THE JOURNAL OF PHYSICAL CHEMISTRY B
A JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Article

Nanoscale Catalyst Chemotaxis Can Drive the Assembly of Functional Pathways

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Cite This: *J. Phys. Chem. B* 2021, 125, 8781–8786

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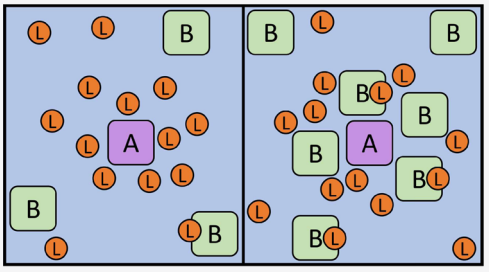
ABSTRACT: Recent experiments demonstrate molecular chemotaxis or altered diffusion rates of enzymes in the presence of their own substrates. We show here an important implication, namely, that if a nanoscale catalyst A produces a small-molecule ligand product L which is the substrate of another catalyst B, the two catalysts will attract each other. We explore this nonequilibrium producer recruitment force (ProRec) in a reaction–diffusion model. The predicted cat–cat association will be the strongest when A is a fast producer of L and B is a tight binder to it. ProRec is a force that could drive a mechanism (the catpath mechanism) by which catalysts could become spatially localized into functional pathways, such as in the biochemical networks in cells, which can achieve complex goals.



INTRODUCTION

Force between Two Agents That Is Based on Functionality. Consider two different challenges: (1) different enzymes or nanoparticles in solution catalyze different reactions. How might a nanoengineer drive different catalysts together in space into multicatalyst pathways that could create desired complex products? (2) How might primitive enzymes have assembled prebiotically to become today's biochemical pathways in cells?

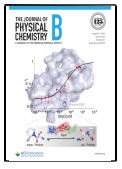
We describe here a type of force of attraction that is based on the functions of the actors. To illustrate what that means, here is a metaphor. One actor, Niagara Falls, is a producer P of energy in a fixed location. The other actor, a company U, is a user of energy and is mobile. If there is a cost to transport energy over a distance, there will be an attraction that drives U to locate near P. We call this the producer–user recruitment force, ProRec for short. These are situations in which users locate near producers. We use the terms function or functionality to refer to the production or usage of some exchangeable good in common between the producer and the user—energy in the Niagara Falls, for example.

Producer–user situations are ubiquitous throughout biology. Cells are users of molecules, taking up food and other components from the surroundings, and they are also producers of molecules that they excrete or export. If user and producer cells experience attraction due to an exchangeable molecule in common, it could be the basis for driving cell assembly into functional tissues. In well-known producer/cheater yeast dynamics, some yeast cells (producers) put out molecules into the surroundings, while other yeast cells (nonproducing "cheaters") utilize the resources made by the producers.[1,2] Producer–user actions also occur at the molecular level. For example, receptors cluster in signaling processes in the immune synapse,[3,4] in the feedback mechanisms of cell-to-cell signaling networks,[5] or in long-term potentiation memory in the brain.[6] In the origins of life, producer–user actions may help explain how randomly dispersed chemical reactions in solution could come to assemble into spatially localized functional biochemical pathways.[7] For concreteness here, our descriptions will be expressed in terms of molecular-level events, where different catalyst molecules, such as enzymes or Janus colloids, act on some common small molecule that is the product of one catalyst and the substrate of the other one. We will call this particular producer–user recruitment setup, where both the producer and user are (macro)molecule-scale catalysts organizing into a chemical pathway, the catpath mechanism, as in Dill and Agozzino.[8] Here, we develop a model of the catpath mechanism that is motivated by earlier work.[7,9] This is related to, but different from, enzyme chemotaxis or enhanced diffusion, as we discuss at the end of the Results and Discussion section.

THEORY

Reaction–Diffusion Model of the ProRec Cat–Cat Attraction. We consider the following mechanism. One catalyst (cat) A is fixed in space. Another cat B is mobile; it is free to diffuse throughout the space. A produces small

Received: May 21, 2021
Revised: July 13, 2021
Published: July 29, 2021



https://doi.org/10.1021/acs.jpcb.1c04498
J. Phys. Chem. B 2021, 125, 8781–8786

molecule ② as its product, and B uses ②'s as the substrate. As long as A continues to make its product, the ②'s will distribute in a concentration gradient away from A, which will facilitate the attraction of B's. The action is shown in Figure 1, where

