Unveiling The Roswell ME Platform

WHITEPAPERS

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15th November 2021

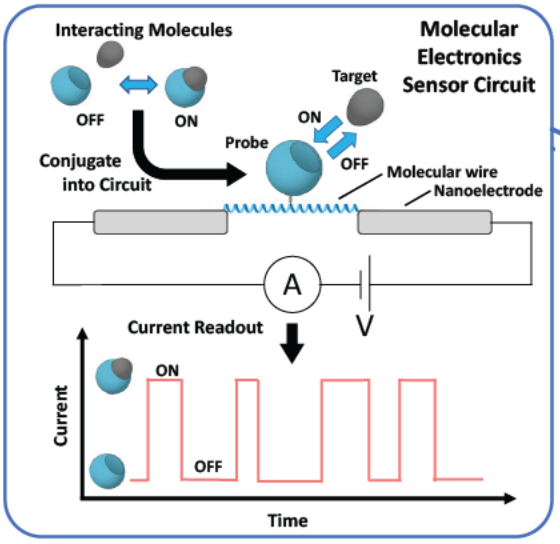
The New Era of Molecular Electronics Chips

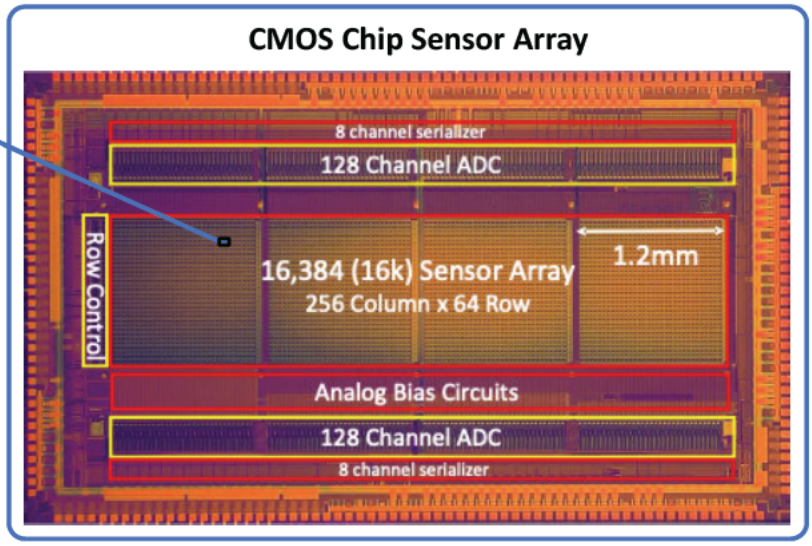
What is New:
The first semiconductor chip to integrate single molecules into circuits.

Powering Disruptions in:
- Drug Discovery
- Point-of-Care Diagnostics
- Telemedicine & Connected Health
- Environmental Sensors

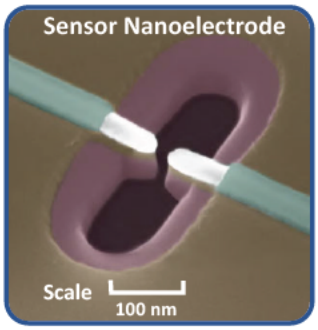
The Problem: Bioanalytical devices are based on legacy technologies that ultimately limit the ability to reduce costs, reduce instrument size, increase information content, and scale to mass manufacturing.

The Roswell Solution: The Roswell Molecular Electronics Chip puts biosensing on modern CMOS chip technology, in a maximally scalable and universal way. This enables a new era of low-cost, small-size, high-information, smart devices for a broad range of biosensing applications.





How We Realized a 50-year-old Technology Vision: Integrating molecules into electronic circuits has long been envisioned as the way to achieve ultimate miniaturization of electronics. Roswell is the first to realize this vision, for the 'killer app' of biosensing, where the wired molecule becomes the sensor element. Each pixel on the chip has a current meter circuit capable of measuring pico-Amp scale currents. The nano-electrodes (right) in each pixel allow a single probe molecule to be wired into the circuit. A voltage is applied across the probe molecule, and the resulting current-versus-time trace provide direct electronic detection of the probe molecule interacting with target molecules in a test sample. This fully scaled sensor provides a maximally scalable chip architecture, where circuits can shrink freely without modifying the sensor.



