Flexible Microsystems-Integrated Urinary Catheters to Aid CAUTI Prevention

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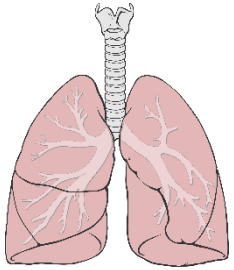
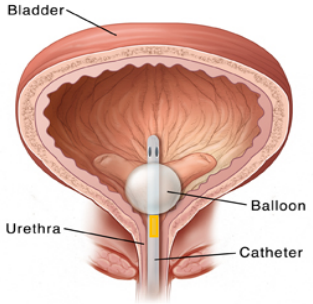
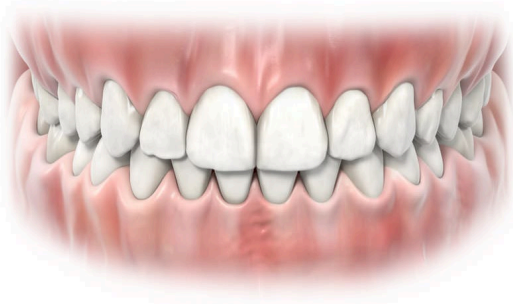
NIH NIDDK CAUTI Technology Workshop

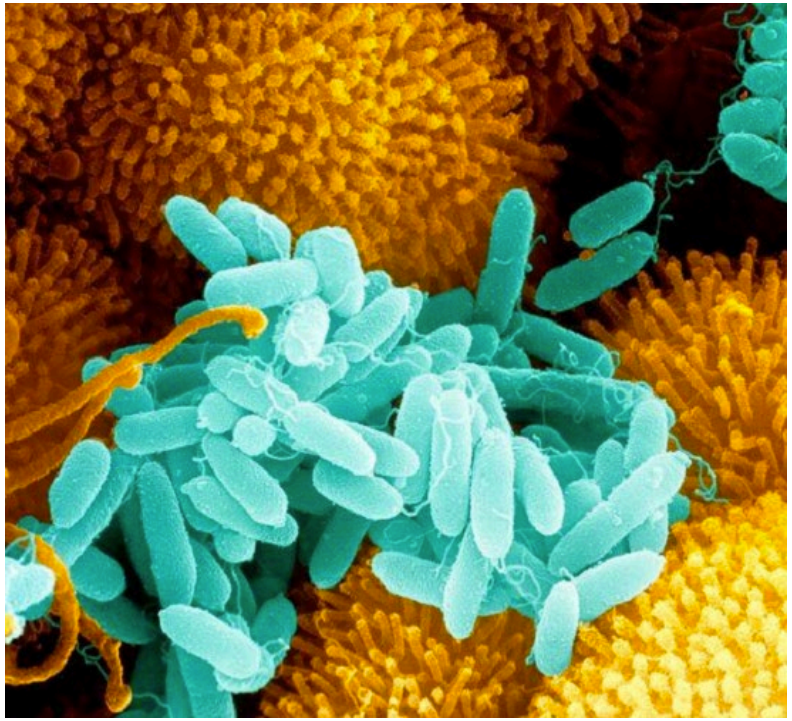
Monday, March 11, 2019

Bacterial Biofilms

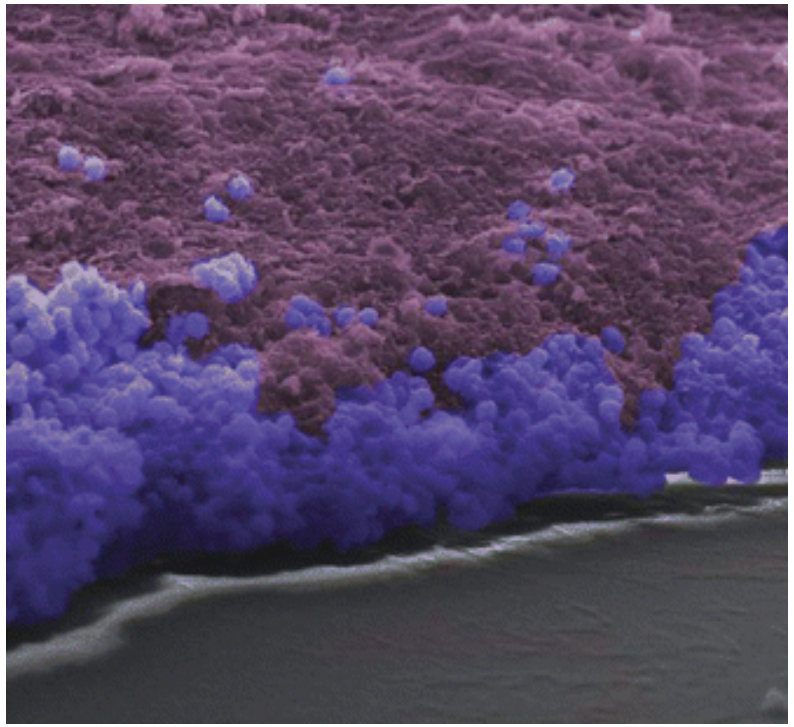




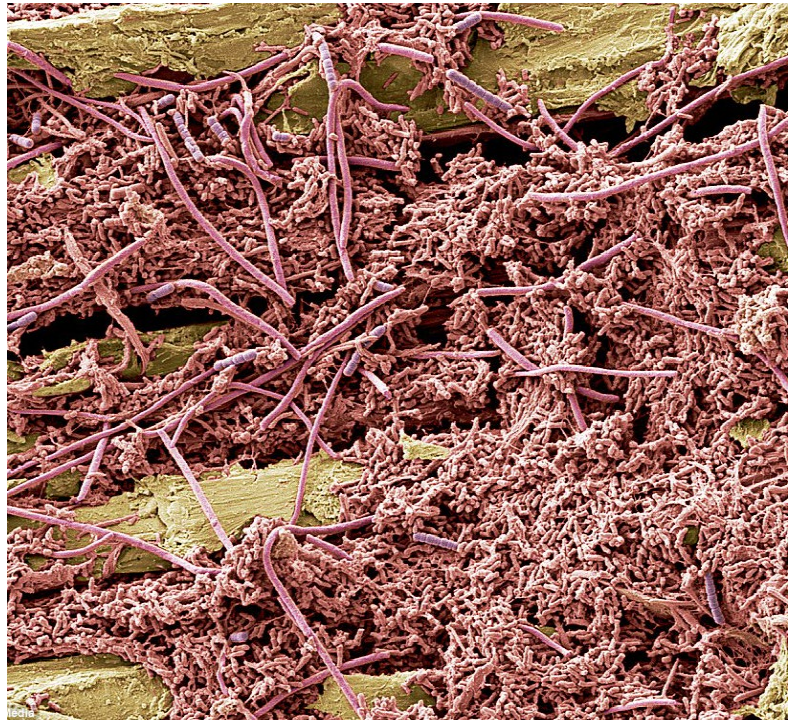




Pseudomonas aeruginosa biofilm in a lung, www.sciencephoto.com



Staphylococcus aureus biofilm in a catheter, www.jimmunol.org



Plaque on teeth, www.dailymail.co.uk

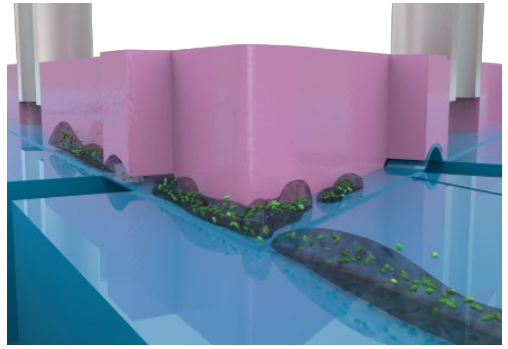
Microdevice Approaches for Biofilms

- **Microfluidic Control**[1]
  - Reproducible biofilm growth
  - Reduced reagent consumption
- **Analog AI-2 Biofilm Inhibition**[2]
  - Quorum sensing inhibitor treatment
  - Synergistic with antibiotics
- **Bioelectric Effect (BE) Treatment**[3]
  - Low-intensity electric field and low dose antimicrobial
  - Synergistic removal effect
  - Reduced antibiotic use
- **Integrated Biofilm Sensors**[4,5]
  - Surface-acoustic-wave sensor
    - Sensitive
    - Complex fabrication
  - Impedance sensor
    - Analog
    - Simple fabrication
- **Feedback-driven System**[5]
  - Threshold-activated biofilm treatment
  - Simple electrical engineering approach

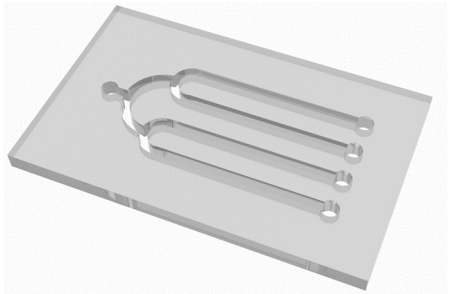
[1] Meyer et al., J Micromech Microeng, 2015
[2] Roy et al., Appl Microbiol Biotechnol, 2013
[3] Kim et al., npj Biofilms Microbiomes, 2015
[4] Kim et al., Sens Actuators A Phys, 2016
[5] Subramanian et al., ACS Appl Mater Interfaces, 2017

