Detecting alterations in genomic profiles : the infinite population case.

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joint work with L. Decreusefond[2], G. Lang[3], S. Robin[4] and P. Vallois[5]

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([5]) IECL

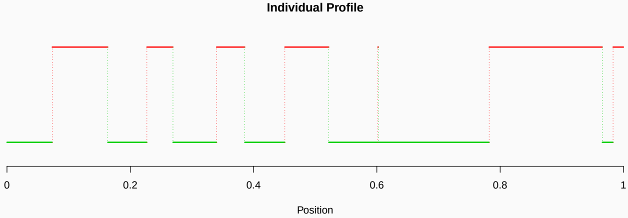
Modelling individual genomic profile, large L

Pure Jump Continuous-time Markov model:

Each profile X_i is a continuous time Markov process $X_i = \{X_i(t)\}_{0 \leq t \leq L}$:

States:	$0 = \text{normal}$	$1 = \text{alteration}$
Transition rates:	$\lambda : 0 \to 1$	$\mu : 1 \to 0.$

Consequence.
Mean length of normal regions = $1/\lambda$ and altered regions = $1/\mu$.



Cumulative Cohort profiles

We are interested in the alterations shared by a large proportion of patients.

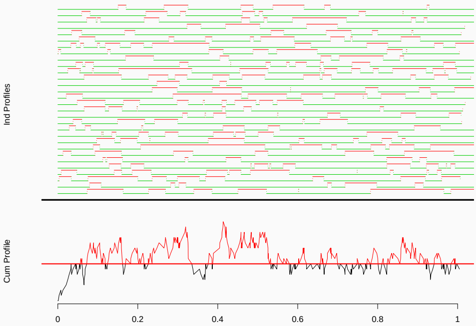
Define the cumulative cohort profile as $S_n = \sum_{i=1}^{n} X_i$.

Focus on the length $E_1, E_2, \ldots.$ of the excursions above a of S_n on $[0,1]$.

Goal : characterizing the distribution of

$$E_*^{a,S_n}(1) = \max_i E_i(1)$$

$$\mathbb{P}\left(E_*^{a,S_n} > l\right) = ??$$



A True Sea Snake

Let's Dare to say it in French *Un véritable serpent de mer*

Rats do not leave the ship

Theoretical behaviour with large number of patients

Cumulative process S_n

The process $\{S_n(t), t \in [0,1]\}$ counts the number of altered profiles at time t. Assuming $\lambda = \mu$, the jumps $\mathbf{U} = (U_1^{(n)}, U_2^{(n)}, \ldots)$ occur at exponential times λn.

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It is a Markovian birth and death process with states $\{0, 1 \ldots, n\}$ and transition rates

$$i \to i+1 \quad \text{('birth' of an alteration) :} \qquad \lambda_i = (n-i) \times \lambda$$

$$i \to i-1 \quad \text{(death = back to normal) :} \qquad \mu_i = i \times \lambda$$

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In the stationary case,

$$X_i(0) \sim \mathcal{B}\left(\frac{1}{2}\right), \quad i = 1, \ldots n,$$

Define $\tau = 2\lambda$, $p = 0.5$, we have:

$$\mathbb{E}\left[S_n(t)\right] = \frac{n}{2}, \quad \mathbb{V}\left[S_n(t)\right] = \frac{n}{4}, \quad \mathbb{C}\mathrm{ov}\left[S_n(s), S_n(s+t)\right] = \frac{n}{4} e^{-\tau t}$$

Consider

$$Z^{(n)}(t) = \frac{S_n(t) - n/2}{\sqrt{n/4}},$$

The perfect suspect $\mathbf{Z} = (Z(t), 0 \le t \le 1)$ solution to

$$dZ(t) = -\tau Z(t)dt + \sqrt{2\tau}dW(t), \quad Z(0) \sim \mathcal{N}(0,1).$$

Cumulative process $S^{(n)}$

Sketch of proof :

