Multidisciplinary Aspects of Developing Small Sensing Devices for Monitoring Chemicals and Biochemicals

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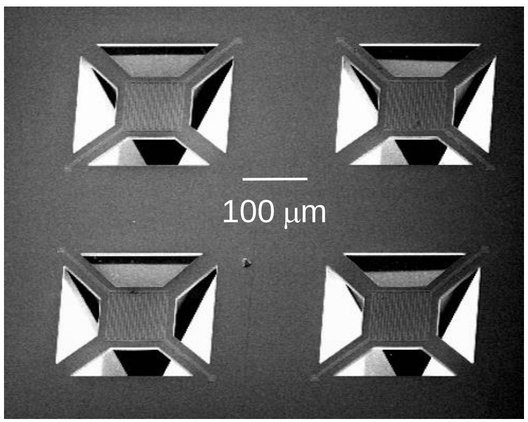
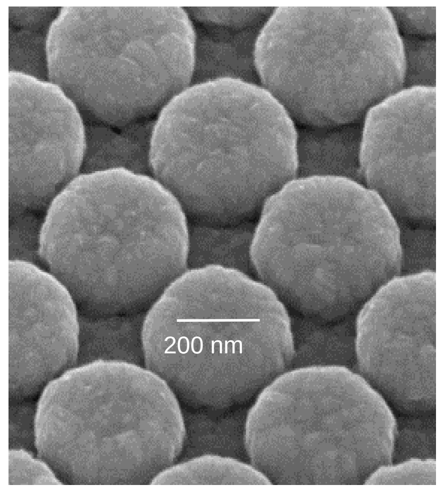
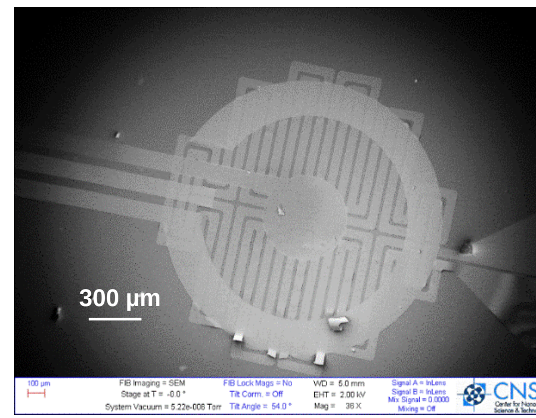


Chemiresistive Gas Sensing



Plasmonic Gas & Solution Sensing



Electrochemical DNA-Based Monitoring

small device platforms, nanomaterials, temperature variation

National Institute of Standards and Technology (NIST)

Gaithersburg, Maryland

Contributors to efforts at NIST:

Materials
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Biosensing
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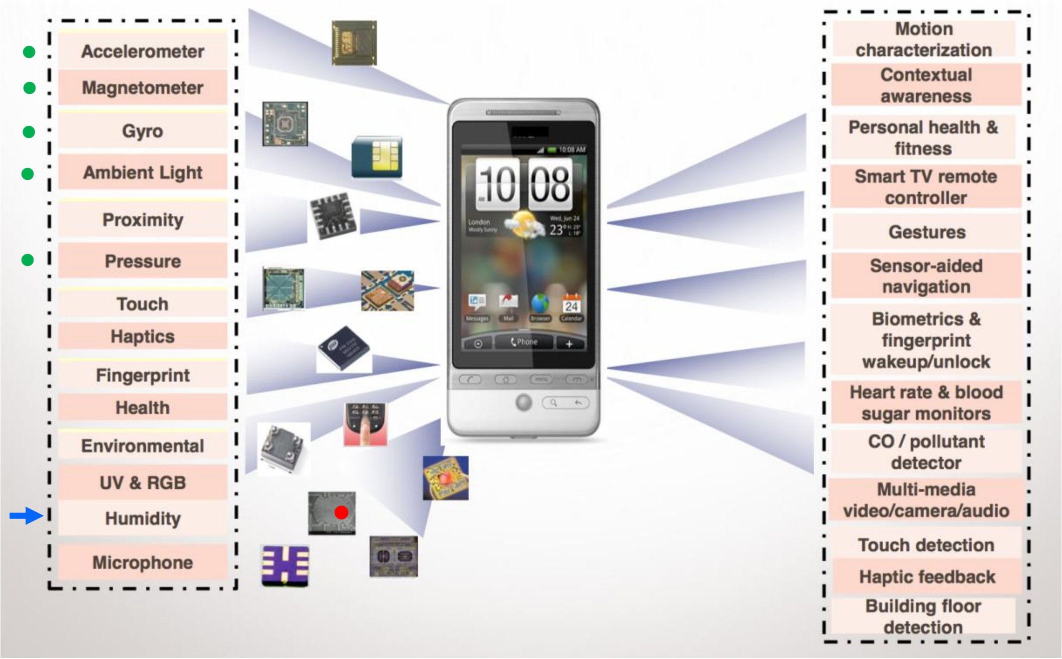
Acknowledgments: Technical Support - Mike Carrier, Chip Montgomery
Funding - *NRC Postdoctoral Associateship Program

Growing Demand for Sensors: Examples

iPhone and tablet apps, wearables


Fitbit

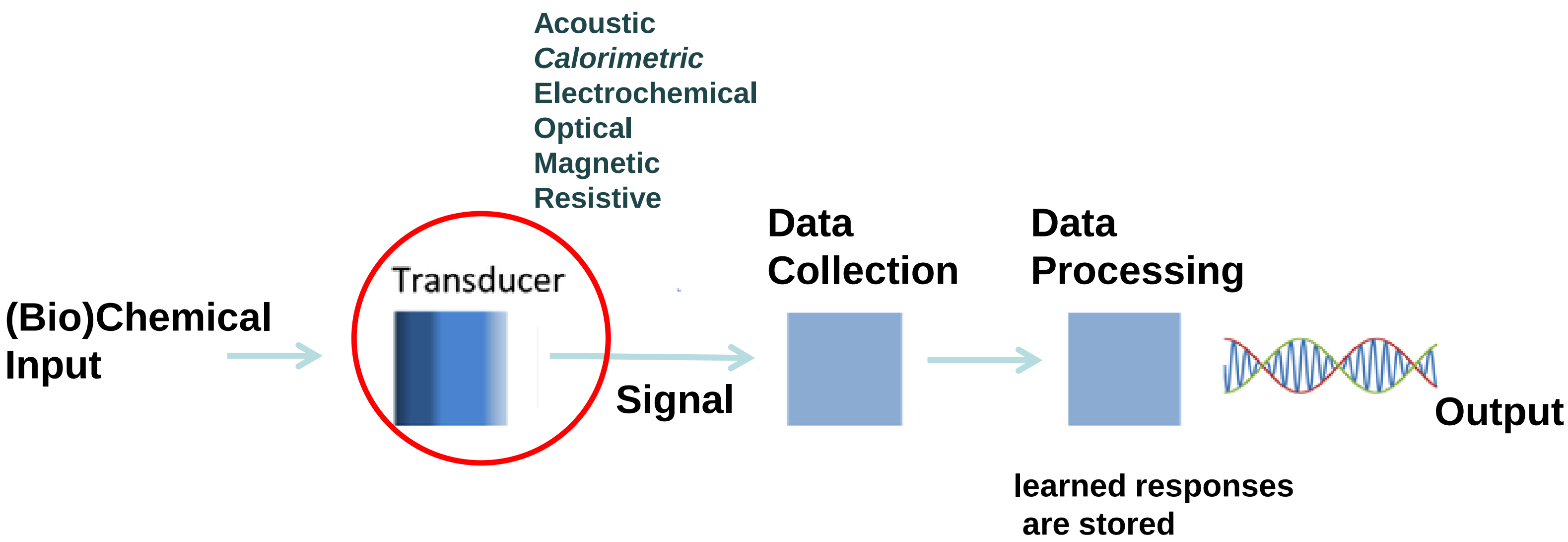


- Electronics/interfacing/communication components are much more mature (low $$)
- Physical sensing is more prominent in commercial devices – easier (fewer degrees of freedom)
- Need good sensor devices for chemicals/biochemicals - reliable "chemical signals"

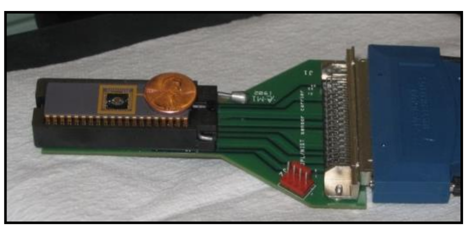
chemical/biochemical interactions produce a richness that is much more challenging (sensitivity, interferences)

Microdevice Sensing Technology

device-based electronic sensing can add convenience at low cost



Themes



- **Functional microplatforms**
- **Integrated nanomaterials for transduction**
- **Signal processing of data streams**
- **Operational concepts and enabling technology**

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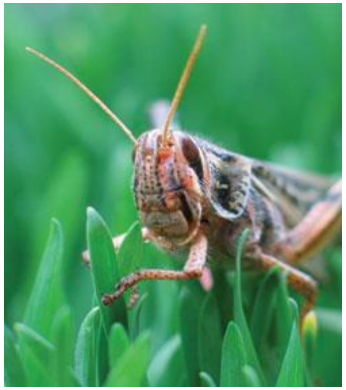
Bio-Inspiration for Chemical Detection

Insects



tracking low molecular conc's.of target molecules to locate food or a mate

Trained Dogs

reliable detection of drugs, explosives and disease [not overly convenient or network friendly]

evolutionary success (biological olfaction) challenges "electronic noses" (artificial olfaction)

InSitu FOUNDATION

"system" is sensitive and fast

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Measurement Choices: Sensors vs Instruments

Instruments

larger, more expensive, "gold standard"

Direct measurement of chemical target

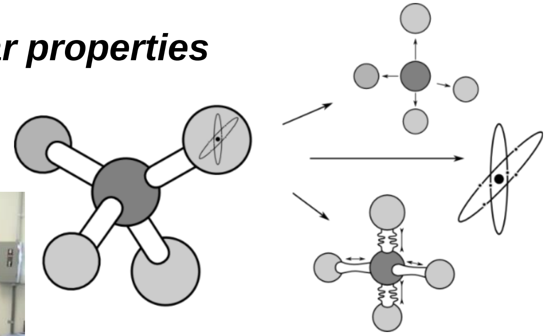
Mass spectrometry

IR-vis-UV/fluorescence spectroscopy

photo-electron spectroscopy

NMR spectroscopy

intrinsic molecular properties



Orbitrap LC/MS
~ $1M

Sensors

smaller, cheaper, less precise, screening/networks

Indirect detection of chemical target

Electrochemical

Colorimetric/Opto-chemical

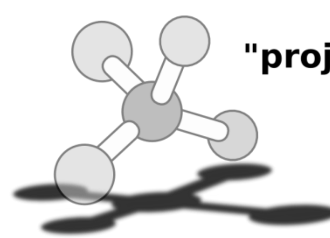
Bio-molecular (assays)

Solid State

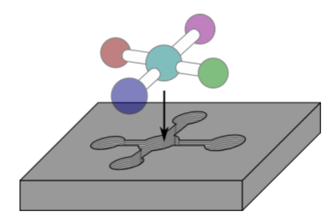
< 1 cm, $10s to $100s

effects from interactions

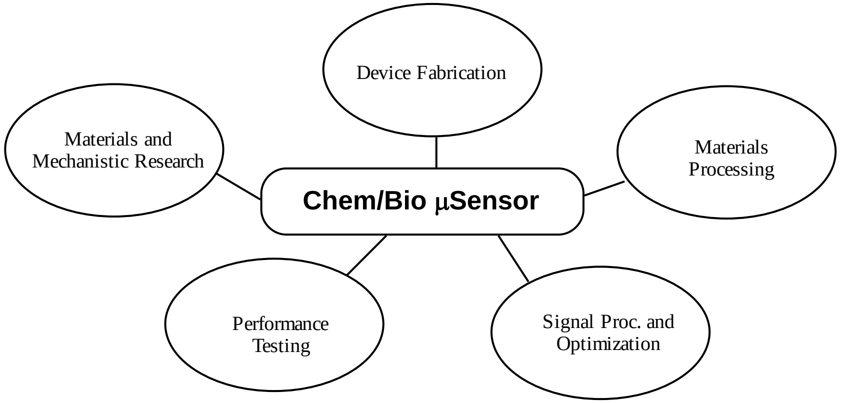
lock and key



"projection"



Multidisciplinary Research



Chemistry

- kinetics, thermodynamics
- surface reactions
- etching/micromachining reactions

Physics

- semiconductor/insulator properties
- electron transfer

Engineering

- design and fabrication of microdevices
- testing equipment

Materials Science

- thin films
- nanomaterials

Math

- data collection
- signal processing

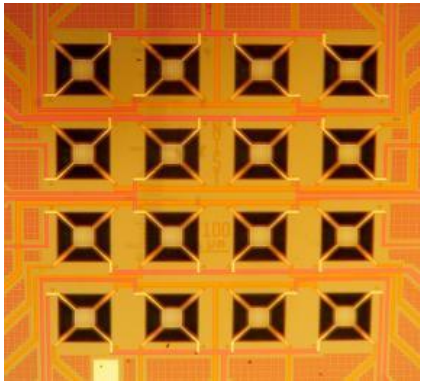
Biology

- biomolecule binding
- medical screening

Outline

- **Chemiresistor Array**

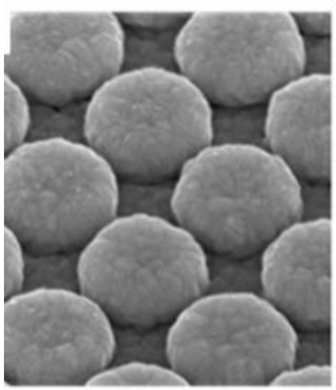
  application-adaptable gas sensing



100 μm elements

- **Plasmonic Optical Sensor Platform**

  gas-phase and condensed-phase sensing

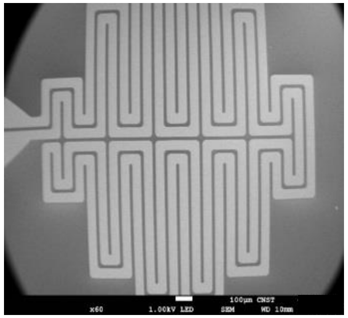


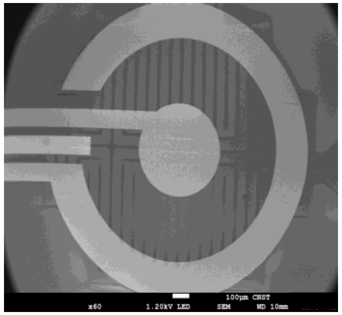
380 nm features

- **Microscale Electrochemical Device**

  biochemical characterization

DNA on 500 μm working electrode





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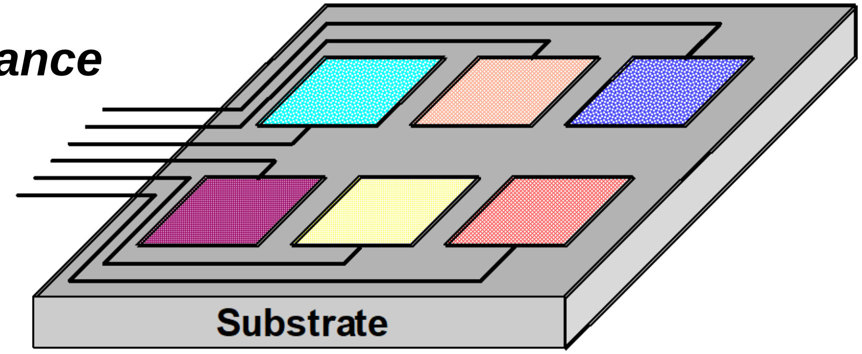
Chemical Sensor Array Concepts: *Adaptable* Platform

Solid State Chemiresistor Devices

Materials

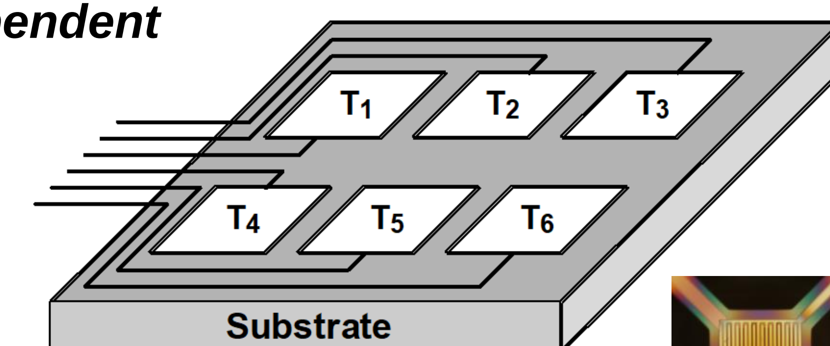


gas-induced changes in electrical conductance

- **semiconducting oxides**
- **conducting polymers**
- **chemical and electronic modifiers**
- **nanotextured and nanostructured films**

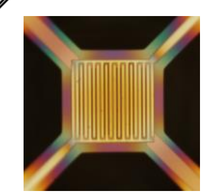
Operating Temperature $T_n(t)$

materials-dependent and temperature-dependent surface interactions



- **adsorption $f_1(T)$**
- **desorption $f_2(T)$**
- **coadsorbate reactions $f_3(T)$**

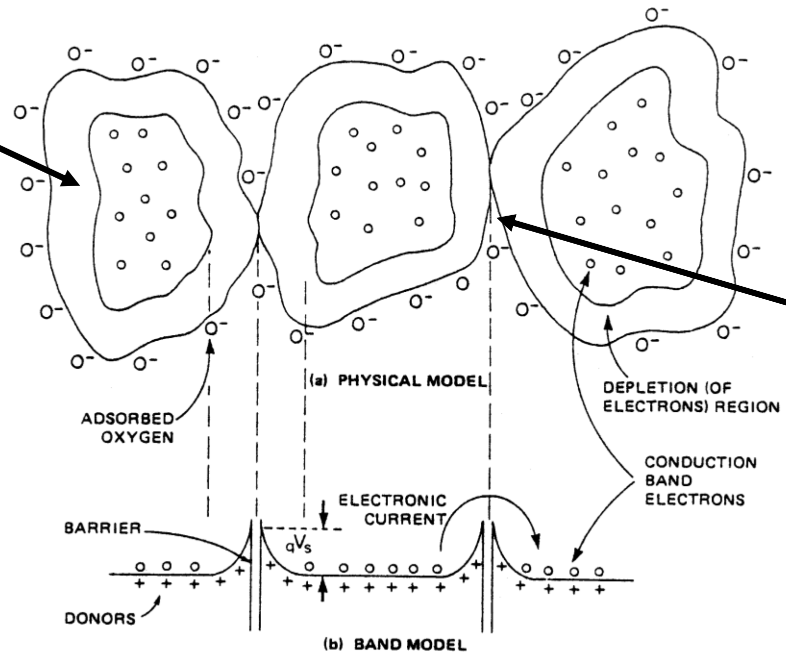
T(t) programming controls these phenomena in time



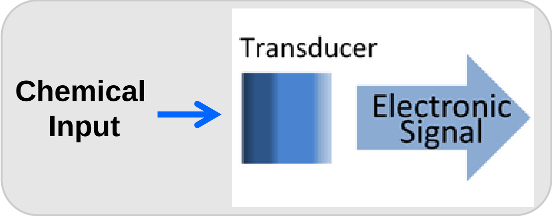
approach produces <u>analytically rich datastreams</u> and allows a <u>tunable technology</u> for varied applications

Chemiresistive Sensing: Mechanistic Effects

Variable electron depletion



Interparticle percolation



- **Oxygen vacancy defects - set base conductance levels for oxide films**
- **Surface charge transfer to bonded adsorbates**
- **Adsorbates react to control adsorbed oxygen (air background)**

