Noise in nanopore sensors: Sources, models, reduction, and benchmarking

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\textbf{A B S T R A C T}

Label-free nanopore sensors have emerged as a new generation technology of DNA sequencing and have been widely used for single molecule analysis. Since the first \(\alpha\)-hemolysin biological nanopore, various types of nanopores made of different materials have been under extensive development. Noise represents a common challenge among all types of nanopore sensors. The nanopore noise can be decomposed into four components in the frequency domain (1/f noise, white noise, dielectric noise, and amplifier noise). In this work, we reviewed and summarized the physical models, origins, and reduction methods for each of these noise components. For the first time, we quantitatively benchmarked the root mean square (RMS) noise levels for different types of nanopores, demonstrating a clear material-dependent RMS noise. We anticipate this review article will enhance the understanding of nanopore sensor noises and provide an informative tutorial for developing future nanopore sensors with a high signal-to-noise ratio.

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\textbf{1. Introduction}

Nanopores have emerged as a promising label-free biosensor for analyzing various kinds of biomolecules such as DNA,\textsuperscript{1,2} RNA, and proteins.\textsuperscript{3} A nanopore sensor is often operated by applying a constant voltage across two chambers to electrophoretically drive charged polymers through a nanoscale hole. The readout is an ionic current trace with individual dips corresponding to a single molecule translocation, usually called an event. The ionic current shape (e.g., current blockage magnitude, shape, and duration) of each event provides the basis for interpreting the molecule length, shape, charge, and reactivity of the nanopore surface.\textsuperscript{4–7} Various types of nanopores are currently under investigation (Fig. 1). The nanopore concept was first demonstrated with the protein pore \(\alpha\)-hemolysin,\textsuperscript{28} a member of the biological pore family that also includes MspA porin pores.\textsuperscript{29} Biological nanopores have been successfully commercialized in Oxford Nanopore DNA sequencers.\textsuperscript{30,31} In addition to the pore-forming proteins, solid-state nanopores have also been extensively studied in the past decade due to their mechanical robustness, tunable size, thermal robustness, and integration potential.\textsuperscript{32,33} The solid-state nanopore family includes membrane materials such as SiN\textsubscript{x},\textsuperscript{13,34,35} graphene,\textsuperscript{36} glass nanopores (nanopipette),\textsuperscript{37} and polymer nanopores.\textsuperscript{38} While solid-state nanopores have obvious advantages over their biological counterparts due to flexibility in tuning the geometry and surface properties, the noise performance of solid-state nanopores is often worse than their biological counterparts.\textsuperscript{39} In addition, there is a large variation in the noise of different types of nanopores.

Since the signal in the nanopore experiment is often very small, the noise represents a significant challenge that would severely limit the nanopore sensor’s sensitivity and reliability. In general, the nanopore noise power spectral density (PSD) can be decomposed into 1/f noise, white noise, dielectric noise, and amplifier noise,\textsuperscript{37} each dominating at different frequencies. While the nanopore noise has been extensively studied and the mechanisms previously proposed,\textsuperscript{43–46} a systematic review and comparison of the noise performances of different nanopore types are needed.

In this work, we reviewed and summarized the physical models, origins, and reduction methods for each of these noise components. For the first time, we calculated and benchmarked the root mean square (RMS) values for different types of nanopores. There is a clear material-dependent intrinsic nanopore noise performance. The correlation of the noise performance to the nanopore materials may provide...
alternative insight into understanding and controlling the nanopore noise. We anticipate this review article would provide an informative tutorial into developing future nanopore sensors with improved signal-to-noise ratio (SNR).

2. Nanopore noise analysis and model

There are generally two approaches for analyzing the nanopore noise. One approach is to directly calculate the RMS value in the time domain,

\[ I_{\text{rms}} = \sqrt{\Delta^2(t)} \]  

where \( \Delta(t) \) represents the fluctuation of the current \( I(t) \) deviating from its mean value.

