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Estimating a non-homogeneous Gompertz process with jumps as model of tumor dynamics

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Abstract

A non-homogeneous stochastic model based on a type Gompertz diffusion with jumps is proposed to describe the evolution of a solid tumor subject to an intermittent therapeutic program. Each therapeutic application, represented with a jump in the process, instantly reduces the tumor size to a fixed value and, simultaneously, produces an increasing of the growth rate of the model to represent the toxicity of the therapy. This effect is described via the introduction of a time-dependent function in the drift of the process. The resulting model is a combination of non-homogeneous diffusion processes characterized by different drifts for which the transition probability density function and its main characteristics are studied. The estimation of the model is realized discerning if the therapeutic instances are fixed priorly and if they are established with a strategy based on the mean of the first-passage-time through a control threshold. Simulation studies are made for different choices of the involved parameters and time-dependent functions.

Keywords: Non-homogeneous Gompertz diffusion process, Therapeutic application, Intermittent therapy, First-passage-time, Inference.

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1. Introduction

Due to the increasing concrete interest, in the last decades various mathematical models of cancer dynamics are been proposed to analyze the evolution of the illness when a therapy is administered. Moreover, to take in account of some discrepancies existing between clinical data and theoretical predictions, due to more or less intense environment fluctuations, generally the notion of growth in random environment has been formulated (cf., for instance, [1], [2] and references therein). The attention is often placed on the definition of particular time-dependent functions that change the natural growth rates of the cancer by modeling anti-proliferative and pro-apoptotic effects. Another aspect of interest is the interaction between proliferating and quiescent cells (cf. [3]), this one is also studied to analyze the relevant differences between non-specific cycle drugs (that can damage tumor cells in any phase of the cellular cycle) and specific cycle drugs (that act on tumor cells only in a fixed phase of the cellular cycle) (cf., [4], [5]). The problem of model estimation has been also taken into account, by considering first of all the estimation of the natural growth parameters and then contriving ad hoc procedure to estimate the time-dependent functions used to describe the effects of the therapies (cf. [6], [7], [8]).

Recently, following [9] and [10], in [11] a stochastic model was proposed to analyze the effect of a therapeutic program that provides intermittent suppression of cancer cells. In [12] we assumed that each application of the therapeutic program leads the cancer mass to a return state ρ and it produces a deleterious effect on the organism by increasing the growth rate of the cancer cells of a constant quantity. The result was a diffusion process with jumps. Note that, although in different contexts, such processes were recently extensively studied (cf., [13], [14], [15] for instance). Specifically, following the widespread assumption that the Gompertz law is adapter to describe the growth of a solid tumor (cf., for instance, [16], [17], [18], [19]), we assumed that starting from $\rho > 0$ at the initial time, the process evolves according to the Gompertz law with positive parameters $\alpha_0 = \alpha$ and β that represents the natural growth parameters of the tumor cells in the absence of therapies. After a fixed time, a therapy is applied, the effect of which is to reduce the tumor size to ρ on the one hand and to increase the growth rate with a constant amount on the other hand. In this way, the process $X(t)$, describing the tumor size at the time t, consists of independent cycles, each of one is described by a stochastic diffusion process $X_k(t)$ with different time independent growth rates. The effectiveness of the therapeutic program is considerable influenced by the choice of the instants in which the therapy is applied; for this reason in [12] a strategy to select the inter-jump intervals was proposed so that the first-passage-time of $X(t)$ through a constant control boundary is as large as possible and the cancer size remains under this control threshold during the treatment. An estimation of parameters based on the maximum likelihood method was also provided.

In the present paper we modify the model discussed in [12], assuming that after each therapeutic application the process evolves with a time-dependent growth parameter $\alpha_k(t) = \alpha + h_k(t)$, so that the single processes $X_k(t)$, as well as $X(t)$, become time non-homogeneous, and we focus on the estimation of the model.

The paper is organized as follows. In Section 2 the stochastic model is introduced and the main characteristics of the related stochastic process are given. In Section 3 we assume that the instants of therapeutic applications are fixed before the beginning of the experimental phase. In this case only the estimation of the parameters and functions $h_k(t)$ is addressed. In Section 4 we suppose that the time instants are unknown. Here we propose firstly a strategy for determining optimal time instants of therapeutic application based on the first-passage-time of the process through a control threshold. Since determining each time instant involves to know the process until the previous application cycle, a recursive procedure for estimating the model is proposed. Some simulation studies illustrate the procedures of estimation in both scenarios for different choices of the involved parameters and time-dependent functions $h_k(t)$.

2. The Model

Let $X(t)$ be the stochastic process describing the growth of a tumor mass. We assume that each application of the therapy resets the cancer mass to a state ρ and it produces a deleterious effect on the organism by increasing the growth rate of the cancer cells. Let $\tau_0 = 0$ be the initial time, τ_k are the instants of therapeutic application for $k = 1, 2, \ldots, N$ and $\tau_{N+1} = \infty$. We suppose that the return state ρ is equal to the initial tumor mass, i.e. the tumor size recorded at the diagnose's time. Therefore, one has:

$$X(t) = \sum_{k=0}^{N} X_k(t) 1_{[\tau_k, \tau_{k+1})}(t), \tag{1}$$

where $X_0(t)$ represents the natural evolution of the cancer, whereas $X_k(t)$ describes the dynamics of the tumor between the k-th and the $(k+1)$-th therapeutic application. We assume that $X_k(t)$ is a stochastic Gompertz process whose sample paths are solution of

$$\begin{aligned} dX_k(t) &= [\alpha + h_k(t) - \beta \ln X_k(t)]\, X_k(t)dt + \sigma X_k(t) dW(t), \qquad (\tau_k < t < \tau_{k+1}), \\ X_k(\tau_k) &= \rho, \qquad k = 0, 1, 2, \ldots, N. \end{aligned} \tag{2}$$

In Eq. (2), α and β are the natural growth parameters in the absence of therapy, $\sigma > 0$ measures the width of environment fluctuations and $W(t)$ is a standard Brownian motion. The functions $h_k(t)$ represent the harmful effect of the k-th therapeutic application; actually after each jump, the cancer growth rate increases and it is greater in correspondence of more aggressive therapies. This perspective is representative of targeted drugs that have a certain degree of toxicity for the patient. Differently from the past (cf. [12]), we now consider that after an therapeutic application the growth parameter changes according to a time-dependent function. Specifically, we assume that $h_0(t) = 0$ and for $k = 1, 2, \ldots, N$ the functions $h_k(t) \geq 0$ are continuous and increasing with k.

To characterize $X(t)$ we specify each single process $X_k(t)$, for $k = 0, 1, \ldots, N$. Note that Eq. (2) defines a time non-homogeneous Gompertz process with drift and infinitesimal variance

$$A_1^{(k)}(x,t) = [\alpha + h_k(t) - \beta \ln x]x, \qquad A_2^{(k)}(x) = \sigma^2 x^2,$$

respectively. Note that the process $X_k(t)$ can be transformed in a time homogeneous Ornstein-Uhlenbeck stochastic process as shown in the following proposition.

Proposition 1. *The process*

$$Y_k(t) = \log X_k(t) + q_k(t|\tau), \tag{3}$$

with

$$q_k(t|\tau) = -e^{-\beta t} \int_\tau^t h_k(\theta) e^{\beta\theta}\, d\theta, \tag{4}$$

is a time homogeneous Ornstein-Uhlenbeck process characterized by drift and infinitesimal variance

$$B_1^{(k)}(y) = \alpha - \frac{\sigma^2}{2} - \beta\, y, \qquad B_2(y) = \sigma^2. \tag{5}$$

Proof. Let $f_k[X_k(t), t] = Y_k(t)$, for the Ito's lemma we have that $Y_k(t)$ satisfies the following stochastic equation

$$dY_k(t) = \Big[\frac{\partial f_k[X_k,t]}{\partial t} + \frac{\partial f_k[X_k,t]}{\partial x}\, F_k(t) + \frac{1}{2}\, \frac{\partial^2 f[X_k,t]}{\partial x^2}\, G^2(t)\Big]\, dt + \frac{\partial f_k[X_k,t]}{\partial x}\, G(t)\, dW(t),$$

where

$$F_k(t) = [\alpha + h_k(t) - \beta \log x]\, x, \qquad G(t) = \sigma\, x \qquad f_k(x,t) = \log x + q_k(t|\tau)$$

and

$$\frac{\partial f_k(x,t)}{\partial t} = -\beta q_k(t|\tau) - h_k(t), \qquad \frac{\partial f_k(x,t)}{\partial x} = \frac{1}{x}, \qquad \frac{\partial^2 f_k(x,t)}{\partial x^2} = -\frac{1}{x^2}.$$

It follows

$$dY_k(t) = \left[\alpha - \frac{\sigma^2}{2} - \beta\, y\right] dt + \sigma\, dW(t),$$

that is the Ito's equation for the diffusion process $Y_k(t)$ characterized by infinitesimal moments (5). □

Making use of Proposition 1 and recalling that the transition probability density function (pdf) of $Y_k(t)$ defined in (3) is a normal density with mean and variance

$$\mathcal{M}_k(t|u,\tau) = \frac{\alpha - \sigma^2/2}{\beta}\left[1 - e^{-\beta(t-\tau)}\right] + u\, e^{-\beta(t-\tau)}, \qquad \mathcal{V}^2(t|\tau) = \frac{\sigma^2}{2\beta}\left[1 - e^{-2\beta(t-\tau)}\right],$$

respectively, from (4) we have the transition pdf of $X_k(t)$:

$$f_k(x,t|y,\tau) = \frac{1}{x\sqrt{2\pi V^2(t|\tau)}}\exp\left\{-\frac{[\ln x - M_k(t|\ln y,\tau]^2}{2V^2(t|\tau)}\right\}, \qquad \tau_k \le \tau < t$$

where

$$M_k(t|y,\tau) = \frac{\alpha - \sigma^2/2}{\beta}\left[1 - e^{-\beta(t-\tau)}\right] + y\, e^{-\beta(t-\tau)} + e^{-\beta t}\int_\tau^t h_k(\theta) e^{\beta\theta}\, d\theta,$$

$$V^2(t|\tau) = \frac{\sigma^2}{2\beta}\left(1 - e^{-2\beta(t-\tau)}\right).$$

Moreover, $\tau_k \le \tau \le t$ the conditional moments of $X_k(t)$ are:

$$E[X_k^n(t)|X_k(\tau) = y] = \exp\left\{nM_k(t|\ln y,\tau) + \frac{n^2}{2}V^2(t|\tau)\right\}, \qquad n = 1, 2, \ldots.$$

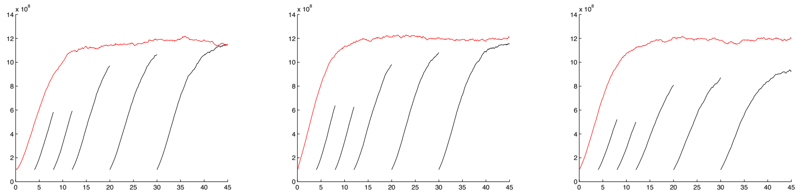
Concerning $X(t)$, from (1) we can easily obtain the mean of $X(t)$:

$$E[X(t)|X(0) = \rho] = \sum_{k=0}^{N} E[X_k(t)|X_k(\tau_k) = \rho] 1_{[\tau_k,\tau_{k+1})}(t).$$

Figures 1 and 2 show some simulated sample paths of $X(t)$ in the interval $[0, 45]$ for several choices of the functions $h_k(t)$. Moreover we assume $N = 5$, being $(4, 8, 12, 20, 30)$ the instants of therapeutic application, and $\sigma = 0.01$ (Figure 1) and $\sigma = 0.1$ (Figure 2). Following [20], in the simulation we have considered $\alpha = 6.46$ year^{-1}, $\beta = 0.314$ year^{-1}, $X_k(\tau_k) = \rho = 10^8$. The tumor size represents the tumor cell density; the value 1.074×10^8 is representative of a 0.1 g tumor mass (namely the smallest diagnosable mass).

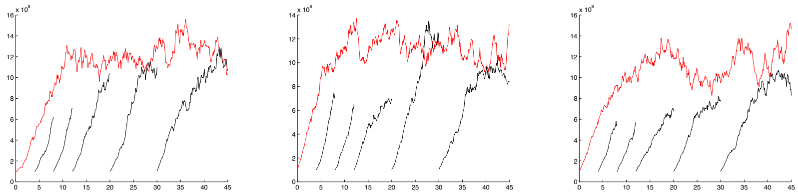
In these simulations almost always the sample paths of $X_0(t)$ (red curves) overhang those of $X(t)$; actually, note that an efficient therapy should keep the tumor size under control and surely at a level lower than the tumor size $X_0(t)$ corresponding at the case in which no therapy is applied. This one suggests the need to find a criterion to choose the instants of therapeutic application in such

a way that the therapy results to be truly effective. Some consideration have been also made in [12] and, for a deterministic model in [21].
Comparing Figure 1 with Figure 2, we note that increasing the value of σ the trends remain unchanged and only the oscillations of the sample paths are more evident.



(a) $h_k(t) = 0.1(k - 1/t)$ (b) $h_k(t) = 0.1(k + 1/t)$ (c) $h_k(t) = 0.1(1 - (\tau_k/t)^k)$

Figure 1: The sample paths of $X(t)$ are plotted for $\rho = 10^8$, $\alpha = 6.46$, $\beta = 0.314$, $\sigma = 0.01$ and different choices of the functions $h_k(t)$; therapeutic application times are $(4, 8, 12, 20, 30)$. The red (upper) curve represents $X_0(t)$.



(a) $h_k(t) = 0.1(k - 1/t)$ (b) $h_k(t) = 0.1(k + 1/t)$ (c) $h_k(t) = 0.1(1 - (\tau_k/t)^k)$

Figure 2: As in Figure 2 for $\sigma = 0.1$.

In order to estimate the model, we will distinguish two situations: the time instants of therapeutic applications are fixed from the beginning of experimentation or they will be determined via some strategies during experimentation.

In the first situation we estimate the parameters α, β and σ^2 and the functions $h_k(t)$. In the second, we propose a strategy similar to that proposed in [12], for determining optimal time instants of therapeutic application based on the first-passage-time of the process through a control threshold. Obviously determining each time instant involves the knowledge of the process until the previous application cycle. This question leads to a recursive procedure for estimating the model: for each cycle the corresponding function h_k is estimated, the estimates of the parameters is updated and the next time instant of application is determined.

In both cases, we consider two situations: a) $h_k(t) \equiv h_k^\gamma(t)$ is known except for a parameter $\gamma > 0$ to be estimated; b) $h_k(t)$ is completely unknown.

3. Model with fixed time instants of therapeutic application

The aim of the present section is to estimate the parameters of $X(t)$ and the function $h_k(t)$ when the therapy is applied at fixed time instants. Then, a simulation study is performed.

3.1. Estimation

In this case, we consider d_k sample paths of each process $X_k(t)$ at times t_{ij}^k with $\tau_k \leq t_{ij}^k < \tau_{k+1}$, $i = 1, \ldots, d_k$; $j = 1 \ldots, n_{i_k}$; $k = 0, \ldots, N$. For each process it may have a different number of sample paths (the experimental subjects may decrease) and each sample path can have a different number of values and be observed at different time instants. Let $\{x_{ij}^k\}$ be the observed values.

a) $h_k(t) \equiv h_k^\gamma(t)$ has a closed functional form except for the value of a parameter γ.

In this case, the estimation of the parameters α, β and σ^2 can be based only on observations of the process $X_0(t)$ (as in [6]). However, it is preferable to use the information of all involved processes and jointly estimate α, β, σ^2 and γ. Here, we assume $h_k^\gamma(t) = \gamma\, r_k(t)$, where $r_k(t)$ is a known positive and increasing function with k, and $r_0(t) = 0, \forall t \in [\tau_0, \tau_1)$.

Denoting by

$$a = \alpha - \frac{\sigma^2}{2}, \quad T_{\beta,k}^{i,j} = \frac{1 - e^{-\beta(t_{ij}^k - t_{i,j-1}^k)}}{\sqrt{\beta\left(1 - e^{-2\beta\,(t_{ij}^k - t_{i,j-1}^k)}\right)}},$$

$$S_{\beta,k}^{i,j} = \frac{\sqrt{\beta}\, e^{-\beta\, t_{ij}^k}}{\sqrt{1 - e^{-2\beta\,(t_{ij}^k - t_{i,j-1}^k)}}} \int_{t_{i,j-1}^k}^{t_{ij}^k} r_k(\theta) e^{\beta\,\theta} d\theta,$$

taking the variable change

$$v_{\beta,k}^{i,j} = \frac{\sqrt{\beta}\left[\log x_{ij}^k - e^{-\beta(t_{ij}^k - t_{i,j-1}^k)} \log x_{i,j-1}^k\right]}{\sqrt{1 - e^{-2\beta(t_{ij}^k - t_{i,j-1}^k)}}},$$

and considering that the processes $X_k(t), \ k = 0, 1, \ldots, N$ are independent, the log-likelihood function for the transformed sample, $\mathbf{v} = \{v_{ij}^k\}$, is

$$\mathbb{L}_{\mathbf{v}}(a, \gamma, \beta, \sigma) = -\frac{M}{2} \log \sigma^2 - \frac{M}{2} \log \pi - \frac{1}{\sigma^2} \sum_{k=0}^{N} \sum_{i=1}^{d} \sum_{j=2}^{n_{i_k}} \left[v_{\beta,k}^{ij} - aT_{\beta,k}^{ij} - \gamma\, S_{\beta,k}^{ij}\right]^2$$

where $M = \displaystyle\sum_{k=0}^{N} \sum_{i=1}^{d_k} (n_{i_k} - 1)$. Deriving the log-likelihood function with respect to $a, \ \gamma, \ \beta$ and σ^2 and making the derivatives equal to zero, one has the following system of equations:

- $$\frac{\partial \mathbb{L}_{\mathbf{v}}(a, \gamma, \beta, \sigma)}{\partial a} = 0 \ \Leftrightarrow \ \sum_{k=0}^{N} \sum_{i=1}^{d_k} \sum_{j=2}^{n_{i_k}} v_{\beta,k}^{ij} T_{\beta,k}^{ij} = a \sum_{k=0}^{N} \sum_{i=1}^{d_k} \sum_{j=2}^{n_{i_k}} (T_{\beta,k}^{ij})^2 + \gamma \sum_{k=1}^{N} \sum_{i=1}^{d_k} \sum_{j=2}^{n_{i_k}} S_{\beta,k}^{ij} T_{\beta,k}^{ij} \qquad (6)$$

- $$\frac{\partial \mathbb{L}_{\mathbf{v}}(a, \gamma, \beta, \sigma)}{\partial \gamma} = 0 \ \Leftrightarrow \ \sum_{k=1}^{n} \sum_{i=1}^{d_k} \sum_{j=2}^{n_{i_k}} v_{\beta,k}^{ij} S_{\beta,k}^{ij} = a \sum_{k=1}^{N} \sum_{i=1}^{d_k} \sum_{j=2}^{n_{i_k}} T_{\beta,k}^{ij} S_{\beta,k}^{ij} + \gamma \sum_{k=1}^{n} \sum_{i=1}^{d_k} \sum_{j=2}^{n_{i_k}} (S_{\beta,k}^{ij})^2 \qquad (7)$$

- $$\frac{\partial \mathbb{L}_{\mathbf{v}}(a,\gamma,\beta,\sigma)}{\partial \beta} = 0 \;\Leftrightarrow\; \sum_{k=0}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} v_{\beta,k}^{ij}\frac{dv_{\beta,k}^{ij}}{d\beta}$$
$$-a\left[\sum_{k=0}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} v_{\beta,k}^{ij}\frac{dT_{\beta,k}^{ij}}{d\beta} + \sum_{k=0}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} T_{\beta,k}^{ij}\frac{dv_{\beta,k}^{ij}}{d\beta}\right]$$
$$+a^2\sum_{k=0}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} T_{\beta,k}^{ij}\frac{dT_{\beta,k}^{ij}}{d\beta}$$
$$-\gamma\left[\sum_{k=1}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} v_{\beta,k}^{ij}\frac{dS_{\beta,k}^{ij}}{d\beta} + \sum_{k=1}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} S_{\beta,k}^{ij}\frac{dv_{\beta,k}^{ij}}{d\beta}\right]$$
$$+\gamma^2\sum_{k=1}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} S_{\beta,k}^{ij}\frac{dS_{\beta,k}^{ij}}{d\beta}$$
$$+a\gamma\left[\sum_{k=1}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} T_{\beta,k}^{ij}\frac{dS_{\beta,k}^{ij}}{d\beta} + \sum_{k=1}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} S_{\beta,k}^{ij}\frac{dT_{\beta,k}^{ij}}{d\beta}\right] = 0 \quad (8)$$

- $$\frac{\partial \log \mathbb{L}_{\mathbf{v}}(a,\gamma,\beta,\sigma)}{\partial \sigma^2} = 0 \;\Leftrightarrow\; M\sigma^2 = 2\sum_{k=0}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}}\left[v_{\beta,k}^{ij} - aT_{\beta,k}^{ij} - \gamma\, S_{\beta,k}^{ij}\right]^2 \quad (9)$$

For arbitrary functions g and h, we denote by

$$X_{g,h}^{\beta,k^*} = \sum_{k=k^*}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} g_{\beta,k}^{i,j}h_{\beta,k}^{i,j}, \qquad Y_{g,h}^{\beta,k^*} = \sum_{k=k^*}^{N}\sum_{i=1}^{d_k}\sum_{j=2}^{n_{i_k}} g_{\beta,k}^{i,j}\frac{dh_{\beta,k}^{ij}}{d\beta}, \quad k^* = 0,1,$$

so that from (6) and (7) one has:

$$X_{vT}^{\beta,0} = aX_{TT}^{\beta,0} + \gamma\, X_{ST}^{\beta,1}$$

$$X_{vS}^{\beta,1} = aX_{TS}^{\beta,1} + \gamma\, X_{SS}^{\beta,1}$$

from which it follows

$$a_\beta = \frac{X_{vT}^{\beta,0}X_{SS}^{\beta,1} - X_{TS}^{\beta,1}X_{vS}^{\beta,1}}{X_{TT}^{\beta,0}X_{SS}^{\beta,1} - (X_{TS}^{\beta,1})^2}, \quad \gamma_\beta = \frac{X_{TT}^{\beta,0}X_{vS}^{\beta,1} - X_{vT}^{\beta,0}X_{ST}^{\beta,1}}{X_{TT}^{\beta,0}X_{SS}^{\beta,1} - (X_{TS}^{\beta,1})^2}.$$

Moreover from (9) one has

$$\sigma_\beta^2 = \frac{2}{M}\left[X_{vv}^{\beta,0} + a_\beta^2 X_{TT}^{\beta,0} + \gamma_\beta^2 X_{SS}^{\beta,1} - 2a_\beta\, X_{vT}^{\beta,0} - 2\gamma_\beta\, X_{vS}^{\beta,1} + 2a_\beta\gamma_\beta\, X_{ST}^{\beta,1}\right].$$

Finally, Eq. (8) becomes

$$Y_{vv}^{\beta,0}-a_\beta\left[Y_{vT}^{\beta,0}+Y_{Tv}^{\beta,0}\right]+a_\beta^2Y_{TT}^{\beta,0}-\gamma_\beta\left[Y_{vS}^{\beta,1}+Y_{Sv}^{\beta,1}\right]+\gamma_\beta^2Y_{SS}^{\beta,1}+a_\beta\gamma_\beta\left[Y_{TS}^{\beta,1}+Y_{ST}^{\beta,1}\right]=0.$$

This last equation in the variable β can be solved with a simple numerical method as the bisection method. After the estimation $\widehat{\beta}$ of β has been obtained, we can find the estimation of $\widehat{a_\beta}=a_{\widehat{\beta}}$, $\widehat{\gamma_\beta}=\gamma_{\widehat{\beta}}$ and $\widehat{\sigma_\beta^2}=\sigma_{\widehat{\beta}}^2$.

