The Michaelis-Menten reaction scheme
as a unified approach towards the optimal restart problem

Tal Rotbart†,∗, Shlomi Reuveni‡,∗, and Michael Urbakh†
†School of Chemistry, Tel-Aviv University, Tel-Aviv 69978, Israel
‡Department of Systems Biology, Harvard Medical School,
200 Longwood Avenue, Boston, Massachusetts 02115, USA.
∗, †T. Rotbart and S. Reuveni had equal contribution to this work.

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 & 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.

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 counter-productive—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 on-growing 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 non-trivial 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 letter, 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 & 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 view point,
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 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 $k_{on}[S]$ ([S] being
the concentration of the substrate), $k_{off}$, and $k_{cat}$
respectively—the single molecule MM equation is at-
tained [33]

$$k_{turn} = \frac{k_{cat}[S]}{[S] + K_M},$$

(1)

with $K_M = (k_{off} + k_{cat})/k_{on}$ (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 memory-less property of the exponential distribution
asserts that the time remaining till 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 $k_{turn}$ is a
monotonically decreasing function of the rate $k_{off}$.

Non-exponential time distributions are, however, quite
common in a variety of complex systems [36–40], and it
has recently been recognized that enzymes are no excep-
tion in that regard [23, 32, 41, 42]. This result is per-
haps 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 devi-
ations from exponentiality and other anomalies [44–48].
Renewal theory can then be invoked to provide a gen-
eralized mathematical treatment of the MMRS [26]. A
completely general analysis of the turnover-unbinding in-
terplay is then very hard, but progress can be made if one
narrows down to the case of exponentially distributed un-
binding times [26, 33]. Letting $k_{off}$ denote the unbinding
rate (assumed to be independent of the catalytic process),
and $f_{cat}(t)$ the probability density function (PDF) of a
generally distributed catalysis time $T_{cat}$, it is possible to
show that [26, 33]

$$k_{turn} = \frac{\hat{f}_{cat}(k_{off})}{\left(T_{on}\right) + k_{off}^{-1} \left[1 - \hat{f}_{cat}(k_{off})\right]},$$

(2)

where $\hat{f}_{cat}(k) = \int f_{cat}(t)e^{-kt}dt$ is the Laplace transform
of $f_{cat}(t)$, and $\langle T_{on} \rangle$ is the mean of a generally distributed
binding time. Equation (2) extends the classical result
of Michaelis & 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 un-
productive unbinding events lead to accelerated turnover
[26]. This type of counter-intuitive behavior is categori-
ically precluded by the classical MM equation and is
therefore considered “non-classical” or “anomalous”.

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

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

$$\Psi(k) = \frac{\hat{f}_{cat}(k)(\hat{f}_{cat}(k) - 1)}{k^2 \hat{f}_{cat}(k)/dk} - \frac{1}{k} = \langle T_{on} \rangle,$$

(3)

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

Equation (3) clarifies the role of binding in our problem.
Restart and the initiation of a new turnover at-
tempt, 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 $k_{turn}$ will de-
velop if and only if $\langle T_{on} \rangle$ drops below the critical value
of $\Psi_{\text{max}} = \max_{k>0} \{\Psi(k)\}$. Indeed, since $k_{\text{turn}}$ is positive and asymptotically decays to zero as $k_{\text{off}} \to \infty$, $\Psi(k)$ 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. 2B.

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 & 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 $f_{\text{cat}}(k) = e^{-kL^2/2D}$ (Laplace space representation of the Lévy-Smirnov distribution), it immediately follows that the mean FPT of the restarted problem is given by $k^{-1}_{\text{turn}}$ in Eq. (2)—and we further note that it is finite for any positive restart rate! In fact, this is true for any $f_{\text{cat}}(k)$, 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 $z^* \simeq 1.59362 \ldots$ is the solution to $z/2 = 1 - e^{-z}$. Clearly, the same modus 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 $f_{\text{cat}}(k) = e^{-(\tau k)^\alpha}$ $(0 < \alpha < 1)$ 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: $f_{\text{cat}}(t) = (1 + a k)/(1 + b k + c k^2)$ (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, $f_{\text{cat}}(t) = \lambda e^{-\lambda t} \left(\lambda > 0\right)$, 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 $a = \frac{1}{\lambda_1} + p \left(\frac{1}{\lambda_2} - \frac{1}{\lambda_1}\right)$, $b = \frac{1}{\lambda_2} + \frac{1}{\lambda_1}$, $c = \frac{1}{\lambda_1 \lambda_2}$, and $\Psi(k) = \left(\frac{k \lambda_1 + (1-p) \lambda_2}{(1-p) \lambda_1 \lambda_2} k^2 + \frac{2 \lambda_1 \lambda_2}{(1-p) \lambda_1 \lambda_2} k \right)$, and $k_{\text{turn}}^{\text{max}}$.

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 $\langle T_{on} \rangle \approx \Psi_0$. When $\langle T_{on} \rangle$ approaches $\Psi_0$, “small $k$” solutions to Eq. (3) are anticipated provided $\Psi_0 > 0$ (see Fig. 2B). One can then try and approximate $\Psi(k)$, at small $k$, considering that in this limit $f_{\text{cat}}(k) \simeq 1 + \sum_{n=1}^{m} \frac{M_n(-k)}{n!}$, where $M_n \equiv (T_{\text{cat}}^n)$ 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 forth order equation and further analytical advancement becomes extremely cumbersome.