The Roswell Chip Roadmap: The scalable chip architecture and fully scaled sensor element allow the future chip roadmap to proceed faster than Moore's Law, advancing through the pre-existing semiconductor chip foundries. The near-term scaling roadmap is shown below.

Chip Generation	Gen 1/2	Gen 3	Gen 4	Gen 5
Timeline	2017-20	2021/22	2022/23	2023/24
N Sensors	256-1024	16k	0.1M – 1M	2M – 20M
Sensor Density	150/sq mm.	2.5K/sq.mm	40K/sq.mm	640K/sq.mm

The Right Chip for Your Applications: Roswell is engaging select partnerships to develop and deploy chips scaled to match your applications. Contact our team to enter this new era of molecular electronics, and put your molecules on our chips. *For more information, contact info@roswellbiotech.com.*

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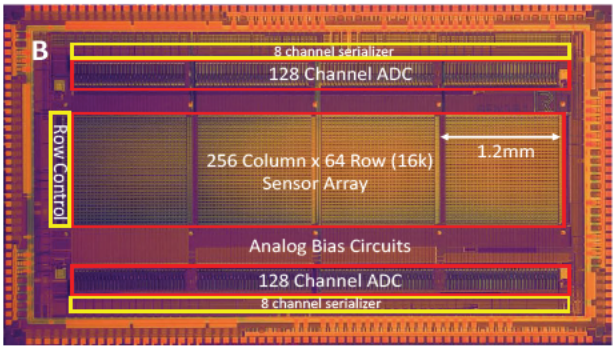
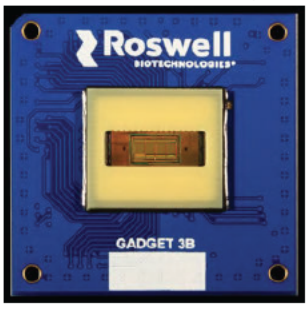
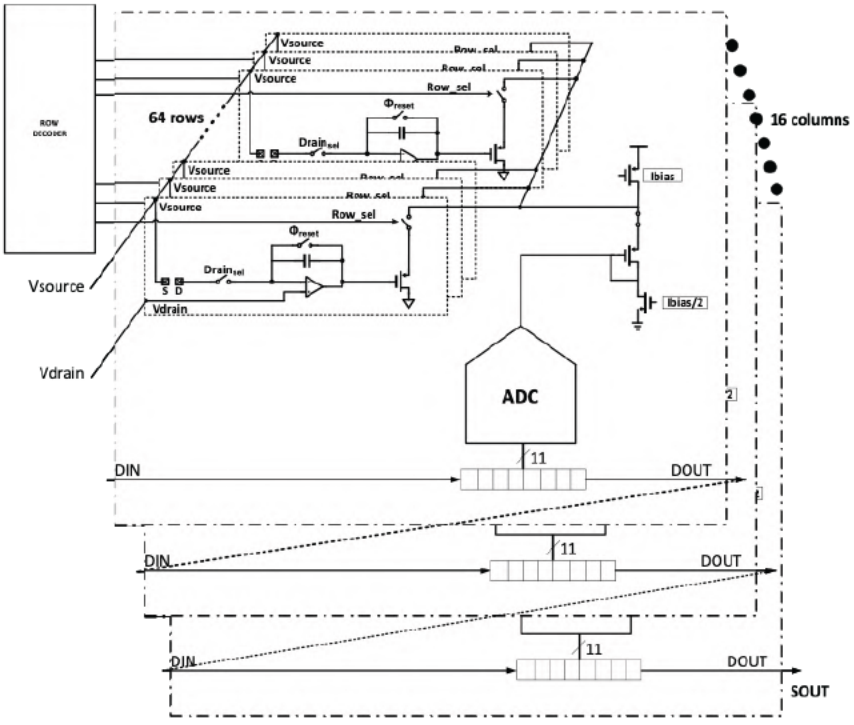
The Roswell Gen 3 Chip Architecture and Specifications.



(Left) Annotated die image for the 16k CMOS sensor array chip. The 16k pixel array is organized as 4 banks of 4k pixels. Readout uses 128 column-pitch-matched ADCs on the top and bottom of the device, to read out a full row of 256 pixels, with the row selection control at left. Serializers on top and bottom read out the digitized data at high speed, supporting 1000 frame-per-second throughput. (Right) Fully packaged die.