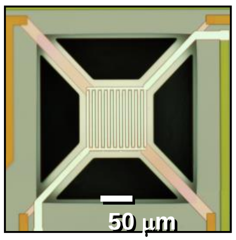
T and microstructure* *are critical to transduction/performance
(chemical and electronic interfacial properties)

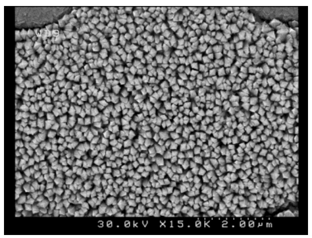
sensitivity, selectivity, stability, speed

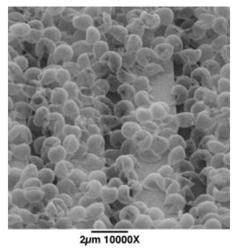
Approach: Trace Detection in Varied Backgrounds

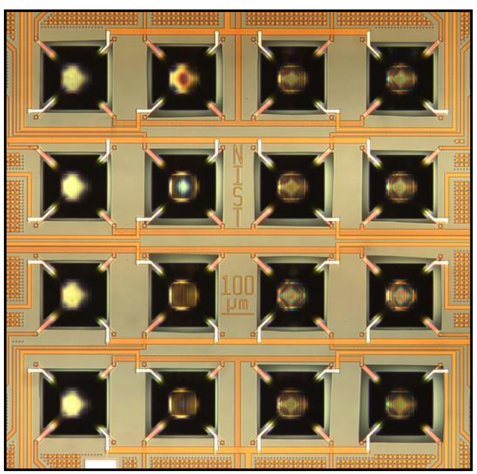
tunable microsensor arrays

- MEMS platforms
- robust chemiresistive nanomaterials
- surface and sensor science
- advanced signal processing

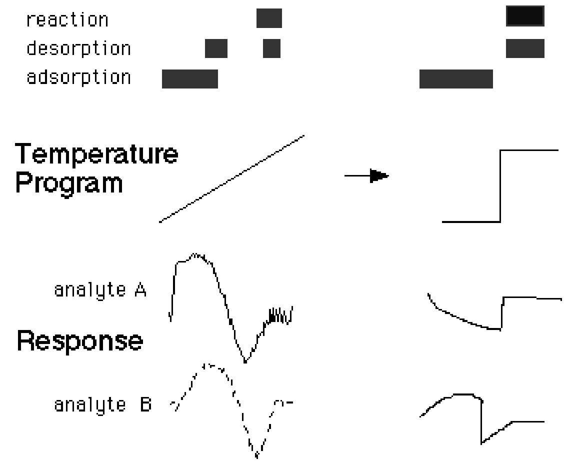




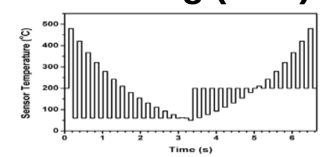




independent chemiresistive MEMS microhotplate array elements



increased analytical content per unit time with Temperature Programmed Sensing (TPS)



large T(t) databases from "virtual sensors"

Signal Processing

target detection/recognition/monitoring

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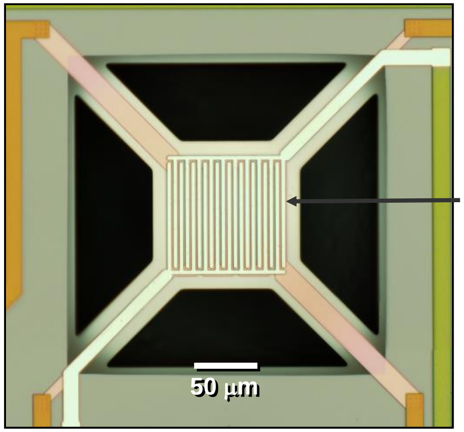
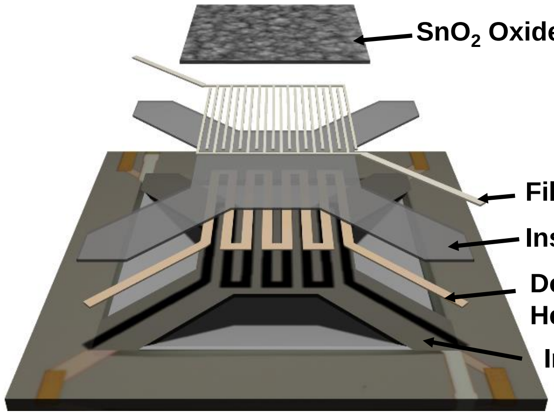
Microhotplate Platforms for Chemiresistive Sensing

single microhotplate element
(mass ~ 250 ng; heating/cooling tc < 5 ms)





layers schematic

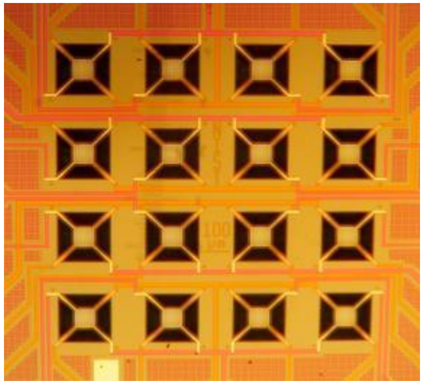
Functionality

- T measurement and control
- electrical characterization

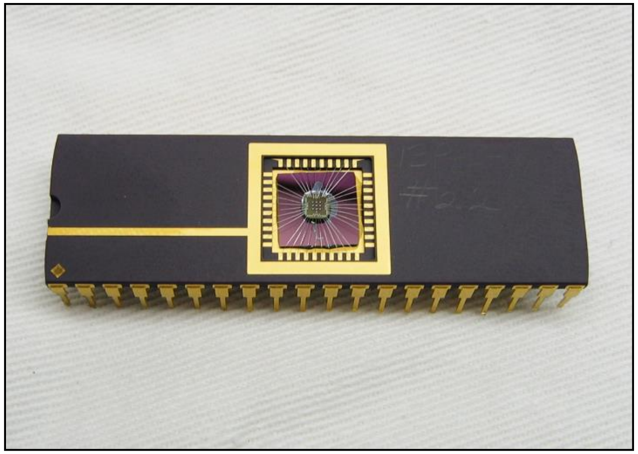
Features

- 20 °C to 500 °C; (~ 20 °C per mW)
- capable of heating rates of 10^5 - 10^6 °C/s
- CMOS design rules

replication to 16-element array



multi-channel electronics used for operation & data collection



packaged device

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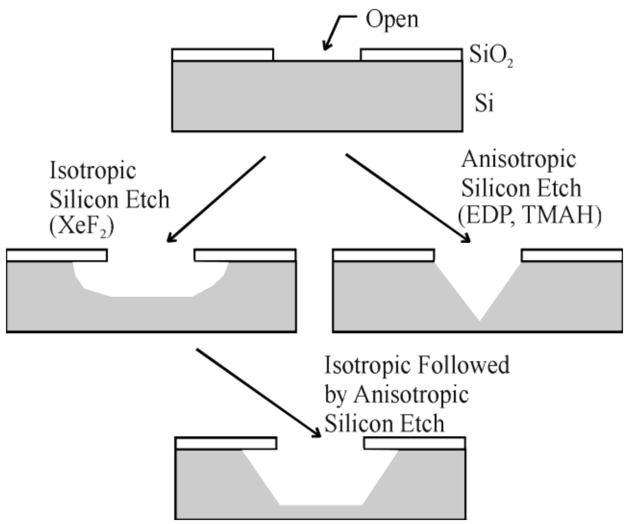
MEMS Platform Fabrication

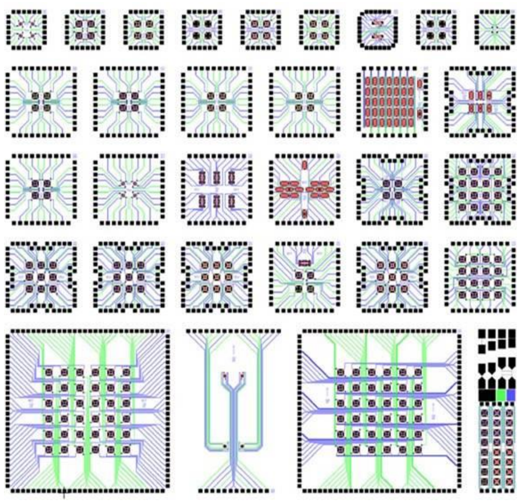
Processing Steps

- Design of multilevel mask set*
- Fab run at Si foundry
- Dicing of wafer and/or die
- Si etch "micromachining"
- Post-processing (e.g. - contacts)
- Mounting/wirebonding

** CMOS design rules*

Top-Surface Si Micromachining





15 mm x 15 mm die with multiple micohotplate-related designs

75 die on 6" wafer
(~ 1500 array devices)

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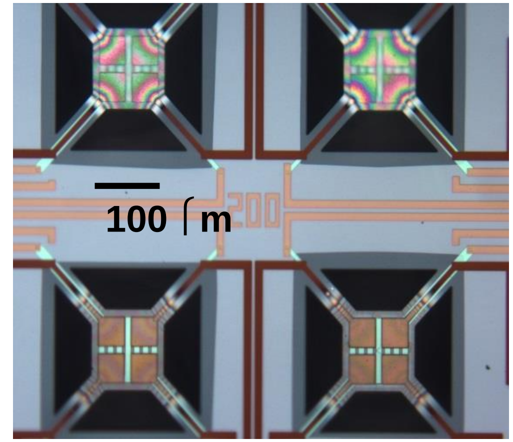
Film Deposition and Processing Methods

Local Heating

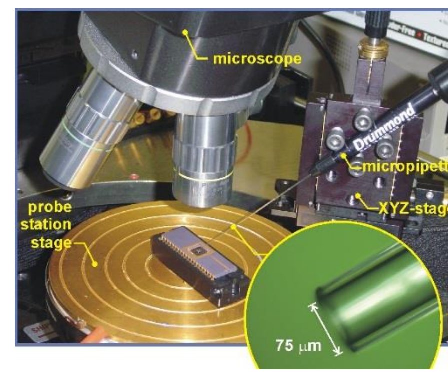
- Thermally-activated CVD
- Sol-gel, suspension drying
- Annealing
- Thermal lithography
- Thermally-assisted imprinting



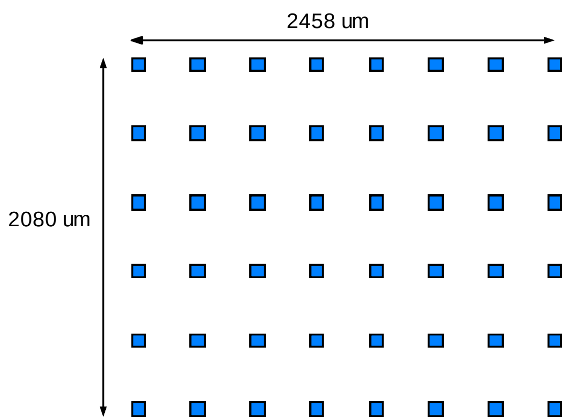
Local Potential Control

- Addressable electrochemical or electrophoretic deposition

Micro-Dispensing (pipetting)



Masking



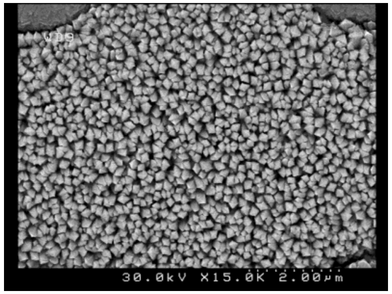
litho-defined shadow mask

all processing done after etching and packaging (to avoid etchants and to use electrical contacts)

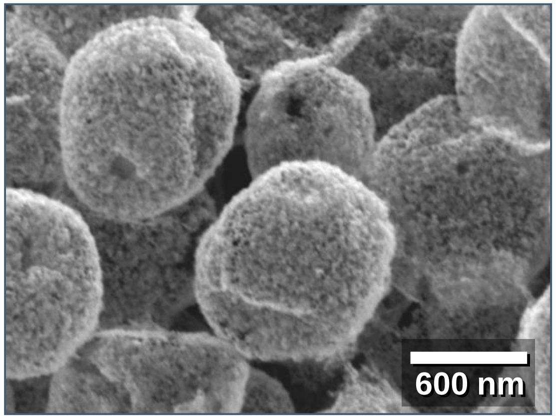
S. Semancik and R. E. Cavicchi, Accounts of Chemical Research 31, 279-287

Examples: Integrated Nanostructured Materials

High Area and Nanoparticle Materials

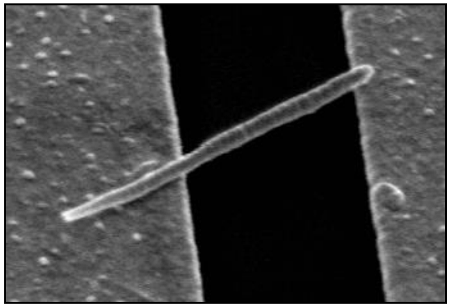


SnO_2 thin film

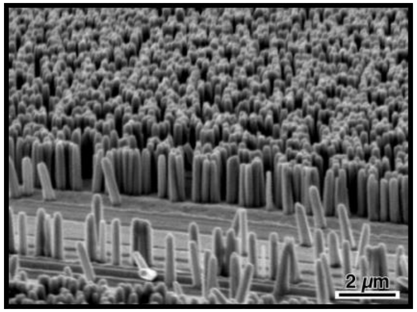


Sb:SnO_2 nanopaticle microshells

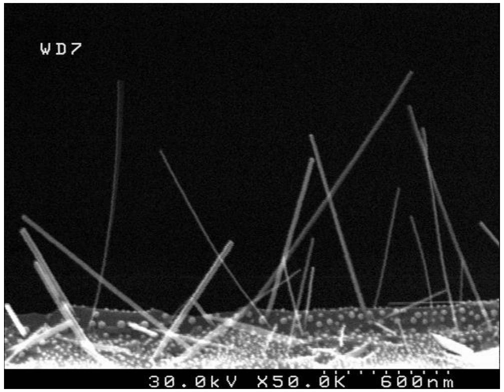
Nanowires, Nanorods and Nanotubes



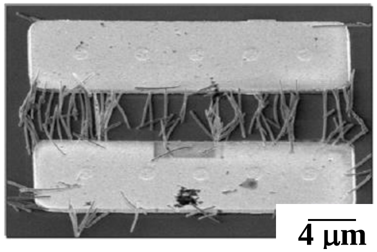
WO_3 wires



ZnO rods

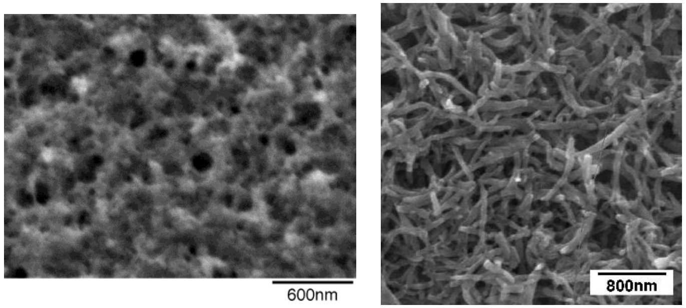


CNTs

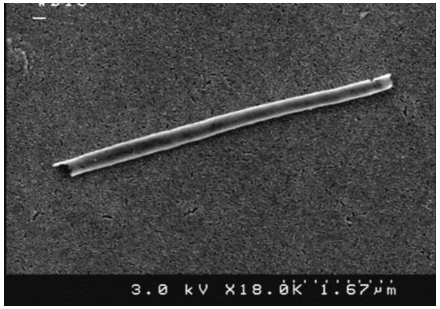


SnO_x nanowires

"Fast" Nanostructured Polymers



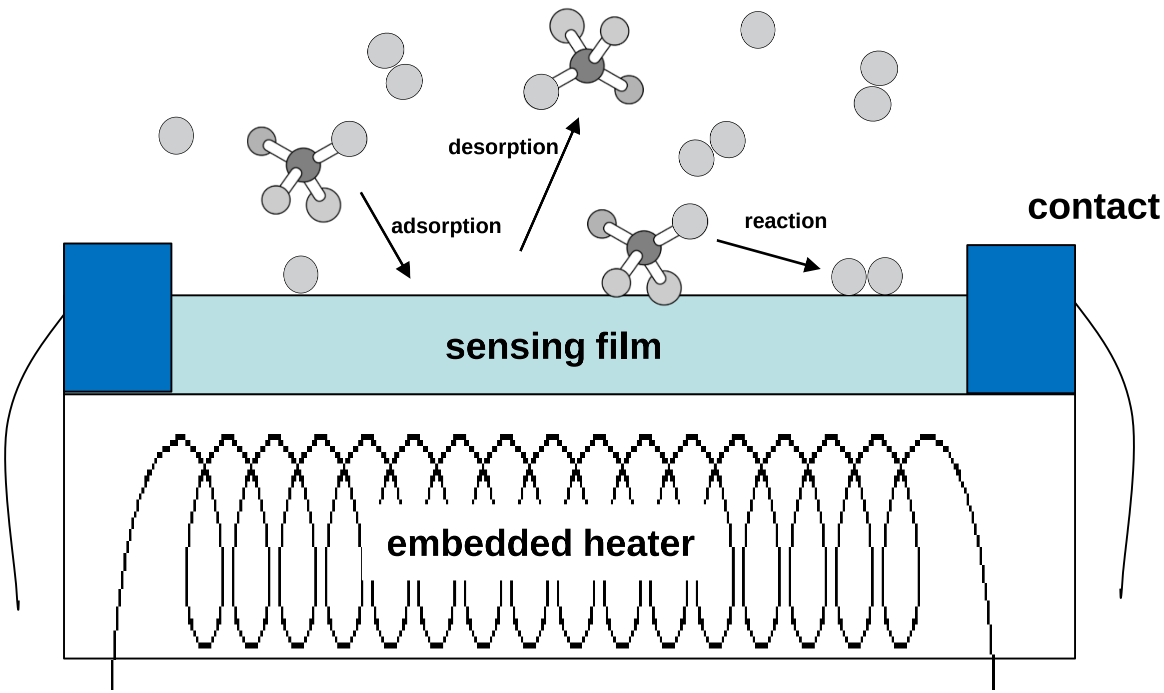
spongy PANI/nafion

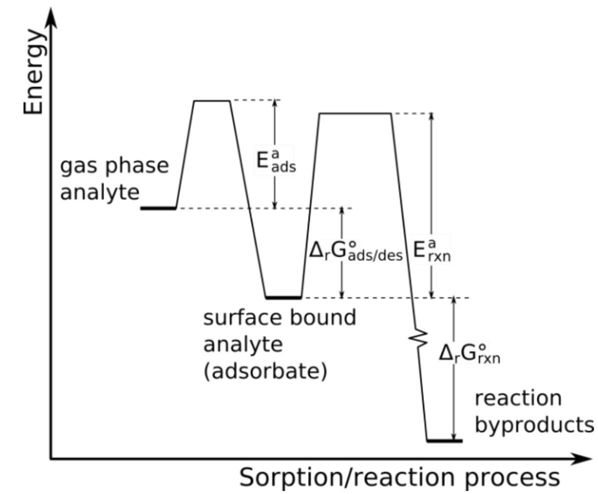


TiO_2 nanotube

Journal of Nanoparticle Research 8, 809-822

Temperature in Gas-Phase Chemical Sensing





s = f (T, Θ)

$$R_{ad} = \frac{d\Theta}{dt} = \frac{s_0}{N_{max}} \cdot f(\Theta) \cdot \frac{P}{\sqrt{2\pi mkT}} \cdot e^{-\frac{E^*_{ad}}{kT}}$$

$$R_{des} = -\frac{d\Theta}{dt} = \nu_x \cdot \Theta^x \cdot N_{max}^{x-1} \cdot e^{-\frac{E_{des}}{kT}}$$