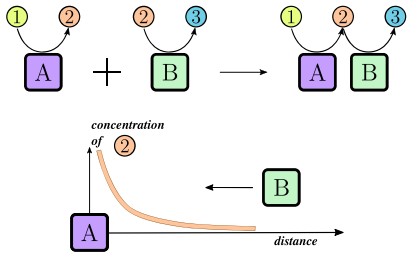


Figure 1. ProRec mechanism. Two catalysts, A (fixed) and B (mobile), share a common substrate/product, which we label as 2. It leads to attraction of B toward A.

the square-box symbols represent two cats of different types, labeled alphabetically. The circles represent the exchangeable molecules, where different types are labeled numerically. The arrows indicate the conversion of the substrate, say ①, to product, say ②, by enzyme catalyst A. Assume that enzyme A is fixed at the origin[a] and that enzyme B is mobile and can diffuse. The system is not in equilibrium because it requires constant input of ①'s to A in order to produce ②'s. Even though the ②'s will diffuse away, there will be a sustained gradient, with ②'s being the most highly concentrated near the A. Producer−user recruitment can be thought of as driving the hand-shaking between two different catalysts that are related through functionality. This mechanism is similar in spirit to the one previously simulated using a computer but not treated so generally or analytically.[7]

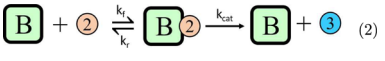
We take the concentration of B's and ②'s to be functions of the distance in space **r** from A. We take the binding of the cats to follow the canonical Michaelis−Menten binding law, and we assume that the unlimited supply of ①'s drives A to constantly produce ②'s at rate $k_2 c_1 \mathrm{A}(r)$.

First, consider the dynamics of the ②'s, where $c_2(\mathbf{r})$ is its concentration as a function of time t and space **r**, in three spatial dimensions. We assume that the ②'s follow reaction−diffusion dynamics and then freely diffuse away according to

$$\left(\frac{\partial c_2(\mathbf{r})}{\partial t}\right)_{\text{total}} = D_2 \nabla^2 c_2(\mathbf{r}) + \left(\frac{\partial c_2(\mathbf{r})}{\partial t}\right)_{\text{reaction}} \tag{1}$$

Now, to obtain the rightmost term in eq 1, we assume that B's bind to ②'s with on-rate k_f, off-rate k_r, and final-step conversion rate k_{cat}.

We will ignore the final step in this reaction for now by taking the binding and unbinding of the catalyst and substrate to be much faster than the catalysis step. Assuming point



(2)

particles and the binding kinetics from eq 2, we can express the reaction dynamics as

$$\left(\frac{\partial c_2(\mathbf{r})}{\partial t}\right)_{\text{reaction}} = k_2 c_1 \mathrm{A}(r) - k_f c_2(r)\mathrm{B}(r) + k_r \mathrm{B}_2(r) \tag{3}$$

where c_1 is the concentration of substrate ①, which is a constant across the region where $\mathrm{A}(r) \neq 0$, and $\mathrm{B}(r)$ and $\mathrm{B}_2(r)$ are the concentrations of the unbound enzyme B and the bound complex B_2 of ②'s bound to B's. If, in addition, the diffusion of the enzyme is slower than the reaction, we have local equilibrium for the catalysis, which is expressed as $k_f c_2(r)\mathrm{B}(r) \approx k_r \mathrm{B}_2(r)$. We can therefore assume that in the entire region where c_2 is significantly nonzero, the first term is dominant $k_2 c_1 \mathrm{A}(r) \gg k_f c_2(r)\mathrm{B}(r) - k_r \mathrm{B}_2(r)$. The last two terms in eq 3 approximately cancel, leading to

$$\left(\frac{\partial c_2(\mathbf{r})}{\partial t}\right)_{\text{reaction}} \simeq k_2 c_1 \mathrm{A}(r) \tag{4}$$

In the steady-state limit, the left-hand side of eq 1 is zero, yielding

$$\nabla^2 c_2(\mathbf{r}) = -\frac{k_2 c_1}{D_2}\mathrm{A}(\mathbf{r}) \tag{5}$$

Equation 5 is readily solved analytically using a Green's function

$$c_2(\mathbf{r}) = \frac{k_2 c_1}{4\pi D_2}\int \mathrm{d}^3\mathbf{x}\frac{\mathrm{A}(\mathbf{x})}{|\mathbf{r}-\mathbf{x}|} \tag{6}$$