- $(Z^{(n)}(t_1), \dots, Z^{(n)}(t_k))$ converges to a Gaussian vector,

$$\sum_{j=1}^{k} \alpha_j Z(t_j) = \sum_{i=1}^{n} \sum_{j=1}^{k} \alpha_j \frac{X_i(t_j) - 0.5}{\sqrt{n/4}} \quad \forall (\alpha_1, \dots, \alpha_C) \in \mathbb{R}^k$$

- The covariance function is

$$\rho(s, s+t) = \mathbb{C}\mathrm{ov}(Z^{(n)}(s), Z^{(n)}(s+t)) = \rho(t) = e^{-\tau t}$$

- The unique stationnary Gaussian process with covariance function $\rho(t) = e^{-\tau t}$ is the Ornstein Uhlenbeck process.
- Tightness

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From a practical point of view, **the rate would be useful** !

Step 0 : Understanding Kubilius

5 years of scientific wandering and convergence rate as rewarding as $N^{1/23}$, which might require large cancer cohort.

Finally, getting inspired by Kęstutis Kubilius[a] (6 citations in Google Scholar).

Theorem ([Kub94])

Let $(\xi_k^{(n)}, \mathcal{F}_k^{(n)})$ be a sequence of square-integrable martingale differences a.s bounded by $n^{-1/2}M$. Denote

$$W^n(t) = \sum_i^n \xi_i^{(n)} + \frac{tV_n^{(n)^2} - V_k^{(n)^2}}{V_{k+1}^{(n)^2} - V_k^{(n)^2}} \xi_i^{(n)}, \quad \text{if } \frac{V_k^{(n)^2}}{V_n^{(n)^2}} < t \leq \frac{V_{k+1}^{(n)^2}}{V_n^{(n)^2}}$$

where $V_k^{(n)^2} = \sum_{i=1}^k \mathbb{E}\left\{(\xi_i^{(n)})^2 | \mathcal{F}_{i-1}^{(n)}\right\}$. There exists a constant C such that

$$\pi(W^{(n)}, W) < C \ln n \left\{ n^{-1/4} + inf_{0<\varepsilon<1} \left(\varepsilon + \mathbb{P}(|V_n^{(n)^2} - 1| > \varepsilon^2) \right) \right\}.$$

π stands for the Prokhorov distance.

[a] K Kubilius. "Rate of convergence in the invariance principle for martingale difference arrays". In: Lithuanian Mathematical Journal 34.4 (1994), pp. 383–392.

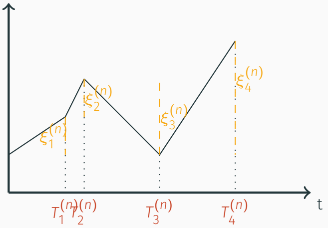
- $\xi_k^{(n)}$ square-integrable martingale differences:

$$\mathbb{E}\left[\sum_{k=1}^{j} \xi_k^{(n)} | \mathcal{F}_{j-1}^{(n)}\right] = \mathbb{E}\left[\xi_j^{(n)} | \mathcal{F}_{j-1}^{(n)}\right] + \sum_{k=1}^{j-1} \xi_k^{(n)}$$

$$\mathbb{E}\left[\xi_j^{(n)} | \mathcal{F}_{j-1}^{(n)}\right] = 0$$

- Handling time

$$T_k^{(n)} = \frac{V_k^{(n)2}}{V_n^{(n)2}}, \quad V_k^{(n)2} = \sum_{i=1}^{k} \mathbb{E}\left[(\xi_i^{(n)})^2 | \mathcal{F}_{i-1}^{(n)}\right]$$



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- The Prokhorov distance π, U et V deux variables à valeurs dans le même espace,

$$\pi(U,V) \leq \varepsilon \text{ iff } \mathbb{P}\{U \in A\} \leq \mathbb{P}\{V \in A^{\varepsilon}\} + \varepsilon$$

