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High fidelity moving Z-score based controlled breakdown fabrication of solid-state nanopore

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Abstract

We investigate the current transport characteristics in the electrolyte-dielectric-electrolyte structure commonly used in the *in situ* controlled breakdown (CBD) fabrication of solid-state nanopores. It is found that the stochastic breakdown process could lead to fidelity issues of false positives (an incorrect indication of a true nanopore formation) and false negatives (inability to detect initial nanopore formation). Robust and deterministic detection of initial physical breakdown to alleviate false positives and false negatives is critical for precise nanopore size control. To this end, we report a high fidelity moving Z-score method based CBD fabrication of solid-state nanopore. We demonstrate 100% success rate of realizing the initial nanopore conductance of 3 ± 1 nS (corresponds to size of 1.7 ± 0.6 nm) regardless of the dielectric membrane characteristics. Our study also elucidates the Joule heating is the dominant mechanism for electric field-based nanopore enlargement. Single DNA molecule sensing using nanopores fabricated by this method was successfully demonstrated. We anticipate the moving Z-score based CBD method could enable broader access to the solid state nanopore-based single molecule analysis.

Supplementary material for this article is available online

Keywords: solid-state nanopore, controlled breakdown, DNA sensing, moving Z-score

(Some figures may appear in colour only in the online journal)

1. Introduction

Due to their mechanical robustness, tunable size, and integration potential, solid-state nanopores emerge as promising label-free sensors for detection of single molecules such as DNAs [1–5], RNAs [6–8], proteins [9–11], and DNA-protein complexes [12–14]. The ionic current blockades during the molecule translocation could provide rich information about the molecule properties [1, 2, 15]. While conventional transmission electron microscopy [16, 17] and focused ion beam [18–21] achieved considerable success for solid-state nanopore research, their accessibility is limited. Controlled breakdown (CBD) method for nanopore fabrication was proposed as an alternative [22]. In this approach, a strong electric field causes a local material failure and results in a nanoscale pore. It works for various materials including silicon nitride (SiN_x) as well as atomically thin two-dimensional materials such as graphene [23, 24] and MoS₂ [25].

Constant voltage stress (CVS) [26–30] and multilevel pulse-voltage injection (MPVI) [31–33] are two primary CBD approaches. The pilot work by Kwok *et al* was based on CVS [26] and showed a nanopore down to sub-2 nm in size could be created by applying a constant voltage across the membrane until a time-dependent dielectric breakdown [34, 35] event occurs. The nanopore formation is signified by the measured membrane current reaching a predetermined cut-off

level [26–28]. Although straightforward to perform, the CVS approach could have several reliability issues. The measured current under CVS is the sum of leakage current (i.e. the trapassisted tunneling current) [36, 37] and the intrinsic nanopore current (if nanopore is formed) [38, 39]. The latter can be overwhelmed by the former at high voltages. In addition, the leakage current varies from membrane to membrane due to the heterogeneous defect profiles. As a result, a universal predetermined cutoff current is impossible to implement. False positive (negative) nanopore formation will occur if the cutoff current is set too low (high) [27, 28, 40, 41]. To solve this issue, MPVI [31] was proposed. In this approach, alternating high and low voltages are used to stress the membrane and to measure the intrinsic nanopore current, respectively. Unfortunately, the repetitive voltage switching creates two fidelity issues due to the capacitive nature of the membrane. The first is the actual voltage across the membrane may not reach the target level if RC time is larger than the high voltage duration. The second is the low voltage measurement after each high voltage pulse must wait until transient current diminishes. Since the RC time is usually unknown and could only be guessed for a specific experiment, long waiting time would be preferred to avoid interfering nanopore current with the transient current. This repeated long waiting time could lead to the total experimental time to be over hours and thus limits the fabrication throughput.

