Optimization and performance analysis of SERS-active suspended core photonic crystal fibers

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Abstract: Recently, surface enhanced Raman spectroscopy (SERS)-active photonic crystal fiber (PCFs) probes have gained great interest for biosensing applications due to the tremendous advantages it has over the conventional planar substrate based SERS measurements, with improvements on the detection sensitivity and reliability in measurements. So far, two main approaches were employed to get the analyte molecule in the vicinity of nanoparticles (NPs) inside PCFs in order to achieve the SERS effect. In the first case, analyte and NPs are pre-mixed and injected inside the holes of the PCF prior to the measurement. In the second approach, controlled anchoring of the NPs inside the inner walls of the PCF was achieved prior to the incorporation of the analyte. Although many studies have been conducted using one configuration or the other, no clear trend is emerging on which one would be the best suited for optimizing the biosensing properties offered by SERS active-PCF. In this paper, we investigate the performances of both configurations along with their interplays with the core size of the PCF probe. We have fabricated several samples of a standard PCF design with different core sizes, and SERS measurements of a standard Raman-active molecule are realized in the same conditions for enabling direct comparisons of the SERS intensity and measurement reliabilities between each configuration, yielding clear directions on the optimization of the SERS-active PCF probe. We envision that this study will pave the way for next-generation clinical biosensors for body fluid analysis, as it exhibits high sensitivity and excellent reliability.

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1. Introduction

Surface enhanced Raman spectroscopy (SERS) is an analytical technique based on the inelastic scattering of light that allows the identification of molecules thanks to their clear vibrational fingerprint. SERS overcomes the weak cross-section of Raman scattering by enhancing the signal by many folds and therefore increasing the detection sensitivity, while maintaining the narrow spectral bands leading to multiplex detection [1–6]. This enhancement occurs when analyte molecules are in the proximity of coinage nanoparticles (NPs) thanks to the localized surface plasmon resonance (LSPR) [7–13]. SERS is mostly studied on nano-roughened planar substrates or with colloidal solutions. Recently, SERS enhancement is also achieved inside photonic crystal fibers (PCFs), which are special optical fibers that possess holes in their cladding, allowing incorporation of liquid or gas analyte inside them [14–17]. In addition of being more flexible than planar substrates, such fibers could further enhance the SERS signal. Indeed, SERS occurs
mainly in the first 10-15 nanometers near the NPs [18–21], therefore limiting the interaction between the excitation light and the analyte to only two dimensions. PCFs allow a third dimension of interaction along the fiber length, which increases the overall interaction area and leads to an improved detection sensitivity [22–28]. Moreover, SERS-active PCF configurations are less prone to irregularities in nanostructures compared to even the best of planar substrates realized with nano-patterning techniques. As a matter of fact, because the light can interact with NPs and analyte over much larger areas, it encounters much more NPs. Therefore, an averaging effect occurs, which limits the impact of a defect in NP disposition. This averaging effect also results in better reproducibility and repeatability. Reproducibility of a SERS sensor indicates the ability to produce uniform SERS-signal from different spatial locations of a unique sensor. Repeatability defines the ability to generate reproducible results from several sensors fabricated at different time under fixed experimental conditions. SERS sensing using PCFs is achieved with two main types of fibers, hollow-core PCFs (HC-PCFs) and solid-core PCFs (SC-PCFs). SC-PCFs exhibit several advantages over HC-PCFs, such as stronger Raman signal enhancement and, fixed and broader transmission bandwidth when filled with liquid [17,29–32]. In these fibers, the light is guided inside the solid core with a fraction leaking in the liquid-channels that enables light-NP-analyte interactions. In SC-PCF, the fraction of evanescent field is mainly governed by the core size (at a given wavelength). The smaller the core is, the more evanescent light will overlap in the holes and interact with NPs and the analyte leading to higher SERS-sensitivity of the PCF probe [33]. However, this configuration may yield stronger absorption of the light by the NPs leading to shorter effective length of interaction along the PCF that reduces its benefits for improving the reliability of SERS measurements. Furthermore, the core size also plays a significant role in the coupling efficiency between the PCF-probe and the Raman spectrometer. In a previous study, we demonstrated the necessity of using a PCF with an optimized core size, not the smallest, to achieve efficient couplings and to limit the effect of operator misalignments on the measurement reliability [34].