Microdevice Approaches for Biofilms

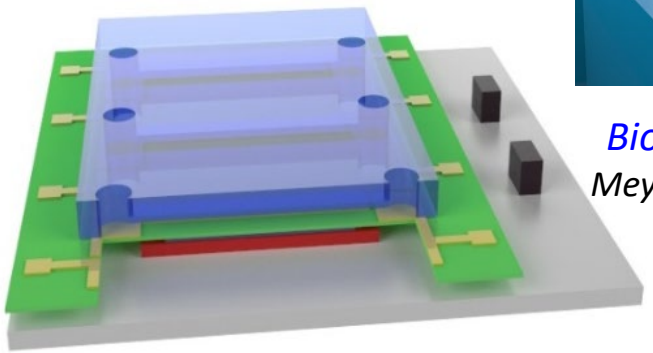
Characterization



Biofilm Sectioning Device
Meyer, J. Micromech Microeng

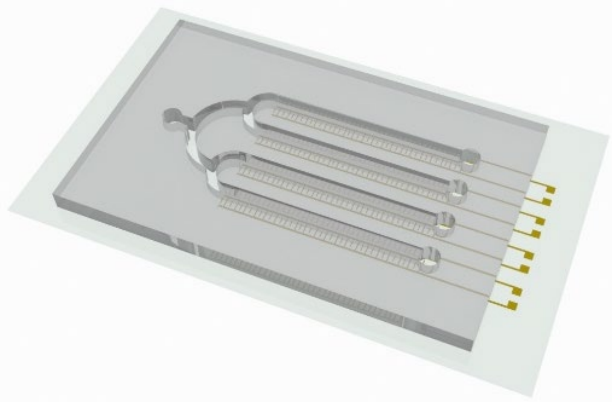


Valveless Bifurcation Sectioning
Subramanian, Transducers '15

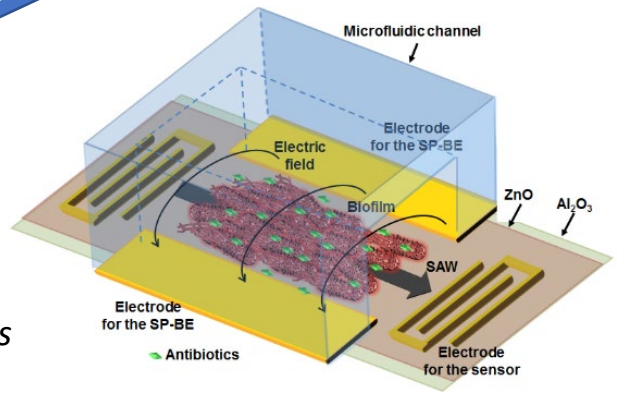


Micro-BOAT Platform
Kim, Hilton Head Workshop '12

2012 2013 2014 2015 2016 2017 2018



Integrated Sensor-Treatment System
Subramanian, Biomed Microdevices

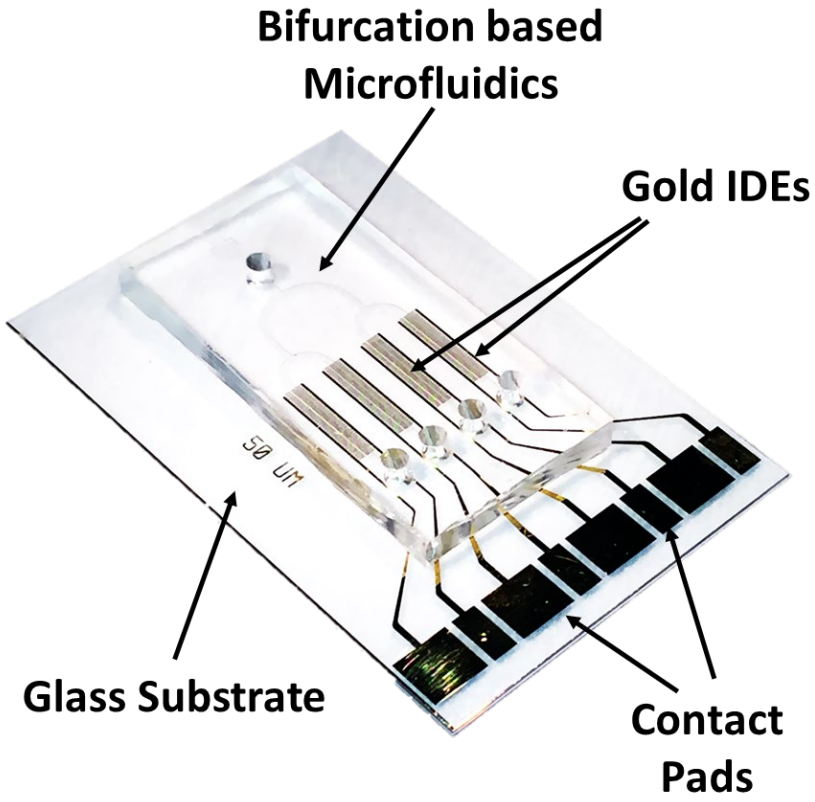


Integrated System
Kim, Sensor Actuat A-Phys

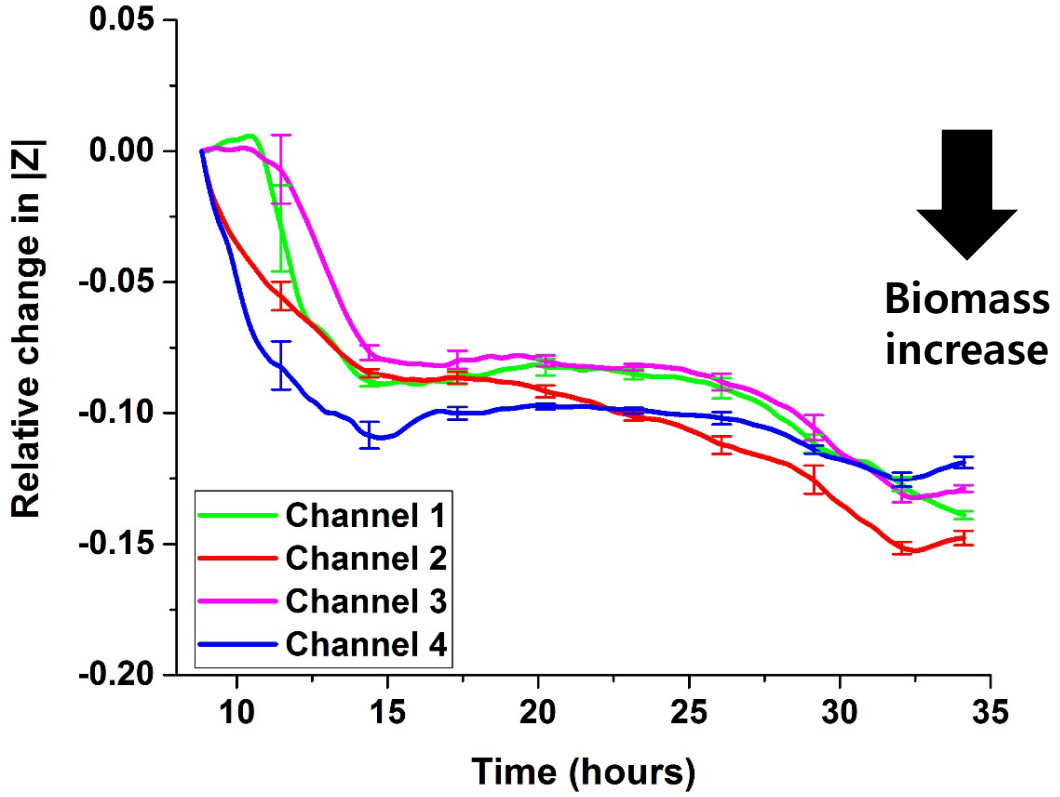
Treatment

Biofilm Monitoring using Impedance Sensor