In this work, we demonstrated a consistent and robust CBD nanopore fabrication using a moving Z-score based adaptive learning approach. It relies on the fact that current anomalousness (e.g. an abrupt jump) is necessary but not sufficient for the initial physical breakdown. This adaptive learning approach monitors the anomalous current event in real time to avoid false negatives. The anomalous event is further examined by IV scanning at low voltages to verify the linearity and conductance consistency to avoid false positives [40] and to reduce the total experimental time. This method could generate a tightly distributed initial nanopore conductance of $3 \pm 1 \text{ nS}$ (corresponds to the size of 1.7 ± 0.6 nm). In addition, we also studied the electric fieldbased nanopore enlargement dynamics and elucidated that the Joule heating is the dominant mechanism for nanopore growth. Successful DNA translocation experiments confirm the reliability and precision of the fabricated nanopore by the moving Z-score approach.

2. Methods

2.1. Materials and chemicals

Low-stress SiN_x membranes on 200 µm thick lightly doped silicon substrate were used in our experiments (Norcada, Canada). The SiN_x membranes are 10 nm in thickness with $50 \times 50 \,\mu\text{m}^2$ window (#NT005Z). Before mounting into our custom-built PMMA based flow cell, the SiN_x membranes were cleaned in oxygen plasma for 120 s at 50 W to facilitate wetting of the membrane surface. Ag/AgCl electrodes were house-made with 0.375 mm Ag wires (Warner Instruments, K A Roshan et al

with a $0.2\,\mu m$ Anotop filter (Whatman).

Hamden, USA). λ -DNA (48.5 kbp, 0.3 µg µl⁻¹) was pur-

chased from ThermoFisher. PBS, KCl and Tris-buffer solu-

tion (pH 8.0) were purchased from Sigma-Aldrich. Ecoflex-5

used as an insulating sealant of the membrane was obtained

2.2. Automated moving Z-scored based nanopore fabrication

The SiN_x membrane was sealed onto a custom-built PMMA flow cell with the cis and trans chamber. Each side of the membrane was wetted with 5 μ l of IPA (isopropyl alcohol) before filling both chambers with 1 M KCl in $1 \times PBS$ buffer. Two Ag/AgCl electrodes were inserted into the KCl solution and electrically connected to a source meter unit (Keithley 2636) through a BNC cable. The chamber opposing the Si etch pit was grounded in our work unless otherwise stated. The entire assembly is shielded inside a Faraday cage to minimize electromagnetic interferences. The assembly leakage or preexisting structural damages (e.g. pinholes, nano-cracks) was examined by measuring the leakage current between ± 100 mV, which should be less than 10 pA. A custom-built LabVIEW program automatically samples the total cis-to-trans current at 50 Hz under a constant stress voltage. The moving Z-score is updated in real time until detecting an anomalous event (Z-score > 6). Triplicate IV scans were performed subsequently to validate if a positive physical breakdown event occurred. This high fidelity detection of initial breakdown could generate nanopores with a narrow size distribution of 1.7 ± 0.6 nm. After the initial breakdown, the nanopore could be further widened to any desirable size through in situ enlargement under 0.5 V nm^{-1} electric field.

2.3. DNA sensing

The nanopore was *in situ* fabricated with 1 M KCl in 10 mM Tris at pH 8 before the single DNA sensing experiment. λ -DNA was added to the *cis* chamber to a final concentration of 10 µg ml⁻¹. The BNC-interfaced Ag/AgCl electrodes were then connected to the Axopatch 200B amplifier (Molecular Devices, CA) with *cis* chamber held at the ground. The ionic current during λ -DNA translocations is amplified in the resistive-feedback voltage-clamp mode. The amplified signal was filtered with a four-pole Bessel set at 10 kHz and digitalized by a 16 bit/100 MHz DAQ card (NI 6363, Texas Instruments). Data analysis was carried out using customdesigned MATLAB software to measure the duration and depth of each current blockade events.

