Optical spectroscopy and biosensors for investigation of biomolecules and their interactions

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Emerging Types of Optical Biosensors I

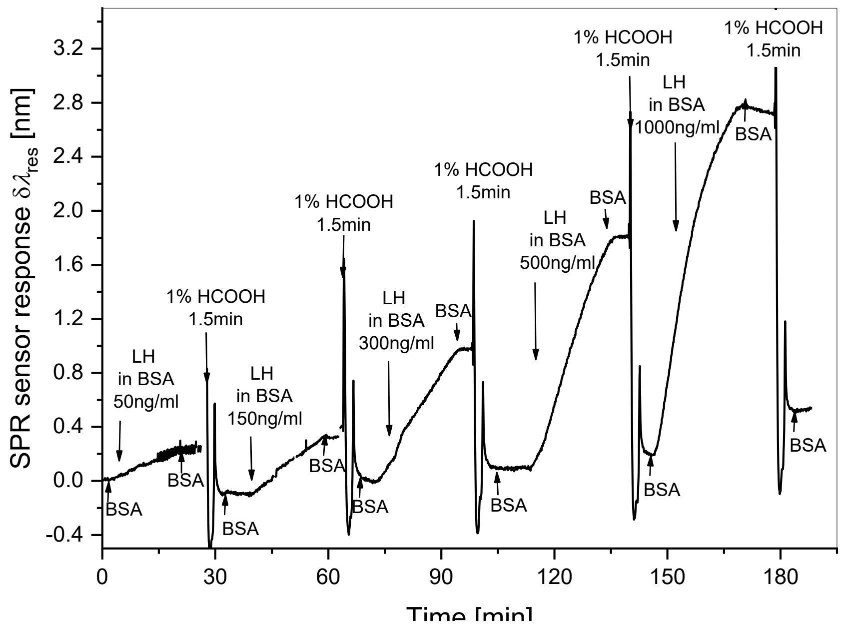
Content

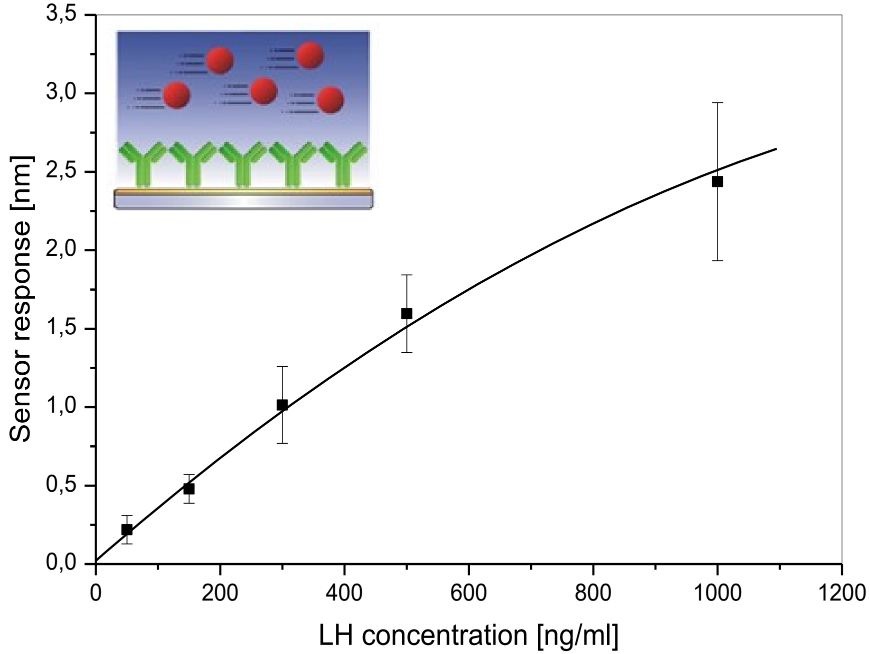
- Weak affinity interactions for reversible binding
- Continuous affinity monitoring biosensors
- Wearable / implanted biosensors operating in sweat, interstitial fluid, tear fluid, saliva.

Reversible Affinity Interactions

SPR Biosensor with Regeneration

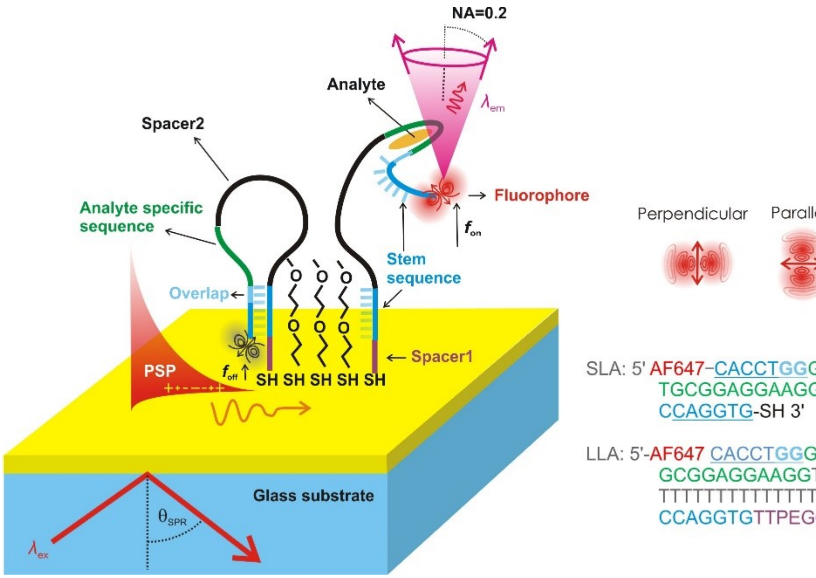
Direct detection of luteinizing hormone (LH, triggers ovulation). Protein with molecular weight of 29 kDa.





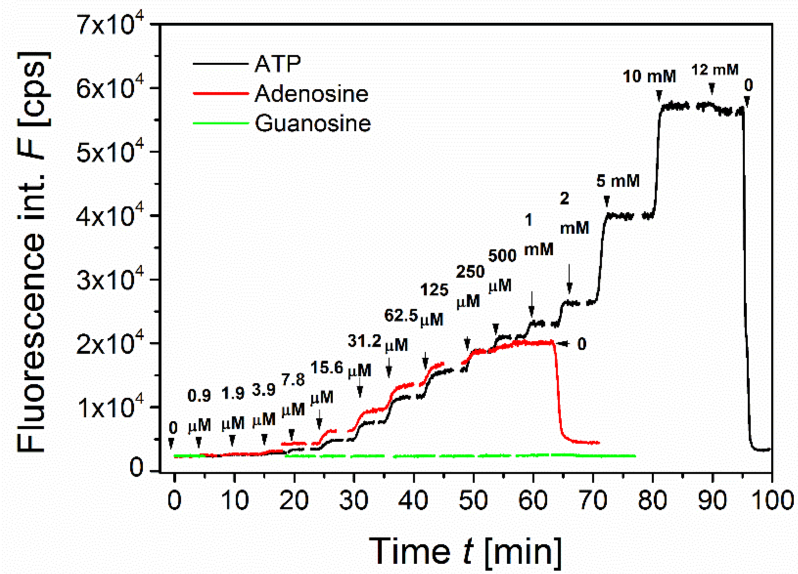
- Binding kinetics for increasing concentrations of LH and regeneration between detection cycles (left) and the calibration curve (right).
- For ligands with low dissociation binding rate, the sensor can be operated in cycles by using regeneration step.

FRET Biosensor with Fast k_{off}



SLA: 5' AF647–CACCTGGGGGAGTAT TGCGGAGGAAGGTT-PEG6-CCAGGTG-SH 3'

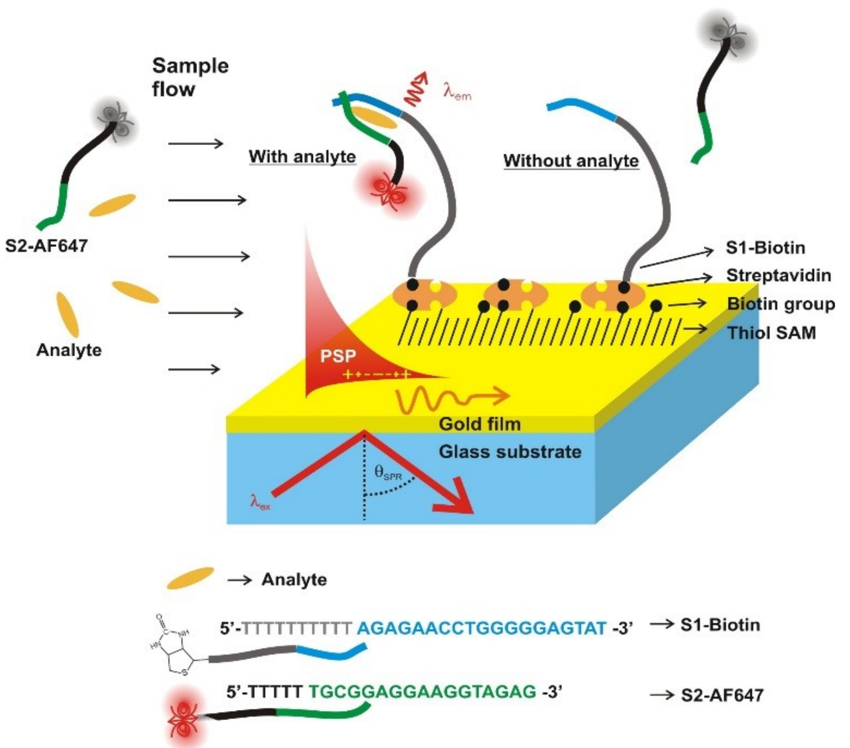
LLA: 5'-AF647 CACCTGGGGGAGTATT GCGGAGGAAGGTT-TTTTTTT TTTTTTTTTTTTTTTTTTTTTTTT CCAGGTGTTPEG6-SH 3'