To circumvent this difficulty, we make use of the widely applied Padé approximation scheme [52] and try $f_{\text{cat}}(k) \simeq (1 + ak)/(1 + bk + ck^2)$. 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 $k \to \infty$—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]: $\Psi(k) \simeq \frac{\Psi_0}{1 + 2R_0(\Psi_0k) + R_0(1 + R_0)(\Psi_0k)^2}$, where $\Psi_0 = (M_2 - 2M_1^2)/2M_1$ and $R_0 = \frac{3(M_2 - 2M_1^2)}{2}$. 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 $\langle T_{on} \rangle < \Psi_0$ since this implies $\frac{dk_{\text{turn}}}{dk_{\text{off}}} \mid_{k_{\text{off}} = 0} > 0$. 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 $\langle T_{on} \rangle < \Psi_0$, if and only if, the mean duration, $\langle T_{on} \rangle + \langle T_{\text{cat}} \rangle$, of a new turnover cycle drops below the mean residual duration $\frac{1}{2}(\langle T_{\text{cat}} \rangle / \langle T_{on} \rangle)$, of an ongoing catalytic step [53]. 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. 2B) and, as $\langle T_{on} \rangle$ approaches $\Psi_0$ from above and crosses over to its other side, a maximum of the turnover rate gradually develops at

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

In particular, setting $\Delta = (\langle T_{on} \rangle)^{-1} - \Psi_0^{-1}$, we observe that to first order $k_{\text{off}}^{\max} \simeq \frac{\Delta}{2R_0}$. 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. 2B), $\Psi(0) > 0$, and $\Psi(k)$ has a local maxima at some $k^* > 0$. Then, as $\langle T_{on} \rangle$ first hits $\Psi(k^*)$ from above, both a minimum and a maximum of $k_{\text{turn}}$ abruptly appear (see “jump” in $k_{\text{off}}^{\max}$, inset of Fig. 2B). As $\langle T_{on} \rangle$ 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 $\langle T_{on} \rangle$ drops below $\Psi_0$, this minimum necessarily disappears—leaving behind a maximum of $k_{\text{turn}}$ at a point $k_{\text{off}}^{\max}$ 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—$\Psi(k \to 0) = \infty$ and the introduction of unbinding is asserted to speed up turnover regardless of $\langle T_{on} \rangle$. The asymptotic behavior of $k_{\text{off}}^{\max}$ at high values of $\langle T_{on} \rangle$ then depends on the tail of the catalysis time distribution ($t \to \infty$), and it can be shown [49] that for $f(t) \sim t^{-(1 + \alpha)}$ with $0 < \alpha < 1 (1 < \alpha < 2)$, $k_{\text{off}}^{\max} \sim (\langle T_{on} \rangle)^{-1}$ ($k_{\text{off}}^{\max} \sim (\langle T_{on} \rangle)^{-1/(2-\alpha)}$). 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 $\langle T_{on} \rangle$ approaches zero, “large $k$” solutions to Eq. (3) are anticipated provided $\Psi(k)$ is asymptotically positive (see Fig. 2B). The behavior of $\Psi(k)$ in this limit is governed by the behavior of $f_{\text{cat}}(t)$ at short times and we progress 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 $k \sim k^{-1}$, and $k_{\text{off}}^{\max} \sim (\langle T_{on} \rangle)^{-1}$. On the other hand, when $\alpha > 0$, $\Psi(k)$ approaches zero from below as

![Figure 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.](image-url)
\( \sim -k^{-1} \), there are no “large \( k \)” solutions to Eq. (3), and \( k_{\text{off}}^{\max} |_{\langle T_{\text{on}} \rangle = 0} \) 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 \( \omega_n = n! \left( \left( -\frac{\partial}{\partial t} \right)^{n-1} f_{\text{cat}}(t) \right) \bigg|_{t=0} \) and note that by construction \( \omega_1 = f_{\text{cat}}(0) > 0 \). Implementing a treatment similar to one given in the previous section we find for \( k \gg 1 \) \cite{49}:

\[ \Psi(k) \simeq \frac{1}{1+2\sqrt{\chi(k)\omega(k)}} + \frac{\chi(k)}{k^2(1+\sqrt{\chi(k)\omega(k)})^2} \text{, where} \quad R_\infty = \frac{2\omega_1\omega_2-3\omega_3^2}{3(\omega_2-2\omega_1)\omega_2-\omega_3^2} \quad \text{and} \quad \chi(k) = \omega_2 - \frac{2\omega_1^2}{3\omega_2} \text{ (compare with } \Psi(k) \text{ for } k \ll 1 \text{ above)}. \]

A large \( k \) solution to Eq. (2) is then found only when \( f_{\text{cat}}(0) < -f_{\text{cat}}^2(0) \iff \chi(k) > 0 \), and is given by

\[ k_{\text{off}}^{\max} = \chi(k) \left( \frac{1}{\langle T_{\text{on}} \rangle \chi(k)} - R_\infty - R_\infty \right) . \] \( (\text{5}) \)

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

Conclusions. In this letter 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 (Fig. 4 for illustration). The results we have obtained are applicable to many fields. In particular, we note that randomized computer algorithms \cite{54, 55} often exhibit heavy tailed run time distributions \cite{56, 57} and restart could hence drastically improve performance in these cases and others \cite{58, 59}.

The optimal restart problem is intimately related with the idea of kinetic proofreading. Independently proposed by Hopfield \cite{60} and Ninio \cite{29}, and studied by multiple authors since \cite{61–69}, 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 (band pass filter), or above/below some cutoff (high/low pass filter). How could this be done? Quite surprisingly, a formal solution to this highly non-trivial problem can be readily obtained by solving Eq. (2) for \( f_{\text{cat}}(k_{\text{off}}) \) given \( k_{\text{turn}}(k_{\text{off}}) \) \cite{70}. This observation paves the way towards intelligent design of “Michaelian Filters”—a concept which we will further develop elsewhere.

Acknowledgments. We gratefully acknowledge support of the German-Israeli Project Cooperation Program (DIP). Schlomi Reuveni gratefully acknowledges support from the James S. McDonnell Foundation via its postdoctoral fellowship in studying complex systems. We thank Haim Diamant for proposing possible continuations to our work. We thank Christopher Moore for turning our attention to applications in computer science and for referring us to relevant literature. We thank an anonymous referee for asking whether the optimal restart problem could be solved for first passage times that are taken from the one sided Lévy distribution.

\[ \text{[1] L. Menten & M.I. Michaelis, Biochem Z, 49, 333, (1913).} \]
In what follows, we use \( \hat{\xi}(k, \sigma) \) to denote, respectively, the expectation and variance of a real-valued random variable \( \xi \).