This result is just the integral equivalent of the differential equation in eq 5 for computing $c_2(\mathbf{r})$ for a given spatial distribution function of the catalyst A. Note that in order to sustain a non-negligible gradient for eq 7, the ②'s must be produced faster than they diffuse away. Note also that the spatial distribution of c_2 will have the same symmetry as A. For simplicity, we will assume spherical symmetry here. If A follows a Gaussian distribution with variance a and a total of N molecules of A, we find

$$c_2(r) = \frac{k_2 c_1 N}{4\pi D_2 r}\mathrm{erf}\left(\frac{r}{\sqrt{2}\,a}\right) \tag{7}$$

Now, we consider the reactions involving the enzyme B, as shown in eq 2, but with a slight augmentation. As shown, eq 2 only gives an on-rate and off-rate of the binding event, with no spatial dependence of that binding interaction. We now also account for a separation-dependent attractive intermolecular potential between B and ②, $V(|\mathbf{r}_B - \mathbf{r}_2|)$, so that we can eventually compute an attractive force of A with B mediated by the ②'s. The resulting reaction−diffusion equations have been extensively studied by Agudo-Canalejo et al.,[9] who have derived the reaction−diffusion equation for the total concentration of $\mathrm{B}_T(r) = \mathrm{B}(r) + \mathrm{B}_2(r)$ by combining the kinetics equations for each type of molecule involved.

In this model, the diffusion of the enzyme B in the presence of ②'s is governed by the equation

$$\partial_t \mathrm{B}_T(r) = \nabla\cdot[D(r)\nabla \mathrm{B}_T(r) - (V_{\text{ph}}(r) + V_{\text{bi}}(r))\mathrm{B}_T(r)] \tag{8}$$

where

$$D(r) = D_B + (D_{B_2} - D_B)\frac{c_2(r)}{K + c_2(r)} \tag{9}$$

https://doi.org/10.1021/acs.jpcb.1c04498
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$$V_{ph}(r) = \frac{k_B T \lambda_B^{\,2}}{\eta}\nabla c_2(r) + \left(\frac{k_B T \lambda_{B_2}^{\,2}}{\eta}\nabla c_2(r) - \frac{k_B T \lambda_B^{\,2}}{\eta}\nabla c_2(r)\right)\frac{c_2(r)}{K + c_2(r)} \tag{10}$$

$$V_{bi}(r) = -(D_{B_2} - D_B)\nabla\left(\frac{c_2(r)}{K + c_2(r)}\right) \tag{11}$$

here, the diffusion coefficients of the free enzyme and the complex are D_B and D_{B_2}, respectively. $V_{ph}(r)$ is the "phoretic" drift velocity, which arises from the nonspecific interaction potentials between B and ② (e.g., van der Waals, electrostatic, and steric interactions, etc.), and it depends on the Derjaguin length[9] λ—the typical length of these interactions, on the order of a few angstroms for weak interactions to the radius of the enzyme for strong interactions—the viscosity of the medium η, and the temperature T. The other term $V_{bi}(r)$, known as the binding velocity, takes into account the difference between the diffusion coefficients of the free enzyme and the complex. The remaining parameter in this equation is the dissociation constant $K = k_r/k_f$.

Note that even in the absence of nonspecific interactions, there is still the possibility that a gradient is created because of the difference in diffusion properties of the free enzyme and the complex (see Appendix A). Now, we derive an expression for this effective force in the case of two enzymes that share a common substrate, and we look for the optimal conditions to see ProRec activity.

RESULTS AND DISCUSSION

Approximate Analytical Expression for the Excess Concentration of the Mobile Cat. We have not found a full analytical solution to 8 over all parameter values. However, in order to study dependences on parameters, we can develop an approximate solution over limited ranges. First, we assume that the substrate concentration is much smaller than the dissociation constant, $c_2(r)/K \ll 1$. We can expand the total B concentration in terms of $c_2(r)/K$, namely

$$B_T(r) = B_u + \sum_{n=1}^{\infty}\left(\frac{c_2(r)}{K}\right)^n f^{(n)}(r) \tag{12}$$

and solve the equation iteratively. Since the distribution of A is fixed and spherically symmetric, so is $c_2(r)$; additionally, we can limit the expansion mentioned above to a first-order expansion $B_T(r) = B_u + fc_2(r)/K$. If we assume that the gradient of the substrate vanishes around A (specifically, $\partial_r c_2(0) = 0$) and that far away from A, there is no substrate[b] ② ($\lim_{r\to\infty} c_2(r) = 0$), then we can show that f is a constant. We will find its value now.

