First Passage Under Restart

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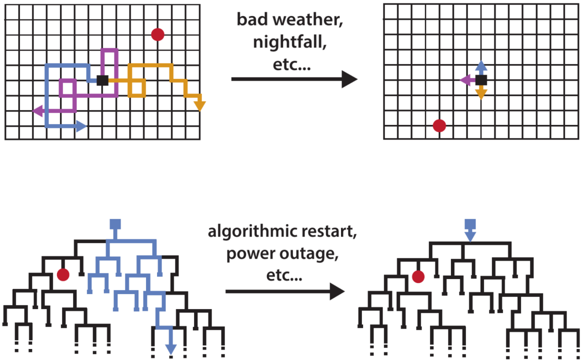
References

- **Non-equilibrium phenomena:** Evans PRL (2011), Kusmierz, PRL (2014), Gupta PRL (2014), **Pal** PRE (2015), **Pal** JPhys A (2016), Mendez PRE (2016), Boyer PRL (2014), **Pal** PRE (2019), **Pal** PRE-R (2019), **Pal** NJP (2019) ...
- **Bio-physical systems:** Rotbart PRE (2015), Roldan PRE-R (2016), Evans JPhys A (2018), Budnar Development Cell (2019), Robin Nat Comm (2019), Breissloff (2020) ....
- **Computer science:** Luby Inf. Proc. Lett (1993), Naksinehaboon IEEE (2008), Keyrouz (2019), Srikant (2020) ....
- **Queueing theory:** Dharmaraja J Stat Phys (2015), Crescenzo Questa (2003), Breissloff (2020) ....
- **Interacting particle systems:** Mercado JPhys A (2018), Falcao JStat Mech (2018), ... **Pal** PRE (2019), Karthika JPhys A (2020), Sadekar JStat Mech (2020)...
- **Thermodynamics:** Seifert EPL (2016), **Pal** PRE (2017), Thierry (2019), Busiello (2019) ... **Pal** PRL (2020), **Pal** under review (2020)...
- **First passage:** Chechkin PRL (2018), Belan PRL (2018), Falcon PRL (2017), Majumdar PRL (2018), Lapeyre PCCP (2019), Redner PRL (2020) ...
    - **A Pal**, S Reuveni PRL 118, 030603 (2017)
    - **A Pal**, R Chatterjee, S Reuveni, A Kundu JPhys A 52 (2019)
    - **A Pal**, VV Prasad PRE 99 (2019)
    - **A Pal**, VV Prasad PRR 1 (2019)
    - **A Pal**, I Eliazar and S Reuveni, PRL 122 (2019)
    - **A Pal**, L Kusmierz, S Reuveni, under review in PNAS (2020)
- **Extensive review:** MR Evans, SN Majumdar, G Schehr – JPhys A, 53 (2020)

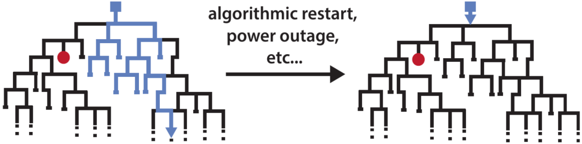
Outlook

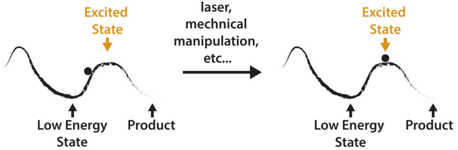
Outlook


bad weather,
nightfall,
etc...
algorithmic restart,
power outage,
etc...

Outlook


bad weather,
nightfall,
etc...


algorithmic restart,
power outage,
etc...


Excited
State
laser,
mechnical
manipulation,
etc...
Excited
State
Low Energy
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Low Energy
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Product

Outlook

Michaelis Menten reaction - 1913'

$$\mathrm{E} + \mathrm{S} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_{cat}} \mathrm{E} + \mathrm{P}$$

