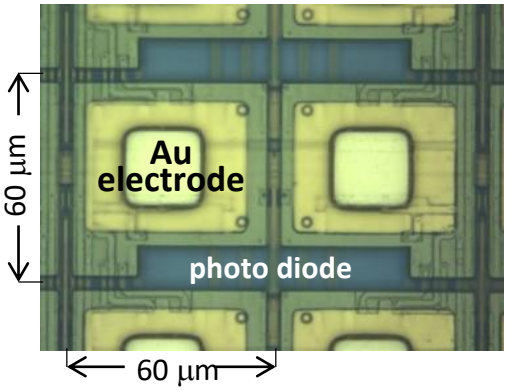
64x64 photo-image
64x64 potential-image

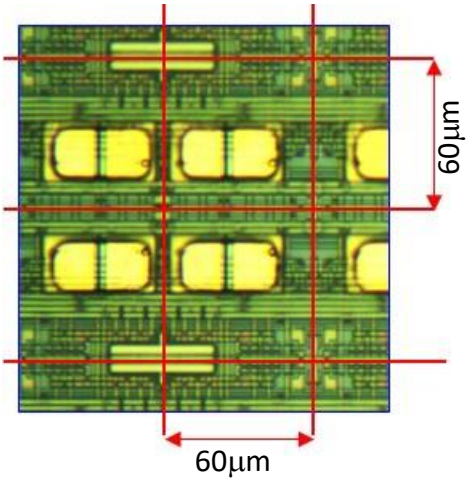



64x64 impedance-image

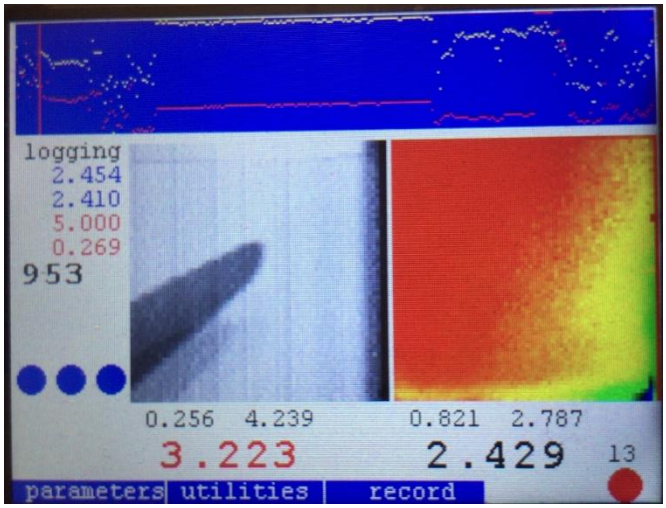


20 pads (SPI IO)