Klaus Christmann

Sticking coefficient, adsorption and desorption rates - enable interesting operating modes when platforms have *time constants in ms range*

(Chemiresistive Sensing)

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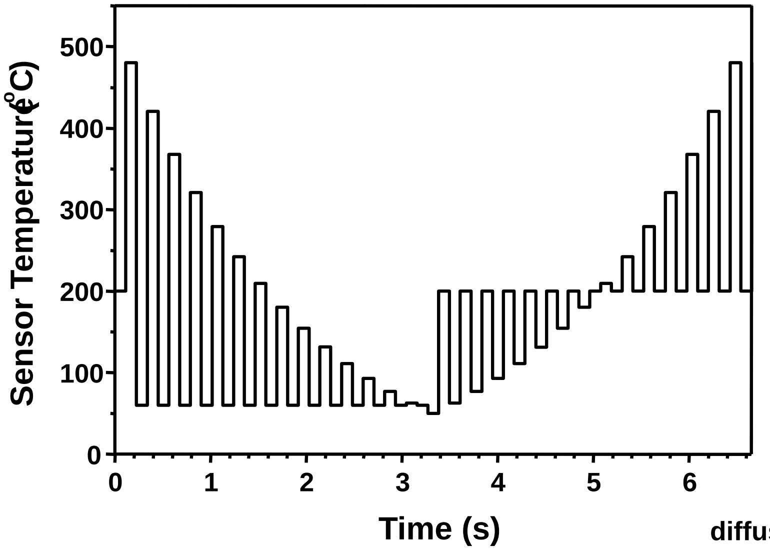
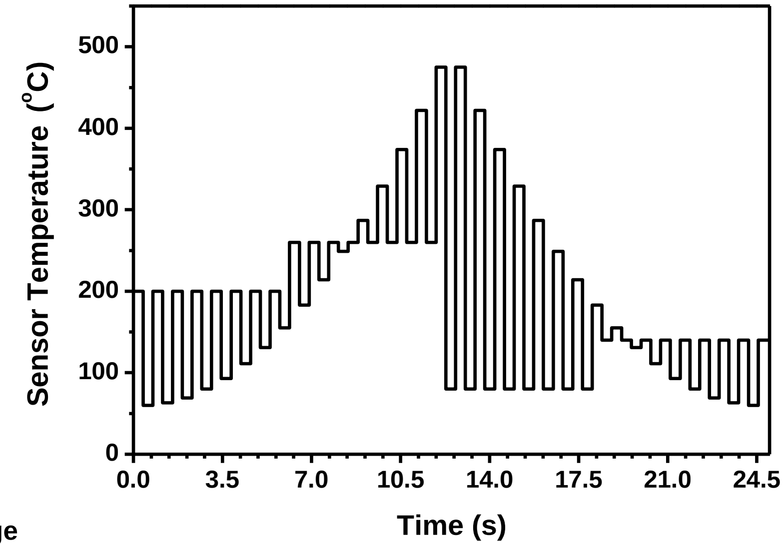
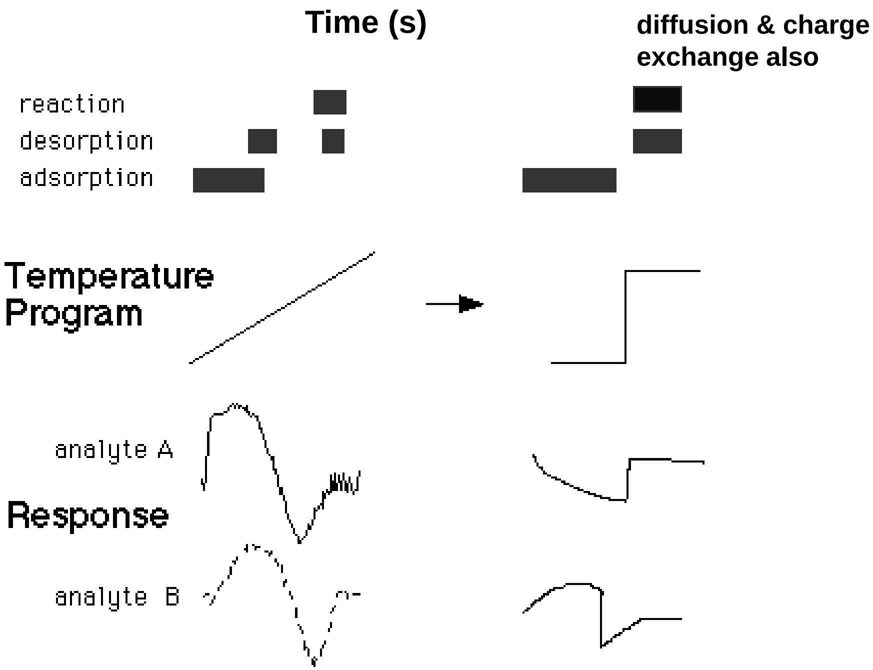
Higher Dimensionality: Temperature Programmed Sensing

2-Base, Exponential TPS Cycle



4-Base, Quadratic TPS Cycle

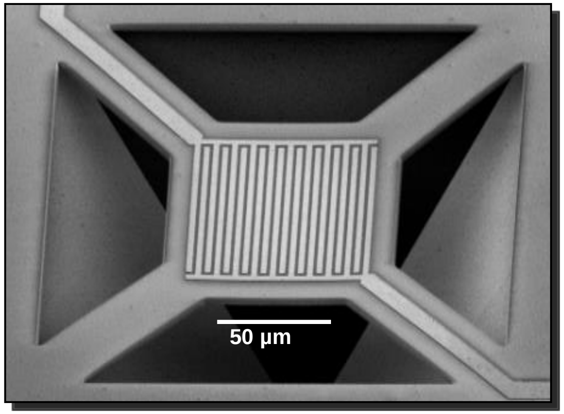




- **gas-film interactions alter film's electronic transport**
- **purposeful temperature excursions as a function of time drive surface phenomena that produce an analytically-rich temporal signal**
- **TPS cycles are run repeatedly to collect environmental information**

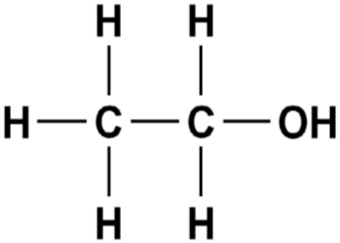
Single Microdevice Sensing

With fast temperature modulation, what discrimination can be accomplished?

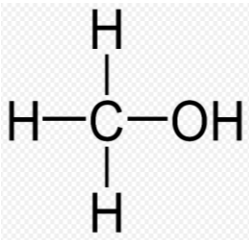


TPS-based operation of a single sensor
(SnO_2 film + ~20A annealed Pd)

Challenge – discriminating 2 similar chemicals



ethanol



methanol

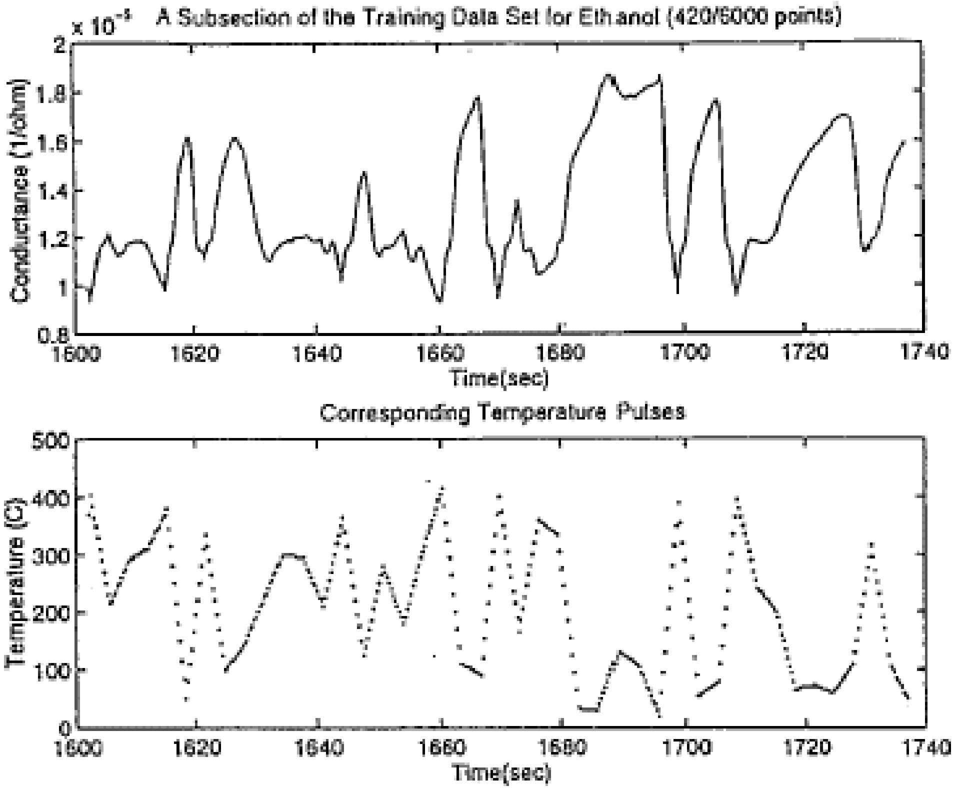
alcohol vapors in air

How should the temperature of the microsensor be varied to best discriminate between the two alcohols?

Let the sensor LEARN the answer ……

Learning about the Sensor’s Response vs T

using semi-random response information to aid discrimination



Measured response (for ethanol)

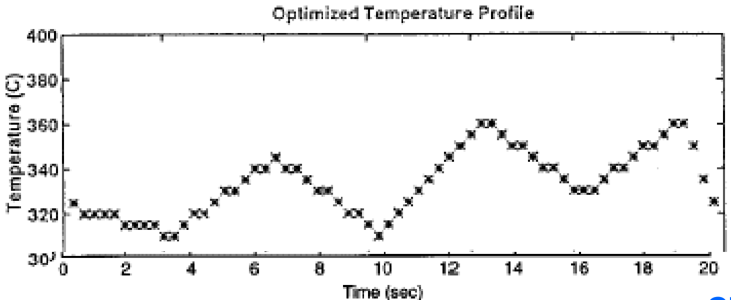
Temperature can be flexibly programmed to vary between ~ 20 °C and 450 °C

Random jumps were found to be too erratic -
but 10 points along randomly generated T slopes worked well, with T reset period ~ 300 ms

T. A. Kunt, T. J. McAvoy, R. E. Cavicchi and S. Semancik, Optimization of temperature programmed sensing for gas identification using micro-hotplate sensors, (Sensors and Actuators B 53, 24-43)

Predicted Response/Measured Response Comparisons

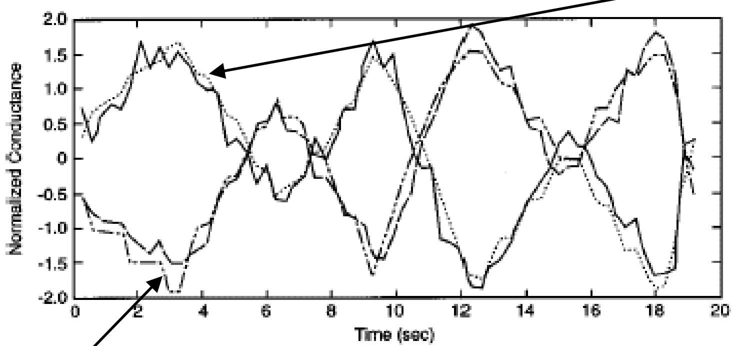
T. A. Kunt, T. J. McAvoy, R. E. Cavicchi and S. Semancik, Optimization of temperature programmed sensing for gas identification using micro-hotplate sensors, (Sensors and Actuators B 53, 24-43)



Predicted optimal discrimination T program
(by maximizing learned response separation)

ethanol prediction

—— ethanol data



Optimized operation predicts “polarity reversals” (out-of-phase) responses for ethanol and methanol *which greatly aids discrimination*

methanol prediction

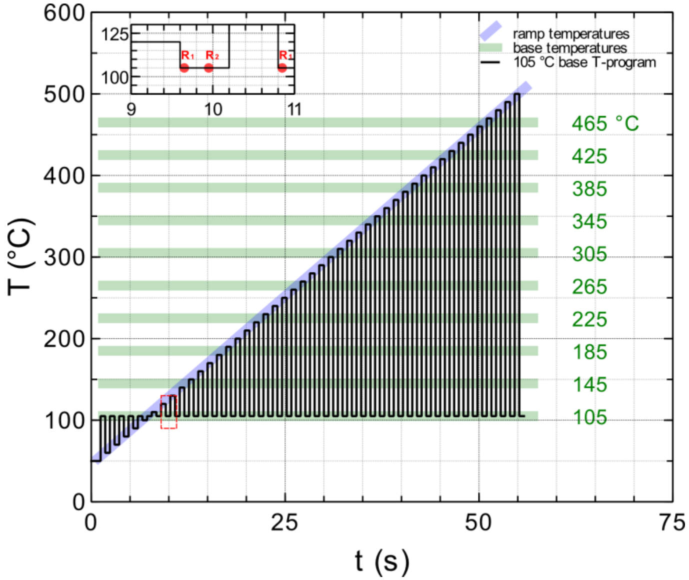
— - — methanol data

(Minimum discrimination time for these alcohols: ~ 2.2 sec)

[with rich data and PCA/LDA can do mixtures]

Systematic Data Acquisition

for development of application-optimized T programs



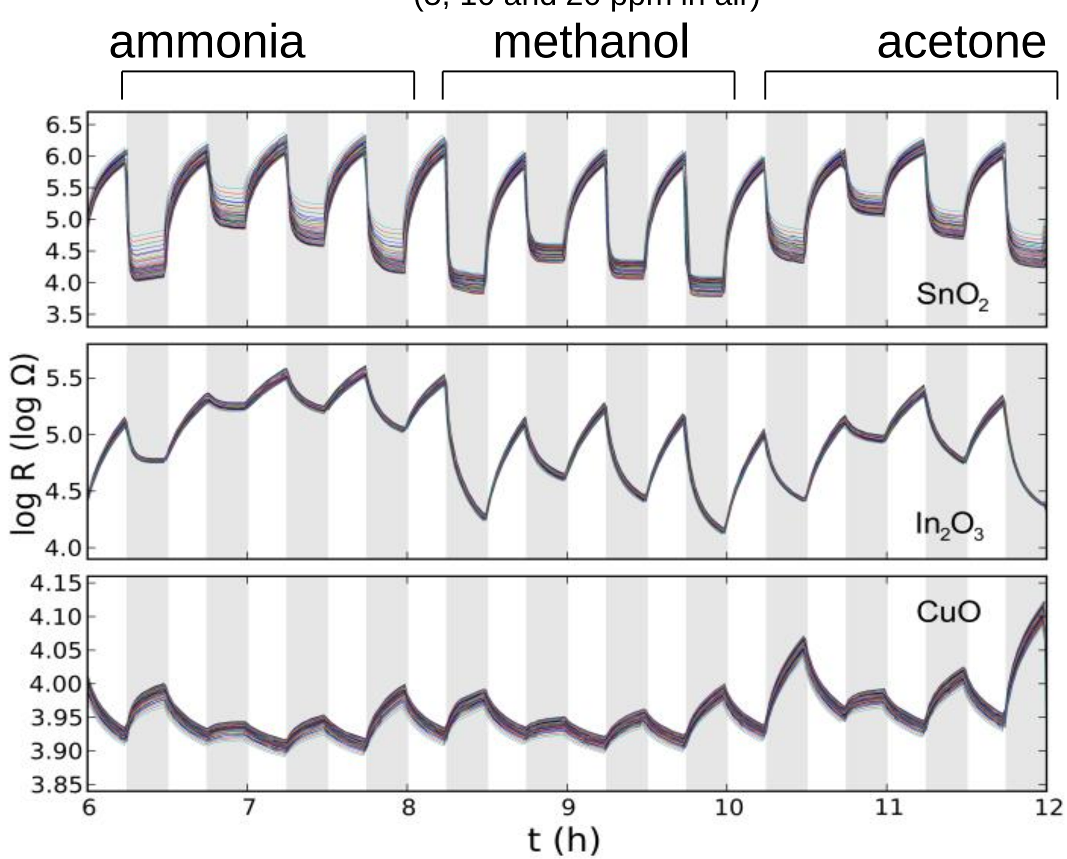
parametric pulsed-ramp programs employed for elements with 3 types of sensing films

46 pseudo-isotherms (for each sensing material below) following all ramp-to-base transitions during the T_{base} = 145 °C 6-hour exposure cycle

[1/10 of systematic database]

trace target exposure period

(5, 10 and 20 ppm in air)



locate high-value portions of TPS datasets via linear discriminant analysis (LDA) cluster separability and biplots

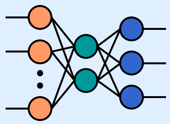
NIST

Signal Processing Methods (AI/ML)

methodology for extracting best analytical information

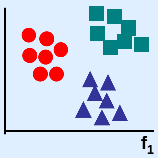
Recognition Classifiers

Artificial Neural Network (ANN)
K-nearest neighbors



Dimensionality Reduction and Data Preprocessing

Principal component analysis (PCA)
Linear discriminant analysis (LDA)
Baseline correction

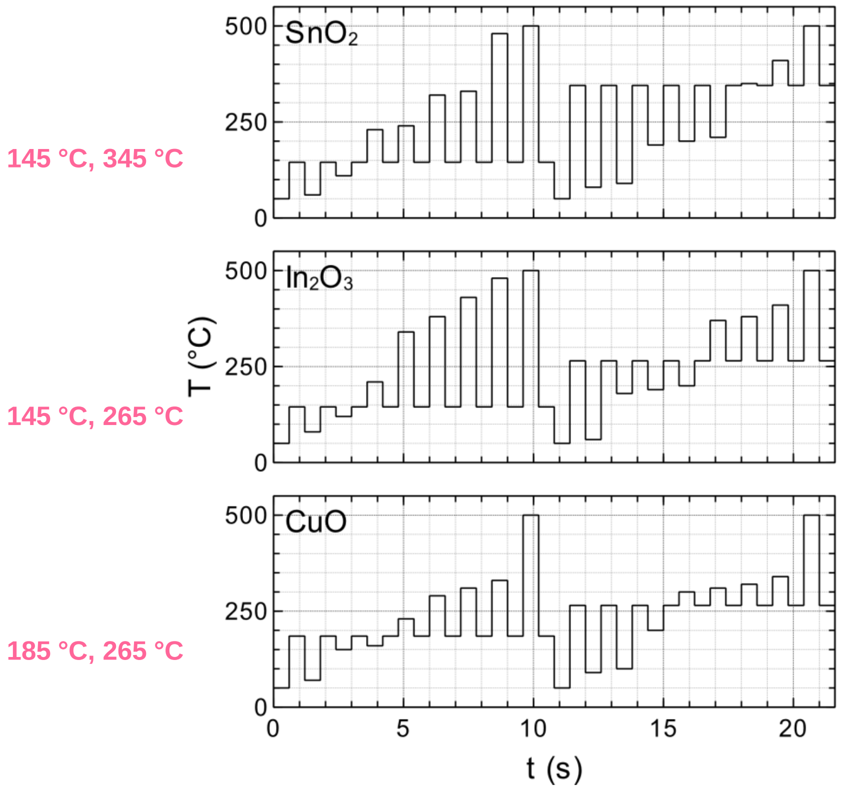


New Techniques for Improving Robustness

Bio-inspired signal processing
– Hierarchical Recognition Method
Event Detection

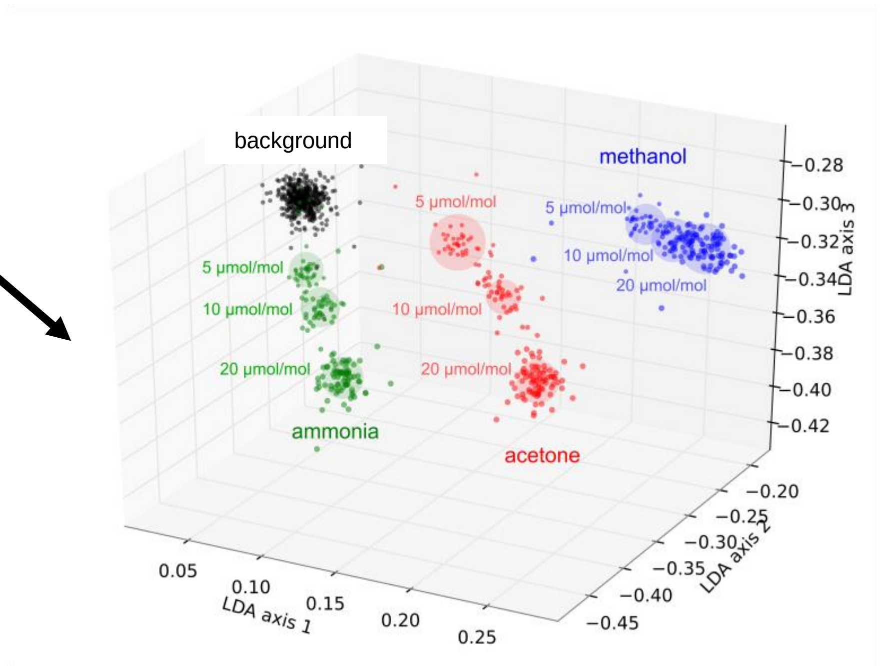
Pruned Optimization Programs/Resulting Performance

sensing material-dependent condensed T program assembled using 2 T_{base} with 9 T_{ramp} inputs each



