Optimal Stochastic Restart Renders Fluctuations in First Passage Times Universal

Shlomi Reuveni[*]
Department of Systems Biology, Harvard Medical School, 200 Longwood Avenue, Boston, Massachusetts 02115, USA

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Stochastic restart may drastically reduce the expected run time of a computer algorithm, expedite the completion of a complex search process, or increase the turnover rate of an enzymatic reaction. These diverse first-passage-time (FPT) processes seem to have very little in common but it is actually quite the other way around. Here we show that the relative standard deviation associated with the FPT of an optimally restarted process, i.e., one that is restarted at a constant (nonzero) rate which brings the mean FPT to a minimum, is always unity. We interpret, further generalize, and discuss this finding and the implications arising from it.

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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. Among these three possibilities the latter is particularly interesting as it suggests that restart can be used to expedite the completion of complex processes involving strong elements of chance. This observation has long been made in the field of computer science [1] where the use of restart is now routine as it drastically improves performance [1–6] of randomized algorithms [7,8]. The latter often display heavy-tailed run time distributions, and diverging variances and even means [2,3,9–12]. Timely restart can then "censor" the tail of the run time distribution and save the algorithm from getting "stuck" in sterile areas of the search space where it is unlikely to find solutions.

Restart is also relevant to many physical, chemical, and biological processes as it is an integral part of the renowned Michaelis-Menten reaction scheme (MMRS) [13]. In its original context the MMRS depicts an enzyme which can reversibly bind a substrate to form a complex. The substrate can then be converted by the enzyme to form a product or, alternatively, unbind and restart the turnover cycle. The MMRS has attracted interest for more than a century [14], and today it is also used to describe heterogeneous catalysis [15–17], *in vivo* target search kinetics [18], and other processes. Two important predictions come from its classical analysis. The rate of an enzymatic reaction should increase as the concentration of the substrate increases and decrease as the unbinding rate increases [13]. And yet, while the first prediction is well established, the second has never been tested experimentally.

Motivated by rapid advancements in single-molecule techniques [19–21] we scrutinized the role attributed to unbinding (restart) in Michaelis-Menten reactions [22]. We showed, via probabilistic—single-molecule level—analysis that unbinding of an enzyme from a substrate can reduce the rate of product formation under some conditions, but that it may also have an opposite effect. Indeed, as substrate concentrations increase, a tipping point can be reached where an increase in the unbinding rate results in an increase, rather than a decrease, of the turnover rate. When this happens, a carefully chosen unbinding rate can bring the enzymatic turnover rate to a maximum (mean FPT to a minimum) by striking the right balance between the need to abort prolonged reaction cycles and the need to avoid premature termination of ongoing ones. Observations similar to ours were also made in the context of search processes [23–25], and a universal condition for the existence of a nonvanishing optimal restart rate was given in Ref. [22]. It was clear, however, that the exact identity of the latter may depend on fine details of the underlying process (conversion of the substrate to a product in the case of enzymatic reactions), and it thus seemed that little can be said in general about optimal stochastic restart.

In this Letter, we address the question of universality in FPT processes subject to stochastic restart. As we have pointed out in Ref. [22], any FPT process [26]—be it the time to target of a simple Brownian particle or that related with a more sophisticated random searcher [27–29] or stochastic process [30–38]—that becomes subject to restart [24,25,39–48] can naturally be described by the MMRS. This observation has recently allowed us to give a unified treatment for the problem of finding a restart rate which brings the mean completion time of a generic process to a minimum (optimal restart) [49], and it will be of value here again. We show that the relative fluctuation in the FPT of an optimally restarted process is always unity. The result is first illustrated, by means of example, on the now classical problem of diffusion mediated search with stochastic restart [25]. We then prove it in a more general setting and further demonstrate its validity for a diverse set of examples. Before concluding, we provide a probabilistic interpretation of our findings and generalize the basic result to account for restart time overheads that inevitably occur in many real life scenarios. In what follows, we use $\langle Z \rangle$, $\sigma^2(Z)$, and $\tilde{Z}(s) \equiv \langle e^{-sZ} \rangle$ to denote, respectively, the expectation, variance, and Laplace transform of a real-valued random variable Z.

