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The opposing effects of isotropic and anisotropic attraction on association kinetics of proteins and colloids

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I. RESULTS

A. Dimer kinetics

1. Dimer association rate constant: decoy and isotropic attraction

In the second row of Fig. 1, we show the effect of the non-specific isotropic interaction on the overall association rate constant, $k_{UT}^{PT}$, computed using Eq. 21 of the Main Article. Clearly the overall association rate constant increases by more than an order of magnitude with the isotropic interaction for low decoy interaction $\epsilon_D$, and eventually levels off for high attraction, i.e. $\epsilon_{iso} \gtrsim 8$. However, the non-specific isotropic interaction does not change the association rate constant for high non-specific decoy interaction $\epsilon_D$. As the decoy patch becomes more attractive, the increase in overall association rate constant gained via the non-specific interaction is lost. It is now just as probable to end up in $D$ as in $T$, since both the target and decoy sites become of equal strength, which consequently retards the overall association toward the target state.

The third row of Fig. 1 shows the same rate constant data, as a function of the non-specific decoy interaction $\epsilon_D$. Here the effect of the decoy strength is clearly to lower the overall association rate constant, for each setting of the $\epsilon_{iso}$. Note that the retardation effect of the decoy site is stronger when there is non-specific isotropic interaction in contrast to no isotropic interaction all.

In the bottom row of Fig. 1, the same data is plotted to show the dependence of the position of the decoy site. The position of the decoy patch only starts to matter for strong decoy interaction in contrast to low decoy interaction. Rebinding from $D$ to $T$ increases when the decoy site is close to the target site, but only noticeably at higher $\epsilon_{iso}$. However, there is almost no difference between $\psi = 120^\circ$ and $\psi = 180^\circ$.

2. Dimer dissociation rate constant: decoy and isotropic attraction

The top row of Fig. 2 shows that the overall dissociation rate constant, $k_{TU}^{PT}$, decreases exponentially with the non-specific isotropic interaction strength, as expected. In contrast, $k_{TU}^{PT}$ varies marginally with the decoy interaction strength $\epsilon_D$. Only when $\epsilon_D > 10k_BT$ the rate constants start to be affected.

3. Normalized association/dissociation rate constants

In the top row of Fig. 3 we plot the same data as in Figs. 1, but now the overall association rate constant is normalized according to: $k_{UT}^{norm} = k_{UT}^{PT}(\epsilon_D, \epsilon_{iso})/k_{UT}^{PT}(\epsilon_D = 0, \epsilon_{iso})$. It demonstrates that at a higher isotropic attraction, the decoy interaction interestingly has relatively a stronger retarding influence on the association rate constant. This could serve as an explanation when upon naively increasing the isotropic interaction (e.g. increasing the concentration of polymers for stronger depletion forces) does not result in a (significantly) higher association rate constant.