22-second programs covering 2 bases and a variety of pulsed excursions

resulting separability of target analytes at different concentrations



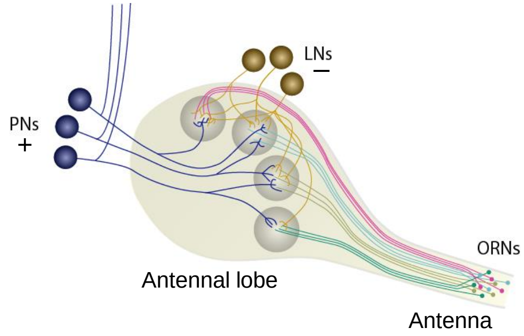
linear, unoptimized TPS	**optimized TPS (at left)**
each 55 sec	**each 22 sec**
0.47 cluster separability	**0.73 cluster separability**

P. H. Rogers, S. Semancik, Sensors and Actuators B 163, 8-19

Recognition and Classification

Taking things a bit further -

toward a hierarchical/bioinspired method for dealing with different types of chemicals



16 materials (2 copies of 8 films)

temperature ramped from 50 to 500 °C (in 1 °C increments)
16 materials x 450 temperatures = 7200 psuedo-sensors

For detecting compounds trained on, and "classifying" the class of unknowns

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Recognize Trained Analytes/Classify Unknowns

Approach Examined:
Hierarchical Method

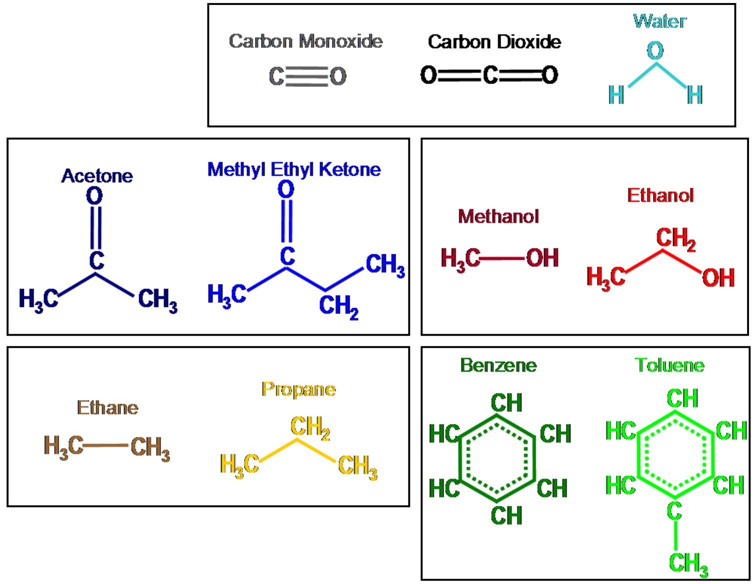
Training

↓

Age the Sensor

↓

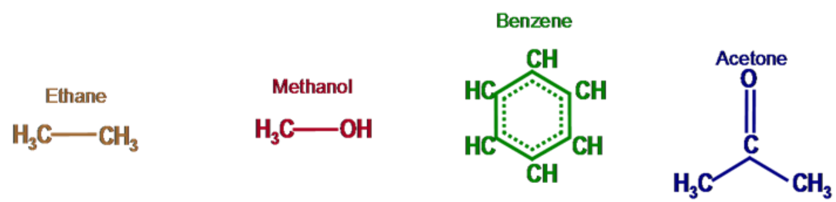
Test



Chemical Classes

Simple Oxides
Ketones
Alcohols
Alkane
Aromatics

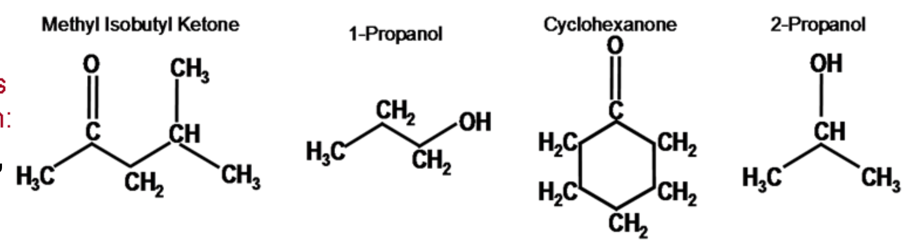
Repeated from training run:



Recognition Task

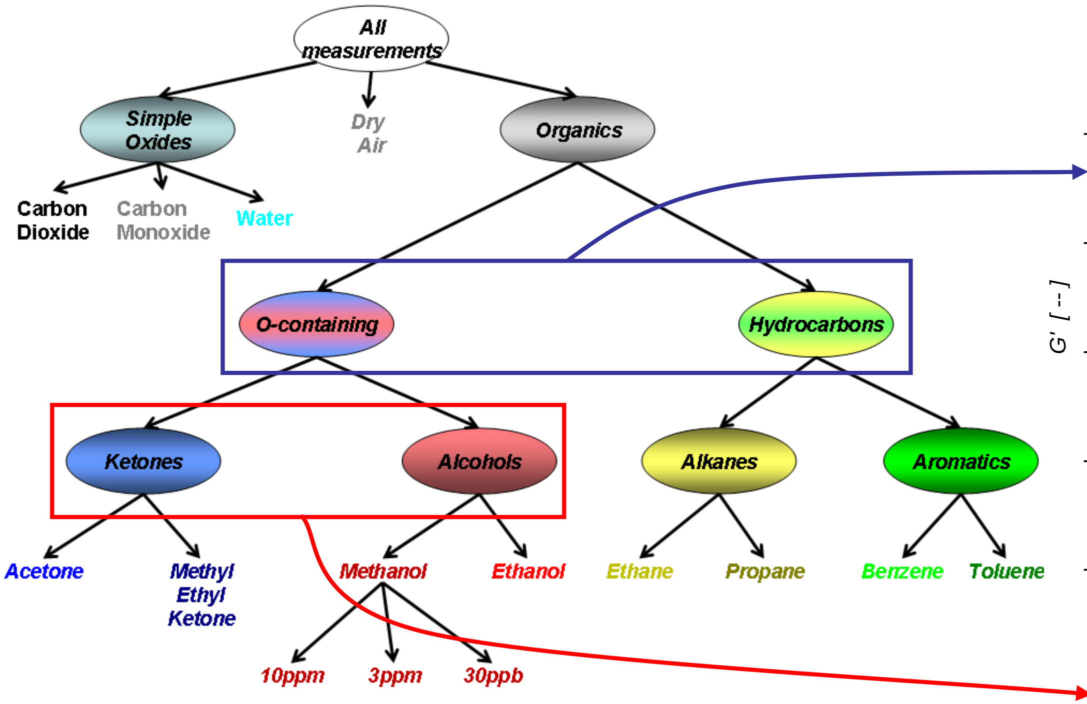
New analytes at ~1-10 ppm:

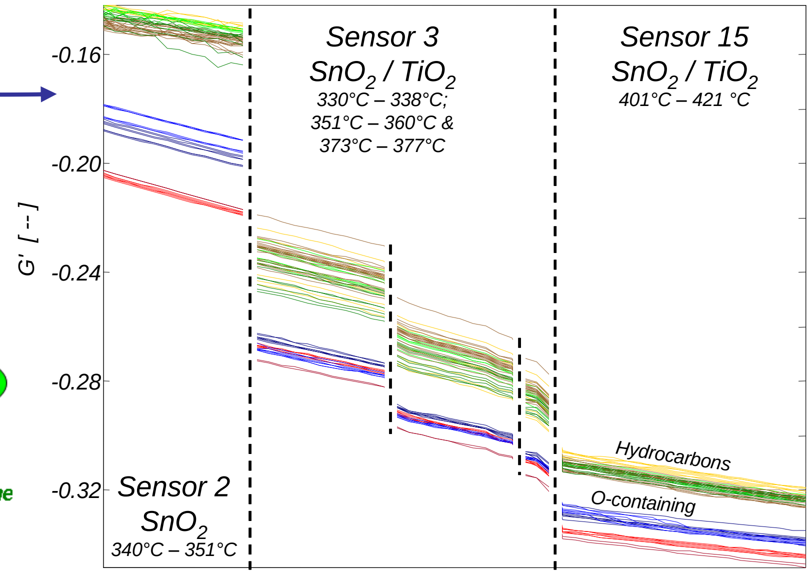
“unknowns”

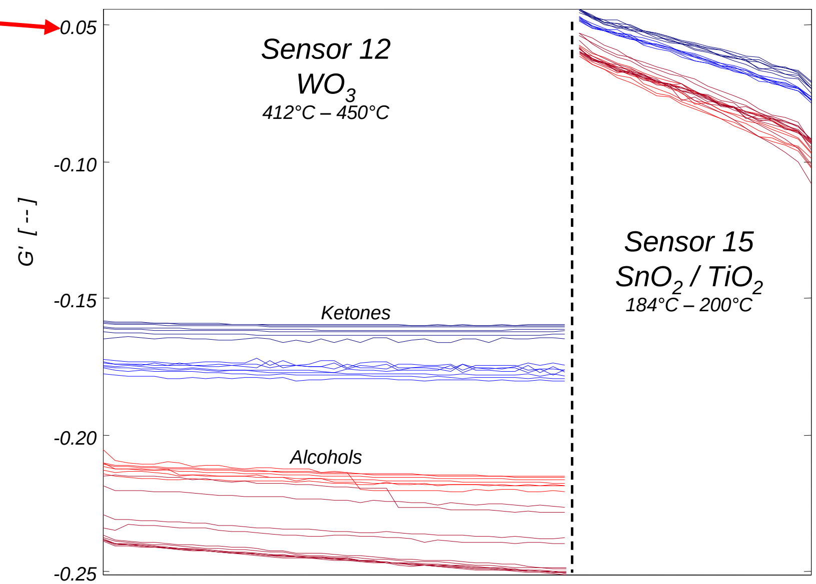


Classification Task

Optimized Analytical Answers from Rich Database







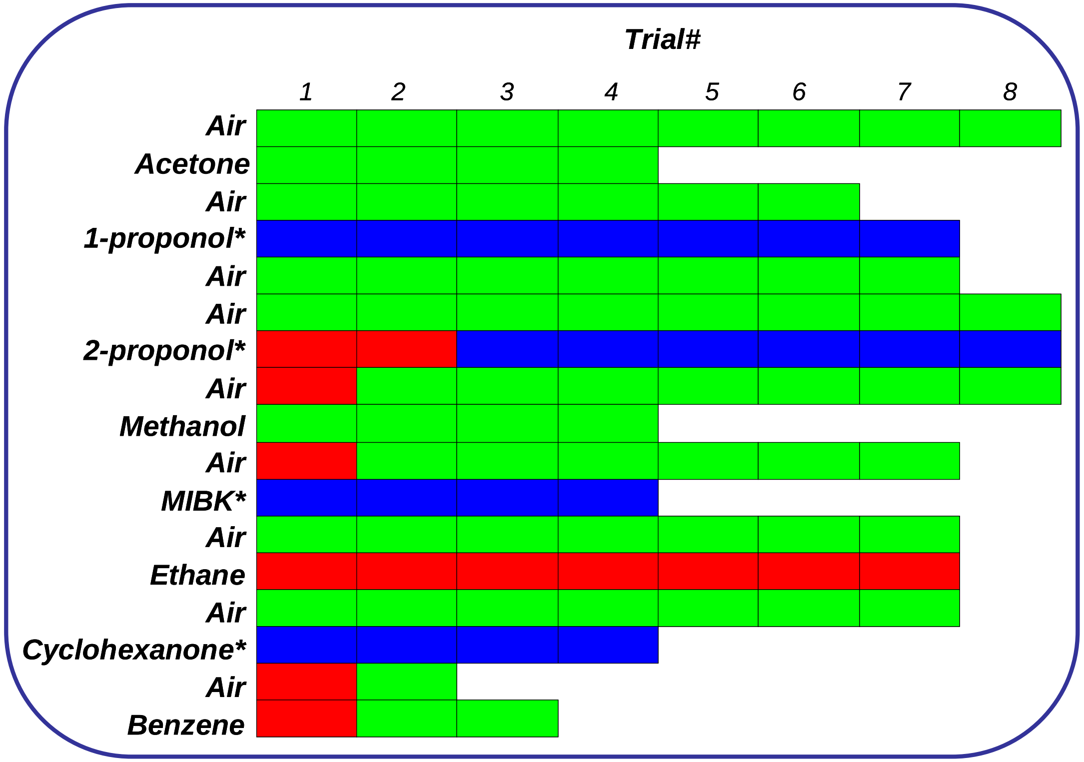
- **Employ (different) optimized regions from the measured materials-dependent and T-dependent training set to address each successive recognition/classification problem**

Bio-Inspired Methodology for Artificial Olfaction
B. Raman, J. Hertz, K. Benkstein, S. Semancik,
Analytical Chemistry 80, 8364-8371

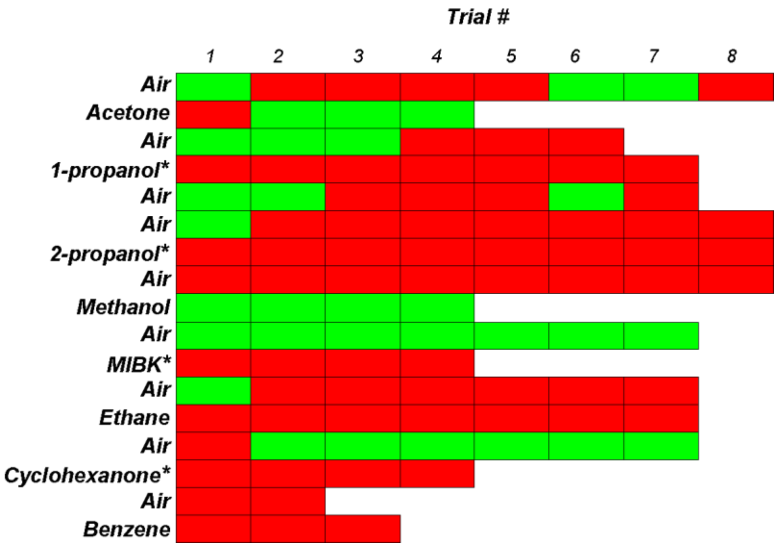
NIST

New Signal Processing Approaches - Hierarchy

Divide-and-Conquer Approach



Old, 'All-at-Once' Approach



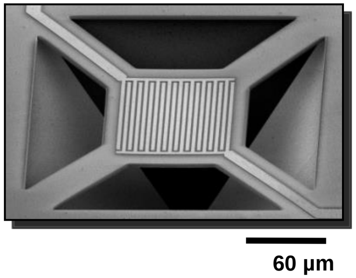
** Indicates chemicals not used in the training set*

Mis-Classification (red) *Correct Recognition* (green) *Correct Classification* (blue)

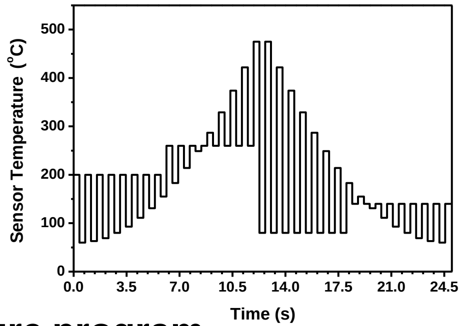
- *good recognition of specific compounds*
- *chemical classification of (untrained) unknowns*
- *method automatically avoids data regions where significant drift occurs*

Adaptability and Tunability with Common MEMS Platform

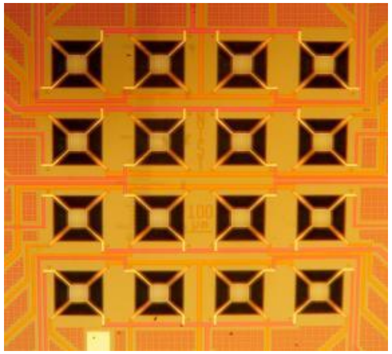
common platform e-nose for application-specific tuning



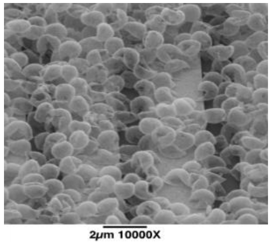
MEMS microhotplate

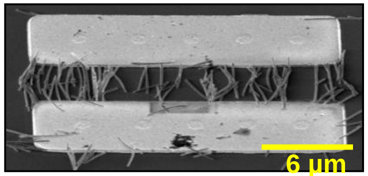


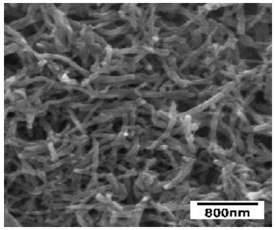
temperature program

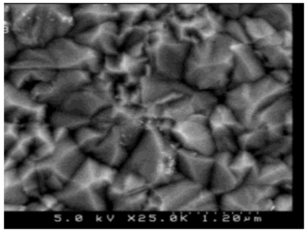


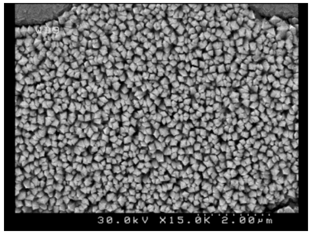
array platform with individually addressable elements



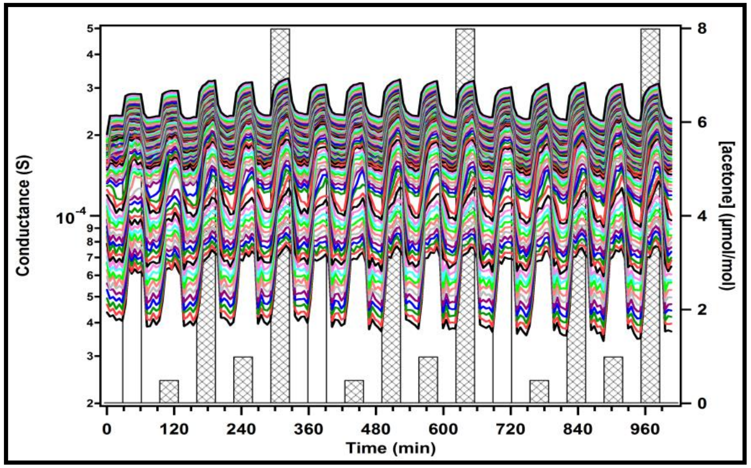




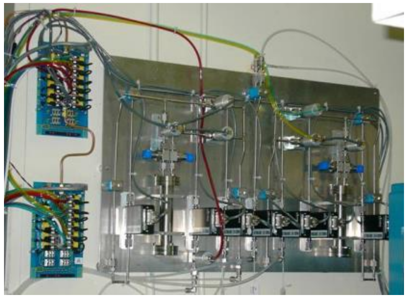




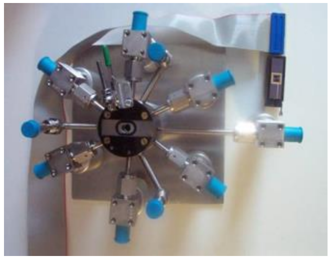
nanomaterials with varied compositions and morphologies



rich data streams



testing facilities



TICs
phosphonates
volatile organics
breath biomarkers

Some Chemicals and Interferences Tested with NIST Conductometric Microsensor Technology

Volatile Organic Compounds	
Acetone	C_3H_6O
Benzene	C_6H_6
Carbon Monoxide	CO
Carbon Tetrachloride	CCl_4
Chloroheptane	$C_7H_{15}Cl$
Dichloromethane	CH_2Cl_2
Ethanol	CH_3CH_2OH
Hydrogen	H_2
Methanol	CH_3OH
Naphthalene	$C_{10}H_8$
Trichloroethylene	$CHClCCl_2$

and others

Chemical Warfare Simulants & Agents

Vap.Press@25℃(torr)

CEES	C_4H_9ClS	3.4
DFP	$C_6H_{14}FO_3P$	0.579
DMMP	$C_3H_9O_3P$	1.2
GA	$C_5H_{11}N_2O_2P$	0.07
GB	$C_4H_{10}FO_2P$	2.9
HD	$C_4H_8Cl_2S$	0.11

Toxic Industrial Chemicals

Acrylonitrile	C_3H_3N	107.8
Ammonia	NH_3	>760
Arsine	AsH_3	>760
Formaldehyde	CH_2O	>760
Hydrogen Cyanide	HCN	≈760
Methyl Isocyanate	C_2H_3NO	348
Parathion	$C_{10}H_{14}NO_5PS$	7.4

and others

Detection at ppm concentrations has been demonstrated for *ALL* analytes; ppb (and high ppt) sensitivity has been demonstrated for some compounds.

