Unified Approach to Gated Reactions on Networks

Yuval Scher* and Shlomi Reuveni†

School of Chemistry, Center for the Physics & Chemistry of Living Systems, Ratner Institute for Single Molecule Chemistry, and the Sackler Center for Computational Molecular & Materials Science, Tel Aviv University, 6997801 Tel Aviv, Israel

(Received 9 January 2021; revised 20 March 2021; accepted 2 June 2021; published 29 June 2021)

For two molecules to react they first have to meet. Yet, reaction times are rarely on par with the first-passage times that govern such molecular encounters. A prime reason for this discrepancy is stochastic transitions between reactive and nonreactive molecular states, which results in effective gating of product formation and altered reaction kinetics. To better understand this phenomenon we develop a unifying approach to gated reactions on networks. We first show that the mean and distribution of the gated reaction time can always be expressed in terms of ungated first-passage and return times. This relation between gated and ungated kinetics is then explored to reveal universal features of gated reactions. The latter are exemplified using a diverse set of case studies which are also used to expose the exotic kinetics that arises due to molecular gating.

DOI: 10.1103/PhysRevLett.127.018301

The first-passage properties of a random walker are central to the study and analysis of stochastic phenomena [1–4]. The classic problem of a random walker in search of a target arises naturally in a variety of fields, be it biology [5–13], finance [14,15], or network science [16–21], to name a few. Markedly, the first-passage problem is central to the theory of diffusion limited reactions, where a reaction between two species can be modeled as stochastic motion that terminates on contact [22–24]. However, while having two molecules at the same place and at the same time is a necessary condition for the occurrence of a chemical reaction, more is oftentimes required for the reaction to actually take place.

It has long been realized that in order to better depict chemical reactions one has to consider the possibility of infertile molecular collisions [25–35]. This realization later matured to the concept of gated reactions, which occur only when molecules collide while in a reactive state (alternatively, the gate is open) [36–51], see Fig. 1. A similar idea of a gated boundary was applied in narrow gated-escape problems [52,53] and search for gated targets [54,55]. Depending on the context, the first time of arriving at the boundary while at the reactive state is interchangeably referred to as reaction time, first-absorption time or first-hitting time. Throughout the years many examples of gated processes were explicitly solved for, but a general understanding of the relations between gated- and ungated-reaction kinetics is still lacking. A notable step in that direction is the formalism developed by Spouge, Szabo, and Weiss [44].

At the heart of this Letter is a renewal approach that is used to build a unified framework to gated reactions on networks. Specifically, we employ this approach to provide simple and general relations between gated and ungated reaction times. These, in turn, are used to show that it is enough to solve for the ungated problem to readily obtain a solution for the corresponding gated problem.

Solving the ungated problem is generally a much simpler task, which, e.g., allows for clean rederivation of classic results that were previously obtained via brute-force methods. Moreover, the relations derived below open the door for systematic and widespread analysis of gated kinetics by providing ready-made solutions in all cases where the underlying, i.e., ungated, problem has already been (or can be) solved. This important feature of our framework has already proven extremely useful in the context of stochastic resetting where similar renewal methods were heavily employed [56–72].

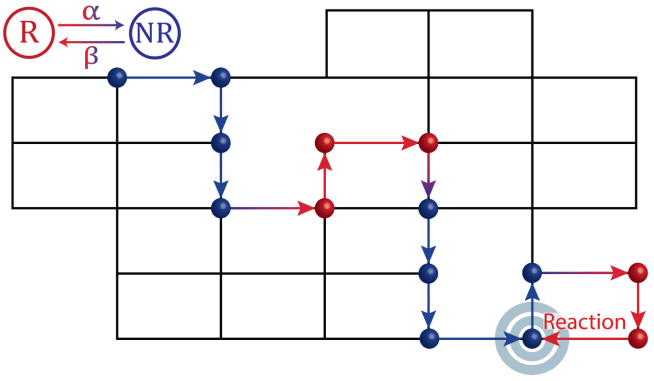

FIG. 1. Illustration of a gated reaction on a network. The reactant, here depicted as a small sphere, performs a continuous-time random walk while switching between the nonreactive (NR, blue) and reactive (R, red) states. Reaction occurs when two conditions are met: (i) the reactant is at the target (shown as bullseye); and (ii) the reactant is in the reactive state.

The framework developed herein is also used to unravel the existence of universal features of gated reactions. Specifically, we point to the effect of fluctuations in the time between consecutive molecular collisions and show that these always lead to an increase in the *mean* completion time of a gated reaction. Moreover, in cases where wild fluctuations lead to diverging means, we show that the exponent governing the heavy-tailed asymptotics of the ungated reaction is inherited by the gated reaction; thus generalizing earlier observations made for simple diffusion [41,42,55]. Finally, the framework is utilized to expose exotic kinetic features that arise due to gating. As we show, these can be observed even in simple model systems such as the 1D random walk, yet they have so far been overlooked. In what follows, we use $\langle Z\rangle$, $\sigma(Z)$, and $\tilde{Z}(s) \equiv \langle e^{-sZ}\rangle$ to denote, respectively, the expectation, standard deviation, and Laplace transform of a real-valued random variable Z.