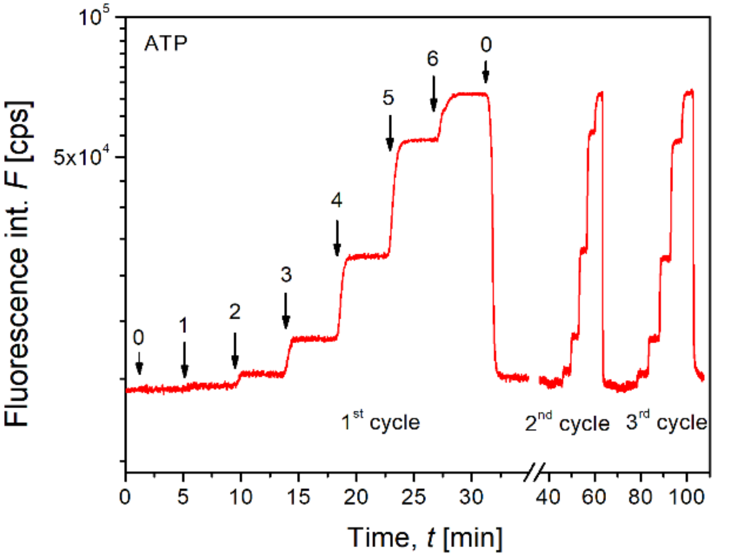


- DNA aptamer specific to ATP was engineered for "on" and "off" by changing distance from f_1 to f_2.
- Design that enables maximize the difference in the fluorescence intensity in the "on" and "off" states

Khulan Sergelen, Stefan Fossati, Aysegül Turupcu, Chris Oostenbrink, Bo Liedberg, Wolfgang Knoll, and Jakub Dostálek, Plasmon field-enhanced fluorescence energy transfer for hairpin aptamer assay readout, ACS Sensors, 2017, 2 (7), 916-923.

Continuous Monitoring with Fast k_{off}



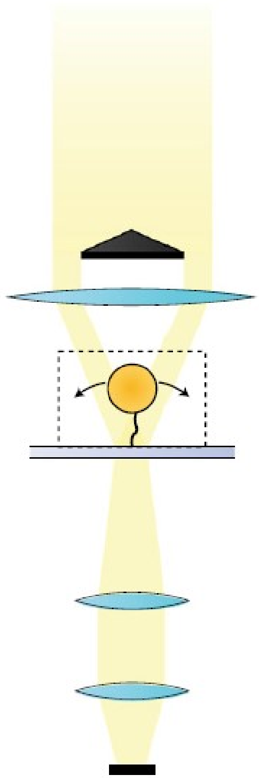


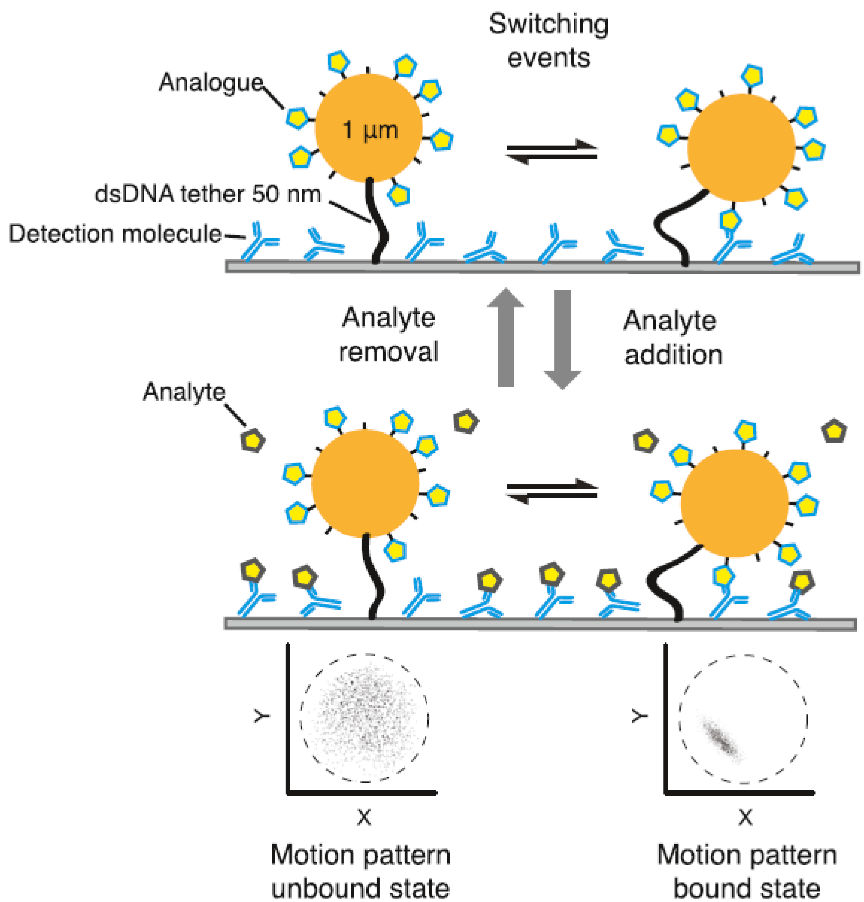
Demonstration of the reversible and reproducible detection of the assay for 3 rounds of ATP detection. Concentrations of analytes are indicated in sequential numbers: 0- 0; 1- 0.062 mM; 2- 0.125 mM; 3- 0.25 mM; 4- 0.5 mM; 5- 1 mM; 6- 2mM; 7- 3 mM; 8- 5 mM, respectively.

- **Sandwich assay can be designed for low molecular weight analyte by splitting the hairpin aptamer sequence.**

Khulan Sergelen, Bo Liedberg, Wolfgang Knoll, and Jakub Dostálek, Surface plasmon field-enhanced fluorescence reversible split aptamer biosensor, Analyst, 2017, 142, 2995-3001.

Scattering-based Continuous Detection of Low Molecular Weight Analyte

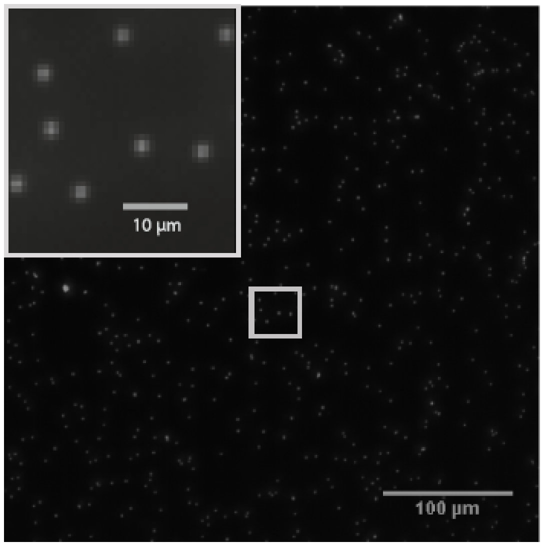




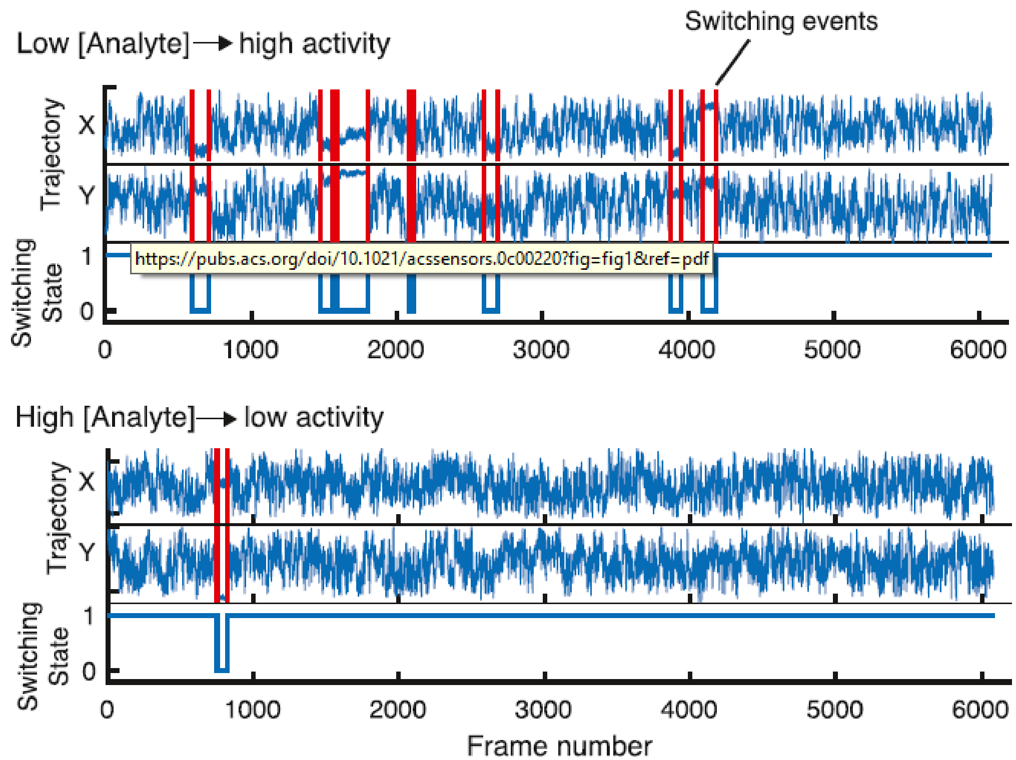
- Monitoring of Brownian motion of microparticles attached via flexible polymer chain.
- Affinity interaction with fast k_{off} used for reversible capturing and releasing the particle.