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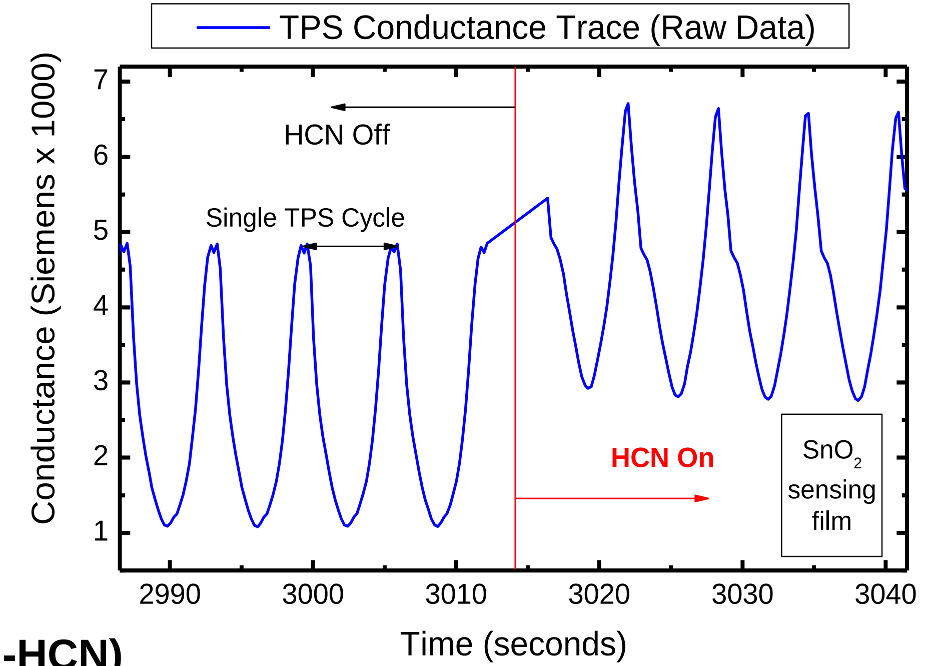
Detecting Chemical Hazards in Challenging Backgrounds

Raw Data (HCN - 1 condition)

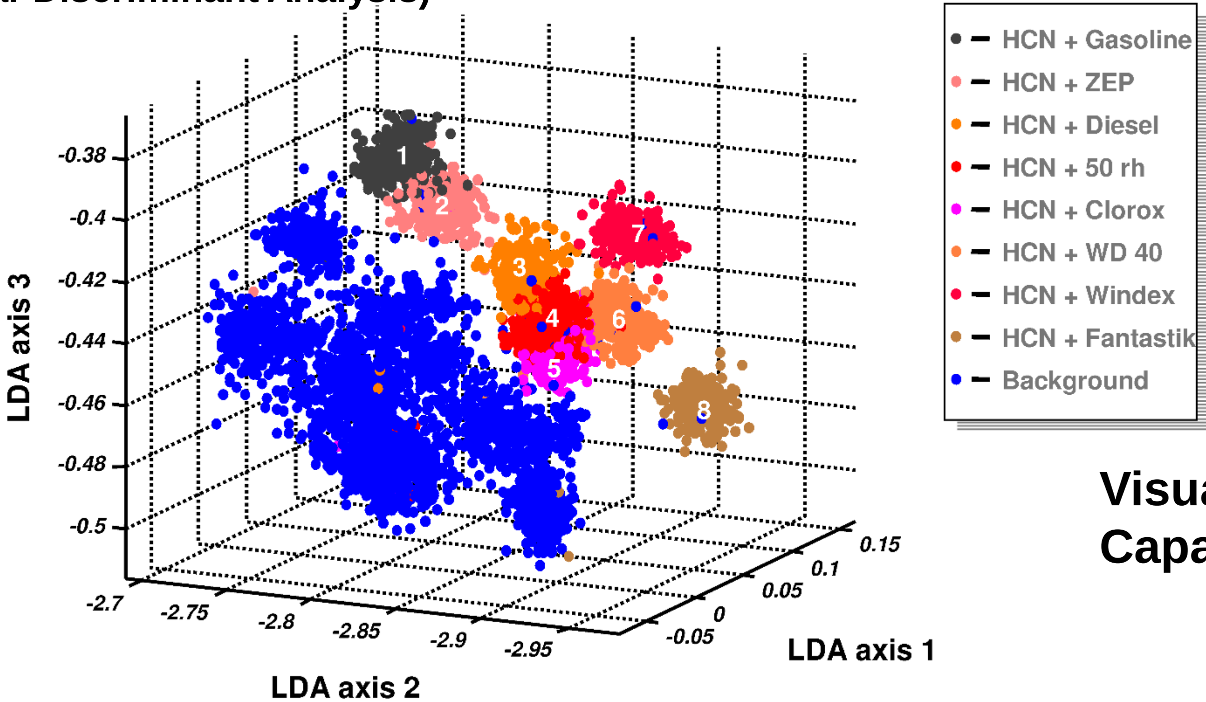
50 ppm HCN, 50% RH

data from <u>single</u> T-programmed SnO_2 element in array (32 T's)



Fully-Processed Data (all HCN and non-HCN)

(Linear Discriminant Analysis)



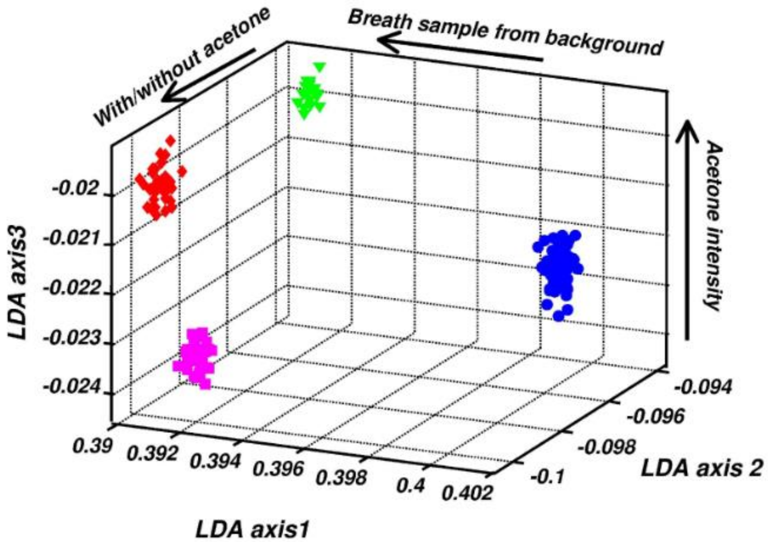
Sensors and Actuators B 137, 617–629

Annual Rev. Anal. Chem. 2:463–84

Visualization of Detection Capability

Preliminary Efforts: Medical Breath Analysis

acetone (diabetes) in synthetic breath



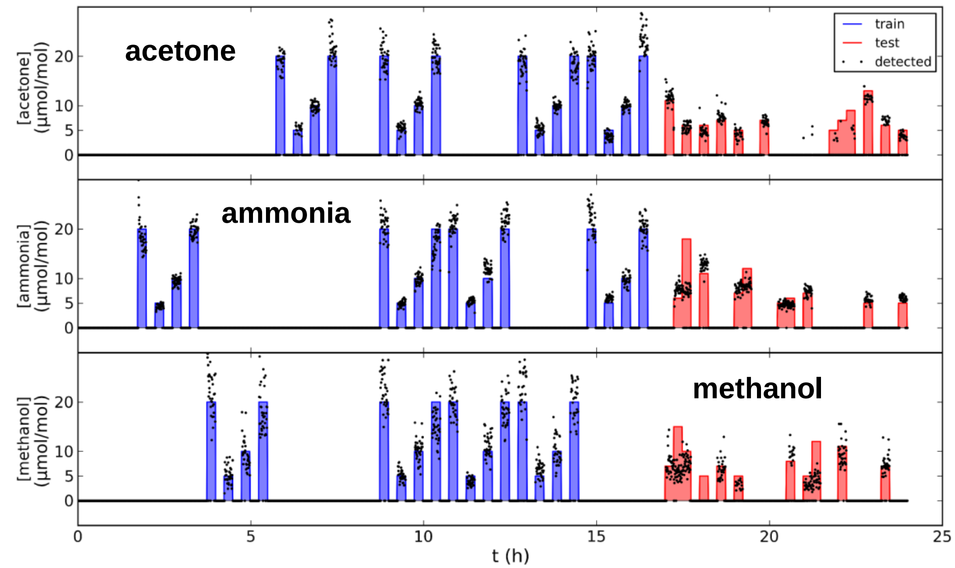
- Background air
- Exhaled breath - clean
- Exhaled breath - acetone low (1 ppm)
- Exhaled breath - acetone high (5 ppm)

IEEE Sensors Journal 10, 137-144

SnO_2 film + Sb:SnO_2 microshell film in TPS mode

multielement TPS with training and testing for 0,1, 2 or 3 target analytes (*biomarkers for diabetes, renal issues*) in synthetic breath

[3 materials, 18 ramp T, 2 base T]



Rogers, Benkstein, Semancik, Analytical Chem. 84, 9774

(machine learning)

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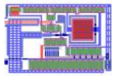
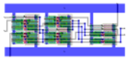
Other Enabling Technical Features

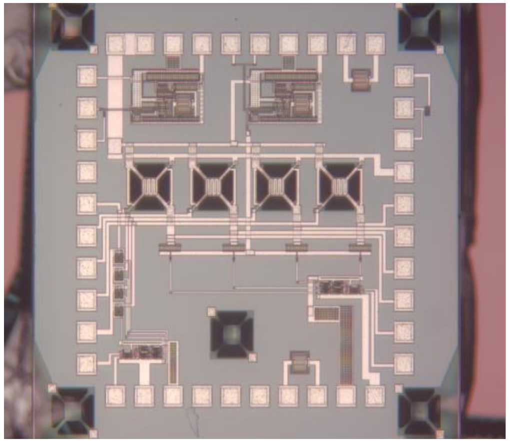
- **Efficient Materials Studies/Optimization**
  combi-array processing/performance evaluations
- **Integration of Support Functions**
  CMOS-based on chip electronics; coupled microfluidics
- **Reliability/Longevity**
  improved materials & contacts, "delayed activation"
  replacement within deployed devices



op-amp



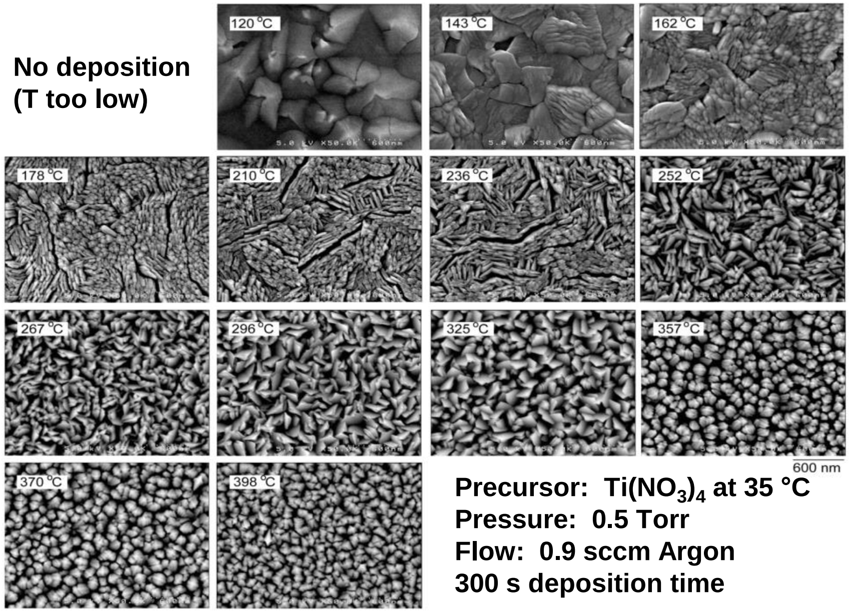
multiplexer



Monolithic Devices & Electronics

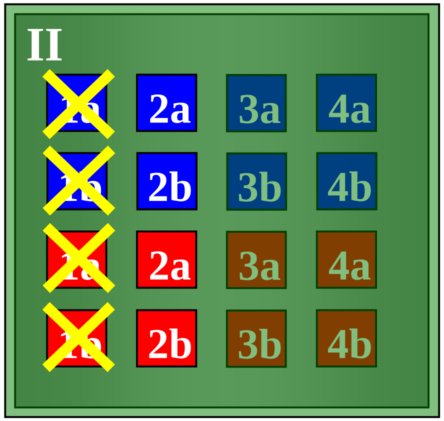
Array-Based Materials Studies

No deposition (T too low)

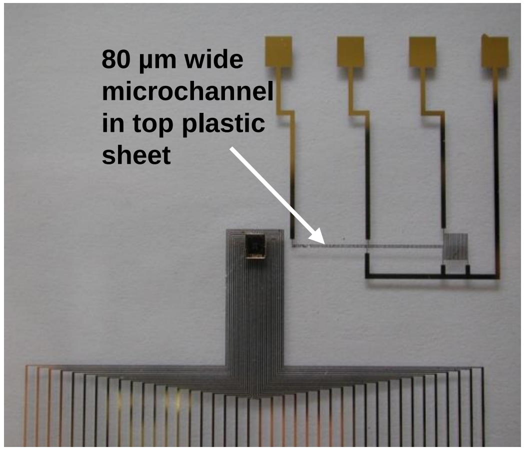


Precursor: $Ti(NO_3)_4$ at 35 °C
Pressure: 0.5 Torr
Flow: 0.9 sccm Argon
300 s deposition time

"Delayed Activation"



Microanalytical Systems



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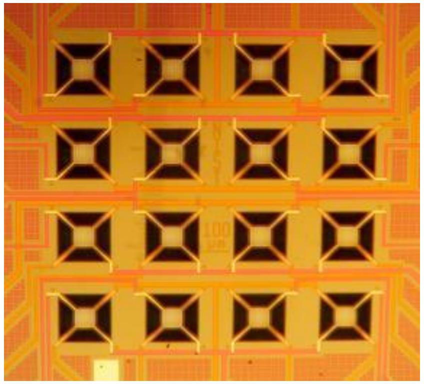
Outline

- **Chemiresistor Array**

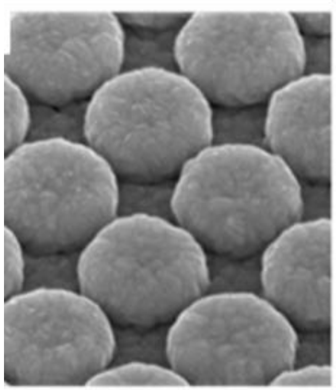
  application-adaptable gas sensing



100 μm elements

- **Plasmonic Optical Sensor Platform**

  gas-phase and condensed-phase sensing

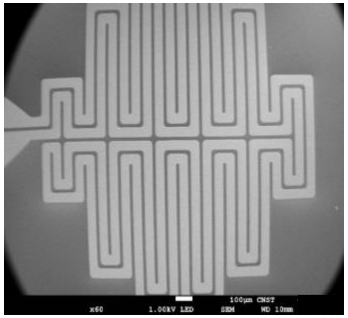


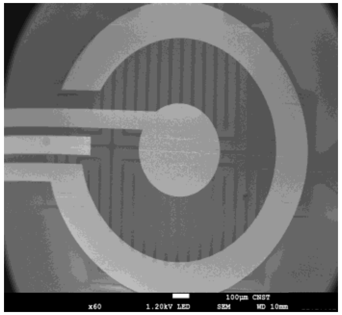
380 nm features

- **Microscale Electrochemical Device**

  biochemical characterization

DNA on 500 μm working electrode

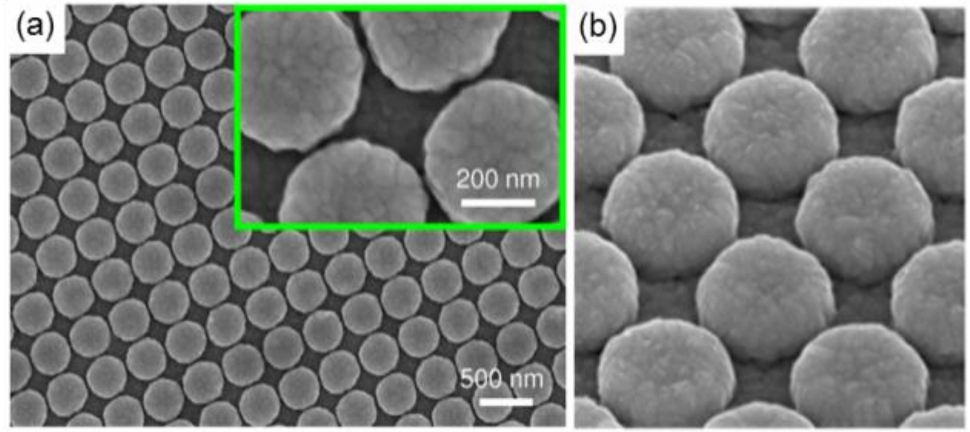


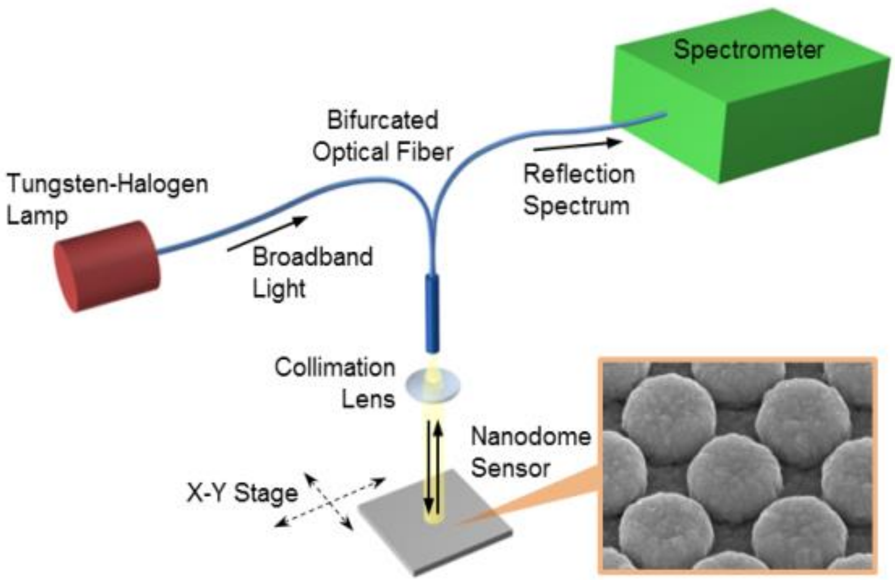


Nanoengineered Materials for Photonic Sensing

Ag Nanodome Arrays

(380 nm diameters, 15-20 nm gaps)





