

**Michaelis-Menten reaction scheme as a unified approach towards the optimal restart problem**Tal Rotbart,<sup>1</sup> Shlomi Reuveni,<sup>2,\*</sup> and Michael Urbakh<sup>1</sup><sup>1</sup>*School of Chemistry, Tel-Aviv University, Tel-Aviv 69978, Israel*<sup>2</sup>*Department of Systems Biology, Harvard Medical School, 200 Longwood Avenue, Boston, Massachusetts 02115, USA*

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We study the effect of restart, and retry, on the mean completion time of a generic process. The need to do so arises in various branches of the sciences and we show that it can naturally be addressed by taking advantage of the classical reaction scheme of Michaelis and Menten. Stopping a process in its midst—only to start it all over again—may prolong, leave unchanged, or even shorten the time taken for its completion. Here we are interested in the optimal restart problem, i.e., in finding a restart rate which brings the mean completion time of a process to a minimum. We derive the governing equation for this problem and show that it is exactly solvable in cases of particular interest. We then continue to discover regimes at which solutions to the problem take on universal, details independent forms which further give rise to optimal scaling laws. The formalism we develop, and the results obtained, can be utilized when optimizing stochastic search processes and randomized computer algorithms. An immediate connection with kinetic proofreading is also noted and discussed.

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**Introduction.** When engaged in a specific task for a time period that extends beyond our initial expectations, we are constantly faced with two alternatives—either keep on going or stop everything and start anew. Every now and then we opt for the latter, hoping that a fresh start will break off an unproductive course of action and expedite the completion of the task at hand. This decision could, however, turn out to be counterproductive—nipping an awaited, but unforeseen, finale in the bud. To restart, or not to restart, that is therefore the question.

Not at all unique to our everyday lives, a “dilemma” similar to the one described above is relevant to virtually any physical, chemical, or biological process that can be restarted. Most notably, restart (or unbinding) is an integral part of the renown Michaelis-Menten reaction scheme (MMRS) illustrated in Fig. 1 [1]. Originally devised to describe enzymatic catalysis, the MMRS has attracted considerable scientific interest for more than a century [2]. Indeed, nature is full with an astonishing variety of Michaelian processes. DNA-DNA hybridization, antigen-antibody binding, and various other molecular processes can all be described by the MMRS [3]. That and more, the simplicity and generality of the scheme have rendered it widely applicable and it is now used to describe anything from heterogeneous catalysis [4–6] to in vivo target search kinetics [7]. As a matter of fact, one can easily convince himself that *any* first passage time (FPT) process [8]—be it the time to target of a simple Brownian particle, or that of more sophisticated stochastic processes [9–12] and random searchers [13–15]—can become subject to restart [16–22] and is then naturally accommodated by the MMRS. Wishing to acquire a unified view on restart phenomena we identify the MMRS as an ideal object of study.

Central to our understanding of the MMRS is the Michaelis-Menten (MM) equation [1]. This equation provides a hundred-year-old prediction by which any increase in the rate of unbinding (restart) will inevitably slow down the rate of enzymatic turnover or, equivalently, prolong the completion time of any process that falls into the MMRS

category. Surprisingly, this prediction was never tested experimentally, but rapid advancements in single-molecule techniques [23–25] have recently motivated us to question it from a theoretical perspective [26]. Contrary to the classical result, we have found that unbinding may also facilitate the successful completion of a reaction. In the emerging picture, a nontrivial solution to the restart dilemma is given by an optimal unbinding rate which strikes the right balance between the need to abort prolonged reaction cycles and the need to avoid premature termination of ongoing ones. Similar observations were made in the context of search processes [17] and, in particular, in the context of DNA search [16] where the authors analyzed facilitated diffusion [27] from a very general perspective. The optimal restart rate depends, however, on the full distribution of the underlying FPT process (catalysis in the case of enzymatic reactions) [26], and the question of what can be said about it in the general case remained open.

In this Rapid Communication, we address the optimal restart problem within the framework of the MMRS. First, the governing equation for this problem, Eq. (3) below, is derived and solved exactly in several cases that are of particular interest. We then show that, in the general case, there are two regimes at which solutions to the problem are universal. These solutions are given in Eqs. (4) and (5). The applicability of our approach is widespread as it allows one to incorporate restart into an existing, generic, FPT problem in an almost plug and play manner.