# simultaneous detection of photo and potential images

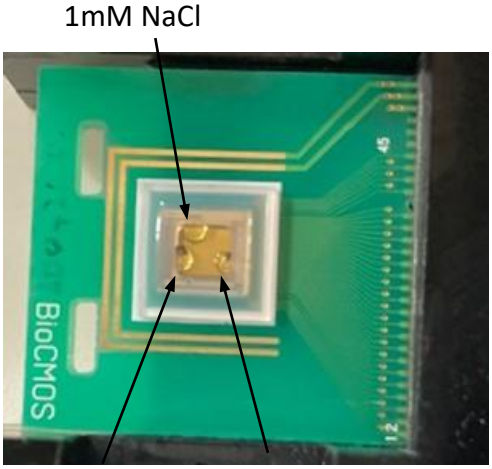


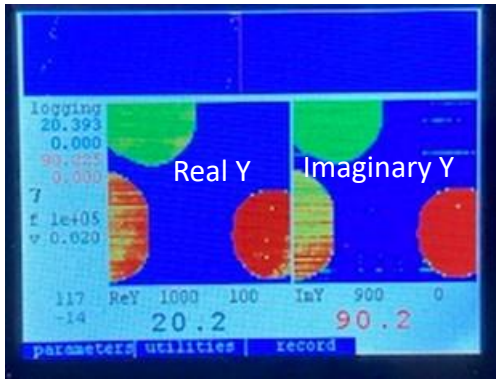

real time
3fps

■ **photometric**
lensless

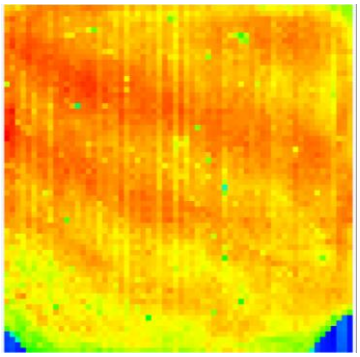
■ **potentiometric**
0.01pH accuracy

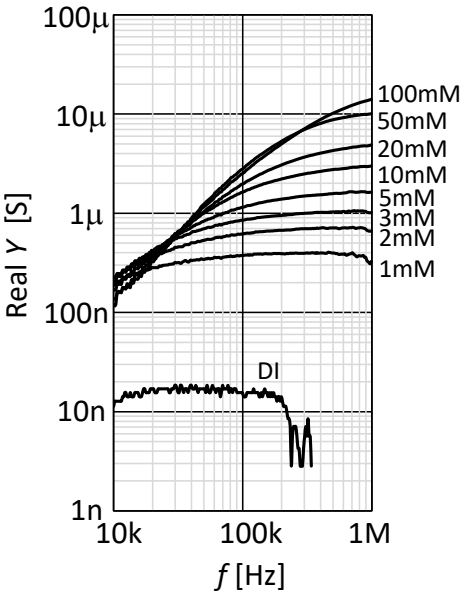
# on-chip impedance detection

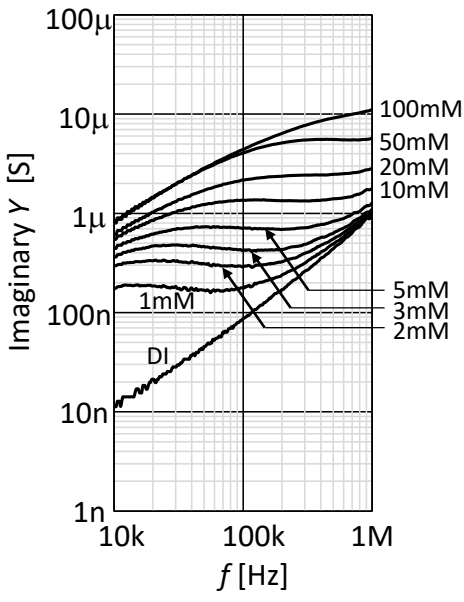


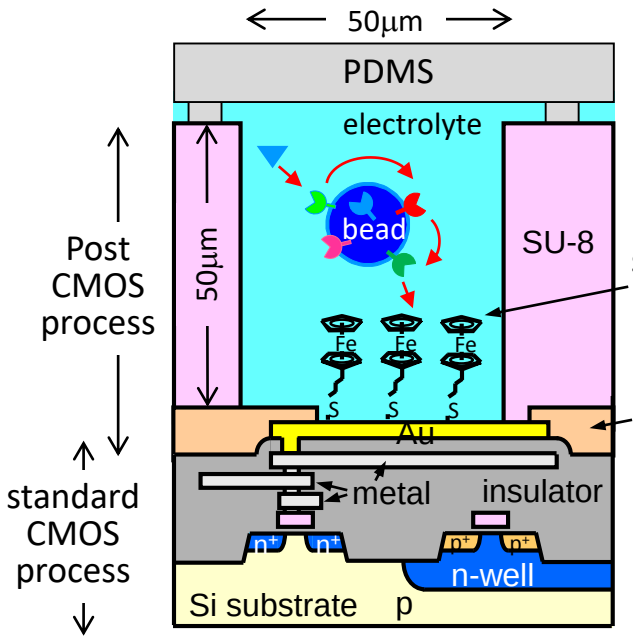

■ **impedimetric**



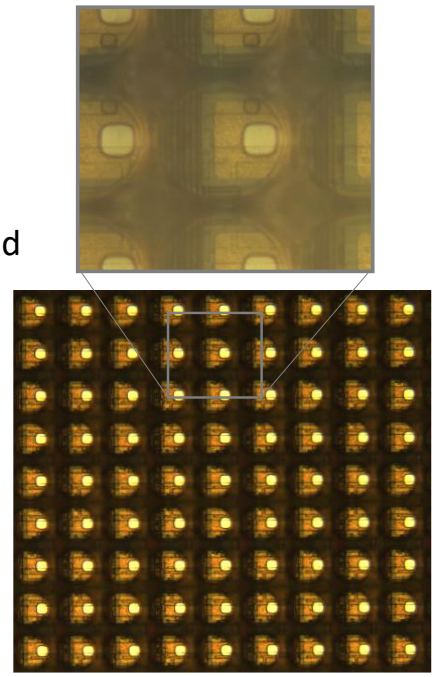


# *enzyme sensor with redox mediator*




schematic cross-section

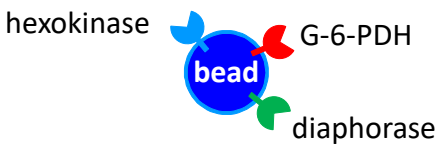


plan view (photomicrograph) of sensor array

▼ target (to be identified)

ψ probe (enzyme, antibody, primer, …)