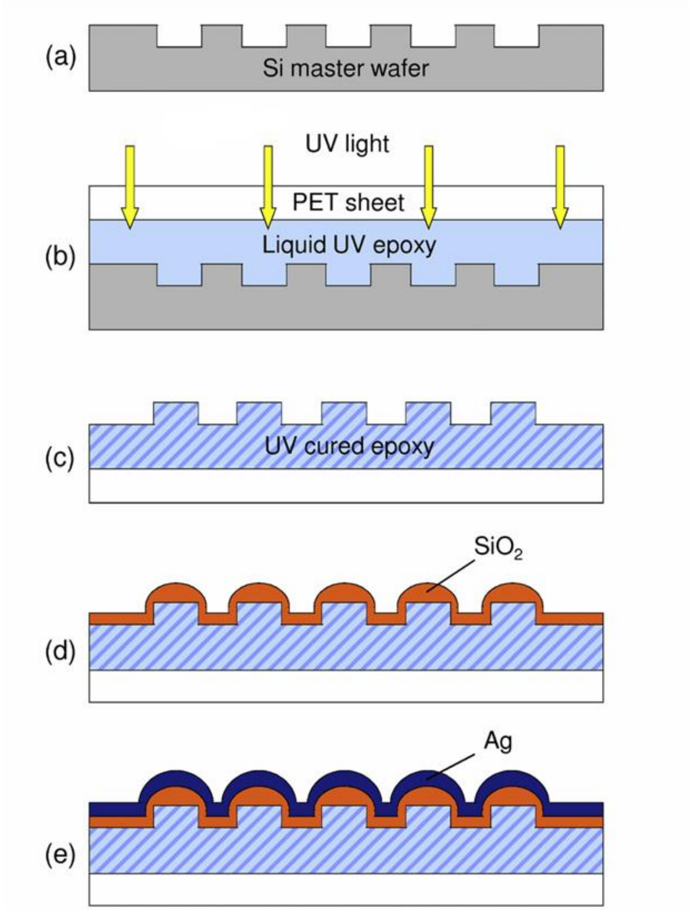
Sensing Signals

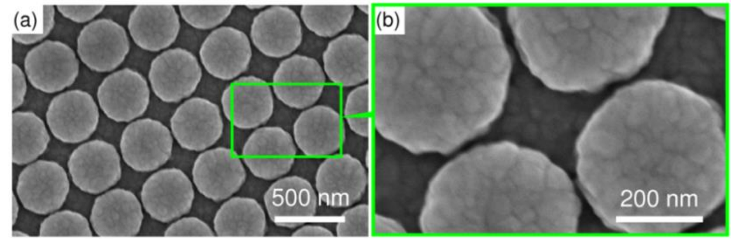
Surface-Enhanced Raman Scattering (SERS)

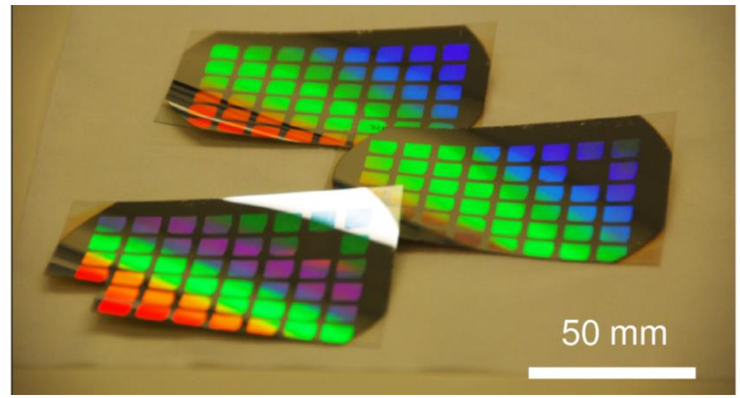
Localized Surface Plasmon Resonance (LSPR) – capture affinity

Nanodome Array Fabrication

Nanoreplica Molding Process



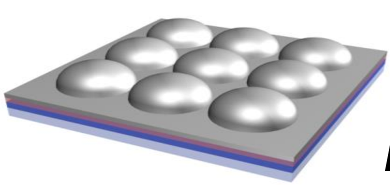




array on flexible polyethylene terephthalate substrate (PET)

- **Room temperature**
- **Low-force molding**
- **Plastic substrate**

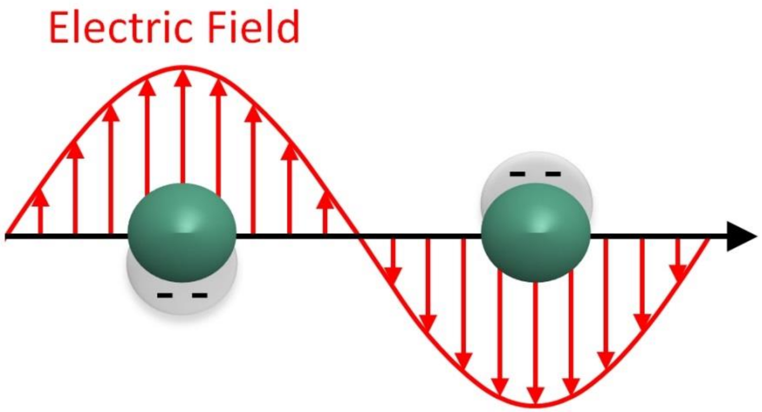
- **Low-cost/disposable**
- **Large-area fabrication**
- **Uniform, reproducible structure**
- **Simple to control gap dimension**



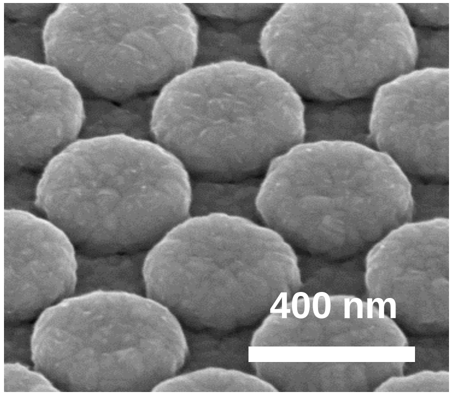
Fabrication at NIST NanoFab

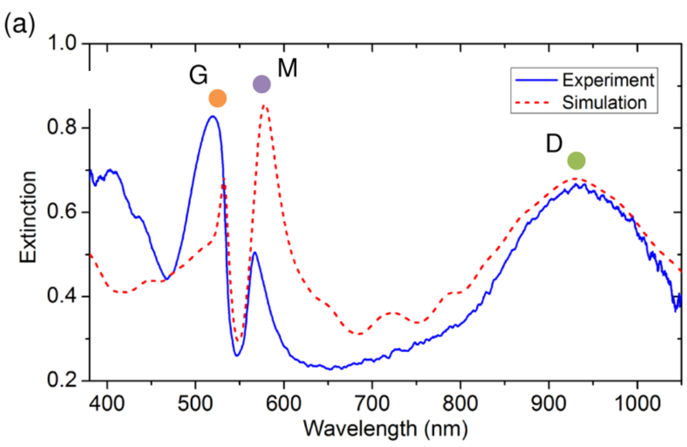
NIST

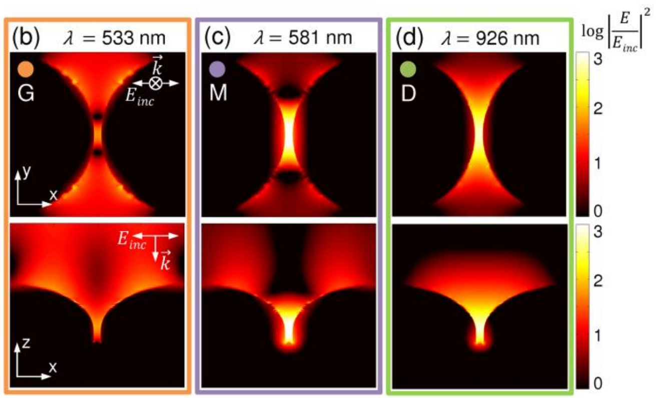
Localized Surface Plasmon Resonance (LSPR)



Plasmonic "Nanodome" Array







Finite Difference Time Domain (FDTD) modeling of photonic modes (spatial/size effects)

Modes

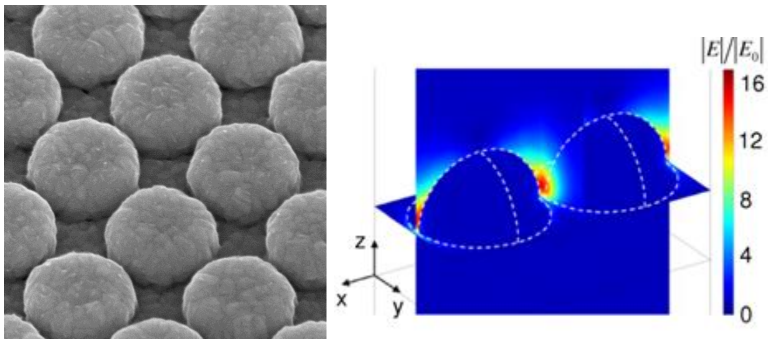
Grating Diffraction (G)
Multipole (M)
Dipole (D)

Choi and Semancik, Optics Express, 21, 28304

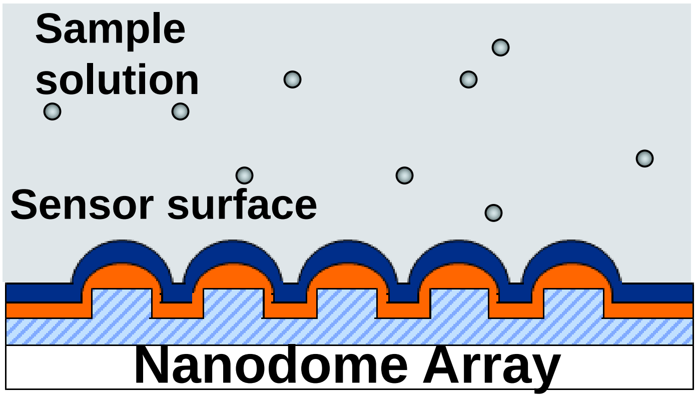
NIST

Label-Free Capture Affinity Biosensor

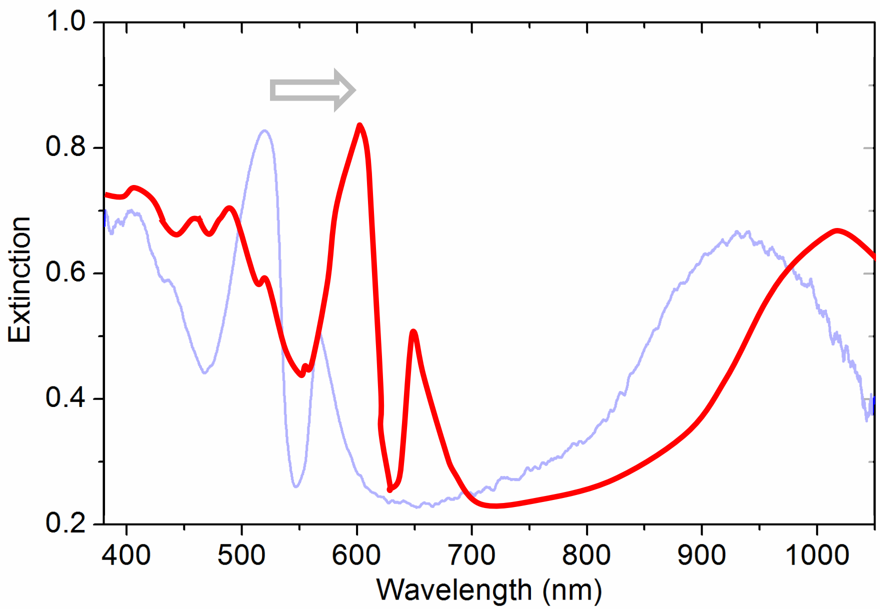
Plasmonic Nanodome Array



- **Biomolecular attachment to sensor surface**



induces shift in resonance of localized modes

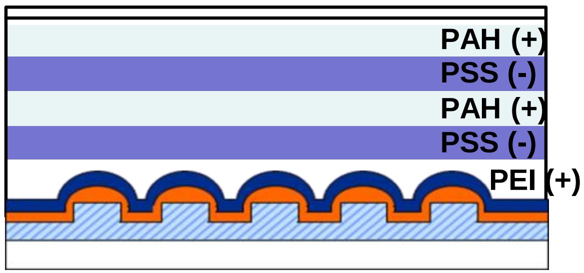


NIST

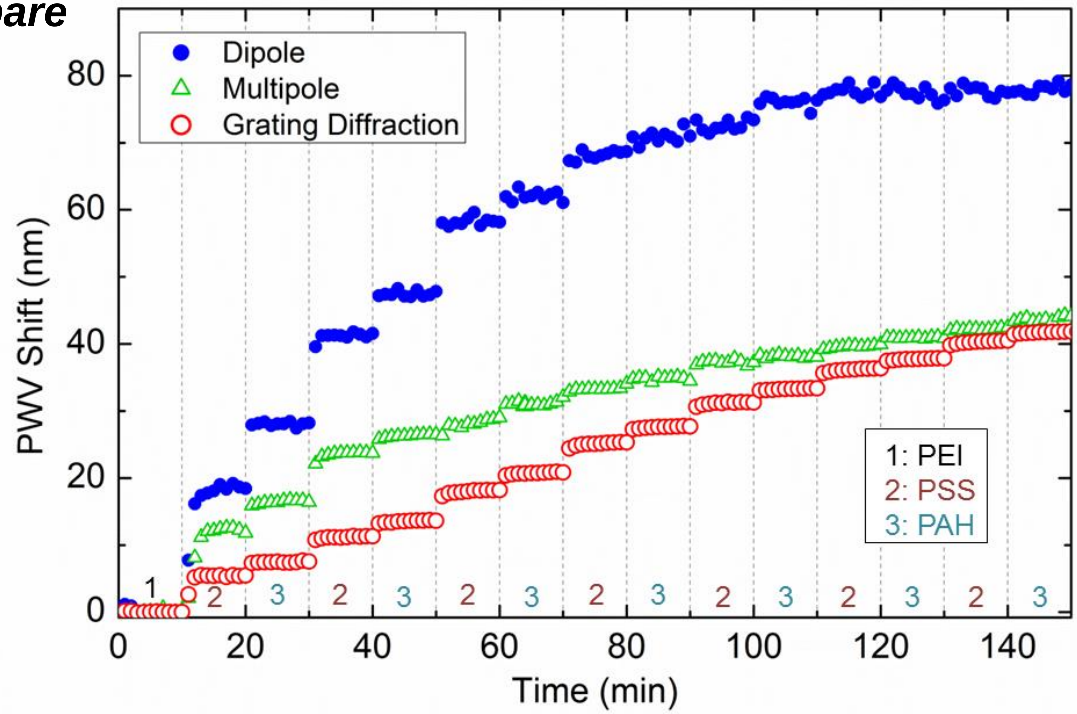
Surface Sensitivity

stacking alternate-charge 5 nm layers to explore surface range and compare to theory

<ins>**Charged polyelectrolyte layers**</ins>



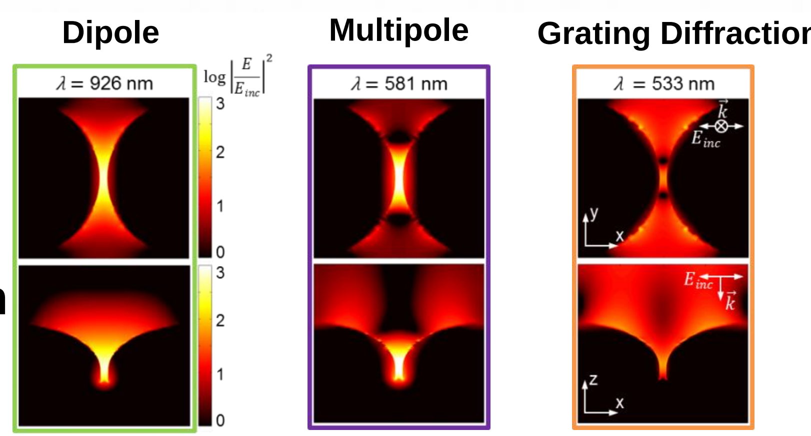
Nanodome Sensor



PEI: poly(ethylenimine)
PSS: poly(sodium 4-styrenesulfonate)
PAH: poly(allylamine hydrochloride)