The RMS current can be directly compared to the molecule translation signal for evaluating the SNR,

\[ \text{SNR} = \frac{\Delta_{\text{ionic}}}{I_{\text{rms}}} \]  

where \( \Delta_{\text{ionic}} \) represents the current blockage amplitude when the charged biopolymers pass through the nanopore.

The other approach is frequency domain analysis of the PSD,\(^{51}\) which can be derived as,

\[ S(f) = \frac{1}{2T} \lim_{T \to \infty} \left| \int_{-T}^{T} \Delta(t)e^{-2\pi ift} dt \right|^2 \]  

The noise RMS can be related to the noise PSD as,

\[ I_{\text{rms}} = \sqrt{\int_{f_1}^{f_2} S(f) df} \]  

Generally, the noise PSD can be decomposed into four components as,

\[ S(f) = S_r(f) + S_w(f) + S_d(f) + S_A(f) \]  

where \( f \) is the frequency; \( S_r, S_w, S_d, \) and \( S_A \) represent the PSD of 1/f noise, white noise, dielectric noise, and amplifier noise, respectively.\(^{33}\)

Fig. 2(a) summarizes the general characteristics of the nanopore noise PSD.\(^{56}\) At low frequencies, noise PSD is mainly contributed to by the 1/f noise. At moderate frequencies, dielectric noise due to dielectric thermal loss starts to become a major source of the noise. At high frequencies, noise is dominated by the amplifier noise. The white noise is spread uniformly at different frequencies and could be overwhelmed by the 1/f and dielectric noise, while being unaffected by the noise PSD.\(^{54,52}\) The transition points where each noise source starts to dominate could vary tremendously among different experiments.\(^{75,52-54}\) Fig. 2(b) shows the equivalent circuit model for describing the noise component in the nanopores.\(^{55}\) In Sections 3 to 6, we review and summarize the general characteristics of each of these noises and discuss approaches for noise reduction.

3. 1/f noise

3.1. 1/f noise origin

A widely accepted theory of 1/f noise is that its spectra consists of a set of Lorentzian noises that come from a group of random telegraph noises (RTNs).\(^{56}\) This model was verified by magnetization current experiments.\(^{57}\) Specifically, the observed 1/f noise is the superposition of many discrete RTNs. 1/f noise often dominates the total noise at frequencies 
\(< 1 \text{kHz} \) and is the most widely studied.\(^{56,51,58,59}\)

The exact origin of the 1/f noise remains controversial. A variety of 1/f noise mechanisms have been proposed, including the channel’s opening–closing process,\(^{60}\) structural flexibility of the nanopore pore walls,\(^{61}\) nanobubbles,\(^{62,63}\) incomplete hydrophilicity of the nanopore surface,\(^{64}\) cooperative fluctuations on ion motion along a confined space,\(^{65}\) surface reversible adsorption of ions combined with the ions’ long-lasting excursions in the reservoirs,\(^{66}\) carbon contaminants surrounding the nanopore surface during transmission electron microscopy (TEM) drilling\(^{67}\) and mechanical vibrations.\(^{68-72}\) These mixed models strongly indicate the 1/f noise stems from many different sources.
In this model, \( E_1 \) and \( E_2 \) represent two different energy states at a single point on the nanopore walls, which correspond to the association and dissociation of the protons. The probability of state \( E_1 \) and \( E_2 \) were given by:

\[
P_1 = \frac{\tau_1}{\tau_1 + \tau_2} = \frac{1}{1 + 10^{pK_a - p}} \quad P_2 = 1 - P_1
\]

Here, \( p \) represents the log form of the equilibrium constant; \( pK_a \) represents the measure of the acidity or basicity of a solution; \( \tau_1 \) and \( \tau_2 \) represent the mean time spent in states \( E_1 \) and \( E_2 \), respectively. The PSD of the Lorentzian RTN noise associated with site \( j \) can be represented as:

\[
S_j(f) = \frac{4(\Delta E_j)^2}{\left(\tau_1 + \tau_2\right)\left[1 + (2nf\tau)^2\right]}
\]

in which \( \tau = \tau_1 + \tau_2/(\tau_1 + \tau_2) \). For sufficiently large numbers of RTN noise, a macro 1/f spectrum could appear. A previous molecular dynamics (MD) simulation demonstrated excellent agreement to the adsorption-desorption model predictions.