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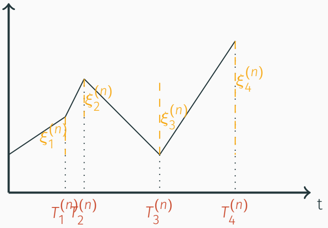

Action Plan

- $Z_k^{(n)} = S^{(n)}(U_k^{(n)})$ for $k = 1, \dots m$ (m the number of jumps)

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- $\mathbb{E}\left[Z_{k+1}^{(n)} | \mathcal{F}_k^{(n)}\right] = \left(1 - \dfrac{2}{n}\right) Z_k^{(n)}$
- $\xi_{k+1}^{(n,m)} = \frac{1}{2}\sqrt{\frac{n}{m}}\left(Z_{k+1}^{(n)} - \left(1 - \frac{2}{n}\right) Z_k^{(n)}\right), \quad 0 \leq k \leq m-1$
- Prokhorov:

$$\begin{aligned}\mathbb{P}(\omega_n \in A) =& \mathbb{P}(\omega_n \in A, \|\omega_n - \omega\|_\infty \leq \varepsilon) + \mathbb{P}(\omega_n \in A, \|\omega_n - \omega\|_\infty > \varepsilon) \\ \leq& \mathbb{P}(\omega \in A^\varepsilon) + \mathbb{P}(\|\omega_n - \omega\|_\infty > \varepsilon)\end{aligned}$$

Step 1: Some random process converges to a Brownian motion

Theorem
Let n and m be two integers satisfying

$$\lambda_1 m \leq n \leq \lambda_2 m, \quad \text{with } 0 < \lambda_1 \leq \lambda_2 \leq n^{1/4},$$

$$W_k^{(n,m)} = \sum_{i=1}^{k} \xi_i^{(n,m)}, \quad 1 \leq k \leq m, \quad W_0^{(n,m)} = 0.$$

Then, there exists a constant $C_1(\lambda_2)$ such that

$$\pi\left(\boldsymbol{W}^{(n,m)}, \mathrm{W}\right) \leq C_1(\lambda_2) n^{-1/4} \ln(n).$$

Step 2: Getting closer from the original process

Let's consider $\boldsymbol{Y}^{(\boldsymbol{n},\boldsymbol{m})} = (Y^{(n,m)}(t), 0 \leq t < 1)$:

$$Y^{(n,m)}(t) = Z_k^{(n)} + \frac{t - t_k^{(n,m)}}{t_{k+1}^{(n,m)} - t_k^{(n,m)}} \left(Z_{k+1}^{(n)} - Z_k^{(n)} \right), \quad t_k^{(n,m)} \leq t < t_{k+1}^{(n,m)}.$$

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The integral representation of a Ornstein uhlenbeck process

$$Z(t) = Z_0 e^{-\tau t} + \sqrt{2\tau} W(t) - \sqrt{2}\tau^{3/2} \int_0^t e^{-\tau(t-s)} W(s) ds, \quad Z_0 \sim \mathcal{N}(0,1).$$

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Let's consider

$$\begin{aligned} F_{n,m}(\omega, x)(t_k^{(n,m)}) &= x\left(1 - \frac{2}{n}\right)^k + 2\sqrt{\frac{m}{n}}\left(1 - \frac{2}{n}\right)^{-1} \omega(t_k^{(n,m)}) \\ &\quad - 4\left(1 - \frac{2}{n}\right)^{-1} \sqrt{\frac{m}{n}} \left(\frac{1}{n} \sum_{i=1}^{k} \left(1 - \frac{2}{n}\right)^{k-i} \omega(t_i^{(n,m)}) \right) \end{aligned} \tag{1}$$

Step 2: Getting closer from the original process

Theorem
Given the previous notations

$$Y^{(n,m)} = F_{n,m}(W^{(n,m)}, Z_0),$$

and if $\left|\frac{M}{n} - 1\right| \leq n^{-1/3}$*, then there exists a constant C such that*

$$\pi(Y^{(n,m)}, \mathrm{Y}) \leq Cn^{-1/4} \ln(n).$$

Step 3: Finally ....

