Transistors à nanofils de silicium pour la détection de ions et protéines

University of Basel

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SNI SWISS NANOSCIENCE INSTITUTE
EINE INITIATIVE DER UNIVERSITÄT BASEL UND DES KANTONS AARGAU

Empa Materials Science and Technology

Since Oct. 1st, 2016, also at
Swiss Federal Laboratories for
Materials Science & Technology
Dübendorf, Switzerland

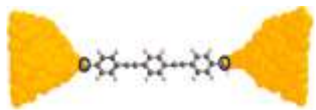
Trends in Micro Nano event, Swiss mnt network, Bienne, October 25, 2016

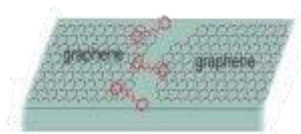
research activities

nanoscale electronics & molecular junctions

Individual molecular junctions

A. Vladyka, J. Overbeck,
M. El Abbassi, *et al.*



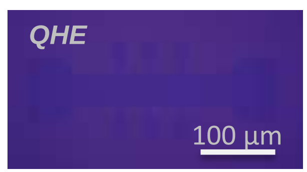


Networks of molecular junctions & hybrid devices

A. Vladyka *et al.*

Graphene & metrology

K. Thodkar, *M. El abbassi,*
A. Vladyka, J. Overbeck et al.



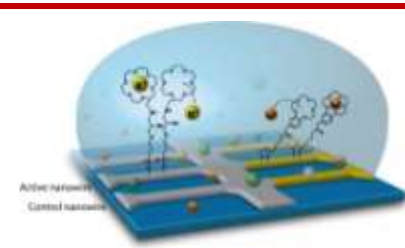
Optoelectronics & plasmonics

J. Overberck, T. Fröhlich *et al.*

ions and biochemicals detection

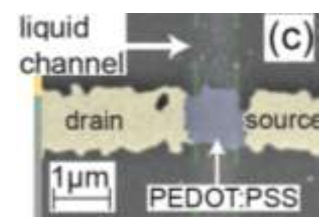
Si nanowires FETs

ions	***pH, Na$^+$, K$^+$, Ca^{2+}, F$^-$***
bio-molecules	***lectin (FimH)***
	sugar binding protein
pathogens	***Avails Medical***



M. Baghernejad, ***A. Fanget,***
O. Synhaivska,
R. Stoop, M. Wipf *et al.*

OECTs



R. Stoop, ***M. Sessolo,***
H. Bolink (Valencia) et al.

Silicon-based transistors for sensing

motivation: diagnostics & drug screening

- *specific detection of biochemicals at low cost*
- *time-resolved, label-free, quantitative, portable*
- *statistically relevant datasets for multiple analytes*

⇨ **simplify point of care-, point of prescription- & possibly home-diagnostics**

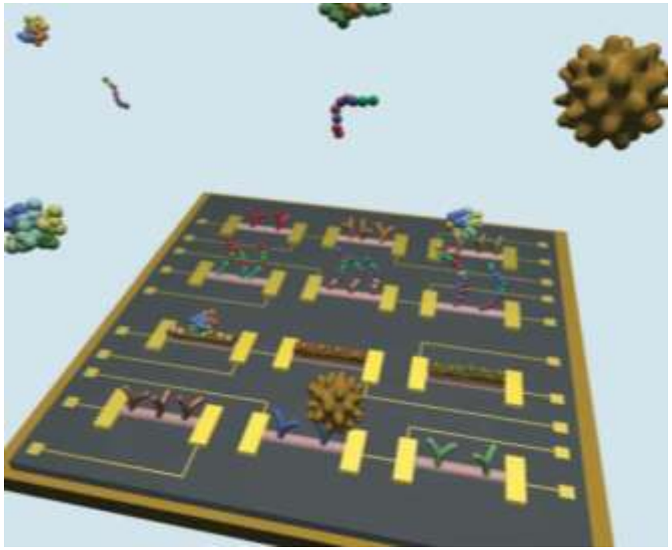
see e.g. Erickson et al., Lab on a chip (2014)
Public Health, Nanotechology & Mobility program (PHeNoM, Cornell)

Silicon-based biochemical sensors

- high-integration
- industrial fabrication processes

⇨***Si nanoribbons*** *operated as* ***ion-sensitive field-effect transistors*** *(ISFETs)*