Gated reactions on networks.—The set of problems we analyze below is formulated as follows. Consider a reactant (particle) performing a continuous-time random walk (CTRW) [73] on a network (see Fig. 1, for an example of a finite network embedded in a 2D lattice). In addition to its spatial motion, the reactant also undergoes stochastic internal dynamics flipping between a reactive state and a nonreactive state. A reaction is deemed to occur if the reactant is found in the reactive state while its spatial position overlaps with the origin—a designated target site which, e.g., harbors a complementary reactant. To keep things general, we make no assumptions on the network on top of which the dynamics takes place, the distributions that govern waiting times in the different sites, and the distributions that govern the random motion (jumps) of the particle between network sites. Importantly, waiting time distributions can be nonexponential, thus allowing for non-Markovian spatial dynamics. In addition, both waiting time and jump distributions can be site dependent, thus allowing treatment of inhomogeneous media of various kinds.

To progress, we assume that the position of the particle is decoupled from its internal state. The strategy is then to "divide and rule." First, we tackle the reactant's internal dynamics which is hereby assumed to be governed by a continuous-time Markov chain composed of two states: reactive (R) and nonreactive (NR). The transition rate from R to NR is denoted by α and the transition rate from NR to R is denoted by β (Fig. 1, top left). We are interested in the conditional probability to be in each of the states after time t, given an initial internal state $q_0 \in \{\mathrm{R}, \mathrm{NR}\}$. For example, when $q_0 = \mathrm{NR}$, this is given by $P(\mathrm{R}, t|\mathrm{NR}) = \pi_{\mathrm{R}}(1 - e^{-\lambda t})$ and $P(\mathrm{NR}, t|\mathrm{NR}) = \pi_{\mathrm{NR}} + \pi_{\mathrm{R}} e^{-\lambda t}$, where $\lambda = \alpha + \beta$ is the effective relaxation rate and with $\pi_{\mathrm{R}} = \beta/\lambda$ and $\pi_{\mathrm{NR}} = \alpha/\lambda$ standing for the equilibrium occupancies.

Consider now the time $T(\mathbf{x}_0)$ it takes the particle to react given an initial location $\mathbf{r}_0$ and an initial internal state q_0

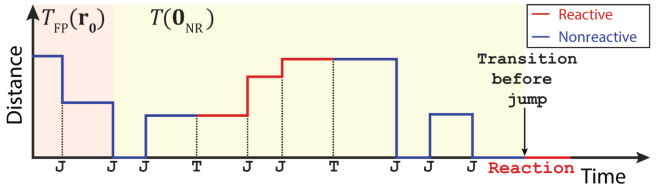

FIG. 2. The gated reaction time $T(\mathbf{x}_0)$ from Eq. (1) has two contributing factors: (i) the first-passage time of the particle to the origin $T_{\mathrm{FP}}(\mathbf{r}_0)$; and (ii) the time it takes the particle to react after it has first reached the origin. In the illustration this time is given by $T(\mathbf{0}_{\mathrm{NR}})$, and I_{FP} in Eq. (1) takes care of situations where the particle arrives at the origin in the reactive state and reacts immediately. On the time axis, J stands for jump and T for transition between internal states.

which we jointly denote by $\mathbf{x}_0 = (\mathbf{r}_0, q_0)$. Two contributions feed into $T(\mathbf{x}_0)$ as illustrated in Fig. 2: (i) $T_{\mathrm{FP}}(\mathbf{r}_0)$ which is the first-passage time of the particle to the origin; and (ii) the time it takes the particle to react after it has first reached the origin. If the particle arrives at the origin in the reactive state it reacts immediately. Otherwise, the particle—which is now found at the origin in the nonreactive state—can be seen to start its motion anew with the following initial conditions $\mathbf{0}_{\mathrm{NR}} \equiv (\mathbf{0}, \mathrm{NR})$. Thus, letting $T(\mathbf{0}_{\mathrm{NR}})$ denote the reaction time starting from $\mathbf{0}_{\mathrm{NR}}$, we have

$$T(\mathbf{x}_0) = T_{\mathrm{FP}}(\mathbf{r}_0) + I_{\mathrm{FP}} T(\mathbf{0}_{\mathrm{NR}}), \tag{1}$$

where I_{FP} is an indicator random variable that receives the value 1 if the particle first arrived at the origin in the nonreactive state and 0 otherwise. Clearly, I_{FP} depends on the initial state q_0 and on the first-passage time $T_{\mathrm{FP}}(\mathbf{r}_0)$, but is independent of $T(\mathbf{0}_{\mathrm{NR}})$ due to renewal [74].

Taking expectations in Eq. (1) we find [74]

$$\langle T(\mathbf{x}_0)\rangle = \langle T_{\mathrm{FP}}(\mathbf{r}_0)\rangle + [\pi_{\mathrm{NR}} \pm (1 - \pi_{q_0})\tilde{T}_{\mathrm{FP}}(\mathbf{r}_0, \lambda)]\langle T(\mathbf{0}_{\mathrm{NR}})\rangle, \tag{2}$$

where we have a plus sign if $q_0 = \mathrm{NR}$, and a minus sign if $q_0 = \mathrm{R}$, and where $\tilde{T}_{\mathrm{FP}}(\mathbf{r}_0, \lambda) = \langle e^{-sT_{\mathrm{FP}}(\mathbf{r}_0)}\rangle|_{s=\lambda}$ is the Laplace transform of $T_{\mathrm{FP}}(\mathbf{r}_0)$ evaluated at λ. Note that as $\mathbf{r}_0$ is pushed far away from the origin, $\tilde{T}_{\mathrm{FP}}(\mathbf{r}_0, \lambda)$ becomes negligible since $e^{-\lambda T_{\mathrm{FP}}(\mathbf{r}_0)}$ is then typically very small. In this limit, the internal state equilibrates before the particle arrives at the origin, and the mean reaction time in Eq. (2) becomes independent of the initial internal state.