When we expand to first order in $c_2(r)/K$, we find $c_2(r)/(K + c_2(r)) \approx c_2(r)/K$ and $V_{ph} \approx k_B T \lambda_B^{\,2}\nabla c_2(r)/\eta + O(c_2^{\,2}/K^2)$. Simplifying eq 8 and keeping only first-order terms in $c_2(r)/K$ gives

$$\frac{B_u K}{D_B}\left(\frac{k_B T \lambda_B^{\,2}}{\eta} - \frac{(D_{B_2} - D_B)}{K}\right)\left(\frac{2}{r}\partial_r c_2 + \partial_r^{\,2} c_2\right) = \left(\frac{2}{r}\partial_r c_2 + \partial_r^{\,2} c_2\right) f + \left(\frac{2}{r}c_2 + 2\partial_r c_2\right)\partial_r f + c_2 \partial_r^{\,2} f \tag{13}$$

The unique solution here is for a constant value of f, with

$$f = \frac{B_u}{D_B}\left(\frac{k_B T \lambda_B^{\,2} K}{\eta} - (D_{B_2} - D_B)\right)$$

The boundary conditions on $B_T(r)$ are that there is no derivative at zero and that it limits to B_u at infinity. As we said above, if c_2 satisfies these, then our solution f = constant is the unique one that satisfies the boundary conditions. Thus, for any such $c_2(r)$, the solution is

$$B_T(r) = B_u + \frac{B_u}{D_B}\left(\frac{k_B T \lambda_B^{\,2} K}{\eta} - (D_{B_2} - D_B)\right)\frac{c_2(r)}{K} \tag{14}$$

Note that, to first order in c_2/K, the effect can lead both to an increase or a decrease in the concentration of the agent B. This is because $\lambda_B^{\,2}$ can be either positive or negative, depending on the type of nonspecific interaction between the enzyme and the substrate.

If we assume that the enzyme is a sphere with radius R, we can use the Stokes–Einstein relation $D = k_B T/6\pi\eta R$ to rewrite eq 14 as

$$B_T(r) = B_u\left[1 + (1 + \gamma - \alpha)\frac{c_2(r)}{K}\right] \tag{15}$$

with the nondimensional parameters $\gamma = 6\pi(R_B \lambda_B^{\,2} K)$, which characterizes the strength of the attraction between B and ②, and $\alpha = D_{B_2}/D_B$, which depends only on the diffusion constants of B and the complex B_2.

Now, we choose the same Gaussian distribution of A that produces the concentrations seen in Figure 2 and test the dependence of the overall phenomenon on the parameters. To do that, we calculate the ratio between the total amount of B enzyme within an arbitrary radius R from the location of the enzyme A, which we call the excess B E_B, and some reference amount of B, denoted as B_u, that would be the distribution in the case where there was no gradient of ②

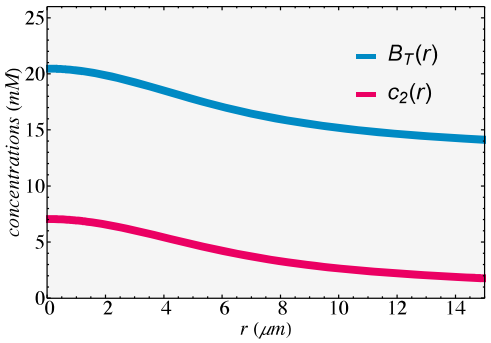

Figure 2. Gradient of the substrate (red) drives recruitment of its cat B (blue) around cat A (localized at the origin) vs distance r.

$$E_B = \frac{\int_R d^3\mathbf{r} B_T(r)}{\frac{4}{3}\pi R^3 B_u} \tag{16}$$

Note that in the case where there is no ② gradient, the excess B is $E_B = 1$.

How the Cat–Cat Attraction Depends on Parameters. Now, we use eq 16 to explore how the cat–cat attraction between A and B depends on the parameters. The diffusion

https://doi.org/10.1021/acs.jpcb.1c04498
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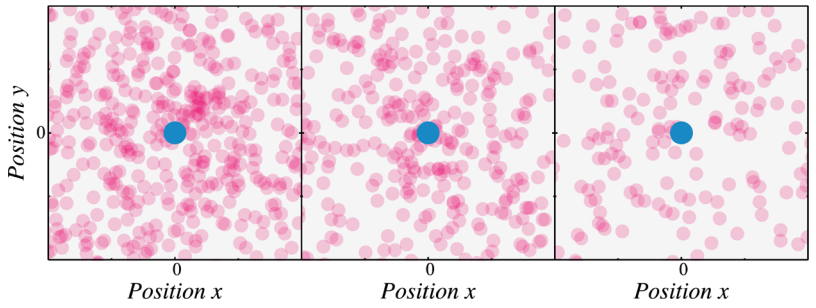

Figure 3. Cloud of B cats around A cats. The three panels from left to right show the effect of decreased affinity (K increases) of B cat to its substrate 2.