Plan

Framework

- First passage under restart
- Effects of restart

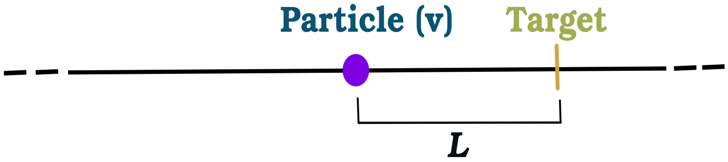
Applications

- Chemical reactions

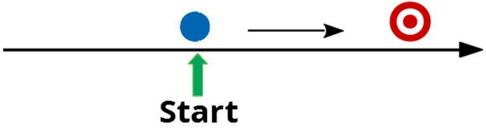
First Passage Under Restart

Target search via constant velocity

- Searcher starting from the origin with constant velocity v, target at L



- First passage time probability $f_T(L,t) = \delta(t - L/v)$
- Mean first passage time (MFPT): $\langle T \rangle = L/v$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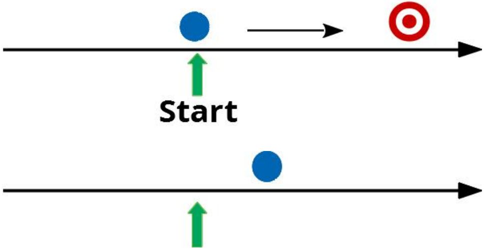
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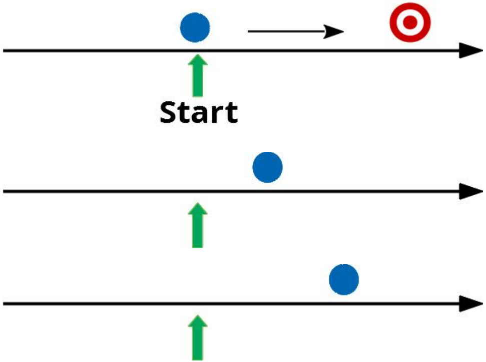
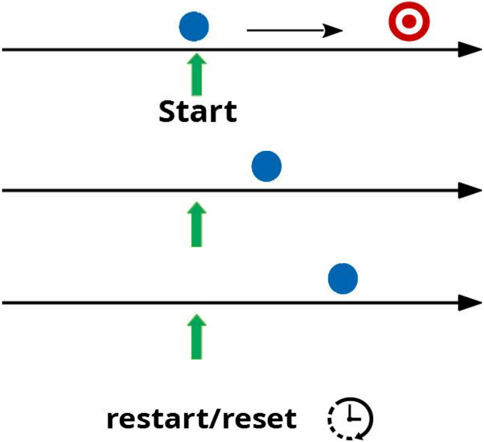
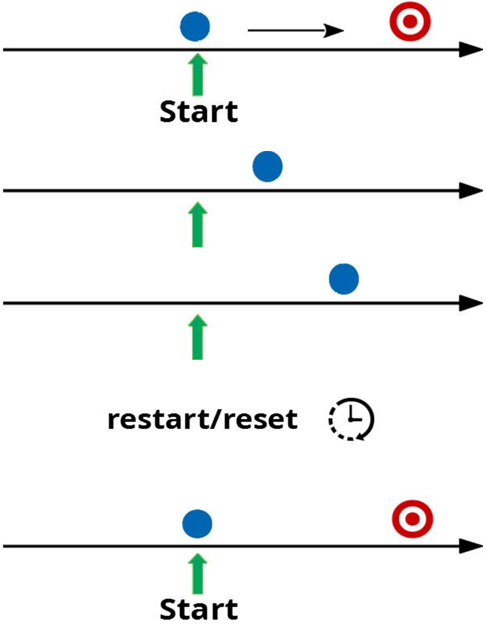
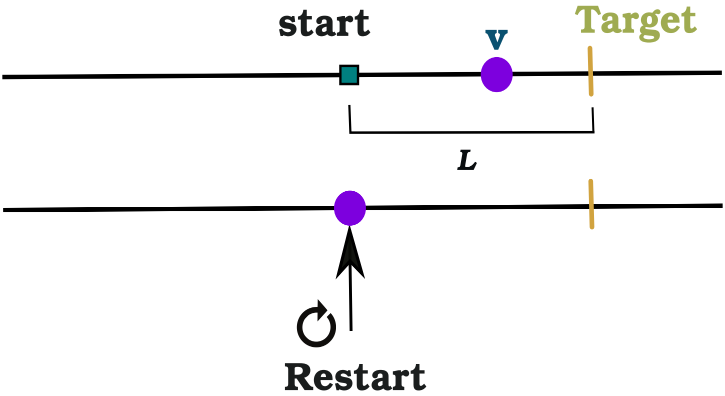

Start


Start
restart/reset


Start
restart/reset
Start

Target search via constant velocity with restart

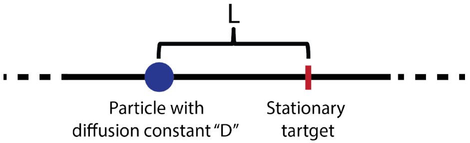
- Relocate the particle at a constant rate r (exponential waiting time)