The distribution of the gated reaction time can also be computed. Taking the Laplace transform of Eq. (1), we find [74]

$$\tilde{T}(\mathbf{x}_0, s) = \tilde{T}_{\mathrm{FP}}(\mathbf{r}_0, s)[\pi_{\mathrm{R}} + \pi_{\mathrm{NR}}\tilde{T}(\mathbf{0}_{\mathrm{NR}}, s)] \pm (1 - \pi_{q_0})\tilde{T}_{\mathrm{FP}}(\mathbf{r}_0, s + \lambda)[\tilde{T}(\mathbf{0}_{\mathrm{NR}}, s) - 1], \tag{3}$$

where we have a plus sign if $q_0 = \mathrm{NR}$, and a minus sign if $q_0 = \mathrm{R}$. Here, too, the above expression simplifies

considerably when $\mathbf{r}_0$ is far away from the origin. In this limit $\tilde{T}_{\mathrm{FP}}(\mathbf{r}_0, s+\lambda)$ is negligible, and one is left with the first term which is independent of the initial internal state.

Examining Eqs. (2) and (3) above reveals that part of the work required to determine the mean and distribution of a gated reaction time can be reduced to the solution of a standard (ungated) first-passage time problem. Namely, one requires $T_{\mathrm{FP}}(\mathbf{r}_0)$ which can be obtained by standard methods [4]. However, we are still left with the task of computing the gated reaction time $T(\mathbf{0}_{\mathrm{NR}})$. The mean and distribution of this random time will be our main focus going forward.

Let $W_{\mathbf{0}}$ denote the random time the particle waits at the origin before jumping to a different site, and let the random variable $\mathbf{X_1}$ stand for the location of the particle following this jump, e.g., ± 1 with equal probability for a symmetric random walk in 1D; and see [74] for further discussion. Setting W_{NR} as the random waiting time of the particle in the nonreactive state, we observe that the gated reaction time $T(\mathbf{0}_{\mathrm{NR}})$ can be written as follows:

$$T(\mathbf{0}_{\mathrm{NR}}) = \begin{cases} W_{\mathrm{NR}} & \text{if } W_{\mathrm{NR}} < W_{\mathbf{0}}, \\ W_{\mathbf{0}} + T_{\mathrm{FP}}(\mathbf{X}_1) + I_{\mathrm{FP}} T'(\mathbf{0}_{\mathrm{NR}}) & \text{if } W_{\mathrm{NR}} \geq W_{\mathbf{0}}, \end{cases} \tag{4}$$

where $T_{\mathrm{FP}}(\mathbf{X_1})$ is the first-passage time to the origin starting from $\mathbf{X_1}$, I_{FP} is the internal state indicator associated with this first-passage process (defined as before), and $T'(\mathbf{0}_{\mathrm{NR}})$ is an IID copy of $T(\mathbf{0}_{\mathrm{NR}})$. Indeed, if $W_{\mathrm{NR}} < W_{\mathbf{0}}$, the particle transitions to the reactive state before jumping out of the origin and a reaction immediately follows. Conversely, if $W_{\mathrm{NR}} \geq W_{\mathbf{0}}$, the particle jumps out of the origin before transitioning to the reactive state. It then requires a time $T_{\mathrm{FP}}(\mathbf{X_1})$ to return to the origin, and an additional gated reaction time $T'(\mathbf{0}_{\mathrm{NR}})$ provided it returned in the nonreactive state. We thus see that the gated reaction time $T(\mathbf{0}_{\mathrm{NR}})$ can be expressed in terms of an ungated first-passage time $T_{\mathrm{FP}}(\mathbf{X_1})$ and the waiting times W_{NR} and $W_{\mathbf{0}}$.

The mean completion time of a gated reaction.—To proceed, we recall that here we assumed Markovian internal dynamics which means that W_{NR} is exponentially distributed with rate β. We will now also assume that $W_{\mathbf{0}}$ is exponentially distributed with rate γ, but note that this assumption is made for clarity and that it can be easily generalized. Also, note that waiting times in other sites are kept general. Taking expectations in Eq. (4) we find [74]

$$\langle T(\mathbf{0}_{\mathrm{NR}})\rangle = \frac{\gamma^{-1} + \langle T_{\mathrm{FP}}(\mathbf{X_1})\rangle}{K_D + \pi_{\mathrm{R}}[1 - \tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, \lambda)]}, \tag{5}$$

where $K_D = \beta/\gamma$, $\pi_{\mathrm{R}} = \beta/\lambda$, and with $\lambda = \alpha + \beta$. Equation (5) asserts that $\langle T(\mathbf{0}_{\mathrm{NR}})\rangle$ can be determined provided the mean and distribution of the ungated return time $T_{\mathrm{FP}}(\mathbf{X_1})$.