Diffusion with stochastic restart—a simple illustration of a general principle.—Consider a particle "searching" for a stationary target via one dimensional diffusion as is illustrated in Fig. 1(a). The particle starts at the origin, the initial distance between the particle and the target is L, and the diffusion coefficient of the particle is D. It has long been known that in this case the mean FPT of the particle to the target diverges [26,35,50]. Consider now a scenario in which, on top of the above, the search process is restarted; i.e., the particle is returned to its initial position, at some constant rate r. What is the mean FPT now? This problem was studied in Ref. [25] by Evans and Majumdar who found that $\langle T_r\rangle$, the mean FPT of the restarted process, is given by

$$\langle T_r\rangle = \frac{e^{\sqrt{rL^2/D}}-1}{r}. \tag{1}$$

As anticipated, $\langle T_r\rangle$ depends on the restart rate but it is interesting to note that it is finite for any $r>0$. Moreover, an optimal restart rate which brings $\langle T_r\rangle$ to a minimum exists, as is illustrated in Fig. 1(b), and one could readily show that it is given by $r^* = (z^*)^2D/L^2$, where $z^*\simeq 1.59362\ldots$ is the solution to $z/2 = 1-e^{-z}$.

Evans and Majumdar continued to compute the full distribution of T_r and found that in Laplace space it is given by

$$\tilde{T}_r(s) = \frac{s+r}{se^{\sqrt{(s+r)L^2/D}}+r}. \tag{2}$$

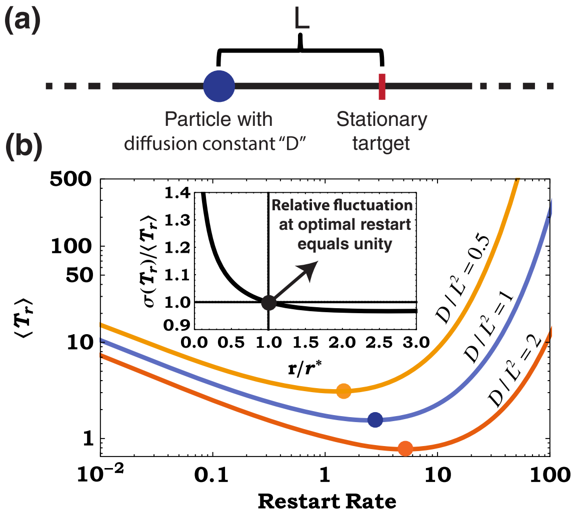

FIG. 1. (a) An illustration of diffusion mediated search at time $t=0$. (b) The mean FPT to target as a function of the restart rate for different values of D/L^2. The higher this ratio is the higher the value of the optimal restart rate r^* which brings $\langle T_r\rangle$ to a minimum (see positions marked with full circles). Inset. The relative standard deviation in the FPT as a function of the restart rate (normalized by the optimal restart rate).

Moments could then be readily computed and we find that $\langle T_r^2\rangle = (2-\sqrt{\frac{rL^2}{D}}e^{-\sqrt{rL^2/D}} - 2e^{-\sqrt{rL^2/D}})/r^2e^{-2\sqrt{rL^2/D}}$, from which it is easy to see that the relative standard deviation in the completion time of the restarted process is given by

$$\frac{\sigma(T_r)}{\langle T_r\rangle} = \sqrt{\frac{e^{2\sqrt{rL^2/D}} - \sqrt{rL^2/D}e^{\sqrt{rL^2/D}} - 1}{(e^{\sqrt{rL^2/D}}-1)^2}}. \tag{3}$$

The right-hand side of Eq. (3) has a form which suggests it should be plotted as a function of r/r^*. We do so in the inset of Fig. 1(b) only to find that when $r=r^*$ the relative fluctuation in T_r is exactly unity

$$\frac{\sigma(T_{r^*})}{\langle T_{r^*}\rangle} = 1. \tag{4}$$

Quite strikingly, and as we will now show, the result in Eq. (4) is not a peculiarity of diffusion but rather a universal property common to all FPT processes subject to stochastic restart.

