

### Supplementary information (S1)

#### First passage time distribution with one surface active site ( $N=1$ )

Following theoretical framework discussed in Ref 18 and 19, the first passage time distribution for product dissociation  $\phi_{on}(s)$  is given by

$$\phi_{on}(s) = \frac{Q_{EP \rightarrow ESP}(s)Q_{ESP \rightarrow ES}(s) + Q_{EP \rightarrow E}(s)}{1 - Q_{EP \rightarrow ESP}(s)Q_{ESP \rightarrow EP}(s)} \quad (S.1)$$

where

$$Q_{EP \rightarrow ESP}(s) = \frac{k_4[S]}{s + k_4[S] + k_3} \quad (S.2a)$$

$$Q_{ESP \rightarrow ES}(s) = \frac{k_5}{s + k_5 + k_{-4}} \quad (S.2b)$$

$$Q_{ESP \rightarrow EP}(s) = \frac{k_{-4}}{s + k_5 + k_{-4}} \quad (S.2c)$$

$$Q_{EP \rightarrow E}(s) = \frac{k_3}{s + k_4[S] + k_3} \quad (S.2d)$$

Here  $[S]$  denotes the substrate concentration.

Substituting these expressions in Eq. A.1, we have

$$\phi_{on}(s) = \frac{k_5 k_4 [S] + k_3 (s + k_{-4} + k_5)}{(s + k_{-4} + k_5)(s + k_4 [S] + k_3) - k_{-4} k_4 [S]} \quad (S.3)$$

In order to obtain the off time distribution, we consider the two parallel dissociation pathways. By applying the first passage time distribution formalism, we get

$$\phi_{off}(s) = C_1 \phi_1(s) + C_2 \phi_2(s) \quad (S.4)$$

where  $C_1$  and  $C_2$  are weight coefficients for the two dissociation pathways such that

$C_1 + C_2 = 1$ . As discussed in Ref 14,  $C_1$  and  $C_2$  are given by

$$C_1 = \frac{k_3(1 + K_2[S])}{k_3(1 + K_2[S]) + k_5 K_2[S]}, C_2 = \frac{k_5 K_2[S]}{k_3(1 + K_2[S]) + k_5 K_2[S]} \quad \text{and} \quad K_2 = \frac{k_4}{k_{-4} + k_5}$$

For the direct dissociation pathway,

$$\phi_1(s) = \frac{Q_{E \rightarrow ES}(s)Q_{ES \rightarrow EP}(s)}{1 - Q_{E \rightarrow ES}(s)Q_{ES \rightarrow E}(s)} \quad (\text{S.5})$$

For the substrate-assisted pathway, the initial state for a single off event is the  $ES$  complex such that,

$$\phi_2(s) = \frac{0}{0} \frac{Q_{ES \rightarrow EP}(s)}{1 - Q_{E \rightarrow ES}(s)Q_{ES \rightarrow E}(s)} \quad (\text{S.6})$$

where

$$Q_{ES \rightarrow EP}(s) = \frac{k_2}{s + k_2 + k_{-1}} \quad (\text{S.7a})$$

$$Q_{ES \rightarrow E}(s) = \frac{k_{-1}}{s + k_2 + k_{-1}} \quad (\text{S.7b})$$

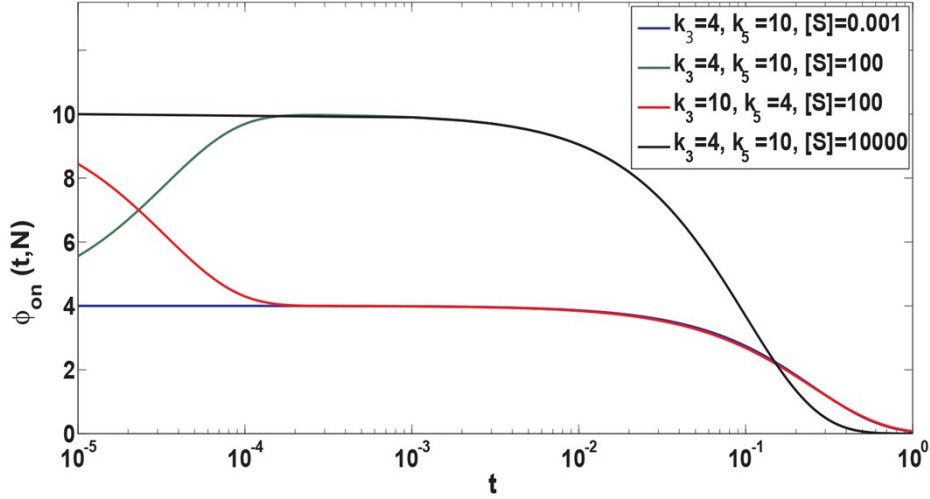
$$Q_{E \rightarrow ES}(s) = \frac{k_1[S]}{s + k_1[S]} \quad (\text{S.7c})$$