- Real-time biofilm growth monitoring with a microfluidic device using interdigitated electrode (IDE) sensors at **5 mV**



A 4-channel microfluidic bifurcation device



Real-time impedance sensing of uniform biofilm growth

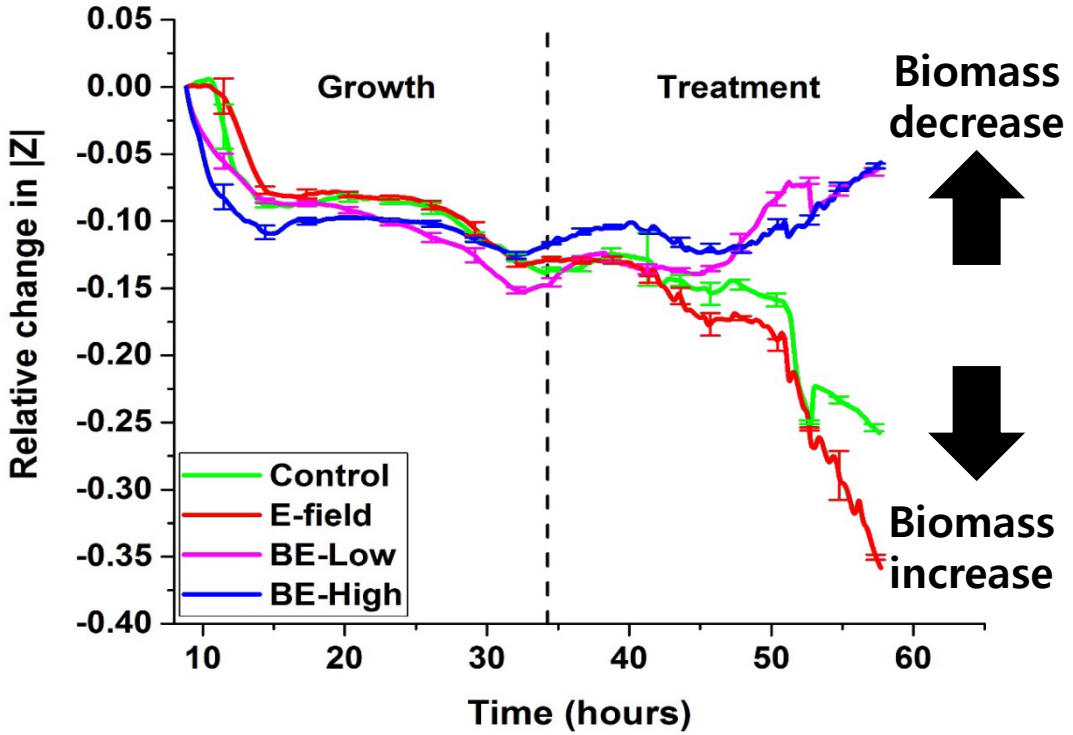
S. Subramanian et al., ACS Appl Mater Interfaces, 2017

Integrated Impedance-BE Microsystem

- IDEs used for **sensing** and **application of the BE treatment**
- Application of **sensing voltage results in treatment** in the BE-low channel

Channel	Sensing	Treatment
Control	5 mV	LB media only
E-field Only	5 mV	LB media + 100mV
BE - low	5 mV	10 µg/ml gentamicin in LB media
BE - high	5 mV	10 µg/ml gentamicin in LB media + 100mV