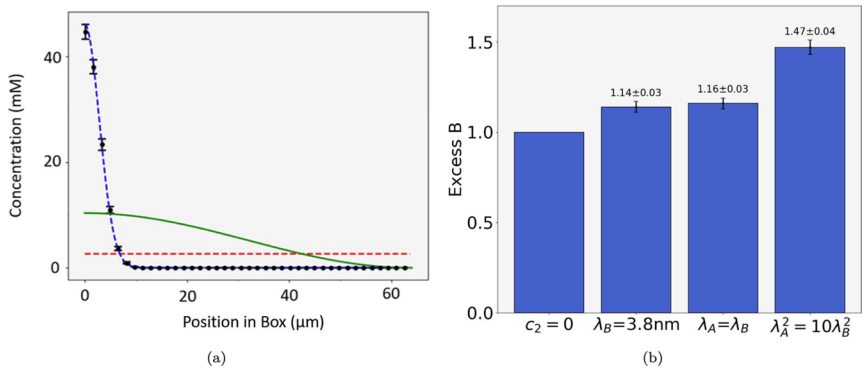

Figure 4. Random walk simulation results demonstrate the catpath effect. (a) Enhancement of cat B around cat A for the c_2 gradient shown in green. The simulated B concentration (black dots) matches the exact B concentration (blue), which can be solved exactly in this case. Cat A is localized near the origin: the ProRec mechanism causes B to be much more abundant in this region than it would be otherwise (the uniform case, shown in red). (b.) Catpath localization is enhanced when a direct A−B attraction is added. When the B−2 attraction parameter λ_B is cranked up to its strongest limits (second bar) and A−B interactions are allowed (third and fourth bars), the amount of total B found around the origin can be 15−50% higher than the uniform case (first bar).

quantity α depends on the change in conformation of the complex with respect to the free enzyme, and its value can range in the interval ∼0.7−1.3, assuming a maximum 30% decrease/increase in the diffusivity of the complex with respect to the free enzyme. In contrast, γ varies throughout the interval $\sim 10^{-4}$ to 10^{-1} (assuming $K \sim 0.1-2$ mM, in the middle of the range for known enzymes, which we believe could be relevant for prebiotic chemistry).

Figure 2 shows the distribution of the total enzyme B compared to the substrate ② when the enzyme A is normally distributed around the origin (see eq 7). Here, we have used[c] K = 2 mM, c_1 = 1 mM, D_2 = 1500 $\mu m^2/s$, a = 3 μm, $N = 10^3$, and the two dimensionless parameters as γ = 0.1 and α = 0.9. As we can see, the presence of the enzyme A localized around the origin forces an excess of B around the same area.

The effect of increasing the parameter K, the dissociation constant of the B−② reaction, is shown in Figure 3. Increasing K decreases the localization of B around A, but only when $\alpha < 1$ (see eq 15, if $\alpha > 1$, the opposite occurs). The weakening of the effect happens because the B molecules spend less time in the slower-diffusing complex when K is larger.

The localization effect is heavily influenced by λ_B, showing more attraction when B and ② have a longer interaction range. The parameter α decreases the localization when it increases, which means that the effect is more evident when the complex diffuses more slowly than the free enzyme. This dependence is the same as the one reported in Mandal and Sen[10] for enzymes exposed to a gradient of their substrate in a microchannel.

Simulations of the Fuller Range of ProRec Dynamical Attractions. Here, we show numerical simulations of the ProRec force in the regime where the localization is very strong; see the Appendix for details. Figure 4a shows that the localization of B is present even with a small gradient of the substrate. The c_2 gradient (green), proportional to cosine squared in this case, created the simulated B distribution shown by the black dots. Each point is time-averaged over 100 simulations steps after the system reached a steady state, with one standard deviation error bars shown. The simulated B concentration is in good agreement with the exact theoretically expected B distribution (the dashed blue curve). The ProRec force led to nearly 9 times the amount of B at the origin when compared to the uniform distribution that would be expected in the absence of ② (the red dashed line).