CMOS Sensor Array Chip Architecture. The major architectural elements of the sensor array chip are as follows, corresponding to the chip-level circuit schematic illustration shown: (1) The chip sensor array organized as 64 rows x 256 columns of pixels (2) Each column is digitized by an ADC operating at 64K samples/second. (3) 16 ADCs are daisy chained and serialized into a single CMOS 1.8V output at (64Kx16) 1M samples/second implying 11Mbps (bit depth of 11 bits/sample) (4) This in turn can be considered one unit cell of the chip; this unit cell is repeated 16 times to create the 64x256 array. This implies there are 16 parallel output lanes that carry data to the off-chip FPGA, which handles primary off-chip data transfer. (5) There are 256 ADCs in the chip, and they are time interleaved between the 64 rows. (6) The row decoder block generates the reset and row select control signals for all the rows and facilitates the time interleaved digitization of the 64 rows by 256 different ADCs.

Roswell Gen 3 Chip Fabrication and Performance Specs: Major chip specs are summarized below.

Technology	180nm CMOS
Min. Feature Size	10nm electrode gap
Die Size	4mm x 6mm
Sensor Density	2,500 / sq.mm
Sensor Count	16,348
Data Rate	1,000 Frames/s (16.3M Samples/s)
Precision	11 bit
Power	60mW @1.8V
Leakage Currents	0.4 pico-Amps
Chip Packaging	Wire-Bonded PCB

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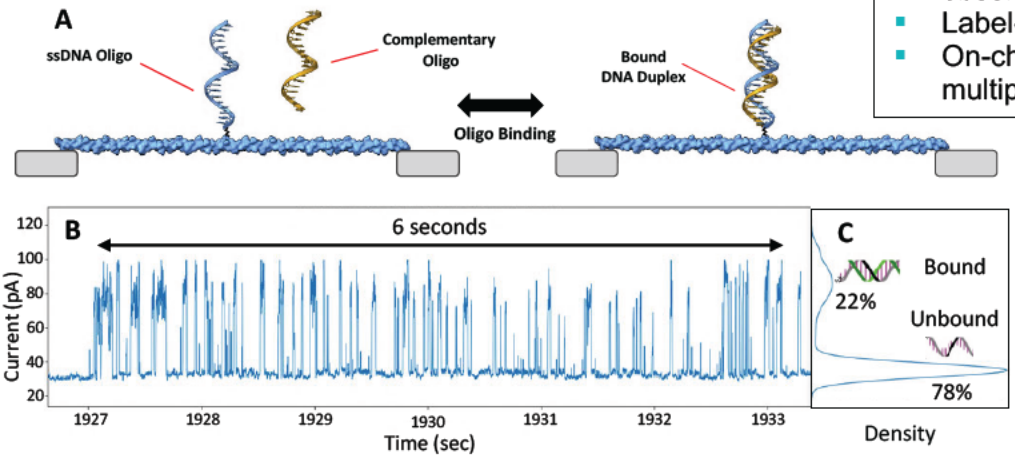
The Roswell Molecular Electronics Sensor: A New Kind of Measurement

The Problem: Measuring molecular interactions is fundamental to many applications in biosensing, but legacy technologies in use have many limitations.

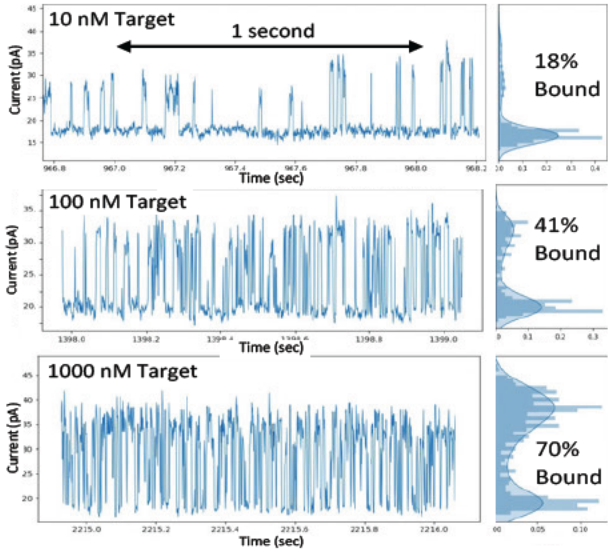
The Roswell Solution: The Roswell molecular electronics sensor offers a fundamentally new and powerful view of molecular interactions: single-molecule, real-time, and all-electronic on-chip. The sensor is also universal: detection targets are programmed by probe molecules wired in the chip.

