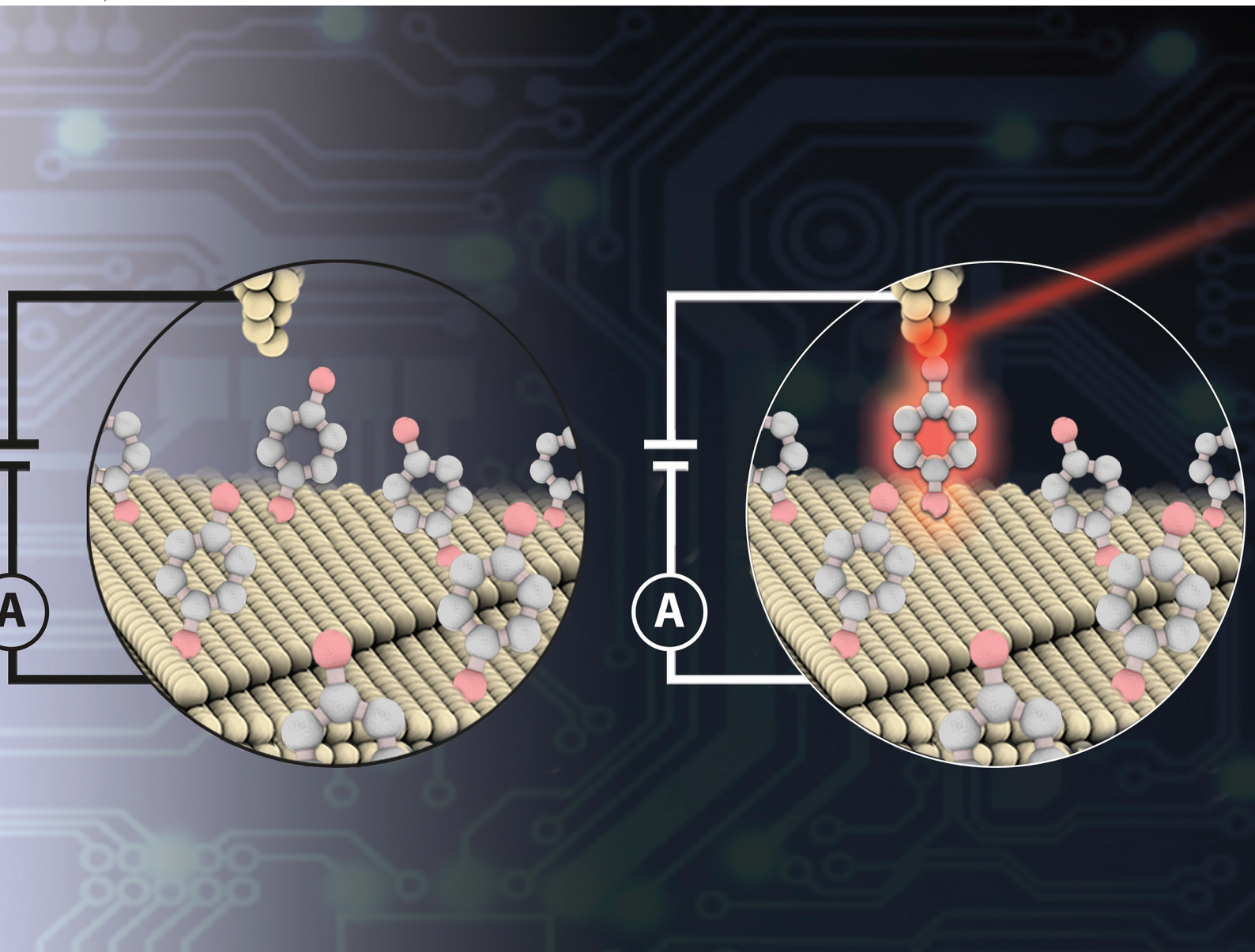


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## Playing *catch and release* with single molecules: mechanistic insights into plasmon-controlled nanogaps†