The surface charge fluctuation can be affected by the pH, ionic concentration, and film material. From the perspective of pH, Fig. 3 (c) and (d) show the nanopore PSD under different pH values, for biological and SiN\(_x\) nanopores, respectively. Both PSDs showed the same trend with pH; the peak PSD appears at intermediate pH values, corresponding to the material’s point of zero charges. From the perspective of ionic concentration, the normalized PSD \( S_2/(G^2) \) increases with decreasing concentrations as the nanopore size is comparable to or even smaller than the Debye length at low ionic concentrations. As a result, ions in the nanopore will be more significantly affected by surface charge fluctuations. From the perspective of the material, the different materials have different surface functional groups with varying densities of charges. As a result, nanopores made of different materials will have different 1/f noise properties. For example, the 1/f noise of a SiN\(_x\) nanopore is usually much larger than that of a biological nanopore or glass nanopore.

Hydrophilicity is another important surface effect that can affect the 1/f noise. It was previously hypothesized that nanobubbles can form at a nanopore surface that produces high 1/f noises when the surface is hydrophobic.

3.1.2. Bulk effect

The bulk and access region of the nanopore is another important source for the 1/f noise (Eq. (7)). The bulk effect mostly comes from ionic mobility fluctuation. The mobility fluctuation can be caused by (1) ionic crowding due to larger ion concentrations in the pore under a voltage bias for a single rectifying conically-shaped nanopore; (2) electrostatic interactions between passing ions and pore walls; and (3) ion species formations at the pore entrance due to the conical geometry. The exact mechanism remains unclear, as illustrated by a variety of models. For example, Fragasso et al. ascribed the carrier free path length fluctuations as the origin for ion mobility fluctuations. Tasserit et al. hypothesized the confinement-induced cooperative fluctuation of ion mobility leads to 1/f noise. The ionic concentration and nanopore geometry will also affect the mobility fluctuations. Wen et al. argued that the bulk region of the nanopore structure plays a dominant role in noise at high concentrations.

3.2. Reducing the 1/f noise

For surface-related 1/f noise sources, improvements in the hydrophilicity are the most common practice (Fig. 4), which can be achieved by atomic layer deposition (ALD) of TiO\(_2\) or Al\(_2\)O\(_3\) (Fig. 4(a) and (b)), piranha cleaning, oxygen plasma, and pulsed voltage treatment (Fig. 4(c)). Among these methods, ALD deposition is capable of reducing the surface charge density, which can also be achieved by changing the pH. Finally, using alternative nanopore materials could also reduce the surface-related 1/f noise.
For bulk-related 1/f noise sources, decreasing the mobility fluctuation can be achieved by increasing the concentration of electrolyte or by choosing nanopores with a large pore diameter. The bulk-related 1/f noise can be improved by enhancing the film mechanical stability (Fig. 4(e)), increasing the film thickness (Fig. 4(f)), and decreasing the film free-standing area. Enhancing the film mechanical stability is of particular importance to reducing the noise of 2D material nanopores.

4. White noise

4.1. White noise origin

A key characteristic of white noise is the PSD is independent of the frequency. There are two sources for the white noise, thermal noise, and shot noise. The general white noise can be written as,

\[ S_{\text{white}} = S_{\text{thermal}} + S_{\text{shot}} = 4kTg + 2qI \]  

(10)

where \( G \) is the conductance, \( K \) is the Boltzmann constant, \( T \) is the temperature, \( q \) is the elementary charge, and \( I \) is the current. The thermal noise (Johnson noise) arises from thermal fluctuations in the charge carriers (i.e., ions in the nanopore sensors). The shot noise (Poisson noise) normally occurs when there is a potential barrier. In the nanopore sensors, the Ag/AgCl interface is an example of a potential barrier. When the electrons/ions cross that barrier, shot noise can be produced. Note that a pure resistor normally does not produce shot noise since there is no potential barrier. Both thermal and shot noises are inherent to a real system, representing fundamental limitations (lower noise floor) in making sensitive measurements.