b) $h_k(t)$ unknown

In this case, the observations of the process $X_0(t)$ must be used to estimate the parameters α, β and σ^2. The results in [6] can be used to estimate the control group by means of a homogeneous Gompertz diffusion process; alternatively we can use the previous results with $\gamma=0$ and $k=0$. In any case we have

$$a_\beta=\frac{\displaystyle\sum_{i=1}^{d_0}\sum_{j=2}^{n_{i_0}}v_{\beta,0}^{ij}T_{\beta,0}^{ij}}{\displaystyle\sum_{i=1}^{d_0}\sum_{j=2}^{n_{i_0}}(T_{\beta,0}^{ij})^2}$$

$$\sigma_\beta^2=\frac{2}{M}\sum_{i=1}^{d_0}\sum_{j=2}^{n_{i_0}}\left[v_{\beta,0}^{ij}-aT_{\beta,0}^{ij}\right]^2$$

$$\sum_{i=1}^{d_0}\sum_{j=2}^{n_{i_0}}v_{\beta,0}^{ij}\frac{dv_{\beta,0}^{ij}}{d\beta}-a_\beta\left[\sum_{i=1}^{d_0}\sum_{j=2}^{n_{i_0}}v_{\beta,0}^{ij}\frac{dT_{\beta,0}^{ij}}{d\beta}+\sum_{i=1}^{d_0}\sum_{j=2}^{n_{i_0}}T_{\beta,0}^{ij}\frac{dv_{\beta,0}^{ij}}{d\beta}\right]+a_\beta^2\sum_{i=1}^{d_0}\sum_{j=2}^{n_{i_0}}T_{\beta,0}^{ij}\frac{dT_{\beta,0}^{ij}}{d\beta}=0$$

Next, following a similar procedure to that proposed in [6] the function $h_k(t)$ can be estimated. Concretely, denoting by $X_{0,k}(t)$ the time homogeneous process with the same infinitesimal moments that $X_0(t)$, but defined in the time interval $[\tau_k,\tau_{k+1})$ with initial condition $X_{0,k}(\tau_k)=\rho$, one has

$$E[X_k(t)]=\exp\left(M_k(t|\log\rho,\tau_k)+\frac{V^2(t|\tau_k)}{2}\right),$$

$$E[X_{0,k}(t)]=\exp\left(M_0(t|\log\rho,\tau_k)+\frac{V^2(t|\tau_k)}{2}\right),$$

and

$$M_k(t|\log\rho,\tau_k)=M_0(t|\log\rho,\tau_k)+e^{-\beta t}\int_{\tau_k}^{t}h_k(\theta)e^{\beta\theta}\,d\theta.$$

Finally, since

$$\frac{E\left[X_k(t)\right]}{E\left[X_{0,k}(t)\right]} = \exp\left(e^{-\beta t}\int_{\tau_k}^{t} h_k(\theta)e^{\beta\theta}\, d\theta\right),$$

it follows

$$h_k(t) = e^{-\beta t}\,\frac{d}{dt}\left\{e^{\beta t}\log\left(\frac{E\left[X_k(t)\right]}{E\left[X_{0,k}(t)\right]}\right)\right\}.$$

So, for each $k = 1, \ldots, N$, from observations $\{x^k_{i,j}\}$, $i = 1, \ldots, d_k, j = 1, \ldots, n_{i_k}$, $E\left[X_k(t)\right]$ can be estimated on each t_j by means of $\sum_{i=1}^{d_k} x^k_{i,j}/d_k$, while $E[X_{0,k}(t_j)]$ can be estimated from the mean of sample paths of the processes $X_{0,k}(t)$ simulated in the same time instants of observations of each process $X_k(t)$. From the estimations of $E[X_k(t_j)]$ and $E[X_{0,k}(t_j)]$, $j = 1, \ldots, n_{i_k}$, the procedure proposed in [6] to approximate the function that model the therapy effect can be used.

3.2. Simulation study

The present simulation study is aimed at validating the estimation procedures described in Subsection 3.1. We consider the following cases:

a) $h_k(t) \equiv h^\gamma_k(t)$ has a functional closed form except for the value of a parameter γ. Concretely we consider

$$h^\gamma_k(t) = \gamma\left(k - \frac{1}{t}\right) \quad \text{and} \quad h^\gamma_k(t) = \gamma\left(k + \frac{1}{t}\right).$$

b) $h_k(t)$ unknown. For this case we consider

$$h_k(t) = \gamma\left(1 - \left(\frac{\tau_k}{t}\right)^k\right).$$

In all cases, the pattern for the simulations is the following:

- We consider 25 simulated sample paths of the process $X(t)$ in the interval $[0, 35]$, with step $h = 0.05$ and time instants of therapeutic application $(5, 10, 15, 20, 25)$.
- We assume $\alpha = 6.46$, $\beta = 0.314$, $\gamma = 0.1 + 0.1(i - 1)$, for $i = 1, \ldots, 5$, and $\sigma = 0.01, 0.05, 0.1$.
- The initial value for each X_k (k=1,...,5) is $\rho = 10^8$.

Lastly, this pattern is replicated 100 times.

Table 1 includes the estimation of the parameters in the case of $h_k^\gamma(t) = \gamma\,(k - 1/t)$ known. The last column includes the relative absolute error between the estimated and the real log-likelihood function. Table 2 is as the previous but considering $h_k^\gamma(t) = \gamma\,(k + 1/t)$. In both cases we conclude that regardless the procedure provides good estimations of the true values. As it is expected, the error on the log-likelihood function increases with σ.

γ	σ	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\gamma}$	$\widehat{\sigma}$	LogLik.Err
0.1	0.010	6.45989	0.31398	0.01000	0.09997	0.000005
	0.025	6.45650	0.31381	0.02498	0.09983	0.000011
	0.050	6.45296	0.31365	0.04991	0.09997	0.000035
	0.075	6.41131	0.31149	0.07503	0.09950	0.000070
	0.100	6.39508	0.31071	0.09965	0.09921	0.000139
0.2	0.010	6.45699	0.31382	0.01000	0.19979	0.000007
	0.025	6.46064	0.31402	0.02497	0.19990	0.000010
	0.050	6.45237	0.31364	0.04996	0.19995	0.000028
	0.075	6.44243	0.31307	0.07489	0.19950	0.000037
	0.100	6.43951	0.31293	0.09989	0.19951	0.000054
0.3	0.010	6.45135	0.31353	0.00998	0.29942	0.000013
	0.025	6.45406	0.31364	0.02500	0.29939	0.000023
	0.050	6.45752	0.31383	0.04982	0.29954	0.000043
	0.075	6.43779	0.31276	0.07471	0.29851	0.000077
	0.100	6.43248	0.31251	0.09986	0.29841	0.000093
0.4	0.010	6.44614	0.31324	0.00998	0.39884	0.000053
	0.025	6.44264	0.31304	0.02492	0.39856	0.000062
	0.050	6.44514	0.31320	0.04997	0.39895	0.000063
	0.075	6.44492	0.31321	0.07488	0.39885	0.000063
	0.100	6.44248	0.31298	0.09964	0.39821	0.000081
0.5	0.010	6.43960	0.31288	0.00999	0.49790	0.000018
	0.025	6.44096	0.31294	0.02492	0.49794	0.000076
	0.050	6.44268	0.31300	0.04982	0.49802	0.000131
	0.075	6.44194	0.31300	0.07457	0.49789	0.000136
	0.100	6.44132	0.31301	0.09964	0.49861	0.000187

Table 1: Parameter estimation in the case of $h_k^\gamma = \gamma\,(k - 1/t)$ known, $\alpha = 6.46$, $\beta = 0.314$, $k = 5$, $\tau_k = (5, 10, 15, 20, 25)$, $\rho = 10^8$.

The case b) is considered in Table 3. Note that in this case $h_k(t)$ is estimated jointly with the parameter γ. This table includes the estimation of the

γ	σ	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\gamma}$	$\widehat{\sigma}$	LogLik.Err
0.1	0.010	6.45936	0.31396	0.01000	0.09997	0.000004
	0.025	6.45270	0.31362	0.02501	0.09988	0.000014
	0.050	6.44246	0.31311	0.04994	0.09990	0.000031
	0.075	6.43412	0.31271	0.07498	0.09991	0.000040
	0.100	6.39841	0.31076	0.10002	0.09893	0.000112
0.2	0.010	6.45407	0.31370	0.01000	0.19980	0.000007
	0.025	6.45746	0.31387	0.02495	0.19991	0.000014
	0.050	6.44925	0.31344	0.05004	0.19965	0.000020
	0.075	6.44847	0.31342	0.07483	0.19974	0.000028
	0.100	6.42806	0.31229	0.09988	0.19894	0.000071
0.3	0.010	6.44932	0.31344	0.00999	0.29943	0.000010
	0.025	6.44975	0.31347	0.02498	0.29949	0.000029
	0.050	6.44827	0.31337	0.04988	0.29932	0.000038
	0.075	6.44362	0.31319	0.07502	0.29948	0.000039
	0.100	6.44301	0.31308	0.09993	0.29899	0.000067
0.4	0.010	6.44388	0.31315	0.00999	0.39883	0.000012
	0.025	6.44554	0.31324	0.02495	0.39891	0.000053
	0.050	6.44313	0.31312	0.04992	0.39881	0.000086
	0.075	6.43778	0.31283	0.07479	0.39853	0.000081
	0.100	6.43608	0.31280	0.09989	0.39878	0.000095
0.5	0.010	6.43690	0.31278	0.01000	0.49797	0.000077
	0.025	6.43619	0.31275	0.02492	0.49793	0.000186
	0.050	6.43159	0.31250	0.04981	0.49762	0.000220
	0.075	6.42700	0.31225	0.07463	0.49725	0.000230
	0.100	6.43500	0.31267	0.09968	0.49771	0.000330

Table 2: Parameter estimation in the case of $h_k^{\gamma} = \gamma\,(k + 1/t)$ known, $\alpha = 6.46$, $\beta = 0.314$, $k = 5$, $\tau_k = (5, 10, 15, 20, 25)$, $\rho = 10^8$.

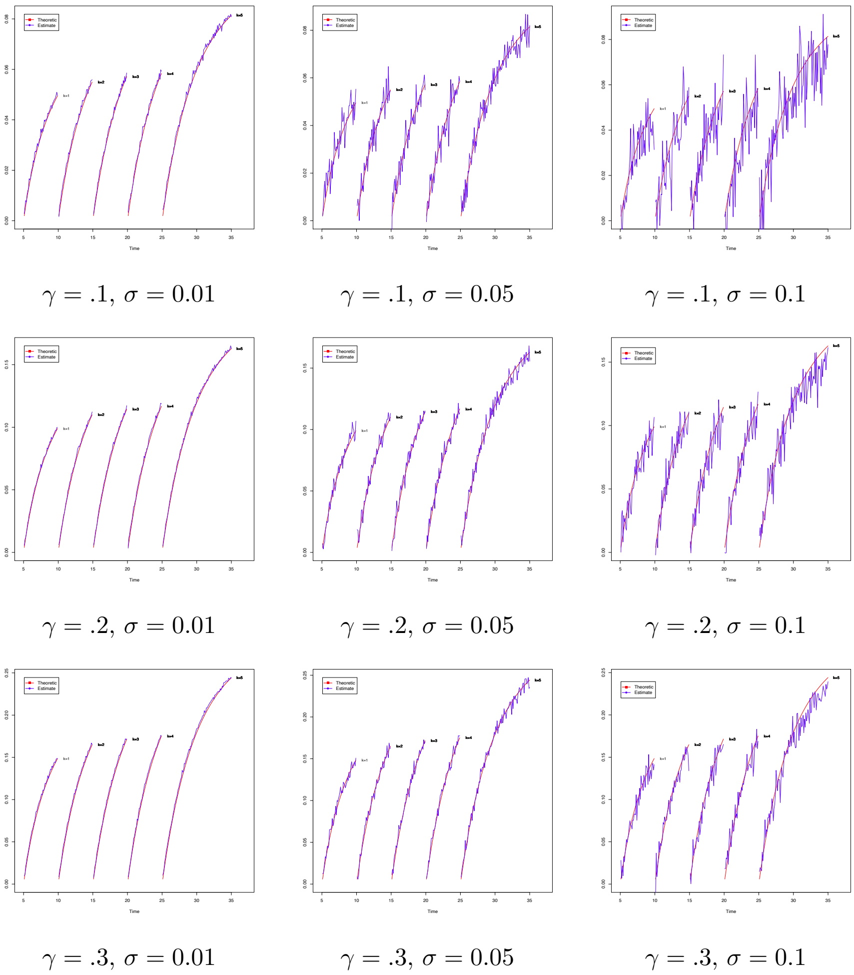
parameters α, β and σ obtained from the data of $X_0(t)$. The last column is a error measure of the estimation of $h_k(t)$ taking that is the relative absolute error between the real $h_k(t)$ functions and their estimations, both of them evaluated at the observation time instants. In this case the procedure for estimating $h_k(t)$ in each interval has been replicated 25 times, that is, after estimating the parameters α, β and σ from the data of X_0, we have considered 25 replications of $X_{0,k}(t)$ in the same time instants of observations of each process $X_k(t)$. For each one the procedure described before is applied and then the mean values are considered.

The value of σ influences the estimation of the parameters, worsening as σ increases, for any γ. It also occurs in the error of the estimation of $h_k(t)$. However, it is interesting to note that as γ increases this error tends to decrease for each value of σ fixed, which seems logical since in this case the growth process is faster, the values of the process are higher and the method allows more accurately capture the differences between the theoretical and estimated models.

γ	σ	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	Error
0.1	0.010	6.45872	0.31393	0.01001	0.05690
	0.025	6.43226	0.31258	0.02494	0.09111
	0.050	6.38698	0.31034	0.04988	0.17905
	0.075	6.15154	0.29816	0.07492	0.22136
	0.100	6.03425	0.29221	0.09940	0.34913
0.2	0.010	6.45541	0.31377	0.00997	0.03972
	0.025	6.44308	0.31313	0.02490	0.05543
	0.050	6.38993	0.31041	0.04987	0.10182
	0.075	6.29227	0.30545	0.07480	0.14929
	0.100	6.06437	0.29371	0.09997	0.17595
0.3	0.010	6.46326	0.31417	0.00996	0.04682
	0.025	6.44978	0.31347	0.02496	0.05273
	0.050	6.36492	0.30912	0.05005	0.06046
	0.075	6.26308	0.30386	0.07479	0.08457
	0.100	6.05824	0.29325	0.09996	0.13916
0.4	0.010	6.45344	0.31366	0.00998	0.04033
	0.025	6.43670	0.31280	0.02485	0.04579
	0.050	6.32423	0.30705	0.04985	0.05339
	0.075	6.19194	0.30023	0.07506	0.07421
	0.100	5.91984	0.28630	0.09960	0.11160
0.5	0.010	6.45321	0.31366	0.01004	0.03351
	0.025	6.44963	0.31348	0.02509	0.04303
	0.050	6.33809	0.30775	0.04998	0.05113
	0.075	6.26878	0.30415	0.07502	0.05551
	0.100	6.06640	0.29384	0.10011	0.08059

Table 3: Estimation in the case of $h_k^\gamma = \gamma\left(1-\left(\frac{\tau_k}{t}\right)^k\right)$ unknown, $\alpha = 6.46$, $\beta = 0.314$, $k = 5$, $\tau_k = (5, 10, 15, 20, 25)$, $\rho = 10^8$.

Figures 3 and 4 shows the estimations of the considered $h_k(t)$ functions for several values of γ and σ.

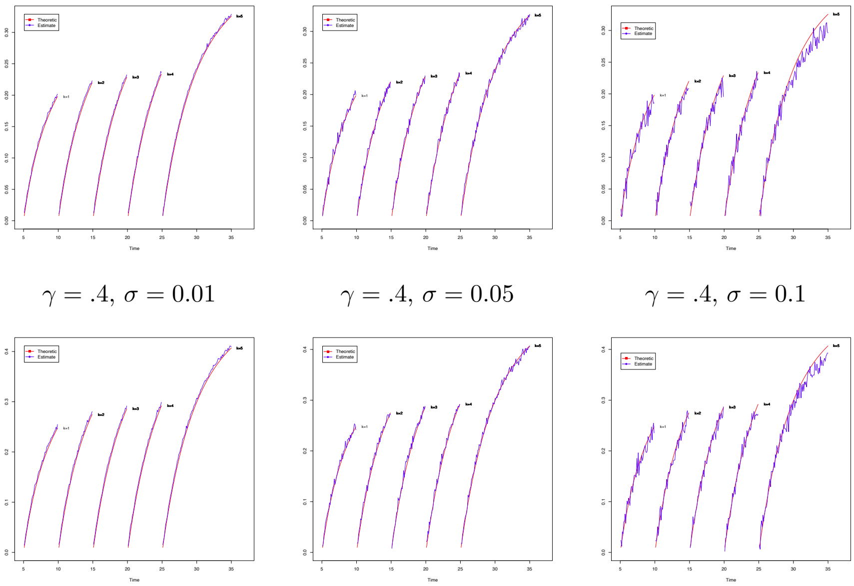


$\gamma = .1,\ \sigma = 0.01$ $\gamma = .1,\ \sigma = 0.05$ $\gamma = .1,\ \sigma = 0.1$

$\gamma = .2,\ \sigma = 0.01$ $\gamma = .2,\ \sigma = 0.05$ $\gamma = .2,\ \sigma = 0.1$

$\gamma = .3,\ \sigma = 0.01$ $\gamma = .3,\ \sigma = 0.05$ $\gamma = .3,\ \sigma = 0.1$

Figure 3: Estimation of the $\gamma\left(1-\left(\frac{\tau_k}{t}\right)^k\right)$ functions in the unknown case for several values of σ and γ for $\alpha = 6.46$, $\beta = 0.314$, $k = 5$, $\tau_k = (5, 10, 15, 20, 25)$, $\rho = 10^8$.



$\gamma = .4$, $\sigma = 0.01$ $\gamma = .4$, $\sigma = 0.05$ $\gamma = .4$, $\sigma = 0.1$

$\gamma = .5$, $\sigma = 0.01$ $\gamma = .5$, $\sigma = 0.05$ $\gamma = .5$, $\sigma = 0.1$

Figure 4: (continued) Estimation of the $\gamma\left(1-\left(\frac{\tau_k}{t}\right)^k\right)$ functions in the unknown case for several values of σ and γ for $\alpha = 6.46$, $\beta = 0.314$, $k = 5$, $\tau_k = (5, 10, 15, 20, 25)$, $\rho = 10^8$.

4. Model with time instants of therapeutic application non established in advance

In this case we assume that the instants of therapeutic application are unknown, so a criterion to establish the times τ_k is formulated.

4.1. Strategy for determining the time instants

The effectiveness of an intermittent treatment depends on the time instants of therapeutic application. The choice of such times have to balance the positive effect (the reduction of the cancer mass) and the negative effect (the survival of the most aggressive clones) of the treatment.

Denoting by S a control threshold, we require that $X(t) < S$ during the treatment. Hence, following [12], we propose to applied therapy before $X(t)$ reaches S. Specifically, for $S > \rho$, we denote by $T_k(S|\rho, \tau_k) = \inf_{t>\tau_k}\{t : X_k(t) > S|X_k(\tau_k) = \rho\}$ the random variable first-passage-time (FPT), by $g_k(S, t|\rho, \tau_k)$ the FPT pdf and $t_k(S|\rho, \tau_k)$ is the mean FPT. As shown in [12], better results can be obtained by applying the therapy as late as possible; so, for $k = 0, 1, \ldots, N-1$, τ_{k+1} can be determined as follows:

$$\tau_{k+1} = 0.99\, t_k(S|\rho, \tau_k). \tag{10}$$

The maximum number of applications N is chosen such that for $k > 0$ one has $\tau_{k+1} - \tau_k > \theta$, where θ can be considered as the minimum waiting time between consecutive applications. Since for $k = 1, 2, \ldots, N$ the processes $X_k(t)$ are time non-homogeneous, a closed form for $t_k(S|\rho, \tau_k)$ is not available. Specifically, being $X_0(t)$ is time homogeneous one has

$$t_0(S|\rho, \tau_0) = \int_\rho^S dz\phi(z) \int_0^z s(u)du, \tag{11}$$

where

$$\phi(x) = \exp\left\{-2\int^x \frac{A_1^{(0)}(\xi)}{A_2^{(0)}(\xi)}d\xi\right\} = x^{-2\alpha/\sigma^2} \exp\Big\{\frac{\beta}{\sigma^2}\ln^2 x\Big\}, \qquad s(x) = \frac{2}{A_2^{(0)}(x)h(x)},$$

are the scale function and speed density of $X_0(t)$, respectively. Instead, for $k = 1, 2, \ldots, N$ the mean $t_k(S|\rho, \tau_k)$ can be evaluated from the numerical approximation of the FPT pdf $g_k(S, t|\rho, \tau_k)$ obtained making use of the package `fptdApprox` of `R` [22], [23]. We ensure that the therapy is efficient by verifying that the mean FPT of $X(t)$ through S, denoted by $E[T(S|\rho)]$[1], is greater than $t_0(S|\rho, \tau_0)$ representing the mean FPT of the process $X_0(t)$ that describes

[1] $E[T(S|\rho)]$ can be computed by using the numerical evaluation of its density function $g(S, t|\rho, \tau_0)$ obtained by means of

$$g(S, t|\rho, \tau_0) = \begin{cases} g_0(S, t|\rho, \tau_0), & t \in I_0 \\ \displaystyle\prod_{j=0}^{k-1}\left[1 - \int_{\tau_j}^{\tau_{j+1}} g_j(S, \tau|\rho, \tau_j)d\tau\right] g_k(S, t|\rho, \tau_k), & t \in I_k. \end{cases}$$

the tumor growth in the absence of therapy. Moreover, we monitor the mean function of $X(t)$ to verify that it is below S until the end of the treatment.

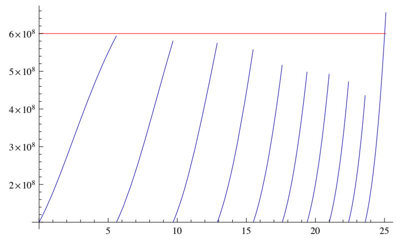
In the following we show the application of the strategy for different choices of the function $h_k(t)$ when it is fully determined. Specifically, we consider $\alpha = 6.46$, $\beta = 0.314$, $\rho = 10^8$, $S = 6 \cdot 10^8$, with $h_k(t) = \gamma\, r_k(t)$ and we analyze how different choices of values of γ, σ and of the functions $r_k(t)$ affect the times of the therapeutic application and hence the mean FPT of $X(t)$ through S. To this aim we consider for σ the values 0.01, 0.05 and 0.1, and for $r_k(t)$ the following choices

$$r_k(t) = k - 1/t, \qquad r_k(t) = k + 1/t, \qquad r_k(t) = 1 - (\tau_k/t)^k,$$

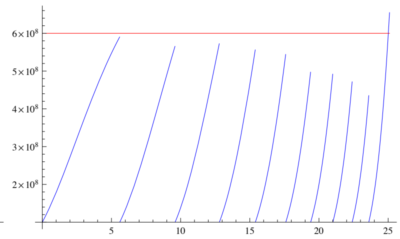
with values of $\gamma = 0.1 + (i-1) \cdot 0.1$, $i = 1, \ldots, 5$.

For each choice of $r_k(t)$ and several values of γ and σ, Tables 4-6 show the values of time instants of therapeutic applications, the mean FPT of each $X_k(t)$ through S and the mean FPT of the process $X(t)$ when the therapy is applied k times. Note that the mean FPT of $X(t)$ and of $X_k(t)$, for fixed values of k, decrease when σ increases. Indeed, due to the more width of the fluctuations, some sample paths reach the control threshold in a shorter time when σ increases. Moreover, when γ increases, the growth of the process becomes more quick so that the values of $t_k(S|\rho, \tau_k)$, as well as those of $E[T(S|\rho)]$, decrease.