Above all, SERS enhancement in PCFs relies on the interactions of the guided light with both the NPs and the analyte. The first configuration (namely “injected”) allowing such interaction consists of mixing a colloidal solution of NPs with analyte and pumping the final mixture inside the fiber [25,29,35,36]. The second strategy (namely “anchored”) consists of pre-functionalizing the PCF by controlled anchoring of the NPs inside the holes, on their inner-surface, and then by pumping the analyte solution that can physically or chemically bind to the NPs [2,3,22,33]. However, SERS based biosensing with high sensitivity (low limit of detection) have been reported in both configurations, with different molecules and PCF designs, leading to arduous comparisons, which are even more complicated with the lack of measurement reliability studies. Therefore, despite the numerous works showing the interests of PCF based SERS sensing, there is no clear direction on which configuration (injected/anchored) is more suitable to benefit from an efficient PCF SERS-probe design that optimizes the sensitivity, reliability offered by long length of interactions and reliable coupling efficiency with the Raman spectrometer. Herein, we investigate these interplays that are crucial for developing next generation of ultra-sensitive PCF SERS-probe compatible with effective uses in real-life applications. We compare and analyze the SERS performance of above mentioned two configurations within the same fiber design, a standard PCF (suspended-core PCF), fabricated with different core sizes. Experiments were realized in the same conditions for enabling direct comparison. We first investigated the effect of the concentration of gold NPs (Au NPs) in the injected configuration in order to determine the optimum concentration that provides the highest signal. Then, we compared the sensitivity and reliability of SERS measurements for both configurations. The impact of the core size on the PCF SERS-probe performances is finally investigated.
2. Experimental

2.1. Fiber fabrication and characterization

Suspended-core PCFs (SuC-PCFs) with three different core sizes (0.9 µm, 1.4 µm and 3.5 µm) were fabricated by using the conventional stack-and-draw process [37]. First, three capillaries were drawn and stacked in a tube. Then, this stack was drawn as a preform down to 2 mm diameter, which in turn was put in a jacket tube and drawn to the final fibers. The additional step of drawing the fiber to 2 mm preform, not mentioned in [37], allowed us to increase the thickness of the cladding to make the fibers easier to handle. In order to get fiber samples with the three different core sizes, the pressure applied in the capillaries, the descent speed of the preform in the furnace and the drawing speed were carefully adjusted during the drawing. Another mandatory requirement was to obtain large enough air holes in the cladding to let average-sized cells pass and to facilitate the incorporation of liquid inside the PCFs. Therefore, an extra care was taken to maintain the holes as large as possible (> 50 µm diameter).

SEM images of the three SuC-PCFs were acquired using a SEM QUANTA 450 W from FEI, to precisely determine their dimensions. A representative SEM image of one of the fibers is given in Fig. 1(a). The entire fiber structure is in silica with a refractive index of \( n_1 = 1.454 \) and the refractive index in the holes depends on the analyte: if the analyte is injected, we consider it as an aqueous solution, i.e. \( n_2 = 1.33 \), and in the anchored configuration, we consider that the holes are filled with air, i.e. \( n_2 = 1 \). The light is preferably guided in the node formed by the three struts due to its larger size, with a small portion of this light leaking in the holes of the cladding, as illustrated in light red near the core of the fibers in Figs. 2(a) and 2(b). As explained previously, this evanescent field is responsible for the interaction with the NPs/analytes. Table 1 summarizes the principal dimensions of each fibers. We have defined the core size as the diameter of the largest circle in the node (as shown in Figs. 1(b)-(d)). As expected, the struts thickness increases with the core diameter.