transducing biochemical reactions in electrical signals



F. Patolsky, C.M. Lieber et al. MRS Bulletin 2007

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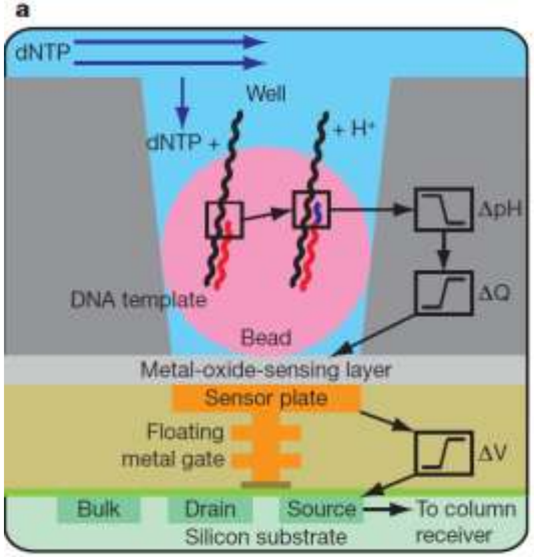
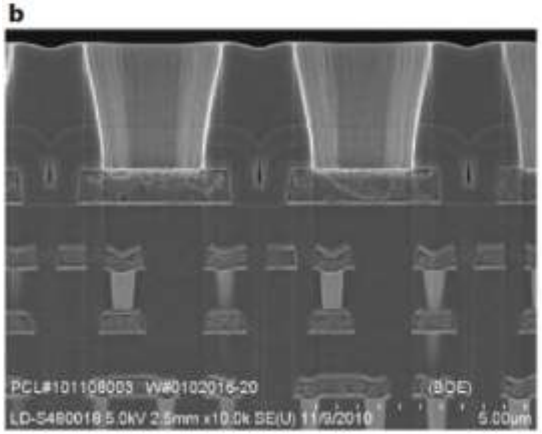
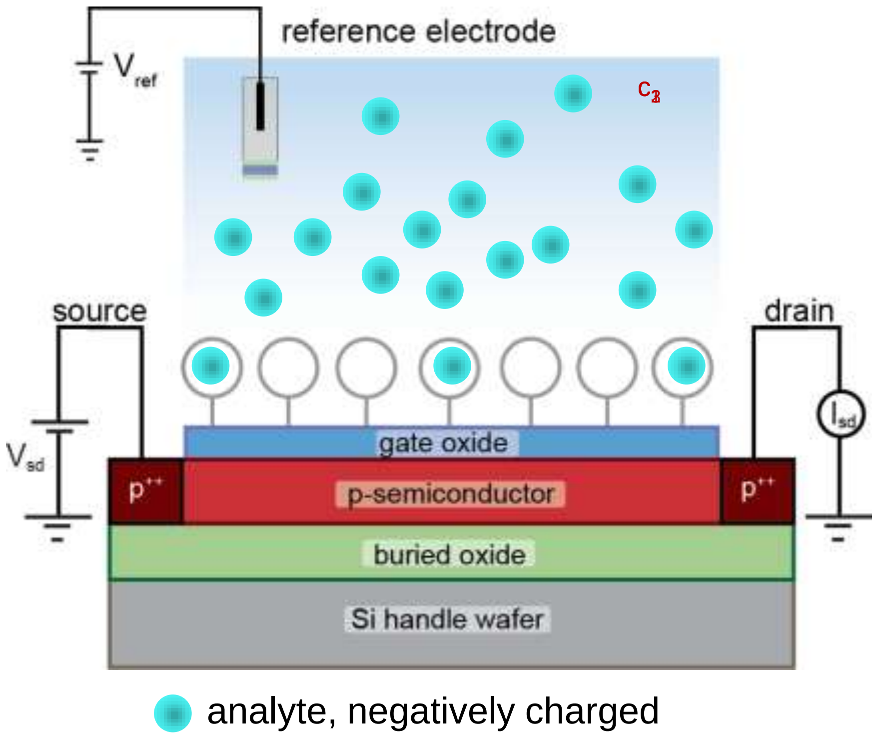
example: non-optical, on-chip sequencing using integrated ISFETs for pH monitoring