To better understand Eq. (5), we observe that the $\langle T(\mathbf{0}_{\mathrm{NR}})\rangle \sim \beta^{-1}$ asymptotics holds for both large and small value of β. Specifically, when $\beta \gg 1$ a reaction is almost sure to happen before the particle leaves the origin. In this limit one can safely neglect $T(\mathbf{0}_{\mathrm{NR}})$ in Eqs. (1) and (2) concluding that the gated and ungated problems are practically equivalent. In the other extreme, $\beta \ll 1$, the transition to the nonreactive state becomes rate limiting and $\langle T(\mathbf{0}_{\mathrm{NR}})\rangle \gg 1$.

Next, consider the limit $\gamma \gg 1$ in which the particle leaves the origin almost instantaneously and without reacting. We then find $\langle T(\mathbf{0}_{\mathrm{NR}})\rangle \simeq \pi_{\mathrm{R}}^{-1}[1 - \tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, \lambda)]^{-1}\langle T_{\mathrm{FP}}(\mathbf{X_1})\rangle$. To understand this result observe that in this limit the probability that the particles return to the origin in the reactive state is given by $p = \pi_{\mathrm{R}}[1 - \tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, \lambda)]$. Thus, on average, the particle returns to the origin $1/p$ times before a reaction occurs with each return taking $\langle T_{\mathrm{FP}}(\mathbf{X_1})\rangle$ time units on average. In the other extreme $\gamma \ll 1$, the particle is slow to leave the origin and a reaction occurs following a transition to the nonreactive state. In this limit we find $\langle T(\mathbf{0}_{\mathrm{NR}})\rangle \simeq 1/\beta$.

The mean reaction time in Eq. (5) scales linearly with the mean of $T_{\mathrm{FP}}(\mathbf{X_1})$ as expected. To better understand how fluctuations in the return time to the origin affect the result, we neglect the dissociation time γ^{-1} and expand $\tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, \lambda)$ by its moments to second order in λ. Doing this we obtain $\langle T(\mathbf{0}_{\mathrm{NR}})\rangle \simeq \beta^{-1} + \frac{1}{2}\pi_{\mathrm{R}}^{-1}(1 + CV^2)\langle T_{\mathrm{FP}}(\mathbf{X_1})\rangle$, where $CV = \sigma(T_{\mathrm{FP}}(\mathbf{X_1}))/\langle T_{\mathrm{FP}}(\mathbf{X_1})\rangle$ stands for the coefficient of variation [74]. We thus see that fluctuations in $T_{\mathrm{FP}}(\mathbf{X_1})$ tend to increase the mean completion time of the gated reaction. In fact, invoking Jensen's inequality we get

$$\langle T(\mathbf{0}_{\mathrm{NR}})\rangle \geq \frac{\gamma^{-1} + \langle T_{\mathrm{FP}}(\mathbf{X_1})\rangle}{K_D + \pi_{\mathrm{R}}[1 - e^{-\lambda\langle T_{\mathrm{FP}}(\mathbf{X_1})\rangle}]}, \tag{6}$$

where the equality holds if and only if $\sigma(T_{\mathrm{FP}}(\mathbf{X_1})) = 0$. A deterministic return time thus yields a universal lower bound for $\langle T(\mathbf{0}_{\mathrm{NR}})\rangle$, and any fluctuation around the mean return time $\langle T_{\mathrm{FP}}(\mathbf{X_1})\rangle$ will necessarily slow down the completion of the gated reaction. This effect is illustrated in Fig. 3.

Beyond the mean.—We now turn attention to the distribution of $T(\mathbf{0}_{\mathrm{NR}})$. Laplace transforming Eq. (4) we get [74]

$$\tilde{T}(\mathbf{0}_{\mathrm{NR}}, s) = \frac{\pi_{\mathrm{R}}^{-1} K_D + \tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, s) - \tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, s+\lambda)}{\pi_{\mathrm{R}}^{-1}[(s/\gamma) + K_D + 1] - K_{eq}\tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, s) - \tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, s+\lambda)}, \tag{7}$$

where $K_{eq} = \alpha/\beta$; and it can once again be appreciated that the gated reaction time can be put in terms of the ungated return time to the origin $T_{\mathrm{FP}}(\mathbf{X_1})$.

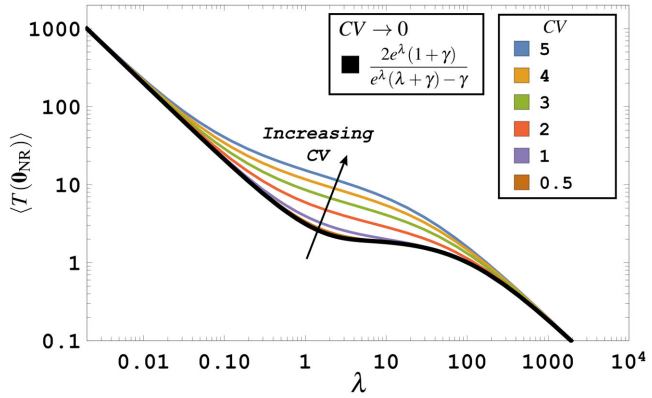

FIG. 3. Fluctuations in the return time to the origin increase the mean completion time of a gated reaction (see [74] for additional details and analysis). The mean reaction time $\langle T(\mathbf{0}_{\mathrm{NR}})\rangle$ from Eq. (5) vs the internal relaxation rate $\lambda = \alpha + \beta$. Here, we consider the symmetric case $\alpha = \beta = \lambda/2$ with $\gamma = 100$, and illustrate the effect by taking the return time $T_{\mathrm{FP}}(\mathbf{X_1})$ from a gamma distribution with unit mean and increasing values of the CV. The black line corresponds to the deterministic, $CV = 0$, case which gives rise to the lower bound in Eq. (6). Higher CVs lead to higher mean completion times as predicted. It can be appreciated that the asymptotic $\langle T(\mathbf{0}_{\mathrm{NR}})\rangle \sim \beta^{-1} \sim \lambda^{-1}$ behavior is common to all curves in both the high and low λ regimes as discussed below Eq. (5).

