Strong defocusing of molecular reaction times results from an interplay of geometry and reaction control

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Textbook concepts of diffusion-versus kinetic-control are well-defined for reaction-kinetics involving macroscopic concentrations of diffusive reactants that are adequately described by rate-constants—the inverse of the mean-first-passage-time to the reaction-event. In contradiction, an open important question is whether the mean-first-passage-time alone is a sufficient measure for biochemical reactions that involve nanomolar reactant concentrations. Here, using a simple yet generic, exactly solvable model we study the effect of diffusion and chemical reaction-limitations on the full reaction-time distribution. We show that it has a complex structure with four distinct regimes delineated by three characteristic time scales spanning a window of several decades. Consequently, the reaction-times are defocused: no unique time-scale characterises the reaction-process, diffusion- and kinetic-control can no longer be disentangled, and it is imperative to know the full reaction-time distribution. We introduce the concepts of geometry- and reaction-control, and also quantify each regime by calculating the corresponding reaction depth.
Reactions between chemically active molecules in condensed matter systems are typically controlled by two factors: the diffusive search of the species for each other\(^1\)-\(^3\) and the intrinsic reactivity \(\kappa\) associated with the probability that a reaction indeed occurs when the particles collide with each other\(^5\). For chemical reactions involving sufficiently high concentrations of particles, which are initially uniformly distributed in the container or reactor such that encounters between reactive species occur more or less uniformly in time, theories based on mean effective reaction rates provide an adequate description of the reaction kinetics\(^1\)-\(^2\)-\(^2\)—apart from some singular and well-known reaction schemes which exhibit anomalous, fluxification-induced kinetics under special physical conditions (see, for instance refs. \(^4\)-\(^6\)-\(^11\)). Since the seminal works by Smoluchowski\(^12\) and Collins and Kimball\(^13\) a vast number of theoretical advances have scrutinised a combined effect of both rate-controlling factors on the mean effective rates providing a comprehensive understanding of this effect\(^13\)-\(^14\)-\(^17\). In particular, the mean reaction time is the sum of two time scales corresponding to the inverse diffusion coefficient and the inverse intrinsic reactivity (see Eq. (5)), such that the influence of diffusion control and (chemical) rate control are separable\(^13\).

For many biochemical reactions, however, the reactive species do not exist in sufficiently abundant amounts to give rise to smooth concentration levels. In contrast, only small numbers of biomolecules, released at certain prescribed positions, are often involved in the reaction process. Indeed, in systems such as the well-studied Lac and phage lambda repressor proteins only few to few tens of molecules are typically present in a living biological cell, corresponding to nanomolar concentrations. The starting positions of biomolecules can either be rather close to the target or relatively far away. Particularly in the context of the rapid search hypothesis of gene expression, it was shown that the geometric distance between two genes, communicating with each other via signalling proteins, is typically kept short by design in biological cells\(^18\), guaranteeing higher-than-average concentrations of proteins around the target in conjunction with fast and reliable signalling\(^19\). Quite generically, many intracellular processes of signalling, regulation, infection, immune reactions, metabolism or transmitter release in neurons are triggered by the arrival of one or few biomolecules to a small spatially localised region\(^20\)-\(^21\). In such cases, it becomes inappropriate to rely on mean rates, and one needs to know the whole distribution of random reaction times, also called the first passage times in the same context. Once the reacting outer boundary can mimic an impenetrable cell membrane, the reaction container’s surface or be an effective virtual front of the “zone of influence” of the target molecule, separating it from other remotely located target molecules.

Assuming that the domain has a spherical shape and placing the target at the origin of this domain renders the model exactly solvable. We note that although such a geometrical setup is simplified as compared with realistic situations (e.g., the target site is not necessarily located at the centre of the domain\(^28\)-\(^29\)) or may be attached to some structure which partially screens it\(^35\), \(^36\), this model captures explicitly two essential ingredients of the reaction process: the diffusive search for the target site and its finite intrinsic reactivity. Importantly, the fact that the model is exactly solvable, permits us to unveil some generic features of the full RTD without resorting to any approximation.

Results

Mathematical model. We consider a model involving a pair of reactive molecules: a partially absorbing, immobile target site of radius \(\rho\) within a bounded domain of radius \(R\) limited by an impenetrable boundary, and a molecule, initially placed at some prescribed position and diffusing with diffusivity \(D\). Once the diffusing particle hits the surface of the target site, it reacts with (binds to) the latter with a finite, intrinsic reaction rate \(\kappa\). The reflecting outer boundary can mimic an impenetrable cell membrane, the reaction container’s surface or be an effective virtual front of the “zone of influence” of the target molecule, separating it from other remotely located target molecules.
The probability density function $H(r, t)$ of the reaction time $t$ for a particle released a radial distance $r - p$ away from the spherical target of radius $p$ is calculated using standard tools27,37,38: one first finds the survival probability $S(r, t)$ of a diffusing particle in a radially symmetric situation subject to the zero-current boundary condition on the outer boundary of the domain, and the "radiation", or partially-reflecting boundary condition$^1$–$^3$,$^39$

$$
\frac{\partial S(r, t)}{\partial r} \bigg|_{r=p} = \kappa S(p, t),
$$

imposed on the surface of the target site. The proportionality factor $\kappa$ in Eq. (2) is an intrinsic rate constant (of dimension length/time) whose value shows how readily the particle reacts with the target site upon encounter. When $\kappa = 0$ no reaction occurs, while the limit $\kappa = \infty$ corresponds to a perfect reaction, when a particle reacts with the target site upon a first encounter. These limiting cases therefore correspond to perfectly reflecting or absorbing boundaries, respectively. The RTD $H(r, t)$ is obtained as the negative derivative of $S(r, t)$ and is valid for arbitrary values of the system parameters. Details of these calculations are presented in the beginning of the Methods section.

Structure of the full distribution of reaction times. The typical shapes of the reaction time density $H(r, t)$ are shown in Fig. 1 for two different release radii $r$ and different values of the dimensionless reactivity $\kappa R/D$. Note that the parameter $\kappa R/D$ represents a combined effect of two factors: based on the definition of the standard chemical constant $K_{on} = 4\pi Dp\kappa$ for a forward reaction and the definition of the so-called Smoluchowski constant $K_S = 4\pi Dp$ we see that $\kappa R/D = (K_{on}/K_S)(R/p)$ and, hence, this is the ratio of the chemical rate and the Smoluchowski rate constant, multiplied by the ratio of the sizes of the domain and of the target site.