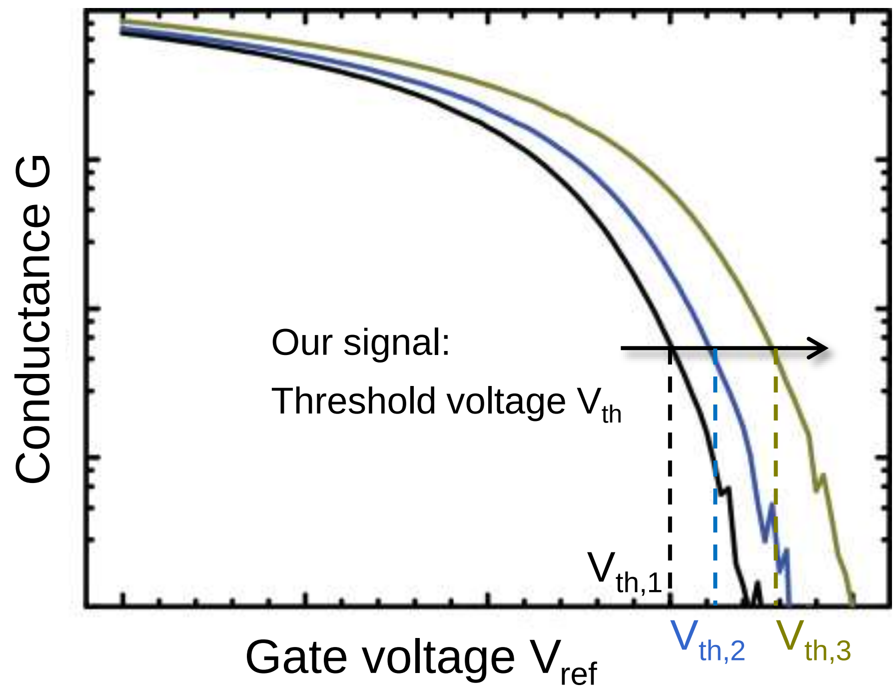




Rothberg et al., Nature (2011)
Ion-Torrent technology

ISFETs as potentiometric biochemical sensors



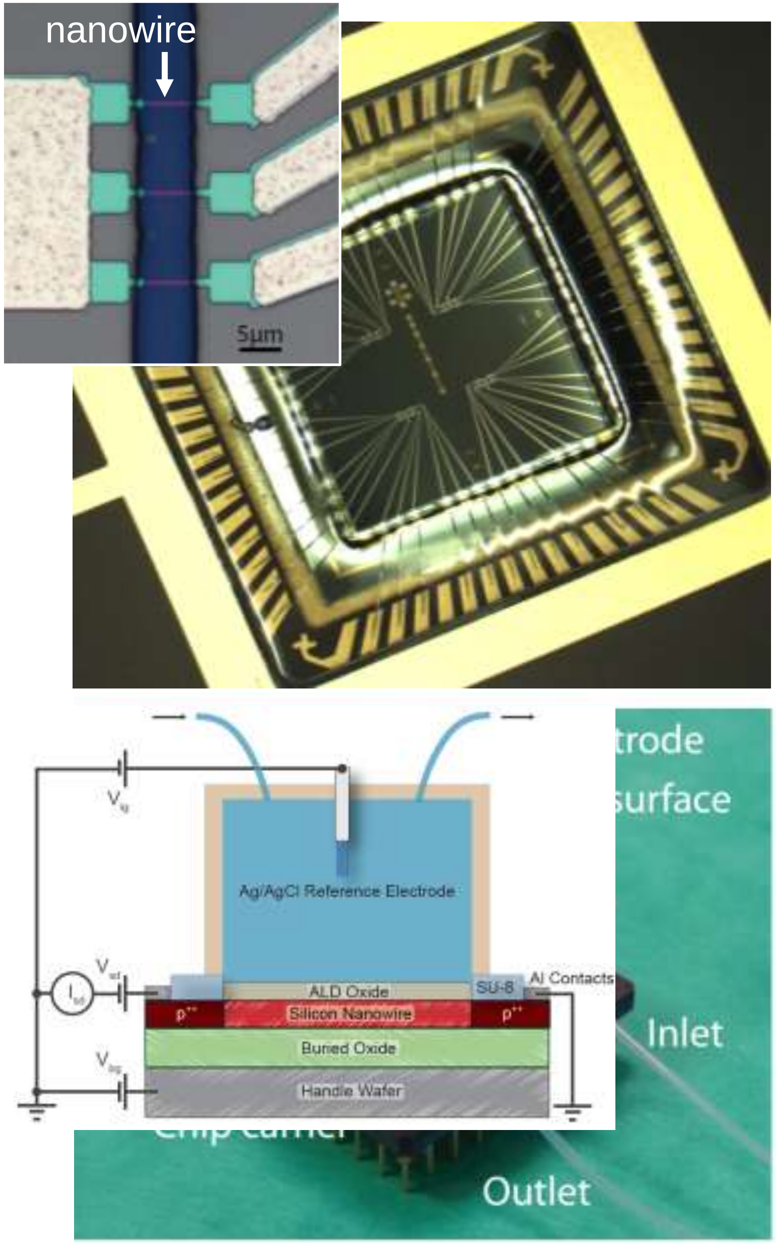


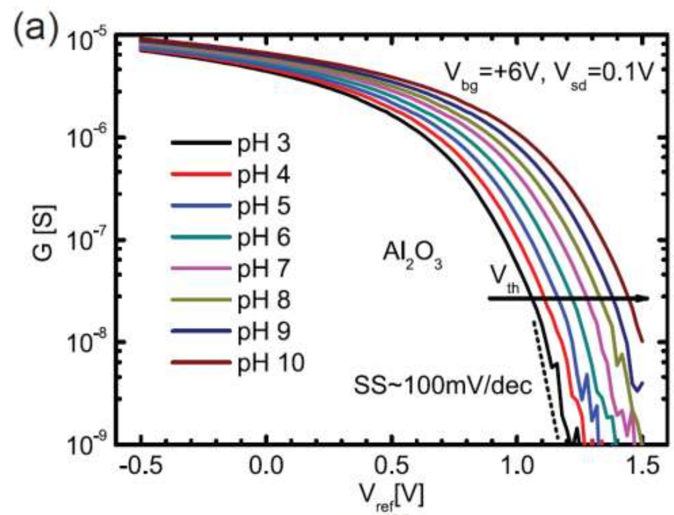
Theoretical limit: Nernst response

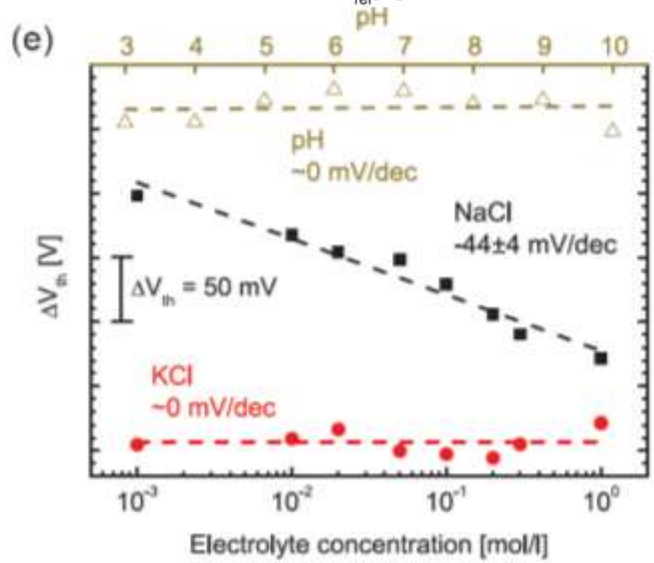
$$\Delta V_{th} = V_{th,2} - V_{th,1} = 2.3\frac{kT}{e}\log_{10}(\frac{c_2}{c_1}) \approx 59.6\,\mathrm{mV}\cdot\log_{10}(\frac{c_2}{c_1})$$

see e.g. Bergveld, IEEE Trans. Biomed. Eng (1970); Bergveld, Sensors & Actuators (2003), IEEE Sensor Conference (2003)

