Resistive-pulse sensing at the micro- and nanoscale

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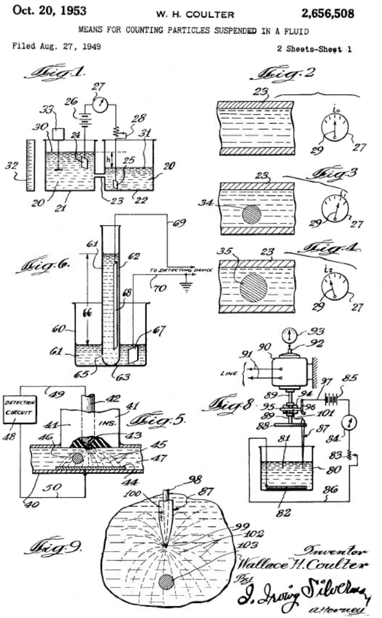
Outline

- 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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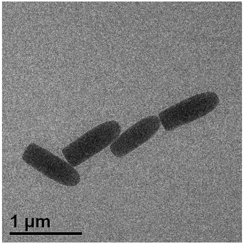

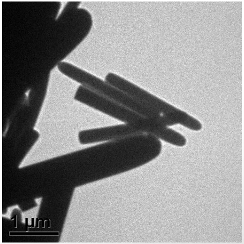

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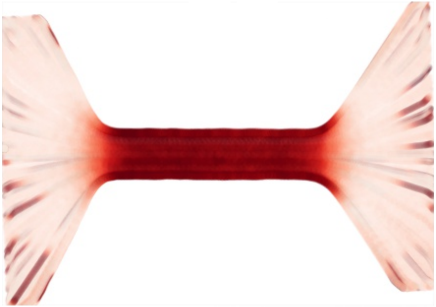

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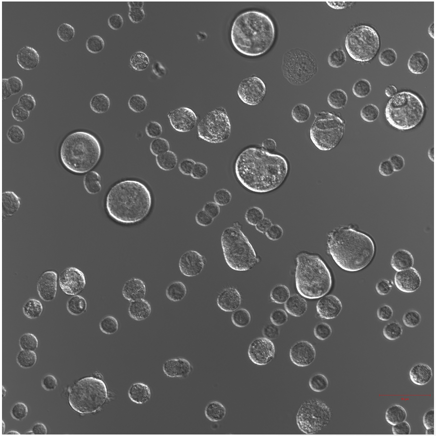
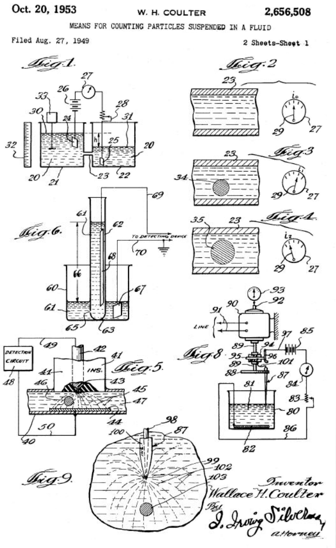


Resistive pulse sensing background

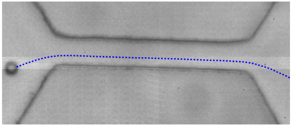
Resistive pulse sensing—description

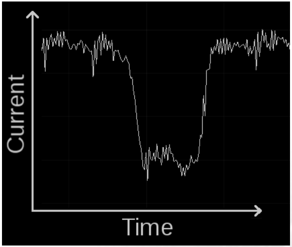
- Resistive pulse sensing (RP) is a method for single particle detection and characterization
- Works at any scale (nano, micro, milli, etc.)
- A diverse range of applications: red blood cell counting (several μm, virus detection $(10 - 100\,\mu$m, and DNA sequencing $(\sim 1\,$nm), among others



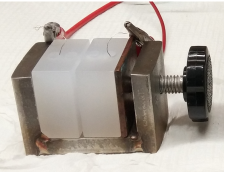
Resistive pulse sensing—how does it work?

