電気通信大学 脳医工学研究センター セミナー，2021年1月19日

マイクロロボティクスの バイオ応用

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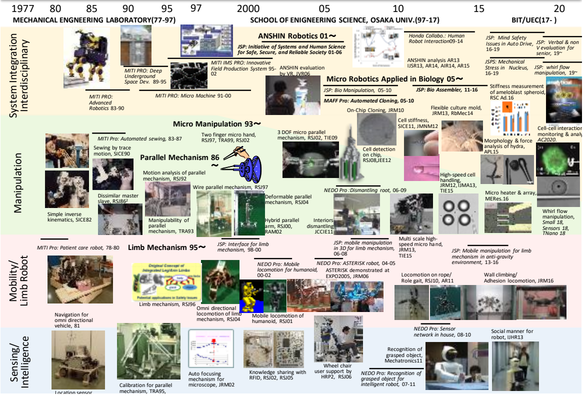
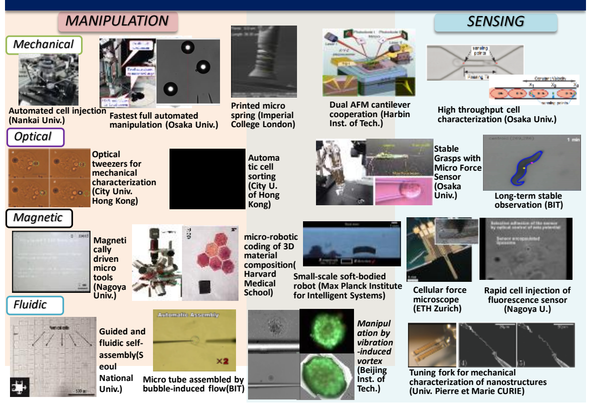
講演内容

- マイクロロボティクスとは
- これまでの成果
- 今後の展望

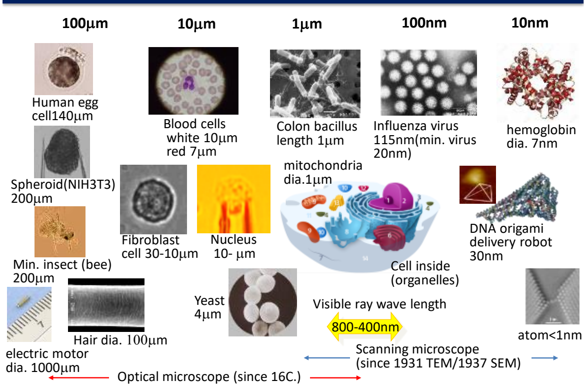
Background



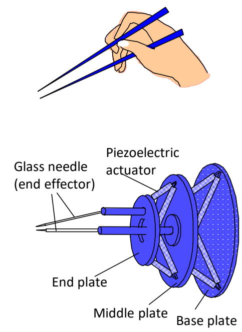
Micro Robotics: MANIPULATION & SENSING



Micro scale in biology



1st prototype with two stories of PM



TRA 99

System and applications

Two-fingered micro hand

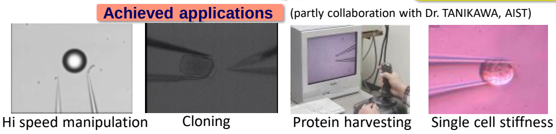
Sensing devices
- Optical microscope
- All in focus imaging
- AFM cantilever
- Fine force sensor

Other tools & devices
- User interfaces including Omni-Device joystick
- Micro drop dispenser & micro gluing
- 6DOF fine motion stage

Low level control
- Tele-operation
- Force control
- Auto focusing
- All in focusing
- 3D auto tracking
- Auto calibration
- Auto capturing

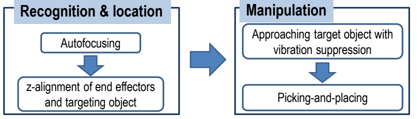
High level control
- Task understanding
- Skill application
- Task planning

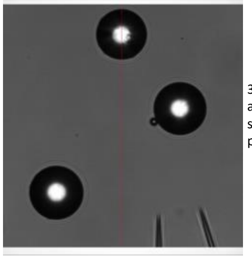
Achieved applications (partly collaboration with Dr. TANIKAWA, AIST)



Hi speed manipulation | Cloning | Protein harvesting | Single cell stiffness

Fast full automation



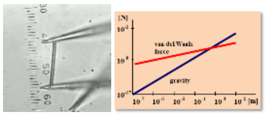


3 microbeads (50μm dia.) alignment at 1,800μm/s high speed. 2 microbead pick & place achieved in 1.2 sec.