ions sensing with Si FETs

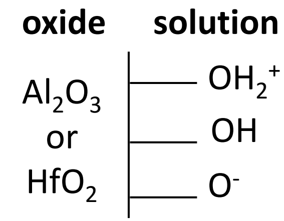






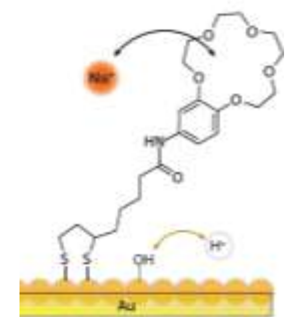
pH sensing

protonation / deprotonation of surface oxide groups



ion sensing

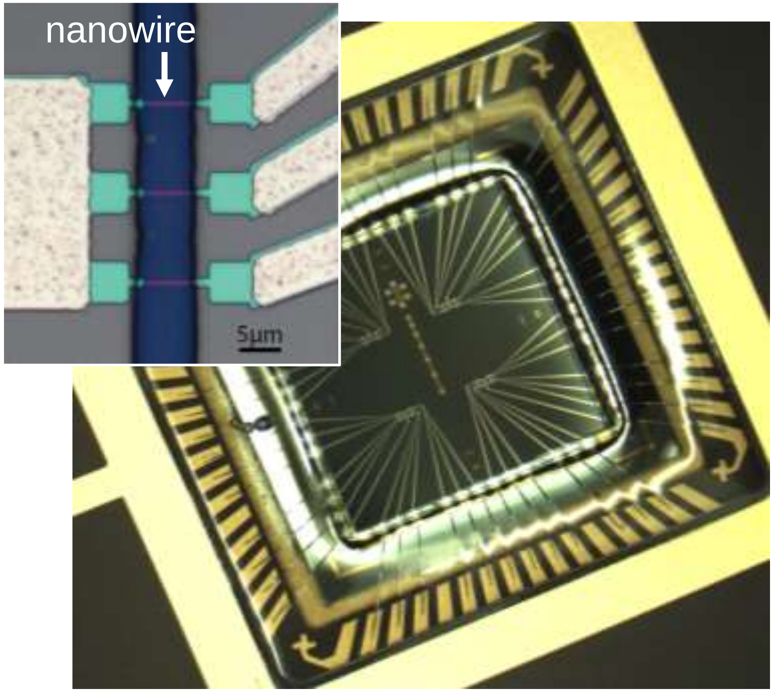
functionalization

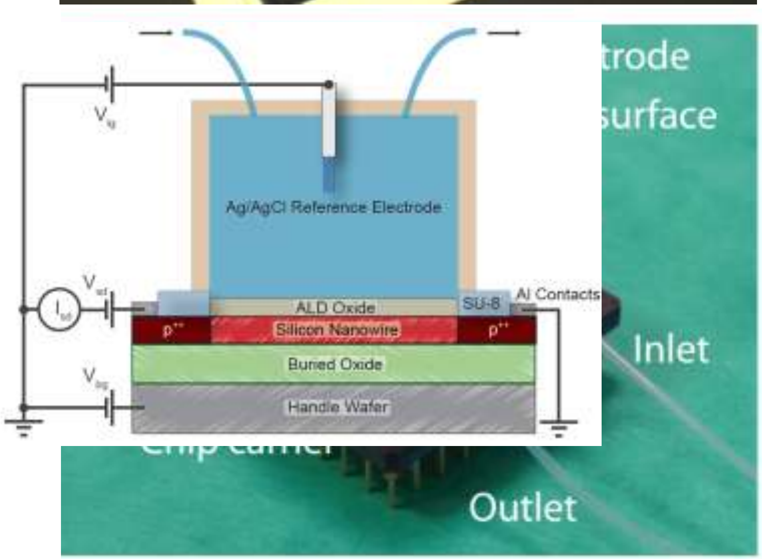


M. Wipf, R. Stoop, et al. ACS Nano (2013)

K. Bedner, V. Guzenko, J. Gobrecht et al., PSI

ions sensing with Si FETs





- **pH** & **surface passivation**
- **ions** **Na^+, K^+, Ca^{2+}, F^-**
  HfO2, Al2O3 or Au surfaces
- **noise, size, s/n ratio, competition effects**

- **quantifying protein-ligand interactions**

  state of the art: surface plasmon resonance (SPR)
  limited throughput, cost-intensive

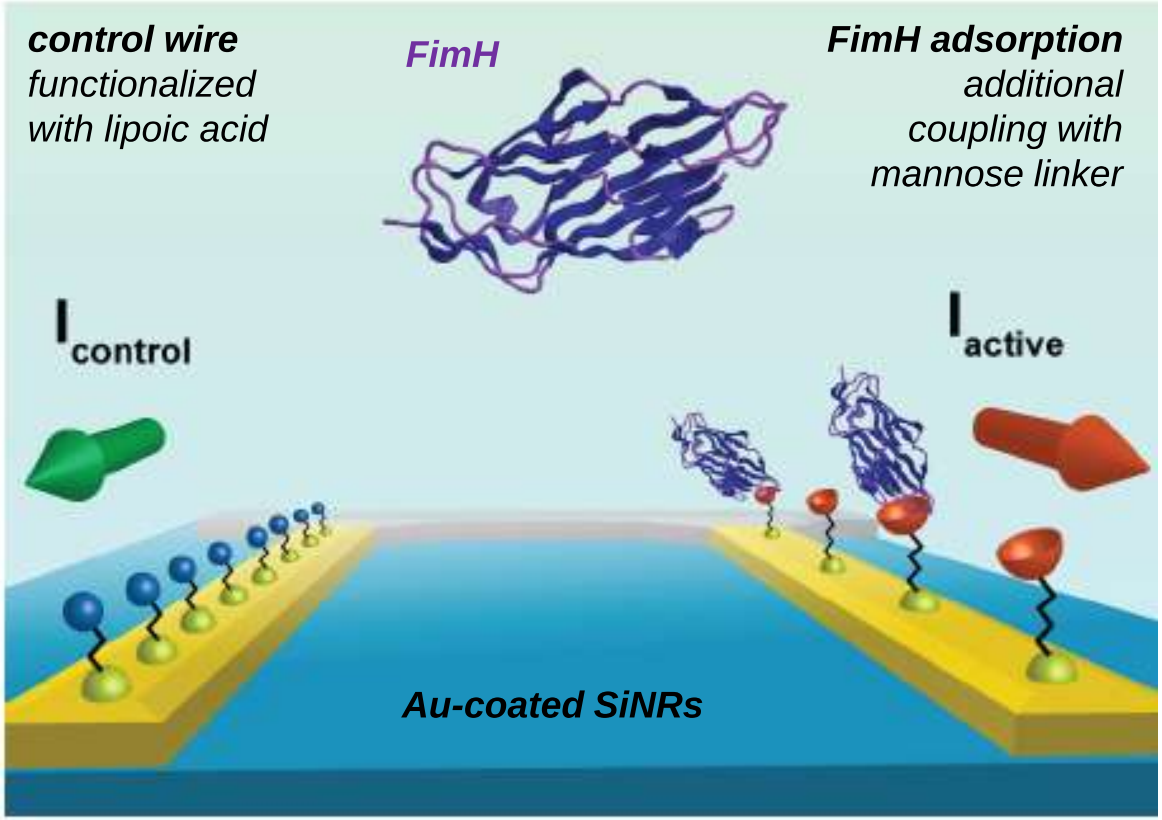
  ⇨ ***can SiNW do the job ?***
  to date mostly DNA and biotin−streptavidin interactions, see e.g. Reed et al.,. Nat. Nano (2012)