<table>
<thead>
<tr>
<th>Core diameter (µm)</th>
<th>Struts thickness (µm)</th>
<th>Outside diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>0.2</td>
<td>200</td>
</tr>
<tr>
<td>1.4</td>
<td>0.5</td>
<td>200</td>
</tr>
<tr>
<td>3.5</td>
<td>1</td>
<td>200</td>
</tr>
</tbody>
</table>

2.2. Injection and anchoring of NPs and analyte

The ‘injected’ configuration of analyte and NPs refers to the pre-mixing of the NPs and the analyte in a beaker and then injecting the mixed solution into a SuC-PCF. Consequently, the analyte-NP mixture will be freely flowing inside the holes of SuC-PCF (as illustrated in Fig. 2(a)). To determine the optimum concentration of Au NPs we diluted the stock of Au NPs solution (1X concentration, 2.6\( \times 10^{10} \) particles/mL, 60 nm diameter, from BBI Solutions) in deionized water to result in 0.25X, 0.5X and 0.75X concentration. 1.5X NP solution was also prepared from the stock solution by centrifuging and re-suspending the colloids after removing one-third of the total volume. Then we mixed each concentration of NPs with an aqueous solution of 4-Aminothiophenol (ATP, Sigma-Aldrich), which is a well-known Raman active molecule. The different solutions were prepared so that the concentration of ATP was constant among all samples, i.e 1 mM. In our previous study [34], we easily detected nM concentrations of ATP and we demonstrated the linearity response of the SuC-PCFs for concentration range from 1 µM to 1 mM. Here, we used 1 mM ATP because we wanted to easily detect the SERS intensity even with very low concentration of Au NPs. If we had used lower concentration of ATP, it might not have been possible to detect consistent SERS signal. Subsequently, 10 cm long fibers were cleaved
Fig. 1. (a) Representative SEM image of 0.9 µm core SuC-PCF. Zoom-in SEM images of the core of three SuC-PCFs with core size of (b) 0.9 µm, (c) 1.4 µm and (d) 3.5 µm. The core size is determined by measuring the diameter of the largest circle in the core, as illustrated by the dotted-circle. Scale bar: (a) 50 µm; (b) 2 µm; (c) 2 µm; (d) 10 µm.

at both ends and one end was glued inside a 27G needle. Using a syringe pump, the solutions were then injected inside the fibers. The free end of each fiber was cleaved again for enabling SERS measurements with the Raman spectrometer without parasitic effects from an overflowing analyte droplet.

The ‘anchored’ NPs configuration refers to the controlled immobilization of the NPs inside the inner walls of the holes and then inject the analyte later, as shown in Fig. 2(b). 10 cm long SuC-PCFs were cleaved and glued into needles and the fibers were cleaned with acetone and dried by pushing air repeatedly inside them. Then, 2% (3-Aminopropyl)triethoxysilane (APTES, Sigma-Aldrich), in acetone, was left to incubate inside the fibers for approximatively fifteen hours in order to functionalize on the silica walls of the fiber. Unbound APTES molecules were then removed by rinsing the fibers with pure acetone and the fibers were dried again. Subsequently, 60 nm AuNPssolution was pumped and left for two hours to allow the binding between Au NPs and previously immobilized APTES. A thorough rinsing with deionized water removed the unbound Au NPs and the fibers were dried. This will result in the formation of Au NPs monolayer inside the fiber. 1 mM ATP solution was pumped inside the SuC-PCFs for ten minutes in order to bind to the anchored Au NPs. Finally, the unbound ATP was removed and the fiber was dried. The free ends of the fibers were then cleaved and SERS measurements were taken.
Fig. 2. Schematics representation of (a) the injected configuration where Au NPs and analyte are pre-mixed and then pumped inside the fiber, (b) the anchored configuration where ATP is pumped inside the fiber so that it binds to immobilized Au NPs inside the fiber holes and (c) the backscattering configuration.