- Mean first passage time (MFPT): $\langle T_r \rangle > L/v$

Target search via diffusion

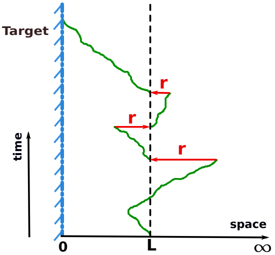
- Brownian searcher starting from the origin, target at L

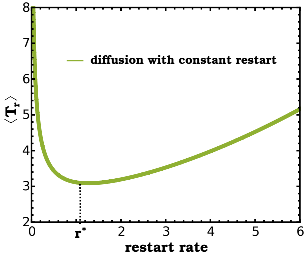


- First passage time probability $f_T(L,t) = \sqrt{L^2/4\pi D t^3}\,\exp[-L^2/4Dt]$
- Mean first passage time (MFPT): $\langle T \rangle \to \infty$

Chandrasekhar, RMP (1943); Feller

Target search via diffusion with restart



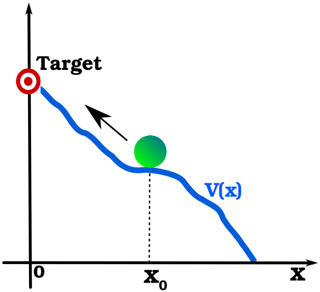


MFPT

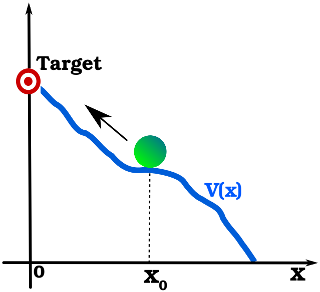
- $\langle T_r \rangle = \frac{1}{r}\left[\exp\left(\alpha_0 L\right) - 1\right], \qquad \alpha_0 = \sqrt{\frac{r}{D}}$
- $r^* \sim \left[\frac{D}{L^2}\right]$

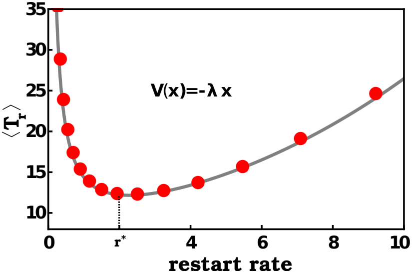
M. R. Evans, and S. N. Majumdar, PRL. 106, (2011)

Target search uphill with restart



Target search uphill with restart





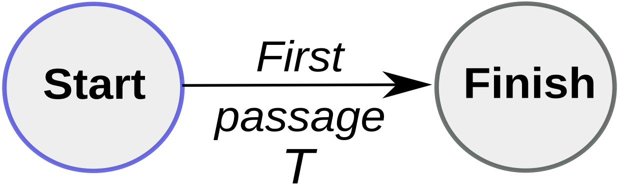
MFPT

$$\langle T_r \rangle = \frac{1}{r}\left[\exp\left(\frac{\lambda + \sqrt{\lambda^2 + 4Dr}}{2D} x_0\right) - 1\right] < \infty$$

A. Pal PRE 91 (2015);
A. Pal et al JPhys A 52 (2019)

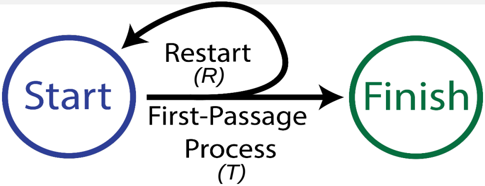
Effect of restart on generic stochastic process?

First Passage Process



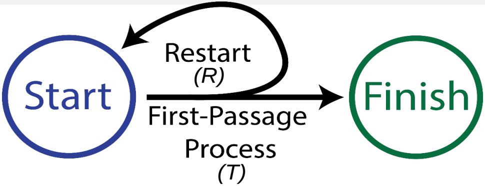
- "T" is a random variable (real valued and positive)
- **Define:** $f_T(t)$ is the probability density function of T
- **Generic notation:** $f_Z(t)$ is the probability density function of a random variable Z

Stochastic Renewal Equation



Completion time $$T_R = \begin{cases} T, & T < R \\ R + T'_R, & R \leq T \end{cases} \tag{1}$$

Stochastic Renewal Equation



Completion time $$T_R = \begin{cases} T, & T < R \\ R + T'_R, & R \le T \end{cases} \quad (1)$$

Renewal equation $$T_R = min(T, R) + I(R \le T)T'_R \quad (2)$$

First Passage
(T)

Restart
(R)

