Nanopore/electrode structures for single-molecule biosensing

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• Introduction
• Nanopore Labs @ Imperial: Background
• Fabrication and structures
• Optical readout vs. electric readout
• Examples: Electrode/nanopore architectures
• Some perspectives
Introduction

Molecular Electronics

Solid-State Nanopores

Protein and Enzyme Electrochemistry

Ionic Liquids at Electrochemical Interfaces

(www.dbu.de)
Molecular Electronics

small transition metal complexes

redox-modified oligonucleotides

tunnelling spectroscopy in ionic liquids

nanoparticles and multiple charge states
Charge transport in electrochemical environments

- Electronic level distribution at the interface: BEEM (Chandrasekhar Natarajan, IMRE/Singapore)
- Charge transport calculations (Robert Stadler, Vienna)

Small nanoparticles and Coulomb charging

$\text{Au}_{145}$ on Pt(111), 0.1 M NaClO$_4$

- $\Delta V(\text{DPV}) = 0.15 \text{ V}, C = 1.08 \text{ aF}$
- $\Delta V(I_t(\eta)) = 0.19 \text{ V}, C = 0.86 \text{ aF}$
- Conductance $G(j) = 2-6 \text{ nS}$
- Consistent with $I_t(V_{\text{bias}})$ and $I_t(z)$ data

Dr Joshua Edel / Dr Tim Albrecht (Chemistry & IBE) since 2006

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Wellcome Trust, HSFP, Corrigan
We are working towards the integration of solid-state nanopores with electrode structures: “Electrode/nanopore architectures”.

- Local gating of ion or biopolymer transport (sieving, sorting)
- Surface modification and specificity
- Translocation control by time-dependent gate fields (sensing)
- Introducing pore functionality (e.g. for optical detection)
Solid-state nanopores: Device fabrication

1. Low-pressure chemical vapor deposition
2. 100nm - 250nm Si$_3$N$_4$
3. Si$_{<100>$}
4. Topside lithography and e-beam metallization
5. Backside lithography and Alignment
6. Au, Si$_3$N$_4$
7. Resist
8. KOH wet etching
9. 50µm
10. Coating removal

Siliconnitride

Silicon

Metal top layer (Au, Pt...)

Cr or Ti adhesion layer

n nanopores
Pore drilling

Dual-beam FIB/SEM

- Drilling into Si₃N₄ or metalized membranes (e.g. ~100 nm (+ ~100 nm Au))
- Single pore or arrays, say 5x5
- Pore diameter ~ 50 -100 nm (≥ 25 nm)
- Different geometries: Pores, slits, etc.

(S)TEM, FEI Titan

- Membrane thicknesses: 30 to 100 nm
- Pore diameter > 2 nm
- Shrinking and enlarging pores
Basic technology and facilities

• Potentiostats, bi- and tripotentiostats, patch-clamp (Axopatch 200B)
• Rigs for single-molecule (fluorophore) optical detection, FLIM…
• Microfluidics (e.g. for high-throughput droplet-based screening)
• Micro- and nanofabrication facilities @ LCN (class 100 clean rooms etc.)
• Surface characterization: optical, SEM, FIB, (S)TEM, EC-STM
Fabrication of small nanopores using electrodeposition and ion current feedback
Ultra-small nanopores difficult and expensive to make (by STEM) alternatives?
Bipotentiostatic control: Two independent WE

In bipotentiostatic mode, two working electrodes (WE) are independently controlled with respect to a common working electrode.

- Set bias between WE2 and CE/RE
- WE1 (Au) “inactive” (e.g. at ocp)
- Ion current $\propto$ Pore conductance
- Change $E(WE1)$ for electrodeposition to occur:

$$[\text{PtCl}_4]^{2-} + 2e^- \rightarrow \text{Pt}^0 + 4\text{Cl}^-$$

During deposition, the pore diameter shrinks, the ion current decreases… stop deposition at pre-defined value!
Active feedback control, example

- Deposition in 100 mM KCl + 10 mM K$_2$[PtCl$_4$]
- Bias = 200 mV
- $E(\text{WE1})_{\text{dep}}$ = 0.35 V
- Bias scans in 100 mM KCl
Calibration and extrapolation: Single digit nanopores?

Apparent pore diameter by SEM, conductance by I/V scan (100 mM KCl)
Some conclusions

- Surface roughness vs. screening length
- Simple scaling law to break down for very small pores
- Apparent size vs. conductance feedback
- Surface modification (SAMs, effect on noise...)
- Range of different materials/metals to be deposited
- Preliminary DNA translocation data
- Fabrication can be extended to array format
Pore arrays

Starting from a 2×2 array of 150 nm pores:

Final pore diameter

- 35 × 29 nm
- 32 × 44 nm
- 39 × 39 nm
- 40 × 48 nm
- ~ 30 - 40 nm

- Pore size decreased by one order of magnitude
- Shrinking fairly uniform across the four pores
Example II

Optical readout of pore translocation: fluorescently labelled $\lambda$-DNA
Fluorescence-based readout

Optical readout (fluorescence), 48 kb λ-DNA

• DNA/RNA fragment sizing and sequencing

• Protein analysis, protein/protein binding, protein/DNA binding

• Applications: Cardiovascular disease, cancer, diabetes...

• Imperial College Healthcare (NHS trust), http://www.imperial.nhs.uk/index.htm
  • Founded in 2007
  • Merger of St. Mary Hospital Trust and Hammersmith Hospitals Trust
  • Headed by Imperial College/Medicine: Imperial College Healthcare Trust
  • “Academic Health Science Centre”
Basic research

What are the problems?

Realistic samples

Realistic testing

Point-of-care diagnostics

Patients
Thank you!