An additional effect that could boost the size of the ProRec localization is the existence of a direct interaction between the A and B molecules, something we have not considered to this point. These types of cat−cat attractions are hypothesized to be important for the origin of life.[8,11] In Figure 4b, we have plotted the excess B close to the origin in four scenarios: (1) the uniform base case where there is no c_2 gradient, which we have scaled to 1, (2) the case where λ_B = 3.8 nm, toward the upper end of its range, (3) the case where we add an attraction between A and B of the same size as the attraction between B and ② from the last scenario, and (4) the case where $\lambda_A^2 = 10\lambda_B^2$. The reported results for the last three bars are the average enhancements over four different simulations of each condition. The localization effect is already apparent in the

https://doi.org/10.1021/acs.jpcb.1c04498
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case where A and B do not interact, but it is nearly doubled when they have a strong attraction.

Computing the Force of ProRec Attraction between Two Cats. Here, we shift focus from concentration enhancement of cat B around A to their driving force of attraction, which is a mean force in the sense of a diffusion force. It is a stochastic force, in the sense that an average force can be expressed for a gradient in Fick's law diffusion. The force enters in the Smoluchowski equation as the drift component; hence, it is equivalent to the product of the velocity multiplied by the viscosity η. The ProRec force can therefore be calculated directly from the expression in eq 8 by considering the corresponding Langevin dynamics. We then approximate this with the first-order term, to obtain

$$F(r) \approx k_B T\left(\lambda_B^2 + \frac{1 - (D_{B_2}/D_B)}{6\pi R_B K}\right)\nabla c_2(r) \tag{17}$$

Not surprisingly, the ProRec force depends on the gradient of the substrate: a steeper gradient will produce a much stronger attraction, arguably at the expense of the range of the attraction. It is increased for the larger length of interaction between the B agent and the substrate ②. Also, we have focused on cases in which the Derjaguin length $\lambda_B^2 > 0$, indicating an attraction between the enzyme and the substrate. Alternatively, the enzyme and substrate could repel, depending on the shape of the potential.[9] In the $\lambda_B^2 > 0$ case, the force is always attractive as long as $\alpha < 1$, when the complex diffuses more slowly than the free enzyme. When $\alpha > 1$, other interesting phenomena would be predicted.

Relationship of the Catpath Mechanism to Enzyme Chemotaxis and Enhanced Diffusion. Two phenomena have recently been observed that are closely related to the catpath mechanism. (1) Enzyme-enhanced diffusion is when an enzyme diffuses faster or slower in the presence of its substrate. (2) Enzyme chemotaxis is when an enzyme moves toward a gradient of its substrate. In (3) the catpath mechanism, one catalyst attracts another catalyst if they share a common substrate/product. For (1), the enhanced diffusion of enzymes in the presence of their substrates has been widely studied.[12−20] In Weistuch and Presse,[21] it was shown that an enzyme undergoing nondirectional enhanced diffusion can be localized if its substrate gradient has a particular form; in their example, however, the cats were repelled by their substrate in a type of *anti*-catpath mechanism. In the ProRec language, users fled from producers. Experimentally, there has been a controversy around the bulk fluorescence correlation spectroscopy (FCS) experiments used in many measurements of enhanced diffusion.[22,23] More granular single-particle methods showed that artifacts from the FCS procedure could give the appearance of a diffusion enhancement when none actually existed.[24−26] Further experiments appear to have shown that only exergonic enzymes undergo enhanced diffusion, with the enhancement proportional to the free energy release rate of the reaction.[27] Therefore, on the one hand, enhanced diffusion is an expected component of the catpath mechanism but that mechanism is not yet proven experimentally.

For (2), catpath localization could also result from enzymes chemotaxing up gradients of their substrates. Enzyme chemotaxis both up[28] and down[20] substrate gradients has been reported; the latter result is consistent with the conclusion of Weistuch and Presse[21] that enzymes undergoing enhanced diffusion flee from their substrate. In both the up and down cases, the enzymes were driven to flow through a multiple-input single-output microfluidic channel next to their substrates, with a fluorescence measurement used to find the enzyme concentration profiles throughout the channel. Our catpath mechanism is not directly comparable to those measurements, which do not measure the system's steady state.[22]