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Single-molecule (SM) detection is essential for investigating processes at the molecular level. Nanogap-based detection approaches have proven to be highly accurate SM capture and detection platforms in the last decade. Unfortunately, these approaches face several inherent drawbacks, such as short detection times and the effects of Brownian motion, that can hinder molecular capture. Nanogap-based SM detection approaches have been successfully coupled to optical-based setups to exploit nearfield-assisted trapping to overcome these drawbacks and thus improve SM capture and detection. Here we present the first mechanistic study of nearfield effects on SM capture and release in nanogaps, using unsupervised machine learning methods based on hidden Markov models. We show that the nearfield strength can manipulate the kinetics of the SM capture and release processes. With increasing field strength, the rate constant of the capture kinetics increase while the release kinetics decrease, favouring the former over the latter. As a result, the SM capture state is more likely and more stable than the release state above a specific threshold nearfield strength. We have also estimated the decrease in the capture free-energy profile and the increase in the release profiles to be around 5 kJ mol<sup>-1</sup> for the laser powers employed, ranging from laser-OFF conditions to 11 mW μm<sup>-2</sup>. We envisage that our findings can be combined with the electrocatalytic capabilities of the (nearfield) nanogap to develop next-generation molecular nanoreactors. This approach will open the door to highly efficient SM catalysis with precise extended monitoring timescales facilitated through the longer residence times of the reactant trapped inside the nanogap.

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## Introduction

Single-molecule (SM) detection is fundamental for investigating individual molecules as well as physical, chemical and biological processes at the molecular level and is therefore one of the most sought-after research objectives in molecular analysis.<sup>1</sup> Besides, SM detection is extremely appropriate for studying systems where analyte species are found in small sample volumes and/or at extremely low concentrations.<sup>2</sup> Nanogaps are undoubtedly the most suitable analytical dimensions for SM detection since they are tiny geometric spaces equivalent to the size of the analyte molecule to be studied.<sup>2,3</sup> They can

provide SM sensitivity with a minimised ensemble effect common in micro and macroscopic measurements.<sup>2,4</sup> Efficient SM detection is based on the precise control of the trapping and release of target species in the nanogap, which is, however, a challenging task because of the prevailing lack of a full understanding of the mechanistic details of SM trapping.<sup>2</sup>

Reliable SM tools based on nanogaps have been developed during the last two decades<sup>5</sup> for high-precision SM trapping and detection to characterise individual molecules, enabling molecular recognition<sup>6</sup> and sensing.<sup>7</sup> Among them, electrically based detection tools<sup>8</sup> are most appealing ones. Electrical current readouts render these approaches label-free, since they rely on molecular electrical capture and release between the individual molecule and the nanogap.<sup>9–14</sup> One of the most versatile electrical approaches to trap and study individual molecules is the one based on fixed and motionless interelectrode nanogaps of precise sub-nanometric dimensions.<sup>10,11,13–15</sup>

Electrical SM detection approaches are facing different inherent problems,<sup>8</sup> because working at room temperature (RT) and under ambient conditions make the localisation of the individual molecules in the reduced geometric space an entropically unfavoured process. On the one hand, the SM

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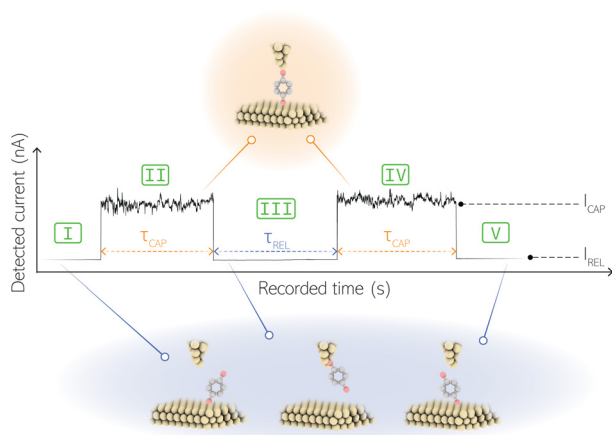
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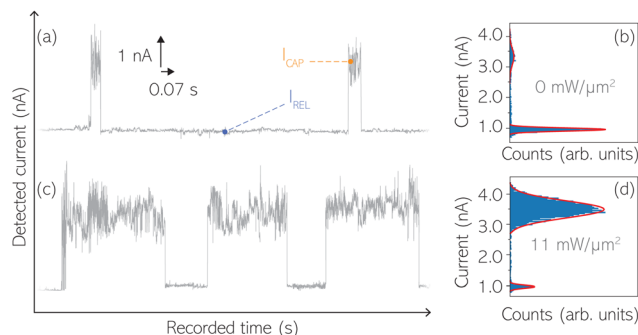