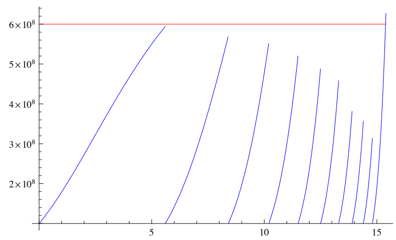
In Figures 5, 6 and 7, the mean of the process $X(t)$ are plotted for some choices of parameters and functions $h_k(t)$ considered (for the sake of brevity we have only considered the cases $\gamma = 0.1, 0.5$ and $\sigma = 0.01, 0.1$). The times τ_k are those obtained from the described strategy as listed in the Tables 4, 5 and 6, respectively. Note that selecting the times of therapeutic application via the proposed strategy, the mean of $X(t)$ results limited by the control boundary S (red line) until the end of treatment.



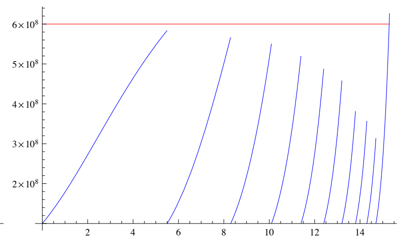
(a) $\gamma = 0.1, \sigma = 0.01$



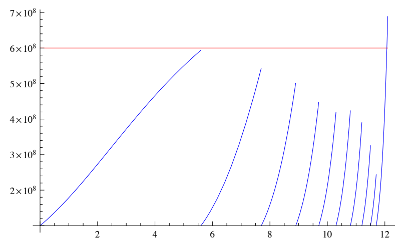
(b) $\gamma = 0.1, \sigma = 0.1$



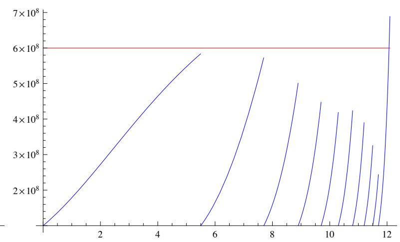
(c) $\gamma = 0.3, \sigma = 0.01$



(d) $\gamma = 0.3, \sigma = 0.1$

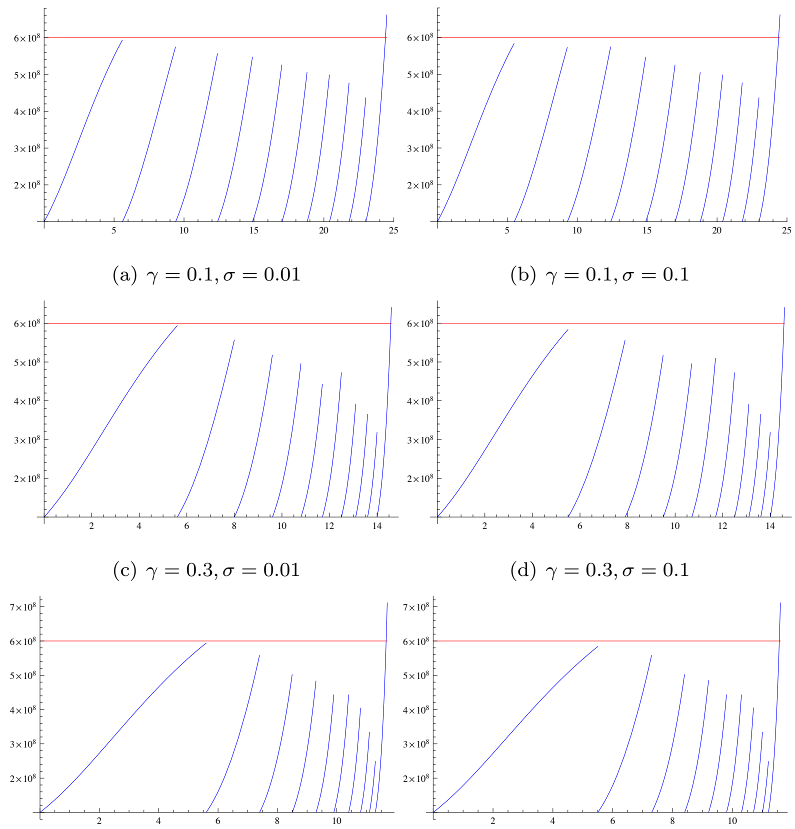


(e) $\gamma = 0.5, \sigma = 0.01$



(f) $\gamma = 0.5, \sigma = 0.1$

Figure 5: For $\rho = 10^8$, $\alpha = 6.46$, $\beta = 0.314$, and $h_k(t) = \gamma(k - 1/t)$ the means of $X(t)$ are plotted for different choices of γ and σ, the therapeutic application times are chosen according to Table 4. The red (upper) line represents the control threshold.



(a) $\gamma = 0.1, \sigma = 0.01$

(b) $\gamma = 0.1, \sigma = 0.1$

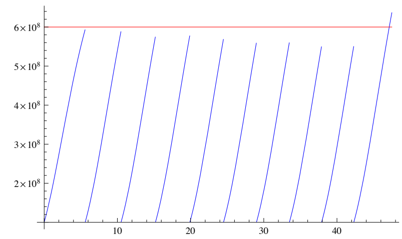
(c) $\gamma = 0.3, \sigma = 0.01$

(d) $\gamma = 0.3, \sigma = 0.1$

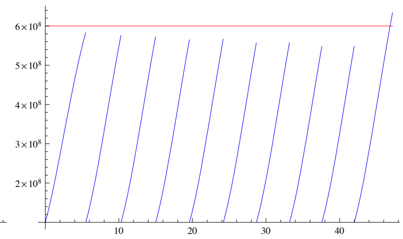
(e) $\gamma = 0.5, \sigma = 0.01$

(f) $\gamma = 0.5, \sigma = 0.1$

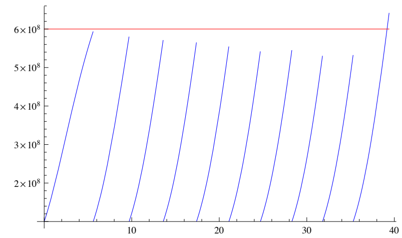
Figure 6: As in Figure 3 with $h_k(t) = \gamma(k + 1/t)$. The times of the therapeutic application are chosen according to Table 5. The red (upper) line represents the control threshold.



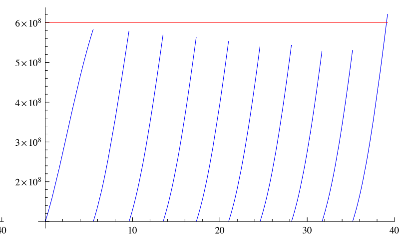
(a) $\gamma = 0.1, \sigma = 0.01$



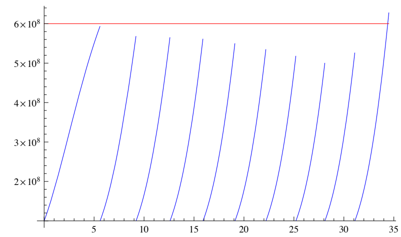
(b) $\gamma = 0.1, \sigma = 0.1$



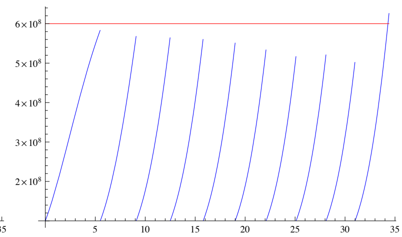
(c) $\gamma = 0.3, \sigma = 0.01$



(d) $\gamma = 0.3, \sigma = 0.1$



(e) $\gamma = 0.5, \sigma = 0.01$



(f) $\gamma = 0.5, \sigma = 0.1$

Figure 7: As in Figure 3 with $h_k^\gamma = \gamma[1 - (\tau_k/t)^k]$. The times of the therapeutic application are chosen according to Table 6. The red (upper) line represents the control threshold.

4.2. Estimation

In this case, to determine the time of the first application τ_1, the observations of the time- homogeneous process $X_0(t)$ are needed until a time instant enough large depending of the used strategy. Moreover, for each $k = 1, 2 \ldots, N$, once τ_k is determined, we observe the process $X_k(t)$, starting at time τ_k, to establish τ_{k+1}. However, both when $h_k^\gamma(t)$ has a functional closed form except for the value of the parameter γ, and when $h_k(t)$ is unknown, the parameters α, β and σ^2 must be estimated from the observations of the process $X_0(t)$ from the initial time to the total time of experimentation T.

a) $h_k(t) \equiv h_k^\gamma(t)$ has a functional closed form except for the value of a parameter γ.

For $k = 1$, from the observations of the processes $X_0(t)$ for $t \in [\tau_0, \tau_1)$ and $X_1(t)$ for $t \in [\tau_1, T]$, we can estimate the parameter γ and update the estimations of the parameters α, β and σ^2 by using the procedure described in 3.1.a). Next, for each $k = 2, \ldots, N$, once obtained each τ_k from observations of the processes $X_0(t), X_1(t), \ldots, X_k(t)$ we can update the estimations of α, β, σ^2 and γ.

b) $h_k(t)$ unknown.

A procedure similar to one described in 3.1.b) can be used, but it is iteratively applied once every τ_k is determined making use of the observations of the process $X_k(t)$ and of the simulations of the process $X_{0,k}(t)$ (i.e. the process $X_0(t)$ defined in $[\tau_k, \tau_{k+1})$ with $X_{0,k}(\tau_k) = \rho$).

4.3. Simulation study

Also in this case we consider the following situations:

a) $h_k(t) \equiv h_k^\gamma(t)$ has functional closed form except for the value of a parameter γ. Specifically,

$$h_k^\gamma(t) = \gamma \left(k - \frac{1}{t} \right) \quad \text{and} \quad h_k^\gamma(t) = \gamma \left(k + \frac{1}{t} \right).$$

b) $h_k(t)$ unknown. For this case we consider

$$h_k(t) = \gamma \left(1 - \left(\frac{\tau_k}{t}\right)^k\right).$$

The pattern for the simulations is the same as that used in Section 3 but considering the time instants of therapeutic application obtained in Subsection 4.1.

Tables 7 to 10 summarize the process of iterative estimation following the procedure established in subsection 4.2. when $h_k^\gamma(t)$ if known. For each choice of σ and γ, the tables include the values τ_k, the successive updated estimates of the parameters obtained from the sample data available at every stage and, from them, the estimated values of the time instants of therapeutic application (τ_k') are calculated. In all cases it can be observed that the real time instants of therapeutic applications (τ_k) and their estimates (τ_k') are very similar. Only a small difference is observed in the first instant of application when $\sigma = 0.1$, although this discrepancy decreases as the number of iterations grows. As regards the estimation of the parameters, the fact most significant is found in the first iteration. Indeed, when only information for $X_0(t)$ is available, the estimates obtained for α, β and σ worsen as σ increases, although the additional information on the successive stages improve the update of these estimates and stabilize them around the real values of the parameters, even in the case $\sigma = 0.1$.

The results when $h_k(t)$ is unknown are summarized in Tables 11 and 12. Again the values of τ_k and τ_k' are quite similar in all cases, showing a behavior similar to the previous case. Consequently, the method proposed for estimating the $h_k(t)$ functions appears useful for the purpose of estimating the time instants of the therapeutic application. As regards the estimates of α, β and σ (note that γ is estimated in conjunction with the $h_k(t)$ function) we can see how they worsen as σ increases, while the update of the estimates presents a behaviour similar to that observed when $h_k(t)$ is known.

		σ = 0.01			σ = 0.05			σ = 0.1		
γ	k	τ_k	$t_k(S\|\rho,\tau_k)$	$E[T(S\|\rho)]$	τ_k	$t_k(S\|\rho,\tau_k)$	$E[T(S\|\rho)]$	τ_k	$t_k(S\|\rho,\tau_k)$	$E[T(S\|\rho)]$
0.10	0	0	5.68727	5.68726	0	5.67102	5.67102	0	5.63108	5.63107
	1	5.6	9.85303	8.94970	5.6	9.85307	7.66324	5.5	9.75642	7.34916
	2	9.7	13.03168	11.44508	9.7	13.03396	8.77928	9.6	12.94221	8.19690
	3	12.9	15.66740	13.51413	12.9	15.66967	9.47694	12.8	15.57754	8.64827
	4	15.5	17.87631	15.24809	15.5	17.87827	10.01571	15.4	17.78504	8.93047
	5	17.6	19.68636	16.66896	17.6	19.68800	10.45545	17.6	19.69365	9.13680
	6	19.4	21.26159	17.90549	19.4	21.26296	10.83777	19.4	21.26776	9.30168
	7	21	22.68171	19.02026	21	22.68286	11.18244	21	22.68696	9.44462
	8	22.4	23.93423	20.00348	22.4	23.93521	11.48644	22.4	23.93874	9.57065
	9	23.6	25.01099	20.84872	23.6	25.01183	11.74778	23.6	25.01489	9.67893
	10	24.7	–	–	24.7	–	–	24.7	–	–
0.20	0	0	5.68727	5.68726	0	5.67102	5.67102	0	5.63108	5.63107
	1	5.6	9.05894	8.32348	5.6	9.06109	7.24768	5.5	8.97097	6.95104
	2	8.9	11.32226	10.10829	8.9	11.32431	8.15098	8.8	11.23176	7.63188
	3	11.2	13.08478	11.49818	11.2	13.08625	8.78300	11.1	12.99144	8.03072
	4	12.9	14.44817	12.57332	12.9	14.44923	9.26944	12.8	14.35299	8.31708
	5	14.3	15.61556	13.49390	14.3	15.61635	9.68550	14.2	15.51919	8.54708
	6	15.4	16.54466	14.22657	15.4	16.54526	10.01635	15.3	16.44748	8.72922
	7	16.3	17.31351	14.83288	16.3	17.31399	10.29014	16.2	17.21576	8.88001
	8	17.1	18.00957	15.38177	17.1	18.00995	10.53802	17	17.91140	9.01653
	9	17.8	18.62510	15.86717	17.8	18.62541	10.75723	17.7	18.52662	9.13727
	10	18.4	–	–	18.4	–	–	18.3	–	–
0.30	0	0	5.68727	5.687267	0	5.67102	5.671021	0	5.63108	5.63107
	1	5.6	8.53607	7.911151	5.6	8.53840	6.973422	5.5	8.44906	6.68650
	2	8.4	10.31692	9.315527	8.4	10.31844	7.735666	8.3	10.22419	7.25314
	3	10.2	11.63785	10.357219	10.2	11.63881	8.276137	10.1	11.54231	7.60759
	4	11.5	12.65383	11.158417	11.5	12.65447	8.689827	11.4	12.55682	7.86568
	5	12.5	13.46467	11.797851	12.5	13.46512	9.019916	12.4	13.36681	8.06964
	6	13.3	14.12929	12.321970	13.3	14.12963	9.290493	13.2	14.03089	8.23671
	7	13.9	14.62749	12.714851	13.9	14.62774	9.493320	13.8	14.52873	8.36194
	8	14.4	15.04807	13.046521	14.4	15.04827	9.664553	14.3	14.94906	8.46768
	9	14.8	15.38436	13.311718	14.8	15.38452	9.801469	14.7	15.28516	8.55222
	10	15.2	–	–	15.2	–	–	15.1	–	–
0.40	0	0	5.68727	5.68726	0	5.67102	5.67102	0	5.63108	5.63107
	1	5.6	8.15990	7.61449	5.6	8.16204	6.77594	5.5	8.07221	6.49549
	2	8	9.59124	8.74326	8	9.59239	7.45482	7.9	9.49691	7.02224
	3	9.4	10.56535	9.51144	9.4	10.56602	7.92180	9.4	10.56826	7.35541
	4	10.4	11.32155	10.10778	10.4	11.32197	8.28437	10.4	11.32344	7.58794
	5	11.2	11.96281	10.61348	11.2	11.96310	8.59186	11.2	11.96413	7.78446
	6	11.8	12.45105	10.99851	11.8	12.45126	8.82598	11.8	12.45203	7.93422
	7	12.3	12.86800	11.32732	12.3	12.86816	9.02593	12.3	12.86874	8.06212
	8	12.7	13.20382	11.59214	12.7	13.20394	9.18697	12.7	13.20440	8.16515
	9	13	13.45272	11.78843	13	13.45282	9.30634	13	13.45319	8.24152
	10	13.3	–	–	13.3	–	–	13.3	–	–
0.50	0	0	5.68727	5.68726	0	5.67102	5.67102	0	5.63108	5.63107
	1	5.6	7.87393	7.38898	5.6	7.87582	6.62576	5.5	7.78524	6.35003
	2	7.7	9.06239	8.32620	7.7	9.06327	7.22814	7.7	9.06619	6.75503
	3	8.9	9.88069	8.97151	8.9	9.88117	7.64313	8.9	9.88282	7.02024
	4	9.7	10.46774	9.43447	9.7	10.46804	7.94091	9.7	10.46909	7.21068
	5	10.3	10.93129	9.80002	10.3	10.93149	8.17605	10.3	10.93221	7.36112
	6	10.8	11.33620	10.11933	10.8	11.33634	8.38147	10.8	11.33687	7.49256
	7	11.2	11.66611	10.37950	11.2	11.66622	8.54885	11.2	11.66662	7.59967
	8	11.5	11.91229	10.57364	11.5	11.91237	8.67374	11.5	11.91269	7.67960
	9	11.7	12.06966	10.69775	11.7	12.06972	8.75358	11.7	12.06997	7.73069
	10	11.9	–	–	11.9	–	–	11.9	–	–

Table 4: Values of τ_k, $t_k(S|\rho,\tau_k)$ and $E[T(S|\rho)]$ for $\alpha = 6.46$, $\beta = 0.314, \rho = 10^8, S = 6 \cdot 10^8$ for $h_k^\gamma = \gamma[(k-1/t)]$ and several choices of γ and σ.

		$\sigma = 0.01$			$\sigma = 0.05$			$\sigma = 0.1$		
γ	k	τ_k	$t_k(S\|\rho, \tau_k)$	$E[T(S\|\rho)]$	τ_k	$t_k(S\|\rho, \tau_k)$	$E[T(S\|\rho)]$	τ_k	$t_k(S\|\rho, \tau_k)$	$E[T(S\|\rho)]$
0.10	0	0	5.68726	5.68726	0	5.67102	5.67102	0	5.63107	5.63107
	1	5.6	9.57927	8.73382	5.6	9.58052	7.52023	5.5	9.48368	7.21092
	2	9.4	12.61701	11.12877	9.4	12.61940	8.67655	9.3	12.52692	8.06532
	3	12.4	15.10470	13.09003	12.4	15.10696	9.53111	12.4	15.11454	8.52702
	4	14.9	17.23697	14.77107	14.9	17.23891	10.23357	14.9	17.24546	8.84380
	5	17	19.05940	16.20785	17	19.06102	10.82845	17	19.06659	9.08672
	6	18.8	20.64201	17.45554	18.8	20.64336	11.34446	18.8	20.64810	9.28477
	7	20.4	22.06688	18.57885	20.4	22.06803	11.80895	20.4	22.07208	9.45865
	8	21.8	23.32263	19.56890	21.8	23.32360	12.21828	21.8	23.32710	9.61098
	9	23	24.40166	20.41959	23	24.40249	12.57001	23	24.40553	9.74148
	10	24.1	–	–	24.1	–	–	24.1	–	–
0.20	0	0	5.68726	5.68726	0	5.67102	5.67102	0	5.63107	5.63107
	1	5.6	8.70517	8.04450	5.6	8.70770	7.06225	5.5	8.61373	6.76997
	2	8.6	10.89282	9.76819	8.6	10.89479	7.86636	8.6	10.80064	7.40219
	3	10.7	12.51883	11.04926	10.7	12.52024	8.46847	10.6	12.42466	7.81750
	4	12.3	13.80852	12.06536	12.3	13.80954	8.94719	12.3	13.81309	8.11249
	5	13.6	14.88931	12.91688	13.6	14.89008	9.34841	13.6	14.89274	8.33868
	6	14.7	15.82606	13.65491	14.7	15.82665	9.69617	14.7	15.82875	8.53305
	7	15.6	16.59966	14.26441	15.6	16.60013	9.98338	15.6	16.60183	8.69344
	8	16.4	17.29889	14.81531	16.4	17.29927	10.24298	16.4	17.30066	8.83842
	9	17.1	17.91664	15.30201	17.1	17.91694	10.47233	17.1	17.91810	8.96651
	10	17.7	–	–	17.8	–	–	17.8	–	–
0.30	0	0	5.68726	5.68726	0	5.67102	5.67102	0	5.63107	5.63107
	1	5.6	8.15830	7.61324	5.6	8.16060	6.77518	5.5	8.06561	6.49214
	2	8	9.78829	8.89865	8	9.78969	7.54535	7.9	9.69360	7.06676
	3	9.6	10.97457	9.83416	9.6	10.97547	8.10838	9.5	10.87816	7.47238
	4	10.8	11.91666	10.57709	10.8	11.91727	8.55563	10.7	11.81918	7.79351
	5	11.7	12.64035	11.14779	11.7	12.64078	8.89921	11.7	12.64231	8.06537
	6	12.5	13.31225	11.67766	12.5	13.31258	9.21823	12.5	13.31374	8.28656
	7	13.1	13.81487	12.07402	13.1	13.81512	9.45688	13.1	13.81603	8.45187
	8	13.6	14.23836	12.40799	13.6	14.23856	9.65796	13.6	14.23929	8.59117
	9	14	14.57665	12.67477	14	14.57681	9.81859	14	14.57742	8.70245
	10	14.4	–	–	14.4	–	–	14.4	–	–
0.40	0	0	5.68726	5.68726	0	5.67102	5.67102	0	5.63107	5.63107
	1	5.6	7.77984	7.31478	5.6	7.78176	6.57640	5.5	7.68549	6.29947
	2	7.7	9.16830	8.40971	7.7	9.16932	7.15560	7.6	9.07199	6.73276
	3	9	10.10593	9.14912	9	10.10653	7.55090	8.9	10.00828	7.03072
	4	10	10.88708	9.76514	10	10.88748	7.88017	9.9	10.78869	7.27163
	5	10.7	11.44044	10.20151	10.7	11.44072	8.11342	10.6	11.34160	7.44155
	6	11.3	11.93544	10.59187	11.3	11.93564	8.32210	11.2	11.83631	7.59358
	7	11.8	12.35652	10.92393	11.8	12.35667	8.49961	11.7	12.25719	7.72292
	8	12.2	12.69503	11.19087	12.2	12.69514	8.64232	12.1	12.59556	7.82690
	9	12.5	12.94576	11.38860	12.5	12.94585	8.74802	12.4	12.84619	7.90393
	10	12.8	–	–	12.8	–	–	12.7	–	–
0.50	0	0	5.68726	5.68726	0	5.67102	5.67102	0	5.63107	5.63107
	1	5.6	7.50098	7.09487	5.6	7.50257	6.42991	5.5	7.40526	6.15743
	2	7.4	8.64562	7.99754	7.4	8.64639	6.97198	7.3	8.54825	6.56993
	3	8.5	9.42515	8.61228	8.5	9.42559	7.34458	8.4	9.32678	6.85714
	4	9.3	10.03569	9.09375	9.3	10.03597	7.63645	9.2	9.93678	7.08188
	5	9.9	10.51056	9.46823	9.9	10.51075	7.86348	9.8	10.41133	7.25656
	6	10.4	10.92179	9.79253	10.4	10.92193	8.06010	10.3	10.82236	7.40786
	7	10.8	11.25554	10.05573	10.8	11.25564	8.21967	10.7	11.15598	7.53067
	8	11.1	11.50420	10.25183	11.1	11.50427	8.33856	11	11.40453	7.62216
	9	11.3	11.66323	10.37723	11.3	11.66329	8.41460	11.2	11.56351	7.68068
	10	11.5	–	–	11.5	–	–	11.4	–	–

Table 5: As in Table 4 for $h_k^\gamma = \gamma(k + 1/t)$.

