On the distributions of time averaged weighted Brownian trajectories

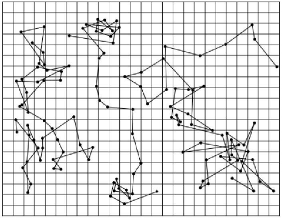
"making the most out of bad statistics"

Denis Boyer, Mexico city

David Dean, Bordeaux

Carlos Mejía-Monasterio, Madrid

Gleb Oshanin, Paris



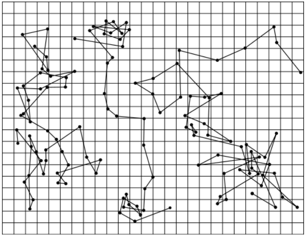
What is the diffusion coefficient?

Diffusion equation with constant force

$$\partial_t p(\mathbf{r}, t|\mathbf{r}_0, t_0) = \partial_{\mathbf{r}} \cdot D(\partial_{\mathbf{r}} - \beta \mathbf{F}(\mathbf{r}))p(\mathbf{r}, t|\mathbf{r}_0, t_0)$$

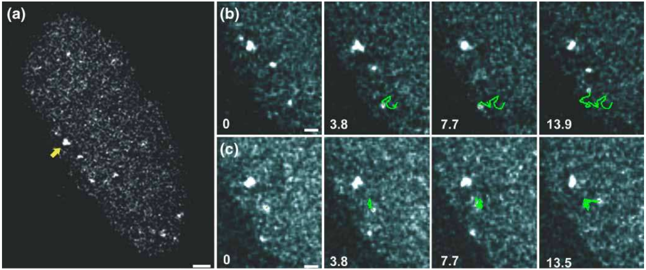
Here D is the emsemble average diffusion coefficient.

How can we estimate D out of a Single Particle Trajectory?



J. Perrin (1909)

Single Particle Tracking



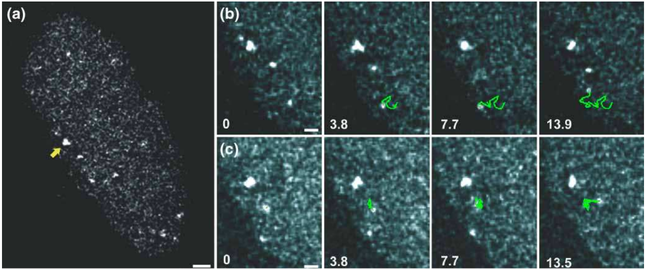
Golding & Cox (2006)

SPT methods are extensively used to study diffusive motion, *e.g.*

- LacI repressor protein along elongated DNA
- in the plasma membrane
- single protein in the cytoplasm and nucleoplasm of mammalian cells.

SPT methods have become instrumental in demonstrating deviations from normal BM of passively moving particles.

Single Particle Tracking

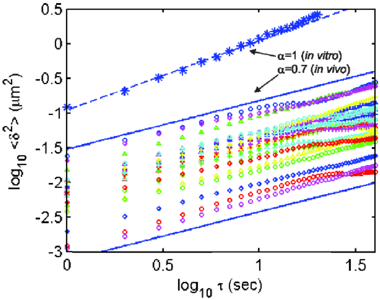


Golding & Cox (2006)

In the cell, the diffusion coefficient determines *e.g.*, binding times, and thus, the kinetic rates of cellular processes.

SPT provides insight into the microscopic rheological properties of complex media and the active motion of biomolecular motors.

Anomalous diffusion



Golding & Cox PRL 96, 098102 (2006)

In vivo experiments: motion is subdiffusive. Robust even at the disruption of cytoskeletal elements

- Macromolecular crowding
- Implications of the anomalous diffusion on the kinetics of bacterial gene regulation.