Experimental conditions during treatment phase



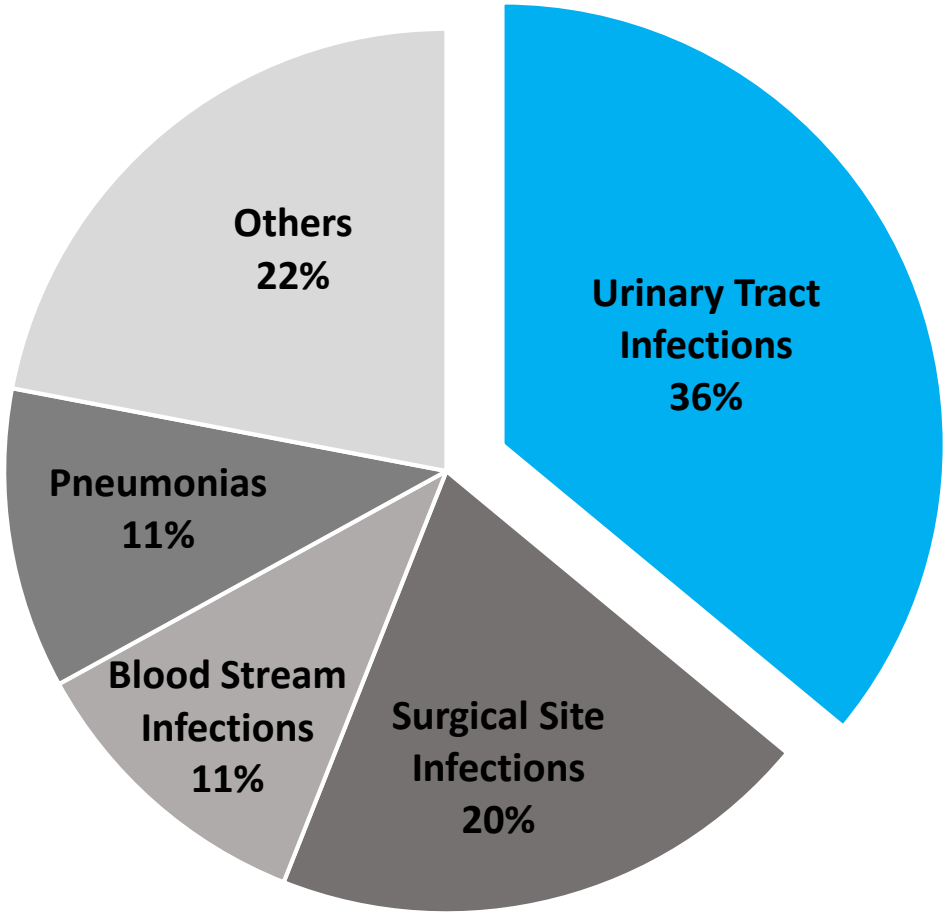
Relative change in absolute impedance during BE treatment of E.coli biofilms

Sensing voltage also causes significant BE

S. Subramanian et al., ACS Appl Mater Interfaces, 2017

Urinary Catheter Infections

- The most common health-care-associated infection in the US
- 530,000 cases
- 13,000 deaths
- $450M in costs
- 5% per day of catheter implantation
- ~75% of urinary tract infections



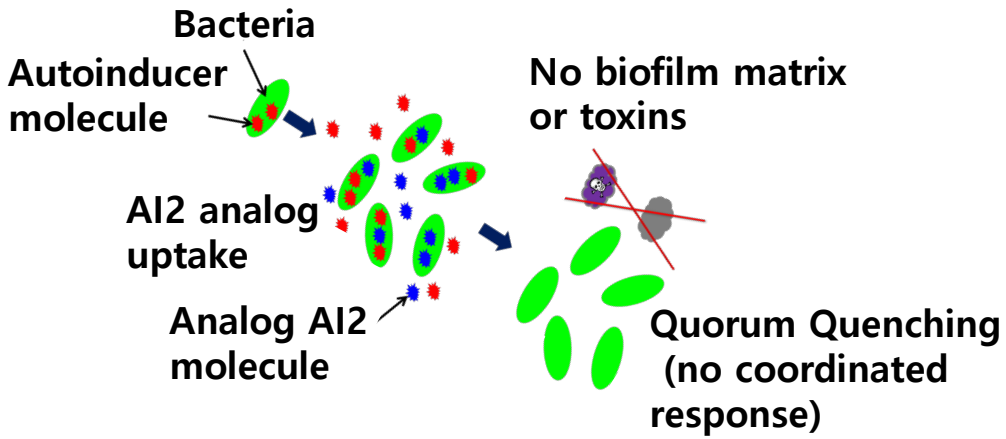
Healthcare-Associated Infections by origin, Klevens et al., Public Health Rep., 2007

"**Catheters are Causing Serious Problems in Hospitals**" – in Tonic (Vice), November, 2018 (https://tonic.vice.com/en_us/article/59vbmx/catheters-are-causing-serious-problems-in-hospitals)

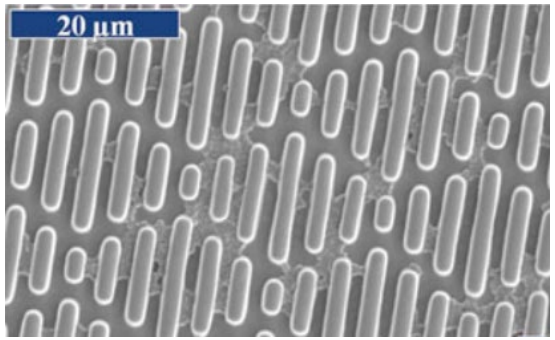
Catheter Infection Management

- Diagnostic: Bacterial Culture
  - Time consuming
- Antibiotics
  - Spread resistance
- Quorum Sensing Inhibitors
- Surface Modifications
  - Micro-topography
  - Chemical modification

Blood agar plate for culturing bacteria, Thermo Fisher



Quorum sensing inhibitors prevent biofilm formation



Sharklet anti-biofilm microstructure, Chung et al., Biointerphases, 2007

Catheter infused with metal ions to kill biofilm, Bard, 2013

In CDC Guideline for CAUTI Prevention

III. Proper Techniques for Urinary Catheter Maintenance

E. Changing indwelling catheters or drainage bags at routine, **fixed intervals is not recommended**. Rather, it is suggested to **change catheters** and drainage bags based **on clinical indications** such as infection, obstruction, or when the closed system is compromised.

F. Unless clinical indications exist (e.g., in patients with bacteriuria upon catheter removal post urologic surgery), **do not use systemic antimicrobials routinely** to prevent CAUTI in patients requiring either short or long-term catheterization.

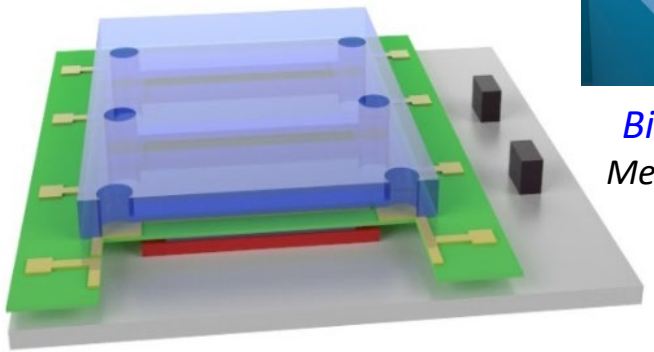
Technological Approach:

Catheter-Integrated Microsystems to Aid Clinical Practices for CAUTI Prevention

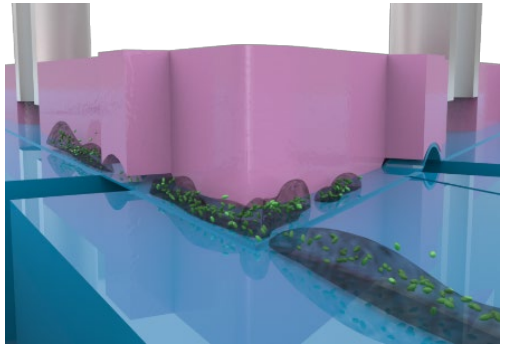
Guideline for Prevention of Catheter Associated Urinary Tract Infections 2009 (Last updated on February 15, 2017)