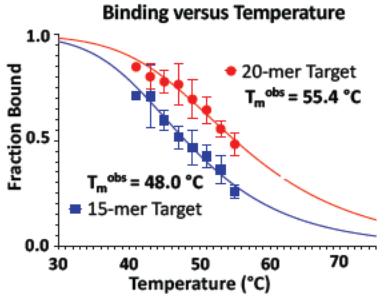
Legacy Measurement Methods:
- Low resolution
- Indirect or label-dependent
- Bulk & static
- Large, costly instruments
- Complex workflows
- Low multiplexing

Roswell ME Platform:
- Single-molecule resolution
- Simple real-time, direct observation of binding kinetics
- Label-free detection
- On-chip for unlimited multiplexing & scalability



The Roswell DNA binding sensor (left) illustrates these principles: (A) a single-stranded DNA oligo probe is conjugated to the sensor bridge molecule, and exposed to a solution containing the target oligo. The subsequent single-molecule binding events are registered as separate curren p ses B Thi provides a rich and unique view of the complete, single-molecule, real time kinetics. For example, this can be used to observe target concentration (left), temperature dependence (melting behavior) (right), and much more





Reversible binding at the s ngle-molecule level is universal in biology. The Roswell platform has demonstrated abilities to quantify this binding kinetics across a broad range of interacting biomolecules This includes DNA DNA int actions, antibody antigen, and proteins interacting with other proteins or small molecules. The sensor can also monitor enzyme activity, such as DNA polymerase and CRISPR-Cas. This comprehensive view of single-molecu e kinetics can provide both a new understanding of molecular interactions, and can unify applications based on binding onto an ideal, scalable, chip platform.

Empower Your Applications with a New Kind of Measurement, On-Chip:
The Roswell sensor provides a new "window" to directly observe molecular interactions at millisecond time scales. We welcome exploring how your applications can enter this new era of digitizing biology. *For more information, contact info@roswellbiotech.com*

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The Roswell Instruments: Connecting Chips to Applications

The Roswell chip-based platform allows for compact, low-cost instruments that are matched to the application. This enables systems for:

- Desktop
- Point-of-Care
- Portable & At-Home

This family begins with the Roswell Trinity instrument, a compact, expandable, desktop platform that can run the current and future Roswell chips for general purpose applications in drug discovery, diagnostics and sequencing.

Future instruments can support ultra-compact form factors with fully integrated sample prep, that are ideal for Point-of-Care diagnostic applications, or highly distributed telemedicine or home-health applications.

The chip-based platform allows unlimited capability to match the instrument to the application, such as future applications for environmental sensors.

The Roswell Trinity Instrument the Trinity instrument is a versatile desktop system capable of running current and future chips, for diverse assays and applications.

Features:

- Fully automated chip-running protocols
- Touchscreen graphical user interface
- Dry instrument: no contact with solutions
- Disposable microfluidic cartridge holds chip and reagent consumables
- Temperature control
- Data analysis on board or in the cloud
- Upgradable for current & future chips

Bring your Applications to the Roswell ME Platform: Join us in creating assays and applications for Trinity, and in defining future instrument formats ideal for your needs. Roswell is engaging select partners to enter this new era of digitizing biology. *For more information, contact info@roswellbiotech.com.*