- 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

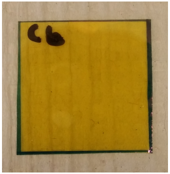




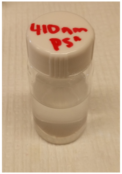
Resistive pulse sensing—system components



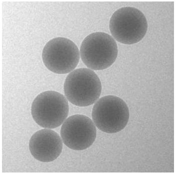
Conductivity cell



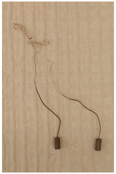
Pore membrane



Electrolyte



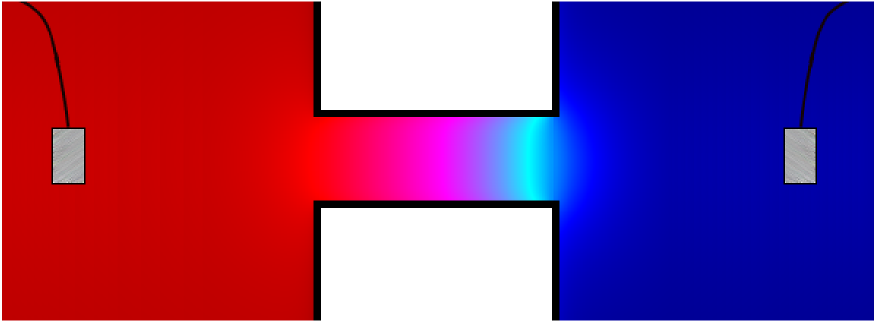
Particles



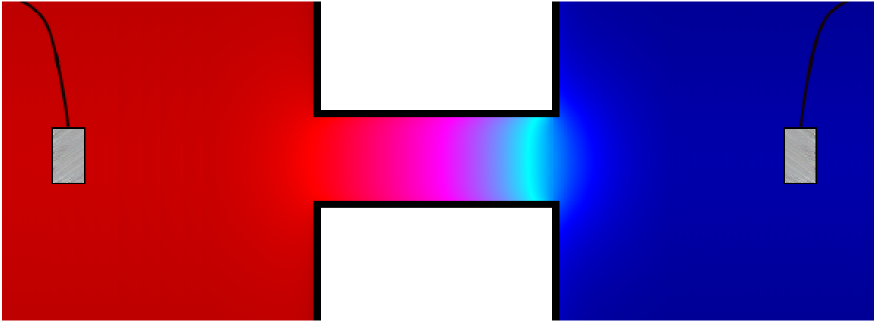
Ag-AgCl electrodes

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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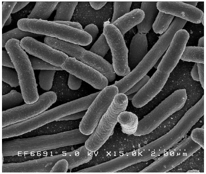
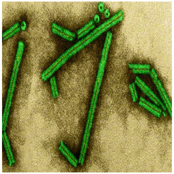
Resistive pulse sensing of high-aspect ratio particles

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

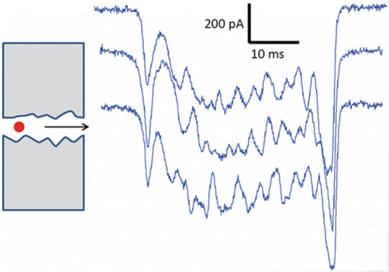
- The ability to measure particle shape is highly desirable for sensing applications
- How can we extend RP sensing to measure length in addition to volume?

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!

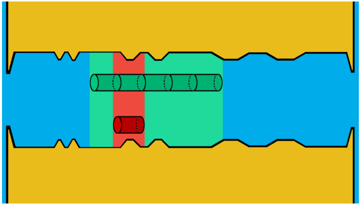


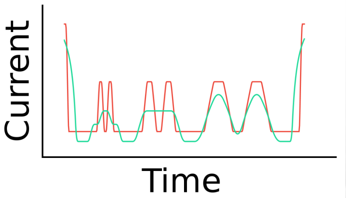
Resistive pulse in non-constant width pores

- For particles with length shorter than characteristic length of changes in pore size, the interior is mapped with high resolution
- Long particles map pore interiors with low resolution because their lengths extend across multiple features

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

Simulated resistive pulses of short and long rods





Length measurement experimental platform

- Resistive pulses can be seen as a map of the pore interior for pores with non-constant radius
- In regions of low diameter, the pulse is deeper; in large diameter regions, the pulse is shallow
- Particles shorter than the length scale of diameter variation accurately map the pore interiors
- Particles longer than the length scale of diameter variation create RP signals that can be seen as a convolution of the pore's interior shape

$$\begin{aligned}\Delta R = R_p - R_0 &= \rho \int_{z=0}^{z=l_P} \frac{dz}{A(z)} - \rho \int_{z=0}^{z=l_P} \frac{dz}{A'(z)} \\ &= \rho \int_{z=z'-l_p/2}^{z=z'+l_p/2} \frac{1}{\pi \left[r_P^2(z) - r_p^2(z) \right]} - \frac{1}{\pi r_P^2(z)}\end{aligned} \tag{1}$$