Similarly we plot the dissociation rate constant $k_{TU}^{norm} = k_{TU}^{PT}(\epsilon_D, \epsilon_{iso})/k_{TU}^{PT}(\epsilon_D = 0, \epsilon_{iso})$ in the bottom row of Fig. 3 which shows that the dissociation is less affected by the decoy strength. This is rationalized by the fact that coming from the target paths are more likely to escape than to find the decoy, while coming from the unbound state the probability to hit the target or decoy are much more even.
FIG. 1. Top Row: Heat map of the overall association rate \( k_{UT}^{PT}(\psi, \epsilon_{iso}, \epsilon_D) \) for \( \psi = 60^\circ \) (left), 120\(^\circ\) (middle), 180\(^\circ\) (right). The diagonal line drawn through each heat map in the top row gives an indication how cooperativity would effect the overall assembly similarly how it occurs for the formation of the constrained tetrahedron (Section III). The diagonal cut shows that for decoy states close to the target state, a higher maximum overall association rate is reached. Second to 4th row: Different cuts through the parameter space for the overall association rate \( k_{UT}^{PT}(\psi, \epsilon_{iso}, \epsilon_D) \). 2nd Row: Overall association rate constant normalized with the rate constant value for \( \epsilon_{iso} = 0 \) for f.l.t.r. \( \psi = 60^\circ \), 120\(^\circ\), 180\(^\circ\) for different decoy strengths, \( \epsilon_D/k_BT = 0 \) (purple), 2 (green), 4 (light blue), 6 (orange), 8 (yellow), 10 (dark blue), 12 (red), 14 (black) and 16 (purple), as function of \( \epsilon_{iso} \). The association rate constant clearly increases with non specific isotropic interaction, however, at high \( \epsilon_D \) values the rate constant decreases. 3rd row: Overall association rate constant for f.l.t.r. \( \psi = 60^\circ \), 120\(^\circ\), 180\(^\circ\) for different isotropic strengths, \( \epsilon_{iso}/k_BT = 0 \) (purple), 2 (green), 4 (light blue), 6 (orange) and 8 (yellow), 10 (blue) as function of \( \epsilon_D \). The association rate constant clearly increases with non specific isotropic interaction, however, at high \( \epsilon_D \) values the rate constant decreases. Bottom row: Overall association rate constant for \( \epsilon_D = 2k_BT \) (left), 8k_BT (middle) and 14k_BT (right) for different positions of the decoy binding site \( \psi = 60^\circ \) (circles), 120\(^\circ\) (squares) and 180\(^\circ\) (triangles) seen as function of \( \epsilon_{iso} \). Clearly, the position of the decoy patch start to matter for strong decoy interaction in contrast to low interaction. Rebinding from \( D \) to \( T \) increases when the decoy site is close to the target site, however, there is no difference between \( \psi = 120^\circ \) and 180\(^\circ\). Note that the scale of the y-axis differs.
FIG. 2. Top Row: Overall dissociation rate constant for f.l.t.r. \( \psi = 60^\circ, 120^\circ, 180^\circ \) for different decoy strengths, \( \epsilon_D/k_BT = 0 \) (purple), 2 (green), 4 (light blue), 6 (orange), 8 (yellow), 10 (dark blue), 12 (red), 14 (black) and 16 (purple), as function of \( \epsilon_{iso} \). The dissociation rate constant behaves roughly Arrhenius-like with non specific isotropic interaction, and is not very sensitive to \( \epsilon_D \). Bottom row: Overall dissociation rate constant for f.l.t.r. \( \psi = 60^\circ, 120^\circ, 180^\circ \) for different isotropic strengths, \( \epsilon_{iso}/k_BT = 0 \) (purple), 2 (green), 4 (light blue), 6 (orange) and 8 (yellow), 10 (blue) as function of \( \epsilon_D \). The dissociation rate constant is not very sensitive to the decoy strength, however, at high \( \epsilon_D \) values the rate constant slightly decreases.

FIG. 3. Top row: Normalized overall association rate constant, \( k_{TU}^{norm} = k_{TU}^{TPT} (\epsilon_D, \epsilon_{iso}) / k_{TU}^{TPT} (\epsilon_D = 0, \epsilon_{iso}) \) for f.l.t.r. \( \psi = 60^\circ, 120^\circ, 180^\circ \) as function of \( \epsilon_D \) for different isotropic interactions with \( \epsilon_{iso}/k_BT = 0 \) (purple), 2 (green), 4 (light blue), 6 (orange) and 8 (yellow), 10 (blue). Bottom row: Normalized overall dissociation rate constant, \( k_{TU}^{norm} = k_{TU}^{TPT} (\epsilon_D, \epsilon_{iso}) / k_{TU}^{TPT} (\epsilon_D = 0, \epsilon_{iso}) \).
FIG. 4. Top: path length distribution of the SRTIS path ensemble for $\epsilon_D = 8$, $\psi = 60^\circ$ (left), and $\psi = 180^\circ$ (right). Bottom: Average path length as a function of $\epsilon_{iso}$ for $\psi = 60^\circ$ (left), and $\psi = 180^\circ$ (right). Note that the length becomes substantially longer for increasing $\epsilon_{iso}$, but saturates at $\epsilon_{iso} > 6k_B T$. Path lengths are reported in units of DMC time steps.