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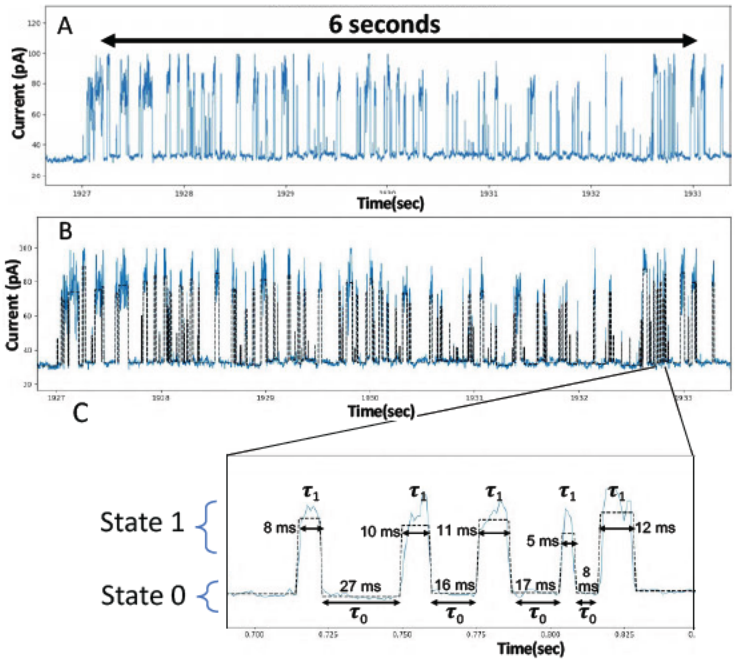
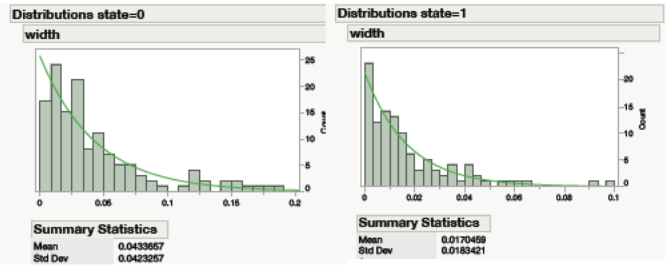
The Roswell Algorithms & Software: Translating Single-Molecule Signals into Answers

The Roswell Molecular Electronics Sensor provides a new view of single-molecule interactions. These real-time signal traces contain extremely rich information. This can be used to deduce target concentration, strength of interaction, temperature dependencies, alternative conformations, and discriminate true targets from background. We are developing powerful algorithms that can convert this high-content data into the answers that drive applications.

Get Answers Locally or In the Cloud: The Roswell Trinity instrument supports powerful on-instrument computing and real-time analysis with on-board GPU, FPGA and CPU processors. Data can also be streamed to The Roswell Cloud to access an extensive analysis suite, elastic computing, databasing of results, and creation of scalable, dynamic knowledgebases for your applications.



Binding Signal Trace Analysis. A Hidden Markov Model (HMM) is used to quantify current-time traces and extract single-molecule interaction kinetic data: (A) Raw data trace from the DNA binding probe sensor (1kHz raw sample rate). (B) A 2-state HMM model fit is shown (black dashed line) and enlarged in (C) to show the waiting time ($\tau 0$) and dwell time ($\tau 1$) parameters for each binding event. Histograms of the observed $\tau 0$ and $\tau 1$ times are shown below; these fit to an exponential distribution (green line), as expected from Boltzmann kinetics.



Put Your Molecules on Our Chips—and Get Your Answers from our Software. A new kind of measurement requires a new kind of analysis, and the scalability of chips requires powerful hardware and seamless access to the cloud. We are providing all of this to select development partners, to build fully integrated and accessible applications. *For more information, contact info@roswellbiotech.com.*

Software & Analysis Capabilities:

- Single-molecule kinetics analysis tools
- On-instrument and in-cloud analysis
- Support for developing custom on-instrument applications and reporting
- Support for developing cloud-based analysis pipelines and dynamic knowledgebases for connected AI-driven applications at all scales

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Drug Discovery Applications: New Understanding from a New View of Target Interactions

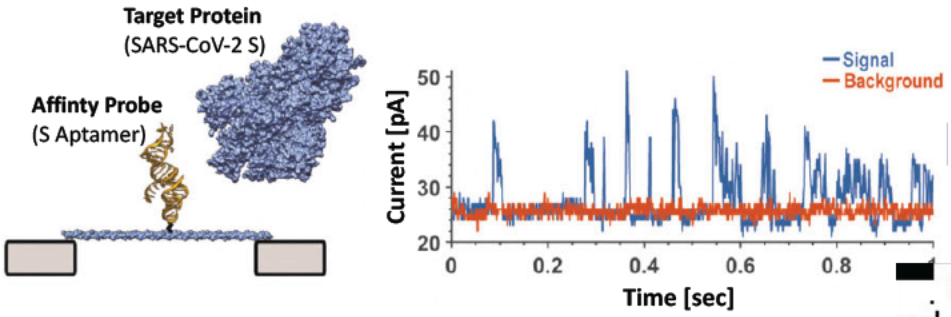
The Problem: Measurement of molecular interactions is fundamental to drug discovery, but current methods are based on legacy technologies limited by