**Fig. 1** Example of a  $I(t)$  readout of stochastic SM capture and release current signatures at a fixed interelectrode nanogap distance. The telegraphic  $I(t)$  readout oscillates between two levels: (i) the low-current regime  $I_{REL}$  (scenario I, III and V) occurs when the molecule releases from one of the electrodes and only background (tunnelling) current is detected. (ii) The high-current regime  $I_{CAP}$  (scenarios II and IV) occurs when the molecule is captured in between both electrodes and closes the electric circuit between them. The lifetime of a SM junction is the capture dwell-time ( $\tau_{CAP}$ ) and the timeframe between two consecutive SM capture current signatures is the release dwell-time ( $\tau_{REL}$ ).

current is detected ( $I_{REL}$ ). The other level is related to the high-current regime (Fig. 1, panels II and IV) when the molecule is captured between both electrodes ( $I_{CAP}$ ). The (stochastic) capture of the molecule causes the sudden increase in the detected current (Fig. 1, scenario I to II) from  $I_{REL}$  to  $I_{CAP}$ . Upon release, *i.e.* the stochastic release, of the molecule, the current returns from  $I_{CAP}$  to  $I_{REL}$  level (Fig. 1, panels II to III and IV to V). The duration of a SM capture stage has a characteristic lifetime or dwell-time ( $\tau_{CAP}$ ). The duration of the release stage, *i.e.* the time between two consecutive SM capture current signatures, is defined by the release dwell-time ( $\tau_{REL}$ ). We have employed 1,4-benzenedithiol (BDT) as target molecule (see sample preparation details in ESI S1.3†). Current detection focused on the BDT characteristic conductance of  $1 \times 10^{-2} G_0$ , related to a bridge contact geometry,<sup>35,36</sup> that for our setup and experimental conditions equals to a current signature of 2.3 nA. The detected current signature of the BDT is not affected by the laser illumination. This is because there is a mismatch between the energy distribution of the Au hot carriers (holes),<sup>37</sup> created due to the presence of the nearfield,<sup>38</sup> and the HOMO level of the BDT. This mismatch prevents a hot-carrier contribution to the detectable current.<sup>37,39</sup> The mismatch is significant, with the HOMO level being approximately 1.2 eV away from the Fermi level of the Au electrodes,<sup>37,40</sup> while the applied (small) bias voltage is only 3 mV.

Time-dependent electrical characterisation was performed with a sampling rate of 10 kHz to monitor the SM capture and release current signatures of individual BDT molecules in the nanogap. Representative  $I(t)$  readouts are presented in Fig. 2a and c. They show how the SM capture and release states are



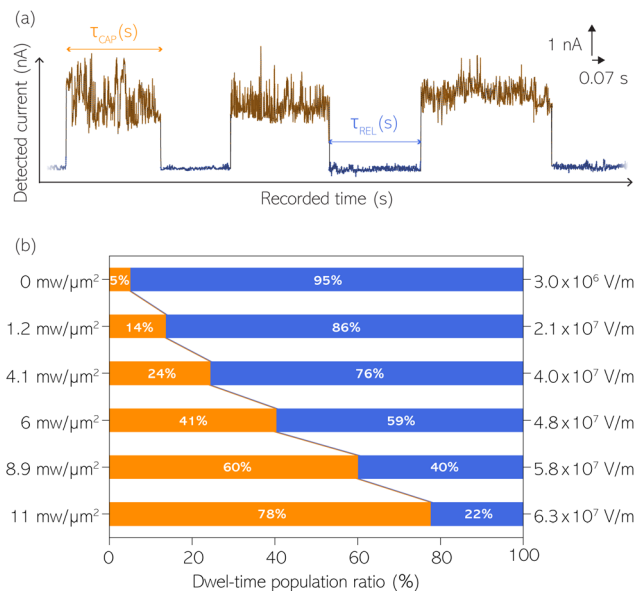
**Fig. 2** Representative  $I(t)$  nanogap readouts for laser-OFF conditions (a) and with a laser power density of  $11 \text{ mW } \mu\text{m}^{-2}$  (b) with the respective 1D histograms corresponding to the entire  $I(t)$  datasets acquired under the same laser power density conditions of a and c (b and d). 1D histograms have been normalised by the total amount of accumulated samples. The different dispersion of the high-current and low-current regimes (amplitude of each current signal level) yields to the difference in total peak area in (b) and (d).