Fluctuations in the first-passage-time of an optimally restarted process are universal.—In deriving the main result of this paper we consider the setting illustrated in Fig. 2. This setting captures the model of diffusion with stochastic restart as a special case and further allows us to generalize lessons learned from it. A generic process starts at time zero and, if allowed to take place without interruptions, will finish after a random time T. The process is, however, restarted at some *constant* rate r. Thus, if the process is completed prior to restart the story there ends. Otherwise, the process will start from scratch and begin completely anew. This procedure repeats itself until the process reaches completion.

Denoting the random completion time of the restarted process by T_r it can then be seen that

$$T_r = \begin{cases} T & \text{if } T<R \\ R+T_r' & \text{if } R\le T, \end{cases} \tag{5}$$

where R is an exponentially distributed random variable with rate r and T_r' an independent and identically distributed copy of T_r. Taking the Laplace transform of T_r we find (see Supplemental Material [51])

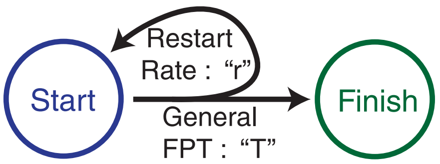

FIG. 2. An illustration of a generic process subject to stochastic restart.

$$\tilde{T}_r(s) = \frac{\tilde{T}(s+r)}{\frac{s}{s+r} + \frac{r}{s+r}\tilde{T}(s+r)}, \tag{6}$$

and note that Eq. (6) generalizes Eq. (2). Indeed, in the case of diffusion mediated search $\tilde{T}(s) = e^{-\sqrt{sL^2/D}}$ (Laplace space representation of the Lévy-Smirnov distribution [35]) and direct substitution of this expression into Eq. (6) verifies our claim. For a discrete-time analog of Eq. (6) we refer the reader to Ref. [40].

Using Eq. (6) we compute the first two moments of T_r:

$$\langle T_r \rangle = \frac{1 - \tilde{T}(r)}{\tilde{T}(r)} \frac{1}{r},$$

$$\langle T_r^2 \rangle = \frac{2(r\frac{d\tilde{T}(r)}{dr} - \tilde{T}(r) + 1)}{r^2 \tilde{T}(r)^2}. \tag{7}$$

Now, if the mean FPT of the restarted process attains a minimum (or a maximum) at some $r^* > 0$ we have $[d\tilde{T}(r)/dr]|_{r^*} = \tilde{T}(r^*)(\tilde{T}(r^*) - 1)/r^*$ simply by taking the first derivative of $\langle T_r \rangle$ and equating it to zero at $r = r^*$. Substituting this result back into Eq. (7) gives $\langle T_{r^*}^2 \rangle = 2(\tilde{T}^2(r^*) - 2\tilde{T}(r^*) + 1)/((r^*)^2\tilde{T}(r^*)^2)$, from which it is easy to see that $\sigma^2(T_{r^*}) = (\tilde{T}(r^*) - 1)^2/((r^*)^2\tilde{T}(r^*)^2)$. Comparing this result with Eq. (7) we conclude that Eq. (4) holds for an arbitrary FPT process, and as long as the restart time R is taken from the exponential distribution (constant restart rate). It is important to emphasize that the result holds regardless of the distribution of the random time T (see Fig. 3 for examples), be it with heavy tails, or even with an atom at $T = \infty$, and note that a classical example of the latter case is diffusion mediated search in three (or more) dimensions. Deviations from Eq. (4) may occur when R is not taken from the exponential distribution. These will be discussed elsewhere.