- Low resolution
- Indirect or label-dependent measurements
- Bulk, static measurements
- Large, costly instruments and complex workflows

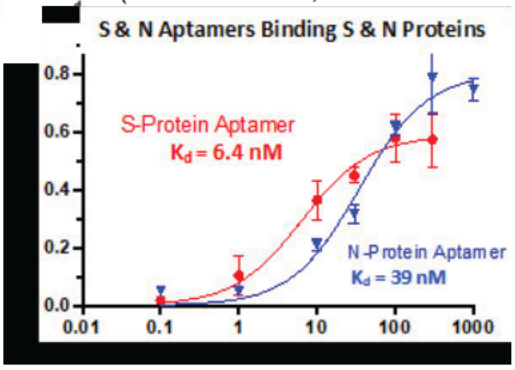
Interaction Types and Applications

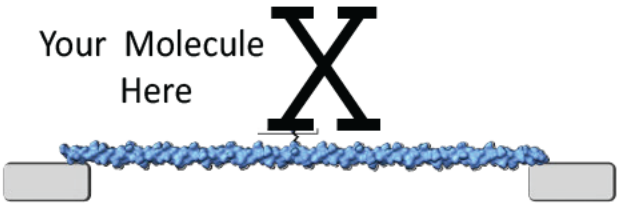
- Antibody – Protein / Antigen
- Aptamer – Protein
- Small Molecule – Receptor
- Affinity Reagent screening
- Inhibitor screening
- Protein biomarker detection
- DNA Encoded Library screening

The Roswell Solution: The Roswell Molecular Electronics Platform offers a fundamentally new and powerful view of molecular interactions: single-molecule, real-time, direct, and all-electronic on-chip. This new view provides rich information to characterize weak interactions, to address challenging "undruggable" targets, or expose off-target interactions. The scalable electronic chip format enables low-cost, high-throughput screens of large libraries.



Example of Aptamer Affinity Sensors. Aptamer Sensors were constructed targeting the SARS-CoV-2 S Protein with a 57-mer DNA aptamer (shown, left), and for the SARS-CoV-2 N-Protein with a 97-mer DNA aptamer (not shown), taken from the literature (*Anal. Chem.* **92**, 9895–9900 (2020)). A typical sensor current-vs-time signal trace is shown (right), with signal spikes corresponding to aptamer-target interactions. Super-imposed in red is the typical baseline, when no target is present. At right are concentration titration response curves for both the S-aptamer and N-aptamer sensors, for a range of applied target protein concentrations; the y-axis is the fraction of time the sensor is in the bound state. The aptamer binding affinities, Kd, derived from these curves (6.4nM, 39nM) are comparable to those reported from standard bulk binding assays.





Put Your Molecules on our Chips:
Roswell is providing the "X-bridge" family of bridges supporting diverse immobilization chemistries, making it convenient to put your existing molecule libraries on our sensor chips. This includes support for conjugating to molecules with His-tags, FLAG-tags, Spytags, lysine or cysteine residues, biotin, or DNA encoding tags.

Advancing Through Partnerships: Roswell is engaging select partnerships to develop drug-discovery assays leveraging this new view of molecular interactions: single-molecule, real-time, label-free, and with on-chip scalability for multiplexing and throughput. Contact our team to be part of the new era of drug discovery powered by the Roswell Molecular Electronics Chip. *For more information, contact info@roswellbiotech.com.*

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Diagnostics: The Platform for a New Era of Testing "Everyone, Everywhere, for Everything"