Test system: FimH *(bacterial lectin)*

with B. Ernst, G. Navarra, Dpt. Pharmacology, Uni Basel

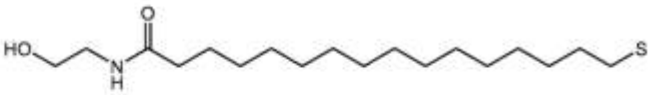
UTI therapy: high-affinity FimH antagonists
⇨ affinity screening tests: **SPR**
Ernst et al., J. Med. Chem. 2010, 2012; Chemmedchem 2012

FimH detection kinetics

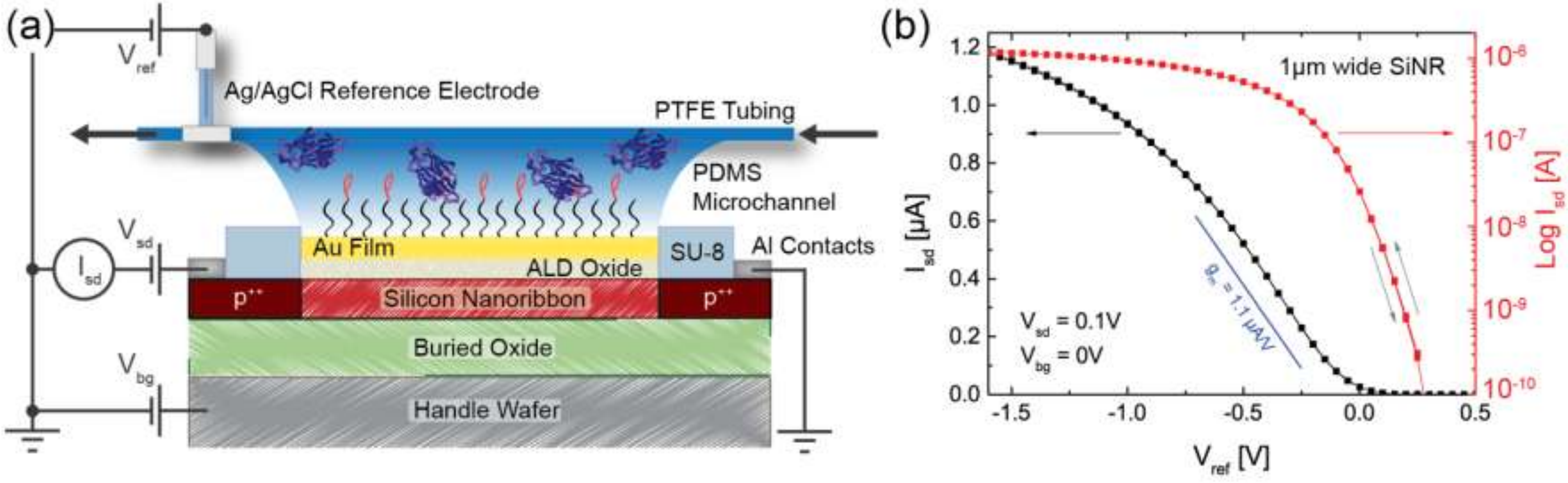


functionalization
- mercaptohexadecanoic acid (MHDA)
- amine coupling for ligand

Control



beyond ions

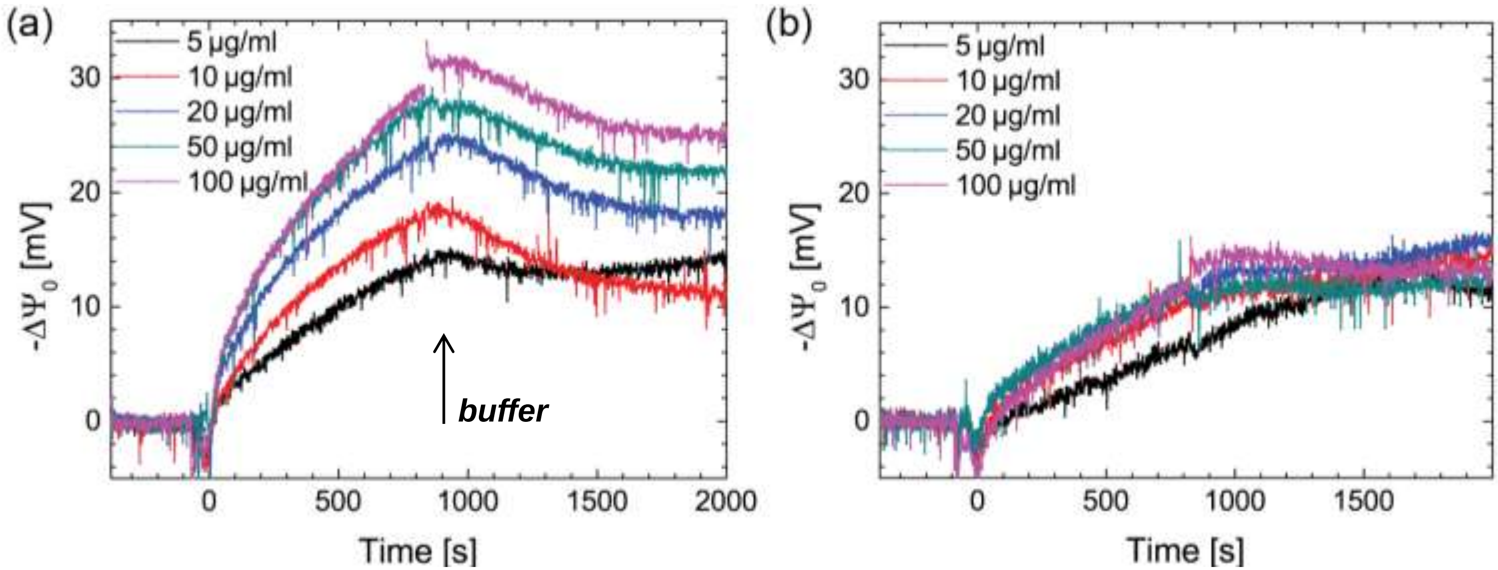


- reduced ionic strength buffer: 10mM HEPES, pH 8 (Debye length $\lambda_D \geq 3$ nm)
  ensure that the proteins are within the electrical double to affect the surface potential
- at pH 8: FimH neg. charged ⇨ I_{sd} increase upon binding
- SiNW operated in **linear region (constant transconductance g_m)**