clearly affected by the presence of the nearfield. Their characteristic  $\tau_{CAP}$  and  $\tau_{REL}$  dwell-times are modified by the laser illumination conditions, namely enlarged and shortened, respectively with increasing laser power. The  $\tau_{CAP}$  enlargement dependence on the nearfield strength is in agreement with our recently reported works,<sup>21,27</sup> where the SM release is stabilised by increasing nearfield gradients, which leads to an increase of the SM detection timescale. We have built 1D histograms for the entire  $I(t)$  datapoint readouts under laser-OFF and under laser illumination conditions of  $11 \text{ mW } \mu\text{m}^{-2}$  (see power laser density calculations from (far)field laser power in ESI S2†) that are shown in Fig. 2b and d, respectively. Under laser-OFF conditions, the prominent peak corresponds to the  $\tau_{REL}$  population, and contrarily, in the presence of the nearfield (laser-ON conditions), the peak corresponding to the  $\tau_{CAP}$  population is the prominent one. The integrated peak area ratio ( $\tau_{CAP} : \tau_{REL}$ ) for laser-OFF conditions is 1 : 17, and under illumination conditions of  $11 \text{ mW } \mu\text{m}^{-2}$  is 4 : 1. It attests a clear population inversion between  $\tau_{CAP}$  and  $\tau_{REL}$  peaks for the two laser conditions.

### Clustering and statistics of capture and release states

With the aim to perform a quantitative analysis of the  $\tau_{CAP}$  and  $\tau_{REL}$  dependence on the nearfield gradients, we have monitored  $I(t)$  readouts at four different laser power densities of 1.2, 4.1, 6.0 and  $8.9 \text{ mW } \mu\text{m}^{-2}$ , in addition to the maximum power of  $11 \text{ mW } \mu\text{m}^{-2}$  and laser-OFF conditions. To perform a complete analysis of a whole cycle of SM junction formation and disruption (*i.e.* SM capture and release pair), it was necessary to include also the  $\tau_{TIMREL}$  extracted from the SM release current signatures besides the  $\tau_{CAP}$  extracted from the SM capture signatures. This analysis procedure goes beyond the common practise in molecular electronics and SM detection studies in which the focus lies solely on the capture current signatures of the molecule in the nanogap ( $\tau_{CAP}$ ).<sup>13,15,29,30,32,34</sup> To carry out the analysis of the telegraphic signal in an





**Fig. 3** (a) Example of data clustering of a 5-second timeframe  $I(t)$  readout with classified SM capture (orange) and release (blue) states. Examples of SM capture and release state dwell-times ( $\tau_{CAP}$  and  $\tau_{REL}$ ) are labelled in the figure. The  $I(t)$  readout was acquired employing a laser power density of  $11 \text{ mW } \mu\text{m}^{-2}$ . (b) Population ratio between  $\tau_{CAP}$  and  $\tau_{REL}$  extracted from the classified entire  $I(t)$  dataset for each laser power density, respectively (values indicated in figure). Nearfield strength equivalents are indicated on the right.

unbiased way and hence exclude any (biased) manual data inspection, we have developed an automatised states finder based on the hidden Markov model (HMM) formalism.<sup>41</sup> Our tool is an unsupervised machine learning framework for time-series analysis based on a continuous-time algorithm that maximizes the likelihood of a sequence of intervals.<sup>42</sup> Accordingly, this framework identifies and clusters (classifies)<sup>43</sup> the different current levels detected in the  $I(t)$  readout (see ESI S3.1† for a detailed description). Our states finder tool is based on two HMM states attributed to the SM capture and release discrete states in time, to identify and cluster the  $I_{CAP}$  and  $I_{REL}$  levels (see Fig. 3a and ESI S3.2†). This approach results in an efficient clustering (see ESI S3.3†). Facilitated by the HMM clustering, the total  $\tau_{CAP}$  and  $\tau_{REL}$  can be extracted by classifying all datapoints of the  $I(t)$  readout datasets for each investigated laser power density. In this way, we explore the ratios between the populations of the two states (Fig. 3b) and assess potential correlations of the respective populations with the nearfield strength.