3. Results and discussion

3.1. Membrane current characteristics

The total current through the membrane consists of both the nanopore current (if pore is formed) and the leakage current. The leakage current assumes a similar transport mechanism to the trap-assisted tunneling current (I_{tat}) through the gate dielectrics in semiconductor transistors [42, 43]. Figure 1(A)



Figure 1. Membrane current characteristics. (A) Schematic of the testing assembly. The membrane is assembled between two reservoirs filled with 1 M KCl in PBS. A biasing voltage is applied to the Ag/AgCl electrodes immersed in the reservoirs. (B) Comparison between the measured current through a pristine silicon nitride membrane (open circles) and the calculated ohmic current through a 1 nm nanopore (filled squares). An accurate determination of I_{np} would require measurement at low voltages (i.e. $V_{\text{bias}} < 2 \text{ V}$) where I_{tat} is negligible. (C) Time-traces of the total current through multiple SiN_x membranes biased at different DC voltages. Setting up a proper cut-off current is challenging thanks to the randomly distributed and fluctuated leakage current.

shows the assembly schematic for evaluating the membrane current under CVS. Figure 1(B) shows the measured current (open circle) through a pristine 10 nm thick SiN_x membrane. It ranges from 3.9 pA to 300 nA (five orders of magnitude change) when the voltage scans from 0.1 to 10 V. This leakage current is highly nonlinear and strongly voltage-dependent. As a comparison, the intrinsic nanopore current (I_{np} , assuming 1 nm in size, filled squares) would have an ohmic behavior. It is clear from figure 1(B) that I_{tat} dominates the measured current at high voltages (>3 V). Accurate determination of intrinsic I_{np} would not be possible in this region.

Figure 1(C) shows the representative time-traces of the total current for multiple SiN_x membranes exposed to various constant voltages. Three features were observed. The first is the random distribution of the leakage current baseline. High voltage bias does not necessarily result in a larger leakage current, which is likely due to the heterogeneous defect profile in different membranes. The second is the leakage current could randomly decrease or increase before the breakdown events. This feature was also observed in previous studies [26, 44]. The third is the temporary spike of the current, which does not necessarily correlate to a physical breakdown. For example, a transient current spike was observed at the time \sim 825 s for the membrane biased at 7 V, which is however a false physical breakdown since the current eventually decays to the baseline. This temporary spike could be ascribed to soft-breakdown [45] or burst noise [46]. These characteristics of the membrane current create fidelity issue for CBD-based nanopore fabrication. Setting the cut-off current too high would result in false negative and un-necessary nanopore enlargement [26, 27, 41, 47], while setting it too low would result in false positives [40].

3.2. Membrane capacitance

Although stressing the membrane at a high voltage with certain duration and measuring the current at low voltage [31] would solve the aforementioned interfering I_{tat} issue, the repetitive switching between high and low voltages on the capacitive membrane could result in transient phenomena that need to be examined in more detail. The inset of figure 2 shows the simplified equivalent circuit model of the



Figure 2. Membrane capacitance results in *RC*-dependent transmembrane voltage and transient current. The purple and green curves represent the transmembrane voltage when *RC* is less and larger than the high voltage duration, respectively. The inset shows a simplified equivalent circuit model of the device before the initial breakdown.

electrolyte-dielectric-electrolyte system before the breakdown. The membrane capacitance could lead to two fidelity issues. One is the actual voltage appearing across the membrane $(V_{membrane})$ is hard to determine due to its RC time dependence. Figure 2 schematically shows the applied voltage and the $V_{membrane}$ as a function of time for two representative cases. When RC is much larger than the high voltage stress duration (thigh), Vmembrane will fall very short of the intended level. The other issue is the interfering capacitive transient current $(I_{transient})$ when switching to a low voltage level for evaluating the intrinsic nanopore current [48]. A waiting time longer than RC is needed for $I_{transient}$ to be negligible. The RC constant for most CBD setup is around a few seconds. This repetitive waiting time could lead to a long experimental time over several hours, although the cumulative t_{high} is only a few seconds. In addition, this waiting time is only guess-based since a prior knowledge about the RC is usually unknown for a specific membrane and setup.