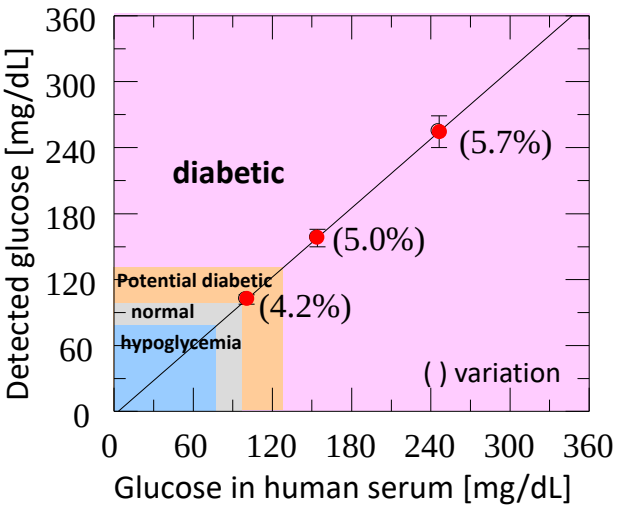
## *Glucose sensor*

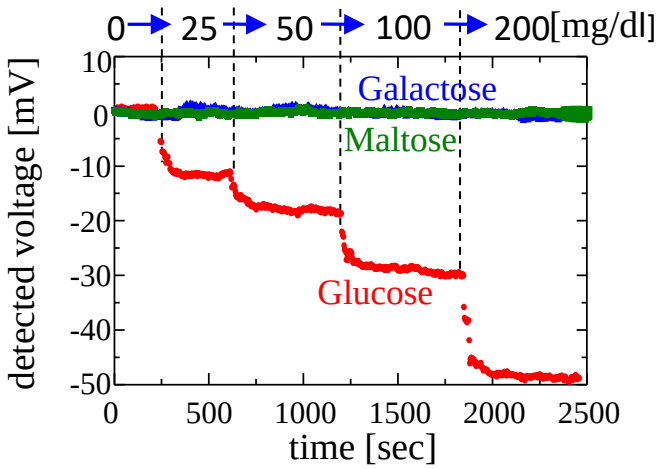



$$\text{Glucose} + \text{ATP} \xrightarrow{\text{hexokinase}} \text{G6P} + \text{ADP}$$

$$\text{G6P} + \text{NAD} \xrightarrow{\text{G-6-PDH}} \text{G6P} + \text{NADH}$$

$$\text{NADH} + 2[\text{Fe(CN)}_6]^{3-} \xrightarrow{\text{diaphorase}} \text{NAD} + 2[\text{Fe(CN)}_6]^{4-}$$





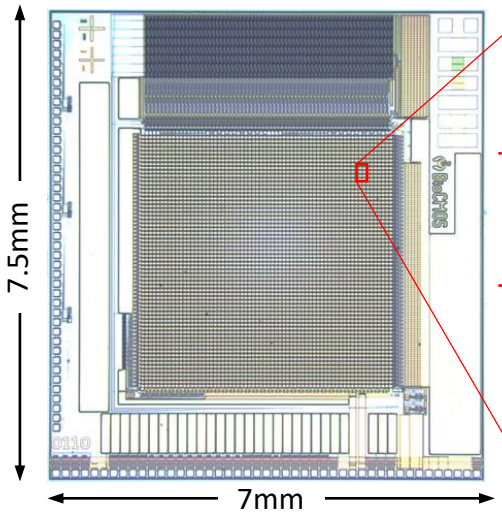
H. Anan, M. Kamahori, Y. Ishige, and K. Nakazato, *Sensors and Actuators B: Chemical* **187**, p. 254, 2013

H. Komori, K. Niitsu, J. Tanaka, Y. Ishige, M. Kamahori, and K. Nakazato, in *Proc. IEEE BioCAS* 2014, p. 464

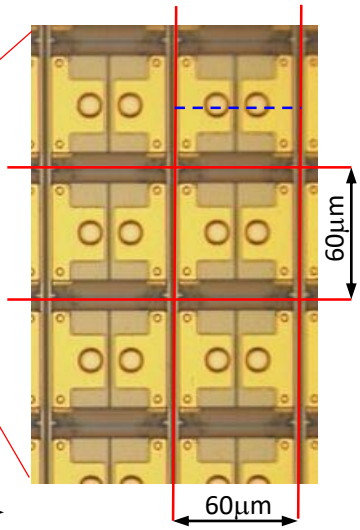

Many kinds of biomolecules can be detected by enzyme sensor with redox mediator, Cholesterol (T. Ishige et al, *Biosensors Bioelectron.* **24**, p.1096, 2009) , Uric Acid (W. Guan et al., *Biosensors Bioelectron.* **51**, p.225, 2014), DNA (H. Ishihara et al, *Jpn. J. Appl. Phys.* **54**, 04DL05, 2015) , ...

