Alcuni sistemi in evoluzione stocastica di tipo frazionario

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The Fractional Birth Process with Power-Law Immigration

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Mutation models

Mutation models are probabilistic descriptions of the growth of a population of cells, in which scarce mutations randomly occur.

Any classic mutation model can be interpreted as the result of the three following ingredients:

- a growing *wild-type* population
- mutants appearing randomly
- evolving *clones* of mutant cells

A (short) historical summary of mutation models

- Luria-Delbrück (1943)
  Both wild-type and mutant populations grow deterministically (exponentially), with mutant initiation events being the sole source of randomness
- Lea and Culson (1949) The wild-type population grows deterministically while stochastic mutant growth in the form of the pure birth process is considered
- Bartlett (1955) The normal cells and the mutant cells grow according to a Markovian birth process

Hypotheses and models

We adopt a semi-stochastic approach, assuming a deterministic growth model for the wild-type cells and a stochastic one for the mutants.

Motivated by population with environmental restrictions, our work differs from previous approaches in two ways:

- non-exponential wild-type growth
- non-Markovian stochastic growth of the mutant population evolving with dormancy and bursty effects

Our three-ingredients approach

The system is observed at a fixed time t.

- Number of wild-type individuals: $n_\tau = \tau^\rho$, $0 \leq \tau \leq t$, $\rho \geq 0$
- The number of clones that have been initiated by t: a Poisson random variable K_t with mean

  $$\mathbb{E}(K_t) = \int_o^t \mu n_\tau d\tau,$$

  $\mu > 0$ being the mutation rate
- If $K_t > 0$, the size of a mutant clone sampled uniformly from the K_t initiated clones: Y_t, $t > 0$

Stochastic growth of mutants will follow a fractional pure birth process.

Let $\mathcal{N}_\nu(t)$ be the number of individuals in a fractional linear birth process, with birth rate $\lambda > 0$, up to time $t > 0$. The state probabilities $p_k^\nu(t) = \mathbb{P}\{\mathcal{N}_\nu(t) = k | \mathcal{N}_\nu(0) = 1\}$ are governed by the following fractional difference-differential equations of order $0 < \nu \leq 1$

$$\frac{\mathrm{d}^\nu p_k^\nu}{\mathrm{d}t^\nu} = -\lambda\, k\, p_k^\nu + \lambda\,(k-1)\, p_{k-1}^\nu, \qquad k \geq 1,$$

with initial condition given by the Kronecker delta $p_k^\nu(0) = \delta_{k,1}$.

The fractional derivative is considered in the Caputo sense and is defined as

$$\frac{\mathrm{d}^{\nu} p_k^{\nu}}{\mathrm{d}t^{\nu}} = \frac{1}{\Gamma(1-\nu)} \int_0^t (t-s)^{-\nu} \frac{\mathrm{d}p_k^{\nu}(s)}{\mathrm{d}s} \mathrm{d}s.$$

It is known that, for $k \geq 1$, $t > 0$,

$$p_k^{\nu}(t) = \sum_{j=1}^{k} \binom{k-1}{j-1} (-1)^{j-1} E_{\nu,1}(-\lambda j t^{\nu}), \qquad \sum_{k=1}^{+\infty} p_k^{\nu}(t) = 1,$$

where the function

$$E_{\alpha,\beta}(z) = \sum_{r=0}^{\infty} \frac{z^r}{\Gamma(\alpha r + \beta)}, \quad \alpha, \beta \in \mathbb{C}, \; Re(\alpha), Re(\beta) > 0,$$

is the two-parametric Mittag-Leffler function.

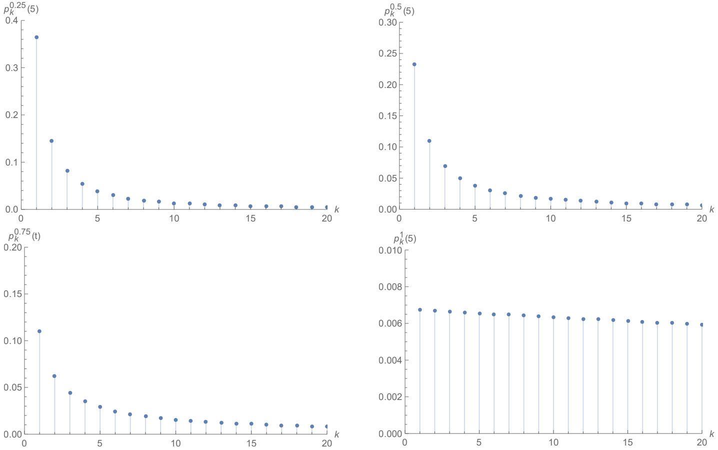

Figura 1: Probability distribution $p_k^{\nu}(t)$ for $t = 5$, $\lambda = 1$ and various choices of ν. From left to right, from top to bottom, the displayed probability masses are respectively 0.859314, 0.711049, 0.486945, 0.126472.