Junhong Yan, Laura van Smeden, Maarten Merkx, Peter Zijlstra, and Menno W. J. Prins, Continuous Small-Molecule Monitoring with a Digital Single-Particle Switch, ACS Sens. 2020, 5, 1168−1176.
Emiel W.A. Visser, Junhong Yan, Leo J. van IJzendoorn, Menno W.J. Prins, Continuous biomarker monitoring by particle mobility sensing with single molecule resolution, DOI: 10.1038/s41467-018-04802-8 |www.nature.com/naturecommunications

Scattering-based Continuous Detection of Low Molecular Weight Analyte



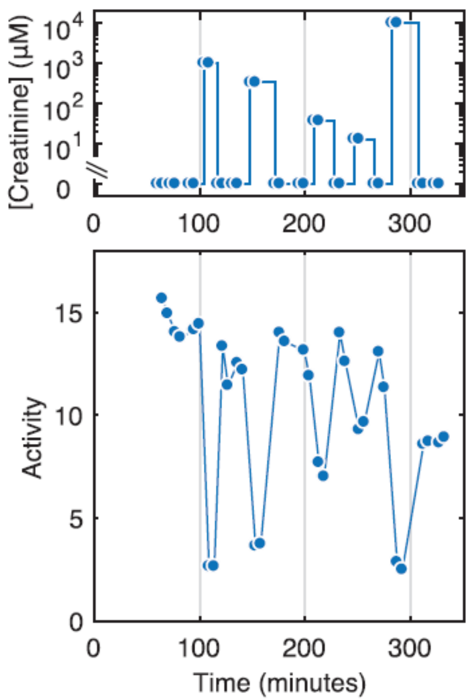
$$Activity = \frac{N_{events}}{N_{particles}}$$

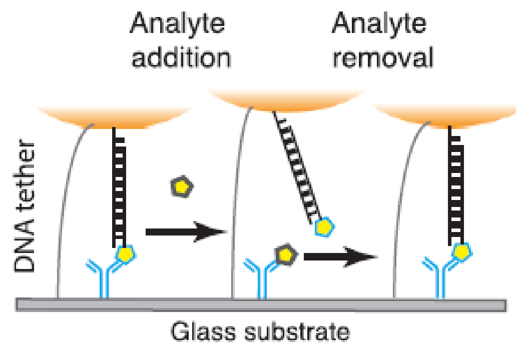


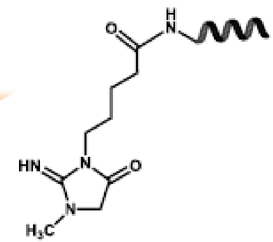
- **Monitoring of particle trajectory with series of affinity binding events**

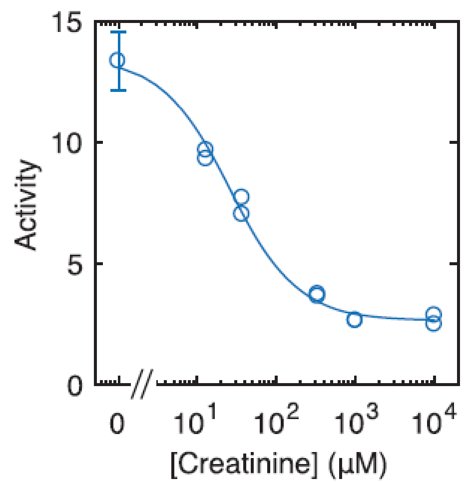
Junhong Yan, Laura van Smeden, Maarten Merkx, Peter Zijlstra, and Menno W. J. Prins, Continuous Small-Molecule Monitoring with a Digital Single-Particle Switch, ACS Sens. 2020, 5, 1168−1176.

FRET Aptamer Biosensor for Direct Detection of Small Analyte







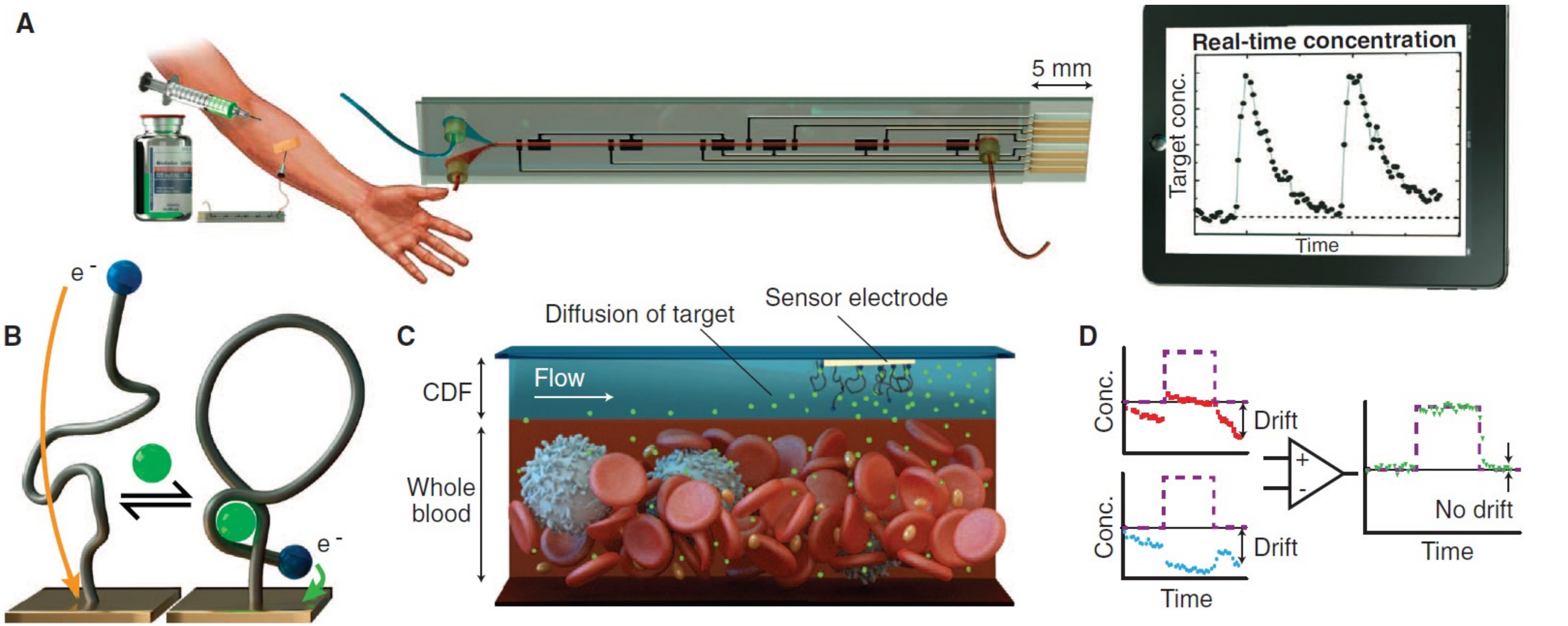


- **Continuous monitoring of creatinine – kidney biomarker at concentrations anti-creatinine antibody and competitive assay format.**

Junhong Yan, Laura van Smeden, Maarten Merkx, Peter Zijlstra, and Menno W. J. Prins, Continuous Small-Molecule Monitoring with a Digital Single-Particle Switch, ACS Sens. 2020, 5, 1168−1176.

Continuous Monitoring

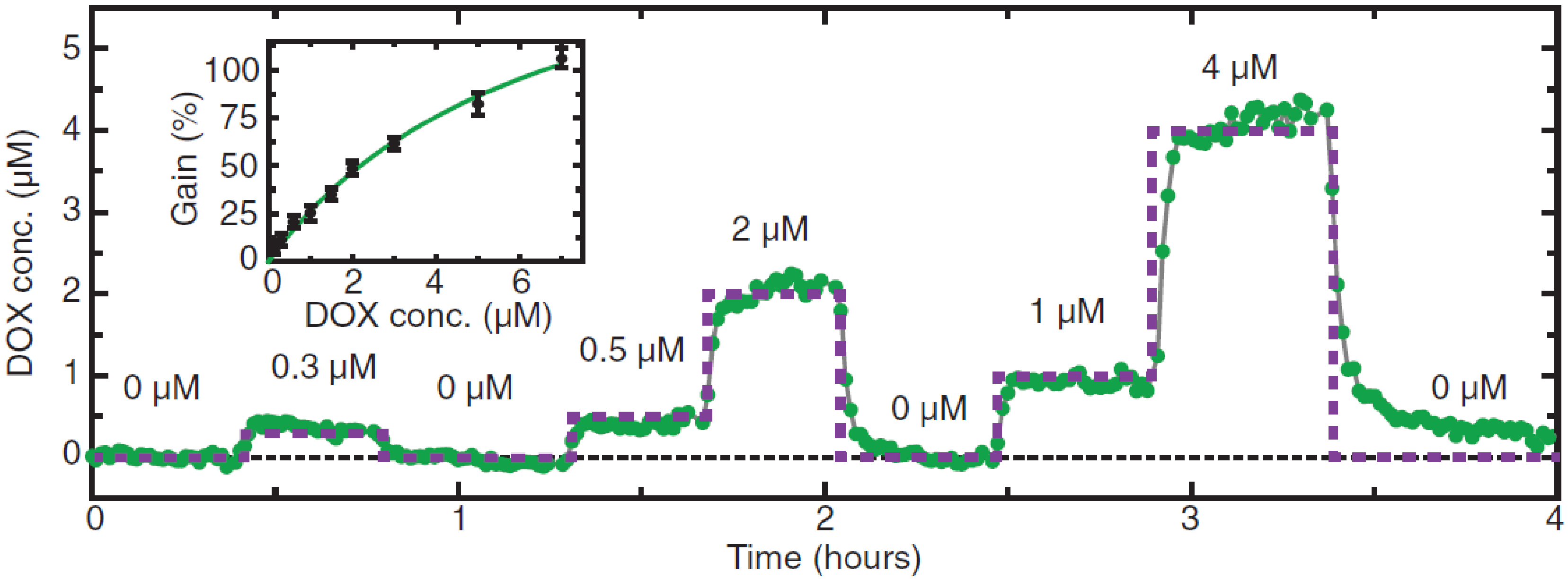
Monitoring of Drugs with Narrow Therapeutic Range



- Measuring therapeutic in vivo concentrations of doxorubicin (a chemotherapeutic) and kanamycin (an antibiotic)

Brian Scott Ferguson, David A. Hoggarth, Dan Maliniak, Kyle Ploense, Ryan J. White, Nick Woodward, Kuangwen Hsieh, Andrew J. Bonham, Michael Eisenstein, Tod E. Kippin, Kevin W. Plaxco, Hyongsok Tom Soh, Real-Time, Aptamer-Based Tracking of CirculatingTherapeutic Agents in Living Animals, 2013 Nov 27;5(213):213ra165. doi: 10.1126/scitranslmed.3007095

Monitoring of Drugs with Narrow Therapeutic Range



- Real-time measurement of DOX in vitro in human whole blood.