# *Detection of single pathogenic microorganism (virus, bacterium, parasite)*

## *Measurement of small impedance in pico-liter solution*

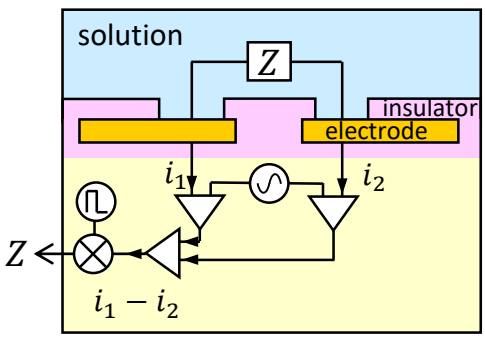



Optical microphotograph of chip




Sensor array part

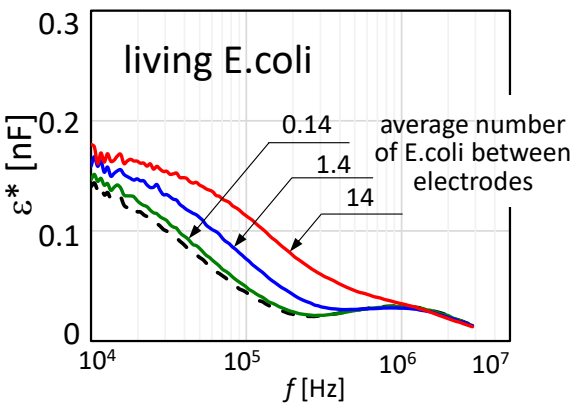
64x64 sensor array
frequency: DC, 100Hz-1MHz
supply voltage to sample : *Vp-p* 10mV – 2V
detection current: 1nA – 1μA




