Resistive-pulse sensing at the micro- and nanoscale

Preston Hinkle

University of California, Irvine

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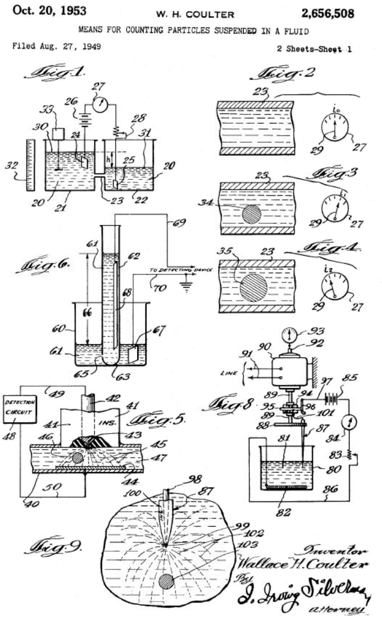
Outline

- Resistive pulse sensing background
- Resistive pulse sensing of high-aspect ratio particles
- Microscale resistive pulse sensing
  - Simultaneous imaging and resistive pulse studies
  - Cancer cell deformability cytometry



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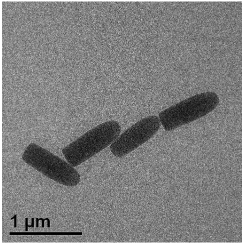

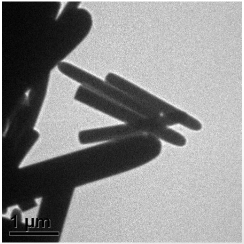

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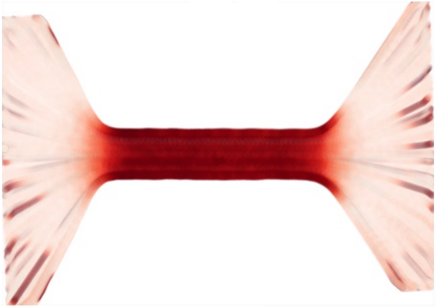

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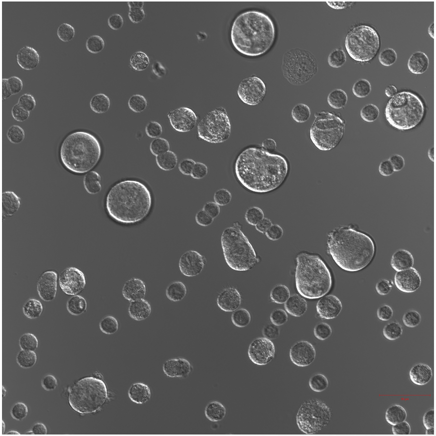
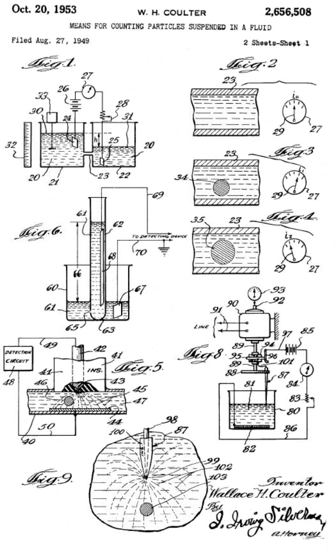


Resistive pulse sensing background

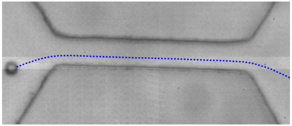
Resistive pulse sensing—description

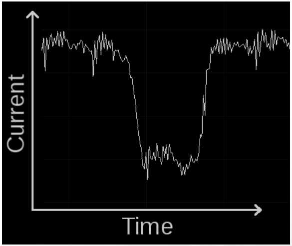
- Resistive pulse sensing (RP) is a method for single particle detection and characterization
- Works at any scale (nano, micro, milli, etc.)
- A diverse range of applications: red blood cell counting (several μm, virus detection ($10 - 100\,\mu$m, and DNA sequencing ($\sim 1\,$nm), among others

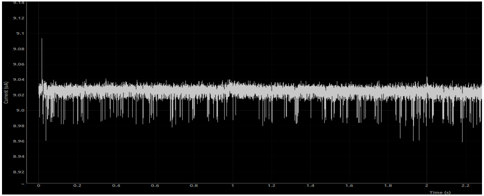


Resistive pulse sensing—how does it work?