Brian Scott Ferguson, David A. Hoggarth, Dan Maliniak, Kyle Ploense, Ryan J. White, Nick Woodward, Kuangwen Hsieh, Andrew J. Bonham, Michael Eisenstein, Tod E. Kippin, Kevin W. Plaxco, Hyongsok Tom Soh, Real-Time, Aptamer-Based Tracking of CirculatingTherapeutic Agents in Living Animals, 2013 Nov 27;5(213):213ra165. doi: 10.1126/scitranslmed.3007095

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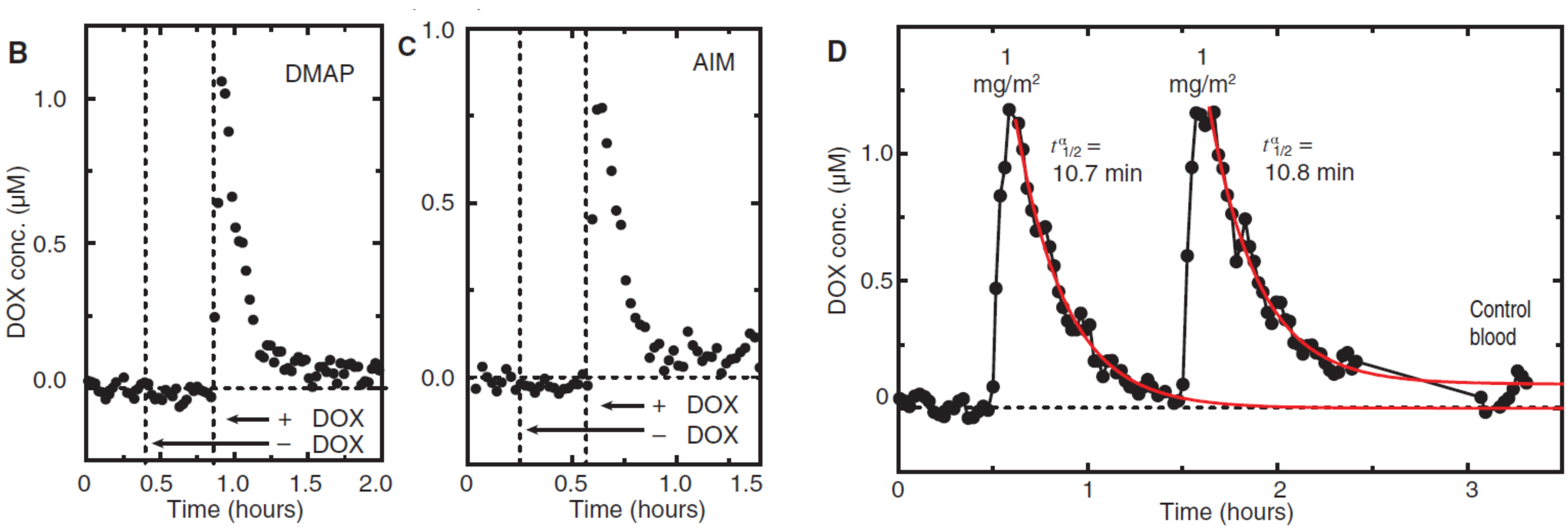
Pharmacokinetics



- Sensor specificity demonstrated in vivo in rats. We subjected rats to chemotherapy cocktails DMAP (B) and AIM (C) in the absence or presence of DOX. Peak concentrations and ta1/2 after two intravenous injections of DOX into a rat.

Brian Scott Ferguson, David A. Hoggarth, Dan Maliniak, Kyle Ploense, Ryan J. White, Nick Woodward, Kuangwen Hsieh, Andrew J. Bonham, Michael Eisenstein, Tod E. Kippin, Kevin W. Plaxco, Hyongsok Tom Soh, Real-Time, Aptamer-Based Tracking of CirculatingTherapeutic Agents in Living Animals, 2013 Nov 27;5(213):213ra165. doi: 10.1126/scitranslmed.3007095

Wearable Biosensors

Glucose Biosensor Solutions

Table 1 | Selected examples of commercial noninvasive or minimally invasive biosensors

Product, company	Analyte, sample	Wearable platform	Monitoring mechanism	Current stage	Website
Smart contact lens, Google and Novartis	Glucose in tears	Contact lens	Electrochemistry	Last update in 2018; this project is now on hold	https://verily.com/projects/sensors/smart-lens-program/
GlucoWatch, Cygnus Inc.	Glucose in ISF	Watch type	Electrochemistry	FDA approved, but retracted from market	No longer available
BioMKR, Prediktor Medical	Blood glucose	Wrist strap similar to a smart watch	Near infrared spectroscopy, bioimpedance	Under clinical testing for approval and market launch in Europe	https://www.prediktormedical.com/
GlucoWise, MediWise	Blood glucose	Finger clip	Radio frequency	Under development, running clinical trials with healthy volunteers	http://www.gluco-wise.com/
Freestyle Libre, Abbott	Glucose in ISF	Patch	Electrochemistry	FDA approved in US in July 2018	https://www.freestylelibre.us/
Dexcom G6 CGM, Dexcom	Glucose in ISF	Patch	Electrochemistry	FDA approved	https://www.dexcom.com/
GlucoTrack, Integrity Applications	Blood glucose	Finger clip	Ultrasonic, electromagnetic, thermal waves	Type 2 diabetes, approved in Europe	http://www.glucotrack.com/
Eversense, Senseonics	ISF glucose	Subcutaneous small stick implant	Fluorescence	Recently received FDA approval	https://www.eversensediabetes.com/
NovioSense tear glucose sensor, NovioSense	Tear glucose	Small stick (spiral type) placed under the lower eyelid	Electrochemistry	Tested in animals and human subjects	http://noviosense.com/

Jayoung Kim, Alan S. Campbell, Berta Esteban-Fernández de Ávila and Joseph Wang, Wearable biosensors for healthcare monitoring, *Nat Biotechnol* **37,** 389–406 (2019). https://doi.org/10.1038/s41587-019-0045-y

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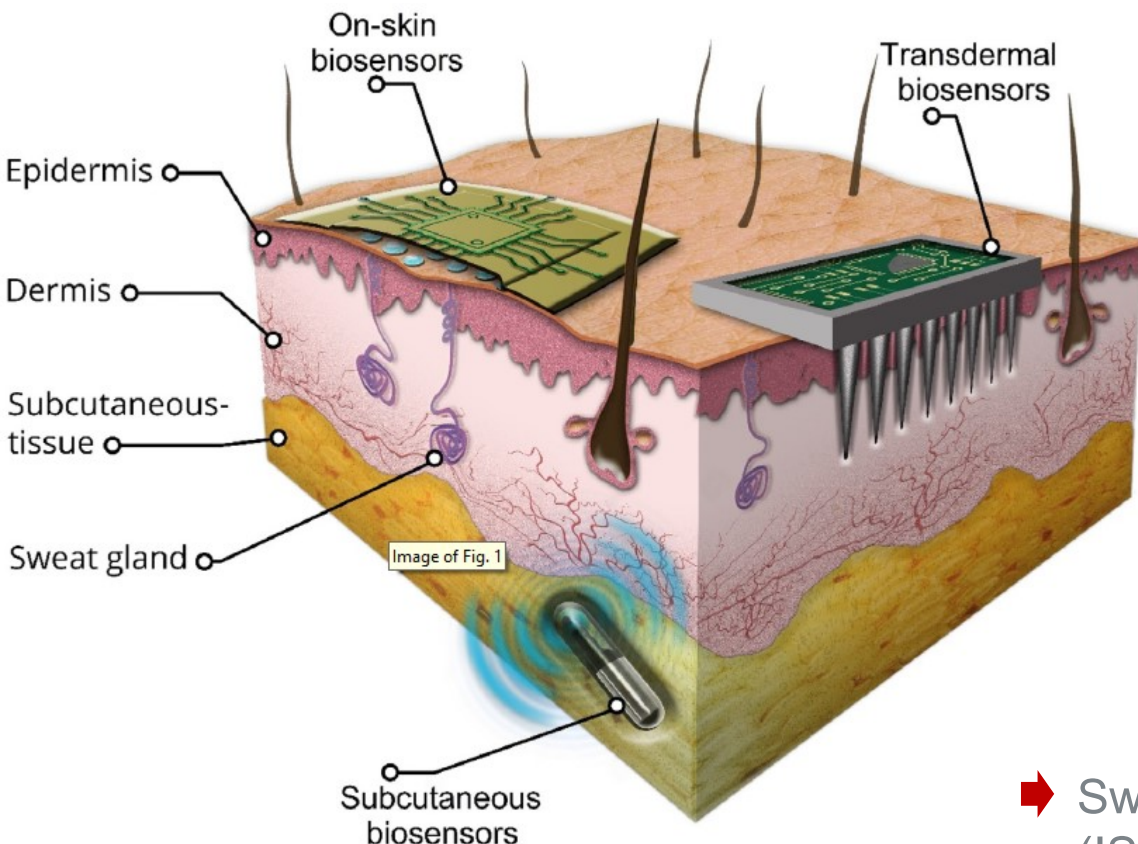
Skin-Contacted / Embedded Biosensors



- Sweat, interstitial fluid (ISF)

Muamer Dervisevica, Maria Albaa, Beatriz Prieto-Simona, Nicolas H. Voelckera, Skin in the diagnostics game: Wearable biosensor nano- and microsystems for medical diagnostics, Nano Today 30 (2020) 100828

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Skin-Contacted / Embedded Biosensors

Table 1
Comparison of several analytes' concentrations found in blood, ISF and sweat.