[1] J. Nino, Biochimie, 57 (5), 587, (1975).
[2] H.P. Lu et al., Science, 282, 1877, (1998).
[3] L. Edman et al., J. Phys. Chem. 247, 11, (1999).
[4] O. Flomenbom et al., Proc. Natl. Acad. Sci. U.S.A., 102, 2368, (2005).
[5] S.C. Kou et al., J. Phys. Chem. B, 109, 19068, (2005).
[6] J. Cao & R. J. Silbey, JPC B, 112, 12876, (2008).
[7] J. Cao, J. Phys. Chem. B, 115, 5493, (2011).
[8] J. Klafter & I.M. Sokolov, First Steps in Random Walks, Oxford University Press, (2011).
[9] S. Reuveni, R. Granek and J. Klafter, Phys. Rev. E, 82, 041132, (2010).
[10] S. Reuveni, I. Eliazar and U. Yechiali, Phys. Rev. Lett., 109, 020603, (2012).
[11] S. Reuveni, I. Eliazar and U. Yechiali, Phys. Rev. E, 86, 061133, (2012).
[12] S. Reuveni et al., Phys. Rev. E, 89, 042109, (2014).
[13] S. Yang et al., Biophysical Journal, 101, 519, (2011).
[14] J.R. Moffitt & C. Bustamante, FEBS J., 281 (2), 498, (2014).
[15] L. Edman & R. Rigler, Proc. Natl. Acad. Sci. U.S.A., 97, 8266, (2000).
[16] R. Granek and J. Klafter, Phys. Rev. Lett., 95, 098106, (2005).
[17] S. Reuveni, R. Granek and J. Klafter, Phys. Rev. Lett., 100, 208101, (2008).
[18] S. Reuveni, R. Granek and J. Klafter, PNAS, 107, 13696, (2010).
[19] S. Reuveni, J. Klafter and R. Granek, Phys. Rev. Lett., 108, 068101, (2012).
[20] S. Reuveni, J. Klafter and R. Granek, Phys. Rev. E., 85, 011906, (2012).
[21] See Supplemental Material at [URL will be inserted by publisher] for details, derivations and supplementary figures.
[22] The converse would contradictory imply that \( \partial k_{rate} / \partial k_{off} > 0 \) from some point onward.
[23] Abramowitz, Milton; Stegun, Irene A., eds. (1972), Handbook of Mathematical Functions with Formulas, Graphs, and Mathematical Tables, New York: Dover Publications.
[24] G.A. Baker Jr. & P. Graves-Morris, Padé Approximants, Cambridge U.P., (1996).
[25] See definition and formula of the time-averaged residual life time of a renewal process in: R. G. Gallager, Stochastic Processes: Theory for Applications, Cambridge University Press, (2013).
[26] L. Lovasz, Random walks on graphs: A survey in Combinatorics (Bolyai Society for Mathematical Studies, 1996), Vol. 2, p. I.
[27] C. Moore & S. Mertens, The Nature of Computation, Oxford University Press, (2011).
[28] A. Montanari and R. Zecchina, Phys. Rev. Lett. 88, 178701 (2002).
[29] J.J. Hopfield, Proc. Natl. Acad. Sci. U.S.A., 71 (10), 4135, (1974).
[30] J.J. Hopfield et al., Proc. Natl. Acad. Sci. U.S.A., 73 (4), 1164–8, (1976).
[31] R. Bar-Ziv, T. Thusty and A. Libchaber, Proc. Natl. Acad. Sci. U.S.A., 99 (18), 11589–92, (2002).
[32] T. Thusty, R. Bar-Ziv and A. Libchaber, Phys. Rev. Lett. 93 (25), 258103, (2004).
[33] D. Sagi, T. Thusty and J. Stavans, Nucleic Acids Res. 34 (18), 5021–31, (2006).
[34] J.T. Reardon & A. Sancar, Cell Cycle 3 (2), 141–4, (2004).
[35] G. Bel, B. Munsch and I. Nemenman, Phys Biol 7 (1), 016003, (2010).
[36] B. Munsch, I. Nemenman and G. Bel, J. Chem. Phys. 131 (23), 235103, (2009).
[37] A. Murugan, D. Huse and S. Leibler, Proc. Natl. Acad. Sci. U.S.A., 109 (30), 12034–9, (2012).
[38] A. Murugan, D. A. Huse and S. Leibler, Phys. Rev. X 4, 021016, (2014).
[39] One should then also verify that \( \hat{\xi}_{cat}(k_{off}) \) is a Laplace transform of a “Kosher” probability distribution as this is not guaranteed.
Supplementary Material

The Michaelis-Menten reaction scheme
as a unified approach towards the optimal restart problem

Tal Rotbart†, Shlomi Reuveni‡, and Michael Urbakh†

†School of Chemistry, Tel-Aviv University, Tel-Aviv 69978, Israel
‡Department of Systems Biology, Harvard University, 200 Longwood Avenue,
Boston, Massachusetts 02115, USA.

* T. Rotbart and S. Reuveni had equal contribution to this work.

Corresponding Author: Shlomi Reuveni

Email: shlomireuveni@hotmail.com
1 Supplementary information for figures

1.1 Details of distributions used in Fig. 2

Turnover rates were calculated for catalysis time distributions with $\langle T_{\text{cat}} \rangle = 1$, and the mean binding time was taken to be $\langle T_{\text{on}} \rangle = 0.1$ in all cases. The following distributions were used (numbers match lines No. 1-6 in Figure 2):

1. Log-Normal distribution:

$$f_{\text{cat}}(t) = \frac{1}{\sqrt{2\pi \alpha t}} \exp \left[ -\frac{(\ln(t) - \beta)^2}{2\alpha^2} \right],$$

with $\alpha = \sqrt{\ln(3)}$, and $\beta = -\ln(3)/2$. The variance of this distribution is $\sigma^2(T_{\text{cat}}) = 2$.

2. Double-Exponential distribution (a.k.a. Hyper-Exponential):

$$f_{\text{cat}}(t) = pk_1 e^{-k_1 t} + (1-p)k_2 e^{-k_2 t},$$

with $k_1 = 0.5$, $k_2 = 2$, and $p = 1/3$. The variance of this distribution is $\sigma^2(T_{\text{cat}}) = 2$.