Properties

- The fractional linear birth process has a mode at 1
- The tail of the probability mass function of the fractional linear birth process decreases more slowly than any exponential tail, but faster than any power law tail as $k \to +\infty$
- The mean number of individuals at time t is

$$\mathbb{E}\left[\mathcal{N}_\nu(t)\right] = E_{\nu,1}\left(\lambda t^\nu\right), \qquad t > 0,$$

As $t \to +\infty$, it grows as

$$\mathbb{E}\left[\mathcal{N}_\nu(t)\right] \sim \frac{1}{\nu} e^{\lambda^{1/\nu} t}$$

The inter-birth time T_i^ν, $i \geq 1$, is Mittag-Leffler distributed with rate $i\lambda$, with density

$$f_{T_i^\nu(t)} = i\lambda t^{\nu-1} E_{\nu,\nu}\left(-i\lambda t^\nu\right), \quad i \geq 1.$$

Moreover,

$$f_{T_i^\nu(t)} \sim \begin{cases} t^{\nu-1} & \text{if } t \to 0 \\ \frac{1}{t^\nu+1} & \text{if } t \to +\infty \end{cases}$$

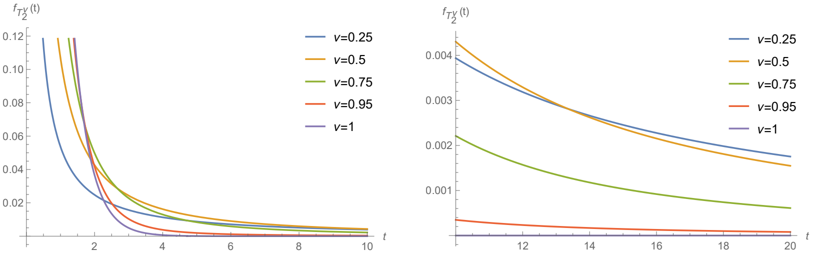

Figura 2: Probability density function of T_2^ν for $\lambda = 1$ and various choices of ν.

Mutant Clone Size Distribution

The size of the clone is dictated not only by the initiation time but also by its manner of growth, here the fractional linear birth process. Hence, by conditioning on the arrival time, we have

$$\mathbb{P}\{Y_t = k\} = \frac{\mu}{\mathbb{E}(K_t)} \int_0^t n_\tau \mathbb{P}\{\mathcal{N}_\nu(t-\tau) = k\}\, d\tau.$$

Proposition

For $\rho \geq 0$, $\lambda > 0$ and $0 < \nu \leq 1$, probability mass function of the mutant clone size reads

$$\mathbb{P}\{Y_t = k\} = \Gamma(\rho+2) \sum_{j=1}^{k} \binom{k-1}{j-1} (-1)^{j-1} E_{\nu,\rho+2}(-\lambda j t^\nu), \qquad k \in \mathbb{N}.$$

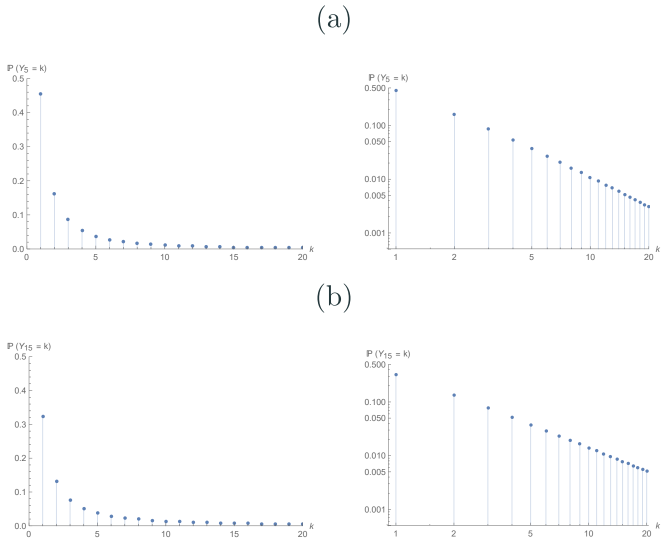

Figura 3: Probability distribution of Y_t for $k = 0, 1, \dots, 30$, with $\rho = 2$, $\nu = 0.5$, $\lambda = 1$, (a) $t = 5$ and (b) $t = 15$. The displayed probability mass is 0.935651 in (a) and 0.802939 in (b). Corresponding log-log plots are depicted on the right-hand side.