$$\phi_{off}(s) = \frac{k_2[S](k_1k_3(k_{-4} + k_5) + k_4k_5s + k_1k_4(k_3 + k_5)[S])}{(k_3(k_{-4} + k_5) + k_4(k_3 + k_5)[S])(k_{-1}s + (k_2 + s)(s + k_1[S]))} \quad (\text{S.8})$$

Similarly we can calculate the on time distribution using this first passage time formalism.

$$\phi_{on}(s) = \frac{k_5 + k_4[S] + k_3(s + k_5 + k_{-4})}{(s + k_5 + k_{-4})(s + k_4[S] + k_3) - k_4k_{-4}[S]} \quad (\text{S.9})$$

The inverse Laplace Transform of Eq. S.8 and S.9 give eqns 3a and 3b respectively.



**Figure S1a:**

The on time distribution in real time  $\phi_{on}(t)$  of a single nanoparticle with one surface active site ( $N=1$ ). The distribution is monoexponential at low and high  $[S]$  (blue and black line) respectively. Multiexponential distribution with  $k_3=4$  and  $k_5=10$  (green line) and  $k_3=10$  and  $k_5=4$  (red line) at  $[S]=100$ . Common parameter values are  $k_4=300$ , and  $k_{-4}=3$ .

In the Laplace space, the mean reaction time is related to first passage time distribution as

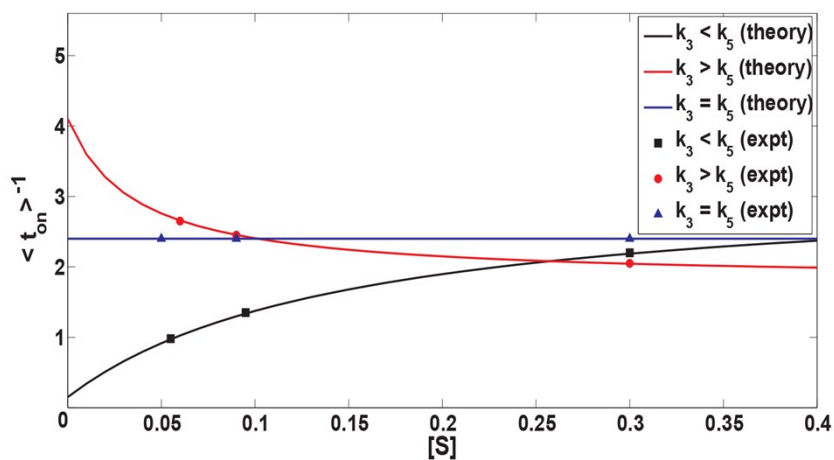
$$\langle t \rangle_{off/on} = \lim_{s \rightarrow 0} (-1) \frac{\partial \phi_{off/on}(s)}{\partial s} \quad (\text{S.10})$$

Using eqns S.10 and S.2, one can calculate the product dissociation rate  $\langle t_{on} \rangle^{-1}$  as function of substrate concentration

$$\langle t_{on} \rangle^{-1} = \frac{k_5 K_2 [S] + k_3}{1 + K_2 [S]} \quad (\text{S.11})$$

Fig. S2 b shows a comparison  $\langle t_{on} \rangle^{-1}$  calculated from eqn S.11 with the experimental data reported by Xu *et. al* in Ref 3. For three different sets of  $k_3$  and  $k_5$ ,  $\langle t_{on} \rangle^{-1}$  shows

a different behavior. The experimental data show excellent agreement with the theoretical work.



**Figure S1b**

$\langle t_{on} \rangle^{-1}$  for one catalytic site calculated from the first passage time distribution formalism. The black, red and blue depict three types of kinetic behaviors for the product dissociation pathways using eqn S.11. The experimental data of the dependence of  $\langle t_{on} \rangle^{-1}$  on [S] are shown by colored symbols. Data adapted from Fig 3b in Ref 3 with  $k_5= 3.2$ ,  $k_3= 0.15$ ,  $K_2= 6.7$  (black line),  $k_5= 1.8$ ,  $k_3= 4.1$ ,  $K_2= 28$  (red line) and  $k_5= k_3= 2.4$ ,  $K_2= 0$  (blue line)