We notice that $H(r, t)$ has a much richer structure than the previously proposed simple form in Eq. (1). The RTD consists of four distinct time domains seen in Figs. 1–3: first, a sharp exponential cut-off at short reaction times terminating at the most probable time $t_{mp}$ second, a region spanning from the most probable reaction time to the crossover time $t_c$ in which $H(r, t)$ shows a slow power-law decrease; third, an extended plateau region beyond $t_c$ which stretches up to the mean reaction time $t_{mean}$; and fourth, an ultimate long-time exponential cut-off. The shape of the RTD for varying reactivities highlighting the geometry-controlled Lévy–Smirnov hump and the reaction-controlled plateau region is our central result. In order to get a deeper understanding of the time scales involved in the reaction process we also introduce and analyse in the Methods section the forms of two complementary characteristic times: the harmonic mean reaction time $t_{harm} = 1/(\langle D/t \rangle)$ and the typical reaction time $t_{typ} = t_c \exp(\langle \ln(t/t_b) \rangle)$, where the angular brackets denote averaging with respect to the RTD depicted in Figs. 1 and 2, and $t_b$ is an arbitrary time scale. Since the logarithm is a slowly varying function, its average value is dominated by the most frequent values of $t$, while anomalously large/small values corresponding to rare events provide a negligible contribution. Such an averaged value is widely used to estimate a typical behaviour in diverse situations$^{40,41}$.

Three characteristic time scales. The most probable reaction time, corresponding to the very pronounced maximum, can be

![Fig. 1 Reaction control. Reaction time density $H(r, t)$ for a reaction on an inner target of radius $p = R = 0.01$, with starting point $a$ $r = 0.2$ and $b$ $r = 0.02$ for four progressively decreasing (from top to bottom) values of the dimensionless reactivity $\kappa' = \kappa R/D$ indicated in the plot. Note that $\kappa'$ includes $R$ and $D$ such that smaller values of $\kappa'$ can also be achieved at a fixed $x$ upon lowering $R$ or by increasing the values of $D$. The coloured vertical arrows indicate the mean reaction times for these cases. The vertical black dashed line indicates the crossover time $t_c = 2(R - p)^2/(4\pi Dp)$ above which the contribution of higher order Laplacian eigenmodes become negligible. This characteristic time marks the end of the hump-like region (Lévy–Smirnov region specific to an unbounded system, see below and the Methods section for more details) and indicates the crossover to a plateau region with equiprobable realisations of the reaction times. This plateau region spans a considerable window of reaction times, especially for lower reactivity values. Thin coloured lines show the reaction time density $H_{on}(r, t)$ from Eq. (6) for the unbounded case ($R = \infty$). Length and time units are fixed by setting $R = 1$ and $D/T^2 = 1$. Note the extremely broad range of relevant reaction times (the horizontal axis) spanning over 12 orders of magnitude for the panel b. Coloured bar-codes c, d indicate the cumulative depths corresponding to four considered values of $\kappa'$ in decreasing order from top to bottom. Each bar-code is split into ten regions of alternating brightness, representing ten 10%-quantiles of the distribution (e.g., the first dark blue region of the top bar-code in panel c indicates that 10% of reaction events occur till $Dt/R^2 \approx 1$).
Eq. (6) for the unbounded case (densities in panel b). The coloured vertical arrows indicate the mean reaction times for these cases (note that some arrows coincide). The vertical black dashed line indicates the crossover time that does depend neither on reactivity, nor on distance. 

When the reactivity $\kappa$ decreases (with $r/R = 0.2$ being fixed), the distribution becomes much broader and extends towards longer reaction times. 

When the distance to the target decreases (with $r/R = 0.02$ fixed), the most probable reaction time shifts to the left, whereas the mean reaction time remains constant.

Interestingly, this simple estimate, which depends only on the diffusion coefficient and the initial distance to the target site, appears to be very robust: $t_{\text{mp}}$ indeed shows very little variation with the reactivity $\kappa$, as one may infer from Figs. 1 and 3. In the Methods section, we show that when $\kappa$ decreases from infinity to zero, the value of $t_{\text{mp}}$ varies only by a factor of 3. This characteristic time is always strongly skewed towards the left tail of the distribution, that is, to short reaction times: $t_{\text{mp}}$, in fact corresponds to particles moving relatively directly from their starting point to the target followed by an immediate reaction and thus generalises the concept of direct, purely geometry-controlled trajectories\textsuperscript{22} to systems with reaction control. Note that expression (3) is different from the diffusion-controlled additive contribution proportional to $1/D$ in the mean reaction time (5).

The second characteristic time scale is the crossover time $t_c$ from the hump-like Lévy–Smirnov region to a plateau-like one. Thinned and thick lines show the reaction time density $H_c(r, t)$ from Eq. (6) for the unbounded case ($R \to \infty$). The length and time units are fixed by setting $R = 1$ and $R^2/D = 1$. Clearly the positions of the most probable reaction times are geometry-controlled by the initial distance to the target. Not surprisingly, for the largest initial distance the solution for the unbounded case underestimates the RTD hump. Note the extremely broad range of relevant reaction times (horizontal axis) spanning over 12 orders of magnitude in panel b. Coloured bar-codes c, d indicate the cumulative depths corresponding to four considered values of $r/R$ in increasing order from top to bottom. Each bar-code is split into ten regions of alternating brightness, representing ten 10%-quantiles of the distribution. In spite of distinctions in the probability densities in panel b, the corresponding cumulative distributions are close to each other and result in very similar reaction depths.
unbounded system, to the plateau region. Hence, \( t_c \) can be interpreted as the time at which a molecule starts to feel the confinement. This can be nicely discerned from comparison with the density \( H_\rho (r, t) \) for the unbounded case (Fig. 2). Thus, reaction times beyond \( t_c \) correspond to indirect trajectories\(^2\). From the result

\[
 t_c = 2(R - \rho)^3/(\pi^2 D)
\]

obtained in the Methods section, we see that \( t_c \) is independent of the starting point and of the reactivity \( \kappa \) being entirely dominated by the diffusivity and the difference between the sizes of the domain \( R \) and of the target. Writing \( t_{\text{mp}}(\kappa, r) = \pi^2 (r - \rho)^2/[12(R - \rho)^2] \), one realises that the crossover time can be comparable with the most probable time (such that the hump-like region shrinks), but may also become much larger than the latter when \( r \) is close to \( \rho \), as it happens, e.g., when proteins are produced in a close vicinity of a first gene activated at \( t = 0 \). In this case, of course, the hump-like region will be most pronounced (Fig. 2).