		$\sigma = 0.01$			$\sigma = 0.05$			$\sigma = 0.1$		
γ	k	τ_k	$t_k(S\|\rho,\tau_k)$	$E[T(S\|\rho)]$	τ_k	$t_k(S\|\rho,\tau_k)$	$E[T(S\|\rho)]$	τ_k	$t_k(S\|\rho,\tau_k)$	$E[T(S\|\rho)]$
0.10	0	0	5.68727	5.68726	0	5.67102	5.67102	0	5.63108	5.63108
	1	5.6	10.60672	9.54406	5.6	10.60128	8.05584	5.5	10.48243	7.71716
	2	10.5	15.43612	13.06243	10.4	15.32781	9.70663	10.3	15.21313	8.96870
	3	15.2	20.10349	16.45730	15.1	19.99641	10.91375	15	19.88345	9.71552
	4	19.9	24.78593	19.85767	19.7	24.57751	11.87111	19.6	24.46552	10.18012
	5	24.5	29.37330	23.18837	24.3	29.16563	12.62656	24.2	29.05423	10.47747
	6	29	33.86321	26.44830	28.8	33.65605	13.25413	28.7	33.54509	10.67451
	7	33.5	38.35583	29.71020	33.3	38.14903	13.80125	33.2	38.03837	10.80656
	8	37.9	42.74910	32.89997	37.7	42.54257	14.29198	37.6	42.43216	10.90462
	9	42.3	47.14377	36.09076	42.1	46.93744	14.73815	42	46.82723	10.97419
	10	46.6	–	–	46.4	–	–	46.3	–	–
0.20	0	0	5.68727	5.68726	0	5.67102	5.67102	0	5.63108	5.63108
	1	5.6	10.15805	9.19024	5.6	10.15632	7.82236	5.5	10.04430	7.49508
	2	10	14.43612	12.55139	10	14.43502	9.32969	9.9	14.32809	8.63962
	3	14.2	18.58101	15.80811	14.2	18.58013	10.50743	14.1	18.47535	9.35591
	4	18.3	22.64836	19.00391	18.3	22.64759	11.49874	18.2	22.54400	9.85966
	5	22.4	26.72789	22.20928	22.4	26.72717	12.32404	22.3	26.62433	10.19701
	6	26.4	30.71172	25.33945	26.4	30.71101	13.05765	26.3	30.60872	10.43497
	7	30.4	34.69989	28.47304	30.4	34.69919	13.70868	30.3	34.59728	10.60951
	8	34.3	38.58921	31.52895	34.3	38.58851	14.31012	34.2	38.48692	10.74358
	9	38.2	42.48078	34.58663	38.2	42.48006	14.88063	38.1	42.37871	10.84712
	10	42	–	–	42	–	–	41.9	–	–
0.30	0	0	5.68727	5.68726	0	5.67102	5.67102	0	5.63108	5.63108
	1	5.6	9.82835	8.93024	5.6	9.82822	7.65020	5.5	9.71886	7.33013
	2	9.7	13.77290	12.02712	9.7	13.77325	9.05618	9.6	13.66914	8.42208
	3	13.6	17.60335	15.03412	13.6	17.60386	10.13267	13.5	17.50194	9.09544
	4	17.4	21.36237	17.98505	17.4	21.36294	11.01427	17.3	21.26225	9.54687
	5	21.1	25.03368	20.86712	21.1	25.03428	11.79084	21	24.93439	9.86134
	6	24.7	28.61136	23.67569	24.7	28.61199	12.50716	24.6	28.51265	10.11472
	7	28.3	32.19502	26.48896	28.3	32.19565	13.18662	28.2	32.09672	10.30522
	8	31.8	35.68053	29.22517	31.8	35.68115	13.82877	31.7	35.58255	10.46490
	9	35.3	39.16907	31.96377	35.3	39.16968	14.45565	35.2	39.07133	10.60091
	10	38.7	–	–	38.7	–	–	38.6	–	–
0.40	0	0	5.68727	5.68726	0	5.67102	5.67102	0	5.63108	5.63108
	1	5.6	9.57060	8.72698	5.6	9.57127	7.51538	5.5	9.46302	7.20045
	2	9.4	13.18612	11.57811	9.4	13.18712	8.97648	9.3	13.08403	8.30996
	3	13	16.70392	14.35219	13	16.70503	10.17493	12.9	16.60413	9.05127
	4	16.5	20.15561	17.07413	16.5	20.15676	11.20212	16.4	20.05709	9.56433
	5	19.9	23.52192	19.72874	19.9	23.52309	12.14432	19.8	23.42421	9.94772
	6	23.2	26.79583	22.31049	23.2	26.79700	13.03671	23.1	26.69868	10.26372
	7	26.5	30.07671	24.89773	26.5	30.07787	13.89713	26.4	29.97996	10.51930
	8	29.7	33.25983	27.40788	29.7	33.26099	14.72235	29.6	33.16339	10.73798
	9	32.9	36.44648	29.92081	32.9	36.44762	15.53760	32.8	36.35027	10.92540
	10	36	–	–	36	–	–	35.9	–	–
0.50	0	0	5.68727	5.68726	0	5.67102	5.67102	0	5.63108	5.63108
	1	5.6	9.36082	8.56154	5.6	9.36189	7.40552	5.5	9.25411	7.09456
	2	9.2	12.75685	11.23965	9.2	12.75816	8.83338	9.1	12.65537	8.17000
	3	12.6	16.06621	13.84940	12.6	16.06757	9.97747	12.5	15.96694	8.87010
	4	15.9	19.31301	16.40981	15.9	19.31439	10.94471	15.8	19.21496	9.34659
	5	19.1	22.47599	18.90412	19.1	22.47736	11.81680	19	22.37871	9.70783
	6	22.2	25.54738	21.32620	22.2	25.54875	12.64575	22.1	25.45064	10.00296
	7	25.2	28.52367	23.67330	25.2	28.52504	13.44043	25.1	28.42733	10.25911
	8	28.2	31.50549	26.02475	28.2	31.50685	14.22807	28.1	31.40945	10.48397
	9	31.1	34.38891	28.29860	31.1	34.39025	14.98949	31	34.29310	10.68440
	10	34	–	–	34	–	–	33.9	–	–

Table 6: As in Table 4 for $h_k^\gamma = \gamma[1 - (\tau_k/t)^k]$.

σ	k	$\gamma = .1$						$\gamma = .2$						$\gamma = .3$					
		τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	$\widehat{\gamma}$	τ'_k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	$\widehat{\gamma}$	τ'_k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	$\widehat{\gamma}$	τ'_k
0.01	0	0	6.45431	0.31372	0.01000		5.6	0	6.45477	0.31373	0.01001		5.6	0	6.45335	0.31367	0.01000		5.6
	1	5.6	6.45827	0.31389	0.01000	0.09962	9.7	5.6	6.46454	0.31423	0.00999	0.20040	8.9	5.6	6.46582	0.31429	0.01001	0.30051	8.4
	2	9.7	6.46137	0.31406	0.01000	0.09999	12.9	8.9	6.46214	0.31411	0.00999	0.20016	11.2	8.4	6.46194	0.31409	0.00998	0.30007	10.2
	3	12.9	6.46121	0.31405	0.01002	0.09997	15.5	11.2	6.46257	0.31411	0.01001	0.19999	12.9	10.2	6.45833	0.31390	0.01001	0.29981	11.5
	4	15.5	6.46050	0.31402	0.01001	0.09995	17.6	12.9	6.45892	0.31394	0.01001	0.19994	14.3	11.5	6.45747	0.31385	0.00999	0.29976	12.5
	5	17.6	6.45802	0.31389	0.01002	0.09995	19.4	14.3	6.45653	0.31381	0.00998	0.19981	15.4	12.5	6.45324	0.31363	0.01000	0.29951	13.3
	6	19.4	6.46060	0.31402	0.00999	0.09996	21.0	15.4	6.45536	0.31374	0.00999	0.19973	16.3	13.3	6.44748	0.31333	0.00996	0.29918	13.9
	7	21	6.46004	0.31400	0.00999	0.09997	22.4	16.3	6.45347	0.31364	0.01000	0.19966	17.1	13.9	6.44433	0.31315	0.01001	0.29898	14.4
	8	22.4	6.45794	0.31389	0.01000	0.09994	23.6	17.1	6.45012	0.31346	0.00998	0.19953	17.8	14.4	6.43845	0.31285	0.00999	0.29870	14.8
	9	23.6	6.45469	0.31371	0.01001	0.09988	24.7	17.8	6.44597	0.31324	0.01001	0.19938	18.4	14.8	6.43297	0.31254	0.01002	0.29836	15.2
	10	24.7	6.45517	0.31374	0.01002	0.09989		18.4	6.44420	0.31315	0.00999	0.19933		15.2	6.42639	0.31219	0.01003	0.29800	
0.05	0	0	6.31880	0.30707	0.04986		5.6	0	6.31396	0.30680	0.04999		5.7	0.0	6.31990	0.30713	0.05002		5.7
	1	5.6	6.41876	0.31183	0.04990	0.09622	9.7	5.6	6.43357	0.31263	0.05002	0.19741	8.9	5.6	6.44296	0.31308	0.04997	0.29780	8.4
	2	9.7	6.42766	0.31232	0.04996	0.09867	12.9	8.9	6.45495	0.31375	0.04995	0.20018	11.2	8.4	6.44734	0.31334	0.05002	0.29913	10.2
	3	12.9	6.43424	0.31266	0.04999	0.09911	15.5	11.2	6.44735	0.31331	0.04999	0.19926	12.9	10.2	6.45960	0.31400	0.04991	0.30015	11.5
	4	15.5	6.45034	0.31353	0.04996	0.09989	17.6	12.9	6.45498	0.31374	0.04992	0.19976	14.3	11.5	6.45143	0.31352	0.04995	0.29931	12.5
	5	17.6	6.44846	0.31340	0.05001	0.09977	19.4	14.3	6.45809	0.31392	0.04996	0.20001	15.4	12.5	6.45433	0.31369	0.04995	0.29965	13.3
	6	19.4	6.44661	0.31329	0.04996	0.09965	21.0	15.4	6.45315	0.31365	0.05001	0.19979	16.3	13.3	6.44686	0.31326	0.04993	0.29910	13.9
	7	21	6.45909	0.31397	0.05004	0.10004	22.4	16.3	6.44603	0.31322	0.04988	0.19926	17.1	13.9	6.43807	0.31284	0.04985	0.29881	14.4
	8	22.4	6.45004	0.31351	0.04997	0.10001	23.6	17.1	6.44463	0.31314	0.04994	0.19926	17.8	14.4	6.44033	0.31291	0.04988	0.29871	14.9
	9	23.6	6.44814	0.31335	0.04994	0.09965	24.7	17.8	6.45022	0.31348	0.04996	0.19953	18.4	14.8	6.43293	0.31256	0.04982	0.29843	15.2
	10	24.7	6.45011	0.31346	0.04987	0.09975		18.4	6.44372	0.31312	0.04983	0.19933		15.2	6.42498	0.31212	0.04978	0.29797	
0.1	0	0	5.93449	0.28818	0.09976		5.9	0	5.89568	0.28630	0.09976		5.9	0.0	5.91774	0.28733	0.09988		5.9
	1	5.6	6.26588	0.30411	0.09998	0.08940	9.7	5.5	6.33462	0.30766	0.09992	0.19362	8.9	5.5	6.40080	0.31093	0.09992	0.29432	8.3
	2	9.6	6.36743	0.30930	0.09994	0.09721	12.8	8.8	6.39168	0.31039	0.09997	0.19524	11.1	8.3	6.43850	0.31273	0.10003	0.29686	10.1
	3	12.8	6.41935	0.31187	0.09983	0.09841	15.4	11.1	6.42452	0.31213	0.09997	0.19807	12.8	10.1	6.45488	0.31367	0.10019	0.29934	11.4
	4	15.4	6.41081	0.31152	0.10004	0.09927	17.6	12.8	6.43616	0.31267	0.10005	0.19834	14.2	11.4	6.45622	0.31386	0.09974	0.30019	12.4
	5	17.6	6.43420	0.31266	0.10001	0.09954	19.5	14.2	6.43791	0.31284	0.09991	0.19913	15.3	12.4	6.45010	0.31356	0.10002	0.29994	13.2
	6	19.4	6.42053	0.31199	0.10000	0.09952	21.0	15.3	6.43421	0.31260	0.09995	0.19888	16.2	13.2	6.44351	0.31309	0.09978	0.29889	13.8
	7	21	6.43965	0.31294	0.10004	0.09972	22.4	16.2	6.43957	0.31292	0.09977	0.19938	17	13.8	6.44428	0.31322	0.09981	0.29928	14.3
	8	22.4	6.43534	0.31271	0.09985	0.09964	23.7	17	6.44502	0.31318	0.09987	0.19942	17.7	14.3	6.43788	0.31285	0.09977	0.29884	14.8
	9	23.6	6.44440	0.31317	0.09980	0.09976	24.7	17.7	6.44791	0.31333	0.09990	0.19953	18.3	14.7	6.43297	0.31256	0.09987	0.29845	15.1
	10	24.7	6.43607	0.31266	0.09987	0.09932		18.3	6.43979	0.31288	0.09971	0.19913		15.1	6.42002	0.31184	0.09965	0.29767	

Table 7: Estimates of the parameters, and real and estimated first-passage-times through $S = 6 \cdot 10^8$ for $h_k(t) = \gamma(k - 1/t)$ $(k = 1, \ldots, 10)$ and $\alpha = 6.46$, $\beta = 0.314$.

		γ = .4						γ = .5					
σ	k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	$\widehat{\gamma}$	τ_k'	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	$\widehat{\gamma}$	τ_k'
0.01	0	0	6.45422	0.31371	0.01001		5.6	0	6.45506	0.31376	0.01000		5.6
	1	5.6	6.46868	0.31444	0.01000	0.40088	8	5.6	6.46834	0.31442	0.00998	0.50082	7.7
	2	8	6.46138	0.31406	0.00999	0.40001	9.4	7.7	6.46078	0.31403	0.00999	0.49999	8.9
	3	9.4	6.46037	0.31401	0.01000	0.39996	10.4	8.9	6.45911	0.31394	0.00999	0.49994	9.7
	4	10.4	6.45786	0.31387	0.01000	0.39977	11.2	9.7	6.45884	0.31393	0.00997	0.49983	10.3
	5	11.2	6.45704	0.31385	0.01000	0.39974	11.8	10.3	6.45539	0.31376	0.01001	0.49954	10.8
	6	11.8	6.45437	0.31369	0.00997	0.39952	12.3	10.8	6.45188	0.31356	0.01001	0.49919	11.2
	7	12.3	6.45317	0.31363	0.00998	0.39942	12.7	11.2	6.44981	0.31344	0.00998	0.49897	11.5
	8	12.7	6.45054	0.31349	0.01001	0.39924	13	11.5	6.44593	0.31324	0.01001	0.49863	11.7
	9	13	6.44783	0.31333	0.00999	0.39900	13.3	11.7	6.44205	0.31304	0.01002	0.49834	11.9
	10	13.3	6.44449	0.31315	0.00999	0.39878		11.9	6.43724	0.31275	0.01002	0.49778	
0.05	0	0	6.32064	0.30714	0.04993		5.6	0	6.31260	0.30673	0.05004		5.6
	1	5.6	6.45107	0.31349	0.05005	0.39800	8	5.6	6.45353	0.31367	0.04998	0.49890	7.7
	2	8	6.46005	0.31396	0.04997	0.39916	9.4	7.7	6.46086	0.31412	0.04992	0.50104	8.9
	3	9.4	6.45319	0.31366	0.04996	0.39964	10.4	8.9	6.45571	0.31368	0.04995	0.49869	9.7
	4	10.4	6.46302	0.31414	0.05001	0.40015	11.2	9.7	6.45071	0.31349	0.04999	0.49895	10.3
	5	11.2	6.45781	0.31384	0.04997	0.39963	11.8	10.3	6.45011	0.31349	0.05001	0.49910	10.8
	6	11.8	6.45288	0.31358	0.05002	0.39929	12.3	10.8	6.45391	0.31366	0.05000	0.49926	11.2
	7	12.3	6.45657	0.31382	0.04997	0.39966	12.7	11.2	6.44715	0.31331	0.04988	0.49870	11.5
	8	12.7	6.45253	0.31357	0.04993	0.39930	13	11.5	6.44520	0.31323	0.04995	0.49866	11.7
	9	13	6.44540	0.31317	0.04993	0.39874	13.3	11.7	6.44031	0.31290	0.04996	0.49800	11.9
	10	13.3	6.44824	0.31334	0.04989	0.39900		11.9	6.43380	0.31262	0.04994	0.49771	
0.1	0	0	5.90189	0.28653	0.09997		5.9	0	5.89744	0.28637	0.10004		5.9
	1	5.5	6.40954	0.31135	0.10002	0.39435	8	5.5	6.45652	0.31370	0.09993	0.49573	7.7
	2	7.9	6.46195	0.31419	0.10006	0.40118	9.4	7.7	6.42944	0.31238	0.10005	0.49621	8.9
	3	9.4	6.45639	0.31364	0.09993	0.39881	10.4	8.9	6.47060	0.31455	0.09994	0.50110	9.7
	4	10.4	6.46895	0.31447	0.10028	0.40078	11.2	9.7	6.45552	0.31379	0.09996	0.49961	10.3
	5	11.2	6.45760	0.31402	0.10000	0.40028	11.8	10.3	6.45620	0.31373	0.10002	0.49901	10.8
	6	11.8	6.44905	0.31353	0.09998	0.39980	12.3	10.8	6.44840	0.31338	0.09973	0.49900	11.2
	7	12.3	6.45783	0.31384	0.09993	0.39958	12.7	11.2	6.44969	0.31336	0.09992	0.49874	11.5
	8	12.7	6.44989	0.31350	0.09993	0.39942	13	11.5	6.44755	0.31319	0.09985	0.49825	11.7
	9	13	6.44457	0.31317	0.09994	0.39878	13.3	11.7	6.44249	0.31310	0.10000	0.49854	11.9
	10	13.3	6.44854	0.31336	0.09966	0.39885		11.9	6.43714	0.31282	0.09962	0.49811	

Table 8: (continued) Estimates of the parameters, and real and estimated first-passage-times through $S = 6 \cdot 10^8$ for $h_k(t) = \gamma(k - 1/t)$ $(k = 1, \ldots, 10)$ and $\alpha = 6.46$, $\beta = 0.314$.

		$\gamma = .1$						$\gamma = .2$						$\gamma = .3$					
σ	k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	$\widehat{\gamma}$	τ'_k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	$\widehat{\gamma}$	τ'_k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	$\widehat{\gamma}$	τ'_k
0.01	0	0	6.45154	0.31358	0.00999		5.6	0	6.45267	0.31364	0.01001		5.6	0	6.45961	0.31398	0.00998		5.6
	1	5.6	6.45429	0.31372	0.01000	0.09992	9.4	5.6	6.45334	0.31366	0.00999	0.19945	8.6	5.6	6.45432	0.31371	0.00999	0.29950	8
	2	9.4	6.45749	0.31387	0.01000	0.09993	12.4	8.6	6.45872	0.31393	0.01000	0.19985	10.7	8.0	6.45503	0.31376	0.01000	0.29974	9.6
	3	12.4	6.45949	0.31398	0.01002	0.10005	14.9	10.7	6.45794	0.31390	0.00999	0.19996	12.3	9.6	6.45463	0.31373	0.00999	0.29966	10.8
	4	14.9	6.45971	0.31398	0.01000	0.09996	17.0	12.3	6.45654	0.31383	0.00999	0.19990	13.6	10.8	6.45310	0.31364	0.01000	0.29955	11.7
	5	17	6.45977	0.31398	0.01000	0.09996	18.8	13.6	6.45473	0.31373	0.00998	0.19980	14.7	11.7	6.44879	0.31342	0.01000	0.29932	12.5
	6	18.8	6.45829	0.31391	0.01000	0.09998	20.4	14.7	6.45254	0.31360	0.00997	0.19966	15.6	12.5	6.44772	0.31336	0.00998	0.29924	13.1
	7	20.4	6.45790	0.31389	0.00998	0.09997	21.8	15.6	6.45081	0.31352	0.00998	0.19963	16.4	13.1	6.44194	0.31306	0.01001	0.29896	13.6
	8	21.8	6.45642	0.31382	0.01000	0.09993	23.0	16.4	6.44986	0.31346	0.01000	0.19956	17.1	13.6	6.43649	0.31276	0.00999	0.29862	14
	9	23	6.45581	0.31378	0.00998	0.09993	24.1	17.1	6.44575	0.31325	0.00998	0.19943	17.7	14.0	6.43063	0.31245	0.01002	0.29831	14.4
	10	24.1	6.45521	0.31374	0.00999	0.09989		17.7	6.44254	0.31307	0.00998	0.19928		14.4	6.42461	0.31211	0.01004	0.29794	
0.05	0	0	6.33081	0.30765	0.04997		5.7	0	6.31380	0.30681	0.04996		5.7	0	6.32035	0.30715	0.04993		5.7
	1	5.6	6.40056	0.31101	0.05005	0.09789	9.5	5.6	6.43053	0.31252	0.05002	0.19796	8.6	5.6	6.43383	0.31264	0.05004	0.29702	8.1
	2	9.4	6.43235	0.31257	0.05000	0.09895	12.5	8.6	6.43112	0.31254	0.05006	0.19889	10.7	8.0	6.44469	0.31324	0.05003	0.29922	9.6
	3	12.4	6.45639	0.31380	0.05003	0.09983	14.9	10.7	6.45317	0.31366	0.05003	0.19960	12.3	9.6	6.44952	0.31343	0.04995	0.29897	10.8
	4	14.9	6.44745	0.31336	0.05014	0.09961	17.0	12.3	6.44409	0.31320	0.04996	0.19945	13.6	10.8	6.45128	0.31356	0.04998	0.29953	11.8
	5	17	6.44866	0.31342	0.04997	0.09978	18.8	13.6	6.45673	0.31385	0.05004	0.19983	14.7	11.7	6.44688	0.31333	0.04998	0.29923	12.5
	6	18.8	6.44341	0.31315	0.04994	0.09970	20.4	14.7	6.44700	0.31333	0.04991	0.19948	15.6	12.5	6.44767	0.31338	0.04996	0.29935	13.1
	7	20.4	6.44843	0.31339	0.04999	0.09974	21.8	15.6	6.44733	0.31333	0.05000	0.19947	16.4	13.1	6.44210	0.31312	0.04987	0.29910	13.6
	8	21.8	6.44910	0.31342	0.04993	0.09979	23.0	16.4	6.44730	0.31336	0.04994	0.19957	17.1	13.6	6.43755	0.31277	0.04991	0.29852	14
	9	23	6.45008	0.31344	0.04991	0.09970	24.1	17.1	6.44757	0.31337	0.04986	0.19954	17.7	14.0	6.43226	0.31253	0.04994	0.29840	14.4
	10	24.1	6.45391	0.31367	0.04998	0.09986		17.7	6.43876	0.31286	0.04986	0.19920		14.4	6.42627	0.31217	0.04990	0.29796	
0.1	0	0	5.93060	0.28799	0.10002		5.9	0	5.93012	0.28795	0.10001		5.9	0.0	5.93379	0.28817	0.09996		5.8
	1	5.5	6.32398	0.30712	0.09997	0.09378	9.4	5.5	6.34179	0.30795	0.10006	0.19233	8.5	5.5	6.42215	0.31201	0.09993	0.29554	8
	2	9.3	6.35873	0.30886	0.09996	0.09729	12.4	8.5	6.42770	0.31230	0.09973	0.19766	10.6	7.9	6.42230	0.31209	0.09978	0.29795	9.6
	3	12.4	6.38295	0.30996	0.10005	0.09774	14.9	10.6	6.42444	0.31219	0.10001	0.19856	12.3	9.5	6.42535	0.31221	0.10005	0.29808	10.7
	4	14.9	6.40965	0.31142	0.10005	0.09925	17.0	12.3	6.44181	0.31303	0.09983	0.19946	13.6	10.7	6.44973	0.31349	0.09986	0.29956	11.7
	5	17	6.42856	0.31234	0.09996	0.09929	18.8	13.6	6.43962	0.31292	0.10001	0.19913	14.7	11.7	6.45166	0.31354	0.09993	0.29934	12.5
	6	18.8	6.42080	0.31187	0.09986	0.09889	20.4	14.7	6.44403	0.31312	0.09994	0.19921	15.6	12.5	6.44741	0.31342	0.09983	0.29967	13.1
	7	20.4	6.43985	0.31297	0.09984	0.09965	21.8	15.6	6.43791	0.31283	0.09977	0.19910	16.4	13.1	6.44612	0.31325	0.09991	0.29904	13.6
	8	21.8	6.43973	0.31294	0.10005	0.09974	23.1	16.4	6.43284	0.31258	0.10001	0.19907	17.1	13.6	6.42846	0.31237	0.09955	0.29842	14.1
	9	23	6.44170	0.31302	0.09995	0.09982	24.1	17.1	6.43051	0.31242	0.09984	0.19885	17.7	14.0	6.43044	0.31243	0.09941	0.29828	14.4
	10	24.1	6.42333	0.31203	0.09983	0.09932		17.7	6.44231	0.31301	0.09969	0.19916		14.4	6.42297	0.31206	0.09947	0.29793	

Table 9: Estimates of the parameters, and real and estimated first-passage-times through $S = 6 \cdot 10^8$ for $h_k(t) = \gamma(k + 1/t)$ $(k = 1, \ldots, 10)$ and $\alpha = 6.46$, $\beta = 0.314$.