T	R	min(T,R)
1.2	2.7	1.2
3.1	0.42	0.42
11.2	0.81	0.81

A. Pal, and S. Reuveni, PRL 118 (2017)

Mean first passage time

MFPT

$$\langle T_R \rangle = \frac{\langle min(T, R) \rangle}{Pr(T < R)}$$

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- One stop **plug and play** solution for **First Passage Under Restart**

Mean first passage time

MFPT

$$\langle T_R \rangle = \frac{\langle min(T, R) \rangle}{Pr(T < R)}$$

- One stop **plug and play** solution for **First Passage Under Restart**

Numerator

$$Pr[min(T, R) \leq t] = 1 - Pr[min(T, R) > t] = 1 - Pr(T > t)Pr(R > t)$$

Mean first passage time

MFPT

$$\langle T_R \rangle = \frac{\langle min(T, R) \rangle}{Pr(T < R)}$$

- One stop **plug and play** solution for **First Passage Under Restart**

Numerator

$$Pr[min(T, R) \leq t] = 1 - Pr[min(T, R) > t] = 1 - Pr(T > t)Pr(R > t)$$

Denominator

$$Pr(T < R) = \int_0^\infty dt\ f_R(t)Pr(T < t) = \int_0^\infty dt\ f_T(t)Pr(R > t)$$

A. Pal, and S. Reuveni, PRL 118 (2017)

Poisson resetting

Constant restart rate or exponential waiting time: $f_R(t) = re^{-rt}$

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

where

$$\tilde{T}(r) = \int_0^{\infty} dt \; e^{-rt} \; f_T(t) \; \ldots \; \text{Laplace transform of } T$$

A. Pal, and S. Reuveni, PRL 118 (2017)

Revisit: diffusion with resetting

First passage time density for diffusion

$$f_T(t) = \sqrt{\frac{L^2}{4\pi D t^3}}\,\exp[-L^2/4Dt]$$

Mean completion time

$$\tilde{T}(r) = e^{-\sqrt{rL^2/D}}$$

$$\langle T_r \rangle = \frac{1-\tilde{T}(r)}{r\,\tilde{T}(r)} = \frac{1}{r}\left(e^{\sqrt{rL^2/D}} - 1\right)$$

Evans & Majumdar, PRL (2011)

Effect of restart

Coefficient of variation (CV) determines effect of restart

$$\text{MFPT:} \quad \langle T_r \rangle = \frac{1-\tilde{T}(r)}{r\tilde{T}(r)}, \quad \text{where} \quad \tilde{T}(r) = \langle e^{-rT} \rangle$$

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Add infinitesimal r

$$\langle T_{\delta r} \rangle = \langle T \rangle + \frac{1}{2} \left[\langle T \rangle^2 - \sigma^2(T) \right] \delta r + \mathcal{O}(\delta r^2) + \cdots$$

When does restart lower the MFPT?

Coefficient of variation (CV) determines effect of restart

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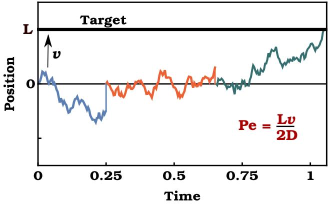
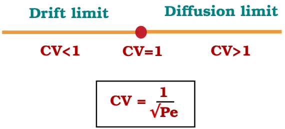
When does restart lower the MFPT?

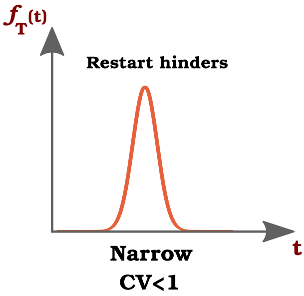
$$CV \equiv \frac{\sigma(T)}{\langle T \rangle} > 1$$

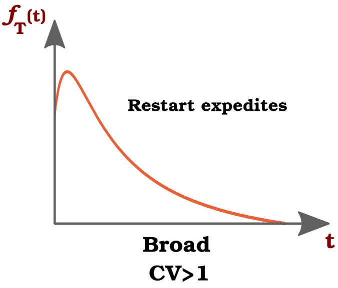
A. Pal, I. Eliazar, and S. Reuveni, PRL 122 (2019)

Restart takes advantage of large stochastic fluctuations









A. Pal, I. Eliazar, and S. Reuveni, PRL 122 (2019)

Summary

- Restart expedites completion of arbitrary stochastic processes.
- Hallmark of restart strategies.
- Universalities: **CV** criterion sets a sharp boundary for restart "speed-up".