Finally, the onset of the right exponential shoulder at long reaction times coincides with the mean reaction time, as indicated by the arrows in Figs. 1 and 2. The latter is obtained from the Laplace transformed distribution (see the Methods section) and is given by the exact formula

\[
 t_{\text{mean}} = \frac{(r - \rho)(2R^3 - 3r\rho + 3\rho^2)}{6D\rho} + \frac{R^3 - \rho^3}{3\kappa\rho^2},
\]

which can be thought of as an analogue of the celebrated Collins–Kimball relation for the apparent reaction rate\(^13\). The first term in Eq. (5) is the standard MFPT to a perfectly reactive target and corresponds to the classical notion of diffusion-controlled rate. The additional contribution to \( t_{\text{mean}} \) proportional to \( \kappa^{-1} \) accounts for the imperfect reaction with finite reactivity, independent of the particle’s starting point. When \( t_{\text{mean}} \) is a unique time scale characterising exhaustively well the reaction kinetics, as it happens for reactions with sufficiently high concentrations of reactants, one can indeed distinguish between diffusion or kinetic control. In contradiction, for reactions with nanomolar concentrations of reactive species, the other time scales \( t_{\text{mp}} \) and \( t_c \) are equally important and no clear-cut separation between diffusion and kinetic control can be made. In the Methods section, we also present an explicit exact expression for the variance of the first reaction time, which permits us to determine the coefficient of variation of the RTD and hence, to quantify its broadness.

**Geometry versus reaction control.** We emphasise that even for perfect reactions, for which \( \kappa = \infty \), the mean reaction time is orders of magnitude longer than the most probable reaction time. For imperfect reactions (finite \( \kappa \) values) the mean reaction time becomes even longer, and diverges as \( 1/\kappa \) when \( \kappa \to 0 \). The fact that the most probable reaction time is very weakly dependent on \( \kappa \) renders the difference between the most probable and the mean reaction times so much more severe for finite \( \kappa \). Another remarkable and so far unnoticed feature is that a pronounced plateau develops beyond \( t_c \), reflecting an emergent regime of reaction-control. This plateau exists even for \( \kappa = \infty \) (Fig. 1) and becomes increasingly longer with decreasing reactivity \( \kappa \), implying that over several decades the values of the reaction time become equally probable. Mathematically speaking this plateau appears due to the fact that the smallest eigenvalue of the boundary value problem—the only eigenvalue with an appreciable dependence on \( \kappa \)—disentangles from the remaining eigenvalues. This point is discussed in more detail in the Methods section. Physically, the emergence of the plateau implies that the first passage process to the reaction event becomes even more defocused with decreasing \( \kappa \), i.e., that the spread of possible reaction times increases significantly. The long spread of reaction times within this plateau region is a consequence of geometrically defocused trajectories exploring the boundary of the reaction volume reinforced by the necessary multiple collisions with the target before a final reaction event due to the reaction-control with finite reactivity. An important consequence of the existence of the extended plateau region is that all positive moments of \( H(r, t) \), not only the mean reaction time, will be dominated by integration over this region. In other words, the resulting RTD of the right exponential shoulder at long reaction times almost coincides for all cases, especially when the reactivity is finite. This part of the reaction time distribution is dominated by trajectories that equilibrate in the volume before eventual reaction (indirect trajectories\(^2\)). In contrast, we see a strong variation of the most probable reaction time. The exponential cut-off at short reaction times and the position of the maximum of the distribution is geometry-controlled, as can be anticipated from the Lévy–Smirnov form for the unbounded problem (see the Methods section): direct trajectories from the initial position to the target need a minimum travel time. For increasing initial distance, the most probable reaction time thus moves to longer times and the relative contribution of the geometry-controlled fraction of direct trajectories becomes less relevant: instead the particles almost fully equilibrate in the confined volume until they finally react with the target. This reaction-control effect is accentuated for decreasing reactivity. We stress that for biological applications, both cases are relevant: shorter initial distances, for instance, are involved when proteins are produced around a first gene activated at time \( t = 0 \) and these proteins then need to move to a close-by second gene, here represented by the inner target. This scenario is very similar to the one discussed in reference\(^{19} \) as an example for the rapid search hypothesis\(^{18} \). Longer initial distances are relevant when a molecular signal passes the cellular membrane or is produced around a cytoplasmic plasmid, and when these molecules then need to diffuse to the nucleoid region in a bacterial cell or pass the nuclear membrane in an eukaryotic cell.

Figure 3 summarises the effects of the finite reactivity and of the distance to the target onto the reaction time distribution in the form of a “heat map”.

**Short- and long-time behaviour.** We now turn to the discussion of the short- and long-time tails of \( H(r, t) \). The long-time behaviour of the density \( H(r, t) \) is determined by the smallest eigenvalue \( \lambda_0 \) of the Laplace operator. For the spherical domain, one can accurately compute this eigenvalue by solving a trigonometric equation (see the Methods section). When both the target and its reactivity are small one gets \( \lambda_0 = \kappa s_2/(DV) \), where the surface area \( S_2 = 4\pi r^2 \) of the target and the volume of the domain \( V = 4\pi R^3/3 \) are introduced. According to Eq. (5), in this limit \( t_{\text{mean}} \approx 1/(D\lambda_0) \), i.e., the mean reaction time is dominated by multiple returns to the target until the reaction occurs. As the target shrinks (\( \rho \) vanishes), the smallest eigenvalue tends to zero. In turn, the other eigenvalues \( \lambda_n \), corresponding to rotation-invariant eigenfunctions of the Laplace operator in the spherical domain, are bounded from below: \( \lambda_n > \pi^2 n^2/2R^2 \) for \( n = 1, 2, \ldots \). As a consequence, there is an intermediate range of times, \( 1/(D\lambda_n) \ll t \ll 1/(D\lambda_0) \), for which the contribution of all higher-order eigenmodes vanishes, that is, \( e^{-D\lambda_n t} \ll 1 \), whereas
the contribution of the lowest eigenmode is almost constant in time, $e^{-D/tc} \approx 1$. This is precisely the reason why the intermediate, plateau-like region emerges, see Fig. 1. Note that this region protrudes over an increasing range of time scales when either the reactivity $\kappa$ or the target radius $\rho$ decrease, or both. Note also that this intermediate regime corresponds approximately to an exponential law which is often evoked in the context of the first passage statistics to small targets, see, for instance, references $^{28,42,43}$.