		Blood	ISF	Sweat
	Na^+	135–145 mM*		10–90 mM [26,27]
Ions	K^+*	3.5–5.5 mM*	Similar to	2–10 mM [27]
	Cl	95–110 mM*	plasma	14–48 mM [28]
	Ca^{2+}	>2.6 mM*		0.37 mM [29]
	Glucose*	3.6-6.0 mM*		36-60 µM [32]
	Lactate	0.5–10 mM	Similar to	5.0–20 mM [33]
Metabolites	Urea*	3.0–7.5 mM*	plasma	13–24 mM [34]
	Cholesterol*	<3.5 mM*		
	Uric acid	0.12-0.45 mM [30]		25-36 µM [34]
	Ascorbic acid	30-80 µM [31]		10-50 µM [35,36]
Hormones	Cortisol	Morning 193–773 nM [37]	Similar to	20-500 nM [38]
		Afternoon 55–496.6 nM	plasma	
	Cytokines	pM to nM	80 % of plasma	<0.1 % of plasma
Proteins	Antibodies e.g. IgA	0.4 –16 mg/mL	15-25 % of plasma	
		~262 mg/mL [39]		0.1–10 ng/mL [40]

- Biomolecules can leach from blood to ISF and sweat, but can be found at many orders of magnitude lower concentrations.

Muamer Dervisevica, Maria Albaa, Beatriz Prieto-Simona, Nicolas H. Voelckera, Skin in the diagnostics game: Wearable biosensor nano- and microsystems for medical diagnostics, Nano Today 30 (2020) 100828

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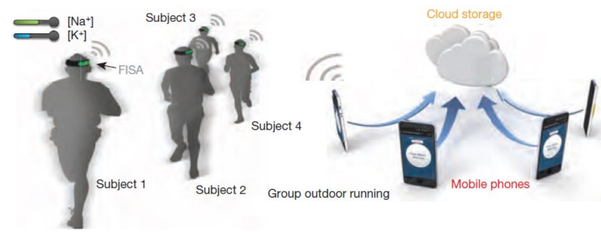
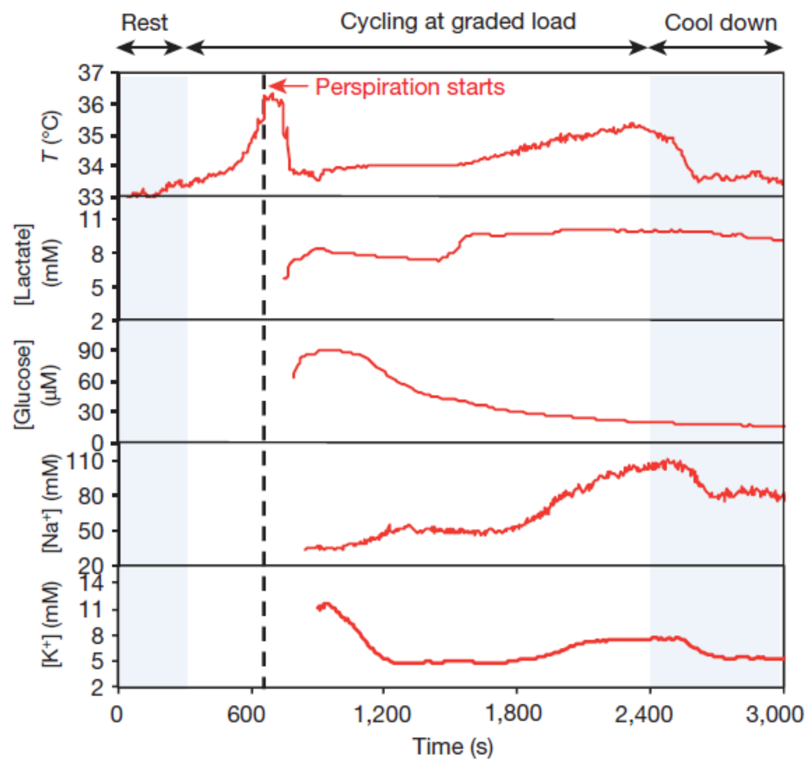
Wearable Sensors – Sweat Analysis

Electrochemical analysis of sweat at molecular level by arrays of sensors in close contact with skin.





Nature 529(7587):509-514 · January 2016
DOI: 10.1038/nature16521

Wearable Sensors – Sweat Analysis

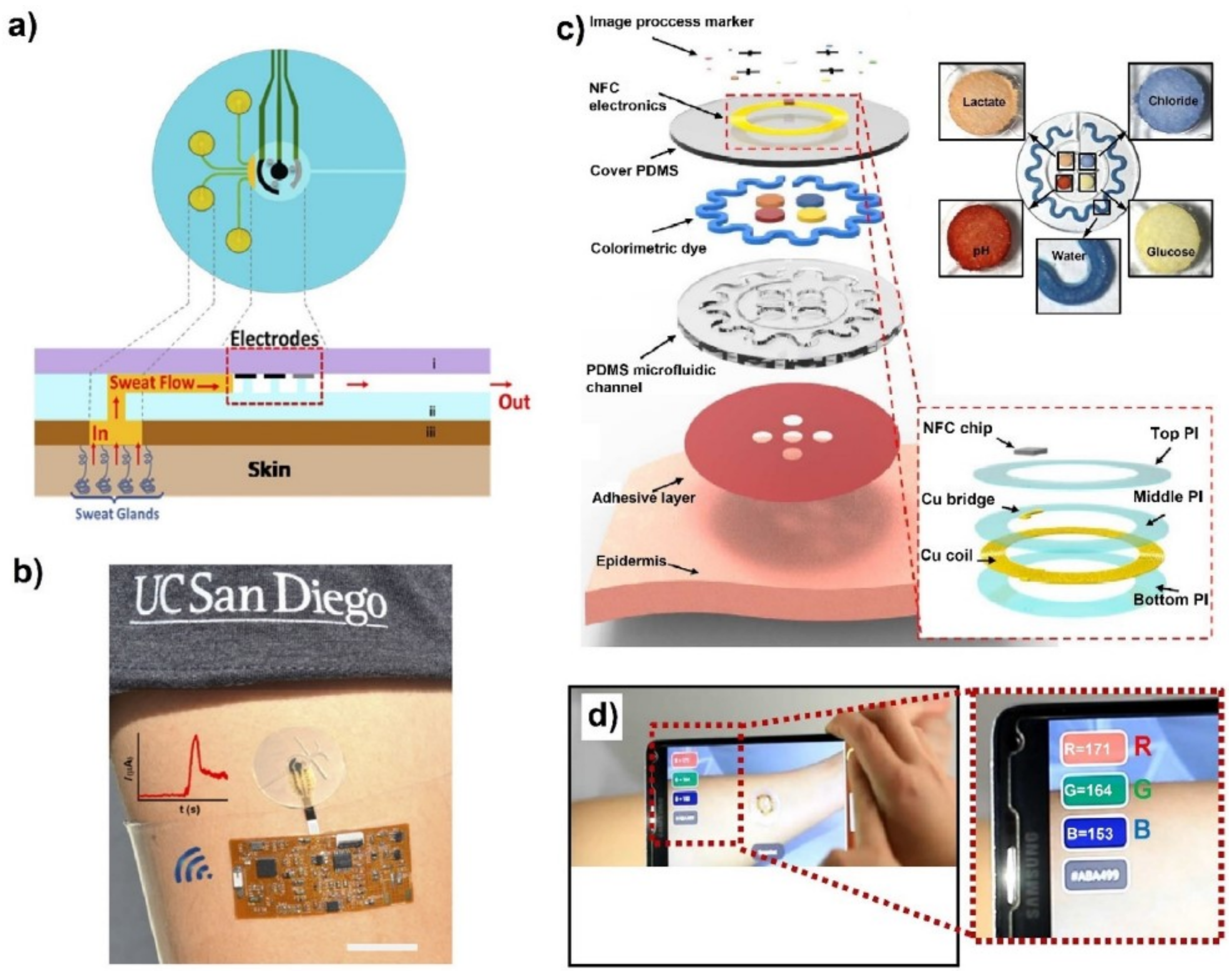
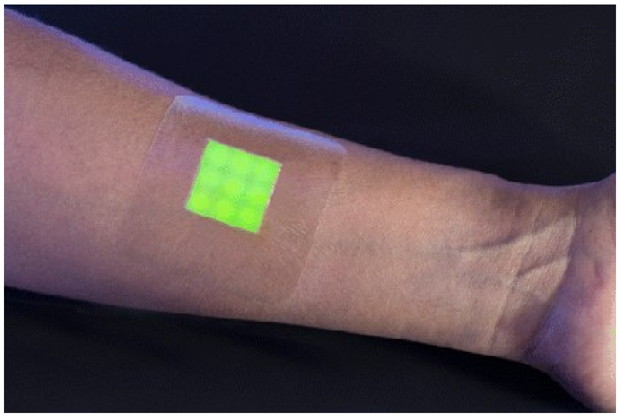
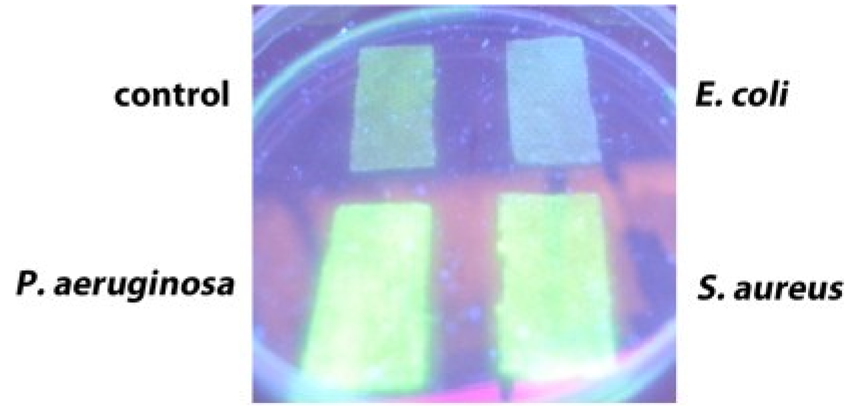