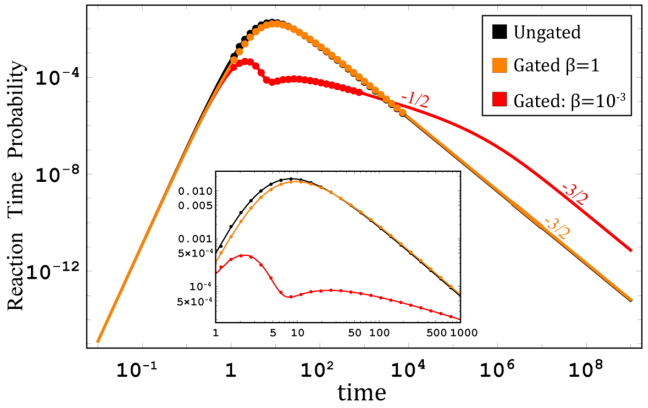

FIG. 4. Gated reaction time distributions for CTRW on a 1D lattice and the ungated behavior for comparison. Here, the particle is taken to start from position $\mathbf{r}_0 = +5$ in the reactive state. The transition rate to the nonreactive state is $\alpha = 1$ and two different rates are considered for the reverse reaction: $\beta = 10^{-3}$ (red) and $\beta = 1$ (orange). The waiting time distribution in all sites (origin included) is taken to be exponential with rate $\gamma = 1$. Solid lines come from numerical inversion of Eq. (3) and full circles from Monte Carlo simulations.

Equation (7) is indispensable in cases where $\langle T_{\mathrm{FP}}(\mathbf{X_1})\rangle$ diverges. Equation (5) then provides little information, but Eq. (7) can still be used to, e.g., show that $T(\mathbf{0}_{\mathrm{NR}})$ inherits the tail asymptotics of $T_{\mathrm{FP}}(\mathbf{X_1})$. Specifically we find that if $\tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, s) \simeq 1 - (\tau s)^{\theta}$ for $s \ll 1$, with $0 < \theta < 1$ and $\tau > 0$, then [74]

$$\tilde{T}(\mathbf{0}_{\mathrm{NR}}, s) \simeq 1 - \frac{\pi_{\mathrm{R}}^{-1}}{1 - \tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, \lambda) + \lambda/\gamma}(\tau s)^{\theta}. \qquad (8)$$

From here it follows that if the survival function of $T_{\mathrm{FP}}(\mathbf{X_1})$ decays as $\sim t^{-\theta}$, then so does that of $T(\mathbf{0}_{\mathrm{NR}})$; and the prefactor can be determined by Eq. (8) and the Tauberian theorem.

Putting it all to work.—To illustrate the applicability of our approach, consider now a simple symmetric random walk on a 1D lattice. Starting the walk at $\mathbf{r}_0$, and working in discrete time, it is well known that the generating function of the first-passage time to the origin is given by $\hat{T}_{\mathrm{FP}}(\mathbf{r}_0, z) = [(1 - \sqrt{1 - z^2})/z]^{|\mathbf{r}_0|}$ [14]. The corresponding solution in continuous time is then given by $\tilde{T}_{\mathrm{FP}}(\mathbf{r}_0, s) = [(1 - \sqrt{1 - \tilde{\psi}(s)^2})/\tilde{\psi}(s)]^{|\mathbf{r}_0|}$, where we have simply replaced z with the Laplace transform of the waiting-time distribution $\tilde{\psi}(s)$ in the CTRW [75]. Finally, we trivially observe that when such a symmetric random walk leaves the origin it will be found at ± 1 with equal probability. As the return time from these lattice points to the origin is equal in law, we have $\tilde{T}_{\mathrm{FP}}(\mathbf{X_1}, s) = \tilde{T}_{\mathrm{FP}}(+1, s)$. Substituting these results into Eq. (7) and then (3), the solution to the corresponding gated problem is readily obtained; and we have verified that this solution identifies with the solution obtained by Budde, Cáceres, and Ré for a particle that is initially prepared in the reactive state [41,42]. In lieu of the general approach developed herein, the latter was obtained with admirable effort.

Continuing with the same example, we plot numerical inversions [76] of the reaction time distribution in Eq. (3) (Fig. 4). Two gated cases, and the corresponding ungated case, are compared. We first observe that the power law governing the long time asymptotics of all distributions is identical to the $\sim t^{-3/2}$ decay which is characteristic to the first-passage probability of the 1D random walk. These asymptotic results agree with the prediction of Eq. (8). However, the behavior at intermediate times differs significantly between gated cases. For the first case (orange), we take $\beta = 1$ which gives an overall behavior that is almost identical to that observed for the ungated case where the particle is always reactive. In the second case (red), we take $\beta = 10^{-3}$ and find that this leads to the emergence of a wide intermediate time window that is governed by a $\sim t^{-1/2}$ power-law decay. This "cryptic regime" was also observed in the analogous diffusion problem studied by Mercado-Vásquez and Boyer [55], but here we see that it can also be accompanied by an additional exotic and previously unobserved kinetic effect which renders the gate reaction time distribution multimodal (Fig. 4, inset). We trace this effect to the existence of two populations of particles: those which reached the origin without ever switching to the nonreactive state and those which switched

prior to reaching. As the latter are blocked from reacting for a mean time $1/\beta \gg 1$ that is much larger than the median return time to the origin, two distinct peaks are formed.