FimH binding kinetics vs concentration

active wire *with mannose linker* ***control wire*** *(lipoic acid)*

SiNRs



SiNRs

- **non-specific adsorption** (control wire)
  lipophilic character of MHDA layer
- **signal only a function of surf. pot. change**
  site binding model see Reed et al., Nat. Nano 2012.

surface bound ligands/m2

charge per analyte

$$\Delta\Psi_0 = -\Delta V_{th} = -\frac{\Delta I_{sd}}{g_m} = \frac{q_A}{C_0}[B]_0 \times \frac{[A]}{K_D + [A]}$$

analyte bulk concentration

$(g_m = \partial I_{sd}/\partial V_{ref})$

equilibrium dissociation constant

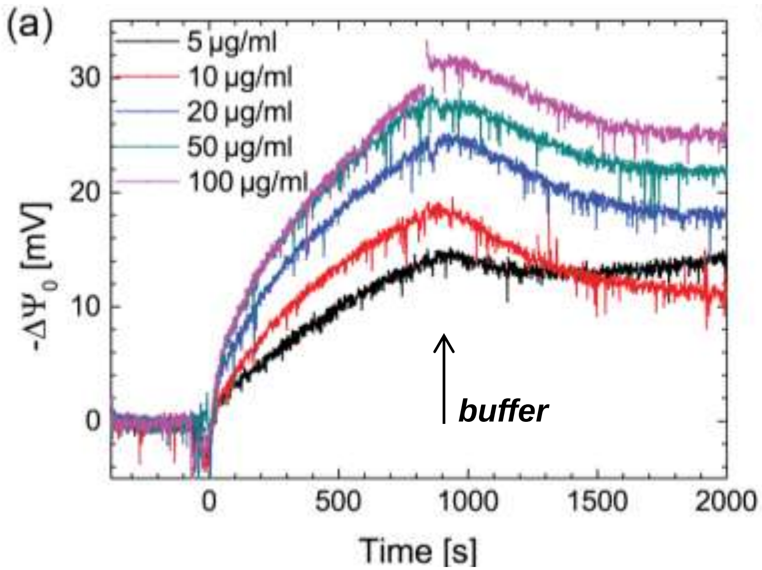
M. Wipf, R. Stoop, et al., ACS Sensors (2016)

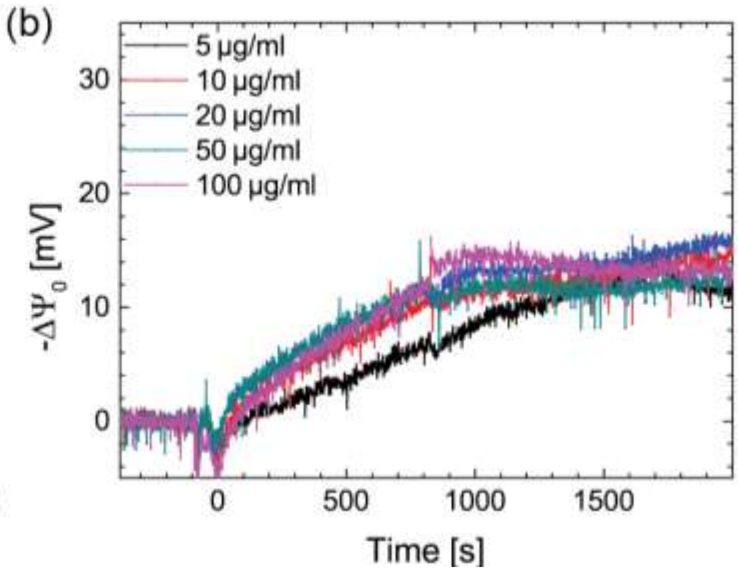
FimH binding kinetics vs concentration

***active wire** with mannose linker*

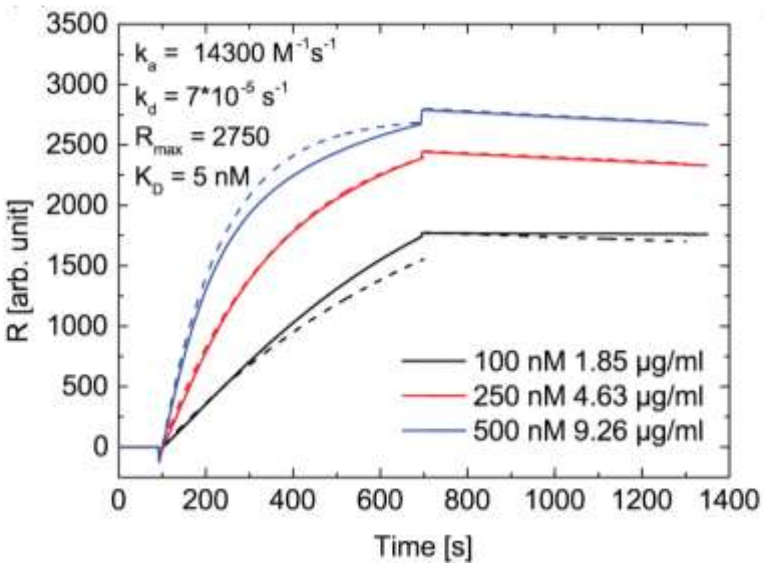
***control wire** (lipoic acid)*

SiNRs





SPR



SiNRs

- **non-specific adsorption** (control wire)
  lipophilic character of MHDA layer
- **signal only a function of surf. pot. change**
  see Reed et al., Nat. Nano 2012.