Equation (4) has an interesting probabilistic interpretation. Examining Fig. 2, one could ask what determines whether $\langle T \rangle$ is larger or smaller than $\langle T_{\delta r} \rangle$ for an infinitesimal δr? When $\langle T \rangle = \infty$, it is always larger than $\langle T_{\delta r} \rangle$ since Eq. (7) asserts that the latter is finite. When $\langle T \rangle$ is finite, the question above can be answered either by examining a small r expansion of $\langle T_r \rangle$ [22,49] or by arguing probabilistically. Letting the original process repeat itself over and over again without restart, one could visit it at a random point in time and ask what is the mean time left until the next completion event occurs? This time is known as the mean residual life time (MRLT) of the process and it is given by $\frac{1}{2}\langle T^2 \rangle / \langle T \rangle$ [52]. When the MRLT is larger (smaller) than $\langle T \rangle$ restart will tend (on average) to speed up (slow down) completion rendering $\langle T_{\delta r} \rangle$ smaller (larger) than $\langle T \rangle$. Applying the same logic to a process which is already subject to restart (simply by seeing it as an original process of itself), we conclude that when a process is restarted at an optimal rate its mean and MRLT must be equal. Indeed, any deviation from equality is in contraindication to optimality as it implies $[d\langle T_r \rangle / dr]|_{r^*} \neq 0$. It thus follows that $\langle T_{r^*} \rangle = \frac{1}{2}\langle T_{r^*}^2 \rangle / \langle T_{r^*} \rangle$, a relation from which Eq. (4) is attained by simple rearrangement.

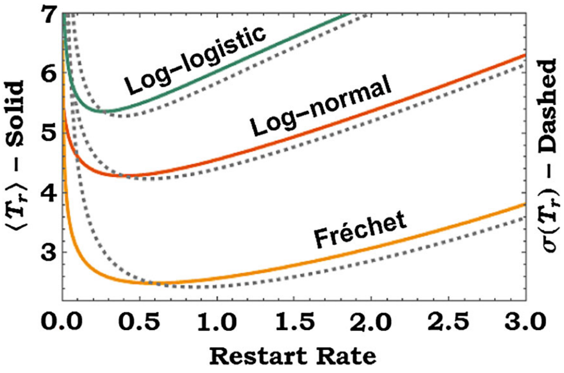

FIG. 3. The mean (solid lines) and standard deviation (dashed lines) in the FPT of a restarted process as a function of the restart rate. Plots are made using Eq. (7) for three different time distributions of the underlying process subject to restart: (i) Fréchet distribution $Pr(T \leq t) = e^{-t^{-\alpha}} (t > 0)$, with $\alpha = 1$; (ii) Log-normal distribution $Pr(T \leq t) = \int_0^t [x\sigma\sqrt{2\pi}]^{-1} \exp[-(\ln(x) - \mu)^2/2\sigma^2] dx (t > 0)$, with $\mu = 1$ and $\sigma = 1.2$; (iii) Log-logistic distribution $Pr(T \leq t) = [1 + (t/\alpha)^{-\beta}]^{-1} (t > 0)$, with $\alpha = 3.4$ and $\beta = 1.45$. Equation (4) asserts that $\sigma(T_r)$ will cut $\langle T_r \rangle$ at the exact point at which the latter attains its minimum.

Recapitulating this section we note that the normalized completion time of an optimally restarted process $T_{r^*}/\langle T_{r^*} \rangle$ has, by definition, mean 1 and, as we have just shown, a standard deviation which also equals unity. It thus follows that $\langle e^{-sT_{r^*}/\langle T_{r^*} \rangle} \rangle \simeq 1 - s + s^2 + o(s^2)$—a form which coincides to second order with the Laplace transform of the exponential distribution $(1 + s)^{-1}$. However, and as we illustrate in Fig. 4, the distribution of $T_{r^*}/\langle T_{r^*} \rangle$ is not universal and deviations from exponentiality may arise for $s \gg 1$.