		$\gamma = .4$						$\gamma = .5$					
σ	k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	$\widehat{\gamma}$	τ'_k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	$\widehat{\gamma}$	τ'_k
0.01	0	0	6.45190	0.31360	0.00998		5.6	0	6.45342	0.31368	0.00999		5.6
	1	5.6	6.45608	0.31380	0.00999	0.39954	7.7	5.6	6.45673	0.31384	0.01001	0.49955	7.4
	2	7.7	6.45749	0.31388	0.01000	0.39974	9	7.4	6.45582	0.31379	0.00999	0.49961	8.5
	3	9.0	6.45701	0.31386	0.01000	0.39985	10	8.5	6.45706	0.31385	0.01000	0.49967	9.3
	4	10.0	6.45671	0.31383	0.00998	0.39974	10.7	9.3	6.45539	0.31377	0.00999	0.49958	9.9
	5	10.7	6.45458	0.31372	0.00999	0.39957	11.3	9.9	6.45289	0.31363	0.00997	0.49933	10.4
	6	11.3	6.45349	0.31366	0.01000	0.39950	11.8	10.4	6.45045	0.31350	0.00999	0.49910	10.8
	7	11.8	6.45099	0.31353	0.00998	0.39932	12.2	10.8	6.44689	0.31330	0.00999	0.49875	11.1
	8	12.2	6.44892	0.31341	0.00998	0.39915	12.5	11.1	6.44362	0.31313	0.01000	0.49847	11.3
	9	12.5	6.44633	0.31327	0.00998	0.39896	12.8	11.3	6.44013	0.31294	0.01001	0.49814	11.5
	10	12.8	6.44323	0.31311	0.00999	0.39876		11.5	6.43663	0.31274	0.01002	0.49782	
0.05	0	0	6.30572	0.30643	0.04993		5.7	0	6.32391	0.30732	0.04999		5.7
	1	5.6	6.45150	0.31358	0.04999	0.39938	7.8	5.6	6.45686	0.31386	0.04994	0.49958	7.5
	2	7.7	6.46424	0.31425	0.04998	0.40048	9.1	7.4	6.44215	0.31308	0.04999	0.49827	8.6
	3	9.0	6.45509	0.31375	0.05004	0.39968	10.1	8.5	6.45753	0.31385	0.04998	0.49946	9.4
	4	10.0	6.46080	0.31404	0.05001	0.39990	10.8	9.3	6.45449	0.31369	0.04996	0.49934	10
	5	10.7	6.45748	0.31388	0.05001	0.39984	11.4	9.9	6.45535	0.31376	0.05002	0.49956	10.5
	6	11.3	6.45393	0.31373	0.04996	0.39979	11.9	10.4	6.44923	0.31349	0.04998	0.49930	10.9
	7	11.8	6.45254	0.31363	0.04994	0.39950	12.3	10.8	6.44453	0.31311	0.05000	0.49823	11.2
	8	12.2	6.44823	0.31337	0.04992	0.39901	12.6	11.1	6.44611	0.31324	0.04992	0.49861	11.4
	9	12.5	6.44276	0.31307	0.04995	0.39866	12.9	11.3	6.43666	0.31277	0.04991	0.49789	11.6
	10	12.8	6.44256	0.31306	0.04993	0.39866		11.5	6.43472	0.31264	0.04988	0.49767	
0.1	0	0	5.93139	0.28804	0.10006		5.9	0	5.91030	0.28699	0.09994		5.9
	1	5.5	6.43175	0.31256	0.10005	0.39713	8	5.5	6.44549	0.31329	0.10004	0.49756	7.7
	2	7.6	6.43369	0.31263	0.09988	0.39780	9.3	7.3	6.45416	0.31370	0.09995	0.49946	8.8
	3	8.9	6.46111	0.31407	0.09996	0.39984	10.3	8.4	6.43016	0.31248	0.09996	0.49747	9.6
	4	9.9	6.45753	0.31387	0.10006	0.39992	11	9.2	6.44227	0.31310	0.09989	0.49868	10.2
	5	10.6	6.45266	0.31362	0.09988	0.39948	11.6	9.8	6.45350	0.31371	0.09991	0.49981	10.7
	6	11.2	6.45409	0.31381	0.10003	0.40013	12.1	10.3	6.44710	0.31324	0.09986	0.49833	11.1
	7	11.7	6.44758	0.31336	0.09997	0.39918	12.5	10.7	6.44353	0.31312	0.09986	0.49834	11.4
	8	12.1	6.45037	0.31346	0.09987	0.39922	12.8	11.0	6.44123	0.31288	0.09995	0.49776	11.6
	9	12.4	6.44185	0.31298	0.09993	0.39845	13.1	11.2	6.44620	0.31314	0.09999	0.49819	11.8
	10	12.7	6.44684	0.31324	0.09986	0.39874		11.4	6.43645	0.31267	0.09974	0.49757	

Table 10: (continued) Estimates of the parameters, and real and estimated first-passage-times through $S = 6 \cdot 10^8$ for $h_k(t) = \gamma(k + 1/t)$ $(k = 1, \ldots, 10)$ and $\alpha = 6.46$, $\beta = 0.314$.

		$\gamma = .1$					$\gamma = .2$					$\gamma = .3$				
σ	k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	τ'_k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	τ'_k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	τ'_k
0.01	0	0	6.45510	0.31376	0.01001	5.6	0	6.44917	0.31347	0.01002	5.6	0	6.45530	0.31377	0.01000	5.6
	1	5.6	6.45812	0.31390	0.00997	10.4	5.6	6.46374	0.31420	0.01001	9.9	5.6	6.46115	0.31403	0.01007	9.6
	2	10.5	6.45236	0.31360	0.01001	15.2	10	6.45487	0.31373	0.00994	14.2	9.7	6.45891	0.31396	0.00999	13.5
	3	15.2	6.46141	0.31409	0.01001	19.8	14.2	6.45984	0.31399	0.00999	18.3	13.6	6.46402	0.31422	0.01002	17.3
	4	19.9	6.45024	0.31351	0.01005	24.4	18.3	6.45344	0.31366	0.01000	22.3	17.4	6.45734	0.31385	0.01004	21
	5	24.5	6.45811	0.31391	0.00998	29	22.4	6.45495	0.31374	0.01004	26.3	21.1	6.46631	0.31431	0.01002	24.7
	6	29	6.45411	0.31369	0.00997	33.4	26.4	6.45354	0.31367	0.00990	30.3	24.7	6.45702	0.31385	0.01000	28.2
	7	33.5	6.46530	0.31427	0.00994	37.8	30.4	6.46116	0.31407	0.00997	34.2	28.3	6.46034	0.31401	0.01004	31.7
	8	37.9	6.45310	0.31365	0.00994	42.2	34.3	6.45962	0.31397	0.01001	38.1	31.8	6.47059	0.31452	0.00998	35.2
	9	42.3	6.46347	0.31417	0.00995	46.5	38.2	6.44725	0.31335	0.01000	41.9	35.3	6.45001	0.31349	0.01001	38.6
	10	46.6	6.45167	0.31358	0.01002		42	6.45626	0.31381	0.01003		38.7	6.46538	0.31427	0.00998	
0.05	0	0	6.25639	0.30405	0.04994	5.7	0	6.22701	0.30261	0.04994	5.7	0	6.24783	0.30364	0.04995	5.7
	1	5.6	6.41562	0.31165	0.04994	10.4	5.6	6.37931	0.30990	0.05002	9.9	5.6	6.35666	0.30866	0.05033	9.6
	2	10.4	6.34560	0.30817	0.05013	15.1	10	6.39403	0.31061	0.05017	14.2	9.7	6.31619	0.30666	0.05023	13.5
	3	15.1	6.36641	0.30919	0.04993	19.7	14.2	6.28693	0.30510	0.05008	18.3	13.6	6.35600	0.30858	0.05034	17.3
	4	19.7	6.36887	0.30928	0.05040	24.2	18.3	6.41469	0.31168	0.04988	22.3	17.4	6.37218	0.30948	0.05011	21
	5	24.3	6.36464	0.30910	0.04981	28.8	22.4	6.38944	0.31041	0.04987	26.3	21.1	6.35081	0.30836	0.04971	24.7
	6	28.8	6.39865	0.31084	0.04954	33.2	26.4	6.41629	0.31179	0.05010	30.3	24.7	6.32654	0.30717	0.05000	28.2
	7	33.3	6.43403	0.31258	0.04968	37.6	30.4	6.40203	0.31102	0.04997	34.2	28.3	6.36073	0.30888	0.04994	31.7
	8	37.7	6.33986	0.30776	0.04971	42	34.3	6.39217	0.31042	0.04984	38	31.8	6.36009	0.30882	0.04997	35.2
	9	42.1	6.32126	0.30684	0.04982	46.3	38.2	6.32749	0.30719	0.04953	41.9	35.3	6.31857	0.30674	0.05005	38.6
	10	46.4	6.36164	0.30894	0.04996		42	6.39625	0.31078	0.05006		38.7	6.33332	0.30753	0.05017	
0.1	0	0	5.61072	0.27245	0.09999	6.2	0	5.62472	0.27312	0.09996	6.2	0	5.65977	0.27483	0.09971	6.2
	1	5.5	6.10696	0.29603	0.09947	10.3	5.5	6.25492	0.30352	0.09978	9.9	5.5	6.03604	0.29218	0.09998	9.5
	2	10.3	5.97104	0.28898	0.09953	14.9	9.9	6.06554	0.29379	0.10001	14.1	9.6	6.07625	0.29442	0.10031	13.4
	3	15	6.00626	0.29080	0.09995	19.5	14.1	6.10820	0.29606	0.09948	18.2	13.5	6.04916	0.29294	0.10030	17.2
	4	19.6	6.06101	0.29351	0.09931	24	18.2	6.00903	0.29091	0.10049	22.2	17.3	6.15329	0.29817	0.09981	20.9
	5	24.2	6.15594	0.29844	0.09960	28.7	22.3	6.10969	0.29610	0.09978	26.2	21	6.20793	0.30092	0.10001	24.5
	6	28.7	6.00011	0.29039	0.09984	33.1	26.3	6.17533	0.29945	0.09950	30.1	24.6	6.07219	0.29418	0.09976	28.1
	7	33.2	6.09340	0.29536	0.09944	37.6	30.3	6.14169	0.29765	0.09981	34.2	28.2	6.09685	0.29543	0.09972	31.7
	8	37.6	6.01552	0.29137	0.09943	41.8	34.2	6.09431	0.29529	0.10027	38	31.7	6.12317	0.29676	0.10002	35.1
	9	42	6.04377	0.29251	0.10045	46.2	38.1	6.12663	0.29690	0.09999	41.9	35.2	6.04534	0.29270	0.09962	38.5
	10	46.3	6.04964	0.29301	0.09989		41.9	6.05152	0.29303	0.09941		38.6	6.10782	0.29587	0.09969	

Table 11: Estimates of the parameters and, and real and estimated first-passage-times through $S = 6 \cdot 10^8$ for $h_k(t) = \gamma[1 - (\tau_k/t)^k]$ $(k = 1, \dots, 10)$ and $\alpha = 6.46$, $\beta = 0.314$.

Conclusions

We propose a cancer growth model based on a time non homogeneous Gompertz diffusion process with jumps to study the effect of an intermittent therapy. We assume that each therapeutic application reduces the cancer size at a fixed level and produces an increase in the growth rate of the cancer cells. The rate increase is expressed via a time dependent function, $h_k(t)$, increasing with the number of applications k. The obtained stochastic process $X(t)$ is time non homogeneous being a combination of different non-homogeneous Gompertz processes, $X_k(t)$, that describe the phenomenon in each inter-jump interval. After the study of the main characteristics of $X(t)$, we focus on the estimation of the model.

Specifically we distinguish two situations: if the instants $(\tau_1, \tau_2, \ldots \tau_N)$ of therapeutical applications are known before that the experimentation or they are unknown priorly. In this second case we determine a strategy based on the FPT mean though a control threshold to chose τ_i. If the instants are priorly fixed, the informations of all involved processes are used to jointly estimate α, β, σ^2 and the functions $h_k(t)$; whereas when the instants are not established in advanced, we use the previous procedure, but it is iteratively applied after the determination of each therapeutic instant so that we can update the estimations at each step. Moreover, in both cases we consider two different situations: if $h_k(t)$ is known except for a parameter $\gamma > 0$ to be estimation and if $h_k(t)$ is completely unknown. This last case is specially interesting because of it mainly represents real situations, together with the case of unknown time instants of therapeutic application.

Extensively simulation studies, performed by using algorithms implemented with `R`, allow to conclude that the procedures provide good estimation of the true values and, as it is expected, the error increases as σ increases.

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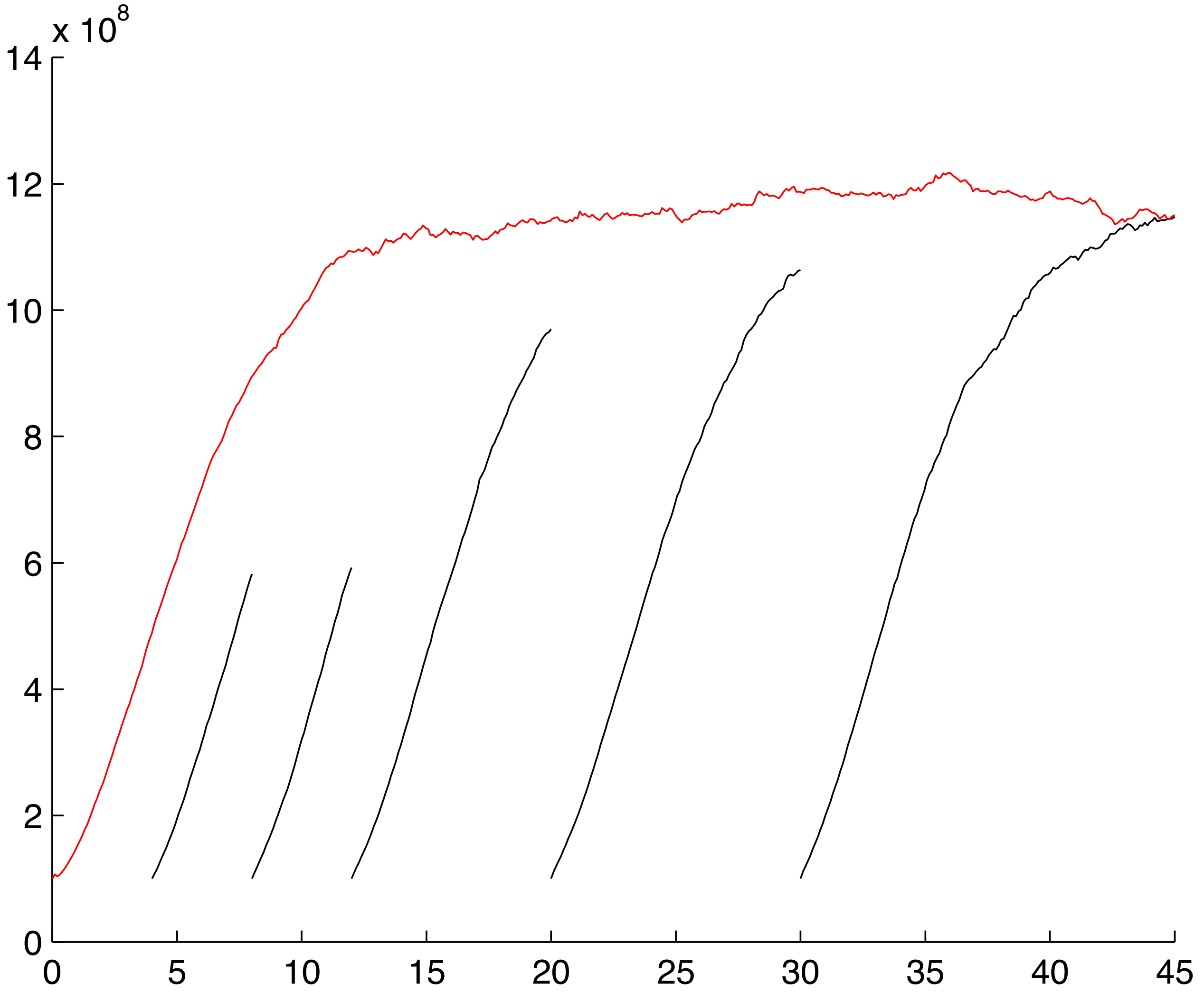
		$\gamma = .4$					$\gamma = .5$				
σ	k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	τ'_k	τ_k	$\widehat{\alpha}$	$\widehat{\beta}$	$\widehat{\sigma}$	τ'_k
0.01	0	0	6.45605	0.31381	0.01000	5.6	0	6.45399	0.31371	0.00998	5.6
	1	5.6	6.45466	0.31373	0.00994	9.4	5.6	6.45509	0.31374	0.01001	9.1
	2	9.4	6.45236	0.31360	0.01003	12.9	9.2	6.45563	0.31376	0.00995	12.5
	3	13	6.44846	0.31340	0.01001	16.4	12.6	6.45722	0.31386	0.00995	15.8
	4	16.5	6.46293	0.31413	0.01006	19.8	15.9	6.44617	0.31328	0.01005	19
	5	19.9	6.44642	0.31332	0.01002	23.2	19.1	6.46050	0.31403	0.00997	22.2
	6	23.2	6.46988	0.31450	0.01004	26.4	22.2	6.46532	0.31426	0.01002	25.1
	7	26.5	6.45160	0.31357	0.01000	29.7	25.2	6.46620	0.31431	0.01006	28.1
	8	29.7	6.43981	0.31297	0.00999	32.8	28.2	6.46572	0.31429	0.01003	31
	9	32.9	6.44764	0.31336	0.01003	35.9	31.1	6.45404	0.31369	0.01000	34
	10	36	6.47173	0.31461	0.00996		34	6.46580	0.31431	0.01003	
0.05	0	0	6.23802	0.30316	0.05008	5.7	0	6.20531	0.30153	0.04992	5.8
	1	5.6	6.36359	0.30910	0.04984	9.4	5.6	6.40388	0.31114	0.05007	9.1
	2	9.4	6.35466	0.30866	0.04984	12.9	9.2	6.39066	0.31050	0.05010	12.5
	3	13	6.44860	0.31342	0.04985	16.4	12.6	6.36026	0.30887	0.05013	15.8
	4	16.5	6.33804	0.30771	0.04994	19.8	15.9	6.38265	0.31001	0.05010	19
	5	19.9	6.40750	0.31134	0.04998	23.2	19.1	6.41111	0.31150	0.05008	22.1
	6	23.2	6.29281	0.30547	0.05000	26.4	22.2	6.34697	0.30821	0.05026	25.2
	7	26.5	6.35181	0.30847	0.04988	29.6	25.2	6.34053	0.30788	0.05045	28.1
	8	29.7	6.40700	0.31139	0.05014	32.8	28.2	6.37038	0.30936	0.05018	31
	9	32.9	6.38814	0.31035	0.04999	35.9	31.1	6.42165	0.31205	0.04967	33.9
	10	36	6.37991	0.30995	0.04997		34	6.31765	0.30669	0.05008	
0.1	0	0	5.64001	0.27387	0.09972	6.2	0	5.65392	0.27456	0.09986	6.2
	1	5.5	6.03754	0.29248	0.09956	9.3	5.5	6.19615	0.30043	0.10003	9
	2	9.3	6.15078	0.29808	0.09933	12.8	9.1	6.06846	0.29394	0.10012	12.4
	3	12.9	6.01161	0.29100	0.09948	16.3	12.5	6.09925	0.29552	0.09997	15.7
	4	16.4	6.08699	0.29472	0.09961	19.7	15.8	6.14507	0.29792	0.09990	18.9
	5	19.8	6.07383	0.29424	0.09962	23.1	19	6.02979	0.29201	0.10006	22
	6	23.1	6.02149	0.29140	0.10007	26.3	22.1	6.17674	0.29950	0.10000	25.1
	7	26.4	6.02436	0.29169	0.09962	29.6	25.1	6.05982	0.29355	0.10019	28
	8	29.6	6.08830	0.29484	0.10061	32.7	28.1	6.05554	0.29324	0.09958	31
	9	32.8	6.07034	0.29427	0.10001	35.9	31	6.06891	0.29388	0.10062	33.8
	10	35.9	6.03297	0.29207	0.09958		33.9	5.97297	0.28906	0.09987	

Table 12: (continued) Estimates of the parameters, and real and estimated first-passage-times through $S = 6 \cdot 10^8$ for $h_k(t) = \gamma[1 - (\tau_k/t)^k]$ $(k = 1, \ldots, 10)$ and $\alpha = 6.46$, $\beta = 0.314$.