By controling the distance between $t_k^{(n,m)}$ and $U_k^{(n)}$, we finally have

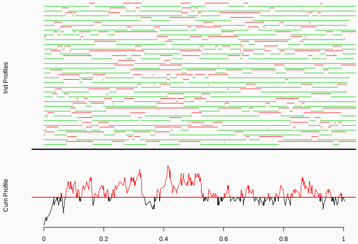
Theorem

For any κ in $]0, 1/4[$, there exists a constant C which only depends on κ such that

$$\pi\left(\mathsf{Z}^{(\mathsf{n})}, \mathsf{Z}\right) \leq \frac{C}{n^{\kappa}}.$$

Did we make any progress ?

Original problem



Characterizing the distribution of

$$E_*^{a,S_n}(1) = \max_i E_i(1)$$

$$\mathbb{P}\left(E_*^{a,S_n} > l\right)$$

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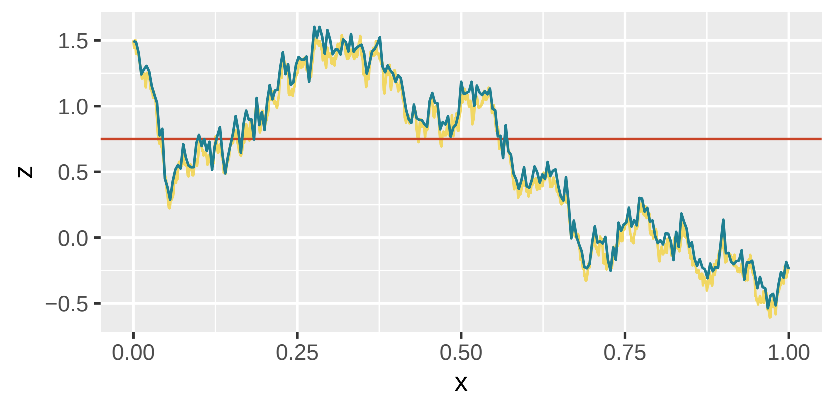

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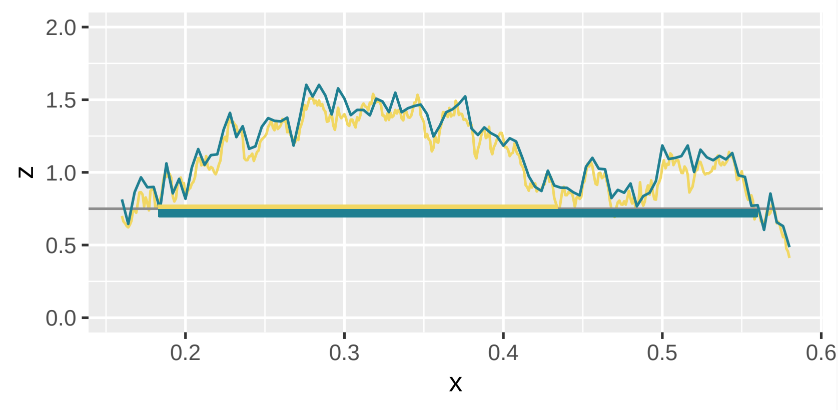

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$$\mathbb{P}\left(E_*^{a,S_n} > \ell\right) = \mathbb{P}\left(\sup_{0\leq s\leq t-l}\left\{\inf_{s\leq u<s+l} S_n(u)\right\} > a\right)$$

This proves the convergence as the event of interest is expressed through a continuous functionnal, but does nt control the rate

Convergence of the longest excursion

Let's denote $H(\omega) = \sup_{0\leq s\leq t-l} \left\{ \inf_{s\leq u<s+l} \omega(u) \right\}$,