From Fig. 3b we can easily note that with increasing laser power density, the  $\tau_{CAP}$  relative population increases and the  $\tau_{REL}$  population decreases (field gradient strength equivalences in Fig. 3b and details in ESI S2†).  $\tau_{CAP}$  rises from an initial mean dwell-time population of 5% under laser-OFF conditions to 78% for the maximum power conditions of  $11 \text{ mW } \mu\text{m}^{-2}$ . On the other hand, the  $\tau_{REL}$  population shows a negative correlation with the nearfield strength and drops from an initial relative value of 95% down to 22% as the laser power grows.

These opposite trends of the dwell-time populations with respect to the laser power are in line with the observations denoted in Fig. 2. Thanks to this complete population-based analysis, we can now define the transition laser-condition from the least likely to the most likely state and *vice versa*. For our experimental conditions, the transition point lies in the range between  $6.0$  and  $8.9 \text{ mW } \mu\text{m}^{-2}$  where  $\tau_{CAP}$  ( $\tau_{REL}$ ) reaches values above (below) 50% of the total population. Below these laser power densities, the release state dominates the  $I(t)$  readout of the nanogap while at stronger nearfield strengths, the capture state is the more probable one.

### Studying the dwell times and modelling the SM kinetics under nearfield conditions

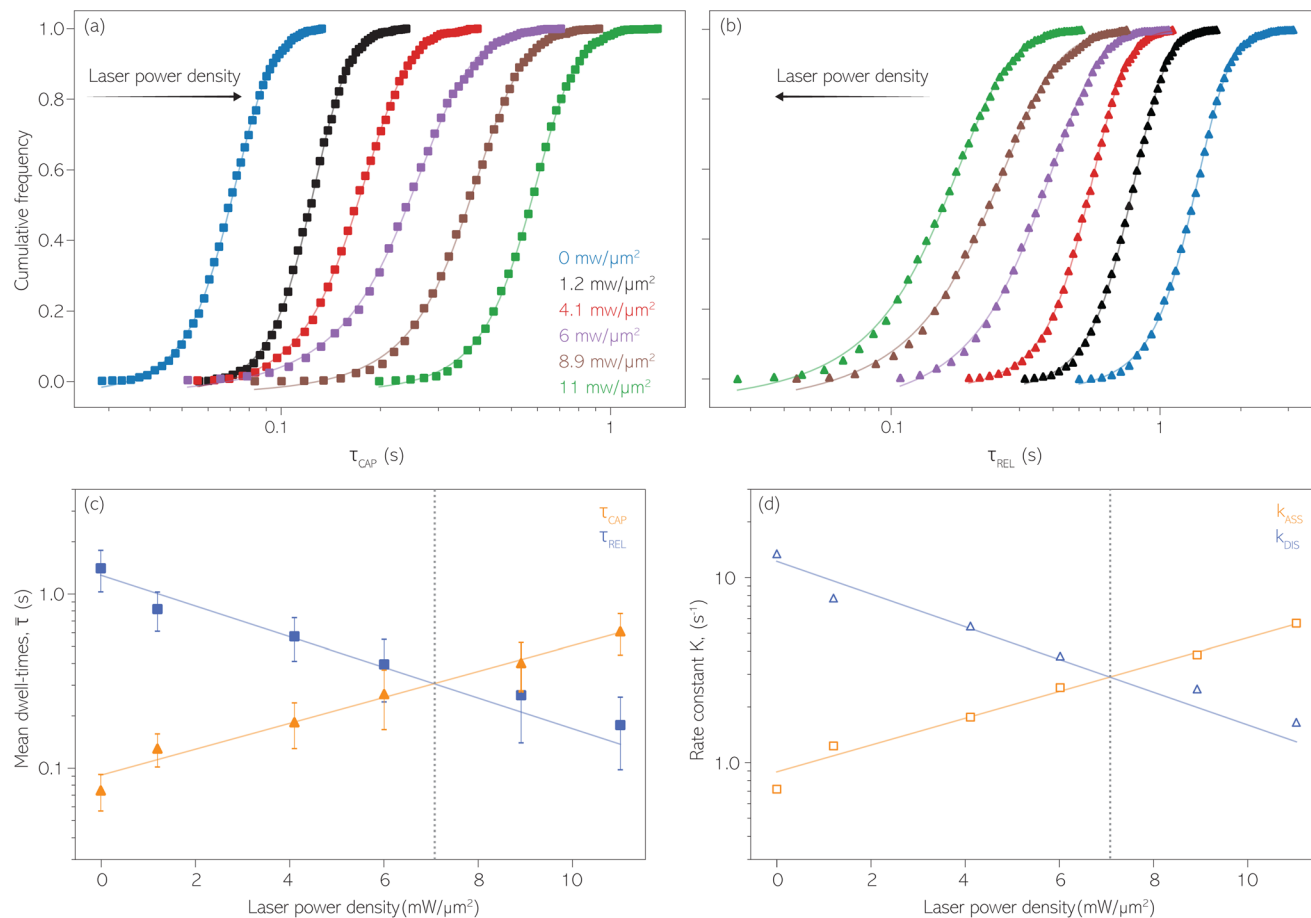
SM capture and release processes in nanogaps can be understood as chemical reactions of different types involving bond formation and bond breaking (commonly desorption), respectively,<sup>31,44,45</sup> each with their own kinetics.<sup>31</sup> As we have seen, the nearfield clearly affects the populations of both SM capture and release states, which implies variations in their kinetics as a function of nearfield strength.<sup>46,47</sup> From the distribution of  $\tau_{CAP}$  and  $\tau_{REL}$  values, clustered from the SM capture and release states in the  $I(t)$  readouts, the hidden kinetic properties of both states can be revealed.<sup>47–49</sup>