2.3. Determination of the sensitivity and reliability of the SuC-PCFs

ATP possesses strong SERS signal exhibiting two intense peaks at 1080 cm\(^{-1}\) and 1590 cm\(^{-1}\), as shown in Fig. 3(a), corresponding to stretching modes \(\nu_{CS, 7a}\) and \(\nu_{CC, 8a}\), respectively \([38–40]\). Intensity of 1080 cm\(^{-1}\) peak was used to monitor the sensitivity and the reliability of SuC-PCFs with 0.9 \(\mu\)m, 1.4 \(\mu\)m and 3.5 \(\mu\)m core diameters. The sensitivity was determined directly by calculating the Raman intensity at fixed experimental conditions; i.e. higher intensity corresponds to better sensitivity. The reliability of a sensor refers to the improved reproducibility and repeatability. A compromise between sensitivity and reliability is mandatory to create a biosensor that has clinical relevance. A sensor that could generate an extremely high SERS signal with poor reproducibility might show false positive results while a sensor that possesses high reproducibility with poor sensitivity could fail in detecting trace level of disease biomarkers. In order to determine the reproducibility, we measured a unique fiber sample eight times and between each measurement, we moved the focus point of the light onto slightly different locations on the core. Then, we calculated the relative standard deviation (RSD) obtained from these eight measurements to deduce the reproducibility. RSD is defined by the ratio of standard deviation by the average calculated across these eight measures. To estimate the repeatability, we prepared fibers from the same batch under exactly same conditions. For each fiber, we averaged the signal over eight measurements. Then, we calculated the RSD from these averaged intensities to deduce the repeatability.
Fig. 3. (a) SERS spectrum of ATP at 785 nm exhibiting two main peaks at 1080 cm\(^{-1}\) and 1590 cm\(^{-1}\), measured within a PCF probe. (b) Variation in SERS intensity of ATP peak at 1080 cm\(^{-1}\), with the concentration of injected Au NPs for fibers with 0.9 \(\mu\)m, 1.4 \(\mu\)m and 3.5 \(\mu\)m core; error bars represent the standard deviation across 8 measurements obtained with the same fiber.

2.4. SERS measurement

The Raman spectrometer (Renishaw InVia) used to measure the SERS signal features a 785 nm laser excitation along with a 1200 l/mm grating. It is coupled to a CCD detector cooled at \(-70^\circ\)C for signal readout through a microscope (Leica). The excitation laser was coupled inside the fiber core using a 50x objective lens (NA = 0.75, Leica) and the emitted SERS signal was collected using the same objective lens in backscattering configuration, as shown in Fig. 2(c). Standard silicon Raman peak at 520 cm\(^{-1}\) was used to calibrate the spectrometer and baseline correction allowed removing the background and fluorescence band. For each measure, the integration time was 10 s and no averaging of the signal was done. Several laser powers were used in this study, ranging from 130 \(\mu\)W to 1.3 mW. We ensured that the output power from the laser was stable between two measurements. We also used the same objective lens resulting in fixed working distance from the fiber. Moreover, we tried to focus the light in the same locations of the core for every single fiber. Therefore, the intensity of the laser entering the front face of fiber is fixed in all measurements.

3. Results and discussion

3.1. Determination of the optimum concentration of Au NPs in the ‘injected’ configuration

The measured Raman intensity of the ATP peak at 1080 cm\(^{-1}\) peak versus the concentration of Au NPs for different fiber core sizes are shown in Fig. 3(b). For sake of clarity, only one representative set of measurement per core size is presented, even though we did several sets per core size. The optimum concentrations of Au NPs across all the measurement sets for the fibers with 0.9 \(\mu\)m and 1.4 \(\mu\)m cores are found to be between 0.5X and 0.75X. For the fiber with 3.5 \(\mu\)m core, the optimum concentration is around 1.5X. However, further increase in the concentration of AuNPs is practically not feasible, as it might result in the creation of NPs aggregates, which, in turn, leads to a decrease in sensitivity and reliability.

In order to explain these trends, it is worth noting that SERS enhancement is achieved thanks to the presence of NPs. However, their presence also generates absorption losses and scattering losses. Thus, the resulting Raman intensity is the sum of the SERS enhancement and the
attenuation losses. This interplay has already been studied for uniformly anchored NPs by Han et al. in forward propagating detection [22]. In backscattering configuration, Zhang et al. have simulated similar conditions and showed that SERS intensity is supposed to reach a plateau after a certain concentration of Au NPs (for a fixed fiber length) [27].

However, here we can observe that for SuC-PCFs with 0.9 µm and 1.4 µm core, the Raman intensity increases up to a concentration of ~0.5X-0.75X and then decreases with the increase in concentration of Au NPs. We hypothesize that the absence of plateau could come from a degradation of SERS enhancement because the attenuation losses inside the fiber at higher NP concentration dominates the enhancement due to SERS. Indeed, the uncontrolled aggregation of Au NPs near the core might result in lower SERS enhancement compared to isolated Au NPs [41]. On the other hand, fiber with 3.5 µm core exhibits stronger SERS enhancement at higher concentration of Au NPs near the core. This can be explained as the fraction of evanescent field that interacts with the NPs and the analyte is smaller for this fiber with a bigger core and hence the loss inherent to NPs are relatively less, which lead to higher SERS enhancement.