3.3. Moving Z-score method

The moving Z-score is an online adaptive learning algorithm for detecting the anomalous points in a time-trace. It measures the number of standard deviations each new observation is



Figure 3. Moving Z-score based nanopore fabrication scheme. (A) A representative time trace of measured current (black) and its moving Z-score (pink). The anomalous event of the abrupt current jump could be missed unless the cutoff current is set precisely. However, it can be readily detected by using Z-score > 6. No assumption about the baseline leakage current is required. (B) Flow-chart of the automated procedure for moving Z-score based CBD nanopore fabrication to avoid false negatives and false positives.

away from the mean over a pre-defined time window length of w

$$Z_{k} = \frac{I_{k} - mean(I_{k-1}: I_{k-w})}{std(I_{k-1}: I_{k-w})}.$$
(1)

Figure 3(A) shows an example current time-trace with corresponding moving Z-score (window size of 10). A current jump event would have been missed unless the cutoff current is set precisely. However, this anomalous event could be easily detected by a Z-score threshold (we used Z-score of 6 in our experiments). It is noteworthy that an abrupt current jump is necessary but not sufficient for positive breakdown due to soft-breakdown [45] or burst noise [46]. The moving Z-score method alleviates false negatives by not missing any suspicious event. Once a suspicious event is identified, subsequent confirmative test at low voltages is performed to avoid false positives. Figure 3(B) shows the overall fabrication flow-chart. A constant biasing voltage is applied to the membrane, and the moving Z-score of the total current is monitored in real time. When an anomalous event with Z-score > 6 is detected, the high biasing voltage is immediately switched off to avoid possible nanopore enlargement [26, 27, 41, 47]. Subsequently, after a waiting time for Itransient to diminish, the membrane conductance is measured by IV scanning at low voltages to confirm if a nanopore is indeed formed. A positive nanopore formation would require triplicate measurements with conductance all bigger than a threshold of 1 nS (corresponding to ~ 0.7 nm pore) and the IV curve linearity (r^2) all larger than 0.85. If the anomalous event turns out to be false positive, the constant biasing voltage will be reinitiated, and the process starts over again. If the anomalous event turns out to be true positive, the initial pore diameter is then estimated using [49]

$$G = \sigma \left(\frac{4h}{\pi D^2} + \frac{1}{D}\right)^{-1},\tag{2}$$

where σ , *h*, and *D* represents the electrolyte conductivity, effective membrane thickness, and the pore diameter, respectively. If larger pores are desirable, this initial nanopore could be *in situ* enlarged by applying electric fields [31, 50]. This moving Z-score fabrication procedure could be fully automated by setting a target nanopore size.

3.4. High fidelity initial physical breakdown detection

High fidelity initial breakdown detection is critical to minimize the nanopore size. Figure 4 shows a representative case for a 10 nm SiN_x membrane under 8 V bias. Before the 8 V stress, the membrane conductance was examined by triplicate IV scans between ± 0.1 V to confirm the assembly is leak-free and the SiN_r membrane is intact (first enlargement view). Subsequently, the 8 V biasing was applied, the current was monitored and the moving Z-score was calculated in real time (top panel of figure 4). Note that the current decay during the first few seconds after the biasing is due to the capacitive transient current. We also observed a general phenomenon of unpredictable increasing or decreasing current over time, consistent with previous reports [26, 27, 44]. A fixed cut-off current would thus be problematic to implement. This slow current drift is likely due to the time-dependent trapping dynamics in the SiN_r membrane [26]. However, the moving Z-scores remain less than 6 during this random fluctuation phase until the first anomalous event detected. To examine if this event is true or false positive, IV scanning between ± 0.1 V was performed. As shown in the second enlargement view of figure 4, a true positive breakdown would require the triplicate conductance and r^2 fall within the shaded area of the scattering plot. The IV scanning result rejected the anomalous event as a true positive. No physical pore was present. Therefore, the 8V biasing was reapplied until the second anomalous event detected. The following triplicate IV scanning confirmed this event was a true positive. The average conductance was determined to be 3.13 nS with excellent linearity (third enlargement view of figure 4). The initial nanopore size is estimated to be around 1.7 nm using equation (2). This high fidelity initial breakdown detection alleviates false negatives by examining all anomalous events that could be otherwise missed if using a predetermined cut-off current. It also avoids false positives by confirming the nanopore presence with triplicate low voltage IV scanning. Unlike the MPVI method, in which switching to the low voltage for characterization happens blindly regardless if there is any sign of pore formation, the moving Z-score method requires only a limited number of anomalous events to be examined by low voltage characterization (supplementary table 1 is available online at stacks.iop.org/NANO/30/095502/mmedia). The total waiting



