First-passage times and reaction kinetics in confined media

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First-passage statistics: First definitions

How long does it take a random walker to reach a target site?

First-passage time

Many physical processes are controlled by first-encounter properties:

- Microscopic scale: diffusion limited reactions
- Macroscopic scale: search processes (animals looking for food ...)

\[ \langle T \rangle : \text{mean first-passage time (MFPT) of a symmetric random walker} \]

- In absence of confinement: \( \langle T \rangle = \infty \)
- In presence of confinement: \( \langle T \rangle < \infty \)

How does \( \langle T \rangle \) depend on the confinement and on the transport process?
Experimental context: Reactivity in confined media

Example: biomolecules (DNA-binding protein) reacting at a **specific location (specific gene)** in a cell.

How \( \langle T \rangle \) depends on:

1. the confining **volume** \( N \)?
   \[ \lim_{N \to \infty} \langle T \rangle = \infty, \]  but how \( \langle T \rangle \) grows with \( N \)?

2. the **distance** \( r \) between S and T?
   Is the **initial position** of the reactant an **important** parameter of the **kinetics**?

3. the **transport** process?
   Effects of crowding, anomalous diffusion...
Theoretical context:
[highly non-exhaustive biblio…]

(quasi) 1D geometries

[Redner…]

Main ingredient: backward equation.

\[ \Delta S \langle T \rangle_S = -1 \quad \text{with} \quad \langle T \rangle_{S=T} = 0; \quad \partial_S \langle T \rangle_{S \in \text{bound.}} = 0 \]

follows from \[ \langle T \rangle_S = 1 + \frac{1}{2} (\langle T \rangle_{S-1} + \langle T \rangle_{S+1}) \]

Averages over starting point

[Montroll…]
**Mean return times**

Blanco, Fournier (2003), Mazzolo (2004):

Pearson walk of velocity \( v \), and reorientation rate \( \lambda \)

\[
\langle t_1 \rangle_{\Sigma} = \frac{\eta_d}{v} \frac{V}{\Sigma} \quad \text{Independent of } \lambda!
\]

Generalizations using Backward Chapman-Kolmogorov equation

- General boundary conditions
  \[
  \langle t_1 \rangle_{\Sigma_{\text{abs}}} = \frac{\eta_d}{v} \frac{V}{\Sigma_{\text{abs}}}
  \]

- Residence time in a subdomain \( V' \)
  \[
  \langle T_1 \rangle_{\Sigma_{\text{abs}}} = \frac{\eta_d}{v} \frac{V'}{\Sigma_{\text{abs}}}
  \]

Discrete case: KAC formula (1947) \[
\langle T \rangle_{\text{return}} = 1/P_{\text{stat}} = N
\]
Outline

I MFPTs of simple random walks

II MFPTs in complex scale-invariant systems
An exact formula for MFPTs

“Renewal equation” : relates
the propagator \( W(\mathbf{r}, t|\mathbf{r}') \)
the first-passage time density \( P(\mathbf{r}, t|\mathbf{r}') \)

\[
W(\mathbf{r}_T, t|\mathbf{r}_S) = \int_0^t P(\mathbf{r}_T, t'|\mathbf{r}_S)W(\mathbf{r}_T, t-t'|\mathbf{r}_T)dt'
\]

*first visit of \( T \) at \( t' \)  \quad \text{return at} \quad T \text{ in } t-t'

\[
\langle T \rangle = N(H(\mathbf{r}_T|\mathbf{r}_T) - H(\mathbf{r}_T|\mathbf{r}_S))
\]

[\text{Noh & Rieger (PRL 2004)}]

where \( H(\mathbf{r}|\mathbf{r}') = \int_0^{\infty} (W(\mathbf{r}, t|\mathbf{r}') - 1/N)dt \)

Exact, but \textbf{formal}
expression of the MFPT

How to go further ???
Large volume asymptotics

$$\lim_{N \to \infty} \frac{\langle T \rangle}{N} = \lim_{N \to \infty} \left( H(r_T|r_T) - H(r_T|r_S) \right)$$

with $$\lim_{N \to \infty} H(r_T|r') = \int_0^\infty W_0(r, t|r') dt = \text{infinite-space Green function}$$

$$\langle T \rangle \simeq N(G_0(0) - G_0(r))$$

$$\langle T \rangle$$ is proportional to the confining volume $$N$$

(This is not a severe infinite-space approximation of the MFPT !)

Explicit dependence in the source-target distance $$r$$

If $$d=3$$, $$\langle T \rangle \simeq N \left( G(0) - \frac{3}{2\pi r} \right)$$ with $$G(0) = 1.516386...$$

If $$d=2$$, $$\langle T \rangle \simeq N \left( \frac{3}{\pi} \ln 2 + \frac{2\gamma}{\pi} + \frac{2}{\pi} \ln r \right)$$
3D Lattice Random Walks

[Condamin et al. PRL (2005)]

\[ \langle T \rangle \simeq N \left( G_0(0) - \frac{3}{2\pi r} \right) \]
Outline

I MFPTs of simple random walks

II MFPTs in complex scale-invariant systems
Other transport mechanisms?