Stochastic restart with time overheads.—Deriving Eq. (4) we have implicitly assumed that restart does not bear with it any time penalty. And yet, when a computer program is stopped restarting it may involve a time overhead. Similarly, when an enzyme unbinds from its substrate time will pass before it binds a new one. This type of complication can be addressed by generalizing the stochastic renewal law in Eq. (5) to read

$$T_r = T_{\text{on}} + \begin{cases} T & \text{if } T < R \\ R + T_r' & \text{if } R \leq T, \end{cases} \tag{8}$$

where T_{on} is a generally distributed random time which collectively accounts for "delays" that may arise prior to any completion attempt. Equation (8) furnishes a mathematical description of the MMRS, and the effect restart has on $\langle T_r \rangle$ in this case was extensively explored in Refs. [22,49]. Here, we will be interested in the effect it has on fluctuations.

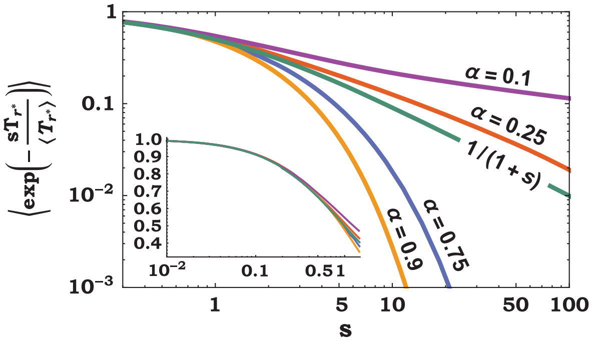

FIG. 4. The distribution of $T_{r^*}/\langle T_{r^*}\rangle$ is nonuniversal. Consider a generalization of diffusion with stochastic restart. Letting $\tilde{T}(s) = e^{-(\tau s)^{\alpha}}$ we note that for $\tau = L^2/D$ and $\alpha = 1/2$ we have the Laplace transform of the Lévy-Smirnov distribution discussed above, and in general for $0 < \alpha < 1$ the Laplace transform of the one sided Lévy distribution [35]. In Ref. [49] we showed that the optimal restart rate for this distribution is given by $r^* = (z^*)^{1/\alpha}/\tau$, where z^* is the solution to $\alpha z = 1 - e^{-z}$. This now allows us to compute $\langle T_{r^*}\rangle$ and plot $\langle e^{-sT_{r^*}/\langle T_{r^*}\rangle}\rangle$ for different values of α while fixing $\tau = 1$ for convenience. It is clearly visible that while all curves fall on top of each other, and on top of $(1+s)^{-1}$, for $s \ll 1$ their behavior for $s \gg 1$ depends on the value of α.

Utilizing Eq. (8) one could show that (see Supplemental Material [51])

$$\tilde{T}_r(s) = \frac{\tilde{T}(s+r)\tilde{T}_{\mathrm{on}}(s)}{1 + \frac{r}{s+r}\tilde{T}_{\mathrm{on}}(s)(\tilde{T}(s+r) - 1)}. \tag{9}$$

Assuming that T_{on} is equipped with a finite mean and variance, we then find $\langle T_r\rangle = (r\langle T_{\mathrm{on}}\rangle + 1 - \tilde{T}(r))/r\tilde{T}(r)$ and $\langle T_r^2\rangle = (2(1-\tilde{T}(r))(1 + r\langle T_{\mathrm{on}}\rangle)^2 + 2r(1 + r\langle T_{\mathrm{on}}\rangle)\times \frac{d\tilde{T}(r)}{dr} + r^2\tilde{T}(r)\langle T_{\mathrm{on}}^2\rangle)/r^2\tilde{T}(r)^2$. Moreover, in Ref. [49] we showed that if $\langle T_r\rangle$ receives a minimum (or a maximum) at some $r^* > 0$ the following equation must hold $[\tilde{T}(r^*)(\tilde{T}(r^*) - 1)/(r^*)^2 \frac{d\tilde{T}(r)}{dr}|_{r^*}] - (1/r^*) = \langle T_{\mathrm{on}}\rangle$. Solving for $[d\tilde{T}(r)/dr]|_{r^*}$ and substituting the result in the expression for $\langle T_{r^*}^2\rangle$ we obtain (see Fig. 5 for illustration)

$$\frac{\sigma(T_{r^*})}{\langle T_{r^*}\rangle} = \sqrt{1 + \frac{\sigma^2(T_{\mathrm{on}}) - \langle T_{\mathrm{on}}\rangle^2}{\tilde{T}(r^*)\langle T_{r^*}\rangle^2}}. \tag{10}$$

Equation (10) generalizes Eq. (4) and while the result is no longer universal [53] it is surprisingly elegant.