Biofilm Microsystems

Characterization



Micro-BOAT Platform
Kim, Hilton Head Workshop '12



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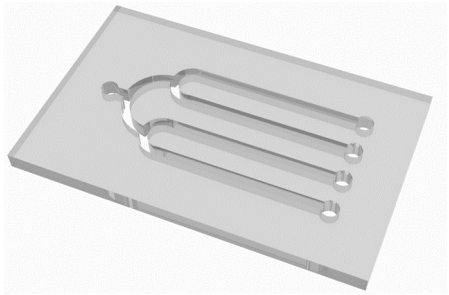

Valveless Bifurcation Sectioning
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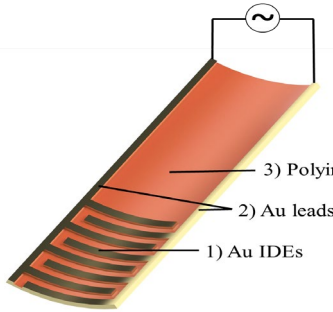
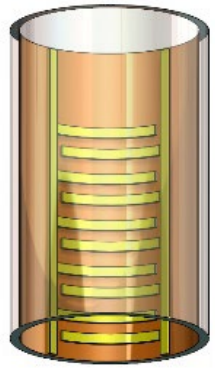
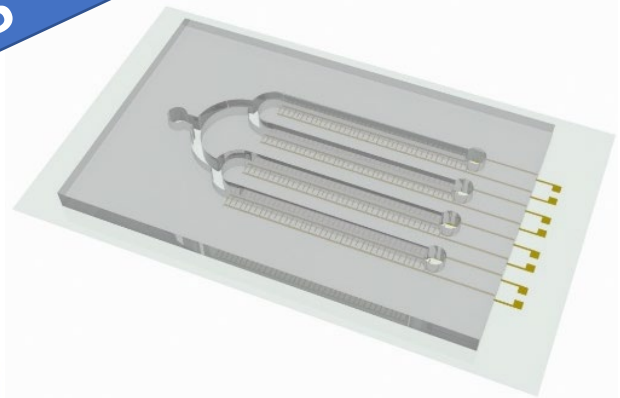


