FAST SIMULATION OF MULTISTAGE CLONAL EXPANSION MODELS FOR COLORECTAL CANCER

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Abstract. We derive and demonstrate a method to simulate the Colorectal cancer model from [2]. The method is faster than previous ones while retaining similar accuracy.

1. Derivation

1.1. **Poisson process with random start time.** We will consider a non-homogeneous Poisson process with rate $\lambda(t) > 0$ which has a random start time $\tau \geq 0$ with distribution p. For fixed τ the number of occurrences at time $t \geq \tau$ given start time τ, $N(t)|\tau$ has the characteristic function [3, chapter 4, eqn. (2.1)]

$$\begin{aligned} \varphi_{N(t)|\tau}(u) &= \exp\left[m(t-\tau)\left\{e^{iu}-1\right\}\right] \\ m(t) &= \int_0^t \lambda(s)\,\mathrm{d}s\,. \end{aligned} \tag{1.1}$$

The by the law of total expectation, the characteristic function of $N(t)$ is given by

$$\begin{aligned} \varphi_{N(t)}(u) &= E\left[\varphi_{N(t)|\tau}(u)\right] \\ &= \int_0^t \exp\left[m(t-\tau)\left\{e^{iu}-1\right\}\right] p(\tau)\,\mathrm{d}\tau + \int_t^\infty p(\tau)\,\mathrm{d}\tau\,. \end{aligned}$$

Comparing this expression to a Poisson process with different rate yields the first theorem.

Theorem 1.1. *Let $N(t)$ follow a non-homogeneous Poisson process with rate $\lambda(t) \geq 0$ starting at a random time $\tau \geq 0$ with probability density function $p(\tau)$. Let $M(t)$ follow a non-homogeneous Poisson process starting at time 0 with rate*

$$\nu(t) = \int_0^t \lambda(t-\tau)\,p(\tau)\,\mathrm{d}s = (\lambda * p)(t)\quad. \tag{1.2}$$

Then for the characteristic functions $\varphi_{N(t)}$ and $\varphi_{M(t)}$ there holds

$$\max_{t\in[0,\sigma]}\left|\varphi_{N(t)} - \varphi_{M(t)}\right| \leq 2\left(\exp\left(2m(\sigma)\right) - 2m(\sigma) - 1\right) = O(m(\sigma)^2) \tag{1.3}$$

where m is the mean value function of $N(t)$ as defined in eqn. (1.1).

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Proof. Let h be the mean value function (eqn. (1.1)) of $M(t)$, then there holds

$$\frac{d}{dt}\int_0^t m(t-\tau)\,p(\tau)\,\mathrm{d}\tau = \int_0^t m'(t-\tau)\,p(\tau)\,\mathrm{d}\tau = \int_0^t \lambda(t-\tau)\,p(\tau)\,\mathrm{d}\tau = \frac{d}{dt}\nu(t)\ .$$

We used the Leibniz integration rule and $m(0) = 0$ in the first step. Because $h(0) = 0$ has to hold, we get

$$h(t) = \int_0^t m(t-\tau)\,p(\tau)\,\mathrm{d}\tau = (m * p)(t)$$

For $\varphi_{N(t)}(u)$, using $k := \left\{e^{iu} - 1\right\}$, we obtain

$$\begin{aligned}\varphi_{N(t)}(u) &= \int_0^t \exp\left[m(t-\tau)\,k\right] p(\tau)\ \mathrm{d}\tau + \int_t^\infty p(\tau)\ \mathrm{d}\tau \\ &= 1 + k\int_0^t m(t-\tau)\,p(\tau)\ \mathrm{d}\tau + \sum_{j=2}^\infty \frac{k^j}{j!}\int_0^t m(t-\tau)^j\,p(\tau)\ \mathrm{d}\tau\,.\end{aligned}$$

For $\varphi_{M(t)}(u)$ we obtain

$$\varphi_{M(t)}(u) = \exp\left(h(t)\,k\right) = 1 + kh(t) + \sum_{j=2}^\infty \frac{k^j}{j!}h(t)^j\ .$$

Let $t \in [0,\sigma]$ then there holds

$$\begin{aligned}\left|\varphi_{N(t)} - \varphi_{M(t)}\right| &= \Big|\sum_{j=2}^\infty \frac{k^j}{j!}\int_0^t m(t-\tau)^j\,p(\tau)\ \mathrm{d}\tau - \sum_{j=2}^\infty \frac{k^j}{j!}h(t)^j\Big| \\ &\le \sum_{j=2}^\infty \frac{|k|^j}{j!}\Big|\int_0^t m(t-\tau)^j\,p(\tau)\ \mathrm{d}\tau - \left(\int_0^t m(t-\tau)\,p(\tau)\ \mathrm{d}\tau\right)^j\Big| \\ &\le \sum_{j=2}^\infty \frac{|k|^j}{j!}\left(|m(\sigma)|^j + |m(\sigma)|^j\right) \\ &= 2\sum_{j=2}^\infty \frac{(2m(\sigma))^j}{j!} \\ &= 2\left(\exp\left(2m(\sigma)\right) - 2m(\sigma) - 1\right)\ .\end{aligned}$$

We used that $\int_0^t p(\tau)\,\mathrm{d}\tau = 1$ and that $m(\cdot)$ is positive and monotonically increasing. $\square$

Remark 1.2. Theorem 1.1 is useful if $m(\sigma) \ll 1$ because it then implies that a Poisson process with random start time can be viewed (and simulated) as a Poisson process with rate $h = (m * p)$. This makes intuitive sense, because if $m(\sigma)$, i.e. the expected number of occurrences for $N(\sigma)$ starting at 0, is much smaller than 1 the correlation that is introduced through the random starting time is negligible.