**The optimal restart problem.** In formulating the optimal restart problem we adopt the terminology of enzymatic reactions (Fig. 1) and consider a scenario in which the processes of binding, unbinding, and catalysis are all stochastic [28]. This probabilistic viewpoint, whose origins can be traced back to the work of Ninio [29], has found one of its prime applications in the analysis of single molecule experiments [23,30–32], and is now well established theoretically [33–35]. Defining the turnover rate  $k_{\text{turn}}$  as the reciprocal of the turnover time—the mean FPT required to complete the reaction cycle—we will be interested in the turnover-unbinding interplay.

When binding, unbinding, and catalysis times are exponentially distributed with rates  $k_{\text{on}}[S]$  ( $[S]$  being the concentration of the substrate),  $k_{\text{off}}$ , and  $k_{\text{cat}}$ , respectively, the single molecule

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FIG. 1. (Color online) The Michaelis-Menten reaction scheme. An enzyme  $E$  can reversibly bind a substrate  $S$  to form a complex  $ES$ . The substrate can then be converted by the enzyme to form a product  $P$  or, alternatively, unbind. The conversion of the substrate to a product is manifested via the process of enzymatic catalysis. Following either catalysis or unbinding, the enzyme is free to act on additional substrate molecules.

MM equation is attained [33]:

$$k_{\text{turn}} = \frac{k_{\text{cat}}[S]}{[S] + K_M}, \quad (1)$$

with  $K_M = (k_{\text{off}} + k_{\text{cat}})/k_{\text{on}}$  (note that, in contrast to other rates in the MM equation, the turnover “rate” is not a rate in the “exponential sense”). In this case, the memoryless property of the exponential distribution asserts that the time remaining until the completion of an ongoing catalytic step, given its age, is exponential and statistically identical to that of a newly started catalytic step. It is therefore clear (see  $K_M$  above) that  $k_{\text{turn}}$  is a monotonically decreasing function of the rate  $k_{\text{off}}$ .

Nonexponential time distributions are, however, quite common in a variety of complex systems [36–40], and it has recently been recognized that enzymes are no exception in that regard [23,32,41,42]. This result is perhaps not surprising as catalysis is intrinsically coupled to the enzyme’s internal degrees of freedom via a complex energy landscape [43] which can give rise to strong deviations from exponentiality and other anomalies [44–48]. Renewal theory can then be invoked to provide a generalized mathematical treatment of the MMRS [26]. A completely general analysis of the turnover-unbinding interplay is then very hard, but progress can be made if

one narrows down to the case of exponentially distributed unbinding times [26,33]. Letting  $k_{\text{off}}$  denote the unbinding rate (assumed to be independent of the catalytic process), and  $f_{\text{cat}}(t)$  the probability density function of a generally distributed catalysis time  $T_{\text{cat}}$ , it is possible to show that [26,33]

$$k_{\text{turn}} = \frac{\hat{f}_{\text{cat}}(k_{\text{off}})}{\langle T_{\text{on}} \rangle + k_{\text{off}}^{-1}[1 - \hat{f}_{\text{cat}}(k_{\text{off}})]}, \quad (2)$$

where  $\hat{f}_{\text{cat}}(k) = \int_0^\infty f_{\text{cat}}(t)e^{-kt} dt$  is the Laplace transform of  $f_{\text{cat}}(t)$ , and  $\langle T_{\text{on}} \rangle$  is the mean of a generally distributed binding time. Equation (2) extends the classical result of Michaelis and Menten and brings new physics. Indeed, an interesting corollary of Eq. (2) is the possibility of restart-facilitated turnover, i.e., a regime in which *unproductive* unbinding events lead to accelerated turnover [26]. This type of counterintuitive behavior is categorically precluded by the classical MM equation and is therefore considered “nonclassical” or “anomalous.”

In Fig. 2(a) we use Eq. (2) to plot  $k_{\text{turn}}$  as a function of  $k_{\text{off}}$  for different catalysis time distributions (CTDs). An asymptotic decay of  $k_{\text{turn}}$  to zero at large  $k_{\text{off}}$  directly follows from Eq. (2), is common to all plots, and is therefore not shown. At intermediate  $k_{\text{off}}$ , however, unbinding can be either *inhibitory* ( $\partial k_{\text{turn}}/\partial k_{\text{off}} < 0$ ) or *excitatory* ( $\partial k_{\text{turn}}/\partial k_{\text{off}} > 0$ ) and the surprise comes from the fact that the latter implies the *breaking* of the classical limit for maximal turnover rates:  $k_{\text{turn}}(0) = (\langle T_{\text{on}} \rangle + \langle T_{\text{cat}} \rangle)^{-1}$ . Maximal turnover rates, and the unbinding rates at which they are attained, can however vary considerably. What therefore determines if unbinding will enhance turnover, and what sets the maximizing unbinding rate  $k_{\text{off}}^{\text{max}}$ ?

