# A CMOS Molecular Electronics Chip for Single-Molecule Biosensing

Drew A Hall<sup>1</sup>, Nagaraj Ananthapadmanabhan<sup>2</sup>, Chulmin Choi<sup>2</sup>, Le Zheng<sup>2</sup>, Paul P Pan<sup>2</sup>, Carl W Fuller<sup>2</sup>, Pius P Padayatti<sup>2</sup>, Calvin Gardner<sup>2</sup>, Daniel Gebhardt<sup>2</sup>, Zsolt Majzik<sup>2</sup>, Prem Sinha<sup>2</sup>, Paul W Mola<sup>2</sup>, <u>Barry Merriman<sup>2</sup></u>



<sup>1</sup>University of California, San Diego, CA <sup>2</sup>Roswell Biotechnology, San Diego, CA

# **Self Introduction**

Dr. Barry Merriman



BS in Math & Physics, University of Washington

- PhD in Applied Mathematics, University of Chicago
- Faculty at UCLA for 20 years, >90 publications, H-index 51
- Lead System Architect for Advanced DNA Sequencing at Thermo Fisher Scientific
- VP of Global Technology Assessment at Human Longevity
- Co-Founder and Chief Science Officer at Roswell Biotechnology
  - >30 years experience in technology development with deep expertise in DNA sequencing

# **Chips Enable Scalable Technologies**

Most bio-analytical instruments are based on detection of light (photons)



The microscope was introduced in the 1660s

# **Chips Enable Scalable Technologies**

Most bio-analytical instruments are based on detection of light (photons)



Based on detection of current (electrons)



The microscope was introduced in the 1660s

Semiconductor chips were introduced in the 1970s

Unlocking the power of microchips for biology will be transformative

## **Classic Biosensors**

Traditional biosensing techniques in the literature and commercialized...



## **Classic Biosensors**

Traditional biosensing techniques in the literature and commercialized...



But: Not single molecule, require labels, not real-time, and have the Morethan-Moore problem: on-chip versions have scaling challenges

How to enable single-molecule, real-time, label-free sensing, fully scaled?

# The Birth of Molecular Electronics



[8]. This electron motion suggests that a rectifier could be built in which electrons would be allowed to

12.6: A CMOS Molecular Electronics Chip for Single-Molecule Biosensing

© 2022 IEEE

# The First Molecular Circuit

SCIENCE • VOL. 278 • 10 OCTOBER 1997

#### **REPORTS**

#### **Conductance of a Molecular Junction**

M. A. Reed,\* C. Zhou, C. J. Muller, T. P. Burgin, J. M. Tour\*

Molecules of benzene-1,4-dithiol were self-assembled onto the two facing gold electrodes of a mechanically controllable break junction to form a statically stable goldsulfur-aryl-sulfur-gold system, allowing for direct observation of charge transport through the molecules. Current-voltage measurements at room temperature demonstrated a highly reproducible apparent gap at about 0.7 volt, and the conductancevoltage curve showed two steps in both bias directions. This study provides a quantative measure of the conductance of a junction containing a single molecule, which is a fundamental step in the emerging area of molecular-scale electronics.

The measurement of charge transport in single organic molecules and the determination of their conductance are long-sought

glued onto a flexible substrate and is fractured by bending of the substrate, after which an adjustable tunneling gap can be

The measurement of charge transport in single organic molecules and the determination of their conductance are long-sought goals. Such measurements are experimen-



ta

or

pr

ce

cc

cc

co

en

qu

. .

Conductance (µS)

0.25

0.125

### The First Wave: A Molecule in a Circuit...

TENT THE BIRTH OF DWARF GALAXIES AND STARBURSTS THE NETWORK INSIDE A CELL

### **Computing With Molecules**

By Mark A. Reed and James M. Tour June 2000



#### BREAKTHROUGH OF THE YEAR

In 2001, scientists assembled molecules into basic circuits, raising hopes for a new world of nanoelectronics

**Molecules Get Wired** 

12.6: A CMOS Molecular Electronics Chip for Single-Molecule Biosensing

© 2022 IEEE International Solid-State Circuits Conference

### **Molecular Electronics Biosensor**



## **Molecular Electronics Biosensor**





# **Molecular Electronics Biosensor**





- ✓ Universal approach to single-molecule sensing
- ✓ All electronic measurement
- ✓ Fully scaled sensor
- $\checkmark$  Can be deployed on a CMOS chip

Direct electronic detection of molecular events – Solving the "more-than-Moore" problem.

# Single-Molecule Biosensor Exemplar



Fully scaled biosensor with a synthesizable molecular wire.

© 2022 IEEE International Solid-State Circuits Conference

# "Bridge" Molecules

#### **DNA Bridge**



- Fully synthesizable
- 10-50 nm long
- >50 GΩ
- 20 pA DR

#### **Peptide Bridge**



- Fully synthesizable
- 10-50 nm long
- >25 GΩ
- 20 pA DR

Selective metal binding on the ends of the bridge with internal conjugation site for probes

Fully synthesizable wires with conjugation sites for electrodes and probe molecule

# Loading the Bridge Molecules

#### Diffusion is *slow*...

Would take >24 hours to bridge!