Conclusions.—The advent of novel single molecule and cell techniques has truly invigorated the experimental [54–62] and theoretical [63–71] study of fluctuation phenomena. Notable in that regard are studies directed towards questions of universality as they allow us to draw broad, model independent conclusions which are in turn widely applicable [32,33,72–75]. In this Letter we studied the effect of stochastic restart on fluctuations in the completion time of a generic process and showed that when the restart rate is optimal, in the sense that it minimizes (or maximizes) the mean FPT of the process, fluctuations are universal. The prevalence of FPT processes in the sciences and the multitude of perspectives that bring one to consider (optimal) restart encourage us to think that the results we have obtained will be of general use. Applications to the field of single molecule enzymology are particularly interesting since enzymes are subject to selective pressure which may have dialed unbinding (restart) rates optimal. Moreover, note that whenever T_{on} arises from the amalgamation of many independent and low intensity events it will admit Poisson statistics for which $\sigma(T_{\mathrm{on}}) = \langle T_{\mathrm{on}}\rangle$. In this case Eq. (10) reduces to Eq. (4) and the common scenario in which numerous substrate molecules compete for the binding of an enzyme is a good example for a situation of that sort. Will it be found that selective pressure towards optimal restart rendered fluctuations in enzymatic turnover rates universal, it would not be the first time that proteins are found occupying a very special niche within a vastly accessible phase space [76,77], and yet another example for the importance of optimality and extremality ideas in biological physics [78].

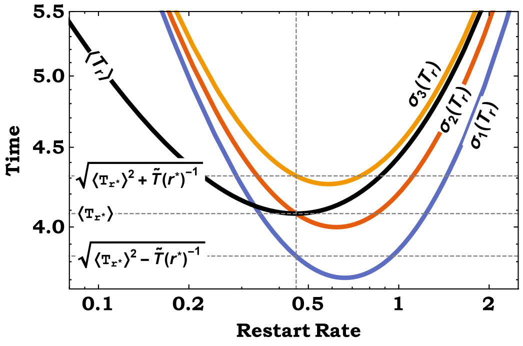

FIG. 5. The mean and standard deviation of T_r for three different cases of diffusion mediated search with stochastic restart and time overheads. In all three cases $\tilde{T}(s) = e^{-\sqrt{s}}$ $(L^2/D = 1)$, $\langle T_{\mathrm{on}}\rangle = 1$, and $\langle T_r\rangle$ is hence one and the same. The standard deviations $\sigma_i(T_r)$ are, however, quite distinct since here we chose $\sigma_i^2(T_{\mathrm{on}}) = i - 1$ for $i = 1, 2, 3$. These values could, for example, be associated with sharp (deterministic), exponential, and Gamma distributed delays (in this order). Note that in all three cases $\sigma_i(T_{r^*}) = \sqrt{\langle T_{r^*}\rangle^2 + [\sigma_i^2(T_{\mathrm{on}}) - \langle T_{\mathrm{on}}\rangle^2]/\tilde{T}(r^*)}$ in accord with Eq. (10).

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[*] shlomireuveni@hotmail.com

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[50] Also see S. Kostinski and A. Amir, Am. J. Phys. **84**, 57 (2016) for a pedagogical derivation of a closely related result.

[51] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.116.170601 for the derivations of Eqs. (6) and (9) in the main text.

[52] See definition and formula of the time-averaged residual lifetime of a renewal process in R. G. Gallager, *Stochastic Processes: Theory for Applications* (Cambridge University Press, Cambridge, England, 2013).

[53] Note dependence on $\bar{T}(r^*)$ and hence on the details of the restarted process.

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