*The fundamental equation of optimal restart.* In order to address the questions presented above we first derive a governing equation for the optimal restart problem. Namely, we show [49] that the stationary points of the turnover rate are

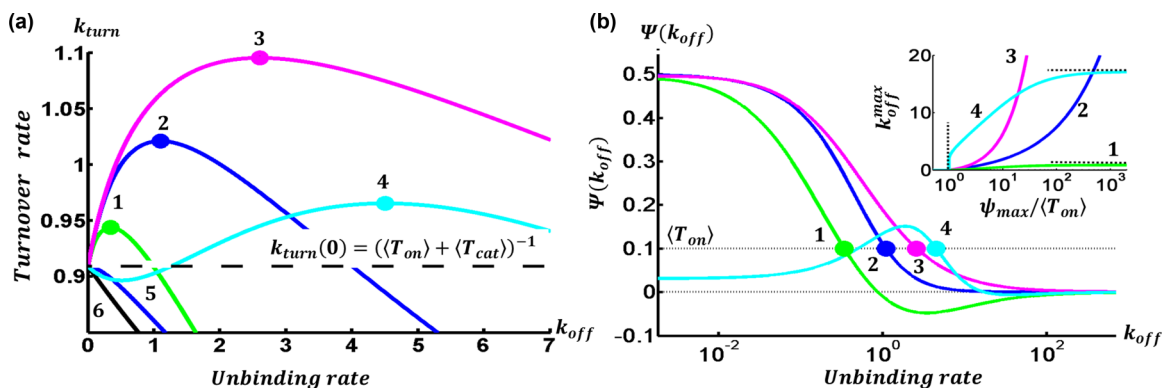


FIG. 2. (Color online) (a) Turnover rate vs unbinding (restart) rate for different catalysis time distributions [(1) log normal, (2) double exponential, (3) Weibul, (4) double Erlang, (5) double exponential, (6) exponential] [49]. Contrary to classical theory, nonmonotonic dependencies are possible and the classical upper limit on turnover rates (dashed) can be broken. Heterogeneity is observed despite the fact that  $\langle T_{\text{on}} \rangle = 0.1$  in all instances, all underlying time distributions share a mean of  $\langle T_{\text{cat}} \rangle = 1$ , and some even share the same variance [ $\sigma^2(T_{\text{cat}}) = 2$  for distributions Nos. 1–3]. Maxima in turnover rates are denoted by full circles. (b) A graphical illustration of the fundamental equation of optimal restart [Eq. (3)]. Extrema of the turnover rate are obtained at points where  $\Psi(k_{\text{off}})$  intersects the mean binding time  $\langle T_{\text{on}} \rangle$ . Maxima from panel (a) are once again denoted by full circles. Lines for distributions Nos. 5–6, where  $\Psi(k) \leq 0$ , are not drawn. Note that line No. 4 intersects  $\langle T_{\text{on}} \rangle$  twice, first with a positive slope (minimum of  $k_{\text{turn}}$ ) and then with a negative slope (maximum of  $k_{\text{turn}}$ ). Inset (b):  $k_{\text{off}}^{\text{max}}$  vs  $\Psi_{\text{max}}/\langle T_{\text{on}} \rangle$ . When  $\langle T_{\text{on}} \rangle > \Psi_{\text{max}}$ ,  $k_{\text{off}}^{\text{max}} = 0$ . As  $\langle T_{\text{on}} \rangle$  drops  $\Psi_{\text{max}}$ , a maxima may develop gradually (lines Nos. 1–3) or abruptly (line No. 4). As  $\langle T_{\text{on}} \rangle$  approaches zero,  $k_{\text{max}}$  can either diverge (lines No. 2 and 3) or asymptotically converge to a plateau (lines No. 1 and 4).

the solutions of

$$\Psi(k) \equiv \frac{\hat{f}_{\text{cat}}(k)[\hat{f}_{\text{cat}}(k) - 1]}{k^2 d \hat{f}_{\text{cat}}(k)/dk} - \frac{1}{k} = \langle T_{\text{on}} \rangle, \quad (3)$$

where the function  $\Psi(k)$  is uniquely determined by the CTD. Moreover, we show that  $\Psi(k)$  has the following property:  $\partial k_{\text{turn}}/\partial k_{\text{off}} > 0 \iff \Psi(k) > \langle T_{\text{on}} \rangle$  and vice versa. Consequently, a local maximum of the turnover rate is attained at an unbinding rate,  $k_{\text{off}}^{\text{max}}$ , which satisfies  $\Psi(k_{\text{off}}^{\text{max}}) = \langle T_{\text{on}} \rangle$  and  $\Psi'(k_{\text{off}}^{\text{max}}) < 0$ .

