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Mini review

Electrochemical sensing with nanopores: A mini review

István Makra [a], Róbert E. Gyurcsányi [b,*]

[a] Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics, Szent Gellért tér 4, H-1111 Budapest, Hungary
[b] MTA-BME "Lendület" Chemical Nanosensors Research Group, Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics, Szent Gellért tér 4, H-1111 Budapest, Hungary

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ABSTRACT

We discuss representative electrochemical nanopore sensing strategies, highlighting their underlying theoretical principles and limitations.

Contents

1. Introduction

The use of nanopores for chemical sensing generally narrows down to nanoporous membranes with straight-through pores of uniform size distribution and ultimately to single nanopore membranes. To understand what makes nanopores so unique in terms of their use for chemical sensing we must consider the extremely small volume defined by their interior. Thus species translocating or residing within a nanopore can effectively change the physical–chemical properties of the nanopore interior (e.g., conductance [1,2] or refractive index [3]), which can be detected in a label-free manner. By having a single nanopore with a volume comparable to that of the targeted species, detection of single species becomes feasible. The use of nanopores for electrochemical sensing originates in the Coulter counter, best known for blood-cell counting in hematology [4]. However, the instrumentation and implementation of biological nanopores additionally benefited from studies on biological ion channels [5,6]. Conventional Coulter counters use a single cylindrical pore to count and size particles suspended in an electrolyte. Pulsewise changes in the pore conductance are detected as insulating particles passing through replace their own volume of highly conducting electrolyte (Fig. 1). The analytical information from a resistive pulse sensing (RPS) measurement is the pulse height (indicative of the volume of the target), pulse frequency

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* Corresponding author.
E-mail addresses: robertgy@mail.bme.hu (R.E. Gyurcsányi).

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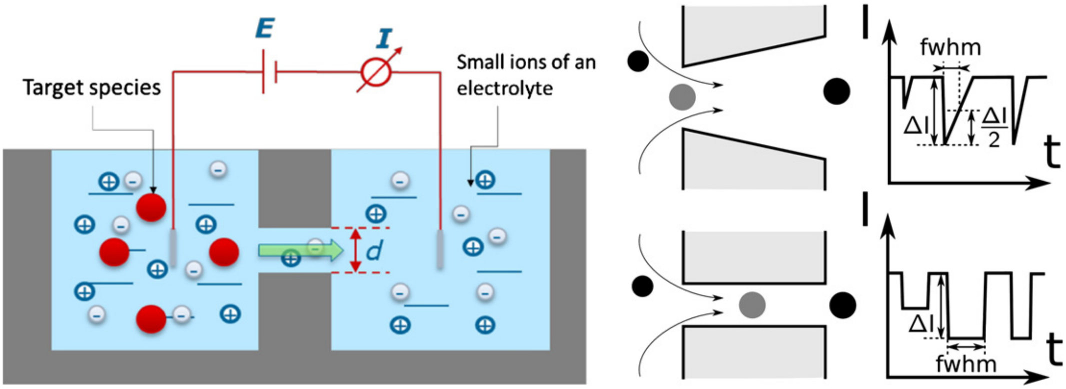

Fig. 1. Schematics of a single nanopore sensor (left) and typical current responses for cylindrical and conical pores (right). The ionic current through the nanopore is maintained by applying a transmembrane voltage between two Ag/AgCl electrodes. The full width at half maximum (fwhm) is a measure of the pulse duration while ΔI of the pulse amplitude [7].

(proportional to target concentration) and pulse duration (depends on the mean translocation velocity and relative lengths of the pore and the target species).

A major strength of the method is the ability to determine particle concentration in a calibration-less manner by relating the number of pulses to the known volume of suspension flown through the pore. The classical apparatus detect species of ca. 2 to 60% of the pore diameter [8] and since the smallest pore diameter is 10 μm the lower size limit of the assessable species is a few hundred nanometers. The reduction of the pore size is an obvious way to extend the applicability of the Coulter principle to species with characteristic dimensions in the lower nanometer range, e.g., nanoparticles of synthetic or biological origin, and macromolecules. However, such a scaling down proved to involve essential changes compared to micropores and to enable new detection methodologies.