Fig. 3. a) Schematic illustration of an electrochemical microfluidic device for glucose and lactate detection, b) optical image of the microfluidic device integrated withelectronic board for wireless transfer of data, adapted with permission from Ref. [77] Copyright (2017) American Chemical Society. c) Schematic illustration of a microfluidicsweat device and its NFC system for colorimetric detection of pH, glucose, lactate and Cl-, d) demonstration of NFC between device and smartphone launch software, adapted with permission from Ref. [91] Copyright (2016) American Association for the Advancement of Science.

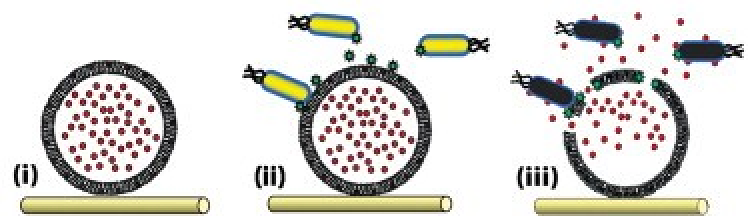
Muamer Dervisevica, Maria Albaa, Beatriz Prieto-Simona, Nicolas H. Voelckera, Skin in the diagnostics game: Wearable biosensor nano- and microsystems for medical diagnostics, Nano Today 30 (2020) 100828

Smart Wound Dressing





Biosensors embedded in wound dressings to monitor bacterial infections. Possible incorporation of triggered release of a drug.



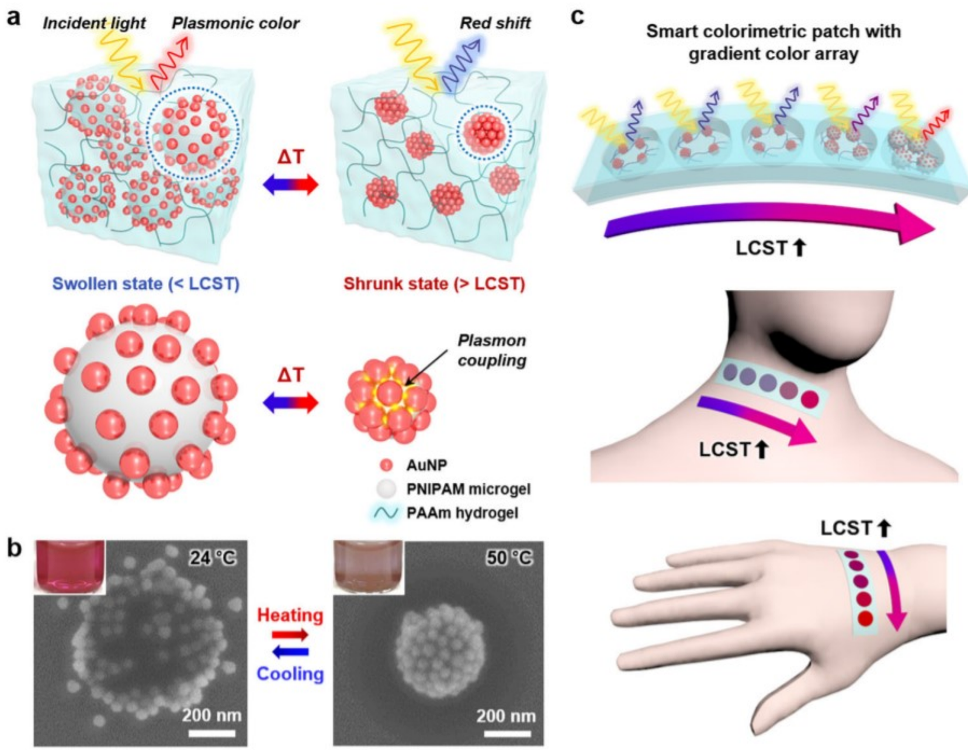
Dye self quenched

Dye bright

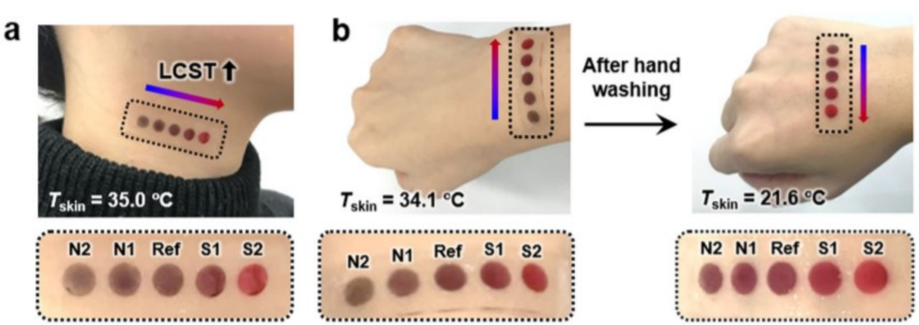
Fluorescent dye loaded to lipid vesicle, toxic bacteria destroy the lipid bilayer wall and leaches the dye reporter.

Toby Jenkins laboratory - 10.1021/acsami.5b07372

Skin Temperature Visualization



- Plasmonic color change, based on near field coupling between gold nanoparticles (plasmonic ruler)
- Actuated by the thermo-responsive microhydrogel volumetric change