The formulas for the mean and the variance are

$$\begin{aligned}
E\left[N\left(\sigma\right)\right] &= h\left(\sigma\right)\ , \\
E\left[M\left(\sigma\right)\right] &= h\left(\sigma\right)\ , \\
Var\left(N\left(\sigma\right)\right) &= h\left(\sigma\right) + \int_0^\sigma m^2\left(t-\tau\right)p\left(\tau\right)\mathrm{d}\tau - \left(\int_0^\sigma m\left(t-\tau\right)p\left(\tau\right)\mathrm{d}\tau\right)^2\ , \\
Var\left(M\left(\sigma\right)\right) &= h\left(\sigma\right)\ .
\end{aligned}$$

While the mean is consistent, the difference in variance is of second order in m.

1.2. **Two Stage Poisson Process.** We will consider a two stage Poisson process. The first process has rate $\nu\left(t\right)$ and each occurrence of the first process is the starting point of a second-stage process with rate $\lambda\left(t\right)$. We are interested in the number $N\left(t\right)$ of occurrences from the first process and the arrival times u_j of the second-stage processes. It is vital that we do not need the arrival times of the first process.

Theorem 1.3. *Let $N\left(t\right)$ be the number of occurrences of a non-homogeneous Poisson process with rate $\nu\left(t\right)$, mean value function $\eta\left(t\right)$ starting at time 0. Let $u_1,\dots,u_{N(t)}$ denote the arrival times of this process.*

For each $j=1,\dots,N\left(t\right)$ let $Y\left(t,u_j\right)$ denote the number of occurrences of a non-homogeneous Poisson process with rate $\lambda\left(t\right)$, mean value function $m\left(t\right)$ starting at time u_j.

The process

$$Y\left(t\right) = \sum_{j=1}^{N(t)} Y\left(t,u_j\right)$$

is called a filtered Poisson process [3, chapter 4, eqn. (5.42)]. For $t\in[0,\sigma]$, if we neglect terms of order $O(m\left(\sigma\right)^2)$:

i) *Conditioned on $N\left(\sigma\right)$ the arrival times of the process $Y\left(t\right)$ follow a Poisson process with rate*

$$\mu_N\left(t\right) = \frac{N\left(\sigma\right)}{\eta\left(\sigma\right)}\left(\nu*\lambda\right)\left(t\right) \qquad \forall t\in\left[0,\sigma\right]\ .$$

Proof. By Proposition 2.206 in [1, p. 147] (*actually this only guarantees the property for a homogeneous process. I am quite certain that this also holds for the non-homogeneous case but I am lacking a source.*) we have that conditioned on $N\left(\sigma\right)$ the distribution for u_j (note that the u_j are not ordered) is given by $p\left(u\right)=\nu\left(u\right)/\eta\left(\sigma\right)$ and all u_j are i.i.d.. Then we know by Theorem 1.1 that $Y\left(t,u_j\right)$ can be approximated up to order 2 by a Poisson process with rate

$$\mu_j\left(t\right) = \int_0^t \lambda\left(t-u\right)\frac{\nu\left(u\right)}{\eta\left(\sigma\right)}\mathrm{d}u = \frac{\left(\lambda*\nu\right)}{\eta\left(\sigma\right)}\left(t\right) \qquad \forall t\in\left[0,\sigma\right]\ .$$

Because the sum of $N\left(\sigma\right)$ independent Poisson process is again a Poisson process, we know that $Y\left(t\right)$ can be approximated up to order 2 by a Poisson process with rate

$$\mu_N\left(t\right) = \frac{N\left(\sigma\right)}{\eta\left(\sigma\right)}\left(\nu*\lambda\right)\left(t\right)\ .$$

□

Remark 1.4. Theorem 1.3 is useful if $m(\sigma) \ll 1$ because it then implies that a two stage Poisson process can be simulated as follows. a) Draw $N(\sigma)$ at random from a Poisson distribution with mean $\eta(\sigma)$. b) Simulate a Poisson process with rate

$$\frac{N(\sigma)}{\eta(\sigma)} (\nu * \lambda)(t) .$$

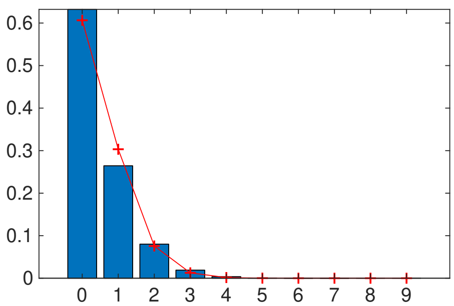
The direct solution would be to simulate the first Poisson process fully and obtain arrival times u_j. For each arrival time one would simulate a Poisson process with rate $\lambda(t - u_j)$. This means on average $\eta(\sigma)$ many Poisson process simulations. The method proposed here can, under the circumstances described, generate a very good approximation with only two Poisson process simulations. This advantage comes from marginalizing out (approximately) the arrival times u_j.