Mapping Distributions: Clone Size to Total Mutant Number

Let B_t be the total number of mutants existing at time $t > 0$. Then

$$B_t := \sum_{i=1}^{K_t} (Y_t)_i \,,$$

where all $(Y_t)_i$ are *iid* random variables specifying the clone sizes. For $\rho \geq 0$, $\lambda > 0$, $\mu > 0$, $0 < \nu \leq 1$ and $m \in \mathbb{N}$, the probability distribution of the total number of mutants B_t is given by

$$\mathbb{P}\left\{B_t = 0\right\} = \exp\left(-\mu \frac{t^{\rho+1}}{\rho+1}\right),$$

$$\mathbb{P}\left\{B_t = m\right\} = \exp\left(-\mu \frac{t^{\rho+1}}{\rho+1}\right) \sum_{h=0}^{m} \frac{\mu^h}{h!} \sum_{j_1+\cdots+j_h=m} \prod_{k=1}^{h} \times \left(\sum_{j=1}^{j_k} \binom{j_k - 1}{j - 1} (-1)^{j-1} \Gamma(\rho+1) t^{\rho+1} E_{\nu,\rho+2}(-\lambda j t^{\nu}) \right).$$

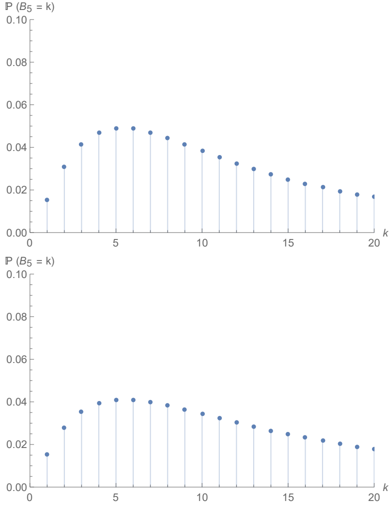

Figura 4: Probability distribution of B_t for $t = 5$, $\lambda = 1$, $\rho = 2$ and various choices of ν. From left to right, from top to bottom, $\nu = 0.25, 0.5, 0.75, 0.95$ and the displayed probability masses are respectively 0.667137, 0.618801, 0.594237, 0.581819.

Moments

$$\mathbb{E}(B_t) = \mu\Gamma(\rho+1)t^{\rho+1}E_{\nu,\rho+2}(\lambda t^{\nu})$$

$$\mathrm{Var}(B_t) = \frac{\mu\, t^{\rho+1}}{\rho+1} + \mu\Gamma(\rho+1)\lambda t^{\nu+\rho+1} \times \left(4E_{\nu,\nu+\rho+2}(2\lambda t^{\nu}) - E_{\nu,\nu+\rho+2}(\lambda t^{\nu})\right)$$

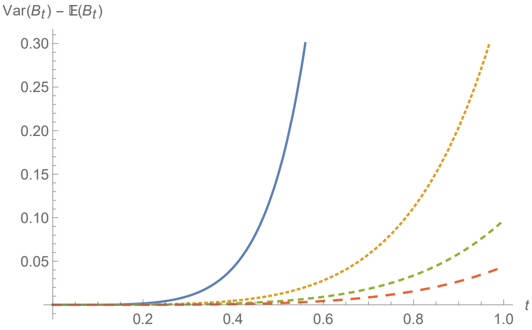

Figura 5: Plots of $\mathrm{Var}(B_t) - \mathbb{E}(B_t)$ versus t, with $(\rho, \mu, \lambda) = \left(2, 10^{-1}, 1\right)$, and $\nu = (0.3, 0.5, 0.7, 0.9)$ from top to bottom.