$Z$ : complex impedance

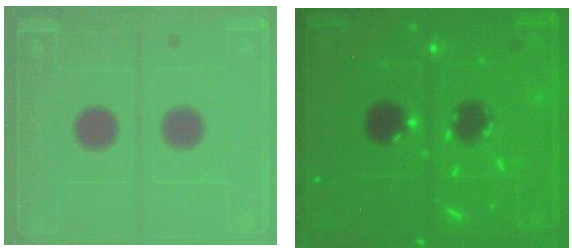
## detection of E.coli

without any reagent

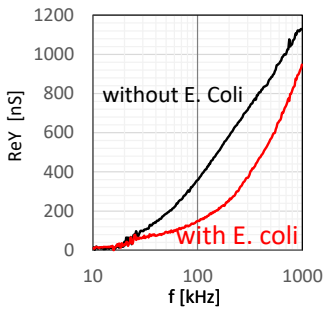


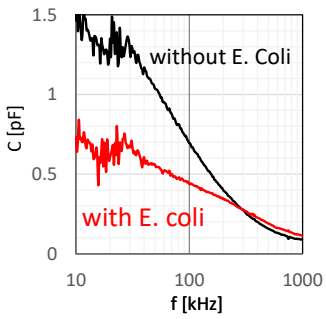

without *Escherichia coli*

*with Escherichia coli* O157:H7 ATCC 43888

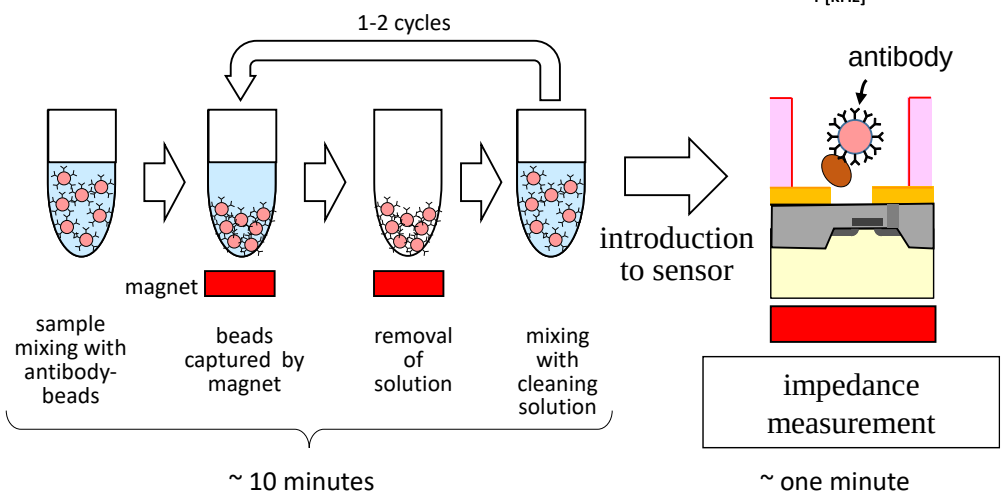



in saline



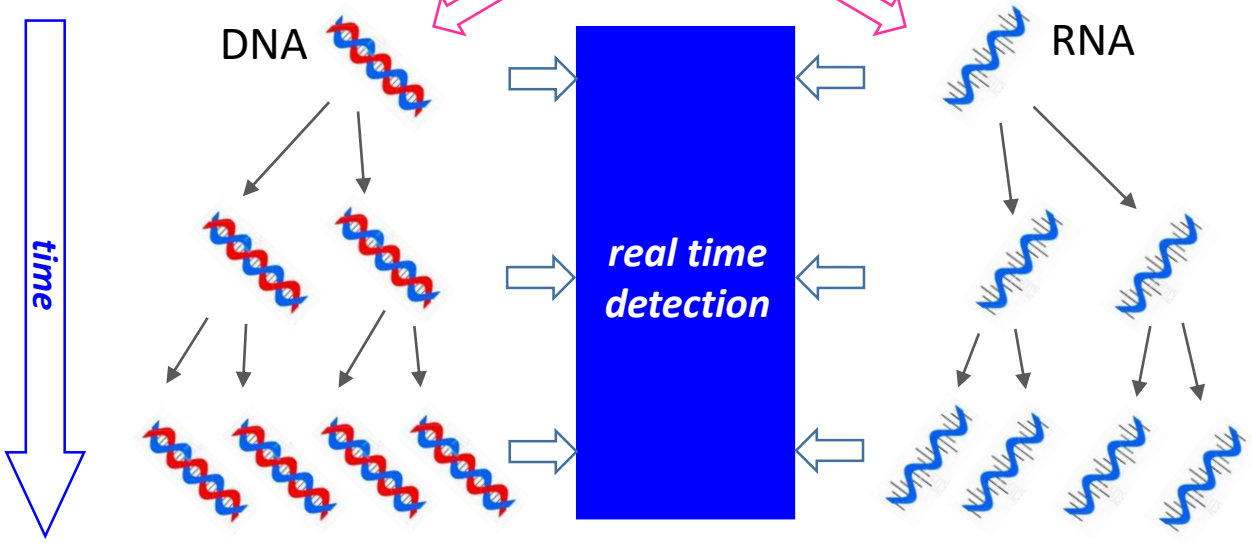

## detection of specific pathogenic microorganism



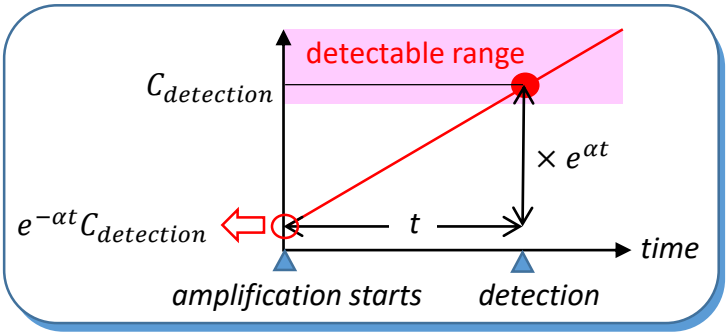
# gene-based diagnostic

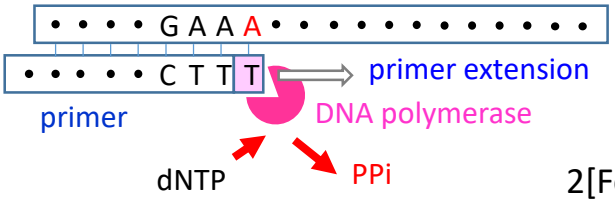

**Real-time LAMP (Loop-Mediated Isothermal Amplification)**

**Real-time NASBA (Nucleic Acid Sequence Based Amplification)**




*The number of specific DNA or RNA is isothermally amplified to a million times in half hour*