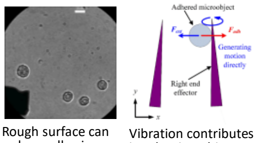
IJMA 13, TIE 15

Issues and challenges

1. Sticky problem



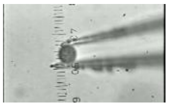
scale effect & dominant surface force



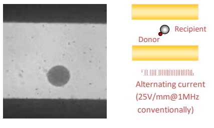
Rough surface can reduce adhesive force. *JMM'15*

Vibration contributes in releasing objects. *Robomech'17*

2. Limited rotational motion



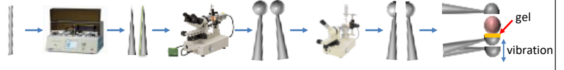
Rotation ranges less than +/-180 deg.



Dielectrophoresis can be applied in rotational manipulation. *JRM'09*

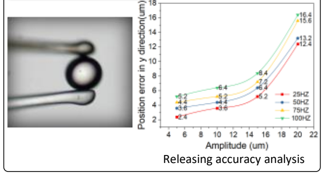
Robust grasping & releasing

Fabrication of gel-coated end-effector



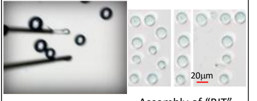
Glass tube → Micropipette puller → Two end parts → Micro forge → Spherical ends → Micro grinder → Polished flat → Gel-coating on vibration effector

Releasing results



Releasing accuracy analysis

Demonstration

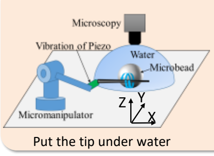


Drawing character 'T'

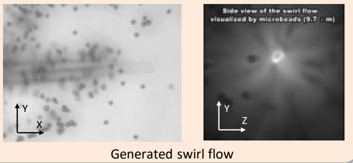
Assembly of "BIT" (Hela cell)

ICMA 2018 (Best paper finalist), MHS 2018

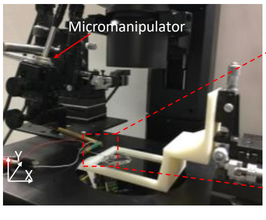
Bio-conscious non-contact manipulation

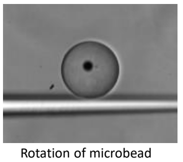


Put the tip under water



Generated swirl flow



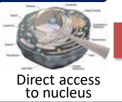


Rotation of microbead (continuous vibration)

TNano18, Sensors18, Small19

Automated Nucleus Injection

Motivation

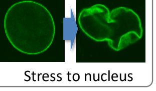


Direct access to nucleus

Expected applications

Drag delivery

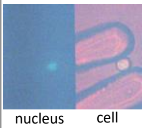
Gene manipulation



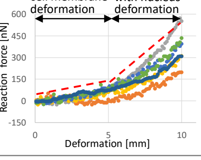
Stress to nucleus

Challenging

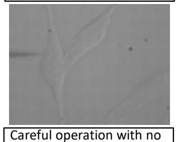
Nucleus is much harder than cell membrane.