Highlights (for review)

- A non-homogeneous Gompertz process with jumps is built as model of tumor dynamics
- In real applications the instants of therapeutical application can be known or not
- The estimation of the model is developed in both cases.
- A strategy for obtaining optimal instants of therapeutical application is developed

Figure



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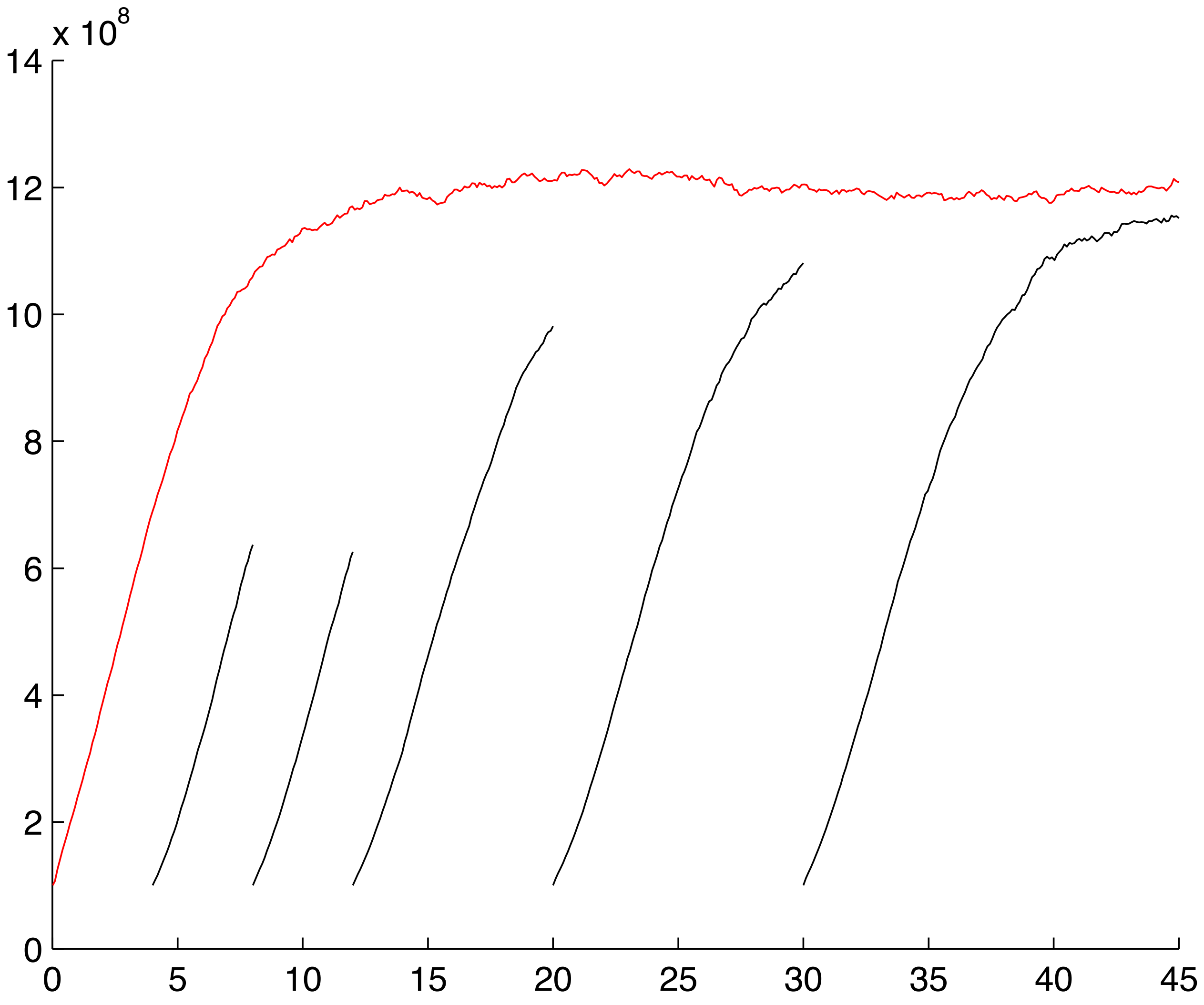

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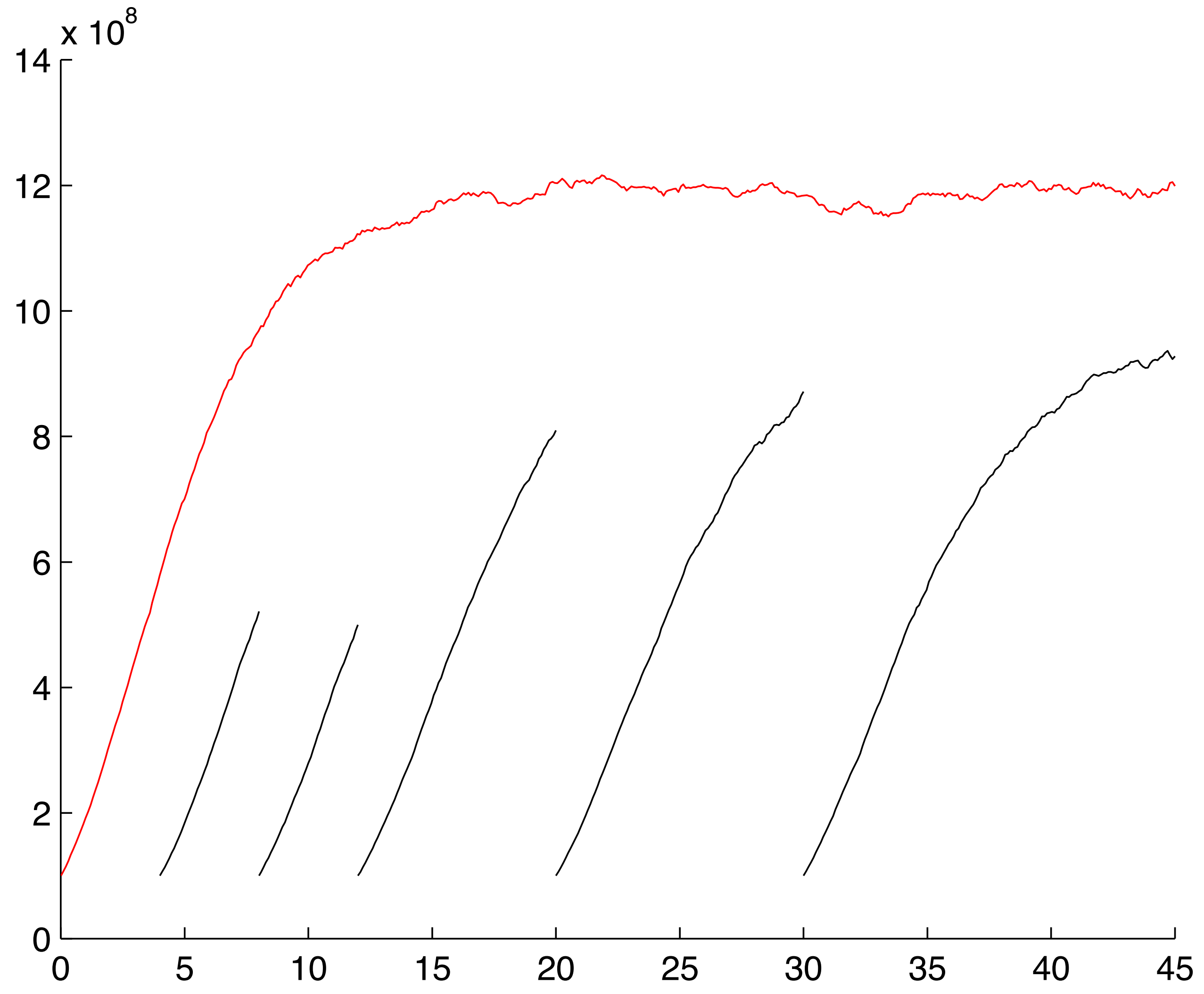

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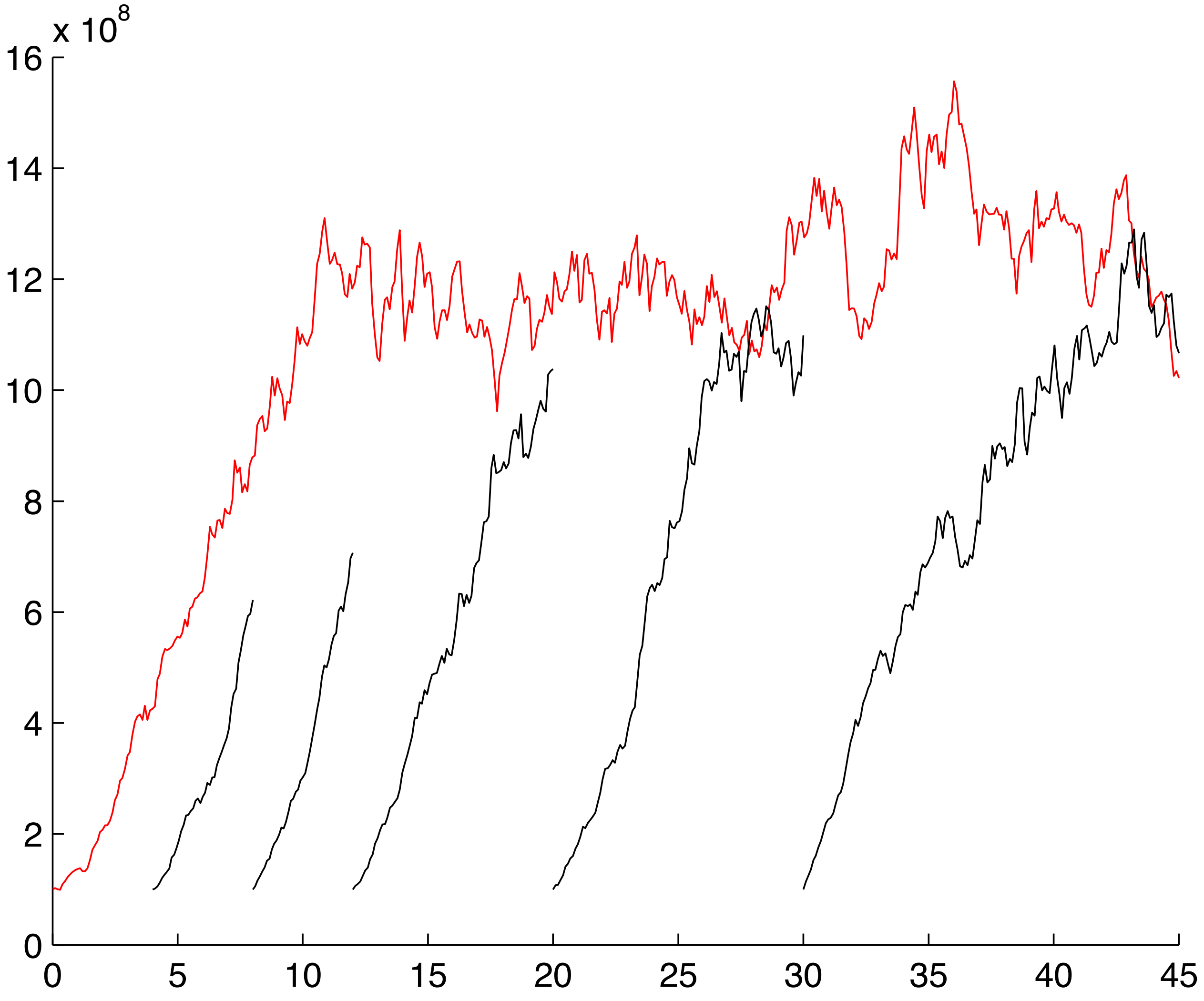

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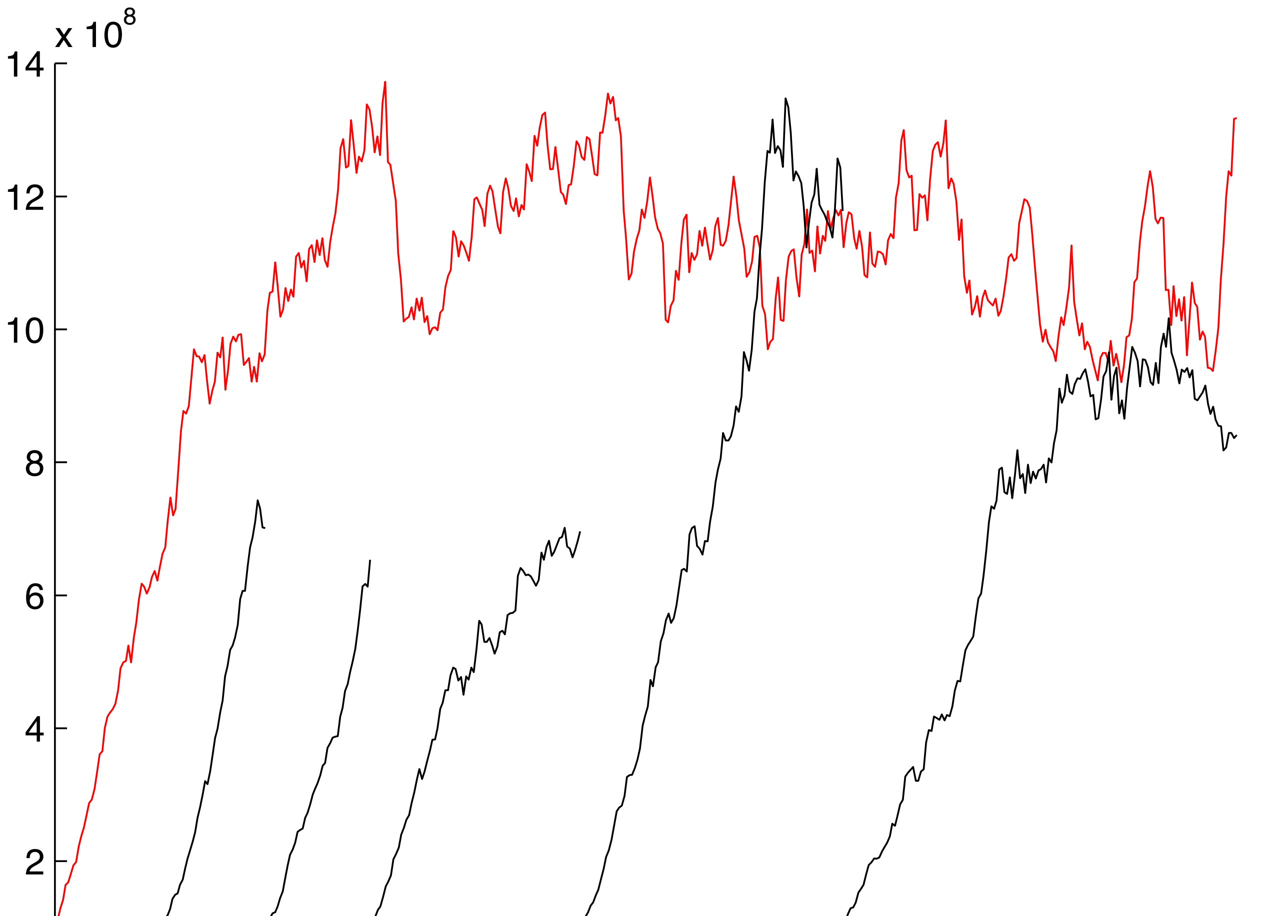

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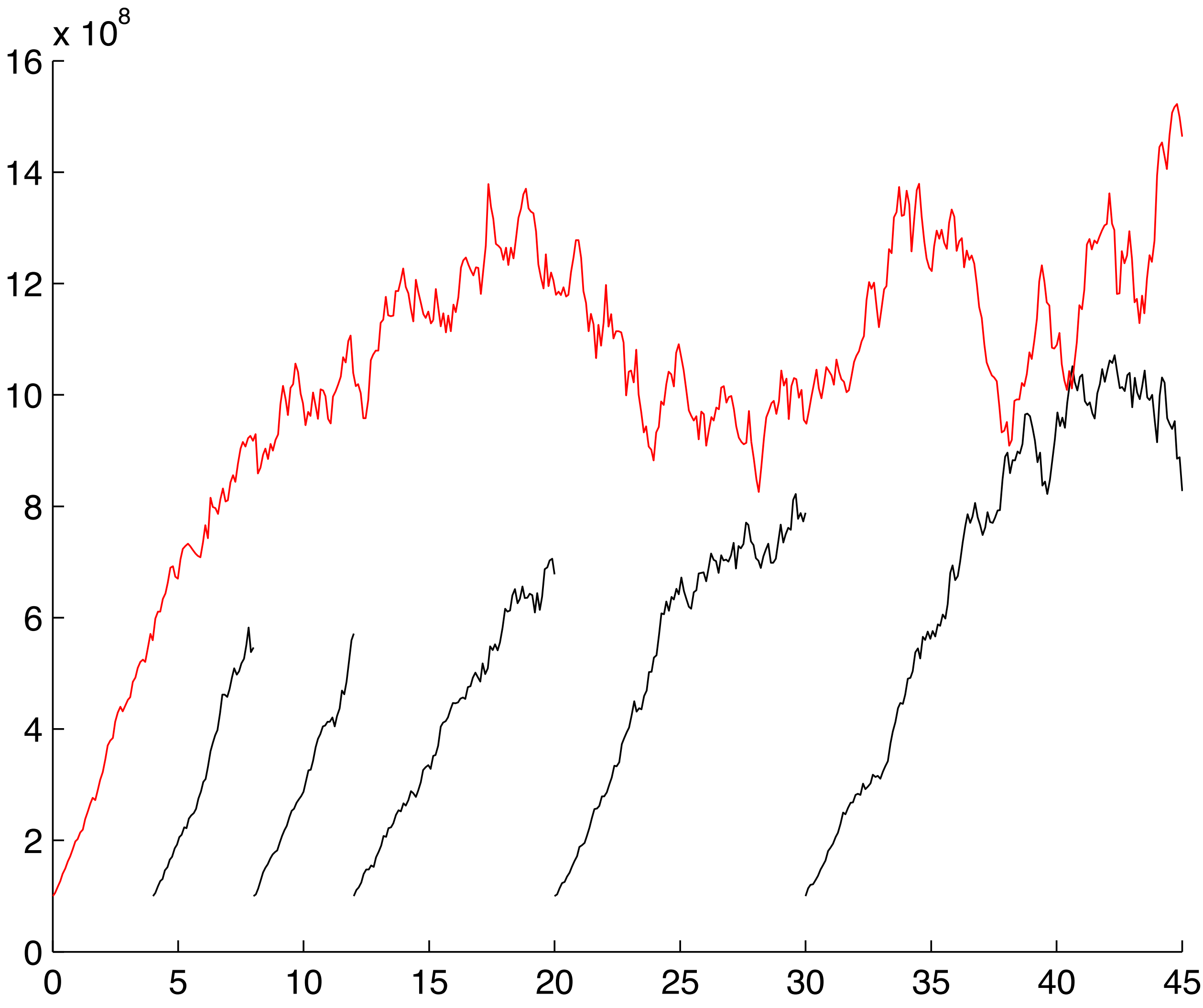

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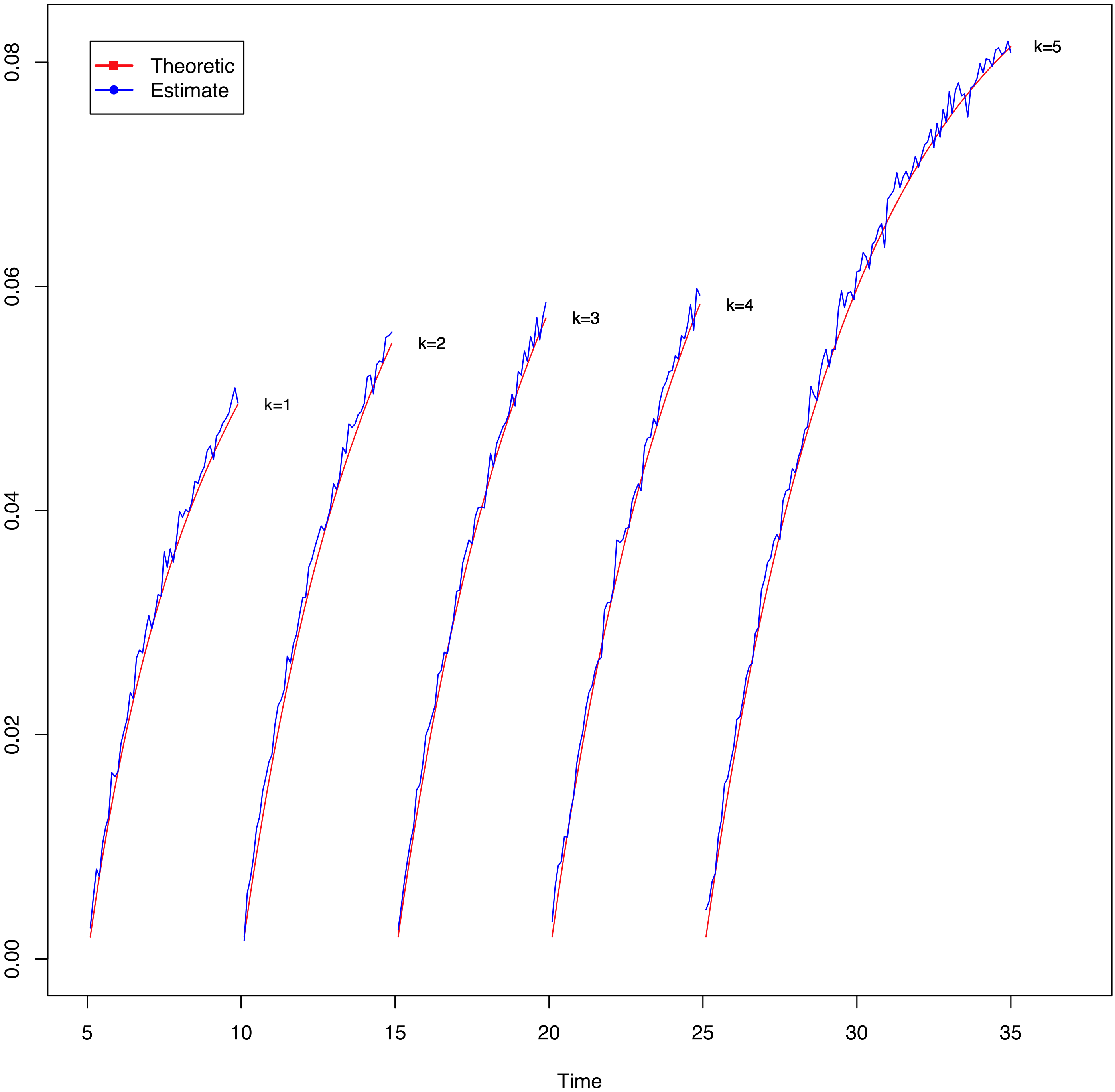
Theoretic
Estimate
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k=2
k=3
k=4
k=5
0.00
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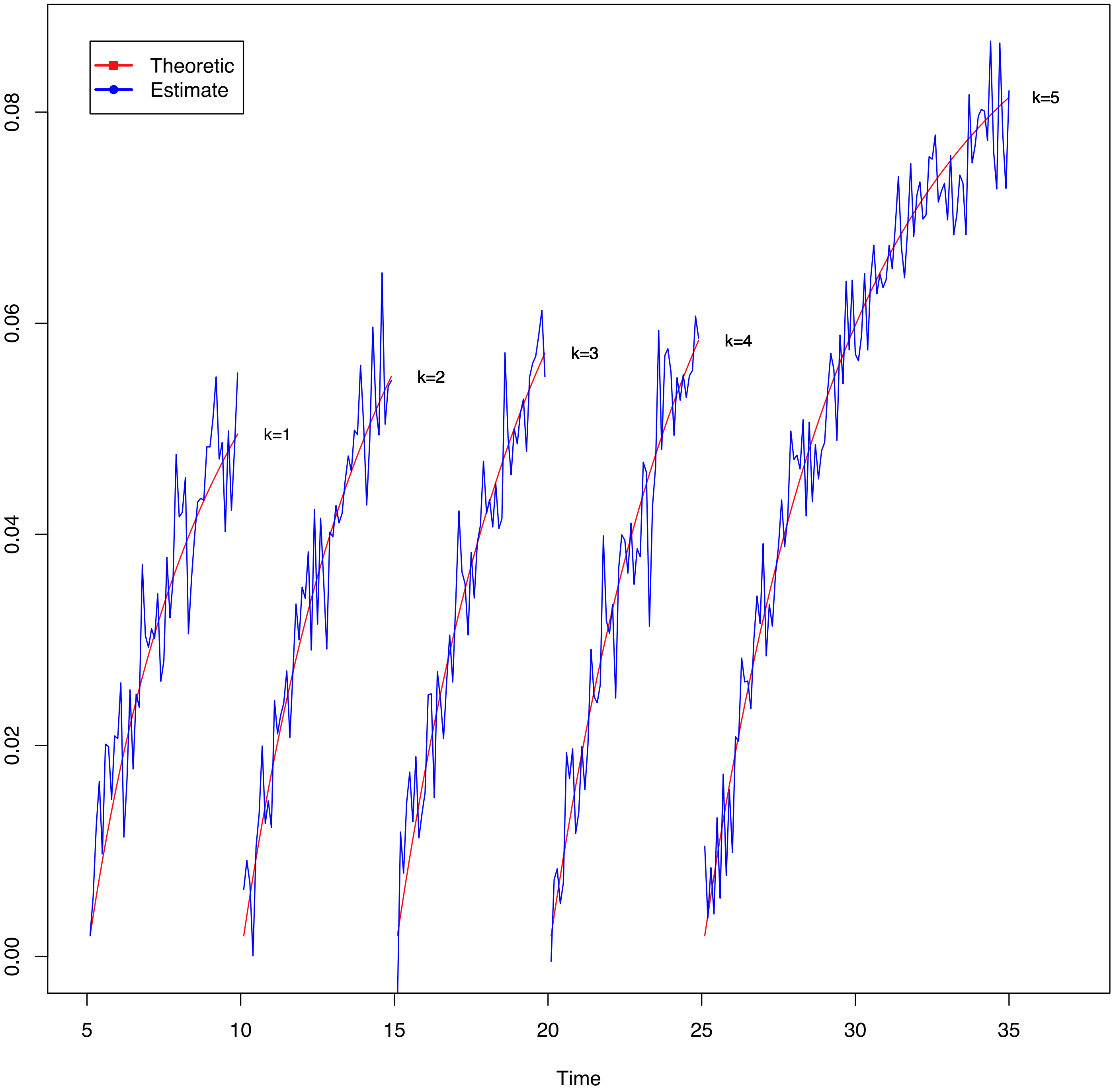
Time