For the Colorectal cancer model from [2] the first rate is of order 10^2, $\sigma = 50$ and the second rate is of order 10^{-6}. The direct approach results in approximately 5000 Poisson process simulations. The approximate method yields a theoretic speedup factor of 1000. Also $m(\sigma) \approx 10^{-4}$ and thus the approximation extremely accurate.

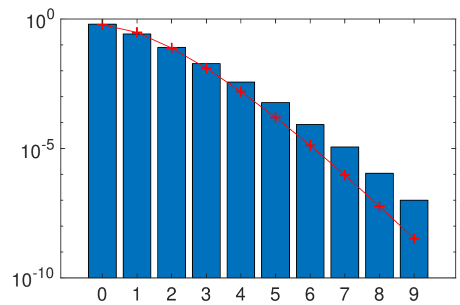
2. Numerical Experiments

In this section we present numerical experiments for all theorems presented in this paper.

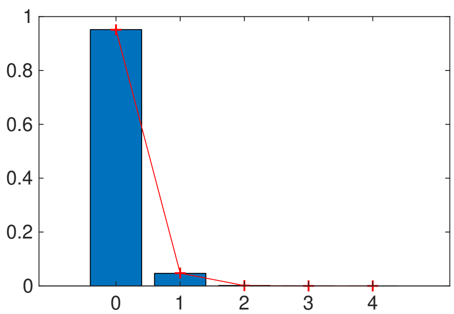
2.1. **Poisson process with random start time.** In Figure 1 the model as described in Theorem 1.1 is simulated with a sample size of 10^7. For $\lambda = 10^{-2}$ the approximation is already very accurate. The relative error in variance is $\lambda/6 \approx 1.7 \times 10^{-3}$ for $\lambda = 10^{-2}$.



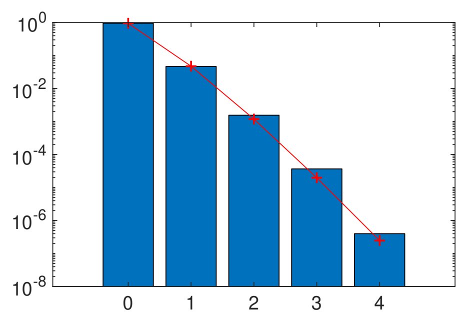
(A) $\lambda \equiv 1$



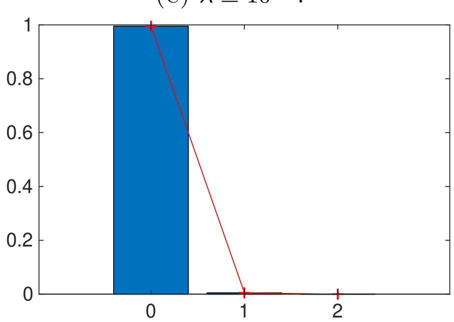
(B) $\lambda \equiv 1$. Log-Scale.



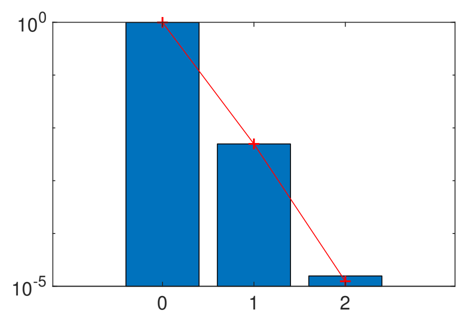
(C) $\lambda \equiv 10^{-1}$.



(D) $\lambda \equiv 10^{-1}$. Log-Scale.



(E) $\lambda \equiv 10^{-2}$.



(F) $\lambda \equiv 10^{-2}$. Log-Scale.

Figure 1. 10^7 samples. $\sigma = 1$. $\tau \sim \mathrm{unif}\,(0, 1)$. For this example there holds $E\,[N] = \lambda/2$ and $Var\,(N) = \lambda/2 + \lambda^2/12$

2.2. **Two Stage Poisson Process.**

References

[1] Vincenzo Capasso and David Bakstein. *An Introduction to Continuous- Time Stochastic Processes*. 2015.

[2] Jihyoun Jeon et al. "Evaluation of screening strategies for pre-malignant lesions using a biomathematical approach". In: *Mathematical biosciences* 213.1 (2008), pp. 56–70.

[3] Emanuel Parzen. *Stochastic processes*. Holden-Day, 1962.