Equation (3) clarifies the role of binding in our problem. Restart and the initiation of a new turnover attempt, inevitably involve a “penalty”—the necessity to go through the binding process all over again. Taking the perspective of turnover rate maximization, lengthy binding times are hence a deterrent against restart and rapid binding an incentive to it. In perfect accord with this intuition, we note that a maximum in  $k_{\text{turn}}$  will develop if and only if  $\langle T_{\text{on}} \rangle$  drops below the critical value of  $\Psi_{\text{max}} \equiv \max_{k>0} \{\Psi(k)\}$ . Indeed, since  $k_{\text{turn}}$  is positive and asymptotically decays to zero as  $k_{\text{off}} \rightarrow \infty$ ,  $\Psi(k)$  will eventually intersect any level in the range  $\Psi_{\text{max}} > \langle T_{\text{on}} \rangle > 0$  with a negative slope (provided  $\Psi_{\text{max}} > 0$ ) [50]. In particular, a maximum in  $k_{\text{turn}}$  will develop whenever  $\langle T_{\text{on}} \rangle$  drops below  $\Psi_0 \equiv \Psi(0)$ —an observation that will come in handy later on. These properties of  $\Psi(k)$  are graphically illustrated in Fig. 2(b).

*A classical example and a family of exactly solvable cases.* The importance of Eq. (3) cannot be overstated as it allows one to find optimal restart rates for generic FPT processes. In order to demonstrate the power of this formalism, we will now reanalyze a problem studied by Evans and Majumdar in [17]. Consider a particle searching for a stationary target via one-dimensional diffusion. Setting the initial distance between the particle and target to  $L$  and the diffusion coefficient to  $D$ , it has long been known that the mean FPT to the target diverges. What happens, however, if the particle is returned (restarted) to its initial position with some given rate  $k_{\text{off}}$  (assume  $\langle T_{\text{on}} \rangle = 0$ )? Well, since the FPT distribution of the original problem is known to be given by  $\hat{f}_{\text{cat}}(k) = e^{-\sqrt{kL^2/D}}$  (Laplace space representation of the Lévy-Smirnov distribution), it immediately follows that the mean FPT of the restarted problem is given by  $k_{\text{turn}}^{-1}$  in Eq. (2)—and we further note that it is finite for any positive restart rate. In fact, this is true for any  $\hat{f}_{\text{cat}}(k)$ , and as long as  $\langle T_{\text{on}} \rangle$  is finite, but is particularly striking when the underlying FPT process is equipped with an infinite mean. Moreover, by solving Eq. (3) one can see that  $k_{\text{off}}^{\text{max}} = (z^*)^2 D/L^2$ , where  $z^* \simeq 1.59362\dots$  is the solution to  $z/2 = 1 - e^{-z}$ . Clearly, the same modulus operandi can also be used to study the effect of restart on many other FPT classics [8]. In particular, one could readily generalize the above example for the one sided Lévy distribution  $\hat{f}_{\text{cat}}(k) = e^{-(\tau k)^\alpha}$  ( $0 < \alpha < 1$ ) to obtain  $k_{\text{off}}^{\text{max}} = (z^*)^{1/\alpha}/\tau$ , where  $z^*$  is the solution to  $\alpha z = 1 - e^{-z}$ .

Analytical solutions to Eq. (3) are hard to find. It is thus interesting to note that whenever the Laplace transform of the CTD has the following form:  $\hat{f}_{\text{cat}}(k) = (1 + ak)/(1 + bk + ck^2)$  (for some constants  $a$ ,  $b$ , and  $c$ ), Eq. (3) reduces to a quadratic and is hence exactly solvable. A particular example in this category is the exponential distribution,  $f_{\text{cat}}(t) = \lambda e^{-\lambda t}$  ( $\lambda > 0$ ), for which  $a = c = 0$ ,  $b = \frac{1}{\lambda}$ , and  $\Psi(k) = 0$ .