Wireless Flexible Sensor
Huiszoon,
Hilton Head Workshop '18

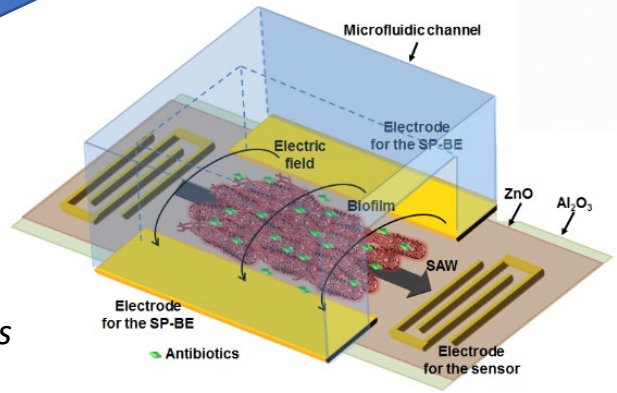


Flexible Sensor-Treatment Platform
Huiszoon, MMB Conference '18

2012 2013 2014 2015 2016 2017 2018



Integrated Sensor-Treatment System
Subramanian, Biomed Microdevices

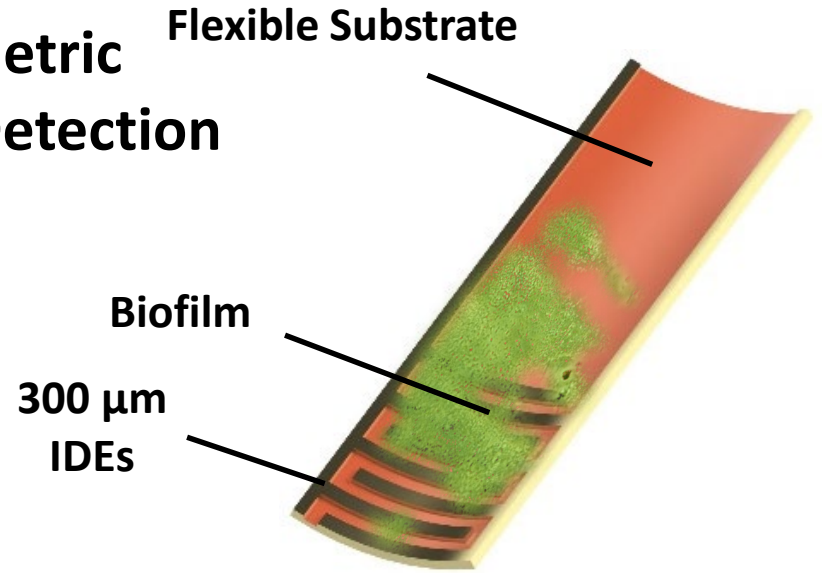


Integrated System
Kim, Sensor Actuat A-Phys

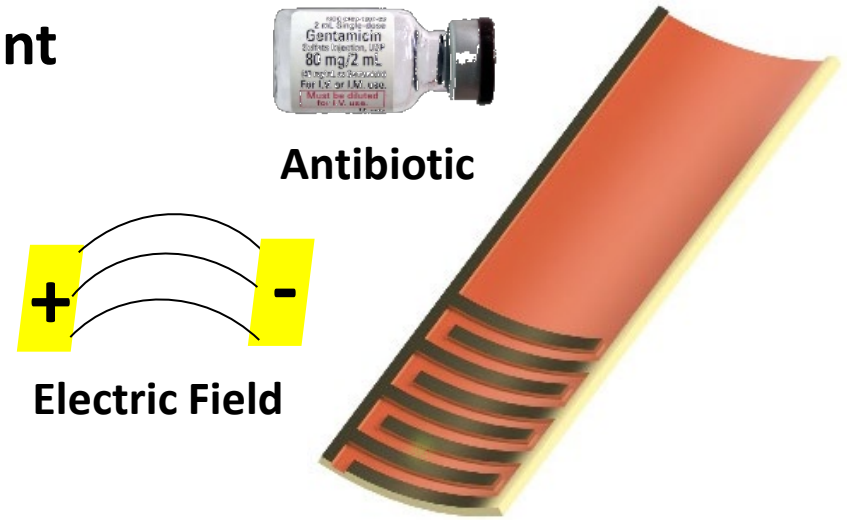
Treatment

Flexible Biofilm Microsystem

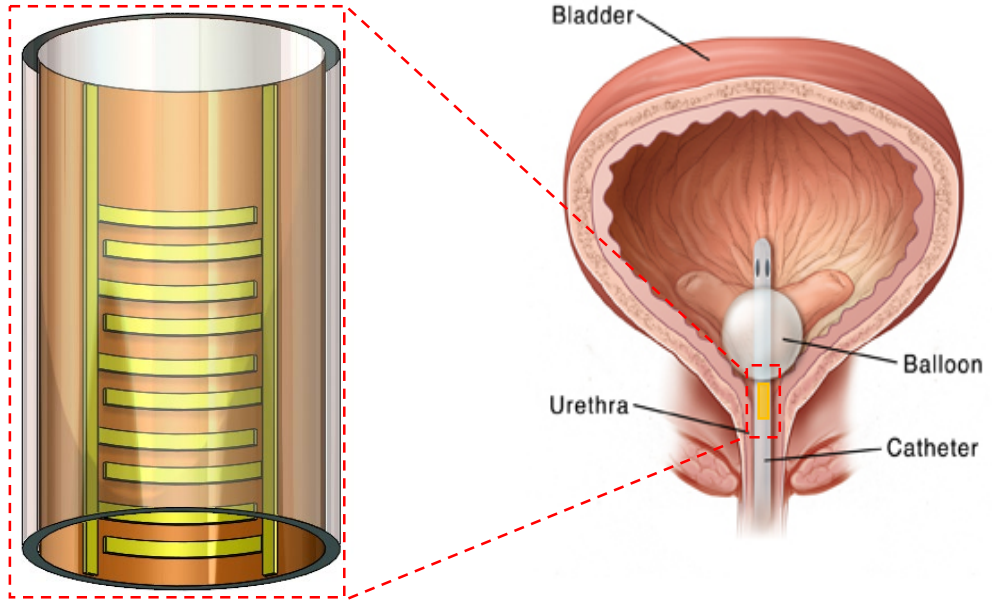
(A) Impedimetric Biofilm Detection



(B) Bioelectric Effect Treatment



(C) Integration with Complex Surface



(A) Flexible platform with interdigitated electrodes for biofilm detection, (B) biofilm removal achieved by combining electric field and antibiotics, (C) schematic of device conforming to lumen of urinary catheter

Flexible Sensing & Treatment Microsystem

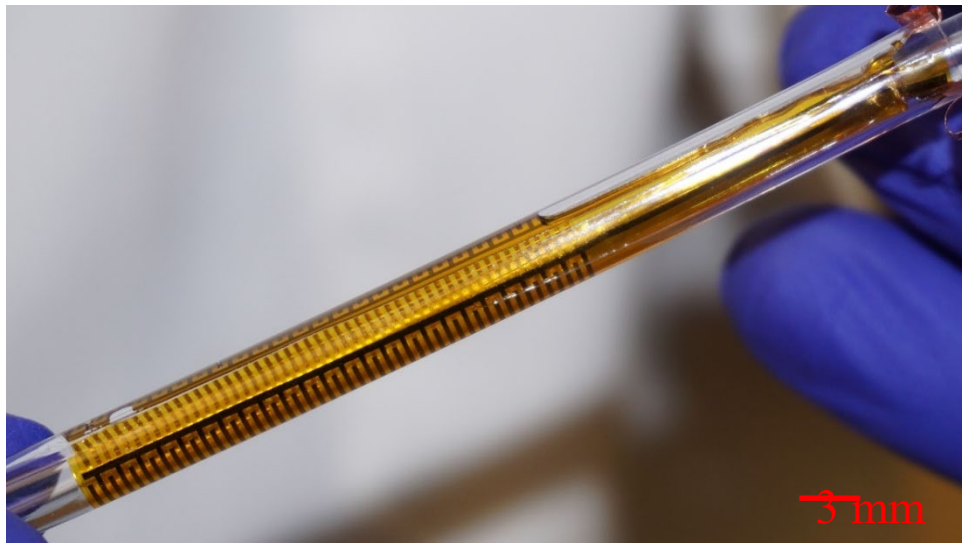
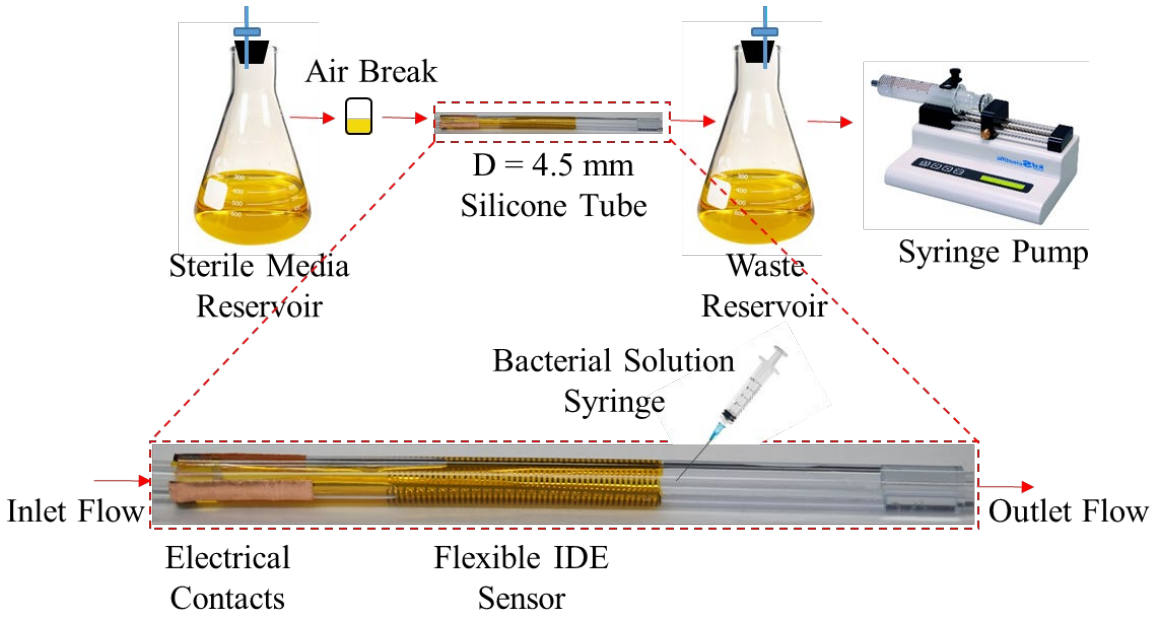


Image of flexible microsystem in a urinary catheter

Sample	Sensing	Condition
Unseeded	50 mV	LB media + No bacteria
Untreated	--	LB media
BE	50 mV	10 μg/ml gentamicin in LB media
Anti-Only	--	10 μg/ml gentamicin in LB media
Sense-Only	50 mV	LB media