Chemical reaction

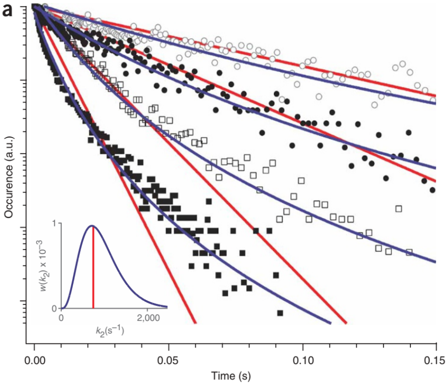
Michaelis Menten reaction - 1913'

$$\mathrm{E} + \mathrm{S} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_{cat}} \mathrm{E} + \mathrm{P}$$

Classical theory, Markov network

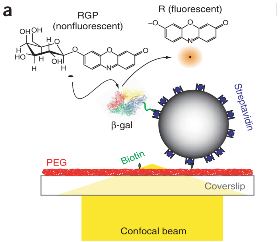
Effect of non-exponential times, unbinding?

Experimental evidence of non-exponential transients



$$\mathrm{E} + \mathrm{S} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_{cat}} \mathrm{E} + \mathrm{P}$$

T_{turn} **?**



English, ..., Xie. Nat Chem Bio, 2(2), p.87 (2006)

Michaelis Menten reaction using FPUR formalism

Generalized Michaelis Menten reaction

$$\mathrm{E} + \mathrm{S} \underset{T_{off}}{\overset{T_{on}}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{T_{cat}} \mathrm{E} + \mathrm{P}$$

Michaelis Menten reaction using FPUR formalism

Generalized Michaelis Menten reaction

$$\mathrm{E} + \mathrm{S} \underset{T_{off}}{\overset{T_{on}}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{T_{cat}} \mathrm{E} + \mathrm{P}$$

Renewal equation

$$T_{turn} = T_{on} + \begin{cases} T_{cat}, & T_{cat} < T_{off} \\ T_{off} + T'_{turn}, & T_{off} \leq T_{cat} \end{cases}$$

Michaelis Menten reaction using FPUR formalism

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MM equation also holds for general transition times!

$$k_{turn}^{-1} \equiv \langle T_{turn} \rangle = \frac{\langle T_{on} \rangle + \langle min(T_{cat}, T_{off}) \rangle}{Pr(T_{cat} < T_{off})}$$

Michaelis Menten reaction using FPUR formalism

Generalized Michaelis Menten reaction

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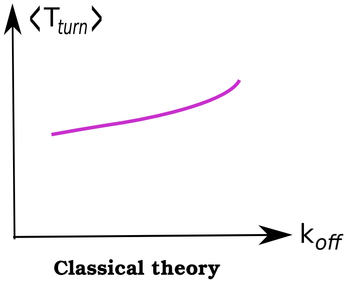
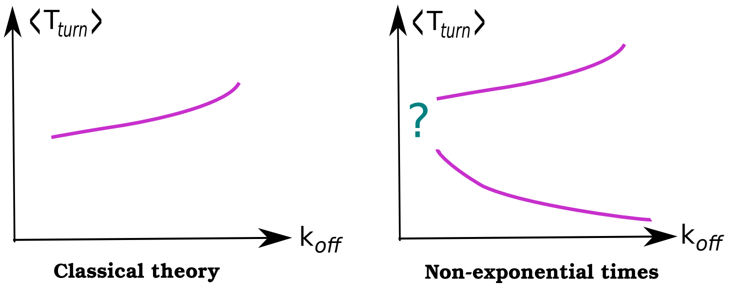
$$k_{turn}^{-1} \equiv \langle T_{turn} \rangle = \frac{\langle T_{on} \rangle + \langle min(T_{cat}, T_{off}) \rangle}{Pr(T_{cat} < T_{off})} \underset{=k_{on}[S]}{\overset{\langle T_{on} \rangle^{-1}}{\Longrightarrow}} k_{turn} = \frac{\tilde{k}_{cat}[S]}{[S] + K_M(k_{off})}$$

Effect of unbinding

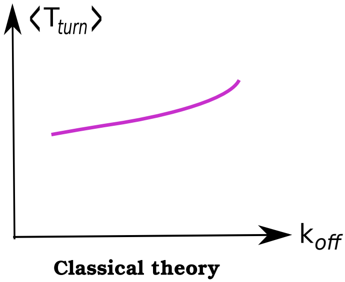


Effect of unbinding



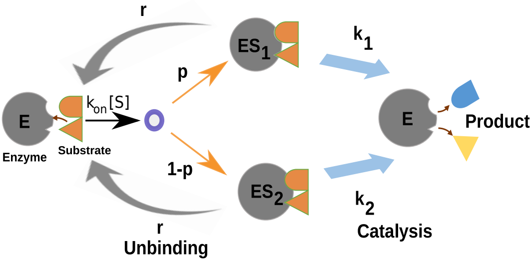
- Unbinding entails a **severe time penalty** for renewed binding and catalysis