Figure 4. High fidelity initial breakdown detection. A representative case for a 10 nm SiN_x membrane under 8 V bias. The top panel shows the current time-trace (black) under constant voltage stress with corresponding moving Z-score (pink). After detecting an anomalous event (Z-score > 6), the membrane conductance is measured at low voltages to confirm nanopore formation. Bottom panel shows scatter plots of membrane conductance and r^2 from the IV scanning. True positive initial breakdown requires all three measurements have the conductance and r^2 within the shaded area of the scattering plot.



Figure 5. Nanopore enlargement kinetics. (A) Nanopore diameter as a function of the cumulative enlargement time at various electric fields from 0.4 to 0.8 V nm⁻¹ for five individual 10 nm thick SiN_x membranes. The inset shows the enlargement rate under each electric field derived by a linear fit. (B) The pore area enlargement rate as a function of the instantaneous nanopore diameter for these devices. A quadratic relationship between the pore area enlargement rate and the instantaneous nanopore diameter was observed.

time (thus the total experimental time) could be reduced tremendously.

3.5. Nanopore growth and enlargement kinetics

It has been shown the nanopore size could be enlarged *in situ* with a sub-nm resolution by exposing to electric field [30, 31, 33, 50]. Nevertheless, a physical understanding of the enlargement mechanism is lacking. We studied the nanopore enlargement kinetics under various applied electric fields to accurately enlarge the nanopore to the desired diameter. The initial nanopore formed by the moving Z-score method was subsequently subjected to multiple enlargement voltage pulses of 5 s in duration. Each pulse was followed by low voltage IV scanning to estimate the pore diameter after a

sufficient waiting time (30 s). Figure 5(A) shows the nanopore diameter as a function of cumulative enlargement time for electric fields ranging from 0.4 to 0.8 V nm^{-1} applied to five individual initial nanopores (size ranging from 1.1 to 2.3 nm). The diameter enlargement rate under each electric field could be derived from a linear fit. In general, nanopore diameter grows faster with the higher electric field. For example, when subjected to 0.4 V nm^{-1} , the enlargement rate is 0.006 nm s^{-1} , whereas the electric field of 0.8 V nm^{-1} could lead to enlargement rate of 2 nm s^{-1} . From a practical perspective, there is a trade-off between sub-nanometer accuracy and total enlargement time. We found that electric field of 0.5 V nm^{-1} works best for enlarging our initial nanopore to a desirable size under 10 nm.



Figure 6. Distribution of nanopore size immediately after the initial breakdown and after fine size tuning that targets 3 nm and 5 nm in diameter, respectively. The enlarged nanopores are within sub-nanometer error to the targeted size.

The inset of figure 5(A) shows the diameter enlargement rate as a function of the electric field. Interestingly, an exponential relationship seems to exist between the diameter enlargement rate and electric field. To understand this dependence, we model the nanopore as a cylinder with timedependent diameter D(t). The instantaneous power dissipation within the nanopore is $P(t) = G(t)V^2$, where G(t) is the dynamic conductance. Without considering the accessing resistance [49], G(t) is determined by the nanopore area $\pi D(t)^2/4$. Thus, the instantaneous power dissipation P(t)within the nanopore would be proportional to $D(t)^2$. As shown in figure 5(B), a quadratic relationship between the pore area enlargement rate and the instantaneous nanopore diameter was observed. This strongly indicates the Joule heating is responsible for removing the material mass along the nanopore. It was found the Joule heating could break the Si–N bonds at the pore aperture area [35, 51, 52]. There are works showing the formation of multiple nanopores during the nanopore enlargement [33, 48, 53, 54]. However, the possibility of additional breakdown at other locations in our experiment is not likely due to the behavior seen in figure 5(B), which strongly indicates the single pore enlargement through the Joule heating around the exiting nanopore.