As another example, think of the double-exponential distribution,  $f_{\text{cat}}(t) = p\lambda_1 e^{-\lambda_1 t} + (1-p)\lambda_2 e^{-\lambda_2 t}$  ( $0 < p < 1, \lambda_1 > 0, \lambda_2 > 0$ ), for which  $a = \frac{1}{\lambda_1} + p(\frac{1}{\lambda_2} - \frac{1}{\lambda_1})$ ,  $b = \frac{1}{\lambda_2} + \frac{1}{\lambda_1}$ ,  $c = \frac{1}{\lambda_1 \lambda_2}$ , and  $\Psi(k) = (\frac{p\lambda_1 + (1-p)\lambda_2}{(1-p)p(\lambda_1 - \lambda_2)^2} k^2 + \frac{2(\lambda_1 \lambda_2)}{(1-p)p(\lambda_1 - \lambda_2)^2} k + \frac{\lambda_1 \lambda_2 [(1-p)\lambda_1 + p\lambda_2]}{(1-p)p(\lambda_1 - \lambda_2)^2})^{-1}$ . Finally, and perhaps most importantly, consider the class of distributions which do not fall into the above-mentioned form, but can rather be *asymptotically* approximated by it. As we hereby show, the basin of attraction for this class is wide, rendering asymptotic solutions to the optimal restart problem (almost) universal.

*Universal behavior at  $\langle T_{\text{on}} \rangle \approx \Psi_0$ .* When  $\langle T_{\text{on}} \rangle$  approaches  $\Psi_0$ , “small  $k$ ” solutions to Eq. (3) are anticipated provided  $\Psi_0 > 0$  [see Fig. 2(b)]. One can then try and approximate  $\Psi(k)$ , at small  $k$ , considering that in this limit  $\hat{f}_{\text{cat}}(k) \simeq 1 + \sum_{n=1}^m \frac{M_n (-k)^n}{n!}$ , where  $M_n \equiv \langle T_{\text{cat}}^n \rangle$  is the  $n$ th moment of the CTD. It can then be verified, utilizing the definition of  $\Psi(k)$ , that this expansion must be carried out to third order in  $k$  ( $m = 3$ ), if it were to correctly capture  $\Psi(k)$  to first order. However, under direct substitution of such an expansion into  $\Psi(k)$ , Eq. (3) becomes a fourth order equation and further analytical advancement becomes extremely cumbersome.

To circumvent this difficulty, we make use of the widely applied Padé approximation scheme [51] and try  $\hat{f}_{\text{cat}}(k) \simeq (1 + ak)/(1 + bk + ck^2)$ . Doing so, we note that this approximation (i) can be made exact to third order in  $k$  by proper choice of the constants  $a$ ,  $b$ , and  $c$  [49]; (ii) decays to zero as  $k \rightarrow \infty$ , as required from a Laplace transform, and in sharp contrast to the divergences of any power series expansion; and (iii) renders the solution to Eq. (3) immediate as it gives for  $k \ll 1$  [49]:  $\Psi(k) \simeq \frac{\Psi_0}{1 + 2R_0(\Psi_0 k) + R_0(1 + R_0)(\Psi_0 k)^2}$ , where  $\Psi_0 = (M_2 - 2M_1^2)/2M_1$  and  $R_0 = \frac{2M_1 M_3 - 3M_2^2}{3(M_2 - 2M_1^2)^2}$ . We now see that in this limit solutions to the optimal unbinding problem are insensitive to fine details of the CTD as they are governed by  $\Psi_0$  and  $R_0$  only.

As we have previously observed, the *introduction* of unbinding is asserted to speed up turnover whenever  $\langle T_{\text{on}} \rangle < \Psi_0$  since this implies  $\frac{\partial k_{\text{turn}}}{\partial k_{\text{off}}}|_{k_{\text{off}}=0} > 0$ . The newly derived expression for  $\Psi_0$  allows us to interpret this result probabilistically. Indeed, setting  $k_{\text{off}}$  to zero, it is easy to see that  $\langle T_{\text{on}} \rangle < \Psi_0$ , if and only if, the mean duration,  $\langle T_{\text{on}} \rangle + \langle T_{\text{cat}} \rangle$ , of a new turnover cycle drops below the mean *residual* duration,  $\frac{1}{2} \langle T_{\text{cat}}^2 \rangle / \langle T_{\text{cat}} \rangle$ , of an ongoing catalytic step [52]. Unbinding will then have an excitatory effect but two distinct scenarios should nevertheless be told apart.