Figure



Theoretic
Estimate
k=1
k=2
k=3
k=4
k=5
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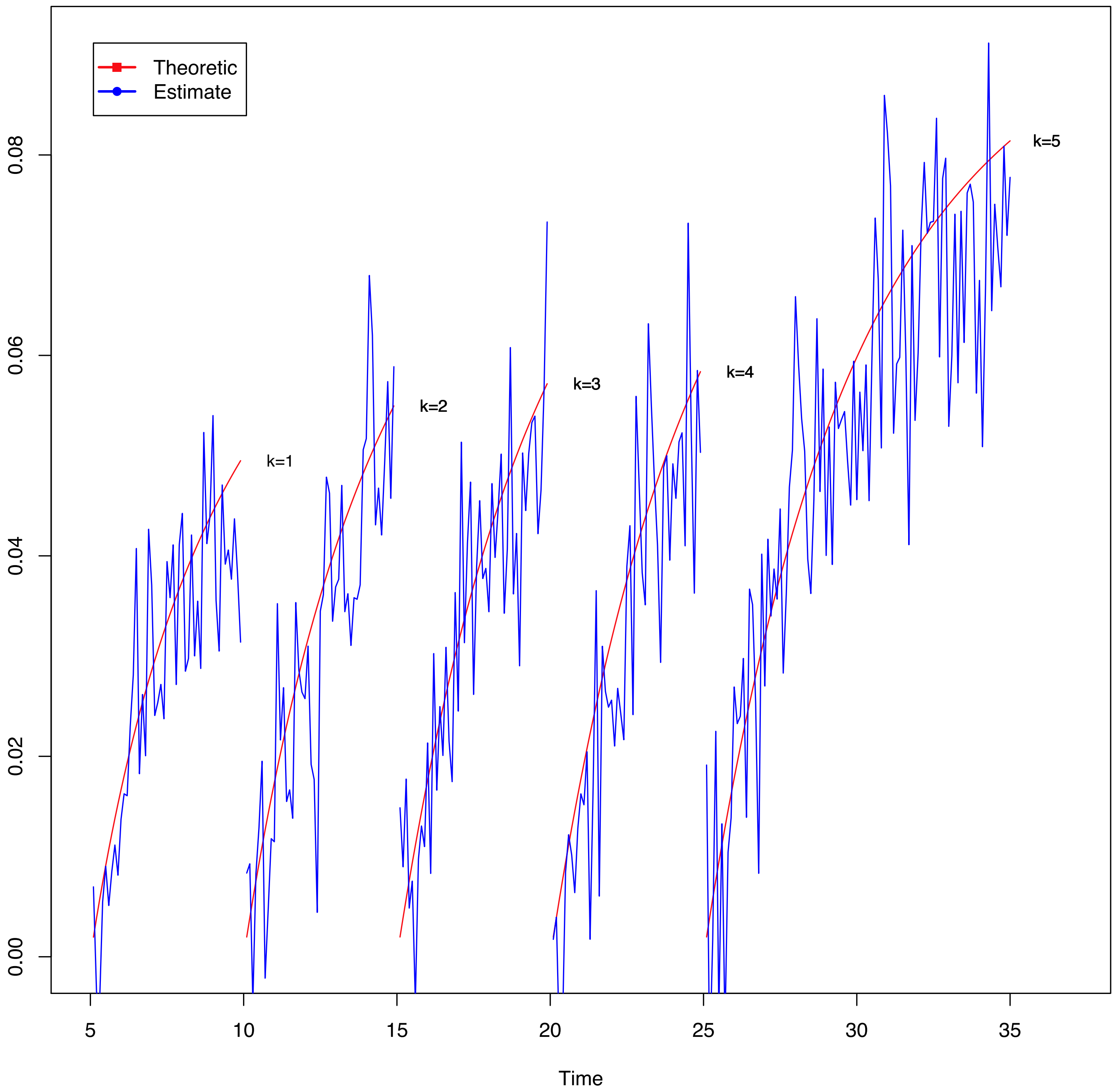
Time

Figure



Theoretic
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k=2
k=3
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k=5
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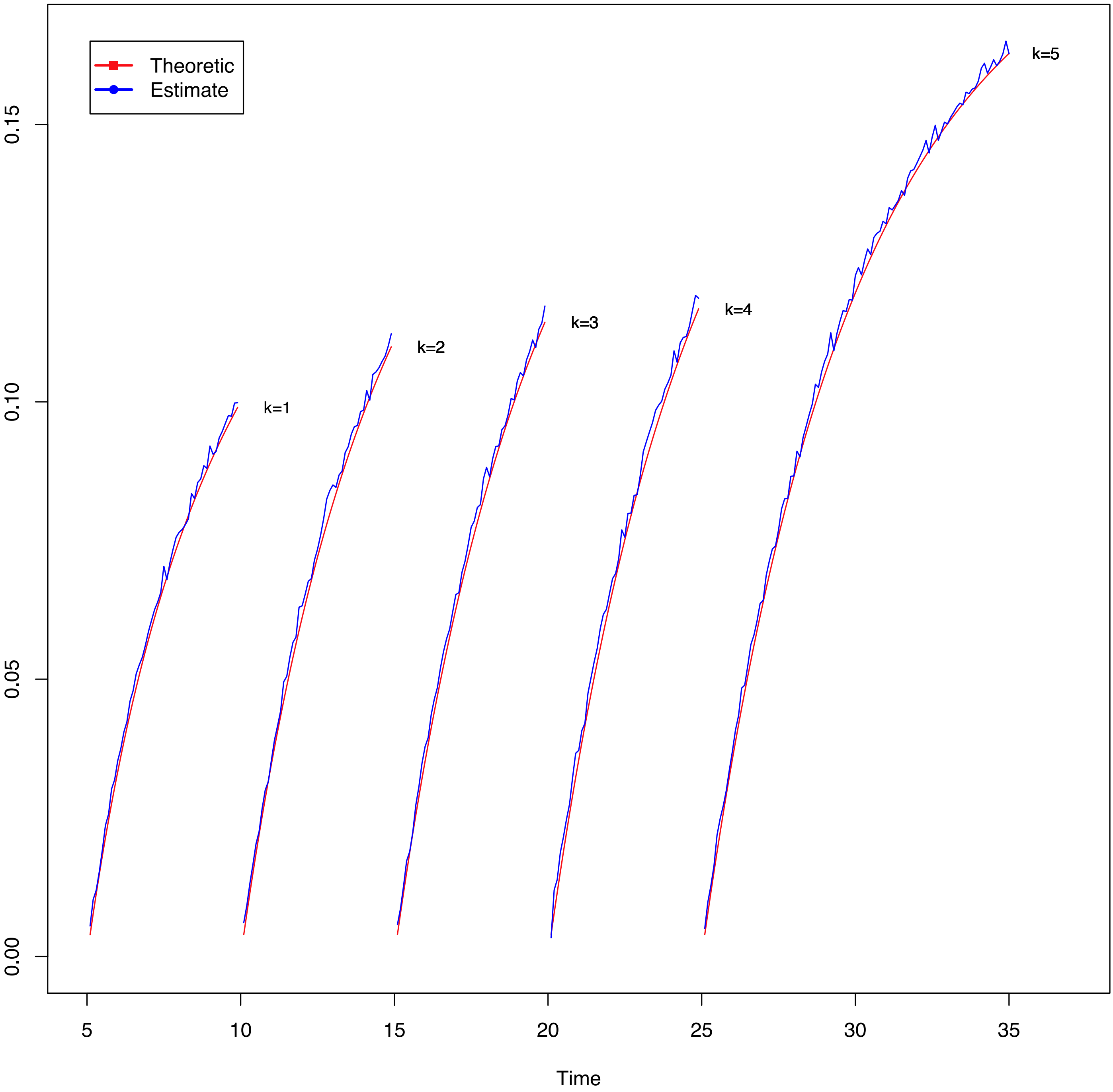
Time

Figure



Theoretic
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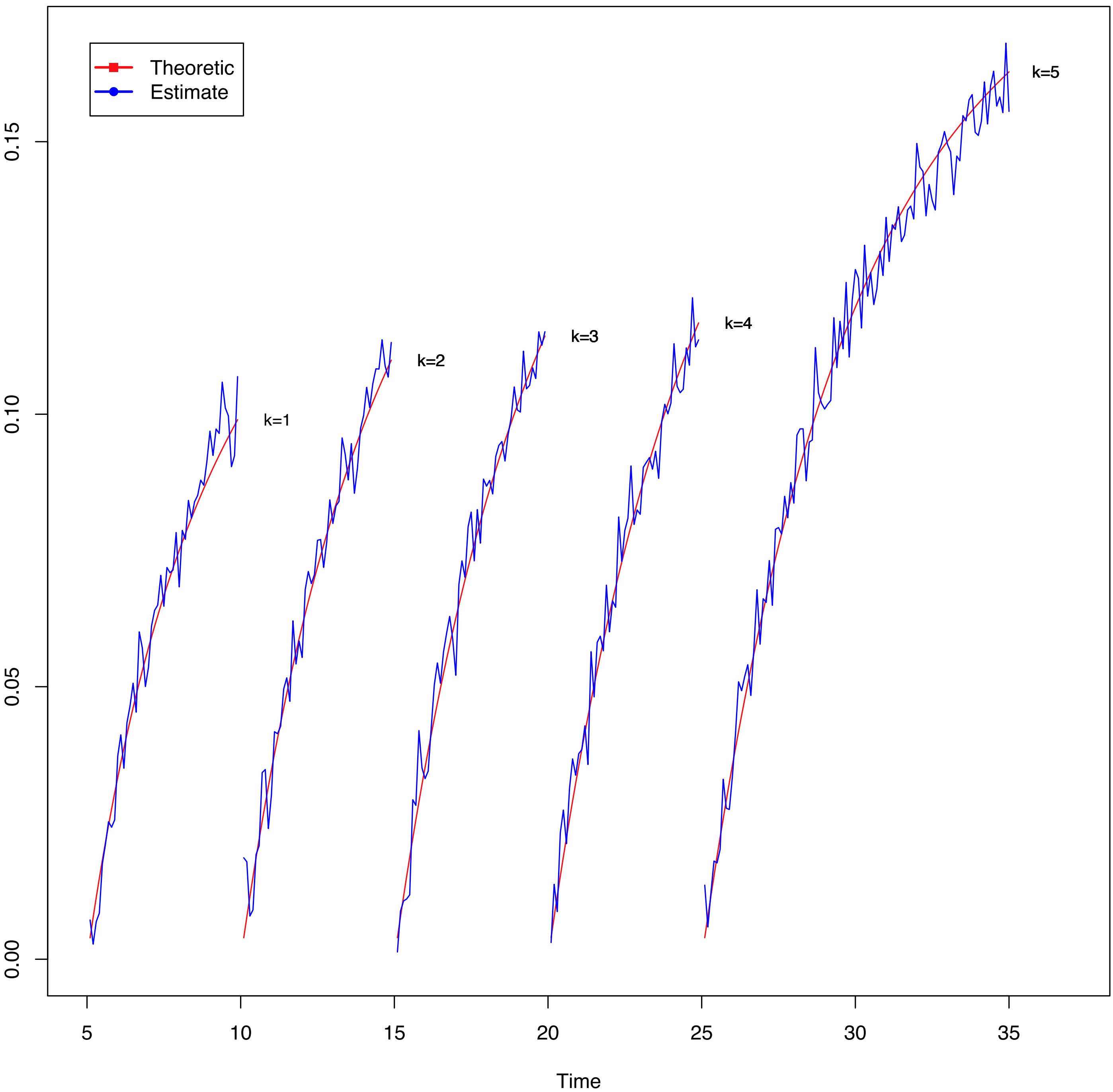
Time

Figure



Theoretic
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Time

Figure

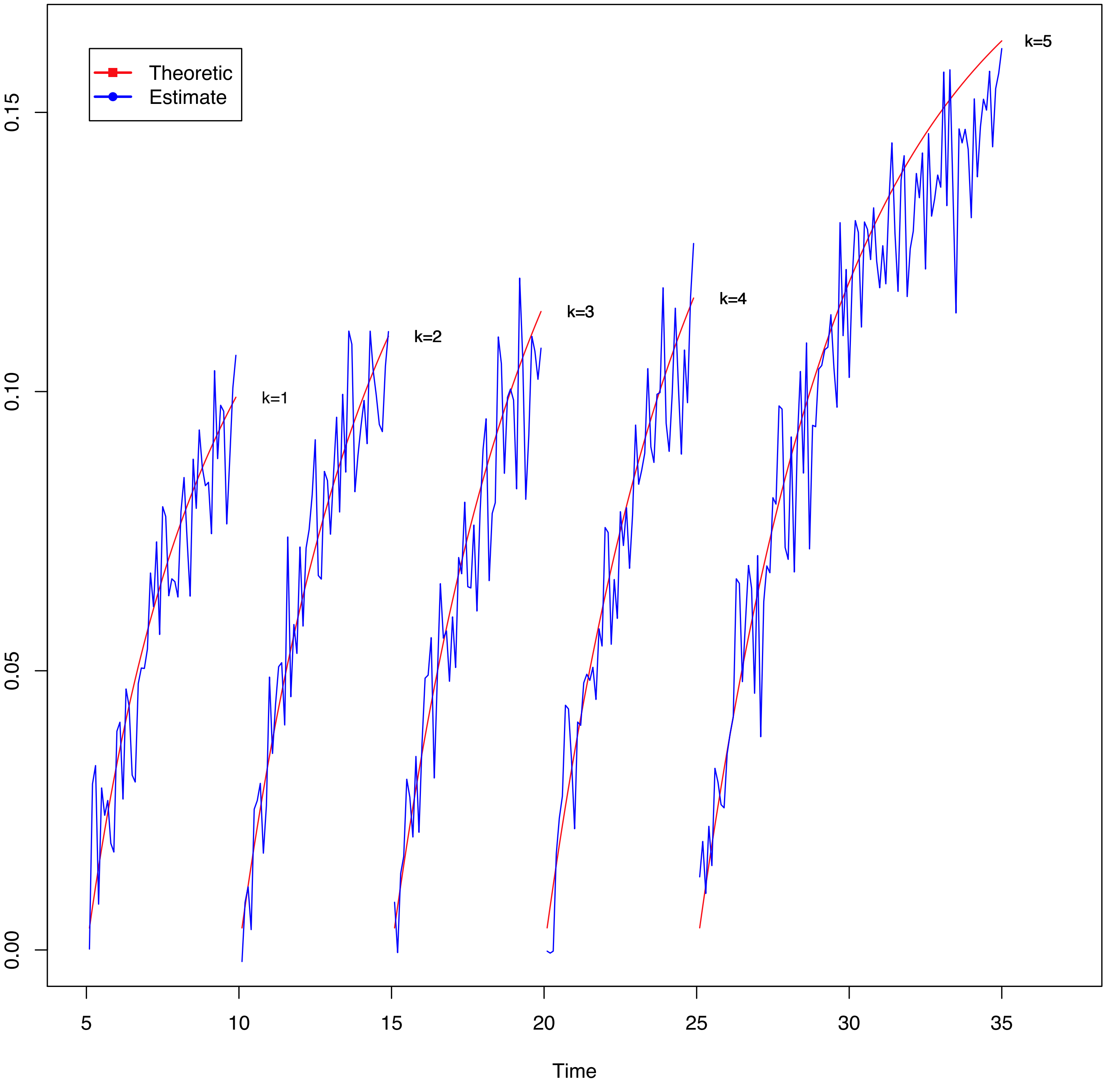
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Figure