3. Weibull distribution:

$$f_{\text{cat}}(t) = \alpha \beta (\beta t)^{\alpha-1} e^{-(\beta t)^\alpha},$$

with $\alpha = 0.7209$, and $\beta = 1.232$. The variance of this distribution is $\sigma^2(T_{\text{cat}}) = 2$.

4. Double-Erlang distribution (a.k.a. Hyper-Erlang):

$$f_{\text{cat}}(t) = pk_1^2 t e^{-k_1 t} + (1-p)k_2^2 t e^{-k_2 t},$$

with $k_1 = 22.8781$, $k_2 = 1.4184$, and $p = 0.31$. The variance of this distribution is $\sigma^2(T_{\text{cat}}) \approx 1.0612$.

5. Double-Exponential distribution (a.k.a. Hyper-Exponential):

$$f_{\text{cat}}(t) = pk_1 e^{-k_1 t} + (1-p)k_2 e^{-k_2 t}$$

with $k_1 = 0.5$, $k_2 = 10/9$, and $p = 1/11$. The variance of this distribution is $\sigma^2(T_{\text{cat}}) = 1.2$.

6. Exponential distribution:

$$f_{\text{cat}}(t) = ke^{-kt},$$

with $k = 1$. The variance of this distribution is $\sigma^2(T_{\text{cat}}) = 1$. 

2
1.2 Details of distributions used in Fig. 4

Maximal turnover rates were calculated for the following catalysis time distributions (by panel order):

A. Double-Exponential distribution:

\[ f_{cat}(t) = pk_1 e^{-k_1 t} + (1-p)k_2 e^{-k_2 t}, \]

with \( k_1 = 1 \), \( k_2 = 10.25 \) and \( p = 0.1025 \).

B. Triple-Exponential distribution:

\[ f_{cat}(t) = p_1 k_1 e^{-k_1 t} + p_2 k_2 e^{-k_2 t} + (1-p_1-p_2) k_3 e^{-k_3 t}, \]

with \( k_1 = 1 \), \( k_2 = 6 \), \( k_3 = 15 \), \( p_1 = 0.1 \) and \( p_2 = 0.3 \).

C. Gamma distribution:

\[ f_{cat}(t) = \frac{\beta}{\Gamma(\alpha)} (\beta t)^{\alpha-1} e^{-\beta t}, \]

with \( \alpha = 0.1942 \) and \( \beta = 1.0221 \).

D. Levi-Smirnoff distribution:

\[ f_{cat}(t) = \sqrt{\frac{\tau}{4D\pi t^3}} e^{\frac{-\tau}{4Dt}}, \]

with \( D = 1 \) and \( \tau = 0.5 \).
Asymptotics of the optimal restart problem, at \( \langle T_{on} \rangle \approx \Psi_0 \), is governed by the first three moments of the catalysis time distribution. Distributions No. 1-4 are all of type Double Erlang with \( \langle T_{cat} \rangle = 1 \) and \( \sigma(T_{cat}) = \sqrt{3} \). They differ, however, by having increasing skewnesses—\( R_0 = \{0.7, 1.5, 3.5, 14.8\} \) respectively (see below). Inset. When \( \langle T_{on} \rangle \approx \Psi_0 \), \( k_{max} \) is linear in \( \Delta = \langle T_{on} \rangle^{-1} - \Psi_0^{-1} \) and inversely proportional to \( R_0 \). As \( R_0 \) increases, the maximizing unbinding rate becomes lower as to avoid premature termination of the catalytic process.

2.1 Details of distributions used in Fig. S1

Distributions No. 1-4 are all of type Double-Erlang

\[
f_{cat}(t) = pk_1^2te^{-k_1t} + (1-p)k_2^2te^{-k_2t}.
\]

The following parameters were used:

| \( p \) | \( k_1 \) | \( k_2 \) | \( \langle T_{cat} \rangle \) | \( \langle T_{cat}^2 \rangle \) | \( R_0 \) |
|---|---|---|---|---|---|
| 1 | 1.93 \times 10^{-1} | 0.55 | 5.437 | 1 | 4 | 0.670 |
| 2 | 1.23 \times 10^{-1} | 0.45 | 3.875 | 1 | 4 | 1.467 |
| 3 | 4.94 \times 10^{-2} | 0.3 | 2.833 | 1 | 4 | 3.477 |
| 4 | 4.6 \times 10^{-3} | 0.1 | 2.19 | 1 | 4 | 14.76 |
3 Supplementary information for text

3.1 Derivation of Eq. 3 in the main text

Before we derive Eq. 3, and the statements which follow it, let us first obtain a preliminary result. Unbinding is said to be excitatory whenever \( \frac{\partial k_{\text{turn}}}{\partial k_{\text{off}}} > 0 \). Utilizing the definition of \( k_{\text{turn}} \) (Eq. 2 in the main text), we see that this condition is equivalent to

\[
\hat{f}_{\text{cat}}(k_{\text{off}}) \left( \frac{1 - \hat{f}_{\text{cat}}(k_{\text{off}})}{(T_{\text{on}}) k_{\text{off}} + \left[ 1 - \hat{f}_{\text{cat}}(k_{\text{off}}) \right]^2} + k_{\text{off}} (1 + k_{\text{off}} (T_{\text{on}})) \right) > 0.
\] (3.1)

Noting that the denominator on the left hand side of Eq. (3.1) is always positive, we multiply both sides by it and rearrange to get

\[
\hat{f}_{\text{cat}}(k_{\text{off}}) \left( 1 - \hat{f}_{\text{cat}}(k_{\text{off}}) \right) > -k_{\text{off}} (1 + k_{\text{off}} (T_{\text{on}})) \frac{\partial \hat{f}_{\text{cat}}(k_{\text{off}})}{\partial k_{\text{off}}}. \] (3.2)

The Laplace transform of a probability density function is monotonically decreasing in \( k_{\text{off}} \). We can thus take Eq. (3.2) and divide both sides by \(-\partial \hat{f}_{\text{cat}}(k_{\text{off}}) / \partial k_{\text{off}}\) to get

\[
\hat{f}_{\text{cat}}(k_{\text{off}}) \left( 1 - \hat{f}_{\text{cat}}(k_{\text{off}}) \right) > k_{\text{off}} (1 + k_{\text{off}} (T_{\text{on}})).
\] (3.3)

Further noting that the unbinding rate is always positive, we rearrange Eq. (3.3) to show that the following condition

\[
\hat{f}_{\text{cat}}(k_{\text{off}}) \left( \hat{f}_{\text{cat}}(k_{\text{off}}) - 1 \right) - \frac{1}{k_{\text{off}}} > (T_{\text{on}}),
\] (3.4)

is equivalent to the existence of excitatory unbinding.