Bias and precision in SPT

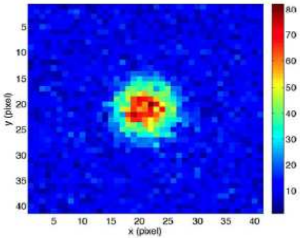
Slinding-time averages

$$\delta_T^2(t) = \int_0^{T-t} dt' \, \frac{(\mathbf{B}(t'+t) - \mathbf{B}(t'))^2}{T-t} \,,$$

yields $\langle \delta_T^2(t) \rangle = 2dDt$.

- static errors due to the spatial resolution of the experimental setup ε
- dynamic errors due to the finite integration time σ

$$\langle \delta_T^2(t) \rangle = 2D(t - \frac{\sigma}{3}) + 2\varepsilon^2$$

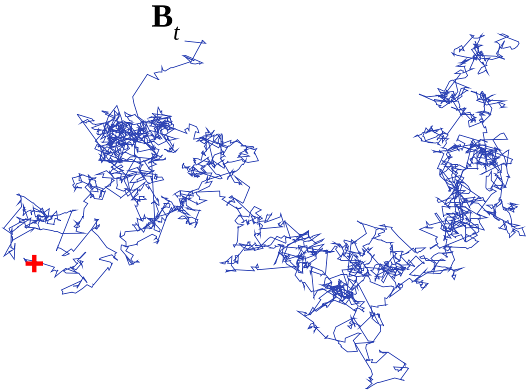


How reliably can one estimate the diffusion coefficient out of few single particle trajectories?

Diffusion coefficient D_f of a single Brownian trajectory $\mathbf{B}_t$

Given a single Brownian trajectory $\mathbf{B}_t$, how to estimate its diffusion coefficient D_f so that it will be most close to the true ensemble average value D?

$$D = \frac{\langle \mathbf{B}_t^2 \rangle}{2dt}$$



A simple-minded *rough* estimate $D_f = \frac{\mathbf{B}_t^2}{2dt}$

D_f is χ^2-distributed with d degrees of freedom

$$P(D_f) = \frac{1}{\Gamma(d/2)} \left(\frac{d}{2D}\right)^{d/2} D_f^{d/2-1} e^{-\frac{d}{2}\frac{D_f}{D}}$$

All moments of $P(D_f)$ exist. However,

- It does not depend on the observation time t. The estimate can not be made more precise upon increasing t. Thus it is not the ergodic "estimator" of D for a single trajectory.
- $d \leq 2$ The maximum is $u = D_f/D = 0$. Most probably we will observe $D_f \ll D$.
- $d > 2$ $P(D_f)$ is bellshaped. Most probable value $u^\star = D_f^\star/D = 1 - 2/d$.
  For $d = 3$ most probably $D_f = D/3$.
- $\mathrm{Var}(u) = 2/d$ is comparable with $\langle u \rangle = 1$.

Estimating the diffusion coefficient

A reliable estimator must possess an ergodic property so that its most probable value converges to the ensemble average one and the variance vanishes as the observation time increases.

- This is often not the case and moreover, ergodicity of a given estimator is not known a priori and has to be tested for each particular form of the estimator.
- On the other hand, knowledge of the distribution of such an estimator could provide a useful gauge to identify effects of the medium complexity as opposed to variations in the underlying thermal noise driving microscopic diffusion.

Generalized "least-squares" estimator

We look for the estimator of D_f that minimizes the generalized "least-squares" functional

$$F_{LS} = \frac{1}{2} \int_0^\tau \frac{w(t)}{t} \left(\mathbf{B}_t^2 - 2dD_f t \right)^2 dt$$

where $w(t)$ is an arbitrary weight function.
Setting the functional derivative $\delta F_{LS} / \delta D_f = 0$, we obtain the generalized least-squares estimator

$$D_f = A \frac{D}{\tau} \int_0^\tau w(t) \mathbf{B}_t^2 dt$$

with A a normalization constant such that $\langle D_f \rangle = D$.