Higher-order moments

Consider the mth-order factorial moment of the fractional linear birth process

$$\mu_{(m)}(t) = \mathbb{E}\left[\mathcal{N}_\nu(t)\left(\mathcal{N}_\nu(t)-1\right)\left(\mathcal{N}_\nu(t)-2\right)\dots\left(\mathcal{N}_\nu(t)-m+1\right)\right].$$

If $m \geq 2$, we have

$$\begin{cases} \frac{\partial^\nu}{\partial t^\nu}\mu_{(m)}(t) = m\lambda\mu_{(m)}(t) + m(m-1)\lambda\,\mu_{(m-1)}(t) \\ \mu_{(m)}(0) = 0 \end{cases}$$

and

$$\mu_{(m)}(t) = m! \sum_{k=0}^{m-1} (-1)^{k+m-1} \binom{m-1}{k} E_{\nu,1}\left(\lambda(k+1)t^\nu\right).$$

As a consequence, the mth-order moment of the fractional linear birth process, $m \geq 2$, reads

$$\mathbb{E}\left[\mathcal{N}_\nu(t)^m\right] = \sum_{r=0}^{m} S(m,r)\, r! \sum_{k=0}^{r-1} (-1)^{k+r-1} \binom{r-1}{k} E_{\nu,1}\left((k+1)\,\lambda t^\nu\right),$$

where $S(m,r)$ is the Stirling number of the second kind. Moreover, the mth-order moment of the clone size has the following form:

$$\begin{aligned}\mathbb{E}\left[Y_t^m\right] &= \frac{\mu}{\mathbb{E}\left[K_t\right]} \int_0^t n_\tau \mathbb{E}\left[\mathcal{N}_\nu\left(t-\tau\right)^m\right] \mathrm{d}\tau \\ &= \Gamma\left(\rho+2\right) \sum_{r=0}^{m} S(m,r)\, r! \\ &\quad \times \sum_{k=0}^{r-1} (-1)^{k+r-1} \binom{r-1}{k} E_{\nu,\rho+2}\left((k+1)\,\lambda t^\nu\right).\end{aligned}$$

Also the tail of Y_t and of B_t exhibits an intermediate decay rate between a power law and an exponential function.

Summary

- We have developed a new model describing the accumulation of mutations over time, capable of embedding both Markovian and non-Markovian dynamics
- We have expressed in closed form the clone size distribution and the mutant number distribution
- We have analysed the moments and behaviour of the tail

Possible extensions

- Cell death
- Cells accumulating multiple mutations, which may be advantageous, neutral or disadvantageous
- Confirmation of experimental data

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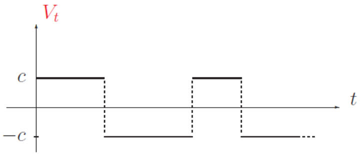
Some results on generalized accelerated motions driven by the telegraph process

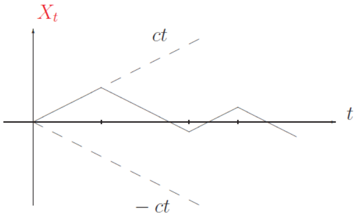
The (integrated) telegraph process

Let $N(t)$, $t \geq 0$, be a homogeneous Poisson process with intensity $\lambda > 0$ and let $\mathrm{P}(V(0) = \pm c) = \frac{1}{2}$.

- Velocity of a particle at time t: $V(t) = V(0)(-1)^{N(t)}$



- Position of a particle at time t: $X(t) = \int_0^t V(s)\,\mathrm{d}s$



If we take

$$A(t) = A(0)(-1)^{N(t)}$$

as the acceleration process (i.e. telegraph signal with values $\pm a$), we can construct the vector process

$$\begin{cases} V(t) = \int_0^t A(s)\,\mathrm{d}s = A(0)\int_0^t (-1)^{N(s)}\,\mathrm{d}s, \\ X(t) = \int_0^t V(s)\,\mathrm{d}s = A(0)\int_0^t (t-s)(-1)^{N(s)}\,\mathrm{d}s. \end{cases}$$

The $n-$times integrated telegraph process

$$\int_0^t \mathrm{d}t_1 \cdots \int_0^{t_{n-1}} (-1)^{N(t_n)}\,\mathrm{d}t_n = \frac{1}{(n-1)!}\int_0^t (t-t_n)^{n-1}(-1)^{N(t_n)}\,\mathrm{d}t_n$$

is a generalization of the accelerated telegraph process and can be generalized into a Riemann-Liouville fractional integral of the telegraph signal.