Effect of unbinding



- Unbinding entails a **severe time penalty** for renewed binding and catalysis
- But unbinding also **prevents** a situation in which the substrate is "stuck" in the ES state for an **undesirably long period of time** $\Longrightarrow$ breakdown of classical theory

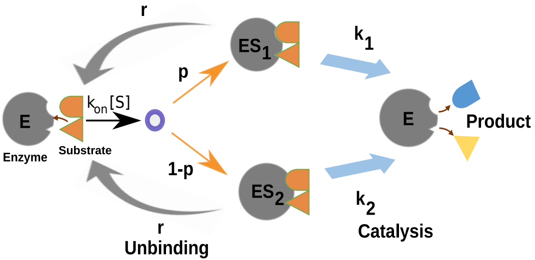
MM-reaction — two pathways



$$f_{unbinding}(t) = re^{-rt}$$

Xie, Single Molecules (2001), J Chem. B (2005); Bushtamante FEBS (2014); Robin Nat Comm (2018)

MM-reaction — two pathways



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Xie, Single Molecules (2001), J Chem. B (2005); Bushtamante FEBS (2014); Robin Nat Comm (2018)

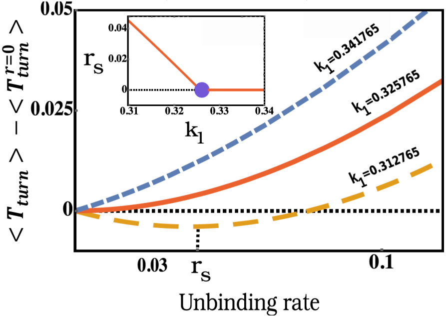
FPUR $\rightarrow$ MM

$$\langle T_R \rangle = \frac{\langle T_{on} \rangle + \langle min(T, R) \rangle}{Pr(T < R)} \implies \langle T_{turn} \rangle = \frac{\langle T_{on} \rangle + 1 - \tilde{T}_{cat}(r)}{r\tilde{T}_{cat}(r)}$$

A. Pal, and VV Prasad, PRR 1 (2019)

Optimal unbinding rate

$(k_2 = 1, p = 1/3)$



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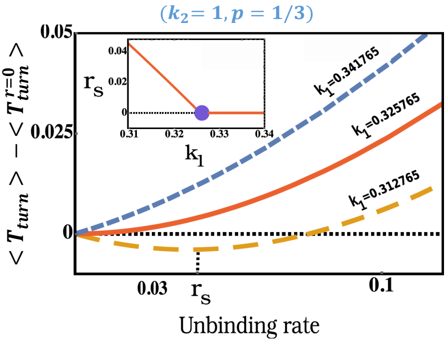
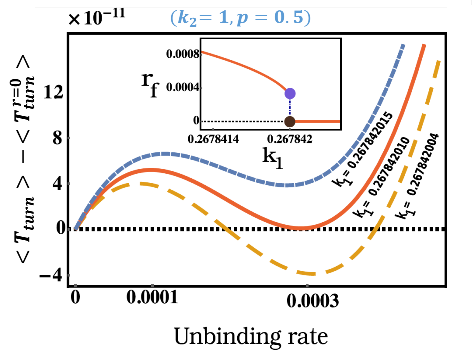


- **Optimal** unbinding rate r_s undergoes a **continuous** phase transition
- unbinding lowers the turnover time $\implies$ breakdown of classical theory
- CV of catalysis affects the turnover (**Recall the CV criterion for restart!!**)

A. Pal, and VV Prasad, PRR 1 (2019)

End of the story?



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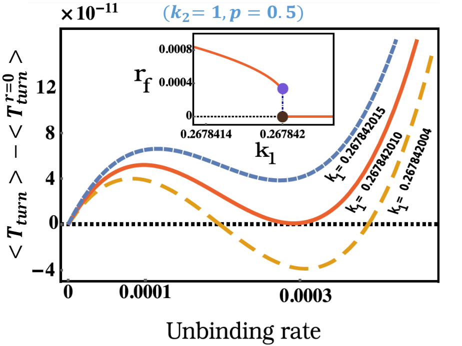
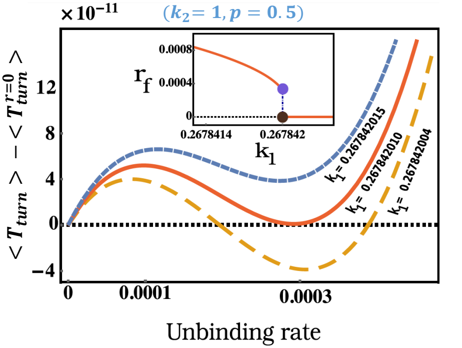


- **Optimal** unbinding rate r_f undergoes a **discontinuous** phase transition

End of the story?