Exponential probability distribution functions,<sup>50</sup> characteristic for Markovian processes,<sup>51</sup> have been vastly employed in SM kinetic studies of molecular stochastic detection<sup>6,52,53</sup> and they have been well described for  $I(t)$  approaches.<sup>48,49</sup> For the research presented here, we have considered single-exponential distributions since we presume a single rate-limiting process for the SM capture and release processes because of two complementary reasons: on the one hand, the molecule|electrode contact interface is equivalent for both contact points (molecule–tip electrode and molecule–substrate electrode) since both electrodes are made of the same material and the molecule is symmetric. On the other hand, all the accumulated current signatures correspond to a *bridge* contact geometry,<sup>35,36</sup> thus the molecule|electrode interfaces of all studied junctions are equivalent. A well-established methodology for analysing the distribution of dwell-times is based on a semilog representation.<sup>50,54</sup> In it, the probability of occurrence or frequency (Y-axis) of each discrete state (here  $\bar{\tau}$ , X-axis) is plotted by adding to its own frequency the sum of the corresponding frequencies of all previous states and normalised by the total accumulated frequency.<sup>55</sup> Using the semilog cumulative frequency distribution (Fig. 4a and b), we extract a mean dwell-time value ( $\bar{\tau}$ ) for each SM capture ( $\bar{\tau}_{CAP}$ ) and release ( $\bar{\tau}_{REL}$ ) state by fitting a single-exponential distribution as a function of  $\tau$ ,<sup>49</sup> in the form of a sigmoidal, according to

$$P(\tau) = 1 - \exp\left(\frac{-\tau}{\bar{\tau}}\right). \quad (1)$$

The cumulative frequency distribution is an intuitive form of representation as the shift between sigmoidal fits is a visual analogy to the trend for the extracted  $\bar{\tau}$  values.





**Fig. 4** 1D semilog cumulative distribution plots for SM capture “ $\tau_{\text{CAP}}$ ” (squares) and release “ $\tau_{\text{REL}}$ ” (triangles) state dwell-times (a and b, respectively) for each laser power density (indicated in figure). Solid lines are the fits based on eqn (1). (c)  $\bar{\tau}_{\text{CAP}}$  (triangle) and  $\bar{\tau}_{\text{REL}}$  (squares) values as a function of employed laser power density. (d) Quantitative kinetic description of  $K_{\text{DIS}}$  (empty triangles) and  $K_{\text{ASS}}$  (empty squares) values as a function of laser power density. Solid lines in c and d are fits with the exponential function  $y = a \exp(-c \cdot x)$ . Error bars in (c) indicate the standard deviation of the dataset for each laser power density. Vertical dashed lines in (c) and (d) indicate the transitions where  $\bar{\tau}_{\text{CAP}}$  becomes larger than  $\bar{\tau}_{\text{REL}}$  and  $K_{\text{ASS}}$  larger than  $K_{\text{DIS}}$ , respectively.