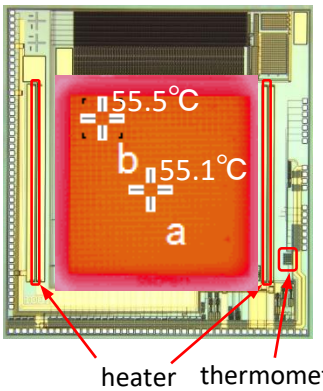



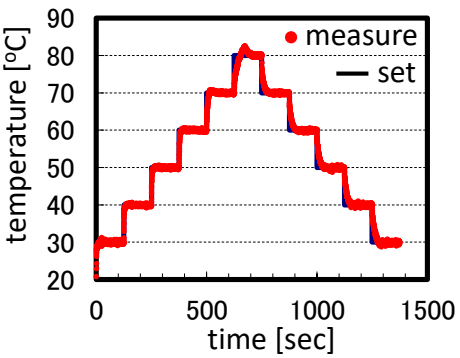

$$PPi + H_2O \xrightarrow{PPase} 2Pi$$

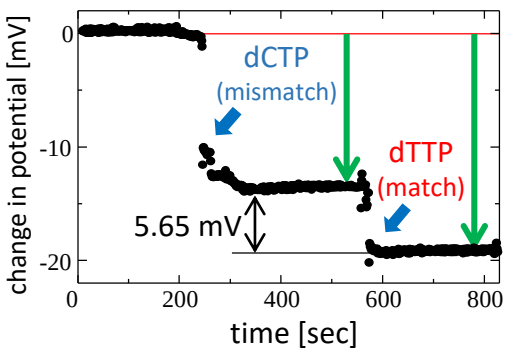
$$Pi + GAP + NAD \xleftrightarrow{GAPDH} 1,3BPG + NADH$$

$$2[Fe(CN)_6]^{3-} + NADH \xleftrightarrow{diaphorase} 2[Fe(CN)_6]^{4-} + NAD$$

*on-chip thermal control*

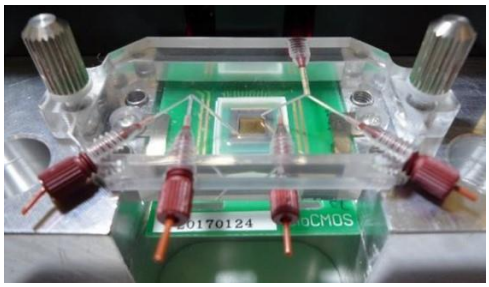


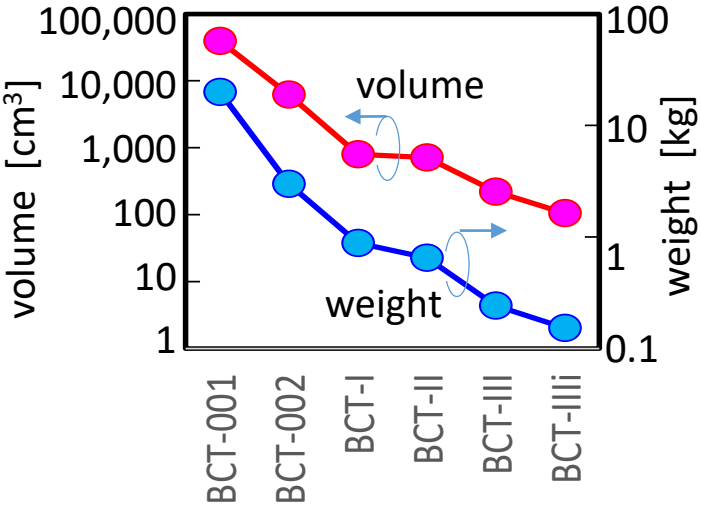



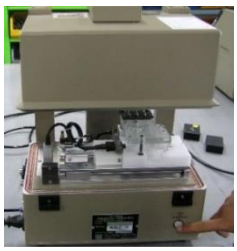

H. Ishihara, K. Niitsu, and K. Nakazato, *Jpn. J. Appl. Phys.* **54**, 04DL05, 2015

# Device






**2014**



BCT-001
250x350x450 mm³
20 kg


BCT-002
150x320x130
3 kg

**2015**
establishment
of BioCMOS

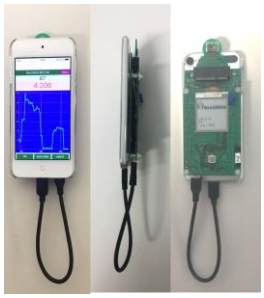
BCT-I
85x170x55
882 g

**2017**

BCT-II
130x100x55
650 g

**2019**

BCT-III
71x135x23
243 g
(including battery)



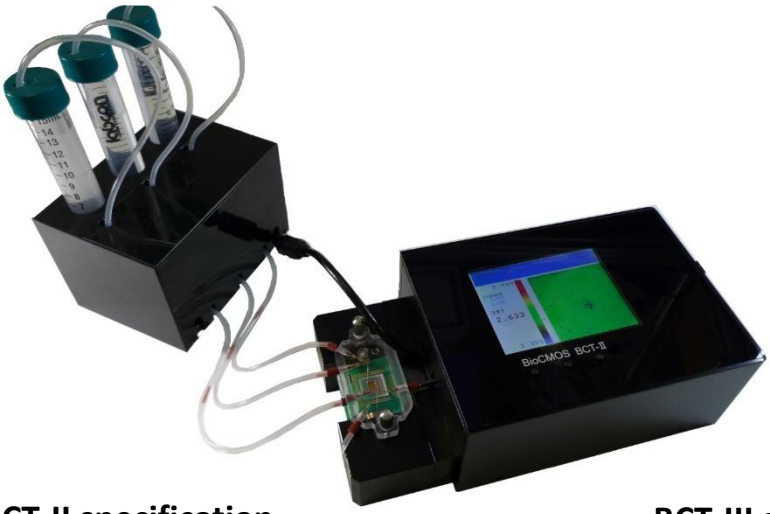
BCT-IIIi
57 x 123 x 15
153 g
(including smartphone)

# BCT-II & BCT-III

BCT-II and BCT-III support the various types of biological sensor system as a hand-held and stand-alone analyzer. BioCMOS chip includes potentiometric, amperometric, impedimetric and photometric sensors; more than 4,000 sensors on a chip with a size of less than 1 square cm.