3.6. Deterministic nanopore size

CBD method for nanopore fabrication could have false positive and false negative problems. The false negative problem means the 'initial phase' of physical pore formation occurred but was not detected, therefore the electrical field keeps on until much bigger pore forms. This essentially leads to a bigger and wider distribution of the pore size (conductance). As shown in figure 6, the moving Z-score method could result in initial nanopore conductance tightly distributed within 3 ± 1 nS with 100% success rate, which corresponds to the pore size of 1.7 ± 0.6 nm using equation (2). Nevertheless, the pore formed in this initial phase is usually too noisy to be practically used as a single molecule sensor. Therefore, we employ the enlargement process to tune the pore to a bigger size and verified the pore with DNA translocation (figure 7). Due to the fine enlargement rate of 1.26 nm min⁻¹ at 0.5 V nm⁻¹ (inset of figure 5(A)), the initial nanopore size could be deterministically enlarged to a predefined size larger than 3 nm within the sub-nanometer resolution (figure 6). This deterministic size tunability of the nanopores makes it suitable for various sensing application. It is noteworthy that a secondary confirmative approach to 'see' the formed nanopore beyond conductance measurement would significantly enhance the conclusion. However, it is experimentally impractical to validate every nanopore after each breakdown, since searching a pore of diameter few nanometers within a window size $50 \times 50 \,\mu\text{m}^2$ is very tedious and error-prone.

3.7. Single DNA molecule detection

To demonstrate the sensing performance of the fabricated nanopores, we performed translocation experiments using 48.5 kbp double-stranded λ -DNA. A nanopore of 9 nm diameter was prepared by the moving Z-score method and the subsequent fine enlargement. Figure 7(A) shows a representative time-trace of current at 200 mV bias. The magnified view shows the ionic current blockade (ΔI) during the DNA molecule translocation. The inset of figure 7(A) shows the current blockade distribution for a total number of N = 604events. The conductance change obtained for the translocation events ($\Delta G \sim 1.6 \text{ nS}$) are in agreement with a 2.2 nm λ -DNA occupying a cylindrical nanopore [49]. Figure 7(B) shows a scatter plot of current blockades versus molecule dwell time. The average dwell time is 6.0 ms which reflects the translocation speed of λ -DNA molecule. We did not observe multiple current blockade levels that would indicate the translocation with folded structure [22, 27, 28, 55, 56]. This could be due to the noise overwhelming the short-lived folded events, although, the exact reason is unknown. Figure 7(C) shows the ionic current power spectrum density for the translocation experiment. At low-frequency range (<1 kHz), the noise level of fabricated nanopores varies as $1/f^{\alpha}$ with $\alpha = 1.6 \pm 0.2$ reaching about 400 pA² Hz⁻¹ at 1 Hz which makes the nanopore suitable for single molecule sensing experiments. This 1/f characteristic at low frequencies was comparable to these in previous studies [57-60].

4. Conclusions

In summary, the time-dependent and membrane-dependent leakage current through a voltage-biased SiN_x membrane could lead to false positives and false negatives in nanopore fabrication by CBD. Here, we reported a robust moving Z-score method for high fidelity nanopore fabrication. By online adaptive learning about the leakage current, false negatives can be alleviated by timely detection of the earliest physical breakdown event without setting an arbitrary cutoff current. This method could generate a tightly distributed initial nanopore conductance of 3 ± 1 nS (corresponds to the size of 1.7 ± 0.6 nm). These initial nanopores could be deterministically enlarged to a predefined diameter larger than



Figure 7. Single DNA molecule sensing. (A) A representative current time-trace during the passage of 48.5 kbp λ -DNA molecules through a 9 nm nanopore at 200 mV bias. The magnified view shows the ionic current blockade during the translocation. The inset shows current blockade distribution for a total of 604 events. (B) Scatter plot of the current blockades versus dwell time. (C) Power spectrum density for the ionic current signal obtained at 200 mV.

3 nm for various single molecule sensing applications. Our studies show that Joule heating is the dominant mechanism for nanopore enlargement. The robust moving Z-score method has the potential to minimize the CBD fabrication variation and increase the nanopore yield for the continued development of solid-state nanopore sensing applications.

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