We hope $\pi\left(H(\mathsf{Z}^{(\mathsf{n})}), H(\mathsf{Z})\right) \leq \varepsilon_n$, i.e. $\forall$ closed set A, $\mathbb{P}(H(\mathsf{Z}^{(\mathsf{n})}) \in A) \leq \mathbb{P}(H(\mathsf{Z}) \in A^{\varepsilon})$

$$\begin{aligned}
\mathbb{P}(H(\mathsf{Z}^{(\mathsf{n})}) > a) &= \mathbb{P}(\mathsf{Z}^{(\mathsf{n})} \in A), \quad \text{with } A = \{\omega, H(\omega) > a\} \\
&\leq \mathbb{P}\left(\mathsf{Z} \in A^{\varepsilon_n}\right) + \varepsilon_n, \\
&\leq \mathbb{P}\left(\mathsf{Z} \in A\right) + \mathbb{P}\left(\mathsf{Z} \in A^{\varepsilon_n} \cap \bar{A}\right) + \varepsilon_n, \\
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$\left\{\mathsf{Z} \in A^{\varepsilon_n} \cap \bar{A}\right\} = \{\exists \omega, H(\omega) > a, \|\omega - \mathsf{Z}\| \le \varepsilon_n, H(\mathsf{Z}) \le a\} \subset \{a - \varepsilon_n < H(\mathsf{Z}) \le a\}$

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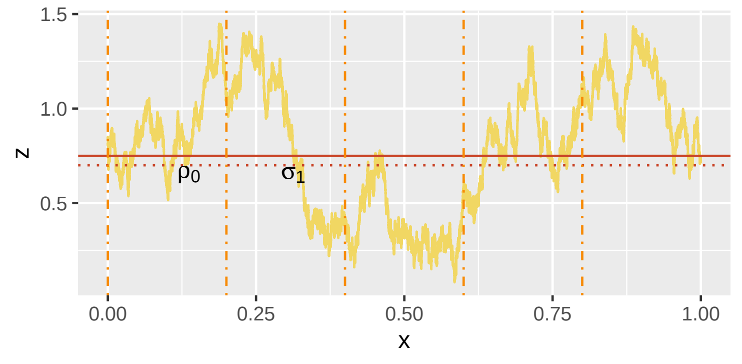
Proposition
There exists $c > 0$ and a sequence ε_n decreasing to zero such that

$$\mathbb{P}^{\lambda}(a - \varepsilon_n < H(\mathsf{Z}) \leq a) \leq c\varepsilon_n$$

Let's denote $F_y^s(a) = \mathbb{P}_{Z(0)=y}\left(\forall t \leq s - l, \inf_{t \leq u \leq t+l} Z(u) \leq a\right)$,
We control $F_y^s(a) - F_y^s(a - \varepsilon)$, reasonning by induction and conditioning on $Z(kl)$



Finally

Theorem
There exists C and $\kappa \in [0, 1/4[$, *such that*

$$\pi(H(\mathsf{Z}^{(\mathsf{n})}), H(\mathsf{Z})) \leq \frac{C}{n^{\kappa}}$$

Conclusion

The bad news

- We prove the convergence of the pure jumps Markov Process to an Ornstein Uhlenbeck Process,
- as well as the convergence of the longest excursion, with the same rate of convergence
- with a descent rate
- in only 10 years,

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- We aim at approximating $\mathbb{P}\left(E_*^{a,S_n} > l\right)$ by $\mathbb{P}\left(E_*^{a,Z} > l\right)$,
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- We have good plan for the 10 years to come.

THANK YOU !

See You in 10 years !

Références

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[Kub94] K Kubilius. "Rate of convergence in the invariance principle for martingale difference arrays". In: Lithuanian Mathematical Journal 34.4 (1994), pp. 383–392.