2. Resistive pulse sensing with single nanopores

While in case of micropores the dominant transport form is the pressure driven flow through the pore, the volume flow rates established through nanopores are orders of magnitude smaller and therefore less efficient. Additionally, in case of charged species or pores the electrophoretic or electroosmotic contributions, respectively, should be considered. In practice, the transport through nanopores occurs through concurrent diffusive, hydrodynamic, electrophoretic, and electroosmotic mechanisms resulting in a mean translocation velocity. Generally, for larger diameter pores ($d > 10$ nm) the dominant mechanism is the hydrodynamic transport owing to its quadratic dependence on the pore diameter. For $d < 10$ nm electrophoresis and electroosmosis dominate; with relative contributions depending on the surface charge density of the pore and the translocating species. Diffusive transport scales with $1/d$ and becomes comparable to electrophoresis only for $d < 1$ nm [9] because diffusion of smaller particles is faster while electrophoresis is practically independent of the pore diameter. Thus, a calibration-less concentration determination is challenging with nanopores unless the hydrodynamic transport prevails. In case of hydrodynamic transport while difficult to determine the minute volume flow rates experimentally, they can be calculated if the pore geometry is known [10]:

$$Q = \frac{3\pi P}{8\eta l}\frac{d_b - d_t}{d_b^3 - d_t^3} d_b^3 d_t^3$$

where, P is the applied pressure, η is the electrolyte dynamic viscosity, l is the pore length, d_b and d_t are the base and tip diameters of the conical pore geometry, respectively. Thus the pore geometry, generally cylindrical or conical, clearly plays an important role in nanopore sensing, by determining the electrical resistance, the shape of the current pulses and the overall sensitivity of the detection. The uniform cross-section of cylindrical pores results in square wave pulses, while the growing cross-section in conical pores causes an asymmetric triangle-like pulse shape [11] (Fig. 1).

2.1. Electrical resistance of nanopores

The general expression of the pore resistance assumes a conical pore geometry (in fact truncated cone) and homogeneous conductivity (valid at high ionic strengths):

$$R_p = \frac{1}{\sigma}\int_{x=0}^{l}\frac{1}{A(x)}dx = \frac{4l}{\pi d_t d_b \sigma}$$

where σ is the electrolyte conductivity, x is the coordinate along the centerline, $A(x)$ is the cross-section at position x, d_b, d_t, and α are the base and tip diameters of the truncated cone, and the half-cone angle, respectively ($d_b = d_t + 2\tan(\alpha)l$).

Since the electric field lines gradually converge into the pore orifice, the changing cross-sections of the ion flux can contribute significantly to the overall pore resistance. This additive component is called the access resistance (R_a) [12]:

$$R_a = \frac{1}{2d\sigma}.$$

Considering R_a at both openings the total resistance of a conical pore is

$$R = \frac{1}{\sigma}\left(\frac{4l}{\pi d_t d_b} + \frac{1}{2d_t} + \frac{1}{2d_b}\right)$$

while for cylindrical pores ($d_t = d_b = d$), $R = \frac{4}{\sigma d\pi}\left(\frac{l}{d} + \frac{\pi}{4}\right)$. The total resistance deviates with only 3% from values simulated at $l/d = 5$ using Nernst–Planck/Poisson equation, as opposed to 20% when the access resistance is unaccounted. The discrepancy is even higher for pores with lower l/d ratio.

2.2. Theoretical models to estimate pulse amplitudes

During particle translocation the maximal resistance change determines the current pulse amplitude or peak height for "triangular" shaped pulses. For simplified models, such as considering uncharged pores, insulating spherical targets and translocation along the pore axis, the pulse amplitude can be calculated analytically. However, in many practical cases one or more of the above assumptions are not valid and therefore numerical solutions of coupled Poisson, Nernst–Planck and Navier–Stokes differential equations [13] are used to provide the pulse amplitudes (and shapes), but at largely increased computation times.