4.2. Reducing the white noise

One possible method to decrease the thermal noise is to decrease the conductance by decreasing the charge carriers’ concentration or the pore size. Increasing the channel length of the nanopore could also decrease the thermal noise, however, this would reduce the sensitivity of the pore.

5. Dielectric noise

5.1. Dielectric noise origin

Dielectric noise is related to dielectric loss due to the non-ideal existence of charge carriers in the dielectric material. In nanopores, while the measured current is exclusively from the ionic current through the nanopore, there is always a leakage current through the non-ideal dielectric membrane (in which charge carriers exist). The thermal fluctuations of this non-ideal leakage current contribute to dielectric noise. To study the dielectric noise induced by non-ideal capacitance \( C_{\text{in}} \), it can be modeled as an ideal capacitor \( C_{\text{in}} \) in parallel with admittance \( Y \) related to the dielectric loss (Fig. 5(a)). Therefore, the dielectric noise can be described as,

\[ S_{\text{D}}(f) = 4kTfY_{\text{f}} = 8nkTC_{\text{in}}Df \]  

(11)

where \( D \) is the dielectric loss constant. It is clear that material with more loss will have greater dielectric noise.
Fig. 5. Model and reduction of dielectric noise. (a) Equivalent circuit model based on Fig. 2(b) for dielectric noise. \( R_i = R_{e1} + R_{e2} \) is the resistance from the nanochannel. \( C_i \) represents the non-ideal membrane capacitance, which is the sum of \( C_m \) and \( C_{i} \) and is expressed in parallel connection of an admittance \( Y_i \) and an ideal capacitance \( C_i \). (b) A SiN \(_x\) chip was coated by polyimide. (c) Polysilicon/SiO\(_2\)/Si (MOS), a multiple-layer structure, was used for nanopore fabrication. (d) The PSD of four different structures, two of which are shown in (b) and (c). (b-d) Redrawing based on reference\(^{52}\) (Republished with permission of Nanotechnology, from [Nanopores in solid-state membranes engineered for single molecule detection, Dimitrov V et al., 21, 065502 (11pp) 2010]; Permission conveyed through Copyright Clearance Center, Inc.). (e) Schematic of a graphene chip with quartz substrate, connected by a thin Si layer. (f) Noise power spectrum density of two chips with Si or quartz substrate. (e-f) Redrawing based on reference\(^{68}\) (Republished with permission of Nanotechnology, from [Noise and its reduction in graphene-based nanopore devices, Kumar A et al., 24, 495503 (7pp) 2013]; Permission conveyed through Copyright Clearance Center, Inc.).

5.2. Reducing dielectric noise

Based on Eq. (11), the dielectric noise is determined by the total capacitance and dielectric loss constant of the material that isolates the electrolyte. Therefore, two clear approaches can be used to reduce the dielectric noise. One is to reduce the total capacitance, which can be done by covering the nanopore chip with insulation materials (e.g., PDMS\(^{39}\) and polyimide\(^{52}\)). Stacked dielectric structures can also be used.\(^{50,82}\) With these methods, the dielectric noise was reduced by 1–2 orders of magnitude, as shown in Fig. 5(b)–(d). The other approach is to use materials with less loss. Since the Si substrate is often the main source of the dielectric loss, another insulation material can be deposited on the substrate or another substrate can be used. It was experimentally observed that the biological and glass nanopores, in general, have better dielectric noise performances than SiN\(_x\) and 2D material nanopores, which can be attributed to the latter’s high loss factor from the Si substrate. Kumar\(^{68}\) used quartz as the substrate of graphene nanopores (Fig. 5(e)) and the dielectric noise was significant decreased (Fig. 5(f)). Other materials, such as Teflon\(^{54}\) and polyimide,\(^{81}\) can also be used to replace Si. Clearly, the dielectric noise can be reduced by combining these two approaches. For example, de Vreede\(^{45}\) nearly completely suppressed the dielectric noise at a wide bandwidth (<100 kHz) using a fused silica substrate and covering it with PDMS.