While the smallest eigenvalue determines the plateau and the ultimate exponential cut-off, the short-time behaviour of the reaction time density $H(r, t)$ is determined by other eigenmodes. Since the limit of a small target ($\rho \ll R$) can alternatively be seen as the limit of large domain size, one can use the density $H_\infty(r, t)$ for diffusion in the exterior of a target, which was first derived by Collins and Kimball,$^{13}$

$$H_\infty(r, t) = \frac{r}{4\pi D t^3} \exp\left(-\frac{(r-r_0)^2}{4Dt}\right),$$

where $erfc(x) = e^{x^2}erfc(x)$ is the scaled complementary error function (its derivation is reproduced in the Methods section). As demonstrated in Fig. 1, Eq. (6) fully captures the geometry-controlled part of the reaction time distribution. In the limit of a perfectly absorbing target, $\kappa \to \infty$, this expression reduces to

$$H_\infty(r, t) = \frac{\rho}{r} \frac{r - \rho}{\sqrt{4\pi Dt^3}} \exp\left(-\frac{(r-r_0)^2}{4Dt}\right),$$

whose normalisation $\rho/r \leq 1$ reflects the transient nature of diffusion in three dimensions. One can easily check that the maximum of this Lévy–Smirnov-type density is given precisely by Eq. (3), as intuitively expected.

**Approximate form of the full distribution.** Combining the short- and long-time contributions, we arrive at the following approximate formula for the reaction time density

$$H(r, t) \approx H_\infty(r, t) + (1 - q) e^{-t/t_{\text{mean}}} \frac{t_{\text{mean}}}{t},$$

where $t_{\text{mean}} = 1/(D\rho_0)$ and

$$q = \int_0^\infty dt H_\infty(r, t) = \frac{\rho/r}{1 + D/(\kappa \rho)} < 1 \quad (9)$$

is the hitting probability of the target. The correct normalisation of $H(r, t)$ is ensured by the prefactor in front of the second term. Result (8) is substantially more general than the simple form (1) suggested in ref. $^{28}$. The form (8) not only extends expression (1) to the partially-reactive case, i.e., for arbitrary finite values of $\kappa$, but also emphasises and provides an explicit form for the contribution from the hump-like region around $t_{\text{mp}}$, which is most relevant for reactions in which the molecule starts close to the target.

Figure 4 illustrates the quality of this approximation, showing that it becomes most accurate when the target radius $\rho$ or reactivity $\kappa$ are small. One observes that it accurately captures both the maximum, the plateau, and the exponential cut-off of the reaction time distribution. In turn, the transition between the maximum and the plateau region is less sharp than in the exact form. A minor inaccuracy of the approximation (8) is that it reaches a constant—set by the second term—in the short-time limit while the exact distribution vanishes as $t \to 0$. This feature can be simply removed by multiplying the second term by a Heaviside step function $\Theta(t - t_{\text{mp}})$ and re-evaluating the normalisation constant. But even in the present form approximation (8) provides a remarkably good insight into the behaviour of the first passage dynamics and can thus be used as an efficient and easy-to-handle fit formula for data analysis or for explicit analytical derivations of follow-up processes.

**Reaction depth.** Lastly, we point out that the contributions of the four different regimes separated by the time scales $t_{\text{mp}}, t_c$, and $t_{\text{mean}}$ can be further quantified by the corresponding reaction depths defining which fraction of trajectories reacted up to a given time. We thus focus now on the cumulative distribution function of reaction times

$$F_r(t) = \int_0^t dt'H(r, t') = 1 - S(r, t), \quad (10)$$

with the evident property $F_r(\infty) = 1$ in a bounded domain in which $H(r, t)$ is normalised, and thus shows explicitly which fraction of trajectories have reacted up to time $t$. The reaction...
depth is illustrated in the Methods section. Table 1 summarises the values of the reaction depths of the three characteristic regions of the RTD: the hump-like region around \( t_{\text{hump}} \), the plateau region, and the exponential tail. We realise that for \( r/R = 0.2 \) the least amount of the reaction events happens within the hump-like region: it is of order of just 4% for perfect reactions, and this fraction rapidly diminishes upon a decrease of \( \kappa \). In turn, a much larger amount of the reaction events is collected within the final exponential region. It is typically of order of almost 37%, independently of the value of \( \kappa \), meaning that for such a value of the ratio \( r/R \) roughly one third of all realisations remain unreacted at time \( t = t_{\text{mean}} \). However, most of realisations of the reaction events occur within the plateau-like regime—it amounts to roughly 59% for perfect reactions, and becomes even bigger for smaller values of \( \kappa \). The situation becomes different for a smaller release radius: \( r/R = 0.02 \). Here, for perfect reactions the majority of trajectories (49% such that \( \tau \) is close to the median time) react within the hump-like region, while the plateau region and the exponential tail contribute only 20 and 30%, respectively. Upon lowering \( \kappa \), the hump-like region is no longer representative, and more reaction events take place during the exponential tail (~37%) and the plateau-like regions (~63%), respectively. In conclusion, the plateau region appears to be the most important part of the RTD, which contributes most to the overall number of reaction events, except for the case \( r/R < 1 \) and \( \kappa R/D \gg 1 \), for which the hump-like region becomes the dominant one. Concurrently, this plateau is the region of the strongest defocusing effect, in particular for increased reaction-control.