# Loading the Bridge Molecules





Dielectrophoretic (DEP) force actively loads the bridge molecules into sensor sites

© 2022 IEEE International Solid-State Circuits Conference

# Outline

### Introduction

### Readout IC

- Sensor Fabrication
- Measurement Results
- Conclusion

### Architecture



Like an image sensor, rolling shutter with readout at 1000 frames/sec

© 2022 IEEE International Solid-State Circuits Conference

### **Pixel**



## **Pixel**



Low-leakage switches ensure <100fA leakage on high impedance node

© 2022 IEEE International Solid-State Circuits Conference

## **Pixel**



Low complexity amplifier given limited area  $(400 \mu m^2)$ 

© 2022 IEEE International Solid-State Circuits Conference

## **Pixel – Reset**



# **Pixel – Integration**



# **Pixel – Calibration**



# **Column Driver**

#### Conventional Source Follower



# **Column Driver**

#### Conventional Source Follower



#### **Split Buffer**



# **Column Driver**

#### Conventional Source Follower



**Split Buffer** 

Current-mode split buffer improves linearity over a conventional source follower

© 2022 IEEE International Solid-State Circuits Conference



# Ramp generator shared with each quadrant (8 total on chip)



Single slope ADC pitch matched to pixel for parallel readout

© 2022 IEEE International Solid-State Circuits Conference

### Serializer



Serialized outputs captured off-chip in an FPGA

© 2022 IEEE International Solid-State Circuits Conference

# **Die Photo and Packaging**

### TSMC 0.18µm Open top packaging for fluidic access



### Instrument

h Alexand



© 2022 IEEE International Solid-State Circuits Conference

# Outline

- Introduction
- Readout IC
- Sensor Fabrication
- Measurement Results
- Conclusion

# **Sensor Fabrication**

CMOS metals Al/Cu are not electrochemically compatible with H<sub>2</sub>O!



#### BEOL spacing rules insufficient for nanoelectrode gaps!

<u>The Challenge</u>: How to get nanoelectrodes with ~10-30nm gaps on CMOS?

# **E-Beam Lithography**



# Ruthenium nanoelectrodes written with e-beam lithography

# Passivation covering electrodes to minimize capacitance

Slow, serial process – but good for exploring electrode size and shapes

# Photolithography



193nm lithography + gap narrowing to reduce from 150nm to 20nm

High volume, foundry-compatible, mass manufacturable process

# Outline

- Introduction
- Readout IC
- Sensor Fabrication
- Measurement Results
- Conclusion

# **Measured Linearity**

Measured through the calibration port across the entire signal path and the ADC



+1.5/-0.7 LSB differential non-linearity (DNL); ±2 LSB integrated non-linearity (INL)

© 2022 IEEE International Solid-State Circuits Conference

# **Measured Leakage and Noise**

Measured without a bridge molecule, minimal dependence on  $V_{DS}$ 



Measured input-referred noise is  $39fA_{rms}$  ( $C_F = 200fF$ ) and  $76fA_{rms}$  ( $C_F = 400fF$ )

#### Low-noise, low-leakage pixel

© 2022 IEEE International Solid-State Circuits Conference

## **Measured Bridge Insertion**



# **Measured Bridge Insertion**



#### **Atomic Force Microscopy (AFM)**

#### Scanning Electron Microscopy (SEM)

**Verification Techniques** 

#### DNA Binding Sensor: Experiment Setup



DNA Binding Sensor: Experiment Setup



#### 1. Raw Signal @ 1kSps

Time (sec)

16 ms

10 ms 🕰 11 ms

2. Machine Learning (HMM) Peak Segmentation

1932

17 ms

ms

1933

2 ms

70

ms







#### 3. Complete Distributions From Single-Molecule





#### 3. Complete Distributions From Single-Molecule



4. Classical Measures From Single-Molecule

Dwell Times: Avg 17 ms  $\rightarrow$  k<sub>off</sub>= 59 sec<sup>-1</sup> Wait Times: Avg 43 ms @ 100nM  $\rightarrow$  k<sub>on</sub>= 2.3×10<sup>8</sup> M<sup>-1</sup>sec<sup>-1</sup>

# **Sensor View of Target Concentration**



© 2022 IEEE

# **Sensor View of Target Concentration**



# **Melting Curve and Mismatch Sensing**



At an ensemble level, single-molecule sensor behaves like a classical biosensor

© 2022 IEEE International Solid-State Circuits Conference

# **Measured COVID-19 Aptamer Binding**

**Aptamer Binding Sensor:** 



Single-molecule detection of COVID-19 antigen using a DNA aptamer

© 2022 IEEE International Solid-State Circuits Conference

# 2-Base Sequencing Exemplar



. ----

# 2-Base Sequencing Exemplar



95% accurate automated base discrimination

© 2022 IEEE International Solid-State Circuits Conference

# Conclusion

- On 50<sup>th</sup> anniversary of the first microprocessor: A new era of integrated <u>molecular</u> electronics
- Demonstrated single-molecule sensing for
  - DNA-DNA hybridization
  - DNA aptamer Target binding
  - Enzyme activity
- Ushering in "The New Era of Digitizing Biology"

# Acknowledgments

- All Roswell employees, former and current
- Jim Tour