Numerical applications.—The approach taken for the 1D CTRW extends to many other first-passage time problems for which analytical results are known. In all such cases, the framework developed herein can be used to readily yield corresponding solutions for gated reaction times. However, in many complicated scenarios analytical results are not available and one must then resort to numerical simulations. We now explain how these can be considerably sped up by taking advantage of the relations derived above. Consider, for example, the mean time of a gated reaction, and imagine that the latter should be determined via numerical simulations for a wide range of rate constants α, β, and γ. While this process can be extremely time consuming, one can instead take advantage of Eq. (5) which only requires numerical determination of the mean and distribution of the ungated first-passage time $T_{\mathrm{FP}}(\mathbf{X_1})$. As the latter does not depend on the above parameters it can be determined once and for all, thus providing a quick and efficient way of getting gated reaction times. Similar reasoning applies to the mean gated reaction time in Eq. (2), which in turn requires determination of one additional ungated first-passage time: $T_{\mathrm{FP}}(\mathbf{r}_0)$. In [74] we exemplify successful implementation of this procedure for the gated reaction depicted in Fig. 1.

Conclusions.—In this Letter, we developed a unified approach to gated reactions on networks, and the results obtained were used to extract considerable insight. Applications cover the entire spectrum of chemical reactions and are especially relevant to the emerging field of single-molecule chemistry where recent technological advancements allow predictions coming from our framework to be tested experimentally. As our framework extends current knowledge on the long studied topic of first-passage it also applies more broadly, and shall be particularly useful in the context of search and foraging where similar ideas also apply.

S. R. acknowledges support from the Azrieli Foundation, from the Raymond and Beverly Sackler Center for Computational Molecular and Materials Science at Tel Aviv University, and from the Israel Science Foundation (Grant No. 394/19). The authors wish to thank Arnab Pal, Somrita Ray, Sarah Kostinski, and Ofek Lauber Bonomo for fruitful conversations and advice.

*yuvalscher@mail.tau.ac.il
†shlomire@tauex.tau.ac.il

[1] S. Redner, *A Guide to First-Passage Processes* (Cambridge University Press, Cambridge, England, 2001).
[2] A. J. Bray, S. N. Majumdar, and G. Schehr, Persistence and first-passage properties in nonequilibrium systems, Adv. Phys. **62**, 225 (2013).
[3] R. Metzler, S. Redner, and G. Oshanin, *First-Passage Phenomena and Their Applications* (World Scientific, Singapore, 2014).
[4] J. Klafter and I. M. Sokolov, *First Steps in Random Walks: From Tools to Applications* (Oxford University Press, New York, 2011).
[5] S. Iyer-Biswas and A. Zilman, First-passage processes in cellular biology, Adv. Chem. Phys. **160**, 261 (2016).
[6] T. Chou and M. R. D'Orsogna, *First Passage Problems in Biology*, First-Passage Phenomena and Their Applications (World Scientific, Singapore, 2014), pp. 306–345.
[7] N. F. Polizzi, M. J. Therien, and D. N. Beratan, Mean first-passage times in biology, Isr. J. Chem. **56**, 816 (2016).
[8] R. A. Alberty and G. G. Hammes, Application of the theory of diffusion-controlled reactions to enzyme kinetics, J. Phys. Chem. **62**, 154 (1958).
[9] A. Szabo, Kinetics of hemoglobin and transition state theory, Proc. Natl. Acad. Sci. U.S.A. **75**, 2108 (1978).
[10] M. Karplus and D. L. Weaver, Diffusion-collision model for protein folding, Biopolymers **18**, 1421 (1979).
[11] D. D. Boehr, R. Nussinov, and P. E. Wright, The role of dynamic conformational ensembles in biomolecular recognition, Nat. Chem. Biol. **5**, 789 (2009).
[12] J. P. Changeux and S. Edelstein, Conformational selection or induced fit? 50 years of debate resolved, F1000 Biol. Rep. **3**, 19 (2011).
[13] A. D. Vogt and E. Di Cera, Conformational selection or induced fit? A critical appraisal of the kinetic mechanism, Biochemistry **51**, 5894 (2012).
[14] M. Steele, *Stochastic Calculus and Financial Applications* (Springer Science & Business Media, New York, 2012).
[15] R. Chicheportiche and J. P. Bouchaud, in Some Applications of First-Passage Ideas to Finance. First-Passage Phenomena and Their Applications (2014), pp. 447–476.
[16] V. Sood, S. Redner, and D. Ben-Avraham, First-passage properties of the Erdős-Renyi random graph, J. Phys. A **38**, 109 (2004).
[17] S. Condamin, O. Bénichou, V. Tejedor, R. Voituriez, and J. Klafter, First-passage times in complex scale-invariant media, Nature (London) **450**, 77 (2007).
[18] V. Tejedor, O. Bénichou, and R. Voituriez, Global mean first-passage times of random walks on complex networks, Phys. Rev. E **80**, 065104 (2009).
[19] S. Reuveni, R. Granek, and J. Klafter, General mapping between random walks and thermal vibrations in elastic networks: Fractal networks as a case study, Phys. Rev. E **82**, 041132 (2010).
[20] S. Hwang, D. S. Lee, and B. Kahng, First Passage Time for Random Walks in Heterogeneous Networks, Phys. Rev. Lett. **109**, 088701 (2012).
[21] I. Tishby, O. Biham, and E. Katzav, The distribution of first hitting times of random walks on Erdős-Rényi networks, J. Phys. A **50**, 115001 (2017).
[22] M. V. Smoluchowski, Drei vortrage uber diffusion. Brownsche bewegung und koagulation von kolloidteilchen, Z. Phys. **17**, 557 (1916).
[23] M. V. Smoluchowski, Versuch einer mathematischen Theorie der Koagulationskinetik kolloider Lösungen, Z. Phys. Chem. **92**, 129 (1918).