When  $R_0 > 0$ ,  $\Psi'(0) < 0$  [e.g., lines No. 1–3 in Fig. 2(b)] and, as  $\langle T_{\text{on}} \rangle$  approaches  $\Psi_0$  from above and crosses over to its other side, a *maximum* of the turnover rate *gradually develops* at

$$k_{\text{off}}^{\text{max}} \simeq \frac{1}{(1 + R_0)\Psi_0} \left( \sqrt{\left(1 + \frac{1}{R_0}\right) \frac{\Psi_0}{\langle T_{\text{on}} \rangle} - \frac{1}{R_0} - 1} \right). \quad (4)$$

In particular, setting  $\Delta = \langle T_{\text{on}} \rangle^{-1} - \Psi_0^{-1}$ , we observe that to first order  $k_{\text{off}}^{\text{max}} \simeq \frac{\Delta}{2R_0}$ . This characteristic dependence is further discussed in Fig. S1 [49].

On the other hand, when  $R_0 < 0$  [e.g., line No. 4 in Fig. 2(b)],  $\Psi'(0) > 0$ , and  $\Psi(k)$  has a local maxima at some  $k^* > 0$ . Then, as  $\langle T_{\text{on}} \rangle$  first hits  $\Psi(k^*)$  from above, both a

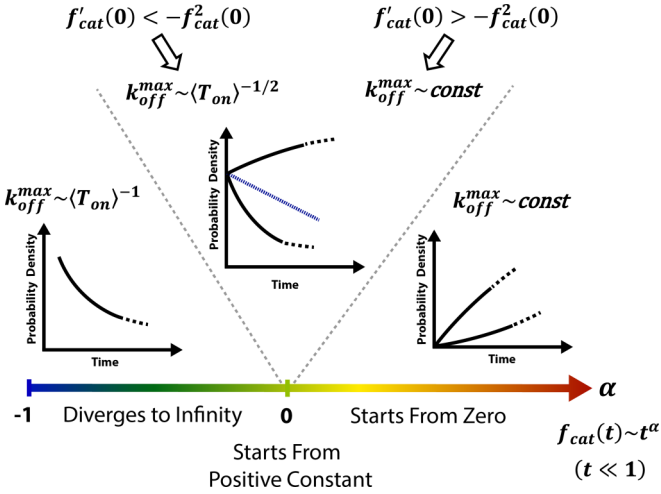


FIG. 3. (Color online) Asymptotics of the optimal restart problem, at fast binding times, is governed by the behavior of the catalysis time distribution near the origin.

minimum and a maximum of  $k_{\text{turn}}^{\text{max}}$  abruptly appear [see “jump” in  $k_{\text{off}}^{\text{max}}$ , inset of Fig. 2(b)]. As  $\langle T_{\text{on}} \rangle$  continues to decrease, these two extrema drift apart and it is important to observe that the small  $k$  solution to Eq. (3) is then a *minimum*, rather than a maximum. As  $\langle T_{\text{on}} \rangle$  drops below  $\Psi_0$ , this minimum necessarily disappears, leaving behind a maximum of  $k_{\text{turn}}^{\text{max}}$  at a point  $k_{\text{off}}^{\text{max}}$  which is *strictly separated* from zero. Before moving forward, we note in passing that  $R_0 < 0$  if and only

if the residual duration of an ongoing catalytic step has a coefficient of variation that is smaller than unity.

We end this section by noting that when the catalysis time distribution is “heavy tailed”, as happens in a wide variety of FPT problems, either one of its first two moments can diverge. An abrupt phase transition is then observed,  $\Psi(k \rightarrow 0) = \infty$ , and the *introduction* of unbinding is asserted to speed up turnover regardless of  $\langle T_{\text{on}} \rangle$ . The asymptotic behavior of  $k_{\text{off}}^{\text{max}}$  at high values of  $\langle T_{\text{on}} \rangle$  then depends on the tail of the catalysis time distribution ( $t \rightarrow \infty$ ), and it can be shown [49] that for  $f(t) \sim t^{-(1+\alpha)}$  with  $0 < \alpha < 1$  ( $1 < \alpha < 2$ ),  $k_{\text{off}}^{\text{max}} \sim \langle T_{\text{on}} \rangle^{-1}$  ( $k_{\text{off}}^{\text{max}} \sim \langle T_{\text{on}} \rangle^{-1/(2-\alpha)}$ ). One example for this type of behavior is the above-mentioned case of diffusion mediated search for which  $\alpha = 1/2$ .