Generalized "least-squares" estimator

We consider the family of least-squares estimators

$$u_\alpha = \frac{D_f}{D} = \frac{A}{\tau}\int_0^\tau w(t)\mathbf{B}_t^2 dt$$

with

$$w(t) = \frac{1}{(t_0 + t)^\alpha}$$

$t_0 > 0$ is a lag time, α an arbitrary real number and A is such that $\langle u_\alpha \rangle = 1$.

If $\alpha < 0$ we give more weight to the behaviour at large times and viceversa, for $\alpha > 0$ the short time behaviour is emphasized.

Generalized "least-squares" estimator

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$t_0 > 0$ is a lag time, α an arbitrary real number and A is such that $\langle u_\alpha \rangle = 1$.

Our goal is to find the optimal value of α for which the least squares estimators most efficiently filter out the fluctuations and hopefully, are ergodic.

Special cases

- LSE ($\alpha = -1$) Least Square Estimator.- Relies on the minimization of
$$\int_0^T dt\,\left(\mathbf{B}_t^2 - l(t)\right)^2$$
If $l(t) = 2dD_f t$ then the LSE becomes
$$u_{LSE} = \frac{A}{T}\int_0^T dt\; t\,\mathbf{B}_t^2.$$
- MLE ($\alpha = 1$) Maximum Likelihood Estimator.- Based on the maximization of the unconditional probability of observing the whole trajectory $\mathbf{B}_t$, assuming that it is drawn from a Brownian process with mean square displacement $2dDt$:
$$u_{MLE} = \frac{A}{T}\int_0^T dt\,\frac{\mathbf{B}_t^2}{t}.$$

Moment generating function of u_α

The moment generating function $\Phi(\sigma)$ of the random variable u_α is

$$\Phi(\sigma) = \mathbb{E}\left[e^{-\sigma \cdot u_\alpha}\right] = \mathbb{E}\left[e^{-\sigma \frac{A}{\tau} \int_0^\tau w(t) \mathbf{B}_t^2 dt}\right]$$

This Laplace transform can be calculated exactly using either

- the Cameron-Martin formula for the Wiener process
- by treating it as a path integral and using Feynmann-Kac formula to obtain the corresponding Schrödinger-type equation

We have determined $\Phi(\sigma)$ exactly for arbitrary d, σ and

$$\varepsilon = \frac{t_0}{\tau}$$

which is a measure of experimental resolution

Moment generating function of u_α

We want to obtain $\Phi(\sigma) = G^d(\sigma)$, where

$$G(\sigma) = \mathbb{E}\left[\exp\left(-\frac{\sigma A}{\tau}\int_0^\tau w(t)\mathbf{B}_t^2 dt\right)\right]$$

Consider the path integral

$$\Psi(x,t) = \mathbb{E}_t^x\left[\exp\left(-\frac{\sigma A}{\tau}\int_t^\tau w(t)\mathbf{B}_t^2 dt\right)\right]$$

where the expectation is conditioned to BM starting at x at time t. Then $G(\sigma) = \Psi(0,0)$.

Moment generating function of u_α

Considering time evolution from t to $t+dt$ during which the BM moves from x to $x+dB_t$ one obtains a Feynman-Kac type formula

$$\begin{aligned}\Psi(x,t) &= \mathbb{E}_{dB}\left[\left(1-\frac{\sigma A_\alpha w(t)}{\tau}x^2 dt\right)\mathbb{E}_{t+dt}^{x+dB_t}\left[\exp\left(-\frac{\sigma A}{\tau}\int_{t+dt}^{\tau} w(t)\mathbf{B}_t^2 dt\right)\right]\right] \\ &= \mathbb{E}_{dB}\left[\left(1-\frac{\sigma A_\alpha w(t)}{\tau}x^2 dt\right)\Psi(x+dB_t, t+dt)\right] \ .\end{aligned}$$

Expanding the rhs in dB_t and dt and performing averaging one finds

$$\partial_t \Psi(x,t) = -D\partial_x^2 \Psi(x,t) + \frac{\sigma A_\alpha w(t)}{\tau}x^2 \Psi(x,t)$$

Schödinger-like equation for a Harmonic oscillator with time dependent frequency.