Example of a percolation cluster in confinement

\[ \text{MFPT to go from S to T?} \]

• Renewal equation

\[
\langle T \rangle = N \left( H(r_T|r_T) - H(r_T|r_S) \right)
\]

where

\[
H(r|r') = \int_0^\infty \left( W(r,t|r') - 1/N \right) dt
\]

• Large volume asymptotics of the MFPT

\[
\lim_{N \to \infty} \frac{\langle T \rangle}{N} = G(0) - G(r)
\]

where

\[
G(|r - r'|) \equiv \int_0^\infty W_\infty(r, t|r') dt
\]

to go further, assumptions on the infinite-space propagator \[ W_\infty(r, t|r') \] needed
Assumptions on the infinite-space problem

- number of sites enclosed in a circle of radius $r$:
  $$M_r \propto r^{d_f}$$
  where $d_f$ is the fractal dimension of the medium
- time taken to a random walker to exit a circle of radius $r$:
  $$T_r \propto r^{d_w}$$
  where $d_w$ is the dimension of the walk
- standard scaling assumption of the infinite-space propagator:
  $$W_\infty(r, t|r') \sim t^{-d_f/d_w} \Pi \left( \frac{|r - r'|}{t^{1/d_w}} \right)$$

[ben-Avraham and Havlin, (2000)]
General scaling of the MFPT

[Condamin et al. Nature (2007)]

\[
\langle T \rangle \sim \begin{cases} 
N(A - Br^{d_w-d_f}) & \text{for } d_w < d_f \\
N(A + B \ln r) & \text{for } d_w = d_f \\
N(A + Br^{d_w-d_f}) & \text{for } d_w > d_f 
\end{cases}
\]

- \( A \) and \( B \) depend \textbf{only} on the infinite-space scaling function \( \Pi \)

- \textbf{Linear dependence on the volume} \( N \)

- \textbf{non-compact} exploration (\( d_w < d_f \)): memory of the initial position \textbf{lost}

- \textbf{compact} exploration (\( d_w \geq d_f \)): the \textbf{initial} position \textbf{always matters}
3D Lattice Random Walks

\[ 2 = d_w < d_f = 3 \]

Non compact exploration

\[ \frac{\text{MFPT}}{N} \]

Source-target distance

- **d=3, cube of side 41, target centred**
- **red: numerical simulations**
- **blue: approximate MFPT**
Critical percolation clusters

[Condamin et al, PNAS (2008)]

d_w > d_f

Compact exploration

\[ \langle T \rangle / N \sim A + Br^{d_w - d_f} \]

- data for different sizes collapse
- good agreement with the theoretical curve
2D Random barrier model

inhomogeneous transition rates $\Gamma$
(quenched disorder)

- power law distribution of transition rates: $\rho(\Gamma) = (\alpha/\Gamma)(\Gamma/\Gamma_0)^\alpha$
- regular diffusion ($d_w = 2$) in dimension 2 ($d_f = 2$)
  with $D_{\text{eff}}$ given by the effective medium approximation

$\langle T \rangle / N \sim \left( A + \frac{1}{2\pi D_{\text{eff}} \ln r} \right)$

![Graph showing MFPT vs. source-target distance]

- 50x50 domain
- 30x30 domain
- 10x10 domain
- theoretical curve
More about A and B:

“Zero” constant formula (compact case)

[Benichou et al. prl (2008)]

\[
\langle T \rangle/N \sim A + Br^{d_w-d_f} \quad \text{for } d_w > d_f
\]

- Continuous space limit gives \( \langle T \rangle (r \to 0) = 0 \) and therefore \( A = 0 \)
- Kac formula gives \( \langle T \rangle (r = 1) = N \) and therefore \( B = 1 \)

Then \( \langle T \rangle/N \sim r^{d_w-d_f} \)
Extension (i) : narrow escape time

Mean time to exit a bounded domain through a narrow aperture:

\[
\lim_{V \to \infty} \frac{\langle T \rangle}{V} = \begin{cases} 
\alpha(a_{w}^{d_{w}} - r_{f}^{d_{w}} - d_{f}) & \text{for } d_{w} < d_{f} \\
\alpha \ln(r/a) & \text{for } d_{w} = d_{f} \\
\alpha(r_{w}^{d_{w}} - a_{w}^{d_{w}} - d_{f}) & \text{for } d_{w} > d_{f}
\end{cases}
\]

Compact exploration
the starting point is important

Non-compact exploration
weak dependence on the starting point
Extension (ii) : case of competitive reactions

Splitting probability $P_1$:
probability to reach the target 1 before the target 2?

$P_1 \sim \frac{A + B(r_{2S}^{d_w-d_f} + r_{12}^{d_w-d_f} - r_{1S}^{d_w-d_f})}{2(A + Br_{12}^{d_w-d_f})}$

**Compact**
exploration

the **furthest** target is
almost never reached first

**Non-compact**
exploration

the **furthest** target has a **finite**
probability to be reached first
FPTs and subdiffusion

\[ \langle \Delta r^2 \rangle \sim t^\beta \text{ with } \beta < 1 \]

“Fractal” static medium

\[ \langle T \rangle / N \sim r^{d_w - d_f} \]

where \( d_w = \frac{2}{\beta} \)

“Dynamic” crowded medium

Continuous Time RW \( \psi(t) \sim C / t^{1+\beta} \)

\[ \text{Prob.}(T = t) \sim C \langle n \rangle / t^{1+\beta} \]

where \( \langle n \rangle \sim N(A - B / r) \) (\( d = 3 \))

Very different dependence on geometry
Concluding remarks: reactivity in confined media like cells?

**Dilute** medium (3d regular diffusion)

\[ \langle T \rangle \]

the initial position doesn’t matter

**Crowded** medium (3d percolation cluster)

\[ \langle T \rangle \]

the initial position is a key parameter

Spatial organization is crucial

Non-compact exploration

Compact exploration
Thanks

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