Fig. 4 shows the 1D semilog cumulative distribution plots for  $\tau_{\text{CAP}}$  (Fig. 4a) and  $\tau_{\text{REL}}$  (Fig. 4b) for each investigated laser power density. The fits of  $\bar{\tau}_{\text{CAP}}$  and  $\bar{\tau}_{\text{REL}}$  show opposite trends. The  $\bar{\tau}_{\text{CAP}}$  variation is correlated with the increasing laser power density (from left to right) while, contrarily,  $\bar{\tau}_{\text{REL}}$  is anticorrelated (from right to left). The extracted values of  $\bar{\tau}_{\text{CAP}}$  range from  $7.5 \times 10^{-2} \pm 1.8 \times 10^{-2}$  s to  $6.1 \times 10^{-1} \pm 1.6 \times 10^{-1}$  s. The ones for  $\bar{\tau}_{\text{REL}}$  range from  $1.4 \pm 3.8 \times 10^{-1}$  s to  $1.8 \times 10^{-1} \pm 7.9 \times 10^{-2}$  s. Over the range of employed laser power densities, the values thus increase by a factor 8.2 ( $\bar{\tau}_{\text{CAP}}$ ) and decrease by a factor of 7.9 ( $\bar{\tau}_{\text{REL}}$ ) between 11  $\text{mW } \mu\text{m}^{-2}$  and laser-OFF conditions. The  $\bar{\tau}_{\text{CAP}}$  and  $\bar{\tau}_{\text{REL}}$  values plotted against the laser power density (Fig. 4c) show a positive exponential dependence for  $\bar{\tau}_{\text{CAP}}$  and a negative one for  $\bar{\tau}_{\text{REL}}$ . The plot reveals that the nearfield effects shorten the release states, besides promoting the capture states. The mechanics of SM trapping by means of a plasmonic nearfield thus turns out to be more complex than revealed by previous studies concentrating on the elongation of the SM trapping lifetimes ( $\tau_{\text{CAP}}$ ).<sup>21,27</sup>

Since the rate constant ( $K$ ) equals the reciprocal of  $\bar{\tau}$ ,<sup>56</sup> we can deduce the SM dissociation and association kinetics to the nanogap ( $K_{\text{DIS}} = 1/\bar{\tau}_{\text{CAP}}$  and  $K_{\text{ASS}} = 1/\bar{\tau}_{\text{REL}}$ , respectively<sup>47,49,56</sup>) at the temperature at which the experiment was performed (RT). Despite the use of low and medium power (far-field) intensities, the photothermal effects (optical heating)<sup>57–59</sup> of exposure of the BDT molecule to laser illumination and the possible repercussions over its capture/release kinetics should be discussed here. As a very recent study revealed,<sup>59</sup> the expected local temperature increase is estimated to be below 3 K for the nearfield in a nanogap of Au-tip|Au-surface configurations in aqueous media using a tip radius of 25 nm, and under the same laser power densities here employed, even considering a field magnification of the order of 50, almost twice that of ours. This temperature increase is insufficient to promote Au–S desorption,<sup>60</sup> Au–Au fracture,<sup>61</sup> or thiol–Au bond instabilities that have been estimated to be significant from a temperature increase of 30 K.<sup>62</sup> Accordingly, the expected small (local) thermal increase will not affect the