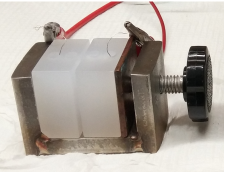
- A nanopore immersed in electrolyte solution acts as an ionic resistor
- Current-Voltage relationship follows Ohm's law $V = IR$
- When a particle enters the channel its resistance changes, yielding a pulse in the measured ionic current
- Pulse properties yield information on size, shape, charge, and concentration of particle



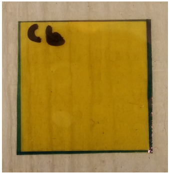




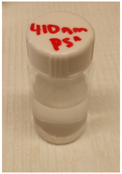
Resistive pulse sensing—system components



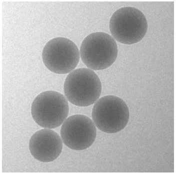
Conductivity cell



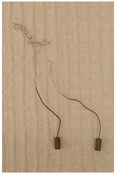
Pore membrane



Electrolyte



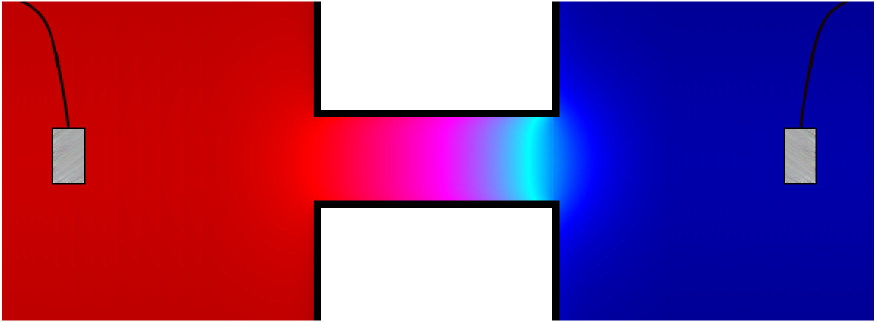
Particles



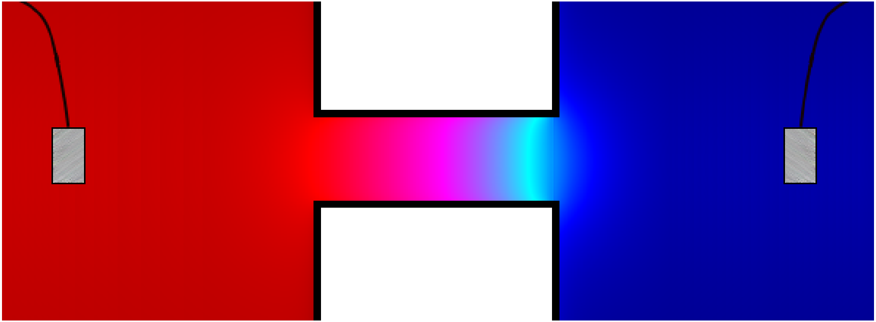
Ag-AgCl electrodes

Voltage amplifier + current recorder

Resistive pulse sensing



Resistive pulse sensing—electrostatic boundary conditions



Resistive pulse sensing—ion transport

- Ion transport is driven by **diffusion**, **convection**, and **electric migration**
- Diffusion: Average flow of ions from high to low concentration
- Convection: Ions move with the fluid/solvent
- Electrical migration: Ions move in electric field

$$\vec{J}_i = \underbrace{z_i e D_i \nabla c_i}_{\text{diffusion}} + \overbrace{z_i e c_i \vec{u}}^{\text{convection}} + \underbrace{z_i e c_i \mu_i \vec{E}}_{\text{migration}}$$

$$I = \sum_i \iint_S \vec{J}_i \cdot \hat{n} dS$$

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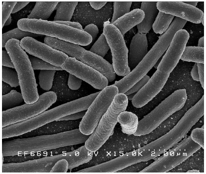
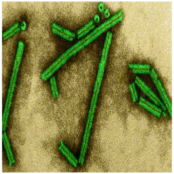
Resistive pulse sensing of high-aspect ratio particles