[24] O. Bénichou, C. Chevalier, J. Klafter, B. Meyer, and R. Voituriez, Geometry-controlled kinetics, Nat. Chem. **2**, 472 (2010).

[25] F. C. Collins and G. E. Kimball, Diffusion-controlled reaction rates, J. Colloid Sci. **4**, 425 (1949).

[26] H. L. Frisch and F. C. Collins, Diffusional processes in the growth of aerosol particles, J. Chem. Phys. **20**, 1797 (1952).

[27] H. Sano and M. Tachiya, Partially diffusion-controlled recombination, J. Chem. Phys. **71**, 1276 (1979).

[28] D. Shoup, G. Lipari, and A. Szabo, Diffusion-controlled bimolecular reaction rates. The effect of rotational diffusion and orientation constraints, Biophys. J. **36**, 697 (1981).

[29] A. Szabo, G. Lamm, and G. H. Weiss, Localized partial traps in diffusion processes and random walks, J. Stat. Phys. **34**, 225 (1984).

[30] A. Szabo, Theory of diffusion-influenced fluorescence quenching, J. Phys. Chem. **93**, 6929 (1989).

[31] S. F. Burlatsky and G. S. Oshanin, Diffusion-controlled reactions with polymers, Phys. Lett. **145A**, 61 (1990).

[32] J. Kim and S. Lee, Theory of diffusion-influenced bimolecular reactions in solution: Effects of a stochastic gating mode, Bull. Korean Chem. Soc. **13**, 398 (1992), https://www.koreascience.or.kr/article/JAKO199213464458050.page.

[33] A. M. Berezhkovskii, Y. A. Makhnovskii, and R. A. Suris, Kinetics of diffusion-controlled reactions, Chem. Phys. **137**, 41 (1989).

[34] D. F. Calef and J. M. Deutch, Diffusion-controlled reactions, Annu. Rev. Phys. Chem. **34**, 493 (1983).

[35] G. H. Weiss, Overview of theoretical models for reaction rates, J. Stat. Phys. **42**, 3 (1986).

[36] J. A. McCammon and S. H. Northrup, Gated binding of ligands to proteins, Nature (London) **293**, 316 (1981).

[37] A. Szabo, K. Schulten, and Z. Schulten, First passage time approach to diffusion controlled reactions, J. Chem. Phys. **72**, 4350 (1980).

[38] A. Szabo, D. Shoup, S. H. Northrup, and J. A. McCammon, Stochastically gated diffusion-influenced reactions, J. Chem. Phys. **77**, 4484 (1982).

[39] A. M. Berezhkovskii, D. Y. Yang, S. H. Lin, Y. A. Makhnovskii, and S. Y. Sheu, Smoluchowski-type theory of stochastically gated diffusion-influenced reactions, J. Chem. Phys. **106**, 6985 (1997).

[40] S. H. Northrup, F. Zarrin, and J. A. McCammon, Rate theory for gated diffusion-influenced ligand binding to proteins, J. Phys. Chem. **86**, 2314 (1982).

[41] C. E. Budde, M. O. Cáceres, and M. A. Ré, Transient behaviour in the absorption probability distribution in the presence of a non-Markovian dynamic trap, Europhys. Lett. **32**, 205 (1995).

[42] M. O. Cáceres, C. E. Budde, and M. A. Ré, Theory of the absorption probability density of diffusing particles in the presence of a dynamic trap, Phys. Rev. E **52**, 3462 (1995).

[43] M. A. Ré, C. E. Budde, and M. O. Cáceres, Survival probability in the presence of a dynamic trap, Phys. Rev. E **54**, 4427 (1996).

[44] J. L. Spouge, A. Szabo, and G. H. Weiss, Single-particle survival in gated trapping, Phys. Rev. E **54**, 2248 (1996).

[45] H. X. Zhou and A. Szabo, Theory and simulation of stochastically-gated diffusion-influenced reactions, J. Phys. Chem. **100**, 2597 (1996).

[46] W. S. Sheu, D. Y. Yang, and S. Y. Sheu, Survival of a walker in gated trapping systems, J. Chem. Phys. **106**, 9050 (1997).

[47] Y. A. Makhnovskii, A. M. Berezhkovskii, S. Y. Sheu, D. Y. Yang, J. Kuo, and S. H. Lin, Stochastic gating influence on the kinetics of diffusion-limited reactions, J. Chem. Phys. **108**, 971 (1998).