Examining the left hand side of Eq. (3.4), we define

\[
\Psi(k) \equiv \frac{\hat{f}_{\text{cat}}(k) \left( \hat{f}_{\text{cat}}(k) - 1 \right)}{\frac{\partial \hat{f}_{\text{cat}}(k)}{\partial k} k^2} - \frac{1}{k},
\] (3.5)

and conclude that

\[
\Psi(k_{\text{off}}) > (T_{\text{on}}) \iff \frac{\partial k_{\text{turn}}}{\partial k_{\text{off}}} > 0.
\] (3.6)

A similar set of steps can then be applied to show that in the case of inhibitory unbinding one gets

\[
\Psi(k_{\text{off}}) < (T_{\text{on}}) \iff \frac{\partial k_{\text{turn}}}{\partial k_{\text{off}}} < 0,
\] (3.7)

as illustrated in the figure below.
Replacing inequalities with equalities in the above derivation, one can readily convince himself that

\[ \Psi(k_{\text{off}}) = \langle T_{\text{on}} \rangle \iff \partial k_{\text{turn}} / \partial k_{\text{off}} = 0, \quad (3.8) \]

i.e., the stationary points of \( k_{\text{turn}} \) are the solutions of \( \Psi(k_{\text{off}}) = \langle T_{\text{on}} \rangle \)—as is stated by Eq. 3 in the main text. We furthermore note that a stationary point of \( k_{\text{turn}} \) for which \( \Psi'(k) < 0 \) (\( \Psi'(k) > 0 \)) is a local maximum (minimum) of the turnover rate. Indeed, the amalgamation of Eqs. (3.6) and (3.7) asserts that \( \partial k_{\text{turn}} / \partial k_{\text{off}} \) is positive (negative) if and only if \( \Psi(k_{\text{off}}) - \langle T_{\text{on}} \rangle \) is positive (negative). Since at a stationary point \( \Psi(k) - \langle T_{\text{on}} \rangle = 0, \ \Psi'(k) < 0 \) (\( \Psi'(k) > 0 \)) implies that at this point \( \partial k_{\text{turn}} / \partial k_{\text{off}} \) transitions from being positive (negative) to being negative (positive), thus resulting in a local maximum (local minimum).
3.2 Approximating $\Psi(k)$

3.2.1 A general recipe

Before obtaining approximations for $\Psi(k)$ at particular limits, we give a recipe illustrating how this could be done in general. Consider the limit $k \to k_{lim}$. An approximation for $\Psi(k)$, at this limit, can be found by taking the following steps:

1. Find the third order power expansion of the Laplace transform $\hat{f}_{cat}(k)$ in the limit $k \to k_{lim}$ (going to third order is required in order to capture the first order behavior of $\Psi(k)$). If the Laplace transform is not analytic, move to step number (5) below.

2. Replace the third order power expansion of $\hat{f}_{cat}(k)$ with the following rational function approximation

$$\hat{f}_{cat}(k) \simeq \frac{1 + ak}{1 + bk + ck^2}.$$  \hfill (3.9)

Choose the parameters $a$, $b$, and $c$ such that the third order power expansion of the right hand side of Eq. (3.9) agrees with that found in step (1) above.

3. Substitute $\hat{f}_{cat}(k)$ in the definition of $\Psi(k)$ (see Eq. 3.5 above) with its approximation as given by Eq. (3.9).

4. Note that, under the approximation made in step (3), $\Psi(k) = \langle T_{on} \rangle$ (Eq. 3 in the main text) is a quadratic equation. Solve it.

5. In cases where a power expansion of $\hat{f}_{cat}(k)$ does not exist, leading order behavior must be extracted in a different manner. In some cases, approximate solutions to Eq. 3 in the main text can still be found. Examples are given below.

3.2.2 Approximating $\Psi(k)$ in the $k \to 0$ limit

1. Power expansion. When all moments of the catalysis time distribution are finite $\hat{f}_{cat}(k)$ can be written in the following form [1]

$$\hat{f}_{cat}(k) = \sum_{n=0}^{\infty} \frac{M_n}{n!} (-k)^n,$$  \hfill (3.10)

where $M_n = \int_0^\infty f_{cat}(t)t^n \, dt$ is the $n^{th}$ moment of the distribution. Truncating the infinite series in Eq. (3.10) to obtain a third order power expansion we have

$$\hat{f}_{cat}(k) \simeq 1 - M_1 k + \frac{M_2}{2} k^2 - \frac{M_3}{6} k^3.$$  \hfill (3.11)

2. Rational function approximation. Note that to third order

$$\frac{1 + ak}{1 + bk + ck^2} \simeq 1 - (b - a) k + (b^2 - ab - c) k^2 - (b^3 - ab^2 + ac - 2bc) k^3.$$  \hfill (3.12)
Equating corresponding coefficients for the power expansions that appear on the right hand side of Eqs. (3.11) and (3.12), one can write equations for the set \( \{ a, b, c \} \) and solve them to obtain

\[
a = \frac{6M_1(M_2 - M_1^2) - M_3}{3(2M_1^2 - M_2)}, \quad b = \frac{3M_1M_2 - M_4}{3(2M_1^2 - M_2)}, \quad c = \frac{3M_2^2 - 3M_1M_3}{6(2M_1^2 - M_2)}.
\]  

(3.13)