Moment generating function of u_α

For $\alpha \neq 2$, we find to leading order in ε

$$\Phi(\sigma) = \begin{cases} \left(\Gamma(\nu) \left(\frac{\sigma}{\chi_1} \right)^{\frac{\nu-1}{2}} \mathrm{I}_{1-\nu}\left(2\sqrt{\frac{\sigma}{\chi_1}} \right) \right)^{-d/2}, & \text{for} \quad \alpha < 2 \\ \left(\Gamma(1-\nu) \left(\frac{\sigma}{\chi_2} \right)^{\frac{\nu}{2}} \mathrm{I}_{-\nu}\left(2\sqrt{\frac{\sigma}{\chi_2}} \right) \right)^{-d/2}, & \text{for} \quad \alpha > 2 \end{cases}$$

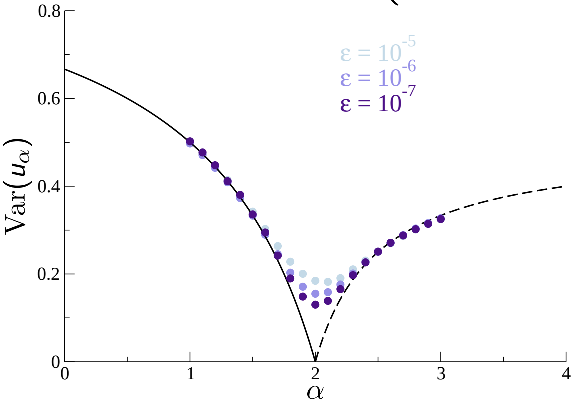
where $\nu = 1/(2-\alpha)$, $\chi_1 = d(2-\alpha)/2$, $\chi_2 = d(\alpha-2)/2(\alpha-1)$ and $I_\mu(z)$ is the modified Bessel function.

Note that ν diverges as $\alpha \to 2$ and χ tends to zero. The case $\alpha = 2$ has to be considered separately.

Variance of the estimator

Differentiating twice with respect to σ we obtain

$$\mathrm{Var}(u_\alpha) = \frac{2}{d} \begin{cases} (2-\alpha)/(3-\alpha), & \alpha < 2, \\ (\alpha-2)/(2\alpha-3), & \alpha > 2. \end{cases}$$



Finite ε corrections are $\mathcal{O}(\epsilon^{2-\alpha})$ Asymptotic behavior attained when $\epsilon \ll \exp\left(-1/(2-\alpha)\right)$.

$$\lim_{\alpha\to 2} \mathrm{Var}(u_\alpha) \to 0$$

but only at expense of increasing the experimental resolution or observation time.

In the leading order in ε, $\mathrm{Var}(u_\alpha)$ can be made arbitrarily small by taking α gradually closer to 2.

Asymptotic behaviour of $P(u_\alpha)$ for $\alpha \neq 2$ and $\varepsilon = 0$

From the exact expression of $\Phi(\sigma)$ we obtain the large- and small-u asymptotics

- the left tail ($u_\alpha \ll 1$)

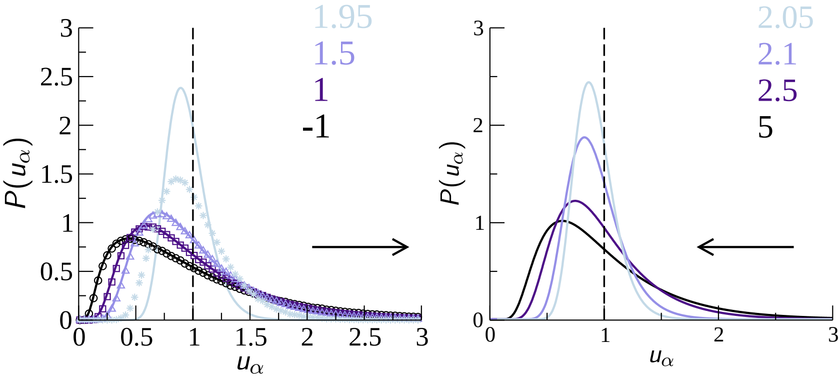
$$P(u_\alpha) \sim \exp\left(-\frac{d^2}{4\chi_{1,2} u_\alpha}\right) \frac{1}{u_\alpha^\zeta}, \; \zeta = \frac{3}{2} + \frac{d}{4} \frac{\alpha}{|2-\alpha|}$$