6. Amplifier noise

6.1. Amplifier noise origin

In a high-frequency range, the noise PSD is proportional to \( f \), corresponding to the amplifier noise. The amplifier noise comes from the interactions of thermal noise at the amplifier input and the total capacitance in the system (including capacitances from the chip and the amplifier).\(^{33}\) The amplifier noise can be expressed as,\(^{33}\)

\[
S_A(f) = (2\pi C_1 e_n)^2 \cdot f^2
\]  
(12)

in which \( e_n \) is the voltage thermal noise, \( C_1 \) is the total capacitance that consists of the nanopore capacitance (\( C_p \)), feedback capacitance (\( C_f \)), and other parasitic capacitance (\( C_b \)), as shown in Fig. 6(a).

6.2. Reducing amplifier noise

According to Eq. (12), the amplifier noise is determined by the total capacitance \( C_i \) and voltage thermal noise, \( e_n \). Reducing the \( C_i \) is a common practice to suppress the amplifier noise, which can be realized two ways. One is to reduce the nanopore capacitance. For example, replacing the intrinsic SiN\(_x\) nanopore (\( C_i = 48.6 \text{ pF} \)) with a glass-passivated nanopore chip with \( C_i < 10 \text{ pF} \) (Fig. 6(b)) can greatly reduce the amplifier noise (Fig. 6(c)). The other way is to use amplifiers with low parasitic capacitance (\( C_p \) and \( C_f \)) as well as reduced voltage thermal noise. For example, replacing the commonly used Axopatch 200B with a CMOS integrated nanopore platform (CNP) (Fig. 6(d))\(^{33}\) is effective in reducing the amplifier noise (Fig. 6(e) and (f)).

7. Material-dependent RMS noise benchmarking

Among the four noise components we discussed, the 1/f and dielectric noise are intrinsic to nanopore materials. To benchmark the noise levels of different materials, we summarized the RMS noise level for biological (Table 1), quartz glass (Table 2), SiN\(_x\) (Table 3), and 2D material
The $I_{\text{rms}}$ values in Tables 1–4 were calculated from the reported PSD data using Eq. (4), or based on the reported $I_{\text{rms}}$ data acquired directly from the text or chart, within the same bandwidth from 1 Hz to 10 kHz for a fair comparison. Fig. 7 shows the RMS noise scattering plot as a function of the nanopore materials. The noise level in the SiN$_x$ nanopore and 2D material nanopore is greater than that in the glass nanopore, while the biological nanopores show the best noise performance. The two populations in the quartz glass nanopore

Table 1
Noise level statistic of biological nanopores.

<table>
<thead>
<tr>
<th>Structure</th>
<th>$I_{\text{rms}}$ (pA)</th>
<th>Diameter (nm)</th>
<th>Ionic strength (Molar)</th>
<th>pH</th>
<th>Bias (mV)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Hemolysin</td>
<td>2.70</td>
<td>n.a.</td>
<td>1.00</td>
<td>8.00</td>
<td>200</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>2.51</td>
<td>1.4</td>
<td>0.20</td>
<td>7.40</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.49</td>
<td>1.4</td>
<td>0.20</td>
<td>7.40</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.47</td>
<td>1.4</td>
<td>1.00</td>
<td>3.50</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.13</td>
<td>1.4</td>
<td>3.50</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FhuA ΔC/Δ4L</td>
<td>2.69</td>
<td>3.1–4.4</td>
<td>0.20</td>
<td>7.40</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.49</td>
<td>3.1–4.4</td>
<td>0.20</td>
<td>7.40</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.13</td>
<td>3.1–4.4</td>
<td>1.00</td>
<td>3.50</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.07</td>
<td>3.8</td>
<td>0.15</td>
<td>7.50</td>
<td>35</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>2.07</td>
<td>3.8</td>
<td>0.15</td>
<td>7.50</td>
<td>−35</td>
<td></td>
</tr>
<tr>
<td>ClyA</td>
<td>2.08</td>
<td>3.8</td>
<td>0.15</td>
<td>7.50</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.07</td>
<td>3.8</td>
<td>0.15</td>
<td>7.50</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 2
Noise level statistic of quartz-based glass nanopores.