The Riemann-Liouville fractional integral $I_{a^+}^{\alpha} f$ of order $\alpha > 0$ is defined by

$$\left(I_{a^+}^{\alpha} f\right)(x) := \frac{1}{\Gamma(\alpha)} \int_a^x \frac{f(t)}{(x-t)^{1-\alpha}} \mathrm{d}t, \quad x > a.$$

Let $\alpha > 0$, $t \geq 0$ and $A(0) = 1$. We consider the conditional distributions

$$\mathbb{P}\left(X^{\alpha}(t) \leq y \,|\, N(t) = n\right), \qquad n \in \mathbb{N},$$

of the process

$$X^{\alpha}(t) := \left(I_{a^+}^{\alpha} A\right)(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-s)^{\alpha-1} (-1)^{N(s)} \mathrm{d}s.$$

For any fixed $t > 0$, $\alpha > 0$ and $n \in \mathbb{N}$, one has $|X_n^\alpha(t)| < \frac{t^\alpha}{\Gamma(\alpha+1)}$.

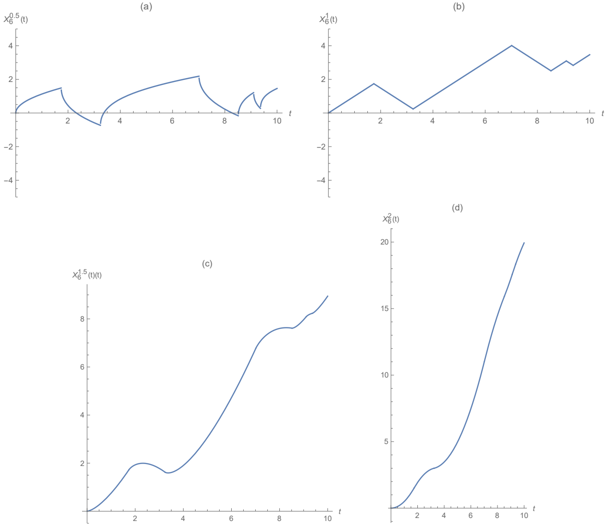
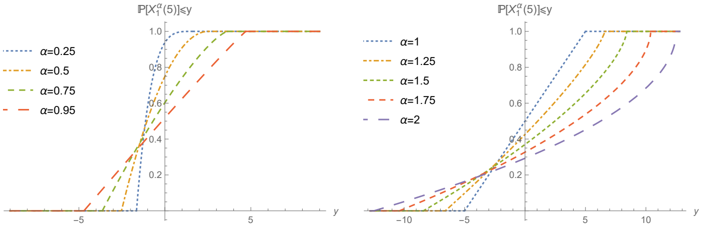


Figura 6: Sample paths of $X_6^\alpha(t)$ with $\lambda = 1$ and (a) $\alpha = 0.5$, (b) $\alpha = 1$, (c) $\alpha = 1.5$, (d) $\alpha = 2$.

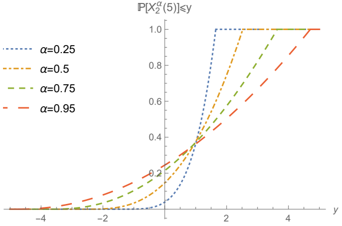
Let $t > 0$, $\alpha > 0$ and $n = 1$. The conditional probability distribution of $X^{\alpha}(t)$ is

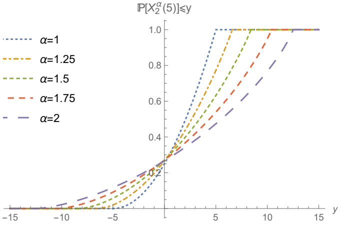
$$\mathrm{P}\left(X_1^{\alpha}(t) \leq y\right) = \begin{cases} 0 & \text{if } y < -\dfrac{t^{\alpha}}{\Gamma(\alpha+1)} \\ 1 - \left(\dfrac{t^{\alpha} - \Gamma(\alpha+1)\, y}{2t^{\alpha}}\right)^{\frac{1}{\alpha}} & \text{if } -\dfrac{t^{\alpha}}{\Gamma(\alpha+1)} \leq y < \dfrac{t^{\alpha}}{\Gamma(\alpha+1)} \\ 1 & \text{if } y \geq \dfrac{t^{\alpha}}{\Gamma(\alpha+1)}. \end{cases}$$