Substituting these parameters into the right hand side of Eq. (3.9) we obtain the following rational function approximation

\[
\hat{f}_{cat}(k) \simeq \frac{1 + \left( \frac{6M_1(M_2 - M_1^2) - M_3}{3(2M_1^2 - M_2)} \right) k}{1 + \left( \frac{3M_1M_2 - M_4}{3(2M_1^2 - M_2)} \right) k + \left( \frac{3M_2^2 - 3M_1M_3}{6(2M_1^2 - M_2)} \right) k^2}.
\]  

(3.14)

3. Approximating \( \Psi(k) \). Substituting Eq. (3.14) into Eq. (3.5) we get

\[
\frac{1}{\Psi(k)} \simeq \left[ \frac{2M_1}{M_2 - 2M_1^2} \right] + 2 \left[ \frac{2M_1M_2 - 3M_2^2}{3(M_2 - 2M_1^2)^2} \right] k
\]

\[
+ \left[ \frac{(6M_1^2 - 6M_2M_1 + M_3)(2M_1M_2 - 3M_2^2)}{9(M_2 - 2M_1^2)^2} \right] k^2.
\]  

(3.15)

Defining

\[
\Psi_0 \equiv \frac{M_2 - 2M_1^2}{2M_1},
\]

(3.16)

and

\[
R_0 \equiv \frac{2M_1M_3 - 3M_2^2}{3(M_2 - 2M_1^2)^2},
\]

(3.17)

we rewrite Eq. (3.15) in a more compact form

\[
\Psi(k) \simeq \Psi_0 \left( 1 + 2R_0 (\Psi_0 k) + [R_0(1 + R_0)] (\Psi_0 k)^2 \right)^{-1}.
\]  

(3.18)

Examining Eq. (3.18), it can be seen that its right hand side depends on two parameters only \( \Psi_0 \) and \( R_0 \). We further note that \( \Psi(k = 0) = \Psi_0 \), and that \( \Psi_0 \) defines a time scale by which we can normalize other times in our problem. Defining

\[
t = \Psi_0 \kappa', \quad k = \Psi_0^{-1} \kappa, \quad \Psi(k) = \Psi_0 \Psi_{norm}(\kappa),
\]

(3.19)

we can write a normalized version of Eq. (3.18)

\[
\Psi_{norm}(\kappa) \simeq \left( 1 + 2R_0 \kappa + [R_0(1 + R_0)] \kappa^2 \right)^{-1},
\]  

(3.20)

in which \( \Psi_0 \) was eliminated, and \( R_0 \)—the only remaining statistic—is dimensionless.

4. Solving the governing equation. Substituting \( \Psi(k) \) in Eq. 3 (main text) with its approximation, as given by Eq. (3.18), we have...
1 + 2R_0 (Ψ_0 k) + [R_0 (1 + R_0)] (Ψ_0 k)^2 = Ψ_0 / ⟨Ton⟩. (3.21)

Equation (3.21) is based on a small k approximation of Ψ(k) and we will hence try to solve in this regime. Small k solutions to Eq. (3.21) can only be found in the ⟨Ton⟩ → Ψ_0 limit and we therefore see that, since ⟨Ton⟩ ≥ 0 by definition, a requirement for their existence is Ψ_0 ≥ 0. Two different scenarios should then be distinguished based on the first order (linear) behavior of the left hand side of Eq. (3.21). If R_0 > 0, a small k solution exists only for 0 < ⟨Ton⟩ < Ψ_0. On the other hand, if R_0 < 0, a small k solution exists only for ⟨Ton⟩ > Ψ_0.

The two solutions of Eq. (3.21) are

\[ k_{\pm}^{\text{ext}} = \frac{1}{(1 + R_0) \Psi_0} \left[ \pm \sqrt{\frac{1}{1 + R_0} \left( \frac{\Psi_0}{⟨Ton⟩} - \frac{1}{R_0} - 1 \right)} \right] \]  

(3.22)

but \( k_{+}^{\text{ext}} \rightarrow 0 \) in the limit ⟨Ton⟩ → Ψ_0, while \( k_{-}^{\text{ext}} \) does not. We therefore choose \( k_{+}^{\text{ext}} \) and continue our analysis.

Utilizing Eqs. (3.19) and (3.22) we write \( k_{+}^{\text{ext}} \) in a normalized form

\[ \kappa_{+}^{\text{ext}} = \frac{1}{(1 + R_0)} \sqrt{\frac{1}{1 + Δ_{on}} \left( \frac{R_0 - Δ_{on}}{R_0} - 1 \right)} \]  

(3.23)

where we have defined \( Δ_{on} = (⟨Ton⟩ - Ψ_0)/Ψ_0 \). Recalling Eq. (3.20), noting that \( 0 < ⟨Ton⟩ < Ψ_0 \Leftrightarrow -1 < Δ_{on} < 0 \), and that \( ⟨Ton⟩ > Ψ_0 \Leftrightarrow Δ_{on} > 0 \), we schematically illustrate the difference between the \( R_0 > 0 \) case and the \( R_0 < 0 \) case in the figure above. Most importantly, we note that from our findings in section (3.1) it follows that when \( R_0 > 0 \) \( (R_0 < 0) \), \( \kappa_{+}^{\text{ext}} \) is a local maximum (minimum) of the turnover rate.

5. Special cases. The analysis given above was based on a power expansion of \( f_{\text{cat}}(k) \) in which we assumed that the first three moments of the catalysis time distribution are finite. In particular, \( Ψ_0 \) was defined based on the first two moments of the distribution and is hence not well defined when these diverge. Divergence of the first two moments can occur if the PDF has a “heavy tail” as happens, for example, when

\[ f_{\text{cat}}(t) \sim \frac{C}{t^{1+α}}, \]  

(3.24)
for $t \gg 1$ and $0 < \alpha < 2$. However, even when this is the case, one can still say something about the behavior of $\Psi(k)$ at small $k$, and we distinguish between two different cases.