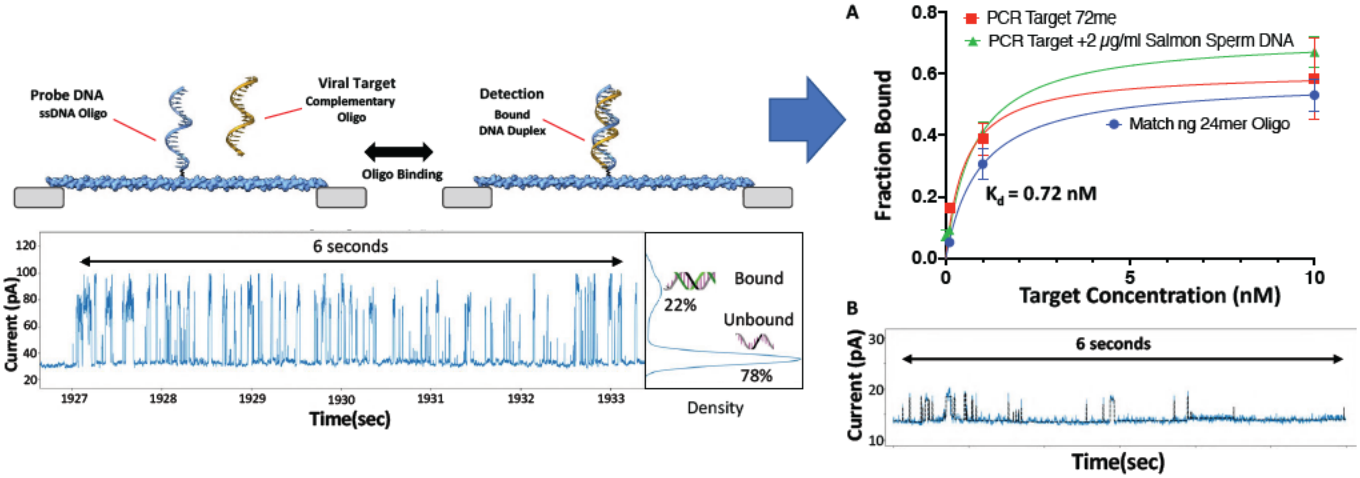
The Problem: Molecular diagnostics platforms are based on many decades-old legacy technologies that ultimately limit access and impact due to

- High testing costs
- Slow testing
- Low multiplexing & Low information
- Complex Instruments and workflows

Molecular Dx targets

- Nucleic acids
- Antibodies
- Antigens
- Proteins
- Metabolites

The Roswell Solution: The Roswell Molecular Electronics sensor chip offers the ability to take the full range of molecular diagnostics and unify them onto a single chip platform. The result is low cost, rapid, highly multiplexable testing in a format that is ideal for deploying on Point-of-Care instruments, and ultimately for telemedicine and home-health applications. For one example, for the future of pandemic viral testing, the platform can support rapid, low-cost, Point-of-Care or at-home testing for many virus strains or different viruses in a single assay. Roswell is currently developing exemplar rapid multi-virus nucleic acid assays for the detection of Influenza (A and B), SARS-CoV-2, and other human respiratory viruses, including operating an internal CLIA lab to support development of LDT and regulated assays



Using the Roswell DNA Binding Sensor to Detect a Viral Target (N gene of Sars-CoV-2) Under Mock Assay Conditions. The DNA binding probe chip is used to detect target PCR products produced from a contrived sample (A) The titration curves show chip sensor response for various concentrations of targets, for (blue) a synthetic 24-mer positive control, (red) unpurified PCR product from a contrived saliva sample, and (green) this PCR product spiked with Salmon Sperm DNA at 2 µg/ml, to mimic genomic DNA contamination. Note this complex background had little impact on the results. (B) A six-second signal trace at the lowest concentration tested, 100 pico-Molar, showing 5.2% fraction of time bound. This illustrates the strong signal spikes and the potential to detect much lower concentrations, through longer observations across multiple sensor pixels.

Advancing Through Partnerships: Roswell will be engaging select partnerships to develop diagnostic assays and point-of-care devices, based on our single-molecule, real-time, label-free, molecular electronics chip platform. Contact our team to be a part of this new era of diagnostics—powered by the first new molecular diagnostics technology in 30 years—towards a future of testing Everyone, Everywhere, for Everything. *For more information, contact info@roswellbiotech.com.*