<table>
<thead>
<tr>
<th>Structure</th>
<th>$I_{\text{rms}}$ (pA)</th>
<th>Diameter (nm)</th>
<th>Ionic strength (Molar)</th>
<th>pH</th>
<th>Bias (mV)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare nanopore</td>
<td>3.09</td>
<td>25.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td>−500</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>1.79</td>
<td>75.0 ± 5.0</td>
<td>1.00</td>
<td>8.0</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27.06</td>
<td>21.0</td>
<td>1.00</td>
<td>8.0</td>
<td>2000</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>24.90</td>
<td>23.0</td>
<td>1.00</td>
<td>8.0</td>
<td>2000</td>
<td>58</td>
</tr>
<tr>
<td>Au deposited</td>
<td>2.91</td>
<td>15.0</td>
<td>0.001</td>
<td>n.a.</td>
<td>−500</td>
<td>88</td>
</tr>
<tr>
<td>Al$_2$O$_3$</td>
<td>17.35</td>
<td>59.0 ± 5.0</td>
<td>1.00</td>
<td>8.0</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16.72</td>
<td>47.0 ± 5.0</td>
<td>1.00</td>
<td>8.0</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20.11</td>
<td>41.0 ± 5.0</td>
<td>1.00</td>
<td>8.0</td>
<td>300</td>
<td></td>
</tr>
</tbody>
</table>
were mainly due to (1) the difference between the bare nanopore and surface-coated nanopores, and (2) the different experimental conditions.

Material-related RMS noise is related to the 1/f noise and dielectric noise dominating the total noise. From the 1/f noise perspective, it is reasonable to hypothesize that different types of nanopores have different surface properties (e.g., surface charge, roughness, and hydrophilicity), geometry, and membrane stability, corresponding to varying levels of 1/f noise. For example, glass nanopores have better hydrophilicity and show less 1/f noise than the SiN$_x$ nanopore. SiN$_x$ nanopores are generally fabricated by TEM or focused ion beam (FIB) during which surface roughness, trapped electrons, or ions could be introduced. The low hydrophilicity of the SiN$_x$ surface may produce nanobubbles more easily than biological and glass nanopores, and may produce more pronounced 1/f noise. Nanopores based on 2D materials have a higher 1/f noise level than other nanopore types, most likely due to mechanical vibrations. In addition, from the dielectric noise perspective, the dielectric loss of the Si substrate would introduce relatively large dielectric noise to SiN$_x$ and 2D material nanopores.