- IDE-based microsystem
- Combination sensing and BE treatment

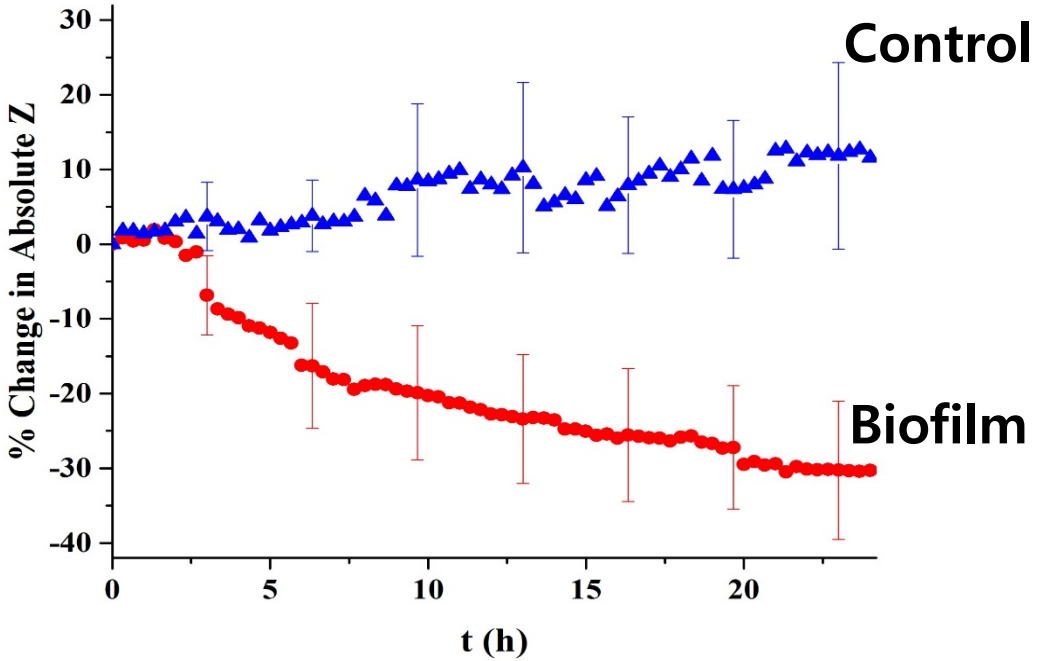


Experimental test setup for flexible device in catheter section

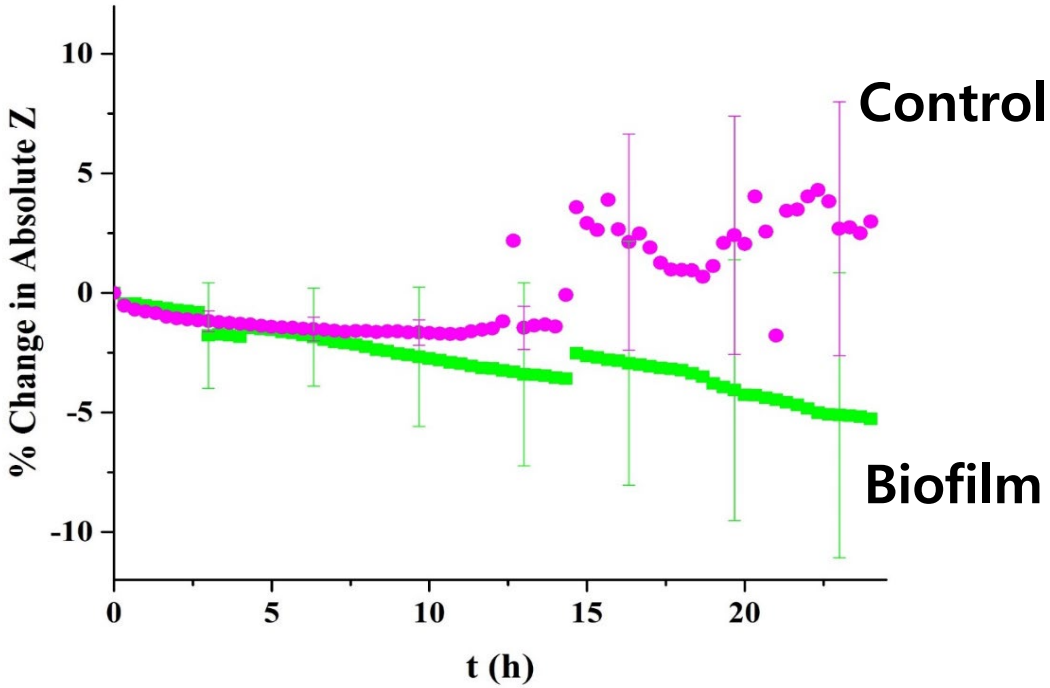
R. Huiszoon et al., IEEE Trans Biomed Eng, 2018

Impedance Sensing

- Impedance response changes in real-time with *E. coli* biofilm growth on IDEs on cylindrical catheter surface
  - >30% decrease in 24 hours
  - Similar sensing trend apparent with potentiostat and impedance converter



Percent change in 100 Hz impedance during 24 h with benchtop potentiostat (N=5)

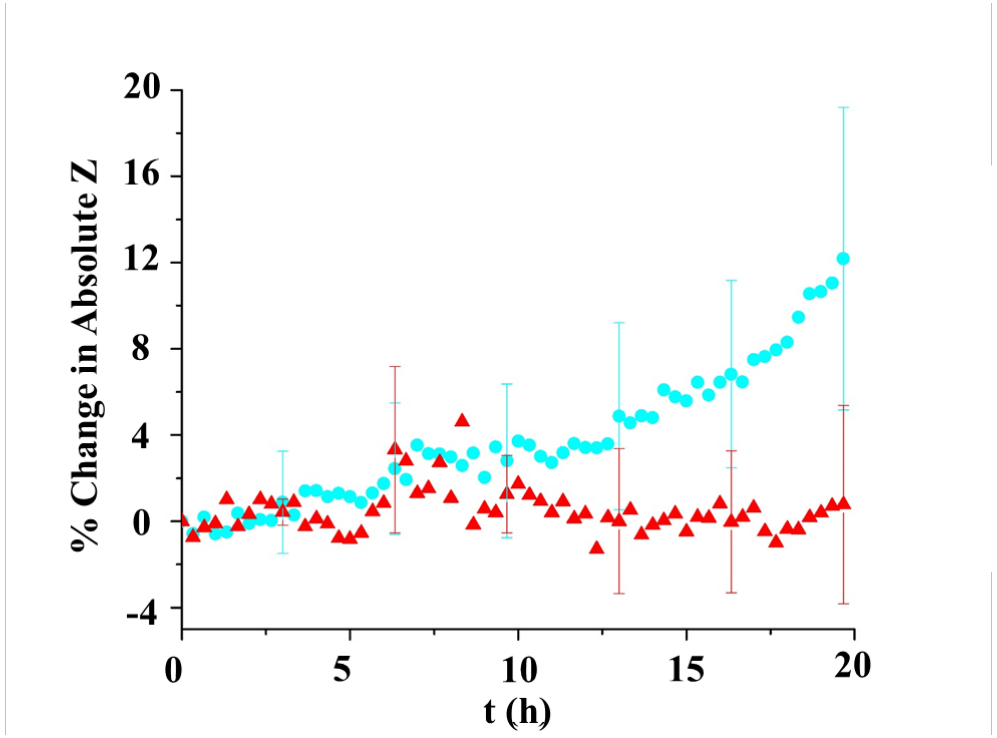


Percent change in 1 kHz impedance during 24 h with impedance converter (N=3)