Finite Difference Time Domain modeling of photonic modes

~ 60 nm



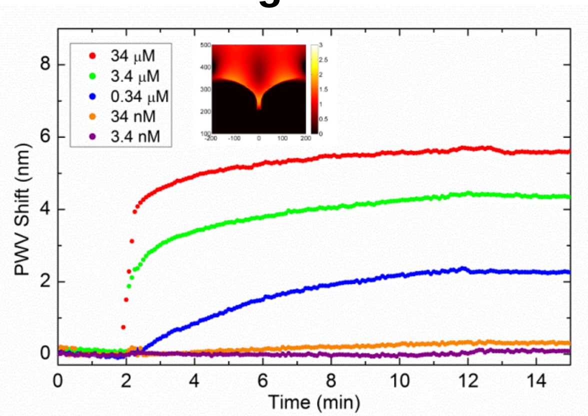
> 75 nm

Choi and Semancik, Nanoscale 5, 8138–8145

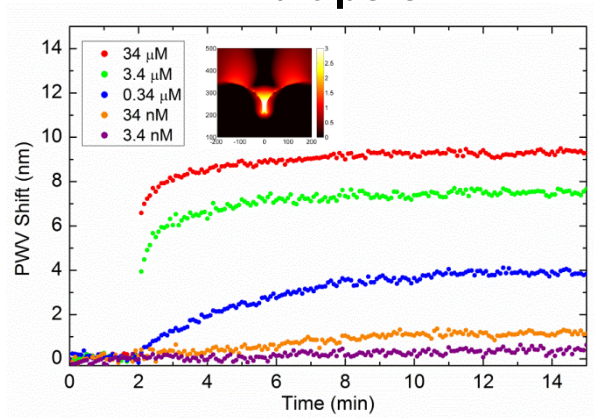
Protein – Protein Binding Assay

Protein A (0.5 mg/mL) adsorbed on nanodome array and exposed to IgG

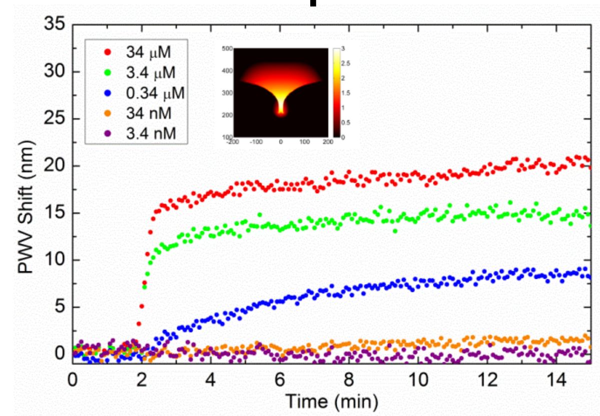
Grating Diffraction

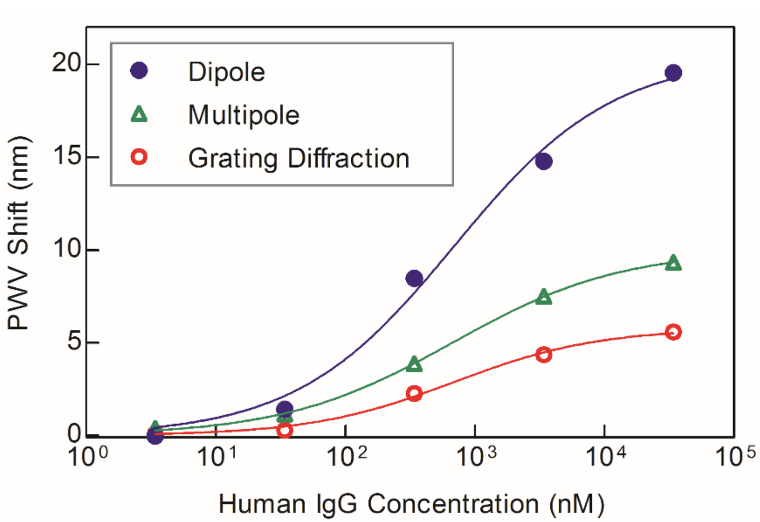


Multipole



Dipole





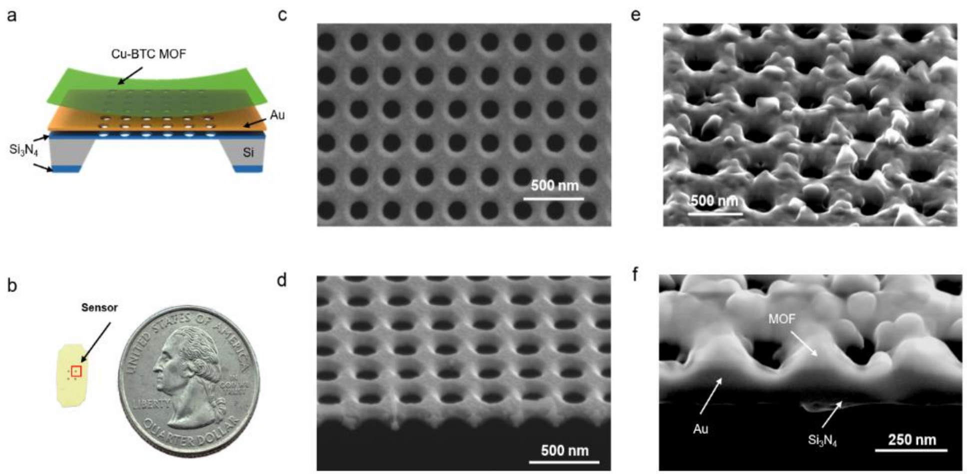
Resonance Mode	K_D (μM)	Detection Limit (nM)
Dipole	0.693	0.131
Multipole	0.672	0.767
Grating Diffraction	0.690	1.69

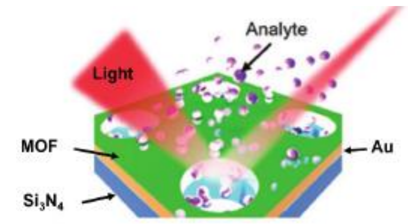
K_D ~ 0.53 μM measured previously
Lu *et al. Appl. Phys. Lett.* 93, 111113

Choi and Semancik, Nanoscale 5, 8138–8145

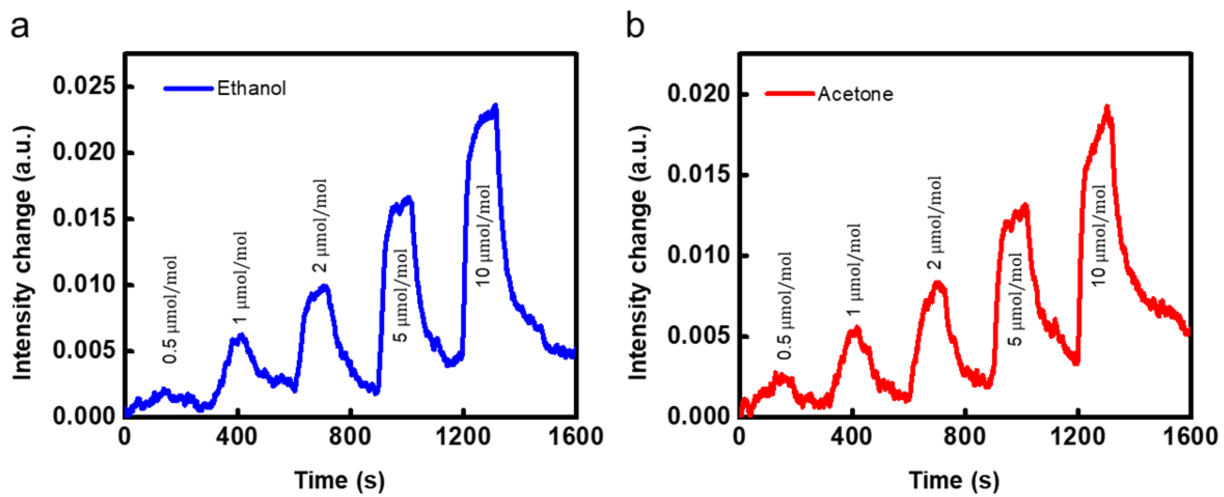
Recent Plasmonics Studies: Gas Sensing with Holes and a Camera

Au nanohole array (NHA) coated with MOF (metal-organic framework)





detection of VOCs at MOF-nanohole interfaces

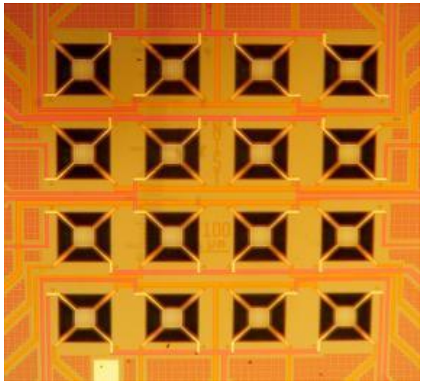


(with George Washington Univ.)

Outline

- **Chemiresistor Array**

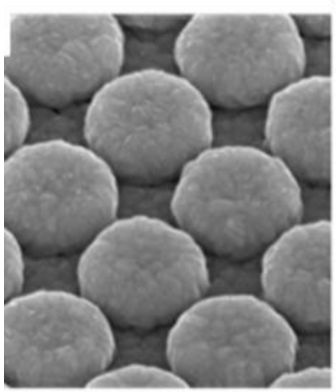
  application-adaptable gas sensing



100 µm elements

- **Plasmonic Optical Sensor Platform**

  gas-phase and condensed-phase sensing

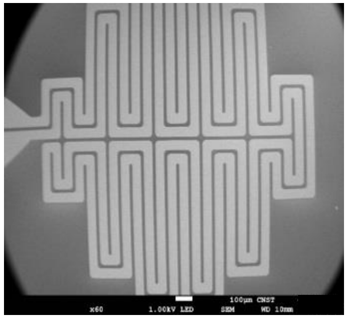


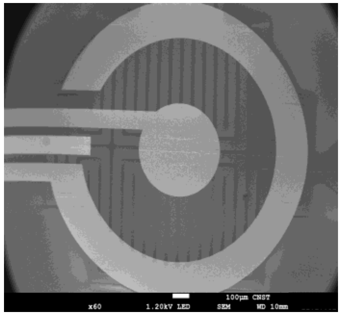
380 nm features

- **Microscale Electrochemical Device**

  biochemical characterization

DNA on 500 µm working electrode



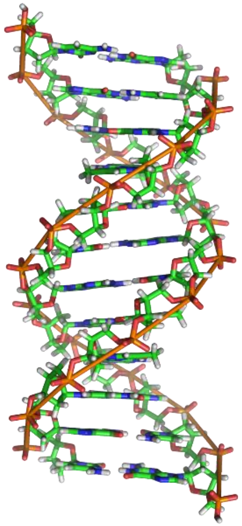


Electrochemical Biosensing

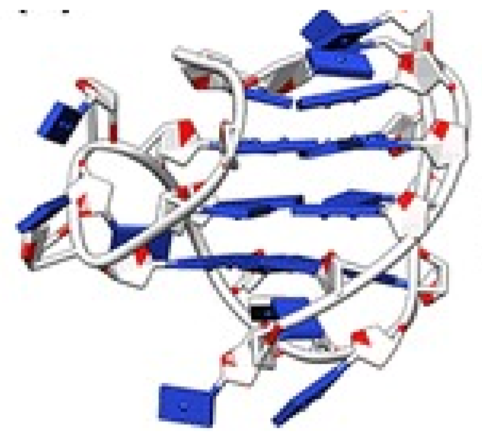
- Surface Immobilized biomolecules
- Microheater-Based T Control, but ~ 20 °C - 80 °C (not 20 °C – 480 °C)
- T_m Measurements as a Property Indicator (biomolecule stability or binding-based change in stability)

Drug discovery & quality control

Medical diagnostics



Duplex DNA



G-Quadruplex DNA

Electrochemical Sensing with Temperature Control

moving toward <u>smaller-volume</u>, <u>electronic</u> devices

Examples of prior electrochemical device research involving temperature:

- **T-dependent hot wire electrochemistry**
  Flechsig, Peter, Hartwich, Wang, Grundler, *Langmuir 21,* 7848-7853
- **Peltier heater-based electrochemical measurements**
  Yang, Hsieh, Patterson, Ferguson, Eisenstein, Plaxco, Soh *Angew. Chem. Int. Ed*. 53, 3163-3167

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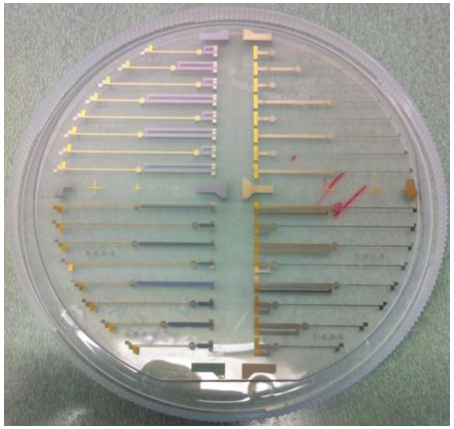
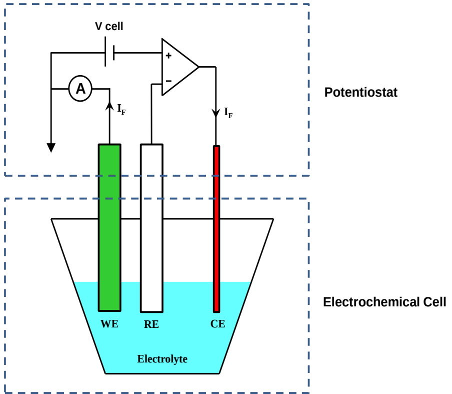
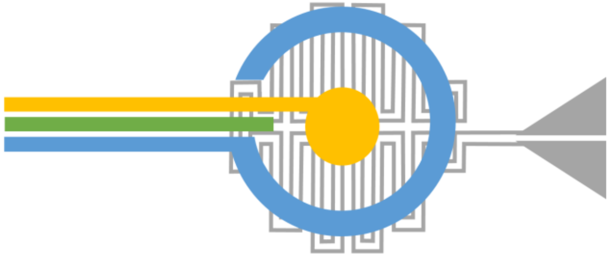


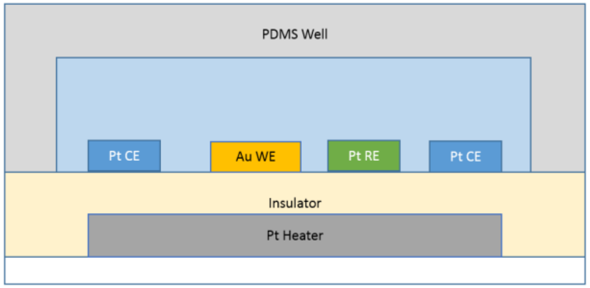
<u>Present work</u>:

- **Wafer-based planar microscale fabrication**
- **Small-footprint elements - *small volume sample analyses***
- **Integrated, localized heater (*dedicated to each element*)**
- **Potentially faster T sweeps and T programming**
- **Compatible with electronic microarray development**





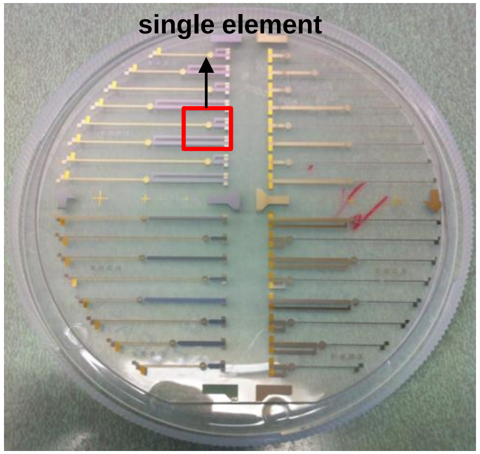
10 µL (moving toward 100nL)

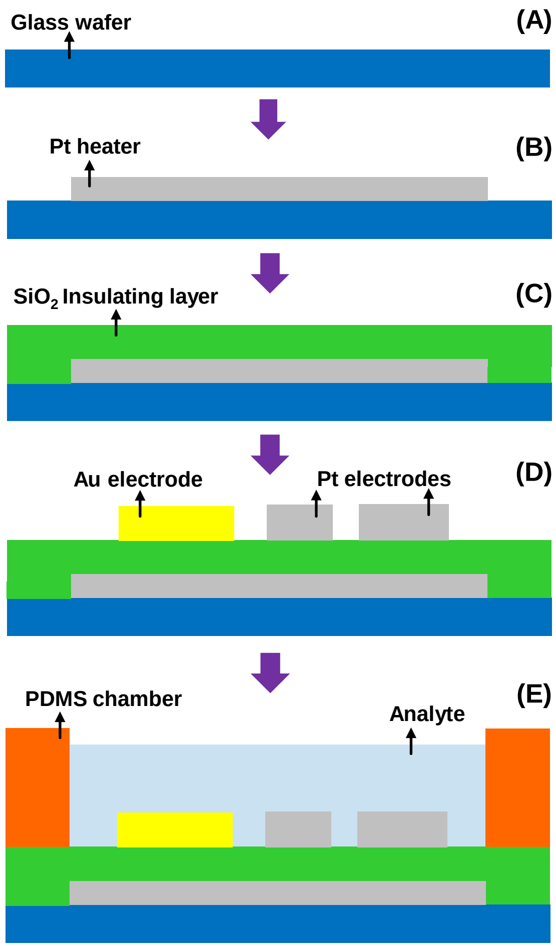


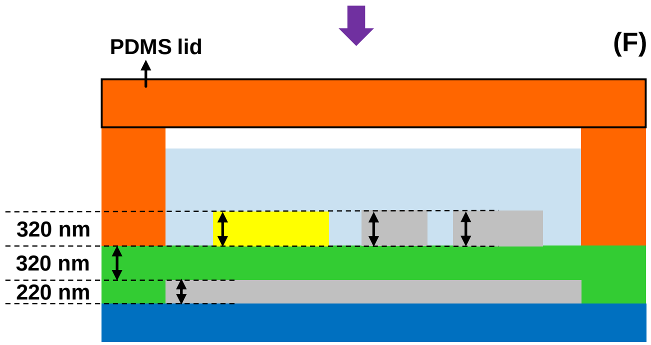
Miniature Temperature-Controlled Electrochemical Device

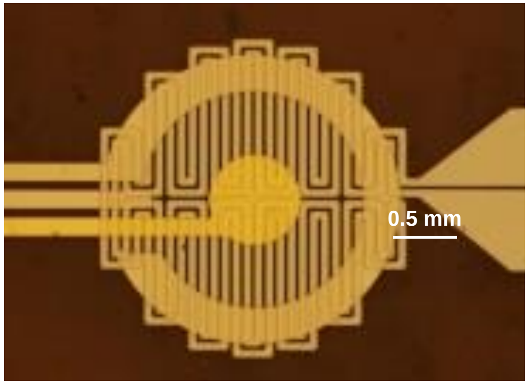
Wafer-Based Planar Fabrication

3-electrode platform with microheater









NIST NanoFab

Sputter Cluster Deposition Tool (Ion Milling Tool – not shown)

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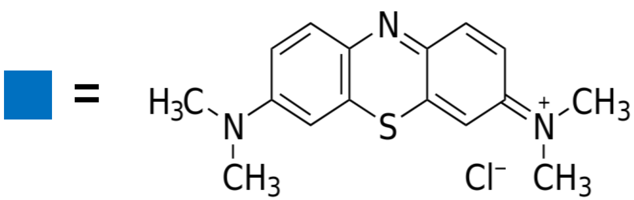
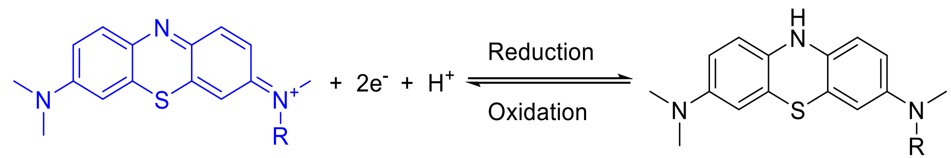
Feasibility for 2 Potential Application Areas

perform studies on hybridization and ligand binding interactions using microscale platforms and thiol-tethered & electroactively tagged biomolecular probes

methylene blue

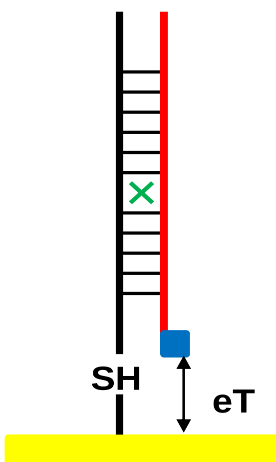


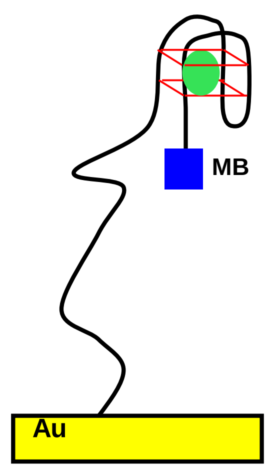
Redox reaction



- ***Disease screening*** **- single nucleotide polymorphism (SNP) detection**

- ***Drug discovery*** **- detection of property changes associated with binding events for (small molecule) drugs**





Monitor:

- binding-based electron transfer (hybridization)