CONCLUSIONS

We have proposed here a type of nonequilibrium force of attraction that can exist between two nanoscale catalysts, such as enzymes, if they share a substrate/product small molecule in common. This force is quite different from equilibrium attractions, which have long been well-known, described as binding affinities of molecules to each other. In particular, the ProRec force should occur even in the absence of any equilibrium affinity of the catalysts for each other. In principle, this force should be readily measurable by creating a gradient of an enzyme's substrate and using methods such as single-molecule force spectroscopy[29] to determine the attraction of a mobile enzyme in solution. Additionally, after a few modifications, our model of the ProRec attraction could be readily applied as a phenomenological description of other producer−user recruitment systems in biology, such as chemotaxing bacteria. Experimental demonstrations of the ProRec force may have implications for the following phenomena: (1) the engineering of assemblies of spatially colocalized nanoscale catalysts of different types in order to create complex chemical processes and (2) explaining early prebiotic chemical steps that led to today's biochemical pathways in cells.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpcb.1c04498.

> Three exact special-case solutions (diffusion only, all parameters the same between B and the complex, and all parameters the same between B and the complex including an attraction to A) for the system in eq 2; more discussion on the parameter λ_A and a plot of its values for various A−B binding affinities; and further simulation results including (1) an example result using the c_2 distribution in eq 7, (2) a study of how the different parameters affect the simulation results, and (3) a further case showing the impact of λ_A (PDF)

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https://doi.org/10.1021/acs.jpcb.1c04498
J. Phys. Chem. B 2021, 125, 8781−8786

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to thank the Laufer Center for Physical and Quantitative Biology for its support. Luca would like to acknowledge financial support from the National Institutes of Health (NIH award R01GM125813).

■ ADDITIONAL NOTES

[a]Fixing the location of A here allows us to simplify the math so as to keep the model analytical using reaction−diffusion differential equation dynamics, without distorting the physics. We believe that this assumption can be lifted, but then, it would require a numerical treatment instead. We would expect the result to be that, if the enzyme moved slowly enough, a sustained gradient of ② could be produced. The source of this gradient, as seen by the B, would be behind the current position of the A enzyme on its path.

[b]Both of these assumptions are satisfied by a c_2 gradient generated by a Gaussian A distribution.

[c]Note that for this value of N, the concentration of A enzyme localized to the sphere of radius approximately a is on the order of 10 s of micromolar.

■ REFERENCES

(1) Gore, J.; Youk, H.; Van Oudenaarden, A. Snowdrift game dynamics and facultative cheating in yeast. *Nature* **2009**, *459*, 253−256.

(2) Yurtsev, E. A.; Chao, H. X.; Datta, M. S.; Artemova, T.; Gore, J. Bacterial cheating drives the population dynamics of cooperative antibiotic resistance plasmids. *Mol. Syst. Biol.* **2013**, *9*, 683.

(3) Lee, K.-H.; Dinner, A. R.; Tu, C.; Campi, G.; Raychaudhuri, S.; Varma, R.; Sims, T. N.; Burack, W. R.; Wu, H.; Wang, J.; et al. The immunological synapse balances T cell receptor signaling and degradation. *science* **2003**, *302*, 1218−1222.

(4) Dustin, M. L.; Groves, J. T. Receptor signaling clusters in the immune synapse. *Annu. Rev. Biophys.* **2012**, *41*, 543−556.

(5) Gartner, Z. J.; Prescher, J. A.; Lavis, L. D. Unraveling cell-to-cell signaling networks with chemical biology. *Nat. Chem. Biol.* **2017**, *13*, 564−568.

(6) Stevens, C. F. Quantal release of neurotransmitter and long-term potentiation. *Cell* **1993**, *72*, 55−63.

(7) Bradford, J. A.; Dill, K. A. Stochastic innovation as a mechanism by which catalysts might self-assemble into chemical reaction networks. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 10098−10103.

(8) Dill, K. A.; Agozzino, L. Driving forces in the origins of life. *Open Biol.* **2021**, *11*, 200324.

(9) Agudo-Canalejo, J.; Illien, P.; Golestanian, R. Phoresis and enhanced diffusion compete in enzyme chemotaxis. *Nano Lett.* **2018**, *18*, 2711−2717.

(10) Mandal, N. S.; Sen, A. The Relative Diffusivities of Bound and Unbound Protein Can Control Chemotactic Directionality. **2021**, arXiv:2103.13469.

(11) Guseva, E.; Zuckermann, R. N.; Dill, K. A. Foldamer hypothesis for the growth and sequence differentiation of prebiotic polymers. *Proc. Natl. Acad. Sci. U.S.A.* **2017**, *114*, E7460−E7468.