Choe et al. NPG Asia Materials (2018) 10: 912-922

Wearable Sensors – ISF Analysis

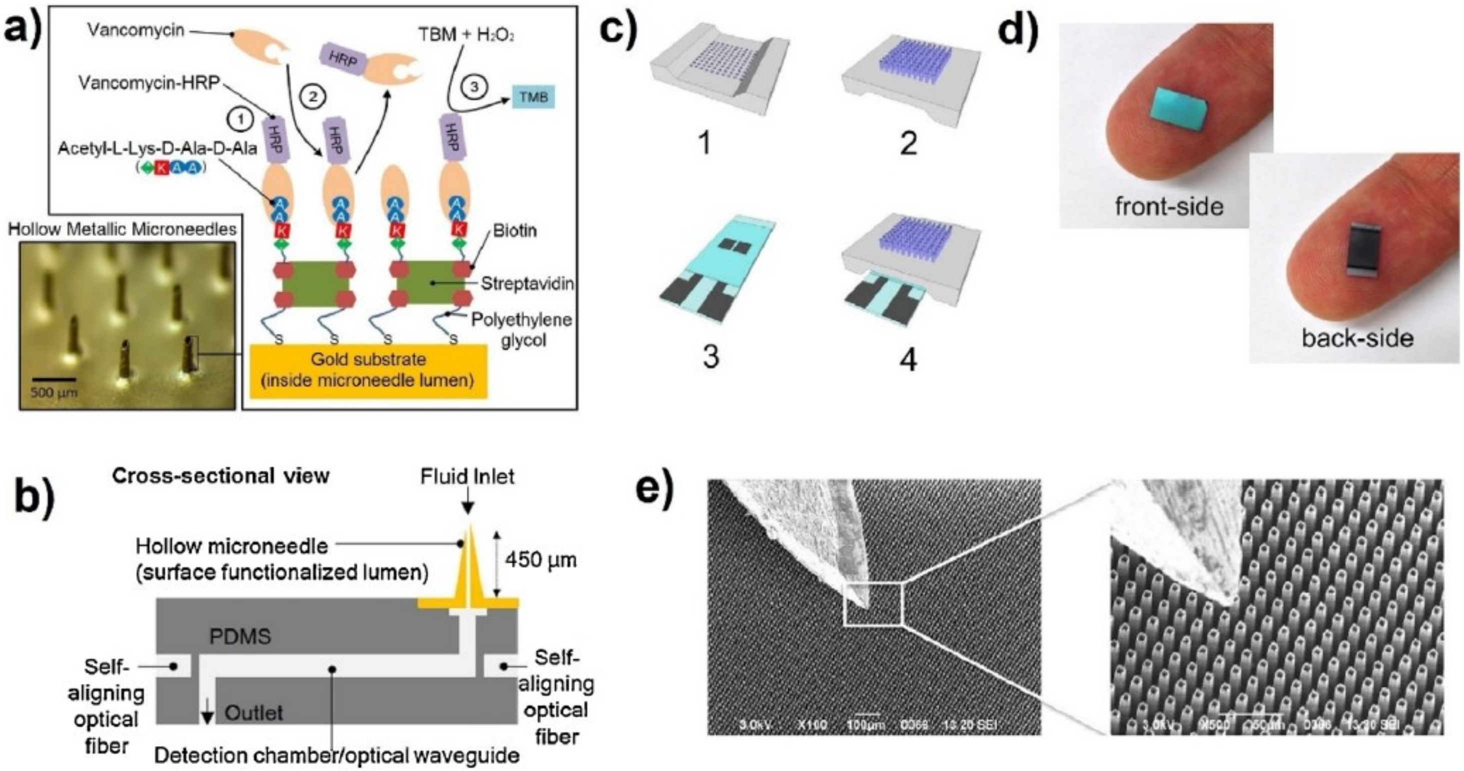
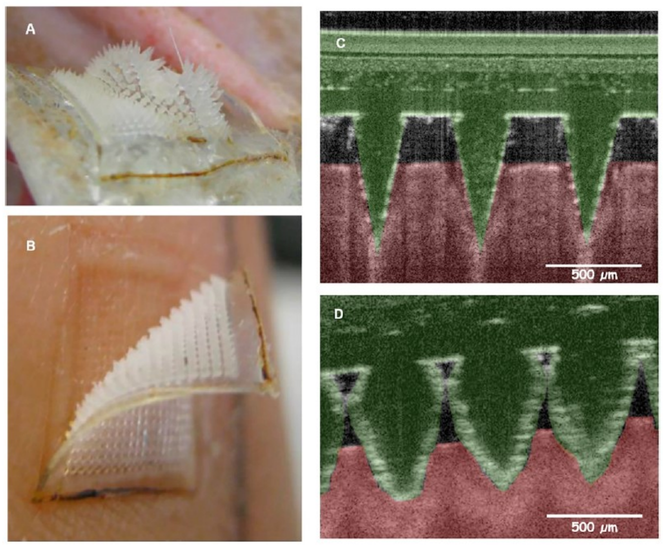
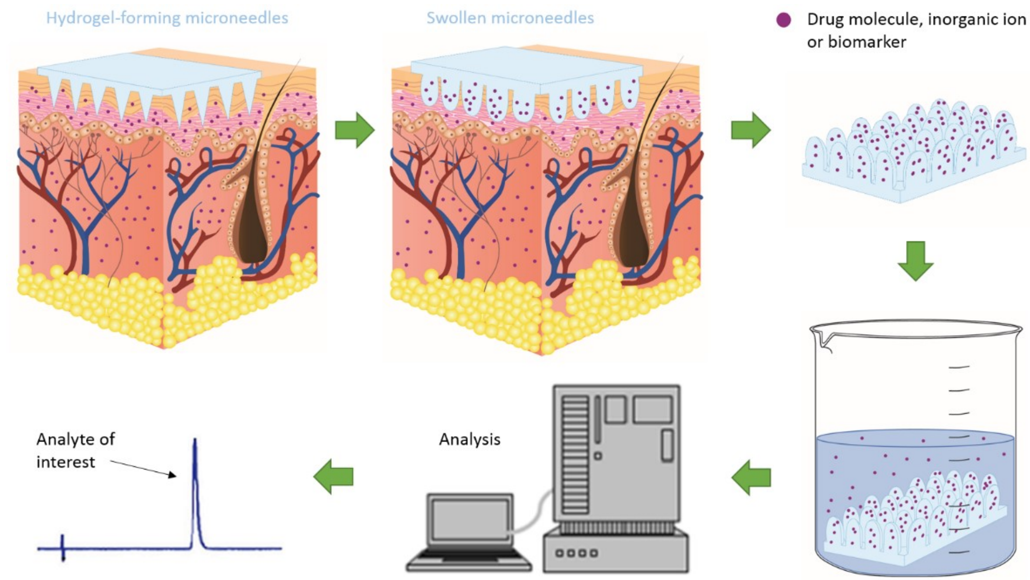


Fig. 5. MNAs integrated into microfluidic systems. **a)** Illustration of the biosensing strategy that relies on a competitive assay, the analyte being vancomycin; **b)** cross-sectional schematic view of MN-based optofluidic biosensor, adapted from Ref. [149]. High density hollow silicon dioxide MNs for measurement of glucose in ISF; **c)** 1-front side and 2-back side of the MNA chip, 3- glucose biosensor, 4- glucose biosensor integrated with MNA chip; **d)** optical images of chips placed on fingertip; **e)** SEM of MNAs compared to the size of a typical insulin hypodermic needle, adapted with permission form Ref. [152] Copyright (2015) Elsevier.

ISF Analysis



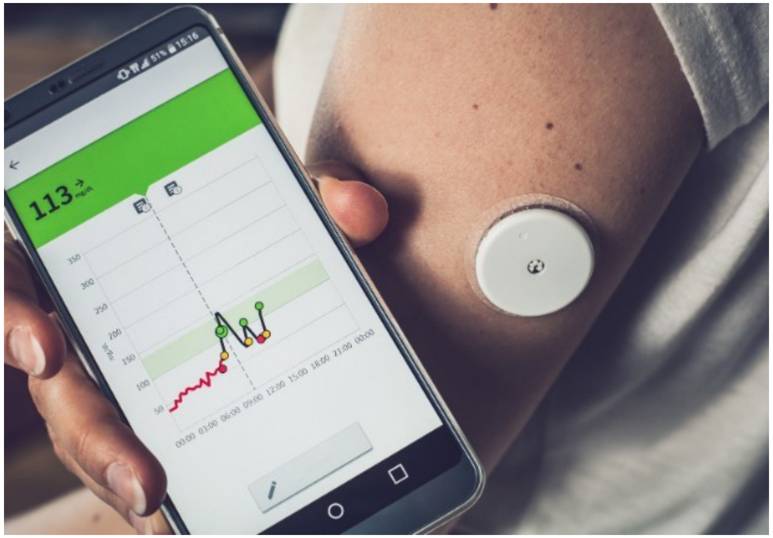


•https://doi.org/10.1371/journal.pone.0145644

- Alternative to collecting of ISF via metallic microneedles based on arrays of hydrogel features swelling the skin.

Caffarel-Salvador, E.; Brady, A.J.; Eltayib, E.; Meng, T.; Alonso-Vicente, A.; Gonzalez-Vazquez, P.; Torrisi, B.M. Vicente-Perez, E.M.; Mooney, K.; Jones, D.S.; et al. Hydrogel-Forming Microneedle Arrays Allow Detection of Drugs and Glucose in Vivo: Potential for use in Diagnosis and Therapeutic Drug Monitoring. PLoS ONE **2015**, 10, e0145644

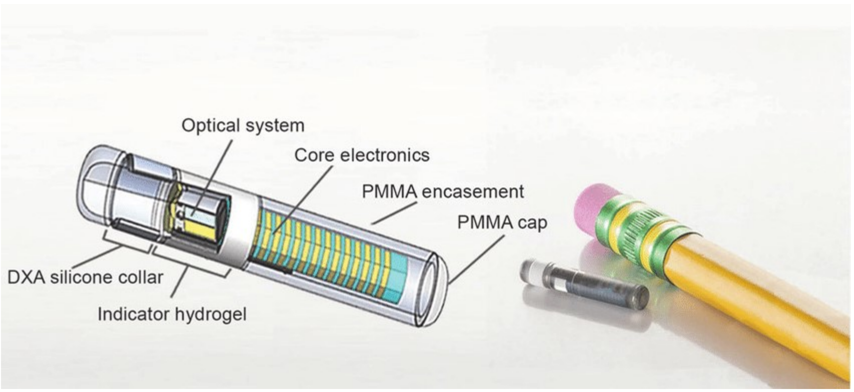
Subcutaneous Glucose Sensing

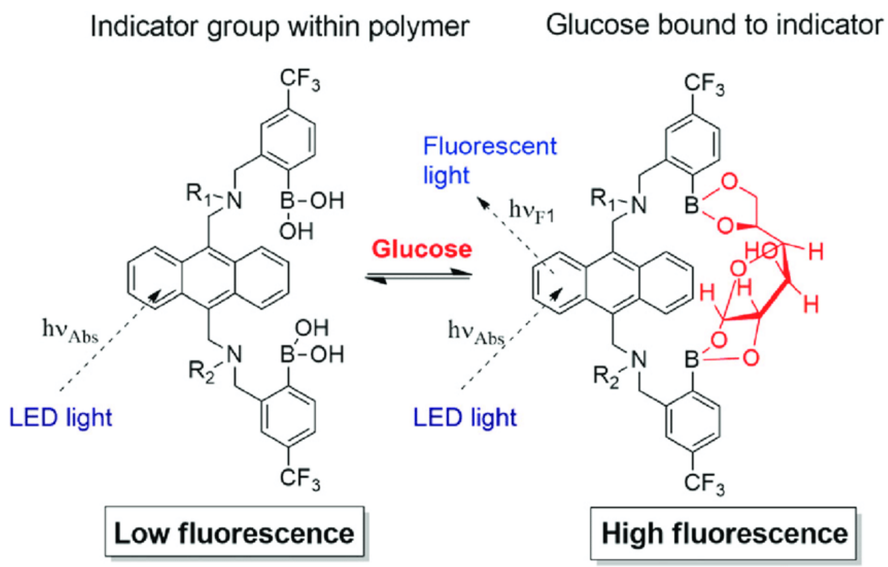


Eversense provides continuous blood glucose monitoring for up to 90 days via an under-the-skin sensor, a removable and rechargeable smart transmitter, and a convenient app for real-time diabetes monitoring and management.