High-aspect ratio resistive pulse sensing—motivation

- Aspherical particles are ubiquitous in biology—e.g., many viruses and bacteria are approximately rod-shaped



e. coli
$L \sim 2\,\mu$m



tobacco mosaic virus
$L \sim 300\,$nm

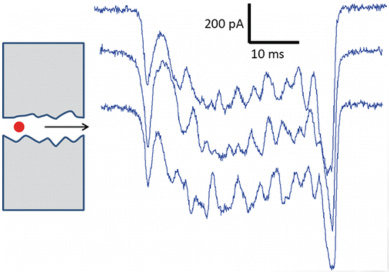
- The ability to measure particle shape is highly desirable for sensing applications
- How can we extend RP sensing to measure length in addition to volume?

Resistive pulse in non-constant width pores

- Consider the RP amplitude for translocation through non-uniform pores

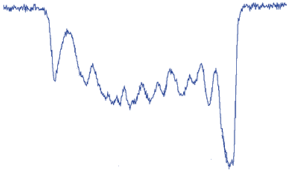
$$\Delta R\left(z'\right) = \frac{\rho}{\pi}\left[\int_{z=z'}^{z=z'+l_p}\left(\frac{1}{r_P^2\left(z\right) - s_p^2\left(z\right)} - \frac{1}{r_P\left(z\right)^2}\right)dz\right]$$

- RP amplitude is a function of the pore geometry **local to the particle's position**
- Particles map the interior of the pore during translocation with their RP signal!

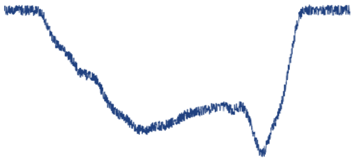


RP signal resolution

- Particles map pore interiors with a length-dependent resolution
- If a particle has length smaller than the characteristic length scale of channel irregularities, the produced signal is a high-resolution mapping
- Particles with lengths longer than characteristic length scale of channel irregularities produce low-resolution mappings



Short particle



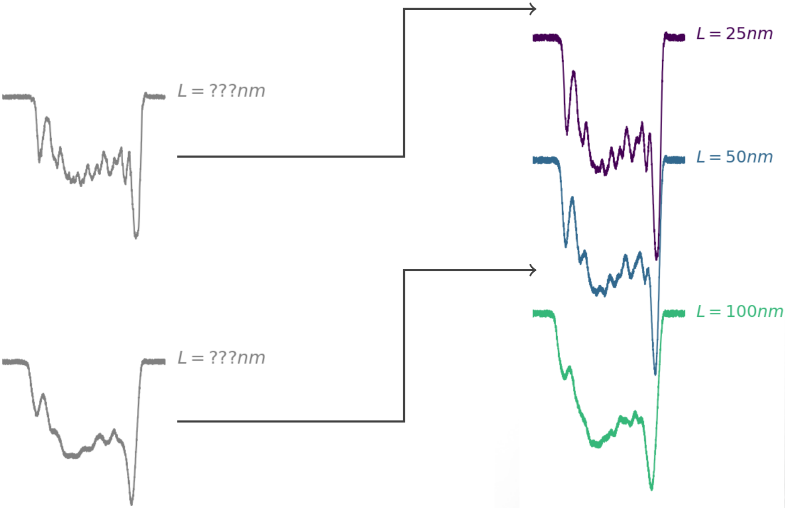
Long particle (simulated)

Can we use this knowledge to measure particle length???