As we previously stated, SM capture and release processes must be coupled since they are mutually dependent, which is in line with the assumption that they can be considered parts of a single metastable state.<sup>64</sup> Interestingly, the same metastable treatment is given to the bond-formation and -breaking processes, which govern the SM capture and release respectively, in the bond-breaking thermodynamic theory for SM junctions,<sup>45</sup> where both processes are understood as counterparts of a dynamical state. Accordingly, we speculate that the near-field gradient (correlated with the laser power density) alters the equilibrium of the dynamic “ $K_{\text{ASS}} \rightleftharpoons K_{\text{DIS}}$ ” state by displacing it toward SM capture. As the laser power density increases (higher  $E_{\text{B}}$ ), the formation of the molecule–electrode bond is promoted,  $\Delta G_{\text{CAP}}$  decreases and the molecule has a higher probability of being captured ( $K_{\text{ASS}}$  increases) while in the counterpart of the equilibrium displacement,  $\Delta G_{\text{REL}}$  increases and the probability of molecule release diminishes ( $K_{\text{DIS}}$  decreases). This idea justifies the mismatch between the observed changes of  $K_{\text{ASS}}$  and  $K_{\text{DIS}}$  under increasing laser power densities in our work and those due to increasing concentrations in earlier studies.<sup>47,56,69,70</sup> In these studies, as explained before, the release process is independent of the concentration change and shows no correlation with the trapping process. We, on the other hand, have observed a negative correlation between  $K_{\text{ASS}}$  and  $K_{\text{DIS}}$  with increasing laser power densities. We can relate this fact to the displacement between the capture and release equilibrium. The anticorrelation between  $K_{\text{ASS}}$  and  $K_{\text{DIS}}$  under growing laser power densities, and their followed behaviour different from the reported by changing the captured molecule’s concentration, lead us to think that the kinetic parameters deduced from the  $I(t)$  read-outs encompass primarily the SM capture and release processes, and disregard the involvement of surface and/or molecular transport,<sup>18,28,60,82</sup> processes out of the equilibrium.

## Conclusions

In summary, thanks to the PBJ technique we have studied mechanistically, for the first time, the manipulation effects of the over the SM capture and release processes in plasmonic nanogaps. The nearfield gradient’s optomechanical stabilisation complementary to the extending SM capture lifetimes, also shortens the release times of the trapped individual molecule with the interelectrode nanogap. The induced changes in the timescales for SM capture and release processes are close to an order of magnitude for the employed laser mid-power range. The stabilisation effect is due to the fact that the near-field alters the capture and release mechanism by changing its kinetics, increasing the capture rate from a  $K_{\text{ASS}}$  of  $7.1 \times 10^{-1} \text{ s}^{-1}$  to  $5.6 \text{ s}^{-1}$ , and decreasing the release rate from a  $K_{\text{DIS}}$  of  $13 \text{ s}^{-1}$  down up to a  $1.6 \text{ s}^{-1}$  in the employed laser range, *i.e.*, the capture kinetics becomes more favourable than the release kinetics. Under laser-OFF conditions and low laser power densities, the release state is the most likely, but above the transition point, found at a power laser density of *ca.* 7.1 mW

$\mu\text{m}^{-2}$ , the capture state dominates over the release. We associate the described kinetics variation with the increase of  $E_{\text{B}}$ , which is dependent on the growth of the nearfield gradient. We have also estimated how the  $\Delta G$  profiles of the capture and release mechanisms vary, decreasing the former and increasing the latter by about  $5 \text{ kJ mol}^{-1}$  for both, thus facilitating the SM capture inside the nanogap. The mechanisms of the SM capture and release processes are clearly tuned by the nearfield gradient. Likewise, they also prove to be coupled and dependent to each other, as their changes in kinetics and thermodynamics show a clear anti-correlation between them, since they can be considered counterparts of the metastable state of the molecule in the junction.

As we have reported in previous works, electrocatalysis at SM level is possible in interelectrode nanogaps under exerted strong electric fields applied *via* accessible voltages by an STM.<sup>13,33</sup> By combining the nanogap’s electrocatalytic capability with the nearfield capacity to affect the molecule’s capture and release mechanism, different applications can be envisaged. On the one hand, the enhanced capture process will improve the efficiency of the SM catalysis, by stabilising the reactant molecules inside the nanogap for extended residence timescales. On the other hand, the enlarged monitoring timescales (*i.e.* higher temporal resolution), yield by the promoted longer capture lifetimes, will allow obtaining hidden insights into catalysed SM reactions. This fact is especially relevant for slow kinetic SM processes that have longer timescales than the common (non-plasmonic) electrical SM detection times.

## Author contributions

K. F. D. acquired funding, contributed to conceptualisation, and performed writing, reviewing and editing. A. C. A. acquired funding, performed writing of the original draft, contributed to conceptualisation, developed the software and data analyses, and performed reviewing and editing.

## Conflicts of interest

There are no conflicts to declare.

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