https://www.eversensediabetes.com/sensor

Subcutaneous Glucose Sensing

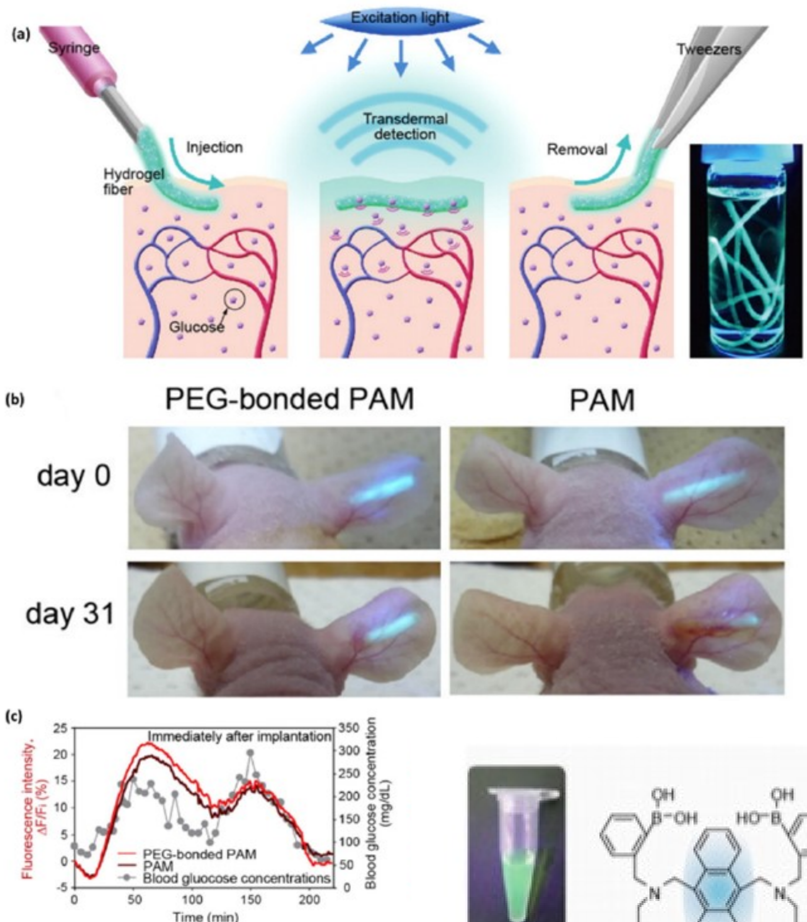




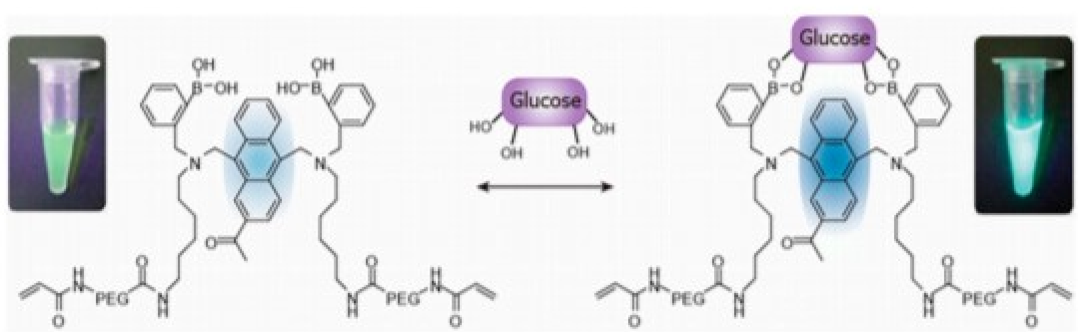
It uses a patented **fluorescent** glucose-indicating polymer technology to measure glucose in the **interstitial fluid** (a thin layer of fluid that surrounds the body's .

https://www.eversensediabetes.com/sensor

Subcutaneous Glucose Sensing



Heo, Y.J.; Shibata, H.; Okitsu, T.; Kawanishi, T.; Takeuchi, S. Long-term in vivo glucose monitoring using fluorescent hydrogel fibers. Proc. Natl. Acad. Sci. USA **2011**, 108, 13399–13403.



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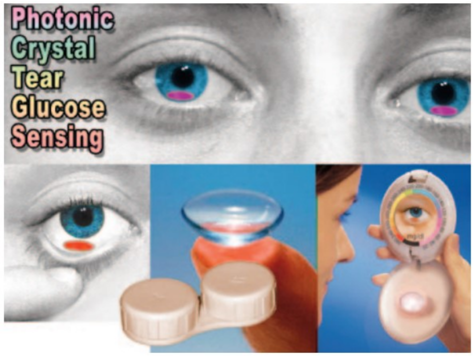
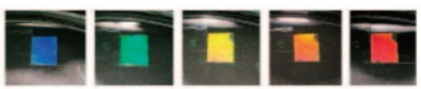
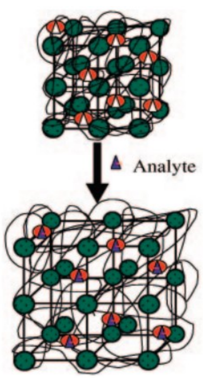
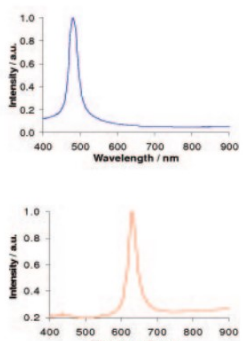
Wearable Sensors - Tear Fluid Analysis

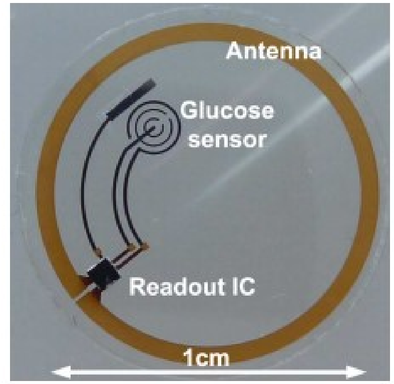


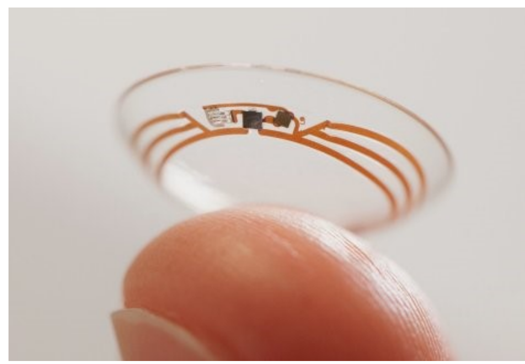






Photonic Crystal Glucose-Sensing Material for Noninvasive Monitoring of Glucose in Tear Fluid," V. Alexeev, S. Das, D.N. Finegold and S.A. Asher, Clinical Chemistry, 50, 2353 - 2360 (2004)





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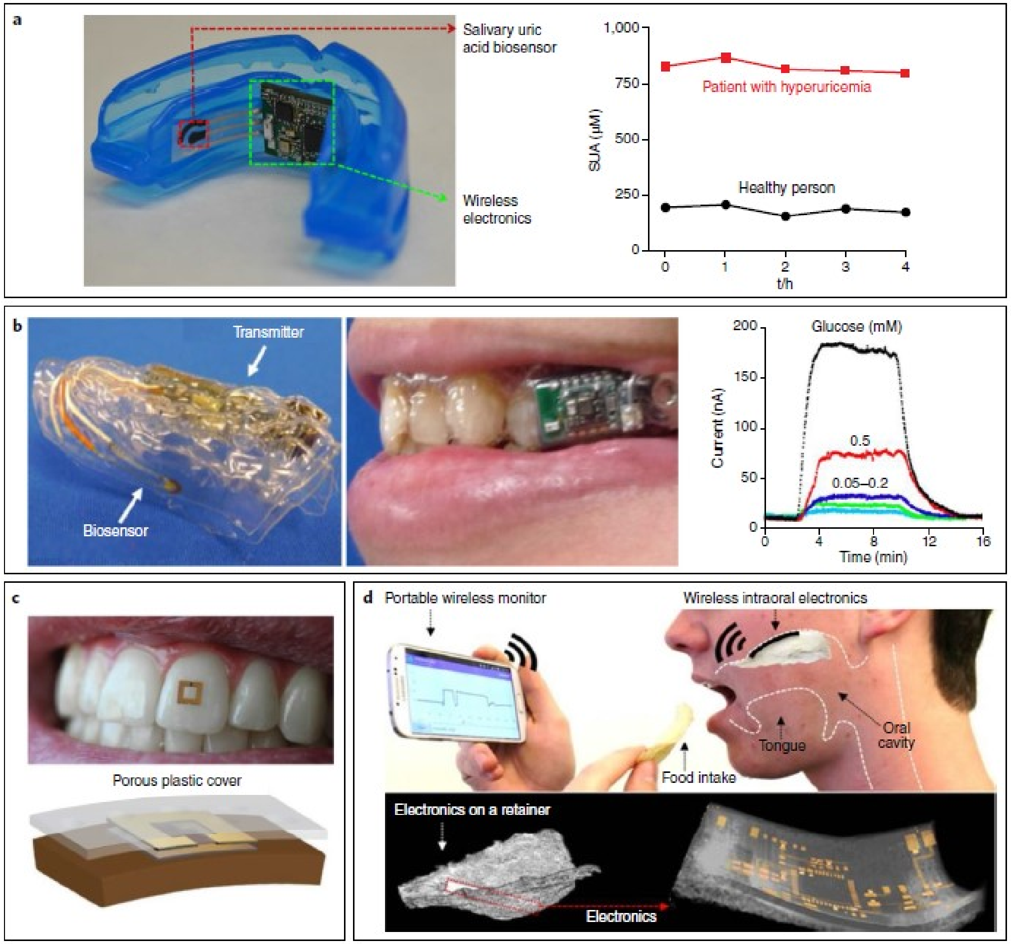

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