Appendix

Practical approach

Practical evaluation of $\mathbb{P}(E_*^{a,Z} > s)$ via MC approach

Several alternatives:

1. Sample a discretized version, named Z^δ of Z,
2. Sample the first hitting time σ_a according to [Alili+2005] and then discretized Z,

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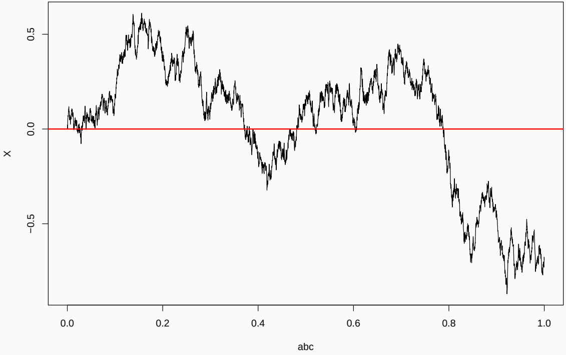
4. Use splitting rare events technics to sample σ_a and use theoretical work for Importance sampling approach.

Validity of the approximation via E_*^{a,Z^δ}



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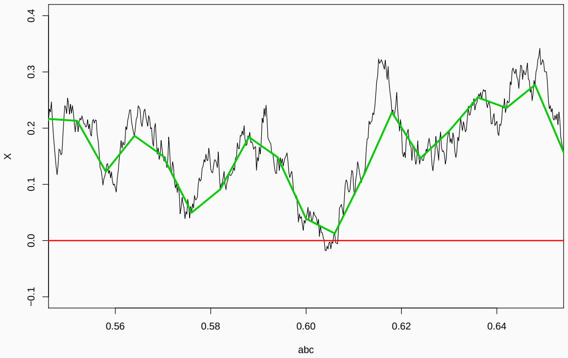

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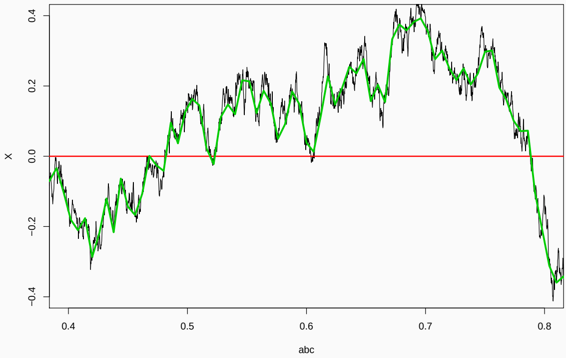

Under regularity conditions, [Azais1990] proves the convergence of the excursion of Z^δ to the excursions of Z, when Z is a Gaussian processes.

Validity of the approximation via E_*^{a,Z^δ}

But poor efficiency

Sample the first hitting time using the density

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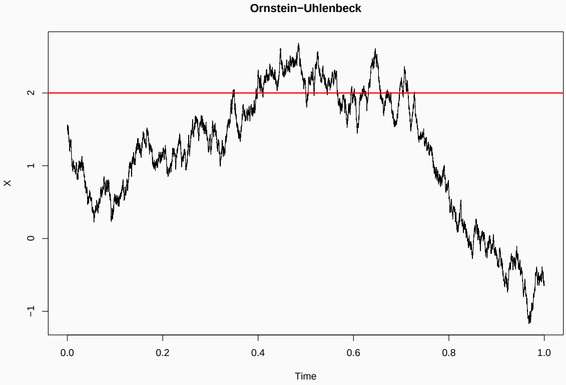
Key idea



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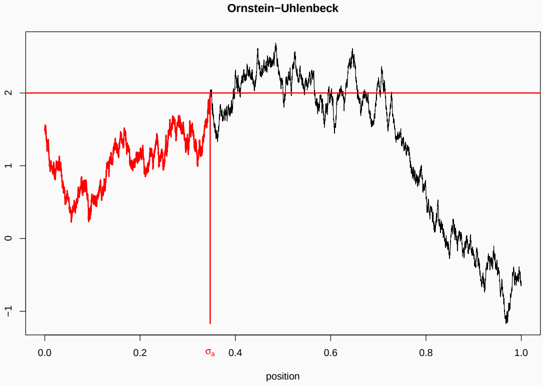