3.2. Comparison between injected and anchored configurations

Previously we have found that for the anchored configuration, 1X concentration of 60 nm Au NPs provides optimum SERS enhancement [34]. In the current study, we anchored the Au NPs inside the SuC-PCFs with 0.9 µm, 1.4 µm and 3.5 µm core and we compared their SERS response to the best concentration of Au NPs in injected configuration, respectively. The average Raman intensity obtained with two to three separate fiber samples for both configurations are plotted in Fig. 4(a). For SuC-PCFs with 0.9 µm core diameter, the anchored configuration exhibits 11% higher SERS signal than the injected one. This result is also verified for SuC-PCFs with 1.4 µm and 3.5 µm core diameter by a signal improvement of 41% and 35%, respectively. The measured values are presented in Table 2. This demonstrates that the anchoring configuration, with our protocol, is preferable to injected one for improving the SERS sensitivity of PCF SERS-probes.

### Table 2. Summary of the measured average Raman intensity, calculated average reproducibility and calculated average repeatability in anchored and injected configurations for 3 core sizes

<table>
<thead>
<tr>
<th>Core Size (µm)</th>
<th>Anchored Average Raman Intensity (a.u.)</th>
<th>Anchored Average RSD in reproducibility</th>
<th>Anchored Average RSD in repeatability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>11113</td>
<td>1.04%</td>
<td>14.02%</td>
</tr>
<tr>
<td>0.9</td>
<td>9869</td>
<td>7.06%</td>
<td>17.62%</td>
</tr>
<tr>
<td>1.4</td>
<td>22037</td>
<td>1.10%</td>
<td>13.87%</td>
</tr>
<tr>
<td>1.4</td>
<td>12985</td>
<td>2.08%</td>
<td>23.54%</td>
</tr>
<tr>
<td>3.5</td>
<td>23524</td>
<td>0.93%</td>
<td>8.79%</td>
</tr>
<tr>
<td>3.5</td>
<td>15203</td>
<td>1.02%</td>
<td>15.12%</td>
</tr>
</tbody>
</table>

Subsequently, we studied the reliability of the different fibers, as this parameter is highly important when developing a clinically viable biosensor. It is worth mentioning that conventional planar substrates have best reproducibility around 5-7% [42–45]. Figure 4(b) depicts the average RSD in reproducibility for all core sizes in the injected and anchored configurations and Table 2 summarizes the exact values. Here, the average reproducibility of both configurations are much better than that in typical planar SERS substrates (except for injected configuration with 0.9 µm core SuC-PCF). The improved reproducibility of our SuC-PCF SERS probes could be explained by the fact that the light can interact with the analyte over several centimeters and thus resulting in an averaging effect that nullifies the variation. Comparatively, in the case of planar substrates, the smallest defect in NPs arrangement can lead to poorer reproducibility because the laser is interacting with the analyte only on the focused spot, which is only few micrometers wide.

In addition, our anchoring protocol further improves the reproducibility of PCFs compared to injected Au NPs. Indeed, for each core size, an anchored SuC-PCF can give the same Raman
Fig. 4. For each core size, comparison between the injected and anchored configurations of (a) the average Raman intensity at 1080 cm\(^{-1}\); error bars represent the standard deviations across two or three samples, (b) the calculated average RSD in reproducibility, (c) the calculated average RSD in repeatability, (d) Variation of average SERS intensity, in the anchored configuration, for fibers with different core sizes.