- conformational/distance-based electron transfer

- thermally-induced dehybridization

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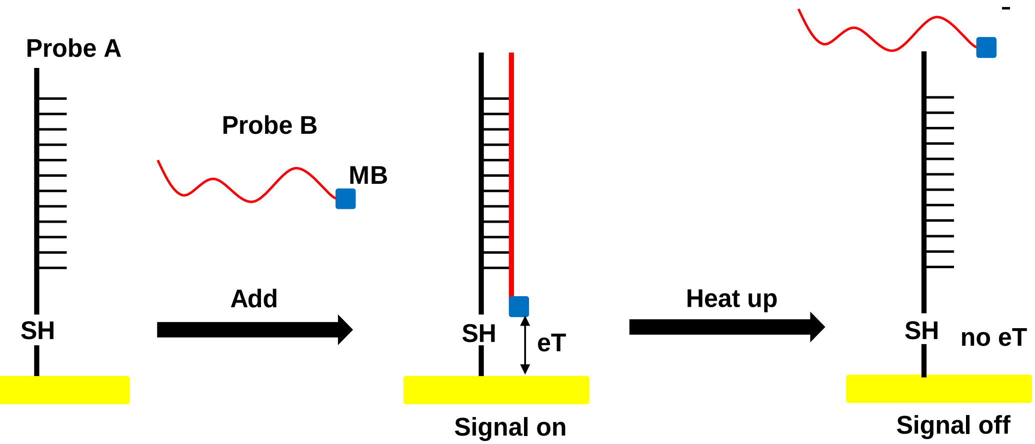
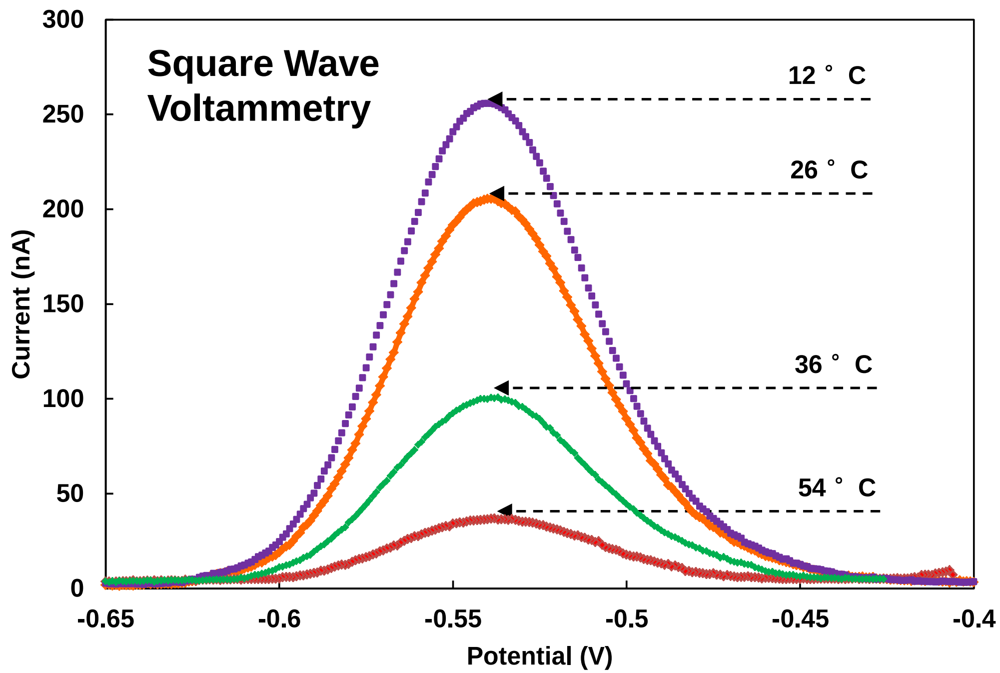
Duplex Melting Curve Analysis

Feasibility: Model studies on DNA duplexes

A)

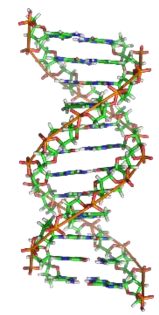


B)



Probe density must be viable:

- **Dense enough to produce measurable signal**
- **Not so dense to create interaction hindrance**



6-mercaptohexanol backfill

1. **Increase the temperature by increasing the heater voltage.**
2. **Wait 5 seconds for equilibrium.**
3. **Take 15 seconds to take electrochemical measurement**

Repeat step 1-3 to collect current at different temperature

The melting curve analysis can be done in ~ 15 mins using electrochemical detection

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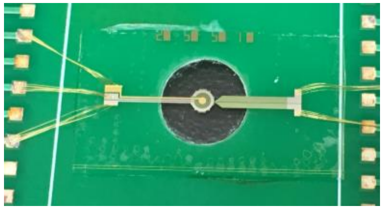
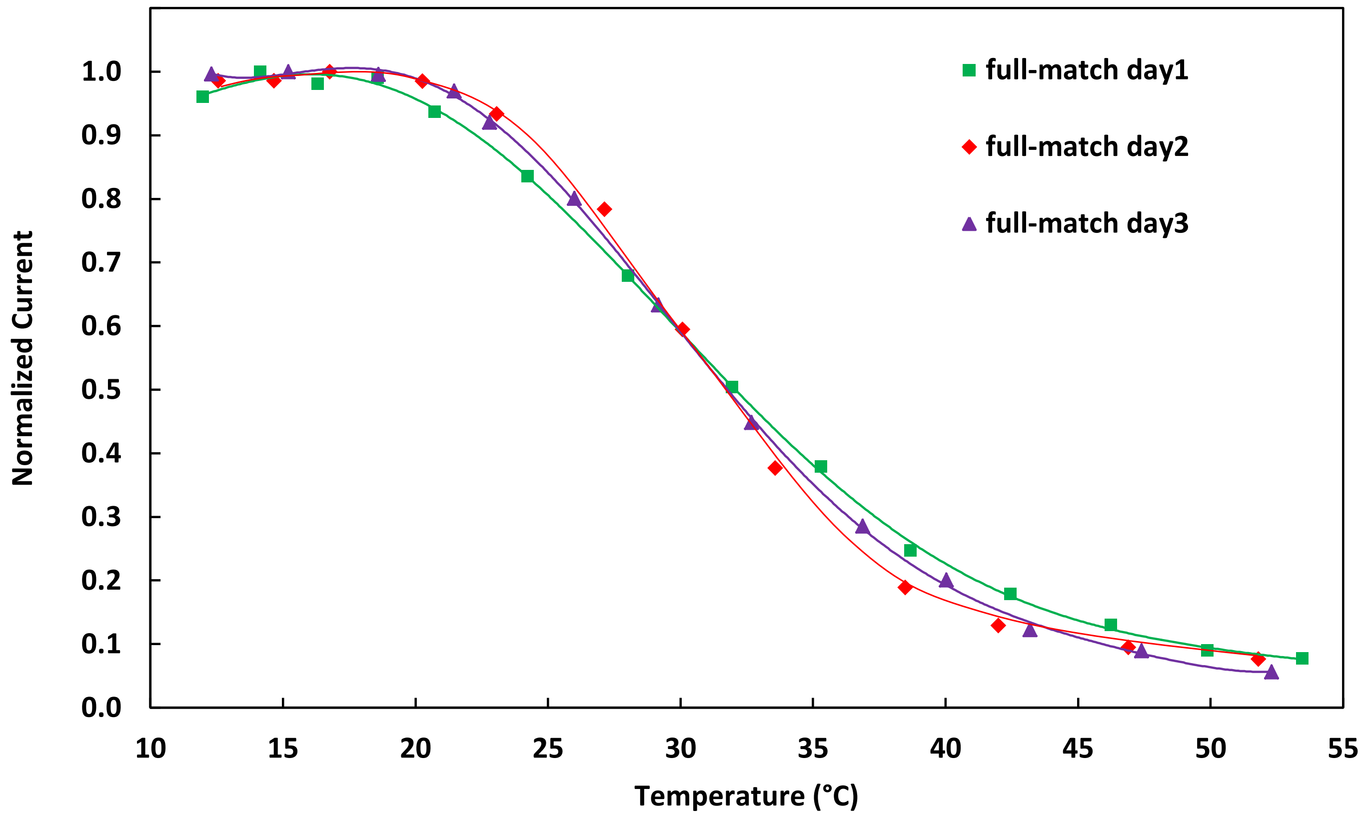
Reproducibility of Duplex Electrochemical Melting





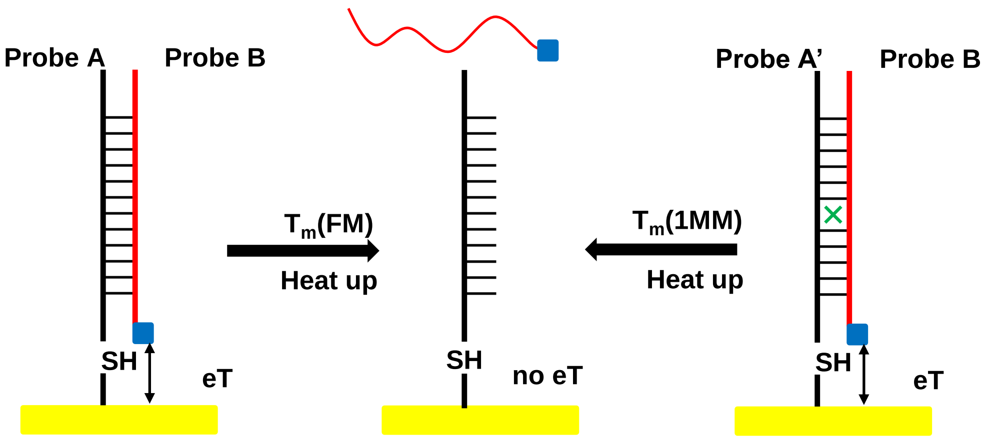
- T_m(day1) = 27.6 ºC, T_m(day2) = 27.1 ºC and T_m(day3) = 28.0 ºC
- T_m(average) = 27.6 $\pm$ 0.4 ºC

Z. Shen, H. O Sintim and S. Semancik, Analytica Chimica Acta 853, 265-270

T_m Detection of Single Nucleotide Polymorphism (SNP)

- SNP detection can be useful for predicting susceptibility to disease and drug metabolism
- Traditionally SNP detection employs optical melt-curve analysis
- Electrochemical measurements offer an electronic alternative

full match



one or more mismatches

explore dehybridization with increased temperature for varied cases

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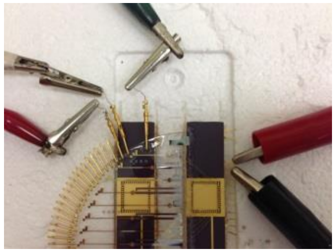
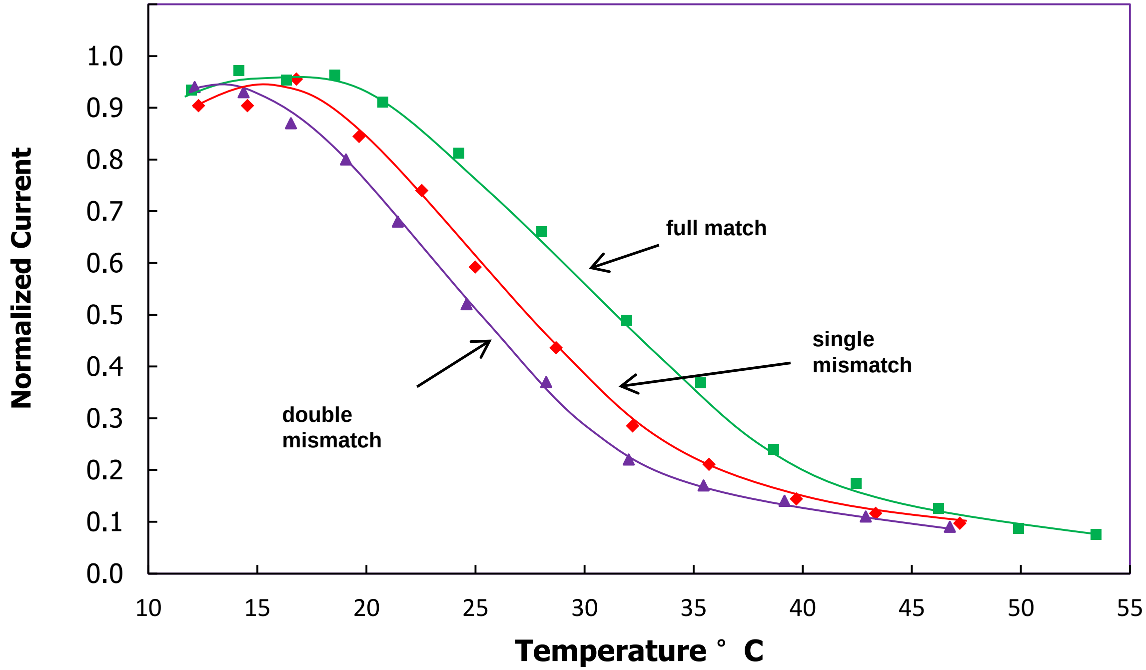
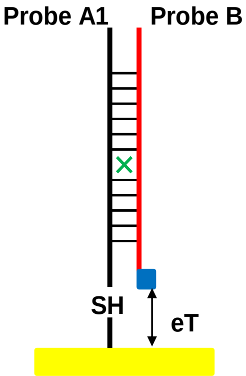
Single Nucleotide Polymorphism (SNP) Detection

Probe A (full match): 5'-SH-C6H12-TTT ACC TTT ATT -3'
Probe A1 (1 mismatch): 5'-SH-C6H12-TTT ACG TTT ATT -3'
Probe A2 (2 mismatch): 5'-SH-C6H12-TTT AGG TTT ATT -3'
Probe B: 3'-MB-AAA TGG AAA TAA CC-5'







single mismatch

- **T_m(FM) = 27.6 ºC, T_m(1MM) = 22.5 ºC and T_m(2MM) = 20.3 ºC**

Z. Shen, H. O Sintim and S. Semancik, Analytica Chimica Acta 853, 265-270

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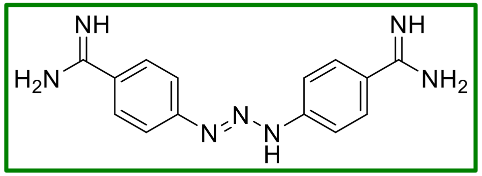
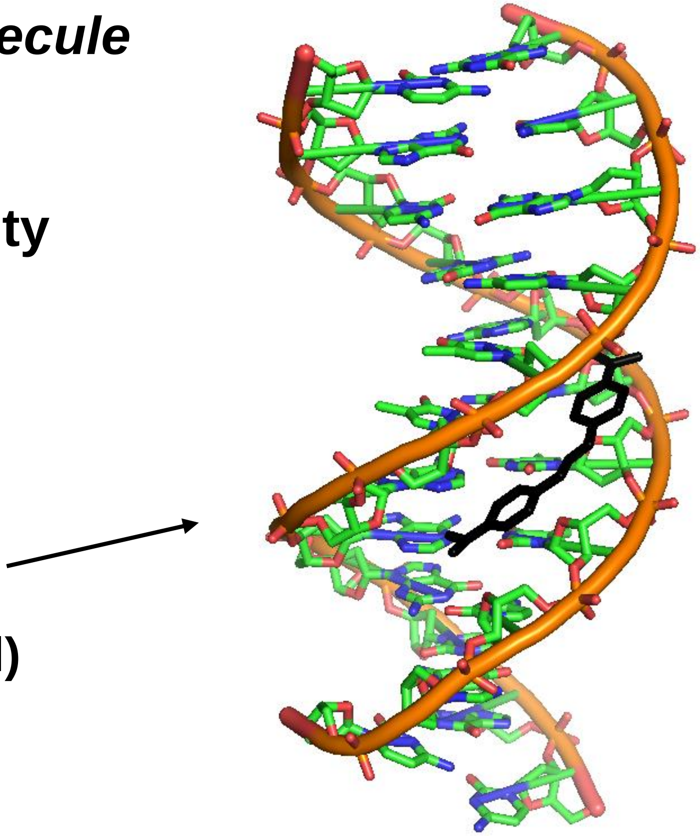
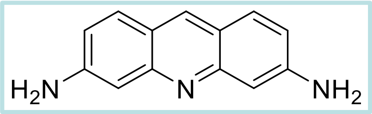
Screening for Drug Stabilization Effects

- Stability changes to detect *small molecule drug* binding
- Binding increases duplex DNA stability (higher T_m)



Diminazene aceturate (DMZ, Berenil)

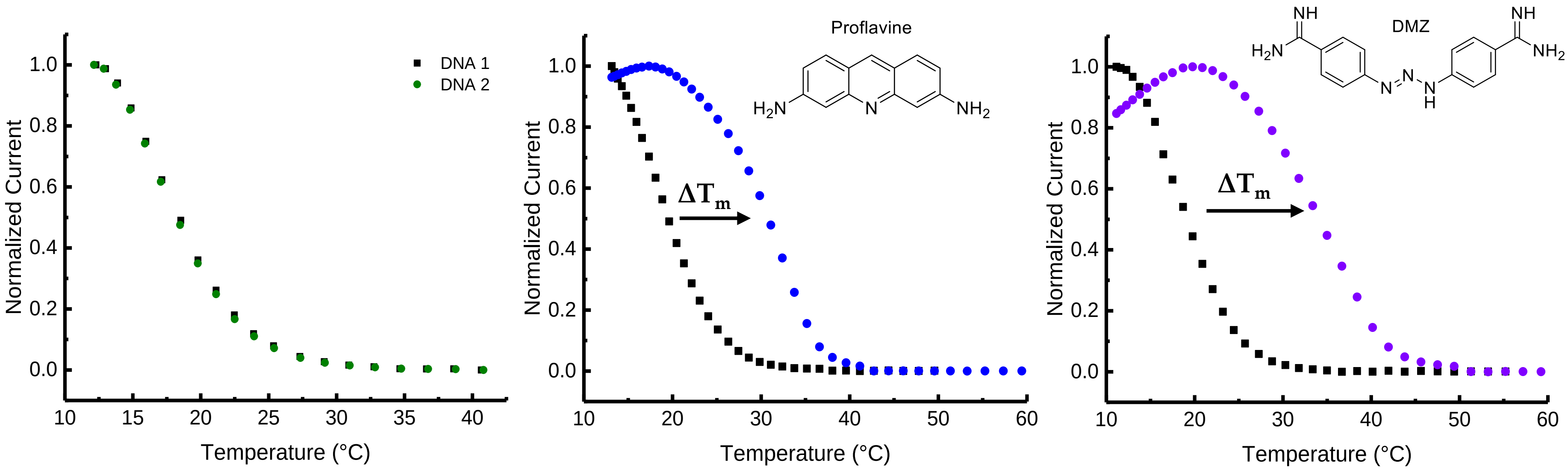




Proflavine

(with U MD and Purdue)

Ligand Stabilization of Duplex DNA



$\Delta T_{m,\ DNA}$ = **-0.3 ± 0.4 °C**

$\Delta T_{m,\ proflavine}$ = **11.8 ± 0.3 °C**

$\Delta T_{m,\ DMZ}$ = **14.6 ± 0.6 °C**

Melting profiles in 10 µL of 2 µmol/L cDNA and 13 µmol/L ligand in 10 mmol/L PBS with 100 mmol/L NaCl pH 7.4.

(standard deviations given for three replicates)

Robinson, S. M.; Shen, Z.; Askim, J. R.; Montgomery, C. B.; Sintim, H. O.; Semancik, S. *Biosensors 9, 54-67.*

NIST

Conclusions

developing measurement concepts for microscale devices that report on chemistry/biochemistry

- **Multidisciplinary research**

↓

- **Platform design and fabrication**
- **Nanomaterials**
- **Surface/interfacial phenomena**
- **Varied application areas**