- the right tail ($u_\alpha \gg 1$)

$$P(u_\alpha) \sim u_\alpha^{d/2-1} \exp\left(-\frac{\chi_{1,2}\gamma_{1-\nu,1}^2}{4} u_\alpha\right)$$

where $\gamma_{\mu,1}$ is the 1st zero of the Bessel function $J_\mu(z)$, and $(\chi_1,\, \mu = \nu - 1)$ or $(\chi_2,\, \mu = -\nu)$ is to be chosen for $\alpha < 2$ or $\alpha > 2$ respectively.

PDF of the estimator



$\alpha < 2$. Increasing α, $P(u_\alpha)$ narrows and its maximum moves towards 1.

$\alpha = 2$. $P(u_\alpha)$ is a δ-function.

$\alpha > 2$.Increasing α, $P(u_\alpha)$ narrows and its maximum starts to move back.

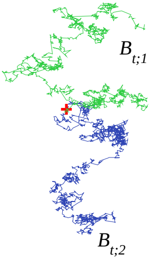
Quantifying the "broadness" of the $P(D_f)$

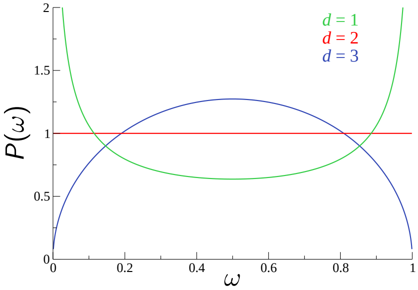
Consider two Brownian trajectories and define

$$\omega = \frac{D_{f;1}}{D_{f;1} + D_{f;2}}$$

which probes the likelihood that diffusion coefficients obtained from two different trajectories are equal. The distribution of ω is

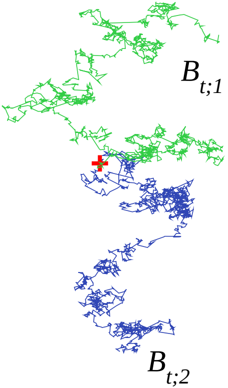
$$P(\omega) = \frac{\Gamma(d)}{\Gamma^2(d/2)} \omega^{d/2-1} (1-\omega)^{d/2-1}$$

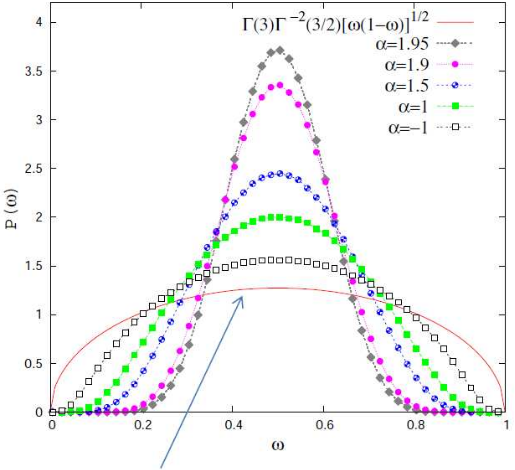




Distribution $P(\omega)$ for $d = 3$, $\alpha \neq 2$ and $\varepsilon = 0$

$$\omega = \frac{D_{f;1}}{D_{f;1} + D_{f;2}}$$





$P(\omega)$ for a simple-minded estimate of D_f

Variance of $P(u_\alpha)$ for $\alpha = 2$ and arbitrary ε

Consider a slightly more general form for $\omega(t)$:

$$\omega(t) = \begin{cases} 2\xi/t_0^2, & \text{for } t < t_0, \\ 1/t^2, & \text{for } t_0 \leq t \leq T, \end{cases}$$

where ξ is a tunable amplitude. For such a choice, the moment generating function is given explicitly by

$$\Phi(\sigma) = \left(\frac{2\,\delta\,\epsilon^{(\delta-1)/2}}{\phi_+} \right)^{d/2} \left[1 + \frac{\phi_-}{\phi_+}\,\epsilon^{\delta} \right]^{-d/2}$$

with

$$\phi_\pm = (\delta \pm 1) \left(\mathrm{ch}\left(\sqrt{2\gamma\xi\sigma}\right) \pm \frac{\delta \mp 1}{2\sqrt{2\gamma\xi\sigma}} \mathrm{sh}\left(\sqrt{2\gamma\xi\sigma}\right) \right)$$

and $\delta = \sqrt{1 + 4\gamma\sigma}$ and $\gamma = 2/d(\xi + \ln(1/\epsilon))$.

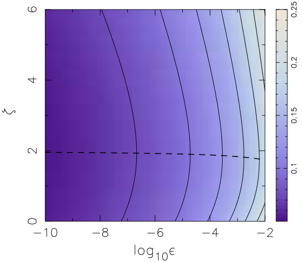
Variance of $P(u_\alpha)$ for $\alpha = 2$ and arbitrary ε

Differentiating $\Phi(\sigma)$ we obtain for the variance

$$\mathrm{Var}(u) = \frac{4}{3d} \frac{3\ln(1/\epsilon) - 3(1-\epsilon) + 2(1-\epsilon)\xi + \xi^2}{(\xi + \ln(1/\epsilon))^2} .$$

This is a non-monotonic function of ξ with a minimum at

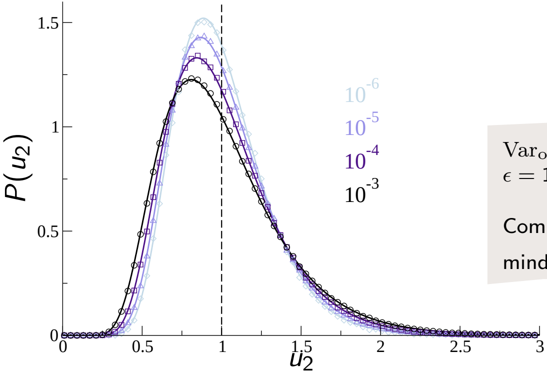
$$\xi = \xi_{\text{opt}} = \frac{(2+\epsilon)\ln(1/\epsilon) - 3(1-\epsilon)}{\ln(1/\epsilon) + \epsilon - 1} .$$



The corresponding optimized variance is given by:

$$\mathrm{Var}_{\text{opt}}(u) = \frac{4}{3d} \frac{3\ln(1/\epsilon) - 4 + 5\epsilon - \epsilon^2}{\ln(1/\epsilon)\,(\ln(1/\epsilon) + 1 + 2\epsilon) - 3(1-\epsilon)}$$

Variance of $P(u_\alpha)$ for $\alpha = 2$ and arbitrary ε



$\mathrm{Var}_{\mathrm{opt}}(u) \approx 0.144,\ 0.096,\ 0.082$ for $\epsilon = 10^{-3}, 10^{-5}, 10^{-6}$, respectively.

Compare this with 0.66 of the simple-minded estimate.

When $\epsilon \to 0$, $\mathrm{Var}_{\mathrm{opt}}(u)$ vanishes as

$$\mathrm{Var}_{\mathrm{opt}}(u) \sim \frac{4}{d} \frac{1}{\ln(1/\epsilon)}$$

The distribution converges to a δ-function so that the estimator with u_2 is the only that possess an ergodic property.