SPR (Biacore T200, Navarra, Ernst et al., Basel)

- **saturation at lower FimH concentrations**
- **dissociation less pronounced**
  dashed lines: Langmuir kinetics, K_D ~ 5nM is obtained.

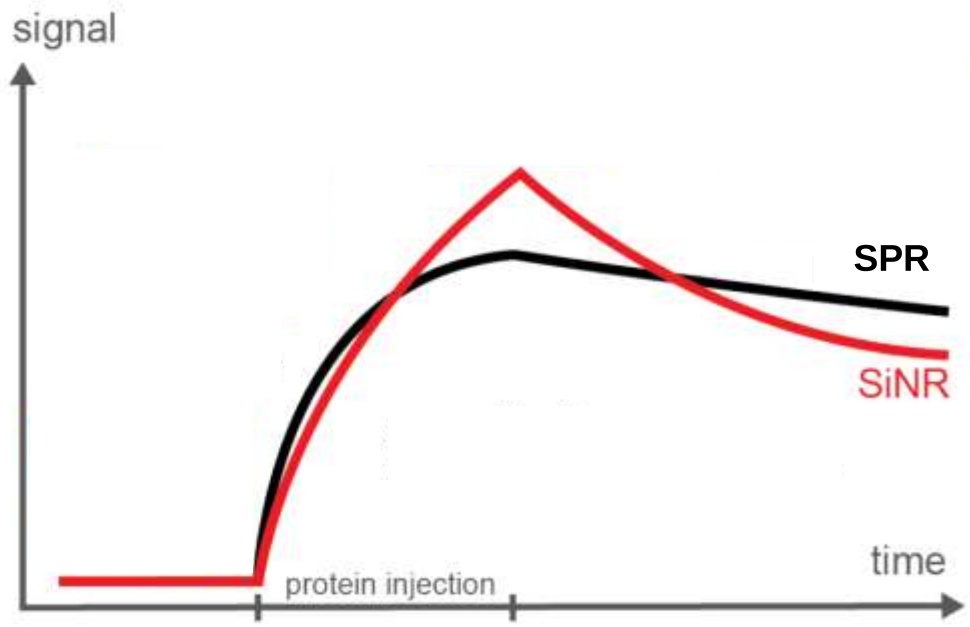
M. Wipf, R. Stoop, et al., ACS Sensors (2016)

FimH binding kinetics vs concentration

comparison SiNRs & SPR

- different **association and disso-ciation rates** (ka, kd)

  NB: variations between SPR systems!
  Cannon et al., Anal. Biochem. 2004; Katsamba et al., Anal. Biochem. 2006



possible origins of differences

- **flow rate at sensor surface & different surface areas**
  *- FimH-mediated bacterial **adhesion affected by shear forces***
  see e.g. Vogel et al., J. Bacteriol. 2007,. J. Biol. Chem. 2008
  ***- re-adsorption** of proteins in flow*

Fluidic channel	BioFET	Biacore
Flow rate	26 μL/min	20 μL/min
Height	100 μm	40 μm
Width	500 μm	500 μm
Length	4 mm	2.4 mm
Volume	$\approx$ 0.2 μL	$\approx$ 0.05 μL

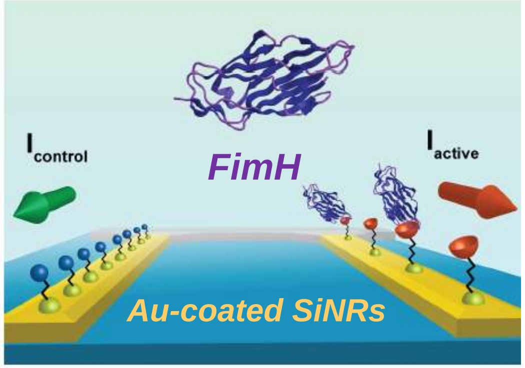
- **different effective protein concentration** *(fluidics)*

- **different sensing mechanisms: optical** (λ_{evan} ~ 300nm) **or charge** (λ_D ~ 3nm)
  ⇨ protein surface rearrangements affect SiNRs stronger than SPR, **longer time const.**
  Rabe et al., Adv. Colloid Interface Sci. 2011, Roach et al., JACS 2005

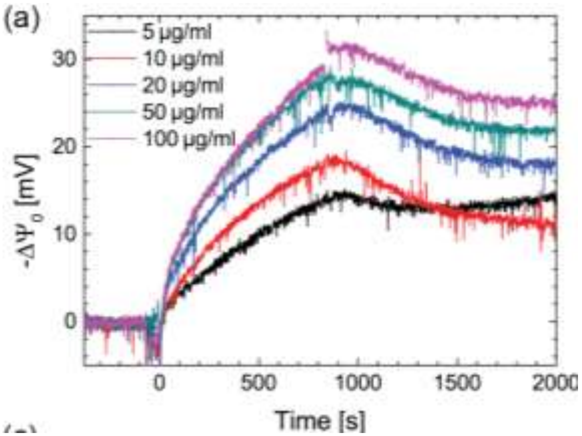
M. Wipf, R. Stoop, et al., ACS Sensors (2016)

conclusion & outlook

Si nanoribbon transistors as biosensors

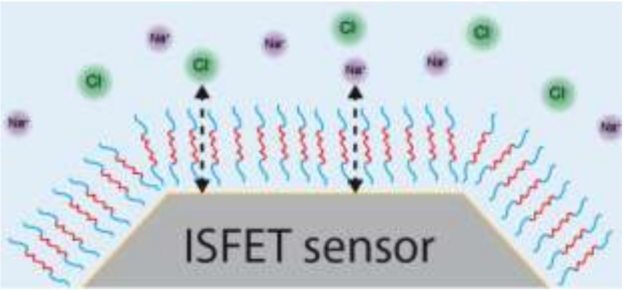


- **time-resolved** & **label-free** detection of FimH with s/n ratio >700
- **Au surface** for strongly reduced pH response & suitable surface chemistry for direct comparison with SPR systems
- quantitative detection by taking into account **competing reactions**
- enhanced **sensitivity to surface rearrangements** as compared to SPR