### Methods

**Exact distribution of reaction times.** We consider a diffusion process in a three-dimensional domain \( \Omega = \{ x \in \mathbb{R}^3 : 0 < |x| < R \} \) between two concentric spheres—a small target and a small surface of radii \( \rho \) and \( R \), respectively. Although the solution of the underlying diffusion problem is well known\(^27\),\(^28\), we revise it here for completeness and to highlight several practical points discussed in the main text. In fact, the Laplace transformed probability density function \( \tilde{h}(x,p) \) satisfies the modified Helmholtz equation

\[
(p - D \Delta) \tilde{h}(x,p) = 0 \quad (x \in \Omega),
\]

subject to the boundary conditions

\[
\left[ \partial_x^\alpha \tilde{h}(x,p) \right]_{|x|=\rho} = 0, \tag{12a}
\]

\[
\left( \frac{D}{\kappa} \partial_x \tilde{h}(x,p) + \tilde{h}(x,p) \right)_{|x|=\rho} = 1. \tag{12b}
\]

Here, \( \Delta \) is the Laplace operator, \( D \) is the diffusion coefficient, \( \kappa \) is the intrinsic reactivity, and \( \partial_x \) is the normal derivative directed outward from the domain \( \Omega \). The rotational symmetry of the domain reduces the partial differential Eq. (11) to an ordinary differential equation with respect to the radial coordinate \( r \):

\[
\tilde{h}''(r,p) + \frac{2}{r} \tilde{h}'(r,p) - \frac{p}{D} \tilde{h}(r,p) = 0,
\]

\[
\tilde{h}'(r,p) = 0,
\]

\[
(\tilde{h}(r,p) - \frac{D}{\kappa} \tilde{h}'(r,p))_{|r=\rho} = 1,
\]

where primes denote derivatives with respect to \( r \). The solution of this equation is

\[
\tilde{h}(r,p) = \frac{g(r)}{g(p) - g'(p)}.
\]

### Table 1 Impact of the target reactivity and proximity onto the reaction depth

| \( r/R \) | region       | \( \kappa' = \infty \) | \( \kappa' = 10 \) | \( \kappa' = 1 \) | \( \kappa' = 0.1 \) |
|---------|--------------|-------------------------|-------------------------|-------------------------|-------------------------|
| 0.2     | Hump-like    | 3.8                     | 0.34                     | 0.04                     | 0.004                   |
|         | Plateau-like | 59.4                    | 62.9                     | 63.2                     | 63.2                    |
| 0.02    | Exponential tail | 36.8                    | 36.8                     | 36.8                     | 36.8                    |
|         | Hump-like    | 49.4                    | 4.4                      | 0.5                      | 0.05                    |
|         | Plateau-like | 20.0                    | 58.8                     | 62.7                     | 63.15                   |
|         | Exponential tail | 30.6                    | 36.8                     | 36.8                     | 36.8                    |

Relative weights (in percents) of three characteristic regions of the reaction time density for \( r/R = 0.2 \): the hump-like region around the most probable reaction time \( t_{\text{mp}} \), extending from 0 till \( t_{\text{mp}} = 2(\kappa' - 1)^2D/\pi \) (and thus merging two subregions discussed in the text: the exponential tail left to \( t_{\text{mp}} \) and the power-law decay right to \( t_{\text{mp}} \)); the plateau-like region stretching from \( t_{\text{mp}} \) to the mean reaction time \( t_{\text{mean}} \) and the exponential tail which persists beyond \( t = t_{\text{mean}} \). Two starting points \( r/R \) and four values of dimensionless reactivity \( \kappa' = \kappa R/D \) are used, corresponding to Fig. 1.
where
\[ g(r) = \frac{R \sqrt{p/D} \cosh \xi - \sinh \xi}{r \sqrt{p/D}}, \]
with \( \xi = (R - r) \sqrt{p/D} \). It follows that
\[ g'(r) = \frac{1}{r^2 \sqrt{p/D}} \]
\[ (1 - R p/D) \sinh \xi - \xi \cosh \xi. \]

The mean reaction time is obtained from the Laplace-transformed density as
\[ t_{\text{mean}} = - \lim_{p \to 0} \frac{\partial}{\partial p} \hat{H}(r, p), \]
from which Eq. (5) follows.

In the limit \( R \to \infty \), Eqs. (16-18) yield
\[ \hat{S}_\infty(r, t) = 1 - \frac{\rho \exp \left( - \frac{(r - \rho)^2}{4D} \right)}{r(1 + \rho \sqrt{D}/(t))} \]
\[ \text{erfcx} \left( \frac{r - \rho}{\sqrt{4D}} \right) - \text{erfc} \left( \frac{r - \rho}{\sqrt{4D}} + \left( 1 + \frac{D}{\rho} \right) \sqrt{Dt} \right). \]

Now we come back to a bounded case with \( R < \infty \). The Laplace inversion of Eq. (14) can be performed by identifying the poles of the function \( \hat{H}(r, p) \) in the complex plane \( p \in \mathbb{C} \), that is, by finding the zeros of the function
\[ F(p) = g(p) - \frac{D}{k} g'(p). \]

For convenience, we introduce dimensionless Laplace variable \( s = (R - \rho)^2 p D \), so that
\[ F(p) = \frac{1}{\rho^2 s^2} \left( (p + \rho - R - \rho^2 s) \sqrt{\cosh s} \right. \]
\[ - \left. (p + \rho - R + \rho^2 s \sinh s) \right). \]

where we defined the dimensionless “dilatoriness” parameter \( \mu \) as
\[ \mu = \frac{D}{\kappa (R - \rho)}. \]

The perfectly reactive target with \( \kappa = \infty \) corresponds to \( \mu = 0 \). In other words, for high reactivity \( \kappa \) the value of the dilatoriness \( \mu \) is small and reactions occur more likely on first encounter, and vice versa. Note that a fully reflecting target with \( \kappa = 0 \) is excluded from our analysis because the reaction time would be infinite. In other words, we always consider \( 0 \leq \mu < \infty \).

The solutions of the equation \( F(p) = 0 \) lie on the negative real axis. Setting \( s = -\alpha^2 \), one gets the trigonometric equation
\[ \tan \alpha = \frac{a(\rho + \rho - R - \rho^2 s)}{\rho(\rho - R) + \rho(\rho - R^2 s) + \rho R \alpha^2}. \]

This equation has infinitely many positive solutions that we denote as \( a_n \), with \( n = 0, 1, 2, \ldots \). Since the function on the right-hand side has the slope \( \frac{\partial}{\partial \rho} (\rho + \rho - R - \rho^2 s) > 0 \) near \( \alpha = 0 \), the smallest solution \( a_0 \) lies in the interval \( (0, \pi/2) \).

More generally, the solution lies in the interval \( \left( \arcsin \left( n \pi + \pi/2 \right) \right) \) and tends, for any fixed \( \kappa \), to the left boundary of the interval as \( n \to \infty \). Note that \( \alpha = 0 \) (or \( p = 0 \)) is not a pole of the function \( \hat{H}(r, p) \).