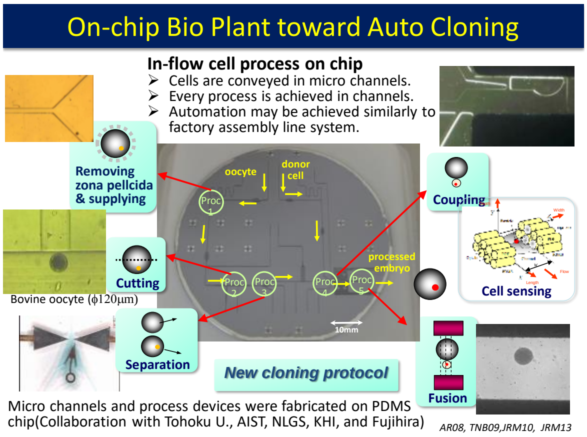
Simultaneous deformation image

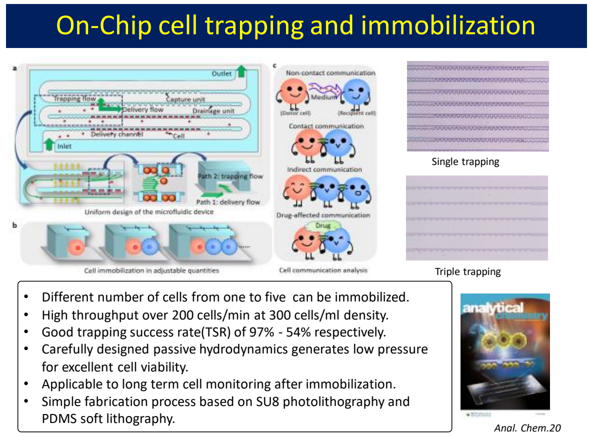


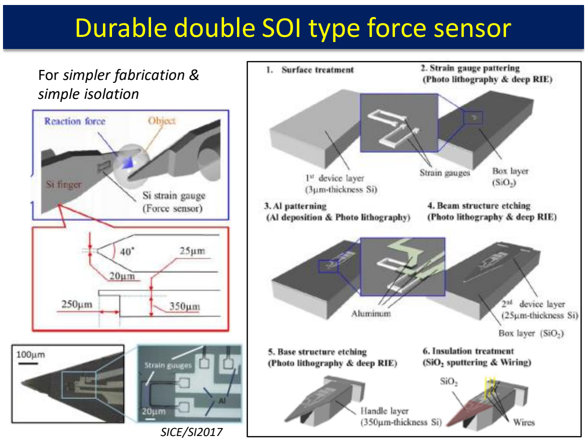
Access should be through cell membrane.

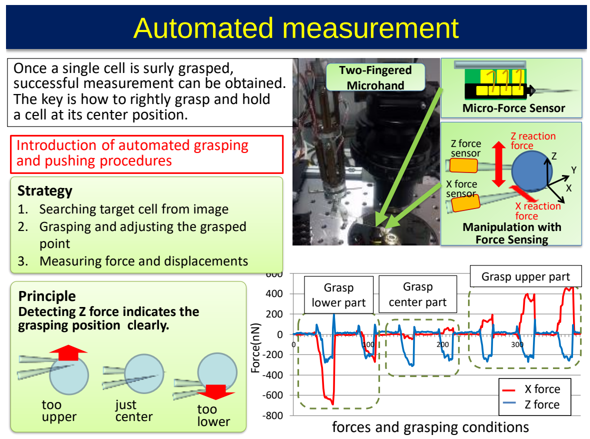


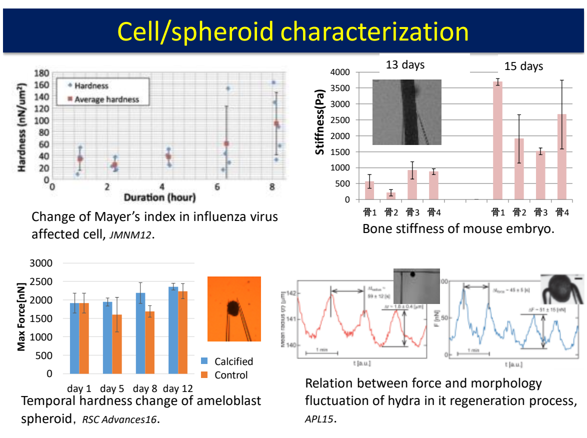
Careful operation with no damage, quick & precise insertion.