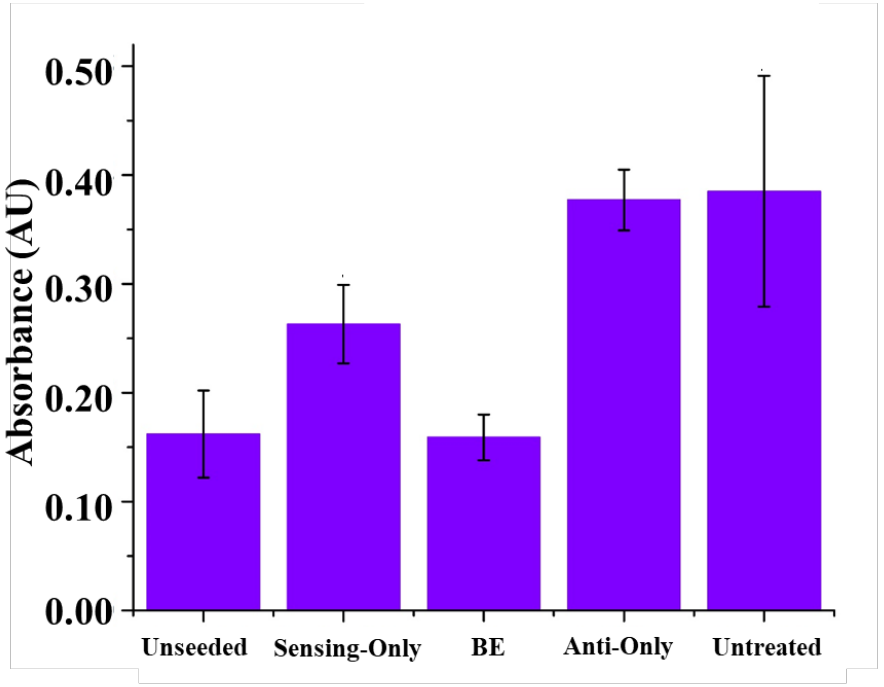
R. Huiszoon et al., IEEE Trans Biomed Eng, 2018

BE Treatment Efficacy

- Impedance characterization and crystal violet biomass quantification of *in situ* BE treatment



Percent change in 100 Hz impedance during treatment (N=3)

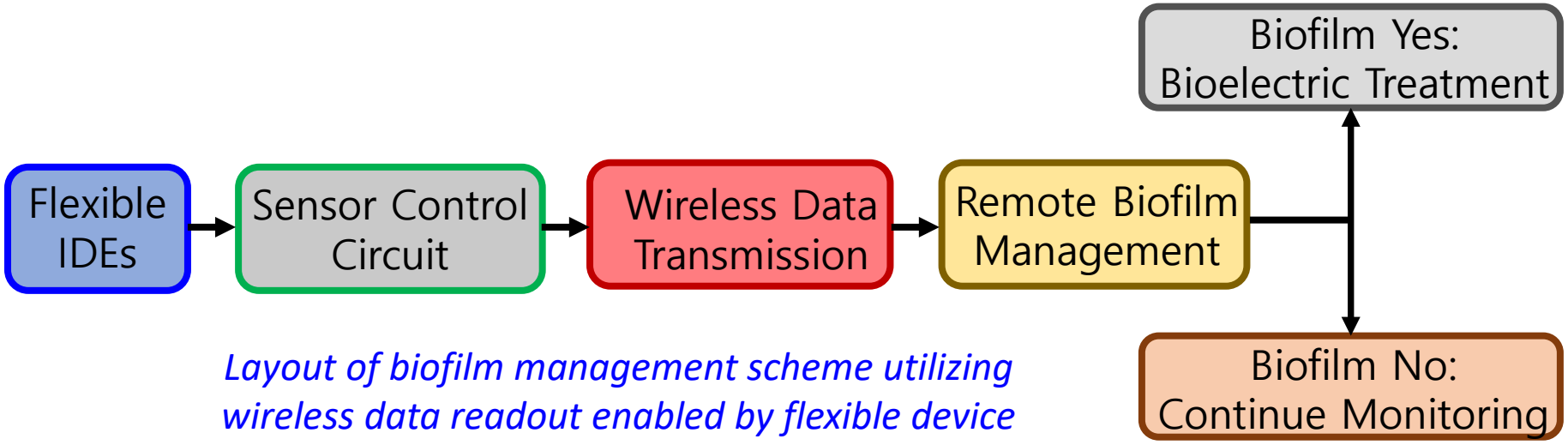


Crystal violet biofilm biomass results (N=3)

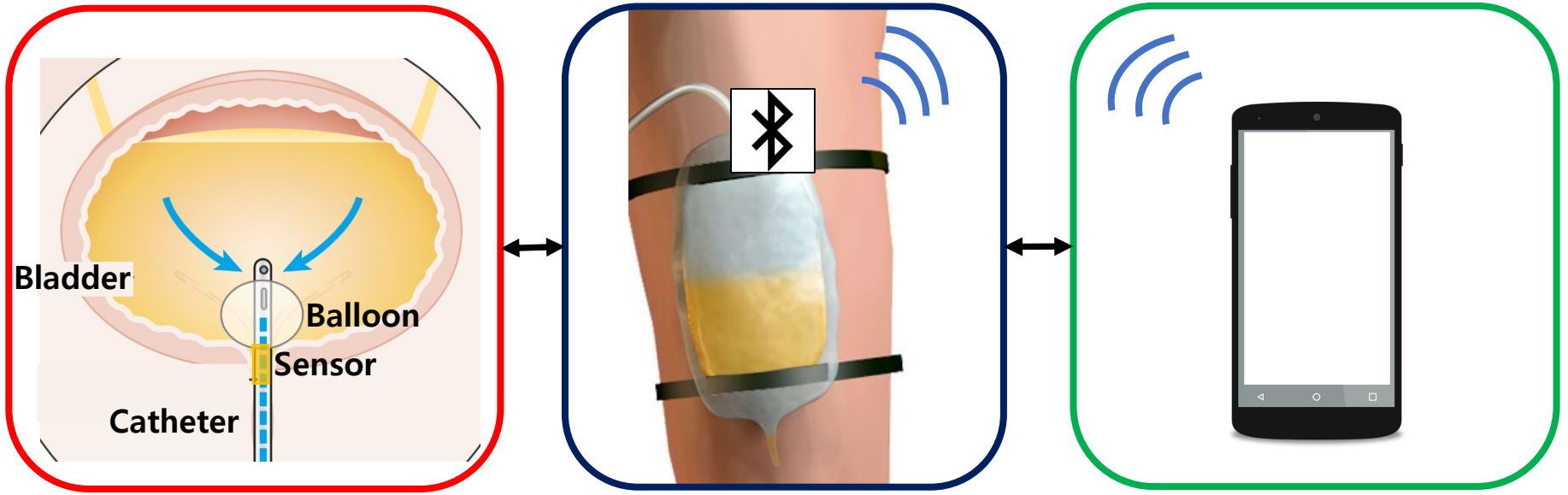
BE treatment yields biomass similar to biofilm-free samples

Patent Pending, US application No 16/107,869

Wireless Biofilm Management



Layout of biofilm management scheme utilizing wireless data readout enabled by flexible device



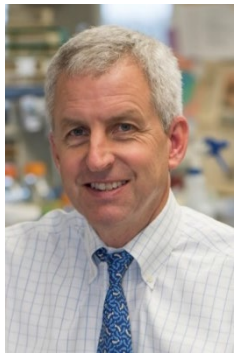
Wireless readout and control approach showing sensor embedded (inserted urinary catheter) on a cylindrical surface

Human-Technology Partnerships

- Reliable sensor performance (sensitivity, selectivity, life time, etc.)
- Standardization in data acquisition, transfer and analysis
- Adaptive, customizable, and secured partnership via integration with machine learning/AI
- Understanding the needs and communication protocols from different disciplines (e.g. engineers, clinicians, biologists, data scientists, etc.)

Our Team / Acknowledgement

MEMS Sensors and Actuators Laboratory



Professor William Bentley

Luke Beardslee M.D./Ph.D.

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