When $0 < \alpha < 1$, the first and second moments of the catalysis time distribution both diverge. A small $k$ approximation of the Laplace transform is then given by [1]

$$\hat{f}_{\text{cat}}(k) \simeq 1 - \frac{C \cdot \Gamma(1 - \alpha)}{\alpha} k^{\alpha}, \quad (3.25)$$

where $\Gamma(x)$ is the Gamma function. Substituting Eq. (3.25) into Eq. (3.5) we see that to first order in this limit

$$\Psi(k) \simeq \frac{1 - \alpha}{\alpha} \frac{1}{k}. \quad (3.26)$$

Neglecting lower order corrections, we see that $\Psi'(k) < 0$ and conclude that as $\langle T_{\text{on}} \rangle \to \infty$ the following asymptotics holds

$$k_{\text{off}}^{\text{max}} \simeq \frac{1 - \alpha}{\alpha} \frac{1}{\langle T_{\text{on}} \rangle}. \quad (3.27)$$

When $1 < \alpha < 2$, the first moment of the catalysis time distribution is finite but the second moment diverges. A small $k$ approximation of the Laplace transform is then given by [1]

$$\hat{f}_{\text{cat}}(k) \simeq 1 - \langle T_{\text{cat}} \rangle k + \frac{C \cdot \Gamma(2 - \alpha)}{\alpha (\alpha - 1)} k^{\alpha}. \quad (3.28)$$

Substituting Eq. (3.28) into Eq. (3.5) we see that in this limit

$$\Psi(k) \simeq \frac{C \cdot \Gamma(2 - \alpha)}{\alpha \langle T_{\text{cat}} \rangle} \frac{1}{k^{2 - \alpha}}. \quad (3.29)$$

Neglecting lower order corrections, we see that $\Psi'(k) < 0$ and conclude that as $\langle T_{\text{on}} \rangle \to \infty$ the following asymptotics holds

$$k_{\text{off}}^{\text{max}} \simeq \left( \frac{C \cdot \Gamma(2 - \alpha)}{\alpha \langle T_{\text{cat}} \rangle \langle T_{\text{on}} \rangle} \right)^{\frac{1}{2 - \alpha}}. \quad (3.30)$$

3.2.3 Approximating $\Psi(k)$ in the $k \to \infty$ limit

1. Power expansion. When the PDF of the catalysis time distribution is analytic in the vicinity of $t = 0$ we can Taylor expand it

$$f_{\text{cat}}(t) = \sum_{n=0}^{\infty} \left[ \left( \frac{\partial}{\partial t} \right)^{n} f(t) \right]_{t=0} \frac{t^{n}}{n!} = \sum_{n=0}^{\infty} \omega_{n+1} \frac{(-t)^{n}}{n!(n+1)!}, \quad (3.31)$$

where we have defined

$$\omega_{n} \equiv n! \left[ \left( - \frac{\partial}{\partial t} \right)^{n-1} f(t) \right]_{t=0}. \quad (3.32)$$

from reasons that will soon become clear. The Laplace transform of such a series can then be written as
\[ \hat{f}_{\text{cat}}(t) = \sum_{n=1}^{\infty} \frac{-\omega_n}{n!} \left( -\frac{1}{k} \right)^n. \]  

(3.33)

Truncating the infinite series in Eq. (3.33) to obtain a third order power expansion we have

\[ \hat{f}_{\text{cat}}(k) \simeq \frac{\omega_1}{k} - \frac{\omega_2}{2k^2} + \frac{\omega_3}{6} \frac{1}{k^3}. \]  

(3.34)

2. Rational function approximation. Note that to third order

\[ \frac{1 + ak}{1 + bk + ck^2} \simeq \frac{a}{c} \left( \frac{1}{k} \right) - \frac{ab - c}{c^2} \left( \frac{1}{k} \right)^2 + \frac{ab^2 - ac - bc}{c^3} \left( \frac{1}{k} \right)^3. \]  

(3.35)

Equating corresponding coefficients for the power expansions that appear on the right hand side of Eqs. (3.34) and (3.35), one can write equations for the set \( \{a, b, c\} \) and solve them to obtain

\[ a = \frac{6\omega_1 (\omega_2 - 2\omega_1^2)}{2\omega_1 \omega_3 - 3\omega_2^2}, \quad b = \frac{2\omega_3 - 6\omega_1 \omega_2}{2\omega_1 \omega_3 - 3\omega_2^2}, \quad c = \frac{6 (\omega_2 - 2\omega_1^2)}{2\omega_1 \omega_3 - 3\omega_2^2}. \]  

(3.36)

Substituting these parameters into the right hand side of Eq. (3.9) we obtain the following rational function approximation

\[ \hat{f}_{\text{cat}}(k) \simeq \frac{1 + \left( \frac{6\omega_1 (\omega_2 - 2\omega_1^2)}{2\omega_1 \omega_3 - 3\omega_2^2} \right)}{1 + \left( \frac{2\omega_3 - 6\omega_1 \omega_2}{2\omega_1 \omega_3 - 3\omega_2^2} \right) k + \left( \frac{6 (\omega_2 - 2\omega_1^2)}{2\omega_1 \omega_3 - 3\omega_2^2} \right) k^2}. \]  

(3.37)

3. Approximating \( \Psi(k) \). Substituting Eq. (3.37) into Eq. (3.5) we get

\[ \frac{1}{\Psi(k)} \simeq \left[ \frac{2\omega_1 \omega_3 - 3\omega_2^2}{\omega_2 - 2\omega_1^2} \right] k^2 + 2 \left[ \frac{2\omega_1 \omega_3 - 3\omega_2^2}{3 (\omega_2 - 2\omega_1^2)} \right] k \]

\[ + \left( \frac{6\omega_3 - 6\omega_2 \omega_1 + \omega_1^2 (2\omega_1 \omega_3 - 3\omega_2^2)}{9 (\omega_2 - 2\omega_1^2)^2} \right). \]  

(3.38)

Defining

\[ \chi_\infty \equiv \frac{\omega_2 - 2\omega_1^2}{2\omega_1}, \]  

(3.39)

and

\[ R_0 \equiv \frac{2\omega_1 \omega_3 - 3\omega_2^2}{3 (\omega_2 - 2\omega_1^2)}, \]  