Once the poles are identified, we determine the residues by taking the derivative of \( F(p) \) at the poles. Applying the theorem of residues to compute the inverse Laplace transform, we finally deduce the exact expression for the probability density \( H(r, t) \) of the reaction time for a particle starting at a distance \( r - \rho \) from the target,
\[ H(r, t) = \sum_{n=0} a_n(r) e^{-\lambda_n t}, \]
with
\[ \lambda_n = a_n^2/(R - \rho)^2, \]

where the expansion coefficients \( a_n \) are given explicitly by the residues as
\[ a_n = \frac{2 \rho^2 a_n^2}{(\rho R + (\mu R^2 + \rho^2)) a_n + \rho(\rho R^2 - \rho) \cos a_n}. \]

**Long-time behaviour of the RTD.** When either the target radius \( \rho \) or the dilatoriness parameter \( \mu \) is large, the slope of the right-hand side of Eq. (23) is close to unity and thus the smallest eigenvalue \( a_0 \) is close to zero. Expanding both sides of Eq. (23) into Taylor series one finally deduces the exact expression for the probability density \( H(r, t) \) of the reaction time for a particle starting at a distance \( r - \rho \) from the target,
\[ H(r, t) = \sum_{n=0} a_n(r) e^{-\lambda_n t}, \]
with
\[ \lambda_n = a_n^2/(R - \rho)^2, \]

where the expansion coefficients \( a_n \) are given explicitly by the residues as
\[ a_n = \frac{2 \rho^2 a_n^2}{(\rho R + (\mu R^2 + \rho^2)) a_n + \rho(\rho R^2 - \rho) \cos a_n}. \]

In particular, for small target radius, \( \rho \to 0 \), at fixed dilatoriness \( \mu \), we see that
\[ a_0 \simeq 3(\rho/R)^2 \mu^{-1/2}. \]

In turn, when \( \mu \to \infty \) with fixed \( \rho \),
\[ a_0 \simeq \sqrt{3}\rho \sqrt{R^2 + \rho^2 + \mu \kappa^2}. \]

In both cases, \( a_0 \) is proportional to \( \rho \) and inversely proportional to \( \sqrt{\mu} \). As a consequence, the term with the slowest decay time behaves as
\[ \lambda_0 \simeq \frac{3\rho^2}{D(R^2 + \rho^2 + \mu \kappa^2) \kappa^2} \simeq \frac{3\rho^2}{D^2 R^2} \simeq \frac{\lambda_0}{\lambda_0}, \]
where in the intermediate approximation we ignored terms of order \( \rho^2 \) and higher, and we introduced the surface area \( S_0 = 4\pi\rho^{2} \) of the target and the volume of the domain \( V = 4\pi R^3/3 \).

We also note that the approximation \( \epsilon_0 = (3\rho/R^2)/((\mu + 3\rho)/(2\mu R)) \) holds for \( \rho \ll R \), and thus \( \epsilon_0 \sim 1/((1 + 3\rho)/(2\mu R)) \), i.e., it is close to unity as long as the dilatoriness \( \mu \) is not too small. Therefore, the survival probability can be accurately approximated as \( S(r, t) \simeq \exp\left(-D t a_0^2 t^2 R^3\right) \) for intermediate and large times. In this case the median reaction time becomes
\[ t_{\text{median}} \approx \frac{R^2 \ln 2}{D \rho^2} \simeq \frac{D \rho^2}{3 \rho^2 R^2} \simeq \frac{R^2 \ln 2}{D \rho^2}, \]
from which the relation \( t_{\text{median}} = t_{\text{median}} \ln 2 \) follows. This median value is close to the mean reaction time, in which the limit \( \rho \ll R \) has the dominant behaviour as \( R^3/(3\rho^2) \) according to Eq. (5). In turn, the most probable reaction time, which is determined by the higher-order eigenmodes, is orders of magnitude smaller. This behaviour is, however, only present for weakly reactive targets. In contrast, the median time for perfect reactions is usually close to the crossover time \( t_c \), while \( t_{\text{mean}} \) is orders of magnitude larger.

**Most probable reaction time.** One may deduce from Fig. 1 that the region around the most probable reaction time is well described by the function in (6), which corresponds to the solution in the limit \( R \to \infty \). Hence, the most probable reaction time \( t_{\text{mp}} \) can be obtained with a good accuracy by merely differentiating this function with respect to \( t \) and setting the result equal to zero:
\[ t_{\text{mp}} = \frac{r - \rho^2}{6D}, \]
where \( z \) is defined implicitly as the solution of the following, rather complicated transcendental equation
\[ \beta^2 z^4 - 3(1 + \beta) z^2 + 9 - \sqrt{\pi/6}\beta^2 z^2 \text{erfcx} \left( \frac{\sqrt{3/2}}{2} + \frac{\beta z}{\sqrt{6}} \right) = 0. \]
where erfc(x) is the scaled complementary error function, and

\[ \beta = \frac{r - \rho}{\rho} \left( 1 + \frac{\kappa p}{D} \right). \]  

(34)

We denote the solution of this equation as \( z_0 \). When \( \beta \) tends to 0, a Taylor expansion of the left-hand side of (33) yields \( z_0^2 = 9 + O(\beta) \), from which \( \beta = O(1) \). In the opposite limit \( \beta \to \infty \), one uses the asymptotic behaviour of the function erfc(x) to get

\[ z_0 \simeq 1 + \frac{3}{\beta^2} + O(\beta^{-3}). \]  

(35)

With some technical efforts, one can prove that \( z_0 \) is a monotonically decreasing function of \( \beta \) (see Fig. 5). We conclude that \( z_0 \) is bounded between \( \sqrt{3} \) and 1 so that the most probable time \( t_{mp} \) lies between \( (r - \rho)^2/(6D) \) (for \( \kappa p \gg 1 \)) and \( (r - \rho)^2/(2D) \) (for \( \kappa p \ll 1 \)). In other words, the most probable reaction time shows remarkably weak dependence on the reactivity \( \kappa \), as illustrated by Fig. 5.