BCT-II is a general-purpose equipment, not specialized for specific application. It is rather development kit to test in laboratory.

BCT-III is a handy and user friendly equipment. It can realize specific applications such as glucose sensor, DNA sequencer, bacteria or viruses counting, ion chromatography, and so on.




**BCT-II specification**

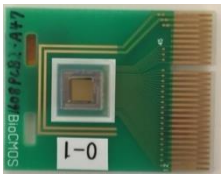
| | |
|---|---|
| **Sensor type** | redox potential, PH, C$^4$D, optical image |
| **Power** | DC 5V (USB port, Type mini-B) |
| **Data storage** | USB storage (USB port, Type A) |
| **Dimensions (mm)** | W130 x D100 x H55 |
| **Weight (g)** | 650 |

**BCT-III specification**

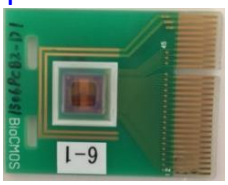
| | |
|---|---|
| **Sensor type** | redox potential, impedance, optical image |
| **Power** | internal battery |
| **Data storage** | internal & WiFi connection |
| **Dimensions (mm)** | W71 x D135 x H23 |
| **Weight (g)** | 243 |

By inserting the BioCMOS chip, sensing mode is automatically selected.