4. Path length distributions

We measure the path length distributions for all ensembles. We plot a few of these distributions and report the average path length (in units of DMC steps) for all simulations in Fig. 4. Clearly for increasing $\epsilon_{iso}$, the average path length increases, until it levels off around $\epsilon_{iso} \approx 7k_B T$. This is caused by the fact that the isotropic potential acts as an intermediate in which the particles can dwell quite a long time before committing to one of the stable states. Note that there is no energetic barrier towards the target state. The long paths represent a purely diffusive random walk.
FIG. 5. Effect of isotropic interaction on reactive path density (RPD) for state $D$ for distance between the centers, $r$, and the sum of the angles of patch vectors with the inter-particle vector, $\phi$ for from left to right $\psi = 60^\circ$, $120^\circ$ and $180^\circ$. From top to bottom the isotropic interaction is $\epsilon_{iso} = 3$, $\epsilon_{iso} = 6k_BT$, and $\epsilon_{iso} = 9$. The decoy interaction strength is set to $\epsilon_D = 12$. Note that integration of a reactive path distribution does not result in unity.

5. Reactive path density

The reactive path density for transitions out of $D$ for the system with isotropic interaction is shown in Fig. 5 (and in Fig. 10 of the Main Article). Here one observes an increase in rebinding probability as the isotropic interaction increases, corresponding to the increased flux ratio $f_{UT}/f_{U,D}T$ in Fig. 4 of the Main Article. The rebinding probability changes dramatically between $\epsilon_{iso} = 2$ and $\epsilon_{iso} = 6k_BT$, but saturates for high $\epsilon_{iso} = 12$. 
FIG. 6. Rate matrix, $K$ for constrained tetrahedron formation as function of $\epsilon_{iso}$. Note that for rate constants from and to $D$ are only defined for $\epsilon_{iso} > 0$.

**B. Constrained Tetramer**

Fig. 6 presents the 12 off diagonal elements of the $4 \times 4$ rate matrix for the constrained tetramer formation as a function of $\epsilon_{iso}$. Note that the most association processes are enhanced due to the nonspecific attraction.

In the Main Article we presented the overall TPT association rate constant for the constrained tetramer as a function of $\epsilon_{iso}$. Strikingly, the rate constant increases first, then decreases with non specific interaction. We report in Fig. 7 the normalized curves for different box volume where the rate constants are scaled according to Eq. 12 of the Main Article. For all cases the rate constant increases by more than an order of magnitude first, then decreases with non-specific isotropic interaction. Remarkably the increase is relatively strongest for the lowest concentration. Note that the behavior of the dissociation rate constant is as expected (see Fig. 8), i.e. it depends roughly exponentially on $\epsilon_{iso}$.

One would think that the case of the constrained tetrahedron would be almost identical to the dimer with a decoy site with only a slightly different geometry. However, as discussed in the Main Article the behavior is rather different due to the cooperativity of the non-specific interaction in the trimer.
FIG. 7. Overall association rate constant for a constrained tetrahedron for different concentrations normalized with the rate constant value for $\epsilon_{\text{iso}} = 0$. The curves correspond to different volumes $V/V_0 = 1.0$ (black), $10.0$ (purple), $10^2$ (green), $10^3$ (blue), $10^4$ (orange), $10^5$ (red). A shift from $4k_BT$ to $8k_BT$ is seen for the maximum association rate constant as function of the volume scaling.

FIG. 8. Overall dissociation rate constant for a constrained tetrahedron showing Arrhenius-like behavior as function of $\epsilon_{\text{iso}}$.

For completeness we investigate whether this behavior is robust with respect to protein concentration (or system volume). We compare in Fig. 9 the volume dependency of the protein dimer formation with the constrained tetrahedron, in where the concentration is decreased hundredfold using the data in Fig. 1. Note that these curves do not show a maximum, although as the concentration is decreased all curves tend to overlap, indicating that the retardation effect due to the decoy state is decreased.

FIG. 9. Overall association rate constant as a for $\psi = 60^\circ$ (left), $120^\circ$ (middle), $180^\circ$ (right), as in Fig. 1 but with the concentration decreased a hundredfold according to Eq. 12 of the Main Article. Colors as in Fig. 1. Note that the retardation effect of the decoy state is relatively decreased. Moreover, the higher rebinding probability for small $\psi$ is better visible.