**Fig. 5** Weak dependence of the most probable reaction time on reactivity. The numerical solution \( z_0 \) of Eq. (33) as a function of \( \beta \) (solid line) and its large-\( \beta \) asymptotic behaviour (35) are shown by the dashed line

Moments of the reaction time. As we have already remarked in the main text, the positive moments of the RTD of an arbitrary order are dominated by the integration over the plateau-like region such that their values appear close to the onset of the crossover to the final region—the exponential decay of the RTD. The exact values of the positive moments of the random reaction time \( t \) can be accessed directly by a mere differentiation of \( H(r, t) \) with respect to the Laplace parameter \( p \) and subsequently taking the limit \( p = 0 \): \n
\[ \langle t^k \rangle = (\sim t)^k \lim_{p \to 0} \frac{d^k H(r, p)}{dp^k}. \]  

(36)

For instance, a lengthy but straightforward calculation yields the exact formula for the variance of the reaction time:

\[ \langle t^2 \rangle - \langle t \rangle^2 = \frac{1}{6\pi [\kappa p D]} \left\{ 10r^2(3r^2 - \rho^2)^2 (D/\kappa) \right. \]

\[ + 4\rho^2(5r^2 + 6\rho^2 + 3\rho^2 + \rho^2)(R - \rho)^2 (D/\kappa) \]

\[ + 2\rho^2(5R^2 + 5R^2 + 5R^2 + 10r^2 - 18\rho^2) \]

\[ - 9r^2(\rho + r)(\rho^2 + \rho^3) \}, \]  

(37)

from which one also gets the coefficient of variation, \( \gamma = \sqrt{\langle t^2 \rangle - \langle t \rangle^2}/\langle t \rangle \), which characterises fluctuations of the random reaction time \( t \) around its mean, i.e., the effective broadness of the reaction time density. As compared with ref. 30, the expressions Eqs. (5) and (37) permit us to quantify the effect of both rate-controlling factors.

For a perfectly reactive target, the coefficient of variation diverges as the starting point \( r \) approaches \( \rho \), in particular, one gets

\[ \gamma^2 \simeq 1 + \frac{2\rho}{r - \rho} + O(1), \]  

(38)

when the target is small or the confining domain is large (\( \rho \ll R \)). In turn, for a partially reactive target, the squared coefficient of variation is finite in the limit \( r \to \rho \) and for a small target reads

\[ \gamma^2 \simeq 1 + \frac{2\rho}{r - \rho}. \]  

(39)

The coefficient of variation \( \gamma \) in Eqs (38) and (39) exceeds 1, allowing one to classify this distribution as broad, according to the standard terminology in statistics.\(^{4,30}\) In both cases, the asymptotic behaviour of \( \gamma \) does not depend on the size of the confining domain, \( R \).

We turn next to the negative order moments of the RTD which are clearly dominated by the region close to the origin and hence, probe the left tail of the distribution. The computation of negative moments (with \( v > 0 \)) involves integration:

\[ \langle t^{-\nu} \rangle = \int_0^{\infty} dt(t^{-\nu} H(r, t)) = \frac{1}{\Gamma(\nu)} \int_0^{\infty} dp p^{\nu-1} \tilde{H}(r, p). \]  

(40)

Although this integral is expressed in terms of the explicitly known Laplace transform \( \tilde{H}(r, p) \) from Eq. (14), its analytical evaluation does not seem to be feasible.

In turn, the integral takes a more tractable form in the limit \( R \to \infty \) corresponding to diffusion in the exterior of a partially reactive target of radius \( \rho \). Due to the transient character of diffusion in three dimensions, the probability density \( H_{\infty}(r, t) \) is not normalised to 1 as the molecule can escape to infinity. The integral of the density \( H(r, t) \) yields the probability of reacting at the target:

\[ q = H_{\infty}(r, p = 0) = \frac{\rho/r}{1 + D/(\kappa p)}. \]  

(41)

The negative order moments of the renormalised density \( H_{\infty}(r, t)/q \) are

\[ \langle t^{-\nu} \rangle_{\infty} = 2 \frac{D}{\Gamma(\nu)} \left( \frac{D}{(r - \rho)^3} \right)^{\nu-1} \int_0^{\infty} dx x^{2\nu-1} e^{-x}/(1 + x/β). \]  

(42)

where \( β \) was defined in (34). In the limit \( \kappa \to \infty \), one finds

\[ \langle t^{-\nu} \rangle_{\infty} = 2 \frac{D}{\Gamma(\nu)} \left( \frac{D}{(r - \rho)^3} \right)^{\nu-1} \Gamma(2\nu). \]  

(43)

While the mean reaction time diverges for the exterior problem, the negative order moments are well-defined and can thus characterise the reaction process. In particular, the harmonic mean reaction time, defined as

\[ t_{harm} = \frac{1}{\langle t^{-1} \rangle_{\infty}}, \]  

is deduced from (42) for \( v = 1 \):

\[ t_{harm} = \frac{(r - \rho)^2}{2D} \]  

(45)

where \( Ei(z) = \int_0^{\infty} dx e^{-xs} / s \) is the exponential integral. The dependence of the harmonic mean on the reactivity \( \kappa \) is fully captured via \( β \). In the limit \( \kappa \to \infty \), this mean approaches

\[ t_{harm} = \frac{(r - \rho)^2}{2D}, \]  

and is thus of the order of the most probable time, representing the relevant time scale of the problem. In the opposite limit \( \kappa \to 0 \), \( β \) approaches a constant, and the harmonic mean reaction time also reaches a constant. One can check that \( t_{harm} \) monotonously decreases as \( β \) (or \( \kappa \)) grows.

Figure 6 illustrates by dashed lines the behaviour of the function in (45), in particular, its approach to the limiting expression (46) as \( \kappa \) increases. One can appreciate a very weak dependence of the harmonic mean reaction time for the exterior problem on the reactivity \( \kappa \). We also show the harmonic mean reaction time in the concentric domain, obtained by a numerical integration in Eq. (46) with \( \nu = 1 \). This mean significantly depends on \( \kappa \) and behaves as \( 1/\kappa \) for small \( \kappa \). Given that the probability density \( H(r, t) \) for the concentric domain can be accurately approximated by \( H_{\infty}(r, t) \) at small times (see Eq. (8)), the harmonic mean reaction time for the concentric domain can be approximated by the expression in (46), multiplied by the reaction probability \( q \). This approximation, shown by solid lines, turns out to be remarkably accurate when the target radius \( \rho \) is small as compared to the radius \( R \) of the confining domain. We can also conclude that the significant variations of \( t_{harm} \) with \( \kappa \) for the concentric domain come from those of \( q \) with \( \kappa \).
Finally, we consider the time scale

\[ t_{\text{mp}} = t_0 \exp(\langle \ln(t/t_0) \rangle) \]  

(47)