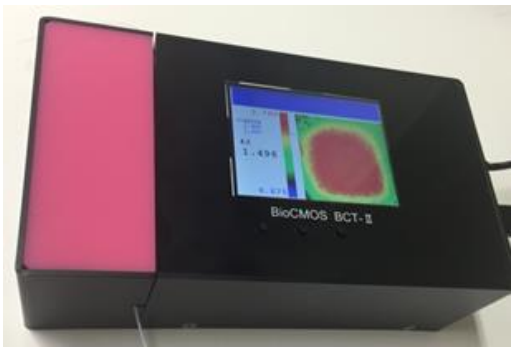
Photo & Potentiometric sensor

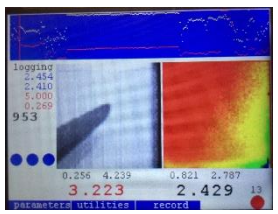


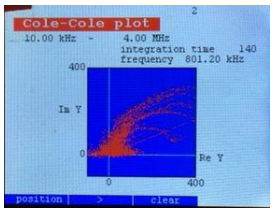

Impedimetric sensor

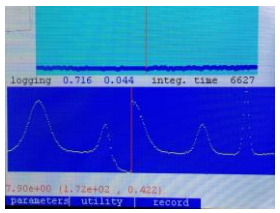



Photometric sensor

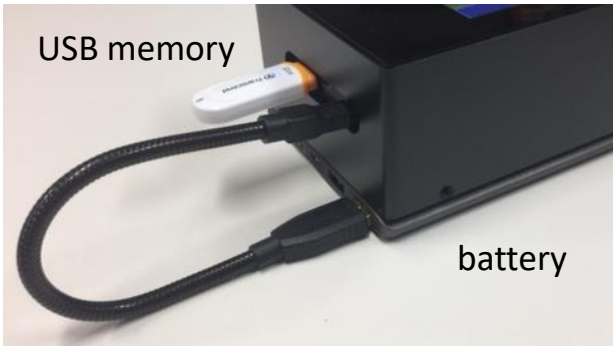



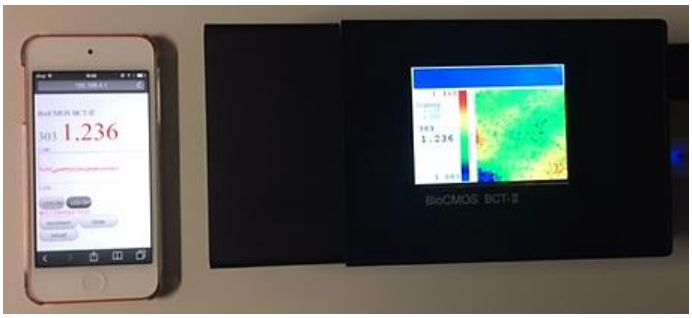
## *stand alone*



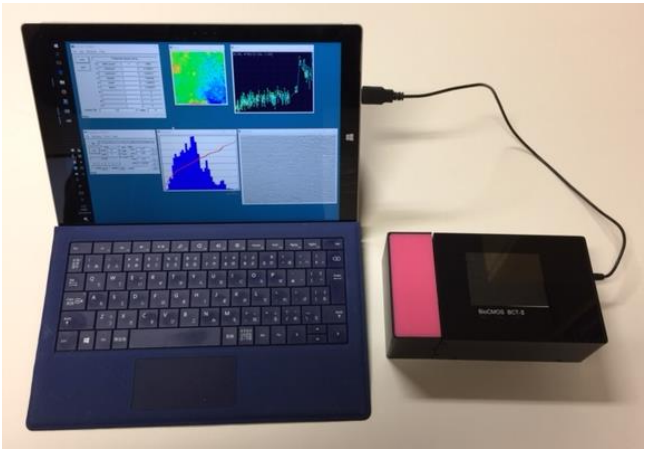

## *from smartphone*

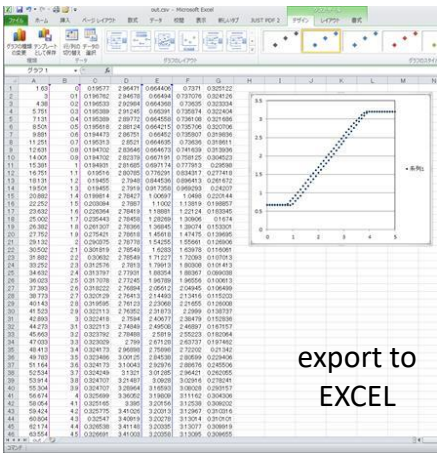
**BCT-III**


**BCT-II**




## *from PC*



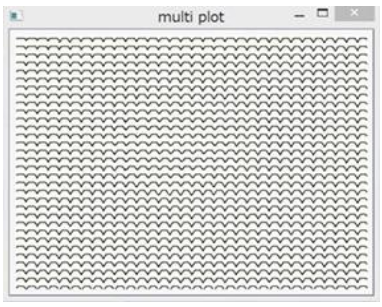


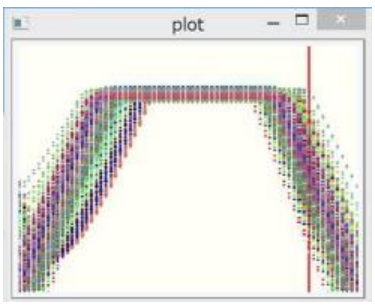
export to EXCEL

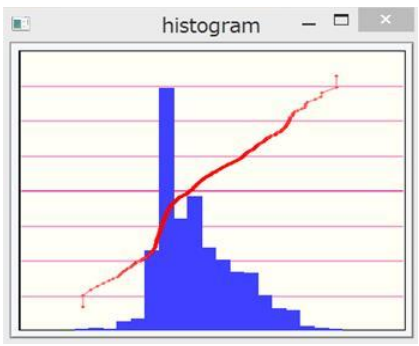
```
{#$$ "Potential array Vref dependence"}
{#$0 "Vref" "0"}
{#$1 "median" ""}
{#$2 "Vref,min"  "0"}
{#$3 "Vref,max"   "5"}
{#$4 "Vref,step"  "0.1"}
{#$5 "SW"  "0"}
{#$6 "array size" "64"}
{#$7 "x" "-1"}
{#$8 "y" "-1"}
{#$9 "step" "1"}

#include ./sub/TR6142.sub

procedure measure;
begin
  call TR6142_putV:r0;
  wait:0.1;
  read:MCU;
  write:MCU;
  r1=data:median;
  plot:r0:r1;
  writeln:r0:(data:min):(data:max):
    (data:median):(data:mean):(data:stddev);
end;

procedure ref_sweep_forward;
begin
  while r0 < r3 do
  begin
    call measure;
    r0 = r0 + r4;
  end;
end;
```

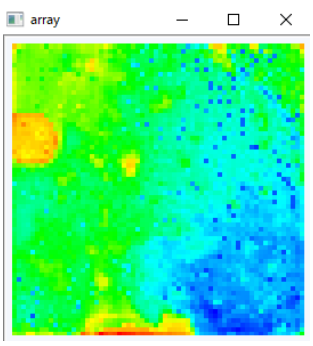
```
#define TR6142 26

procedure TR6142_init;
begin
  send:TR6142:"HV5";
end;

procedure TR6142_putV:v;
begin
  send:TR6142:"D%6.3fE":v;
end;
```

Language designed specifically for programming measurement




data visualization

*The possibilities are infinite.*

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