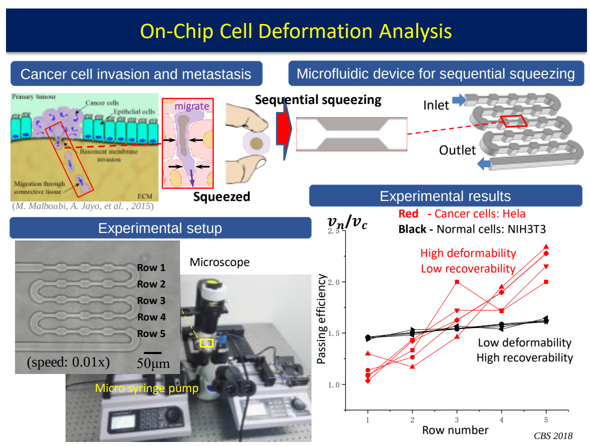

On-chip Bio Plant toward Auto Cloning
In-flow cell process on chip
Cells are conveyed in micro channels.
Every process is achieved in channels.
Automation may be achieved similarly to factory assembly line system.
Removing zona pellcida & supplying
oocyte
donor cell
Coupling
Cell sensing
Cutting
Bovine oocyte (ϕ120μm)
processed embryo
Separation
New cloning protocol
Fusion
10mm
Micro channels and process devices were fabricated on PDMS chip(Collaboration with Tohoku U., AIST, NLGS, KHI, and Fujihira)
AR08, TNB09,JRM10, JRM13


On-Chip cell trapping and immobilization
Single trapping
Triple trapping
Different number of cells from one to five can be immobilized.
High throughput over 200 cells/min at 300 cells/ml density.
Good trapping success rate(TSR) of 97% - 54% respectively.
Carefully designed passive hydrodynamics generates low pressure for excellent cell viability.
Applicable to long term cell monitoring after immobilization.
Simple fabrication process based on SU8 photolithography and PDMS soft lithography.
Anal. Chem.20


Durable double SOI type force sensor
For simpler fabrication & simple isolation
Reaction force
Object
Si finger
Si strain gauge (Force sensor)
1. Surface treatment
2. Strain gauge pattering (Photo lithography & deep RIE)
3. Al patterning (Al deposition & Photo lithography)
4. Beam structure etching (Photo lithography & deep RIE)
5. Base structure etching (Photo lithography & deep RIE)
6. Insulation treatment (SiO_2 sputtering & Wiring)
SICE/SI2017


Automated measurement
Once a single cell is surly grasped, successful measurement can be obtained. The key is how to rightly grasp and hold a cell at its center position.
Introduction of automated grasping and pushing procedures
Strategy
1. Searching target cell from image
2. Grasping and adjusting the grasped point
3. Measuring force and displacements
Principle
Detecting Z force indicates the grasping position clearly.
too upper
just center
too lower
Two-Fingered Microhand
Micro-Force Sensor
Manipulation with Force Sensing
Grasp lower part
Grasp center part
Grasp upper part
X force
Z force
Force(nN)
forces and grasping conditions

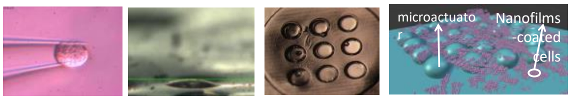

Cell/spheroid characterization
Hardness (nN/um²)
Duration (hour)
Change of Mayer's index in influenza virus affected cell, JMNM12.
13 days
15 days
Stiffness(Pa)
Bone stiffness of mouse embryo.
Max Force[nN]
Calcified
Control
day 1 day 5 day 8 day 12
Temporal hardness change of ameloblast spheroid, RSC Advances16.
Relation between force and morphology fluctuation of hydra in it regeneration process, APL15.