(where \( t_0 \) is an arbitrary time scale), based on the mean logarithm of the reaction time—an important characteristic of the reaction process, which emphasises the typical values of \( t \), i.e., values observed in most of experiments. Indeed, the logarithm is a slowly varying function and its average is supported by the most frequently encountered values of \( t \) with the rare anomalously long- or short-reaction times being effectively filtered out. The estimates based on \( t_{\text{mp}} \) are widely used in the analysis of stochastic reaction-diffusion or transport process in random environments (see, e.g., refs. 40,41 and references therein). Such an averaged value can be formally computed as

\[ \langle \ln(t/t_0) \rangle = \sum_{n=0}^{\infty} u_n(r) \int_0^\infty dt \ln(t/t_0)e^{-Dk_t} \]

\[ = -\sum_{n=0}^{\infty} u_n(r) \frac{\ln(Dk_t)}{Dk_t} \]

\[ = \left( \ln \left( \frac{r-R}{\rho} \right) \right) - \frac{\ln(2\nu)}{\nu} + \sum_{n=0}^{\infty} u_n(r) \frac{\ln^2(2\nu)}{\nu^2}, \]

where \( \gamma = 0.5772... \) is the Euler constant, from which

\[ t_{\text{mp}} = \frac{(r-R)^2}{D} \exp \left( -\gamma - \frac{(r-R)^2}{D} \sum_{n=0}^{\infty} u_n(r) \frac{\ln^2(2\nu)}{\nu^2} \right). \]

(49)

where \( u_n(r) \) are given by (26)

To get a more explicit dependence on the initial radius \( r \), one can again consider the exterior problem \( (R = \infty) \). Rewriting Eq. (42) as

\[ \langle r^{-\nu} \rangle = \left[ \frac{D}{(r-p)^2} \right]^{\nu} \left( \frac{2\nu}{\Gamma(2\nu)} \right)^\nu \frac{1}{\beta} \frac{\Gamma(2\nu)}{\Gamma(\nu)} \int_0^\nu z^{\nu-1} e^z \frac{dz}{1/z^2} \]

(50)

in order to get a Taylor expansion as \( v \to 0 \), one finds

\[ \langle \ln(t/t_0) \rangle = \left\{ \ln \left( \frac{(r-R)^2}{Dk_t} \right) + \frac{\ln(2\nu)}{\nu} + 2e^2E_1(\beta) \right\}, \]

(51)

where the expectation is computed with respect to the renormalised density \( H_r(r,t)/q \). We obtain thus the logarithmic mean time

\[ t_{\text{mp}} = \frac{(r-R)^2}{D} \exp\left(\gamma + 2e^2E_1(\beta)\right). \]

(52)

In the limit \( \kappa \to \infty \), \( e^2E_1(\beta) \) vanishes as 1/\( \beta \), so that for a perfectly reactive target one gets

\[ t_{\text{mp}} = \frac{(r-R)^2}{D} e^2, \]

(53)

which signifies that in the limit \( \kappa = \infty \) the logarithmic mean time is comparable to the most probable reaction time \( t_{\text{mp}} \).

Figure 7 shows the logarithmic mean reaction time, \( t_{\text{mp}} \), as a function of the dimensionless reactivity \( \kappa = rR/D \). For the harmonic mean in Fig. 6, the results for a bounded concentric domain \( (R = 1) \) and for the exterior problem \( (R = \infty) \) differ significantly. The particular definition of the logarithmic time does not allow one to easily renormalise \( t_{\text{mp}} \) for the exterior domain to get an approximation for the bounded domain.

Finally, Fig. 8 compares several mean reaction times for the concentric domain. One can see that the behaviour of the median, the harmonic and the logarithmic means resembles that of the conventional (arithmetic) mean FPT. In particular, all these means behave as 1/\( \kappa \) at small \( \kappa \), indicating that the reaction is limited by the kinetics. Only the most probable FPT exhibits a very different behaviour and shows almost no dependence on the reactivity \( \kappa \), as discussed above.

**Reaction depth.** The reaction depth in Eq. (10) is shown in Fig. 9. Note first that the reaction depths corresponding to the shortest characteristic time \( t_{\text{mp}} \) are evidently the shortest, amounting to only about 4% for perfect reactions and \( r \) close to \( p \). For finite \( x \) or for starting points further away from the target, the reaction depth \( D_t(t_{\text{mp}}) \) diminishes. In turn, in all cases the reaction depth connected to the intermediate plateau is dominant, increasingly so due to the reaction-control at lower reactivities.
computations straightforward, custom routines are available from the corre-
routines for Matlab software. While the explicit form makes these numerical
have been computed by explicit formulas provided in the paper by using custom

Fig. 8 Comparison of several means of the reaction time. They are evaluated as functions of the normalised reactivity, $kR/D$, for an inner target of radius
$R/R = 0.01$ and the starting point $r/R = 0.2$ a and $r/R = 0.02$ b. The length and time units are fixed by setting $R = 1$ and $R^2/D = 1$

Fig. 9 Cumulative distribution function of reaction times, $F(t)$. It is evaluated for the reaction on an inner target of radius $R/R = 0.01$, with the starting point
$a r/R = 0.2$ and $b r/R = 0.02$ and varying reactivity $k$. Symbols indicate the relevant characteristic times: most probable time $t_{mp}$ (asterisks), harmonic
mean $t_{mean}$ (squares), logarithmic mean $t_{log}$ (diamonds), median $t_{median}$ (triangles), and mean time (circles). Note that some most probable times are not
seen at this scale

Data and code availability

All figures have been prepared by means of Matlab software. The plotted quantities
have been computed by explicit formulas provided in the paper by using custom
computations straightforward, custom routines are available from the corre-
sponding author upon request.

Received: 5 September 2018 Accepted: 25 October 2018
Published online: 13 December 2018

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Acknowledgements
D.S.G. acknowledges the support under Grant No. ANR-13-JSV5-0006-01 of the French National Research Agency. RM acknowledges funding from Deutsche Forschungsgemeinschaft (project ME 1535/6-1) and from the Foundation for Polish Science within a Humboldt Polish Honorary Research Scholarship. The authors acknowledge the support of Deutsche Forschungsgemeinschaft (German Research Foundation) and Open Access Publication Fund of Potsdam University.

Author contributions
D.S.G., R.M. and G.O. formulated the problem. D.S.G. performed the mathematical derivations and prepared the figures. D.S.G., R.M. and G.O. analysed the obtained results and wrote the paper.

Additional information
Competing interests: The authors declare no competing interests.

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