(12) Sengupta, S.; Spiering, M. M.; Dey, K. K.; Duan, W.; Patra, D.; Butler, P. J.; Astumian, R. D.; Benkovic, S. J.; Sen, A. DNA polymerase as a molecular motor and pump. *ACS Nano* **2014**, *8*, 2410−2418.

(13) Riedel, C.; Gabizon, R.; Wilson, C. A. M.; Hamadani, K.; Tsekouras, K.; Marqusee, S.; Pressé, S.; Bustamante, C. The heat released during catalytic turnover enhances the diffusion of an enzyme. *Nature* **2015**, *517*, 227−230.

(14) Illien, P.; Zhao, X.; Dey, K. K.; Butler, P. J.; Sen, A.; Golestanian, R. Exothermicity is not a necessary condition for enhanced diffusion of enzymes. *Nano Lett.* **2017**, *17*, 4415−4420.

(15) Giunta, G. Spatio-Temporal Organization of Enzymatic Reactions. Ph.D. Thesis, Technische Universität München, 2020.

(16) Somasundar, A.; Ghosh, S.; Mohajerani, F.; Massenburg, L. N.; Yang, T.; Cremer, P. S.; Velegol, D.; Sen, A. Positive and negative chemotaxis of enzyme-coated liposome motors. *Nat. Nanotechnol.* **2019**, *14*, 1129−1134.

(17) Pressé, S. A thermodynamic perspective on enhanced enzyme diffusion. *Proc. Natl. Acad. Sci. U.S.A.* **2020**, *117*, 32189−32191.

(18) Jee, A.-Y.; Chen, K.; Tlusty, T.; Zhao, J.; Granick, S. Enhanced diffusion and enzyme dissociation at high substrate concentration. *Bull. Am. Phys. Soc.* **2020**, *65*.

(19) Jee, A.-Y.; Cho, Y.-K.; Granick, S.; Tlusty, T. Catalytic enzymes are active matter. *Proc. Natl. Acad. Sci. U.S.A.* **2018**, *115*, E10812−E10821.

(20) Jee, A.-Y.; Dutta, S.; Cho, Y.-K.; Tlusty, T.; Granick, S. Enzyme leaps fuel antichemotaxis. *Proc. Natl. Acad. Sci. U.S.A.* **2018**, *115*, 14−18.

(21) Weistuch, C.; Pressé, S. Spatiotemporal organization of catalysts driven by enhanced diffusion. *J. Phys. Chem. B* **2017**, *122*, 5286−5290.

(22) Feng, M.; Gilson, M. K. Enhanced diffusion and chemotaxis of enzymes. *Annu. Rev. Biophys.* **2020**, *49*, 87−105.

(23) Kandula, H. N.; Jee, A.-Y.; Granick, S. Robustness of FCS (fluorescence correlation spectroscopy) with quenchers present. *J. Phys. Chem. A* **2019**, *123*, 10184−10189.

(24) Chen, Z.; Shaw, A.; Wilson, H.; Woringer, M.; Darzacq, X.; Marqusee, S.; Wang, Q.; Bustamante, C. Single-molecule diffusometry reveals no catalysis-induced diffusion enhancement of alkaline phosphatase as proposed by FCS experiments. *Proc. Natl. Acad. Sci. U.S.A.* **2020**, *117*, 21328−21335.

(25) Xu, M.; Ross, J. L.; Valdez, L.; Sen, A. Direct single molecule imaging of enhanced enzyme diffusion. *Phys. Rev. Lett.* **2019**, *123*, 128101.

(26) Günther, J.-P.; Börsch, M.; Fischer, P. Diffusion measurements of swimming enzymes with fluorescence correlation spectroscopy. *Acc. Chem. Res.* **2018**, *51*, 1911−1920.

(27) Jee, A.-Y.; Tlusty, T.; Granick, S. Master curve of boosted diffusion for 10 catalytic enzymes. *Proc. Natl. Acad. Sci. U.S.A.* **2020**, *117*, 29435−29441.

(28) Zhao, X.; Palacci, H.; Yadav, V.; Spiering, M. M.; Gilson, M. K.; Butler, P. J.; Hess, H.; Benkovic, S. J.; Sen, A. Substrate-driven chemotactic assembly in an enzyme cascade. *Nat. Chem.* **2018**, *10*, 311−317.

(29) Pelz, B.; Žoldák, G.; Zeller, F.; Zacharias, M.; Rief, M. Subnanometre enzyme mechanics probed by single-molecule force spectroscopy. *Nat. Cmmun.* **2016**, *7*, 10848.