*Universal behavior at fast binding times.* When  $\langle T_{\text{on}} \rangle$  approaches zero, “large  $k$ ” solutions to Eq. (3) are anticipated provided  $\Psi(k)$  is asymptotically positive [see Fig. 2(b)]. The behavior of  $\Psi(k)$  in this limit is governed by the behavior of  $f_{\text{cat}}(t)$  at short times and we proceed by assuming that  $f_{\text{cat}}(t) \sim t^\alpha$  ( $t \ll 1$ ). Three different regimes, illustrated in Fig. 3, are then noteworthy [49]. When  $-1 < \alpha < 0$ ,  $\Psi(k)$  approaches zero from above as  $\sim k^{-1}$ , and  $k_{\text{off}}^{\text{max}} \sim \langle T_{\text{on}} \rangle^{-1}$ . On the other hand, when  $\alpha > 0$ ,  $\Psi(k)$  approaches zero from below as  $\sim -k^{-1}$ , there are no “large  $k$ ” solutions to Eq. (3), and  $k_{\text{off}}^{\text{max}}|_{\langle T_{\text{on}} \rangle=0}$  is finite (can be zero).

The case  $\alpha = 0$  is a bit more delicate. Assuming  $f_{\text{cat}}(t)$  has a Taylor expansion near the origin we denote  $\omega_n = n! [(-\frac{\partial}{\partial t})^{n-1} f_{\text{cat}}(t)]|_{t=0}$  and note that by construction  $\omega_1 = f_{\text{cat}}(0) > 0$ . Implementing a treatment similar to the one given in the previous section we find for  $k \gg 1$  [49]:

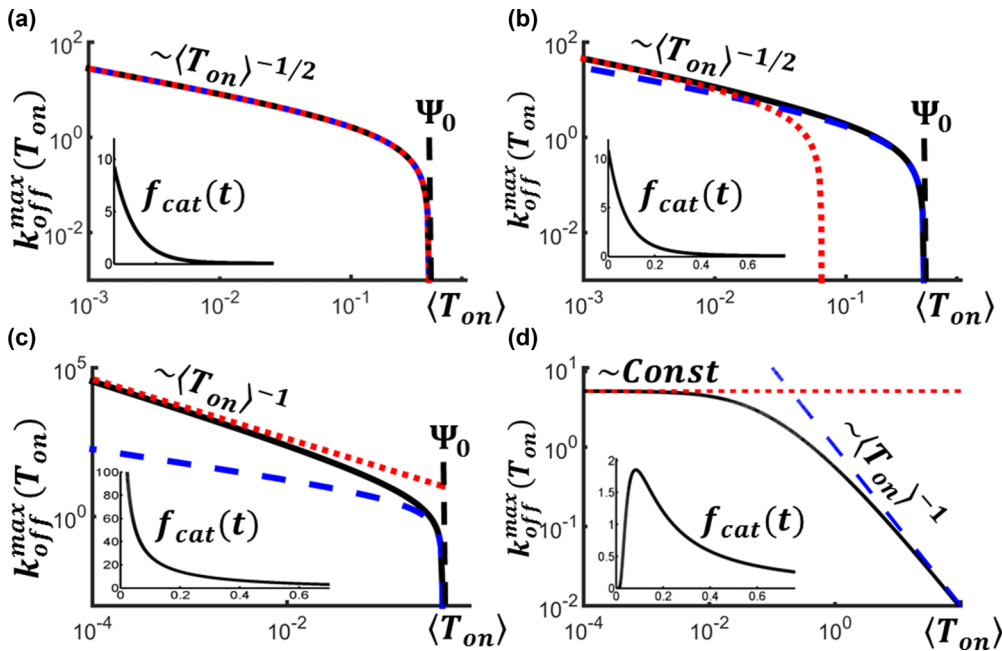


FIG. 4. (Color online) Optimal unbinding (restart) rate vs mean binding time for different catalysis time distributions. The solid (black), dashed (blue), and dotted (red) curves correspond to  $k_{\text{off}}^{\text{max}}$ , and to asymptotic approximations of  $k_{\text{off}}^{\text{max}}$  in the  $\langle T_{\text{on}} \rangle \rightarrow \Psi_0$ , and  $\langle T_{\text{on}} \rangle \rightarrow 0$ , limits respectively. Distributions [(a) double exponential, (b) triple exponential, (c) gamma, and (d) Lévy-Smirnov] are drawn at the bottom left corner of each panel [49]. Dashed (blue) lines in panels (a)–(c) are drawn according to Eq. (4). A phase transition occurs in panel (d) where  $\langle T_{\text{cat}} \rangle = \infty$  and asymptotics is governed by a  $\sim \langle T_{\text{on}} \rangle^{-1}$  scaling law. Dotted (red) lines in panels (a) and (b) are drawn according to Eq. (5). A different behavior is found in panels (c) and (d), in accord with the  $t \rightarrow 0$  asymptotics of  $f_{\text{cat}}(t)$  and the scaling laws that are summarized in Fig. 3. Note how in panel (a) the exact solution coincides with the asymptotic approximations as expected.

$\Psi(k) \simeq \frac{\chi_\infty/k^2}{1+2R_\infty(\chi_\infty/k)+R_\infty(1+R_\infty)(\chi_\infty/k)^2}$ , where  $R_\infty = \frac{2\omega_1\omega_3-3\omega_2^2}{3(\omega_2-2\omega_1^2)^2}$  and  $\chi_\infty = (\omega_2 - 2\omega_1^2)/2\omega_1$  [compare with  $\Psi(k)$  for  $k \ll 1$  above]. A large  $k$  solution to Eq. (2) is then found only when  $f_{\text{cat}}(t)$  decreases steeply enough near the origin, i.e., when  $f'_{\text{cat}}(0) < -f''_{\text{cat}}(0) \iff \chi_\infty > 0$ , and is given by

$$k_{\text{off}}^{\text{max}} = \chi_\infty \left( \sqrt{\frac{1}{\langle T_{\text{on}} \rangle \chi_\infty}} - R_\infty - R_\infty \right). \quad (5)$$

In particular, note that in this case  $k_{\text{off}}^{\text{max}} \sim \langle T_{\text{on}} \rangle^{-1/2}$ . On the other hand, when  $\chi_\infty < 0$ , we once again find that  $k_{\text{off}}^{\text{max}}|_{\langle T_{\text{on}} \rangle=0}$  is a constant.

**Conclusions.** In this Rapid Communication we took advantage of the Michaelis-Menten reaction scheme to provide a unified analysis of the optimal restart problem. The incorporation of restart into an existing first passage time problem modifies its behavior. The mean first passage time then becomes a function of the restart rate and the question of optimality naturally arises. Here, we have developed a formalism which can be used in order to study the effect of restart on generic first passage time problems. A prime corollary of our study is the identification of two regimes at which the optimal restart rate displays universal behavior in the sense that it is solely governed by a handful of key parameters (see Fig. 4 for illustration). The results we have obtained are applicable to many fields. In particular, we note that randomized computer algorithms [53,54] often exhibit heavy tailed run time distributions [55,56] and restart could hence drastically improve performance in these cases and others [57,58].

The optimal restart problem is intimately related with the idea of kinetic proofreading. Independently proposed by Hopfield [59] and Ninio [29], and studied by multiple authors

since [60–68], the kinetic proofreading scheme suggests a way in which an enzyme can amplify *small differences* in the unbinding rates of two substrates—one right, the other one wrong, such that  $k_{\text{off}}^{\text{wrong}} > k_{\text{off}}^{\text{right}}$ —in order to discriminate them with *high fidelity*. The basic idea is that by molding the catalysis time distribution, for example into something that resembles a sharp delay, the ratio between the right and wrong turnover rates can be made arbitrarily large. Consider now a case in which one is provided with a desired profile of the turnover rate as a function of the unbinding (restart) rate, and is then asked to conjure a catalysis (i.e., first passage) time distribution that would yield this profile. For example, think of a scenario in which an enzyme wishes to select only the substrates whose unbinding rates fall within a small range (bandpass filter), or above (below) some cutoff [high (low) pass filter]. How could this be done? Quite surprisingly, a formal solution to this highly nontrivial problem can be readily obtained by solving Eq. (2) for  $\hat{f}_{\text{cat}}(k_{\text{off}})$  given  $k_{\text{turn}}(k_{\text{off}})$  [69]. This observation paves the way towards intelligent design of “Michaelian filters,” a concept which we will further develop elsewhere.

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