[48] W. S. Sheu, First-passage-time-distribution approach to gated trapping problems, J. Chem. Phys. **110**, 5469 (1999).

[49] T. Bandyopadhyay, K. Seki, and M. Tachiya, Theoretical analysis of the influence of stochastic gating on the transient effect in fluorescence quenching by electron transfer, J. Chem. Phys. **112**, 2849 (2000).

[50] O. Bénichou, M. Moreau, and G. Oshanin, Kinetics of stochastically gated diffusion-limited reactions and geometry of random walk trajectories, Phys. Rev. E **61**, 3388 (2000).

[51] A. Godec and R. Metzler, First passage time statistics for two-channel diffusion, J. Phys. A **50**, 084001 (2017).

[52] J. Reingruber and D. Holcman, Gated Narrow Escape Time for Molecular Signaling, Phys. Rev. Lett. **103**, 148102 (2009).

[53] P. C. Bressloff and S. D. Lawley, Escape from subcellular domains with randomly switching boundaries, Multiscale Model. Simul. **13**, 1420 (2015).

[54] J. Shin and A. B. Kolomeisky, Molecular search with conformational change: One-dimensional discrete-state stochastic model, J. Chem. Phys. **149**, 174104 (2018).

[55] G. Mercado-Vásquez and D. Boyer, First Hitting Times to Intermittent Targets, Phys. Rev. Lett. **123**, 250603 (2019).

[56] M. R. Evans and S. N. Majumdar, Diffusion with Stochastic Resetting, Phys. Rev. Lett. **106**, 160601 (2011).

[57] S. Reuveni, M. Urbakh, and J. Klafter, Role of substrate unbinding in Michaelis-Menten enzymatic reactions, Proc. Natl. Acad. Sci. U.S.A. **111**, 4391 (2014).

[58] J. M. Meylahn, S. Sabhapandit, and H. Touchette, Large deviations for Markov processes with resetting, Phys. Rev. E **92**, 062148 (2015).

[59] S. Reuveni, Optimal Stochastic Restart Renders Fluctuations in First Passage Times Universal, Phys. Rev. Lett. **116**, 170601 (2016).

[60] A. Pal and S. Reuveni, First Passage under Restart, Phys. Rev. Lett. **118**, 030603 (2017).

[61] A. Chechkin and I. M. Sokolov, Random Search With Resetting: A Unified Renewal Approach, Phys. Rev. Lett. **121**, 050601 (2018).

[62] M. R. Evans and S. N. Majumdar, Run and tumble particle under resetting: A renewal approach, J. Phys. A **51**, 475003 (2018).

[63] A. Pal, I. Eliazar, and S. Reuveni, First Passage under Restart with Branching, Phys. Rev. Lett. **122**, 020602 (2019).

[64] A S. Bodrova, A. V. Chechkin, and I. M. Sokolov, Scaled Brownian motion with renewal resetting, Phys. Rev. E **100**, 012120 (2019).

[65] S. Ray, D. Mondal, and S. Reuveni, Péclet number governs transition to acceleratory restart in drift-diffusion, J. Phys. A **52**, 255002 (2019).

[66] A. Pal, L. Kusmierz, and S. Reuveni, Search with home returns provides advantage under high uncertainty, Phys. Rev. Research **2**, 043174 (2020).

[67] M. R. Evans, S. N. Majumdar, and G. Schehr, Stochastic resetting and applications, J. Phys. A **53**, 193001 (2020).
[68] D. Gupta, C. A. Plata, and A. Pal, Work Fluctuations and Jarzynski Equality in Stochastic Resetting, Phys. Rev. Lett. **124**, 110608 (2020).
[69] O. Tal-Friedman, A. Pal, A. Sekhon, S. Reuveni, and Y. Roichman, Experimental realization of diffusion with stochastic resetting, J. Phys. Chem. Lett. **11**, 7350 (2020).
[70] S. Ray and S. Reuveni, Diffusion with resetting in a logarithmic potential, J. Chem. Phys. **152**, 234110 (2020).
[71] I. Eliazar and S. Reuveni, Mean-performance of sharp restart I: Statistical roadmap, J. Phys. A **53**, 405004 (2020).
[72] B. De Bruyne, J. Randon-Furling, and S. Redner, Optimization in First-Passage Resetting, Phys. Rev. Lett. **125**, 050602 (2020).
[73] E. W. Montroll and G. H. Weiss, Random walks on lattices. II, J. Math. Phys. (N.Y.) **6**, 167 (1965).
[74] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.127.018301 for: (i) Derivation of Eq. (2) in the main text. (ii) Derivation of Eq. (3) in the main text. (iii) On the meaning of $\mathbf{X_1}$ in Eq. (4). (iv) Derivation of Eq. (5) in the main text. (v) Small λ expansion of $T(\mathbf{0}_{\mathrm{NR}})$ (vi) Gamma-Distributed Return Times. (vii) Derivation of Eq. (7) in the main text. (viii) Derivation of Eq. (8) in the main text. (ix) Analysing the gated reaction depicted in Fig. 1 of the main text.
[75] G. Bel and E. Barkai, Random walk to a nonergodic equilibrium concept, Phys. Rev. E **73**, 016125 (2006).
[76] J. Abate and P. P. Valkó, Multi-precision Laplace transform inversion, Int. J. Numer. Methods Eng. **60**, 979 (2004).