Let $t > 0$, $\alpha > 0$ and $n = 2$. The conditional probability distribution of $X^{\alpha}(t)$ is

$$\mathrm{P}\left(X_2^{\alpha}(t) \le y\right) = \begin{cases} 0 & \text{if } y < -\dfrac{t^{\alpha}}{\Gamma(\alpha+1)} \\ \dfrac{2!}{t^2}\left(\dfrac{t^{\alpha}+\Gamma(\alpha+1)\,y}{2}\right)^{\frac{1}{\alpha}}\left[t-\left(\dfrac{t^{\alpha}-\Gamma(\alpha+1)\,y}{2}\right)^{\frac{1}{\alpha}}\right. & \\ \qquad \left.\times {}_2F_1\left(-\dfrac{1}{\alpha},\dfrac{1}{\alpha};\dfrac{1}{\alpha}+1;-\dfrac{t^{\alpha}+\Gamma(\alpha+1)\,y}{t^{\alpha}-\Gamma(\alpha+1)\,y}\right)\right] & \\ & \text{if } -\dfrac{t^{\alpha}}{\Gamma(\alpha+1)} \le y < \dfrac{t^{\alpha}}{\Gamma(\alpha+1)} \\ 1 & \text{if } y \ge \dfrac{t^{\alpha}}{\Gamma(\alpha+1)}. \end{cases}$$





Let $t > 0$ and $\alpha > 0$. Then the unconditional mean of $X^{\alpha}(t)$ is

$$\mathrm{E}\left[X^{\alpha}(t)\right] = \frac{1}{\Gamma(\alpha+1)} t^{\alpha} e^{-2\lambda t} {}_1F_1(\alpha; 1+\alpha; 2\lambda t).$$

$$\mathrm{E}\left[X^{\alpha}(t)\right] \sim \frac{t^{\alpha-1}}{2\lambda\Gamma(\alpha)} \quad \text{as} \quad t \to +\infty$$

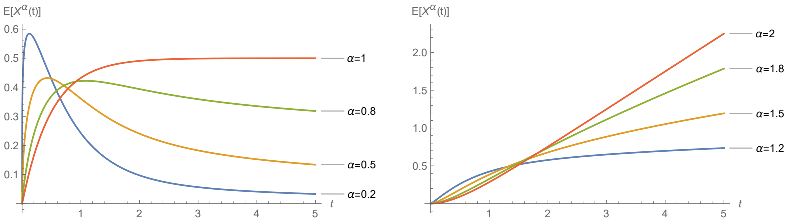


Figura 7: Mean value of $X^{\alpha}(t)$ with $\lambda = 1$ and various choices of α.

Let $t > 0$ and $\alpha > 0$. Then the unconditional variance of $X^{\alpha}(t)$ is

$$\begin{aligned} \mathrm{Var}\left[X^{\alpha}(t)\right] = \frac{2(2\lambda)^{-\alpha}}{\Gamma(\alpha)^2} & \left[t^{\alpha}\Gamma(\alpha) B(\alpha,1)\,{}_1F_1(\alpha;\alpha+1;2\lambda t)\right. \\ & - \frac{t^{2\alpha}(2\lambda)^{\alpha}}{\alpha} B(1,2\alpha)\,{}_2F_2(2\alpha,1;\alpha+1,2\alpha+1;2\lambda t) \\ & \left. - e^{2\lambda t}\Gamma(\alpha;2\lambda t) B(\alpha,1)\, t^{\alpha}\,{}_1F_1(1;\alpha+1;-2\lambda t)\right] \\ & - \left(\frac{1}{\Gamma(\alpha+1)} t^{\alpha} e^{-2\lambda t}\,{}_1F_1(\alpha;1+\alpha;2\lambda t)\right)^2 . \end{aligned}$$

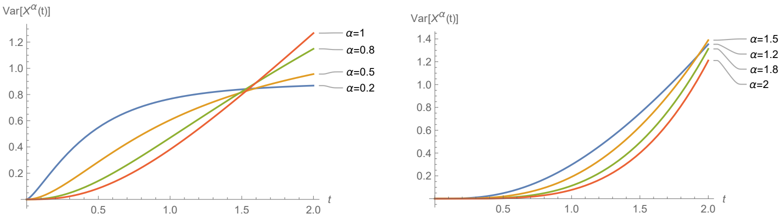


Figura 8: Variance of $X^{\alpha}(t)$ with $\lambda = 1$ and various choices of α.

Summary

- We have introduced a stochastic process describing a motion on the real line, that generalizes a uniformly accelerated motion with Poisson-paced changes of its acceleration
- Various results on the conditional probability distribution and on the unconditional mean and variance have been given

Possible extensions

- Use of the proposed process as an alternative to standard MCMC algorithms

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Thank you!