(3.40)

we rewrite Eq. (3.38) in a more compact form

\[ \Psi(k) \simeq \chi_\infty^{-1} \left( (\chi_\infty^{-1}k)^2 + 2R_\infty \left( (\chi_\infty^{-1}k)^2 + R_\infty (R_\infty + 1) \right)^{-1} + R_\infty \right). \]  

(3.41)
Examining Eq. (3.41), it can be seen that its right hand side depends on two parameters only $\chi_\infty$ and $R_\infty$. We further note that in the limit $k \to \infty$, $\Psi(k) \simeq \chi_\infty k^{-2}$, and that $\chi_\infty^{-1}$ defines a time scale by which we can normalize other times in our problem. Defining

$$t = \chi_0^{-1} t', \ k = \chi_0 K, \ \Psi(k) = \chi_0^{-1} \Psi_{Norm}(K)$$

we can write a normalized version of Eq. (3.41)

$$\Psi_{Norm}(K) \simeq \left( K^2 + 2R_\infty K + R_\infty (R_\infty + 1) \right)^{-1},$$

in which $\chi_\infty$ was eliminated, and $R_\infty$—the only remaining statistic—is dimensionless.

4. Solving the governing equation. Substituting $\Psi(k)$ in Eq. 3 (main text) with its approximation, as given by Eq. (3.41), we have

$$\frac{\chi_\infty / k^2}{1 + 2R_\infty \chi_\infty / k + R_\infty (R_\infty + 1) (\chi_\infty / k)^2} = \langle T_{on} \rangle.$$

Equation (3.44) is based on a large $k$ approximation of $\Psi(k)$ and we will hence try to solve it in this regime. Large $k$ solutions to Eq. (3.44) can only be found in the $\langle T_{on} \rangle \to 0$ limit. Two different scenarios, schematically illustrated in the figure above, should then be distinguished based on the leading order behavior of the left hand side of Eq. (3.44).

When $\chi_\infty > 0$, $\lim_{k \to \infty} \Psi(k) = 0^+$, i.e., $\Psi(k) > 0$ as it approaches zero from above. The two solutions of Eq. (3.44) are then

$$k_{ext}^+ = \chi_\infty \left[ \pm \sqrt{\frac{1}{\chi_\infty \langle T_{on} \rangle} - R_\infty - R_\infty} \right],$$

but $k_{ext}^+ \to \infty$ in the limit $\langle T_{on} \rangle \to 0$, while $k_{ext}^-$ does not. We therefore choose $k_{ext}^-$ and continue by noting that since $\Psi'(k) < 0$ in this limit the findings in section (3.1) assert that $k_{ext}^+$ is a local maximum of the turnover rate. Utilizing Eqs. (3.42) and (3.45) $k_{ext}^+$ can also be written in normalized form

$$K_{ext}^+ = \sqrt{\frac{1}{\delta_{on}} - R_\infty - R_\infty},$$
where we have defined $\delta_{on} = \chi_{\infty} \langle T_{on} \rangle$.

When $\chi_{\infty} < 0$, $\lim_{k \to \infty} \Psi(k) = 0^-$, i.e., $\Psi(k) < 0$ as it approaches zero from below. Since $\langle T_{on} \rangle \geq 0$ by definition, there are no large $k$ solutions to Eq. 3.44 in this case. It is however possible, that $\Psi(k)$ is positive for smaller values of $k$, in which case, the continuity of $\Psi(k)$ and the fact that it is negative at large $k$ guarantees that there is a finite value of $k$, $k_{\text{thresh}}$, for which $\Psi(k_{\text{thresh}}) = 0$. This translates (as visualized in the figure above) to $k_{\text{max}} \to k_{\text{thresh}}$.\[5. Special cases.\] The analysis given above was based on an expansion of $f_{cat}(k)$ in powers of $k^{-1}$. In particular, when defining $\chi_{\infty}$ we have assumed that $0 < f_{cat}(0) = \omega_1 < \infty$. In contrast, let us now consider a power law behavior of the PDF $f_{cat}(t) \simeq \omega_1 t^\alpha$, (3.47) where $t \ll 1$, $\omega_1 > 0$, $\alpha \neq 0$, and $\alpha > -1$ (the PDF cannot be normalized for $\alpha \leq -1$).\[Noting that the large $k$ asymptotics of the Laplace transform is then given by\] $\hat{f}_{cat}(k) \simeq \int_0^\infty \omega_1 t^\alpha e^{-kt} dt = \omega_1 \Gamma(1+\alpha)k^{-(1+\alpha)}$, (3.48) we substitute Eq. (3.48) into Eq. (3.5) and find
\[\Psi(k) \simeq -\frac{\alpha}{\alpha + 1} \frac{1}{k},\] (3.49) to first order in this limit.

Examining Eq. (3.49), we see that two different cases should be told apart. When $-1 < \alpha < 0$, $f_{cat}(t)$ diverges in the limit $t \to 0$, $\Psi(k) > 0$, and $\Psi(k) < 0$.\[Neglecting lower order corrections, we conclude that as $\langle T_{on} \rangle \to 0$ the following asymptotics holds\] $k_{\text{off}}^{\text{max}} \simeq -\frac{\alpha}{\alpha + 1} \frac{1}{\langle T_{on} \rangle}$. (3.50)

On the other hand, when $\alpha > 0$, $f_{cat}(t)$ zeros in the limit $t \to 0$, and $\Psi(k) < 0$. Since $\langle T_{on} \rangle \geq 0$ by definition, there are no large $k$ solutions to Eq. 3.44 in this case. It is however possible, that $\Psi(k)$ is positive for smaller values of $k$, in which case, the continuity of $\Psi(k)$ and the fact that it is negative at large $k$ guarantees that there is a finite value of $k$, $k_{\text{thresh}}$, for which $\Psi(k_{\text{thresh}}) = 0$. In this case, we once again find $k_{\text{off}}^{\text{max}} \to k_{\text{thresh}}$.\[References\]

[1] J. Klafter and I.M. Sokolov, First Steps in Random Walks, Oxford University Press, (2011).