On-Chip Cell Deformation Analysis
Cancer cell invasion and metastasis
Microfluidic device for sequential squeezing
migrate
Sequential squeezing
Squeezed
Inlet
Outlet
(M. Malboubi, A. Jayo, et al. , 2015)
Experimental setup
Row 1
Row 2
Row 3
Row 4
Row 5
Microscope
(speed: 0.01x)
50μm
Micro syringe pump
Experimental results
Red - Cancer cells: Hela
Black - Normal cells: NIH3T3
High deformability
Low recoverability
Low deformability
High recoverability
Passing efficiency
Row number
CBS 2018

More than Mechano Biology

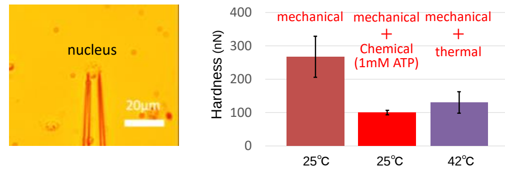
Mechano Biology is to clarify how mechanical stresses are captured and sensed in and around a cell, how they are transformed into signals, then finally what physiological and pathological responses are induced.

according to the JST AMED Project



We can consider many other stresses than just limited mechanical, e.g., thermo, electro, magneto, chemo, wave…

Multi modal stimuli enhances genomics



Giving multi stimuli on nucleus could suggest more than current mechano-biology.

(Collaboration with the Institute of Development, Aging & Cancer, Tohoku Univ. *Non-published.*)

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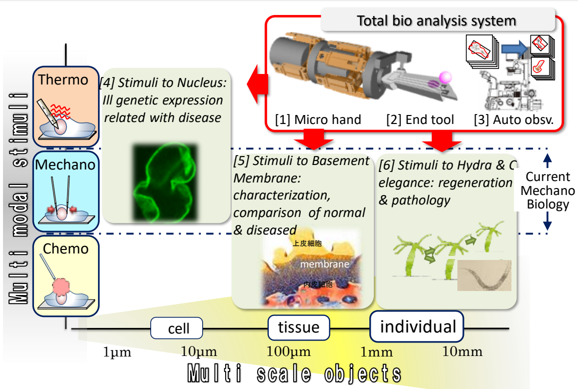
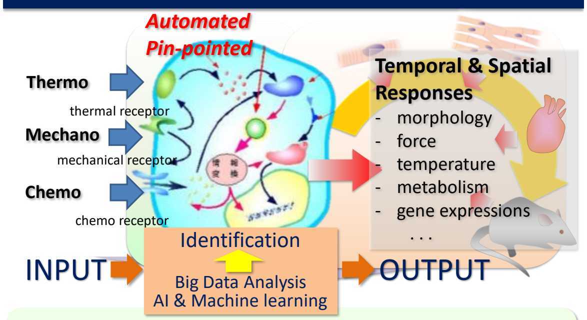
今後の課題



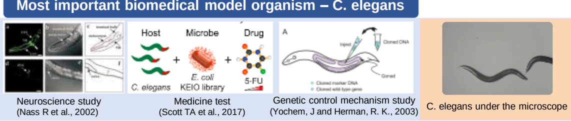
自動で効率的に大量データを収集



Micro robotics and total bio analysis could bring breakthrough in that we could model life phenomena as multi input-multi output system.

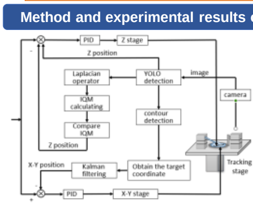
Auto tracking for time lapse observation

Most important biomedical model organism – C. elegans



- ***C. elegans can easily move out of the microscope field***
- ***Difficult to track individual C. elegans manually for long periods of time***

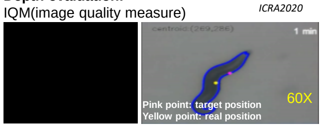
Method and experimental results of time-lapse tracking



Control flowchart

Detection method:
YOLO(deep learning model) & contour detection
Depth evaluation:
IQM(image quality measure)

ICRA2020



Tracking in Z-direction　　Time-lapse tracking

まとめ

- マイクロハンドや微小流路を用いた細胞操作や計測の研究開発例を示した．
- メカノバイオロジーに関連する生命医学応用の一例を示した．
- 今後の研究方向として，マルチスケール・マルチモーダル刺激について紹介した．