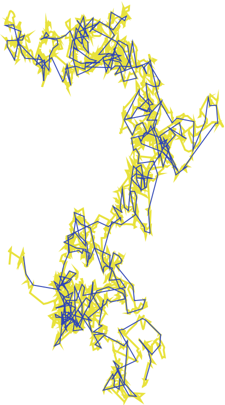
Discrete sets of data. Exact optimization

Collect a set of temporal points t_j, $0 < t_0 < t_1 < \ldots < t_{N-1} = \tau$ and for each of these points B_j, one component of the d-dimensional BM

$$\tilde{u} = \frac{D_f}{D} = \frac{1}{2} \sum_{j=0}^{N-1} w_j \cdot B_{t_j}^2 \ ; \qquad \langle \tilde{u} \rangle = 1$$

The variance is

$$\mathrm{Var}(\tilde{u}) = \sum_{j=0}^{N-1} \sum_{k=0}^{N-1} w_j w_k \min(t_k, t_j)^2 \ .$$



Discrete sets of data. Exact optimization

Exact minimization procedure gives an optimal weight function

$$
\begin{aligned}
w_0 &= \frac{\lambda t_1}{t_0(t_0+t_1)} \\
w_j &= \frac{\lambda}{t_j+t_{j-1}} - \frac{\lambda}{t_j+t_{j+1}} \\
w_{N-1} &= \frac{\lambda}{t_{N-1}+t_{N-2}}
\end{aligned}
$$

and

$$
\lambda = \left(\frac{t_1}{t_0+t_1} + \frac{t_{N-1}}{t_{N-1}+t_{N-2}} + \sum_{j=1}^{N-2} \frac{t_j(t_{j+1}-t_{j-1})}{(t_{j+1}+t_j)(t_{j-1}+t_j)} \right)^{-1}
$$

In the continuous time limit we recover the piece-wise algebraic $w(t)$

Variance of the LS estimators for fBM and $\varepsilon = 0$

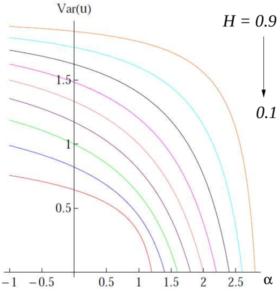
Let B_t be a fBM with a Hurst index H, $0 < H < 1$
exact result for the variance of u_α for $\alpha \leq 1 + 2H$ and $\varepsilon = 0$:

$$\begin{aligned} \mathrm{Var}(u_\alpha) &= \frac{2H+1-\alpha}{2}\left(\frac{1}{1-\alpha} + \frac{2}{1+2H-\alpha} + \frac{1}{1+4H-\alpha}\right. \\ &- \left. 2\frac{\Gamma(1-\alpha)\Gamma(1+2H)}{\Gamma(2+2H-\alpha)} + \frac{\Gamma(1-\alpha)\Gamma(1+2H) - 2\Gamma(1+2H)\Gamma(1+2H-\alpha)}{\Gamma(2+4H-\alpha)}\right) \end{aligned}$$

This result hints that for fBM, the LS estimators

$$u_{\alpha-1+2H} = \frac{A}{\tau}\int_0^\tau \frac{B_t^2}{(t_0+t)^{1+2H}}$$

are ergodic.



To summarize

- We studied weighted LSE of a single Brownian trajectory diffusion coefficient D_f.
- These estimators minimize the leastsquares functionals, approximating D_f.
- For standard BM B_t the LS estimator

$$u_\alpha = \frac{A}{\tau} \int_0^\tau \frac{B_t^2}{(t_0 + t)^\alpha}$$

  is ergodic only for $\alpha = 2$.
- As $t_0/\tau \to 0$, the distribution converges to a δ-function.
- In this case the estimator efficiently filters out the fluctuations and the value of the true, ensemble average D can be obtained from a single trajectory data with any necessary accuracy, but at expense of increasing the observation time τ.
- fBM with Hurst index H the LSE is ergodic for $\alpha = 1 + 2H$.
- For discrete sets of observations the optimal weight function w_j was obtained exactly from the minimization of the variance.