- **Optimal** unbinding rate r_f undergoes a **discontinuous** phase transition

Optimal unbinding rate $\Longrightarrow$ order parameter

A. Pal, and VV Prasad, PRR 1 (2019)

A unified theory?

Landau like theory of "unbinding" transitions

- Transition between $r = 0$ and $r > 0$ phase

Landau like theory of “unbinding” transitions

- Transition between $r = 0$ and $r > 0$ phase

Landau like expansion in optimal unbinding rate

$$\langle T_{turn} \rangle = a_0 + a_1 r + a_2 r^2 + a_3 r^3 + \cdots ,$$

$a_i \implies$ “moments of catalysis process”

Landau like theory of "unbinding" transitions

- Transition between $r = 0$ and $r > 0$ phase

Landau like expansion in optimal unbinding rate

$$\langle T_{turn} \rangle = a_0 + a_1 r + a_2 r^2 + a_3 r^3 + \cdots ,$$

$a_i \implies$ "moments of catalysis process"

- Nature of transitions

$$SO : a_1 = 0$$

$$FO : \langle T_{turn}(r=0) \rangle = \langle T_{turn}(r=r_f) \rangle \quad , \quad \frac{\partial \langle T_{turn} \rangle}{\partial r}|_{r_f} = 0$$

Landau like theory of "unbinding" transitions

- Transition between $r = 0$ and $r > 0$ phase

Landau like expansion in optimal unbinding rate

$$\langle T_{turn} \rangle = a_0 + a_1 r + a_2 r^2 + a_3 r^3 + \cdots ,$$

$$a_i \implies \text{"moments of catalysis process"}$$

- Nature of transitions

$$SO : a_1 = 0$$

$$FO : \langle T_{turn}(r = 0) \rangle = \langle T_{turn}(r = r_f) \rangle \quad , \quad \frac{\partial \langle T_{turn} \rangle}{\partial r}|_{r_f} = 0$$

- Critical points

Landau like theory of "unbinding" transitions

- Transition between $r = 0$ and $r > 0$ phase

Landau like expansion in optimal unbinding rate

$$\langle T_{turn} \rangle = a_0 + a_1 r + a_2 r^2 + a_3 r^3 + \cdots ,$$

$a_i \implies$ "moments of catalysis process"

- Nature of transitions

$$SO : a_1 = 0$$

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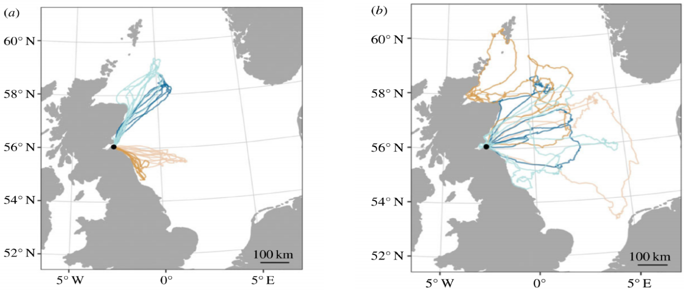
- Critical points
- Higher order critical points

A. Pal, and VV Prasad, PRR 1 (2019)

Summary

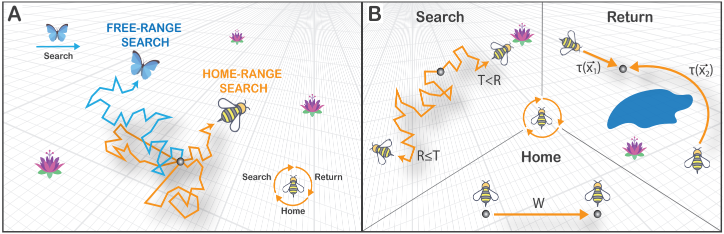
- Novel effects of unbinding: breakdown of classical prediction.
- Unravel striking connection between Landau theory and the transitions in optimal unbinding rate.
- Caveats?
- Landau-like theory for other first passage under restart models?