⇨ ***ISFETs for diagnosis & drug discovery***

Outlook: transmembrane proteins functionality & bacterial activity



M. Baghernejad, A. Fanget et al.,
with C. Palivan, W. Meier et al., (Basel),
D. Fotiadis et al. (Bern)
A. Jesorka et al. (Chalmers)

NCCR Molecular Systems Engineering

EU H2020
***Record It** (FET)*

start-up collaboration

availS MEDICAL

http://www.availsmedical.com/
Menlo Park (CA) USA

"Accurate, rapid, digital detection of infections in any bodily fluid to indicate in real-time which drugs will be most effective at the point-of-prescription"

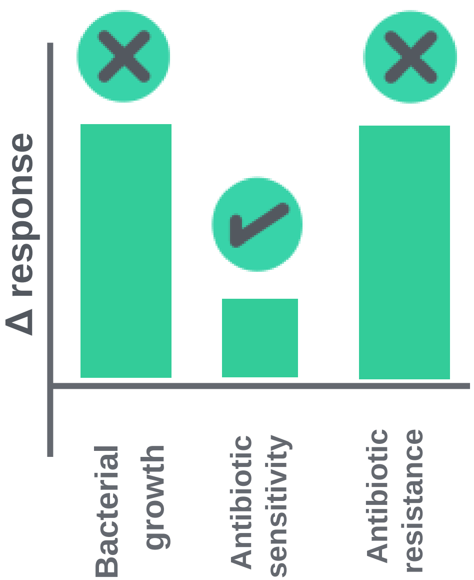
O. Knopfmacher *(CEO)*

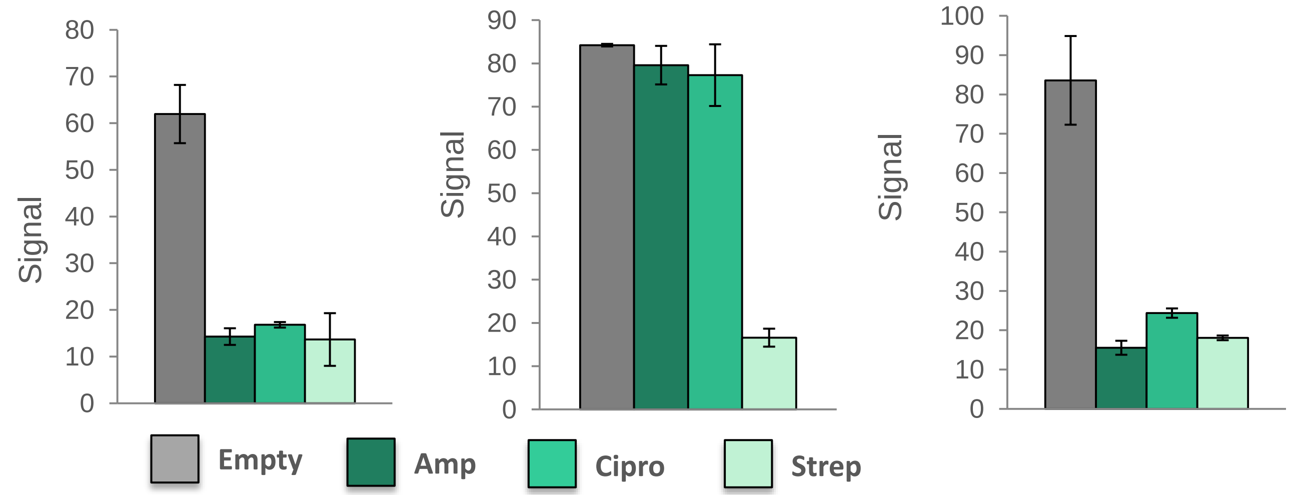
M. Herget *(CTO)*

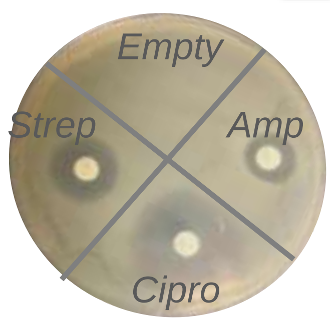
Axel Fanget

Avails AST technology vs disk diffusion to monitor microorganisms resistance to anti-biotics

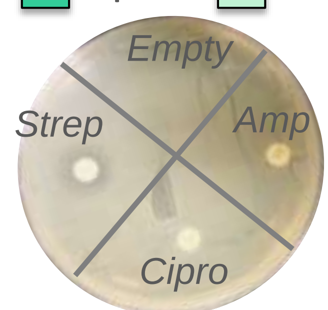
large signal: resistant



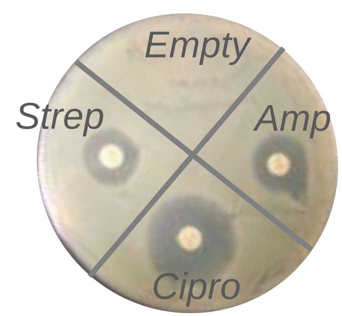




E.Coli



Clinical Sample 15



Clinical Sample 24

Acknowledgment

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- *Kishan Thodkar*
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- *Yves Mermoud*

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C. Schönenberger

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O. Knopmacher, M. Herget (Avails Medical, USA)
E. Constable, C. Housecroft et al. (Basel)
G. Navarra, B. Ernst (Basel)
C. Palivan, W. Meier et al. (Basel)
D. Vuillaume et al. (IEMN, Lille)
A. Jesorka et al. (Chalmers)

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- *SNSF NCCR Molecular Systems Engineering*
- *Avails Medical, USA*
- *nanotera SNSF*

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EINE INITIATIVE DER UNIVERSITÄT BASEL UND DES KANTONS AARGAU

METAS

NCCR Molecular Systems Engineering

EU FP7 & H2020

MOLESCO *(ITN)*
Record It *(FET)*

avails MEDICAL

MOLESCO