spectra with an average variation of approximately 1% over eight measurements. This further demonstrates that even if Au NPs are not well arranged inside the fiber, the final reproducibility achieved is excellent. This could be due to the fact that in the injected configuration, distribution of Au NPs-analyte mixture varies as they move freely inside the holes between two measurements and therefore it might induce a variation in the intensity of the measured spectra. Finally, concerning the repeatability for each core size, measurements between several fibers prepared in the same conditions are able to provide spectrum with less than 15% variations, which is considered more than acceptable in SERS studies [46]. All RSDs in repeatability measurements are given in Table 2 and plotted in Fig. 4(c). It is clear that our anchoring protocol improves the sensitivity and the reliability of the SERS-based PCF sensors. This is in-line with our strategy to develop the next generation of ultra-sensitive PCF SERS-probe compatible with effective uses in real-life applications. Indeed, the injected configuration does not have any interest from a clinical standpoint. It would mean that after collecting body fluids from a patient, the clinicians would have to mix it with a solution of NPs and then inject the NP-analyte solution inside a PCF. However, in a biopsy needle consisting of PCF with functionalized NPs, clinician would only need to collect the body fluid from the patient using the syringe and measure directly its SERS response. We can go further and develop such SuC-PCFs specially functionalized to detect targeted biomarkers in body fluids.

3.3. Impact of the PCF core size on the SERS signal

We also compared the SERS response of the three core sizes in order to determine the best compromise between sensitivity and reliability. Since our anchored protocol showed better
results than the injected configuration in terms of sensitivity and reliability, here we focused only on the effect of core size in the anchored configuration. We found that, fibers with 3.5 µm core diameter give the highest average Raman intensity, as shown in Fig. 4(d).

In addition, as mentioned previously, all three core sizes present an excellent reproducibility and the fiber with 3.5 µm core exhibits significantly better repeatability of less than 9%. In order to achieve the highest coupling efficiency, the light should be launched right at the center of the fiber core. However, practically, some small misalignment could happen and this will add to the variation. For SuC-PCFs with smaller core, precise focusing of the laser beam at the core is extremely challenging and even the slightest misalignment leads to poorer coupling efficiency and therefore lower repeatability.

SuC-PCF with 3.5 µm core seems to be the best compromise to create a highly sensitive and reliable SERS sensor. It exhibits the best sensitivity, reproducibility and repeatability among the three tested fibers and its relatively large core facilitates a proper coupling of the light while maintaining sufficient amount of evanescent field inside the holes to allow a good interaction between the excitation light and the NPs/analyte complex.

4. Conclusion

In this paper, we compared the two main configurations (injected/anchored) used with SERS-active PCF sensors to bring the analyte molecule in the vicinity of NPs. To the best of our knowledge, this study was the first of its kind and it allowed us to compare directly the two configurations in order to determine which one ensured the best sensitivity and reliability for SuC-PCF sensors. We demonstrated that the anchored configuration leads to higher sensitivity, with Raman signals up to 41% more intense. In the case of 3.5 µm core SuC-PCF, the optimum concentration of Au NPs is not yet reached (at 1.5X) in the injected configuration and one might be tempted to increase it further to properly compare it to the anchored configuration. However, this is not practically feasible as it can lead to the aggregation of the NPs, which in turn might yield poor signal reliability. Furthermore, SERS active SuC-PCFs in both configurations exhibit a better reproducibility than conventional planar substrates, specifically anchoring of Au NPs inside SuC-PCF leads to an excellent reproducibility (~ 1%) and repeatability (< 15%). We also showed that, with our anchoring protocol, the SuC-PCF with 3.5 µm core diameter exhibits the highest sensitivity and reliability, with a reproducibility less than 1% and a repeatability less than 9%. The anchored configuration therefore yields more sensitive and reliable SERS-active SuC-PCF sensors, offering very promising perspectives for the next generation of SERS-based PCF sensors. Another advantage of the anchored configuration is its good compatibility with the development of real-life sensors and especially of clinical biosensors compatible with liquid-biopsy requirements. Indeed, there is no practical sense in mixing the body fluid with NPs and then inject it inside the SuC-PCFs. However, SuC-PCFs functionalized with anchored NPs could allow a direct use by clinicians. They would only have to fill the fiber with the body fluid and measure the resulting SERS signal. This would result in a one-step collection and read out process, thus minimizing the actual two-step process.

Even if our protocol shows great potential, it still has to be further optimized in order to create an easy-to-handle biosensor that clinicians could use in operating theatres. For instance, we could envision a biopsy needle composed of a functionalized SERS-active PCF probe that could detect the trace amount of specific biomarkers in body fluids.

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Disclosures

The authors declare no conflicts of interest.

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