Sea bird foraging

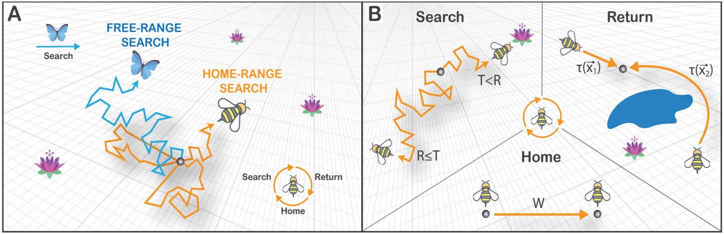


Grecian, J. R. Soc. Interface, 15 (2018)

Home range search — A cyclic process



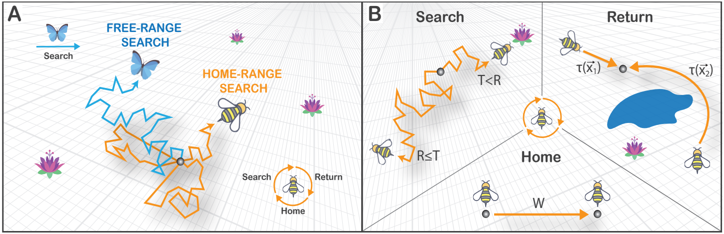
Home range search — A cyclic process



$$T_R = \begin{cases} T & \text{if} \quad T < R \\ R + \tau(\vec{x}) + W + T_R' & \text{if} \quad R \leq T \end{cases}$$

- When is the home-return beneficial?

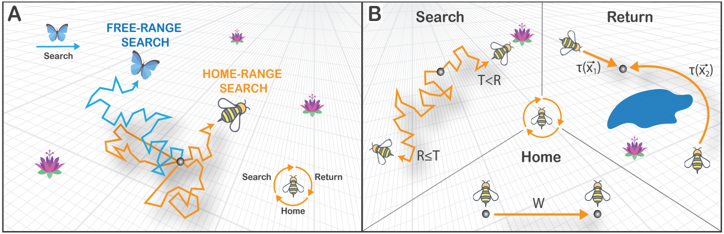
Home range search — A cyclic process



$$T_R = \begin{cases} T & \text{if} \quad T < R \\ R + \tau(\vec{x}) + W + T_R' & \text{if} \quad R \leq T \end{cases}$$

- When is the home-return beneficial?
- Effect of topography?

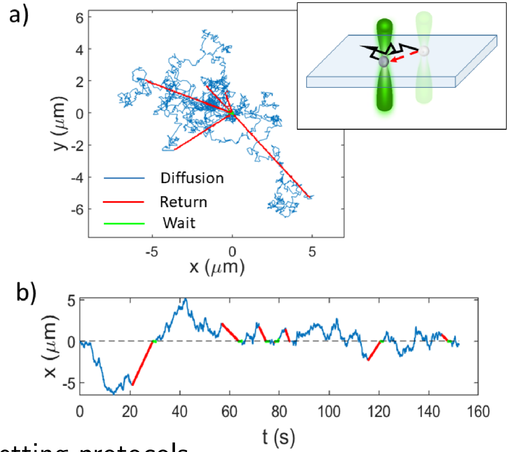
Home range search — A cyclic process



$$T_R = \begin{cases} T & \text{if} \quad T < R \\ R + \tau(\vec{x}) + W + T'_R & \text{if} \quad R \le T \end{cases}$$

- When is the home-return beneficial?
- Effect of topography?
- Cognition & memory

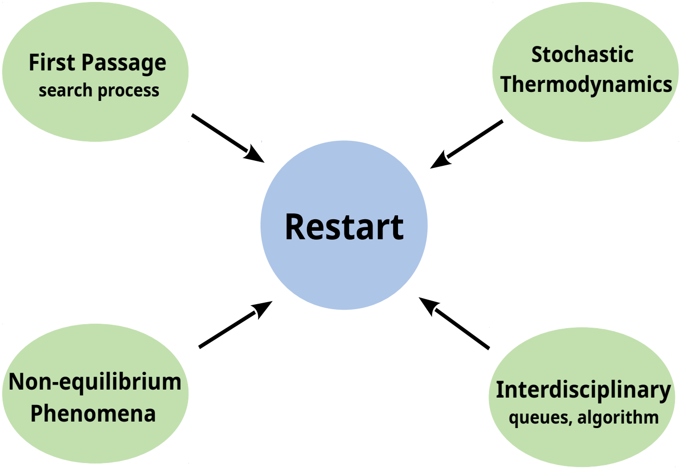
Single particle experiment



- Feasible resetting protocols
- New theoretical challenges

O Friedman, **A Pal**, A Sekhon, S Reuveni and Y Roichman, under review in PRL (2020)

Restart is ubiquitous in nature



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