### Table 3

<table>
<thead>
<tr>
<th>Structure</th>
<th>$I_{\text{rms}}$ (pA)</th>
<th>Diameter (nm)</th>
<th>Ionic strength (Molar)</th>
<th>pH</th>
<th>Bias (mV)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare SiN$_x$</td>
<td>45.58 n/a</td>
<td>1.00</td>
<td>8.0</td>
<td>200</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>63.20 20.0</td>
<td>1.00</td>
<td>8.0</td>
<td>100</td>
<td>99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48.10 20.0</td>
<td>1.00</td>
<td>8.0</td>
<td>100</td>
<td>99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90.47 20.8</td>
<td>1.00</td>
<td>7.5</td>
<td>100</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.07 22.0</td>
<td>1.00</td>
<td>7.5</td>
<td>100</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>147.00 n/a</td>
<td>1.00</td>
<td>8.0</td>
<td>0</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.10 3.3–4.0</td>
<td>1.00</td>
<td>8.0</td>
<td>100</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>131.60 n/a</td>
<td>1.00</td>
<td>8.0</td>
<td>4.5</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38.00 n/a</td>
<td>1.00</td>
<td>8.0</td>
<td>0</td>
<td>54</td>
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<td></td>
</tr>
<tr>
<td>21.90 n/a</td>
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<td>8.0</td>
<td>200</td>
<td>39</td>
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<tr>
<td>28.60 7.0</td>
<td>1.00</td>
<td>8.0</td>
<td>200</td>
<td>64</td>
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<td></td>
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<tr>
<td>Bare SiN$_x$ with zapping treatment</td>
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<td>1.00</td>
<td>8.0</td>
<td>200</td>
<td>64</td>
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</tr>
<tr>
<td>PDMS coated</td>
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<td>8.0</td>
<td>200</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>PI coated</td>
<td>6.40 1.7–2.8</td>
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<td>8.0</td>
<td>100</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>MOS-cap$^b$</td>
<td>6.40 7.1–7.3</td>
<td>1.00</td>
<td>8.0</td>
<td>100</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>SiO$_2$ coated</td>
<td>33.10 20.0</td>
<td>1.00</td>
<td>8.0</td>
<td>100</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>24.50 20.0</td>
<td>1.00</td>
<td>8.0</td>
<td>100</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28.30 20.0</td>
<td>1.00</td>
<td>8.0</td>
<td>100</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stacked</td>
<td>7.11 n/a</td>
<td>1.00</td>
<td>8.0 n/a</td>
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<tr>
<td>Glass-passivated stacked</td>
<td>16.37 n/a</td>
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<td>8.0</td>
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<td>PI substrate</td>
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<td>8.0</td>
<td>100</td>
<td>82</td>
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</table>
| Quartz substrate                   | 12.58 n/a             | 1.00          | 8.0                    | 4.5 | 54

$a$ Driven by constant current.  
$^b$ MOS-cap means the SiN$_x$ membrane was replaced by a MOS structure.

### Table 4

<table>
<thead>
<tr>
<th>Structure</th>
<th>$I_{\text{rms}}$ (pA)</th>
<th>Diameter (nm)</th>
<th>Ionic strength (Molar)</th>
<th>pH</th>
<th>Bias (mV)</th>
<th>Ref.</th>
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<td>Bare graphene</td>
<td>115.39 4.0</td>
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<td>Graphene on quartz</td>
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<td>9.0</td>
<td>100</td>
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<td>9.0</td>
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<td>h-BN</td>
<td>70.45 6.0</td>
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<td>h-BN on quartz</td>
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<td>h-BN on quartz</td>
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<td>8.0</td>
<td>n/a</td>
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<tr>
<td>h-BN on quartz</td>
<td>28.55 5.0</td>
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<td>72</td>
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<td>MoS$_2$</td>
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<td>MoS$_2$</td>
<td>6.05 8.0</td>
<td>1.00</td>
<td>8.0</td>
<td>100</td>
<td>72</td>
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</table>

8. Conclusion and future prospects

In summary, we reviewed and summarized the physical models, origins, and reduction methods for four noise components in nanopore sensors (1/f noise, white noise, dielectric noise, and amplifier noise). For the first time, we calculated and benchmarked the RMS values for different types of nanopores. There is a clear material-specific noise characteristic for nanopore sensors. Biological and glass nanopores show less RMS noise than SiN$_x$ and 2D material nanopores. There are still many unknowns of nanopore noise. The exact origin of the noise, especially the origin of 1/f noise, is still not clear. Without pinpointing the exact noise origins, the noise reduction effort can only be performed by an “error-and-try” approach. We need more theoretical and experimental work in this area. For example, it was previously observed that the nanopore noise can be conditioned by applying an electric field, however, the physical mechanisms of this “conditioning” remain unknown. In addition, we need to develop deeper insight into the impact of nanopore surface properties on the noise performances to control and modify its property. Fabrication methods beyond TEM and FIB may reduce the defect states in the pore-forming material (for reducing the dielectric noise). Lastly, we need to develop high performance, nanopore-integrated amplifiers to reduce the amplifier noise. We anticipate this review article will enhance our understanding of the impact of material properties on the nanopore noise and provide an informative tutorial into developing future nanopore sensors with a high SNR.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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