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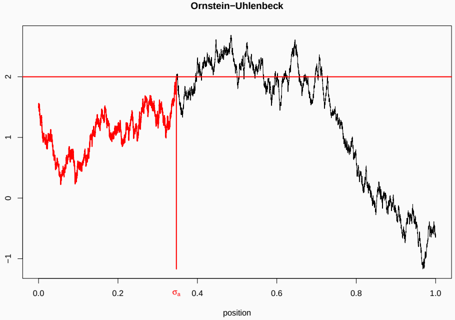

Density of σ_a starting from x.

$$p_{x,\,a}(r) = \frac{|a-x|}{\sqrt{2\pi r^3}} \,\mathbf{exp}\left(-\frac{\tau}{2}(a^2 - x^2 - r) - \frac{(a-x)^2}{2r}\right)$$

$$\times\, \mathbb{E}\mathbf{exp}\left(-\frac{\tau^2}{2}\int_0^r (\mathrm{Bes}_{0,a-x,r}(u) - a)^2 \,\mathrm{d}u\right),$$

where $Bes_{0,a-x,r}$ is a three dimensional Bessel bridge over [0, r] between 0 and $a - x$.

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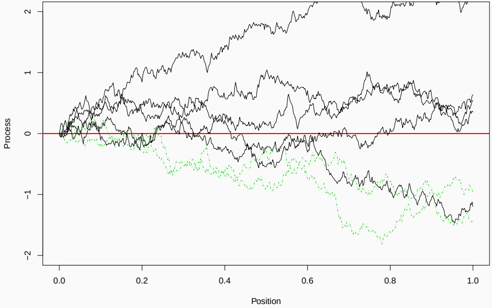

sampling with fixed success: G trajectories have to reach the next level.

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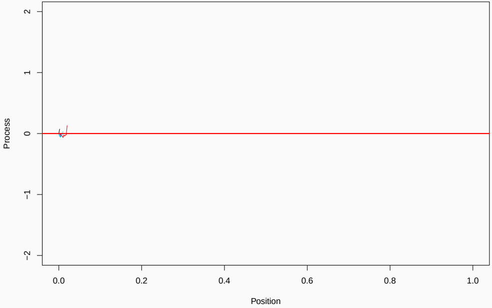

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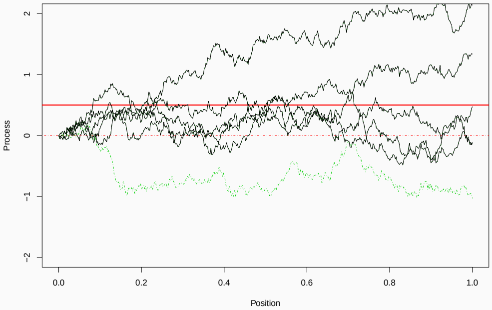

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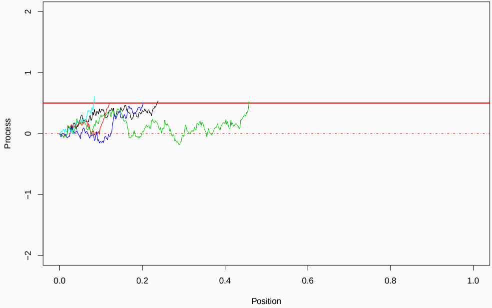

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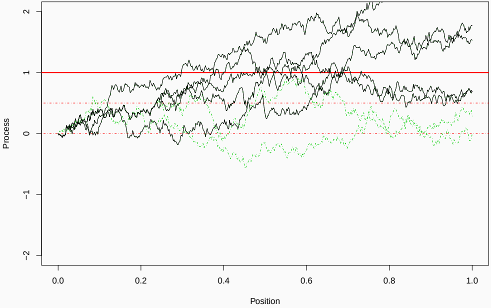

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