Qualitative length comparison

Unidentified particles

Tracer particles



Reexpressing the RP amplitude of a long particle in terms of shorter particles

Because resistances add in series, we can express the RP amplitude of a long particle as a sum over the RP amplitudes of shorter particles

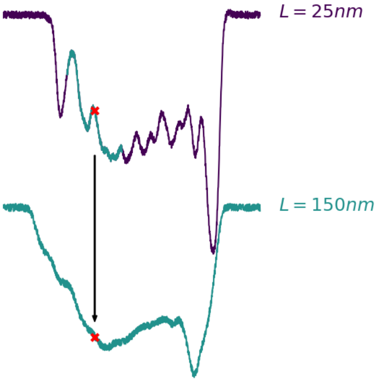
$$
\begin{aligned}
\Delta R_l(z) &= \frac{\rho}{\pi}\left[\int_{z}^{z+l_p}\left(\frac{1}{r_P^2(z')-s_p^2(z')}-\frac{1}{r_P^2(z')}\right)dz'\right] \\
&= \frac{\rho}{\pi}\left[\int_{z}^{z+l_s}\left(\frac{1}{r_P^2(z')-s_p^2(z')}-\frac{1}{r_P^2(z')}\right)dz'\right. \\
&+ \int_{z+l_s}^{z+2l_s}\left(\frac{1}{r_P^2(z')-s_p^2(z')}-\frac{1}{r_P^2(z')}\right)dz + \ldots \\
&+ \left.\int_{z+(n-1)l_s}^{z+nl_s}\left(\frac{1}{r_P^2(z')-s_p^2(z')}-\frac{1}{r_P^2(z')}\right)dz'\right] \\
&= \sum_{i=0}^{n-1}\frac{\rho}{\pi}\left[\int_{z+il_s}^{z+(i+1)l_s}\left(\frac{1}{r_P^2(z')-s_p^2(z')}-\frac{1}{r_P^2(z')}\right)dz'\right] \\
&= \sum_{i=0}^{n-1}\Delta R_s(z+il_s)
\end{aligned}
$$

Quantitative length measurement

Reexpressing the amplitude of long particles in terms of amplitude of short particles suggests a means of measuring length

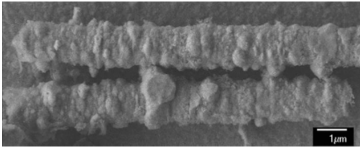
We perform a convolution of the RP amplitude signals of shorter particles over various length intervals

Then, we select the length for which the convolved signal had the greatest similarity to the raw signal of the unknown particle

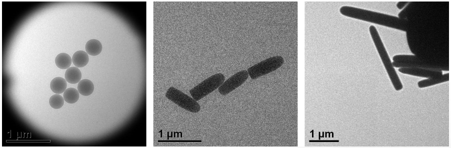


Length measurement experimental test

- Resistive pulse experiments were conducted with PET membranes
- Three types of particles were tested
  - 400 nm polystyrene beads (‘spheres’)
  - 590 nm rods (‘short rods’)
  - 1920 nm rods (‘long rods’)

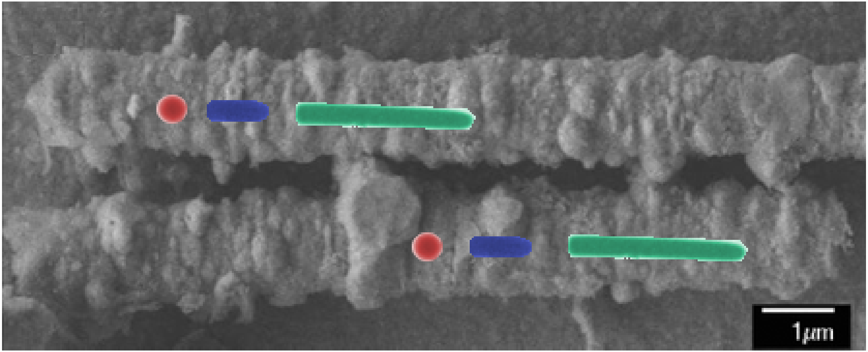


PET pore metal replica



Nanoparticles

Particles to scale



Results—PET7