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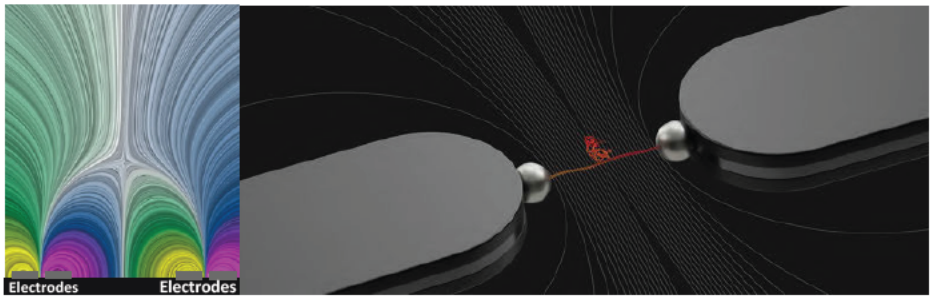
Electronic Target Amplification: A New Route to Rapid Detection at the Single-Molecule Limit

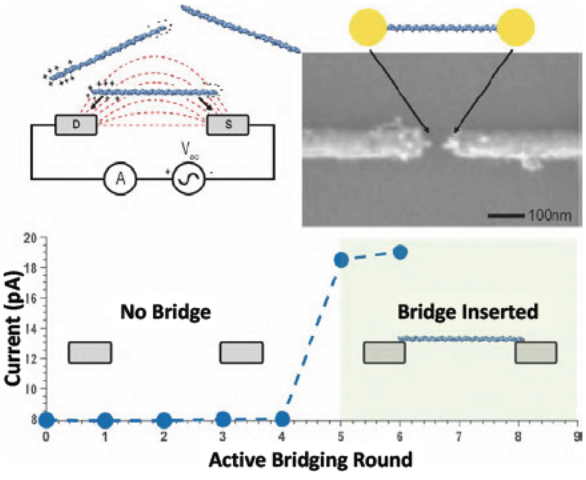
The Problem: In current bioanalytical platforms, approaching the limit of single molecule detection has either required PCR amplification, which is limited to DNA detection, or complex enzymatic cascades such as in ELISA assays. Detection also becomes slower in low-target limits.

Potential Benefits:
- Extremely rapid detection
- Extremely low sample input
- Potential for rapid, PCR-free single molecule detection, for diverse targets: DNA, protein, and small molecules.

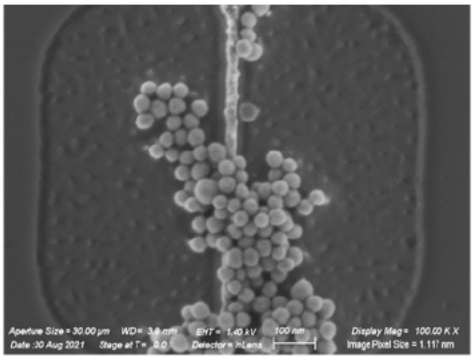
The Roswell Solution: The Roswell Molecular Electronics single-molecule sensor also has a unique capability to electrically attract target molecules, rapidly delivering them to the sensor, even at very low concentration. This capability is currently used to attract the sensor bridges to the electrodes, during sensor assembly. Used more generally, this same effect provides a way to rapidly achieve single-molecule limits of detection without PCR or other complex amplification reactions.



The electric field created by the sensor nano-electrodes (left) can be used to produce a general attractive force (*dielectrophoresis*) that pulls molecules to the vicinity of the electrode gap. This effect is currently used to rapidly assemble the sensor (right) and enables the ability to pull targets to the sensor, increasing the limits of sensitivity.



This attractive dielectrophoresis force is used to assemble the sensors themselves, attracting the bridge molecules to the gaps in less than 10 seconds of applied trapping field, from dilute (pico-Molar) solution, effectively concentrating molecules 1 million-fold near the electrodes. Attracting a bridge molecule to electrodes is shown (left), made visible in SEM with gold bead labels. The increase in current upon bridge insertion is shown, as it occurs during several cycles of applied trapping force.



Similar electronic target concentration can be used to enhance limits of detection of the sensor, by attracting target molecules to the sensor, in effect achieving amplification of the target concentration by *electronic means*. For example, shown (right) is the result of attracting gold nanoparticles to the electrodes, effectively increasing the local nanoparticle concentration by 1-billion-fold in just 10 seconds of electronic amplification.

A New Detection "Super-Power": The latest generation of Roswell chips have general purpose capabilities to apply this force to rapidly concentrate targets near the sensor. Roswell will be working with select partners to develop ultra-sensitive, ultra-rapid assays based on this new method of electronic target amplification, for a new error of sensitive measurement. *Contact us at info@roswellbiotech.com.*

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