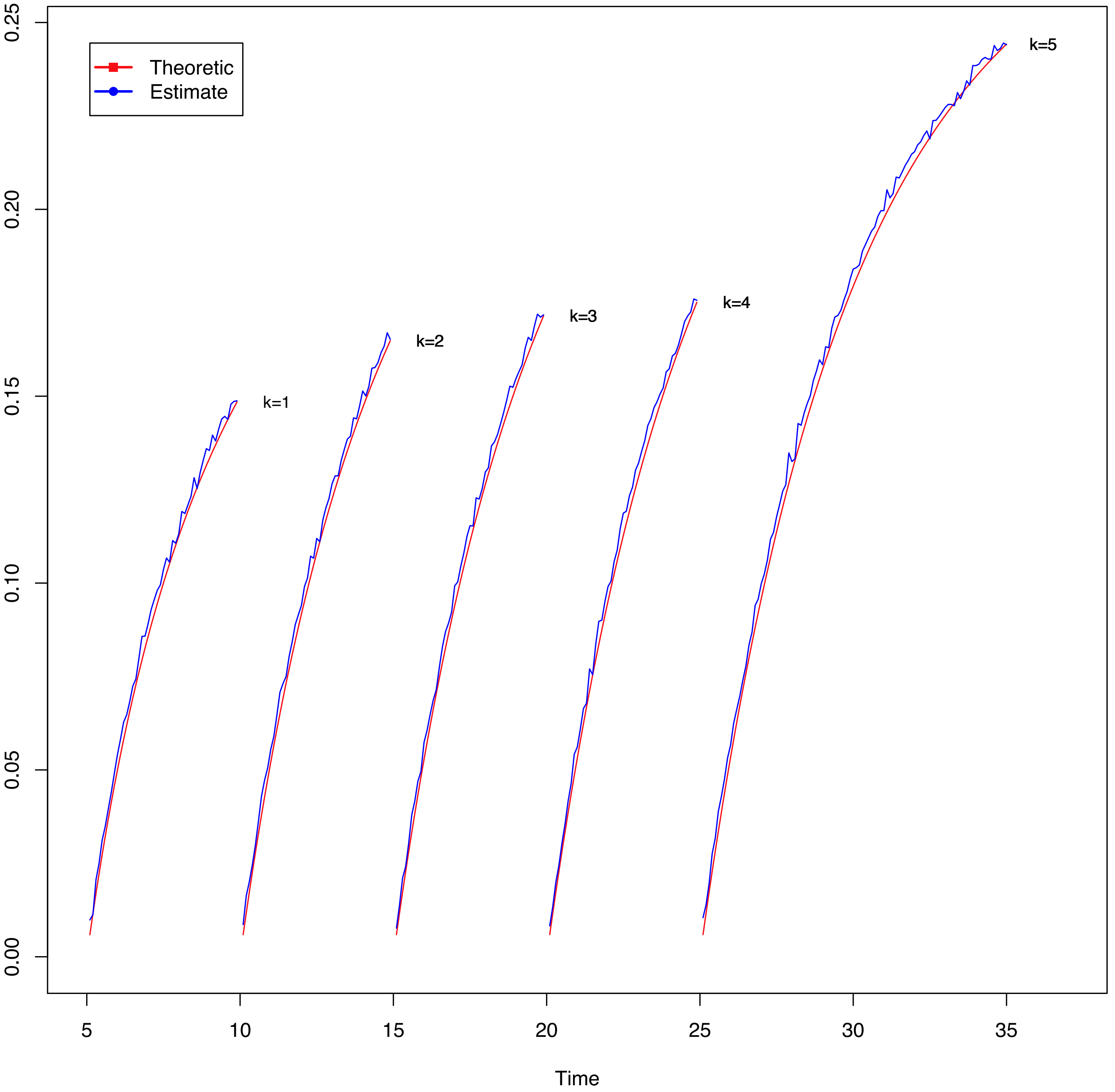

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Figure

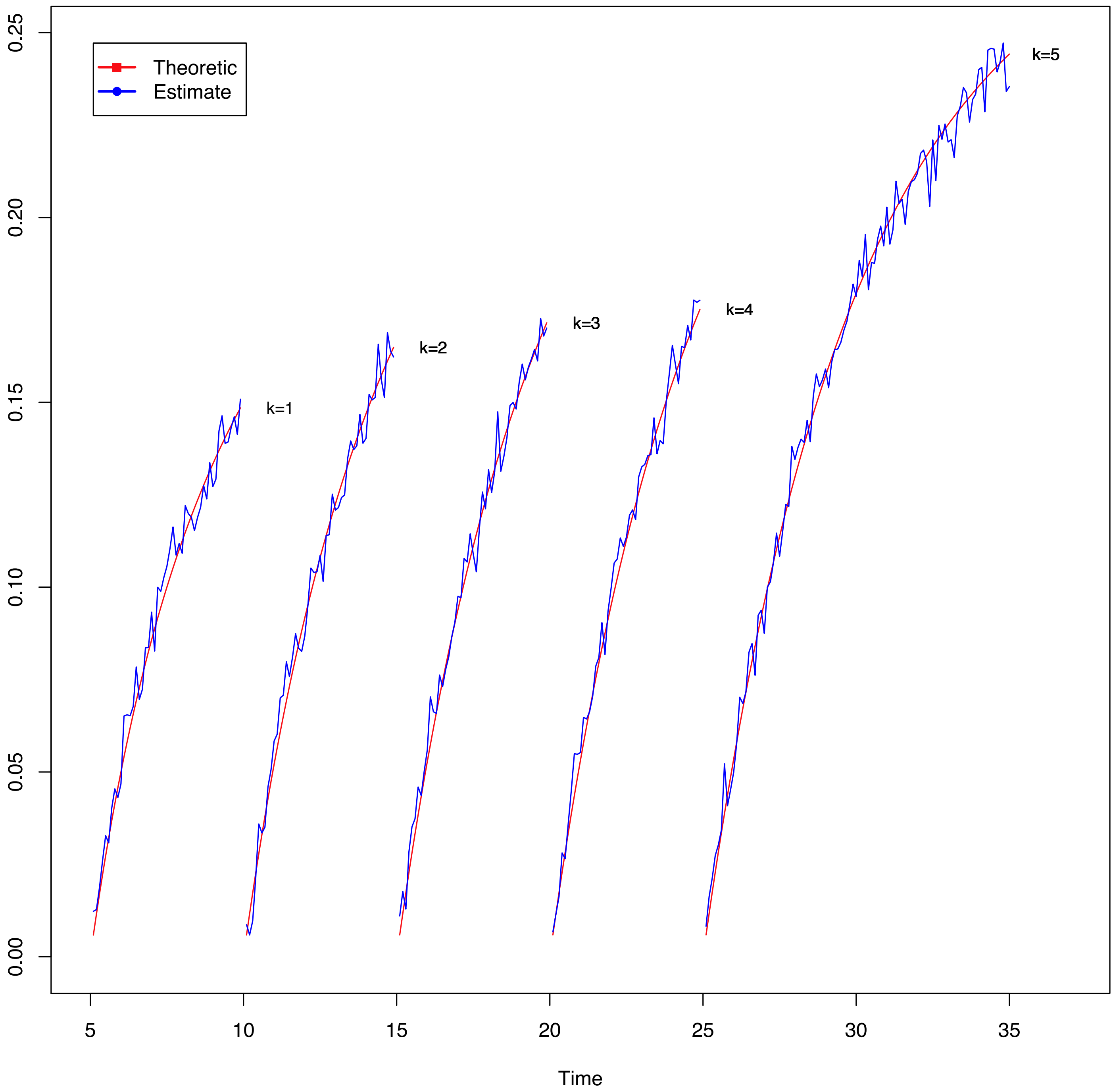

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Figure

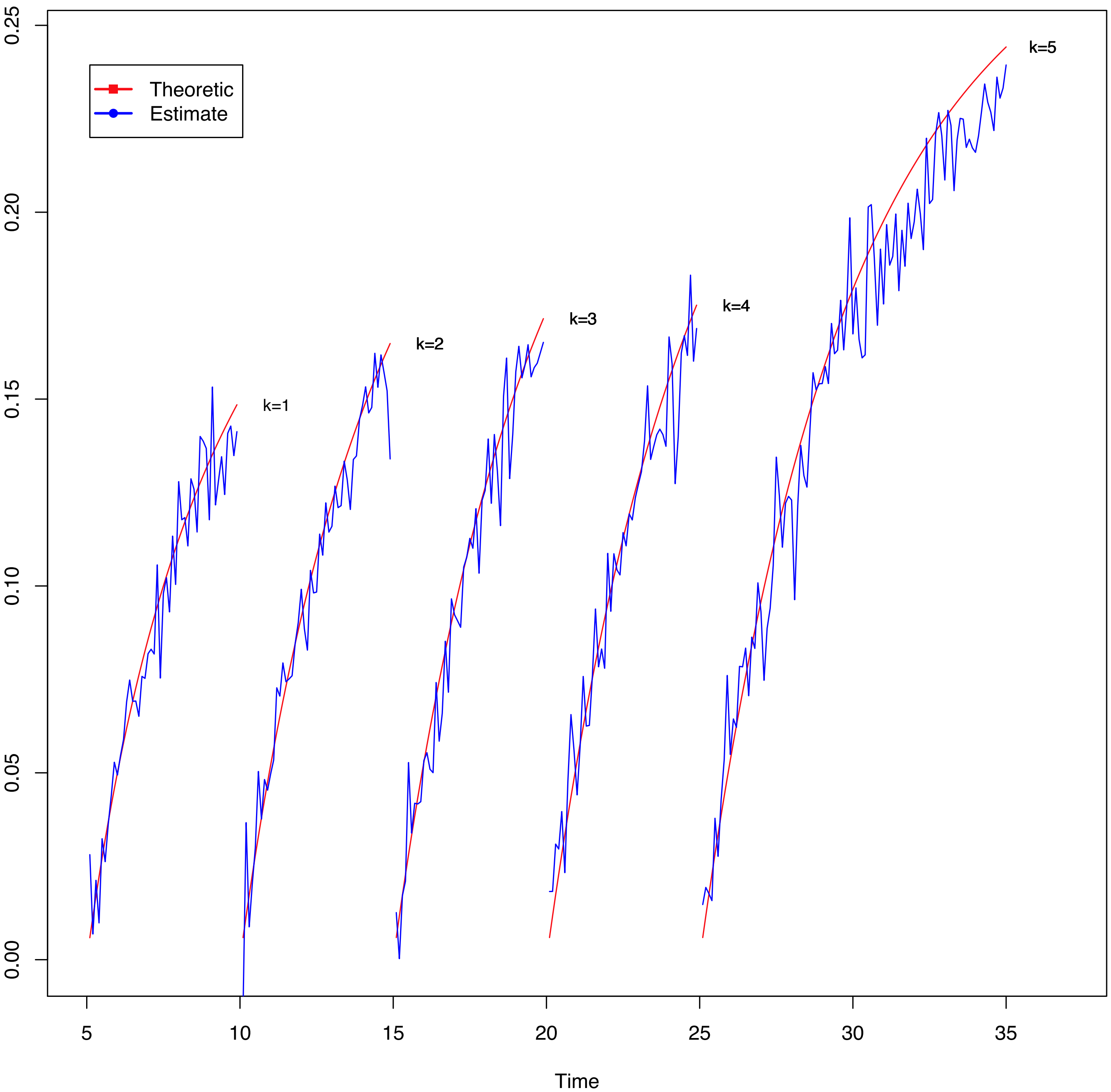

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Figure

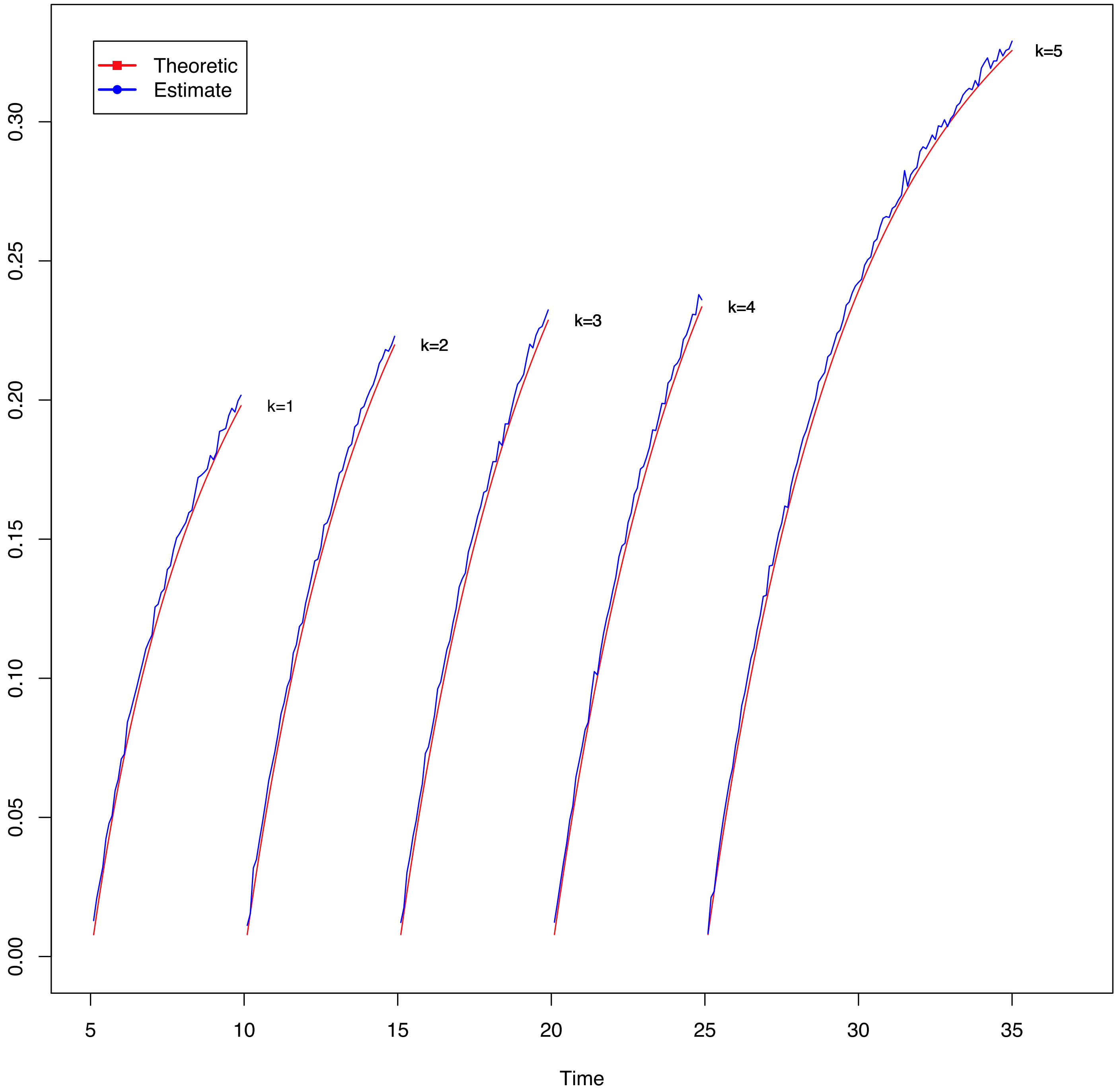
Theoretic
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Figure

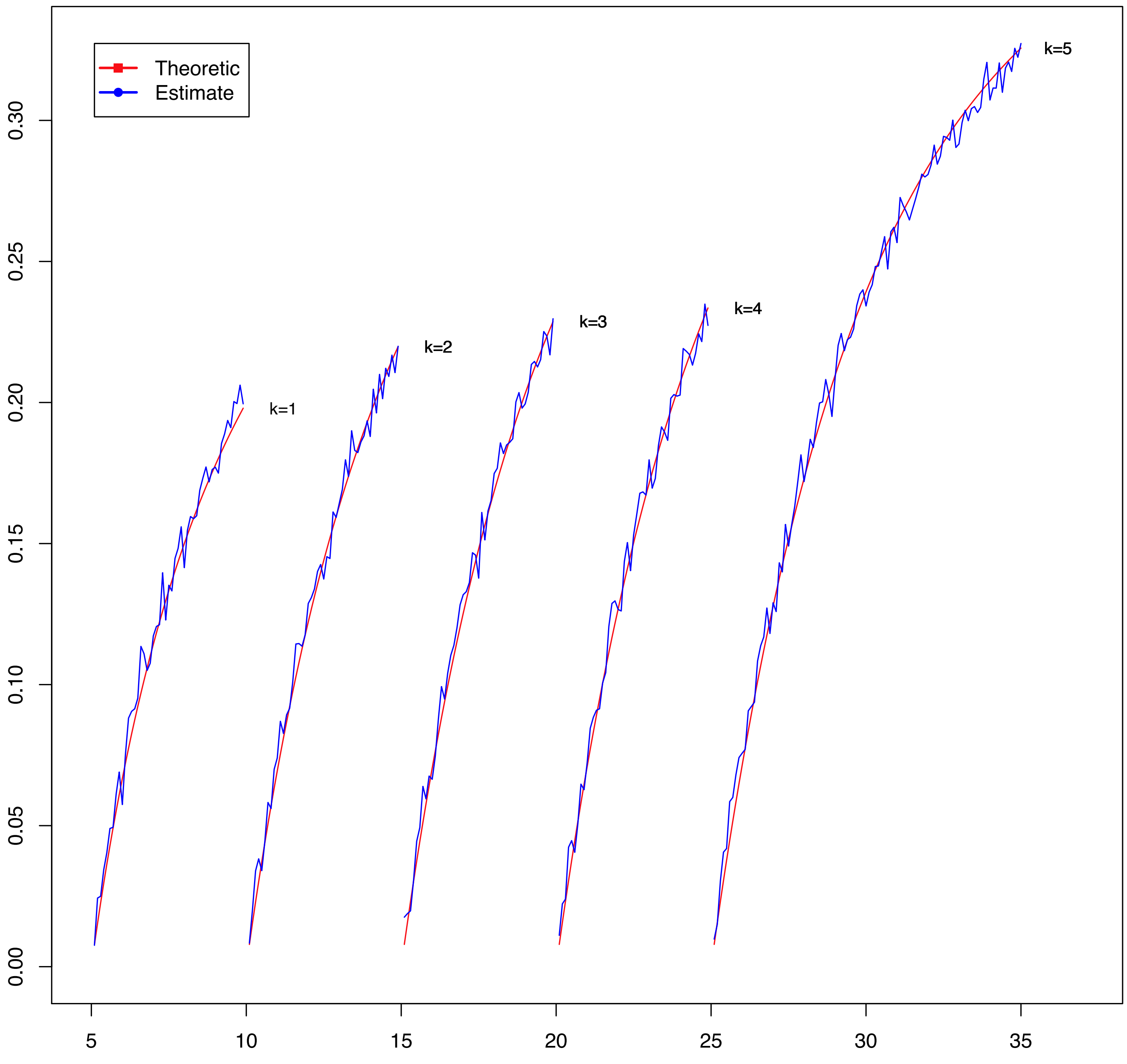
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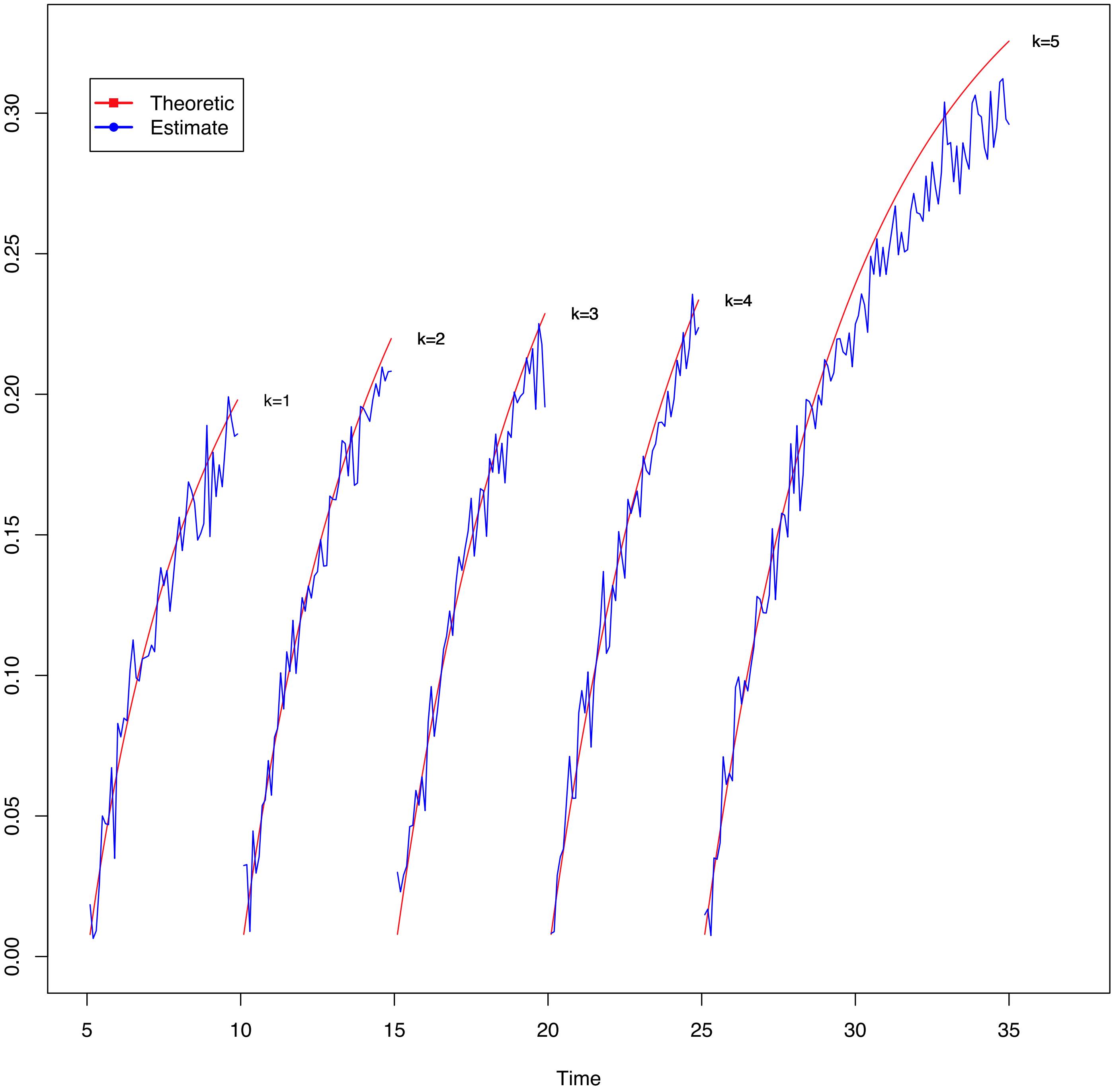
Figure



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Time

Figure

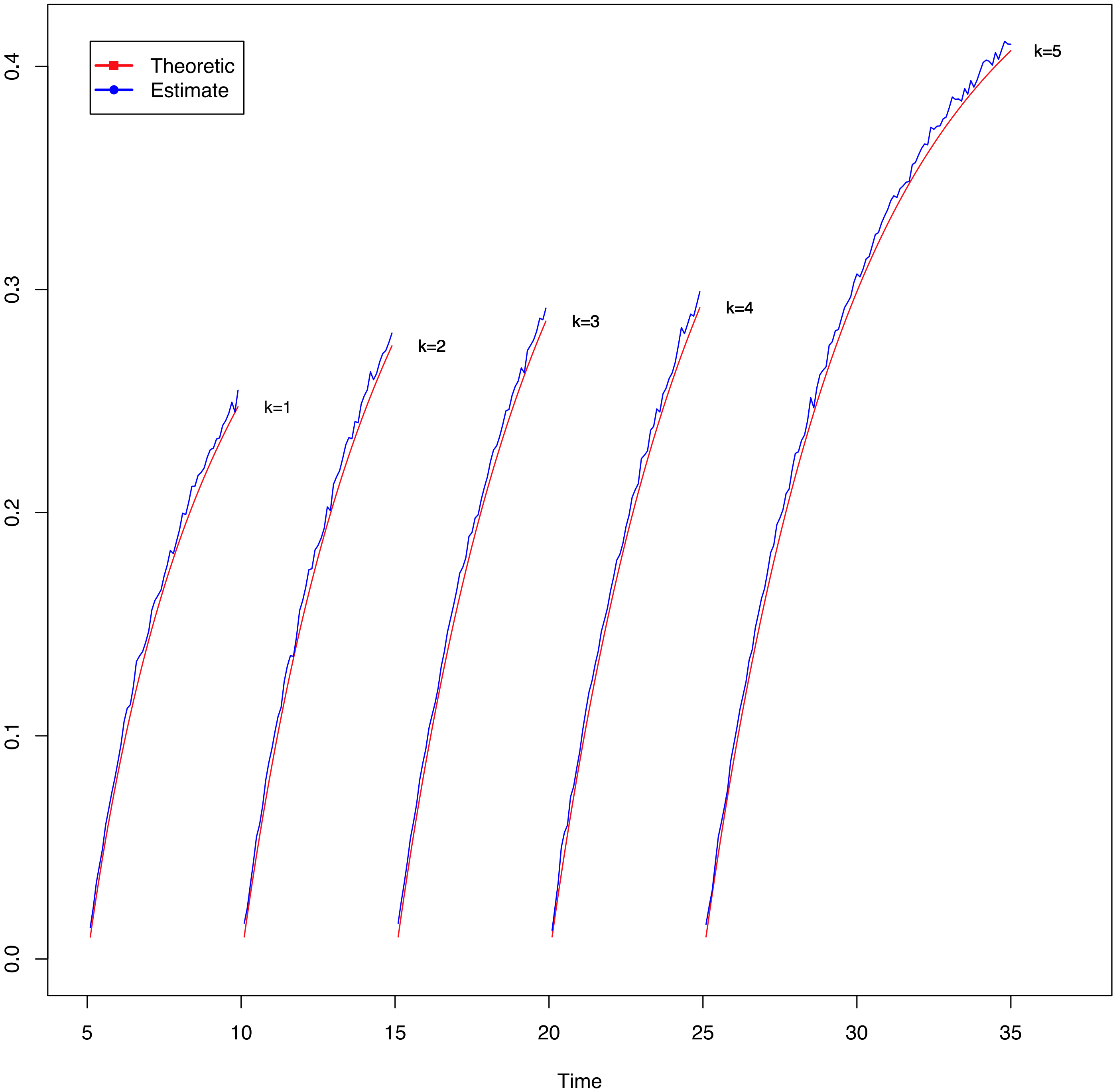
Theoretic
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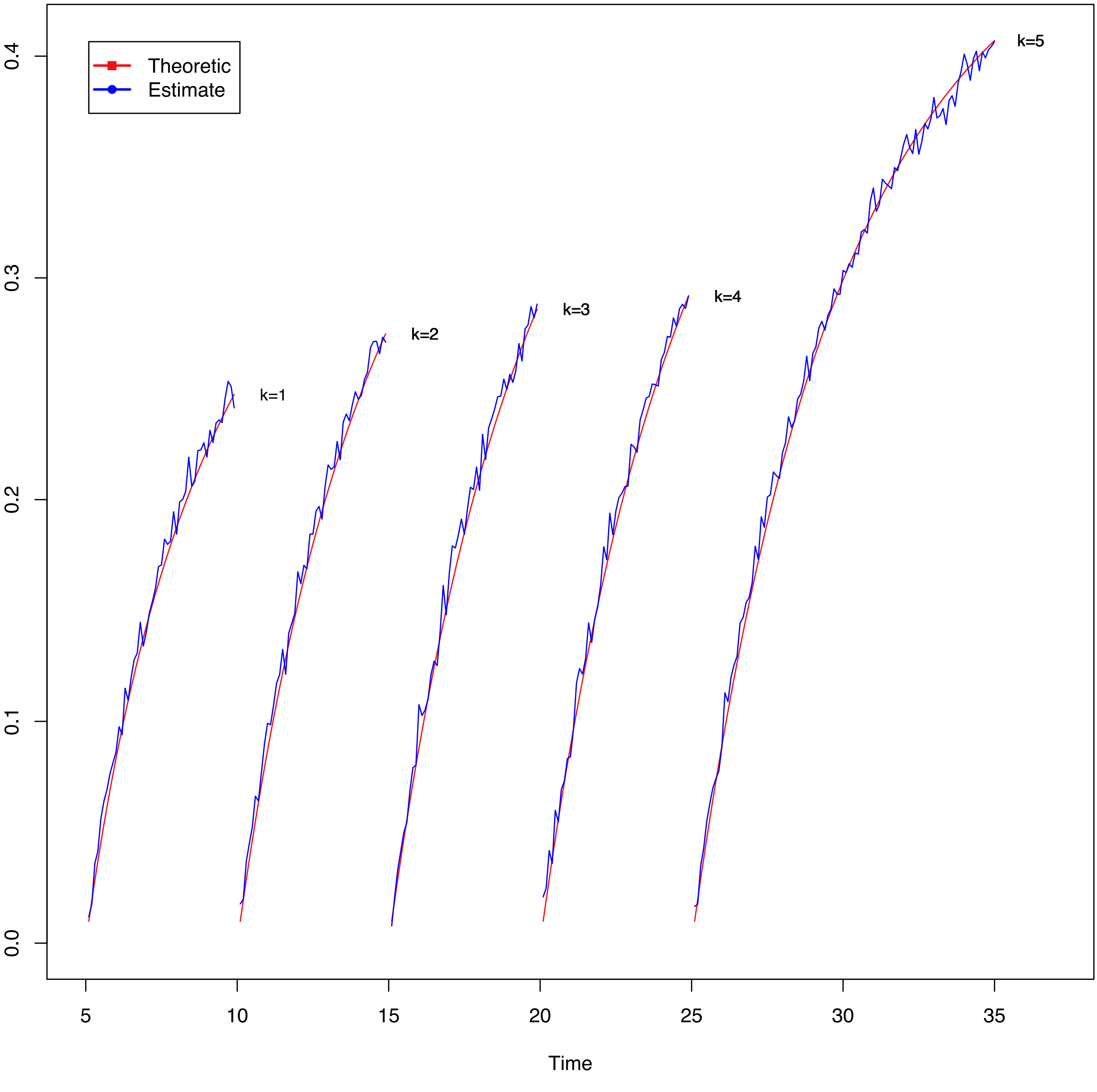
Figure



Theoretic
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Time

Figure

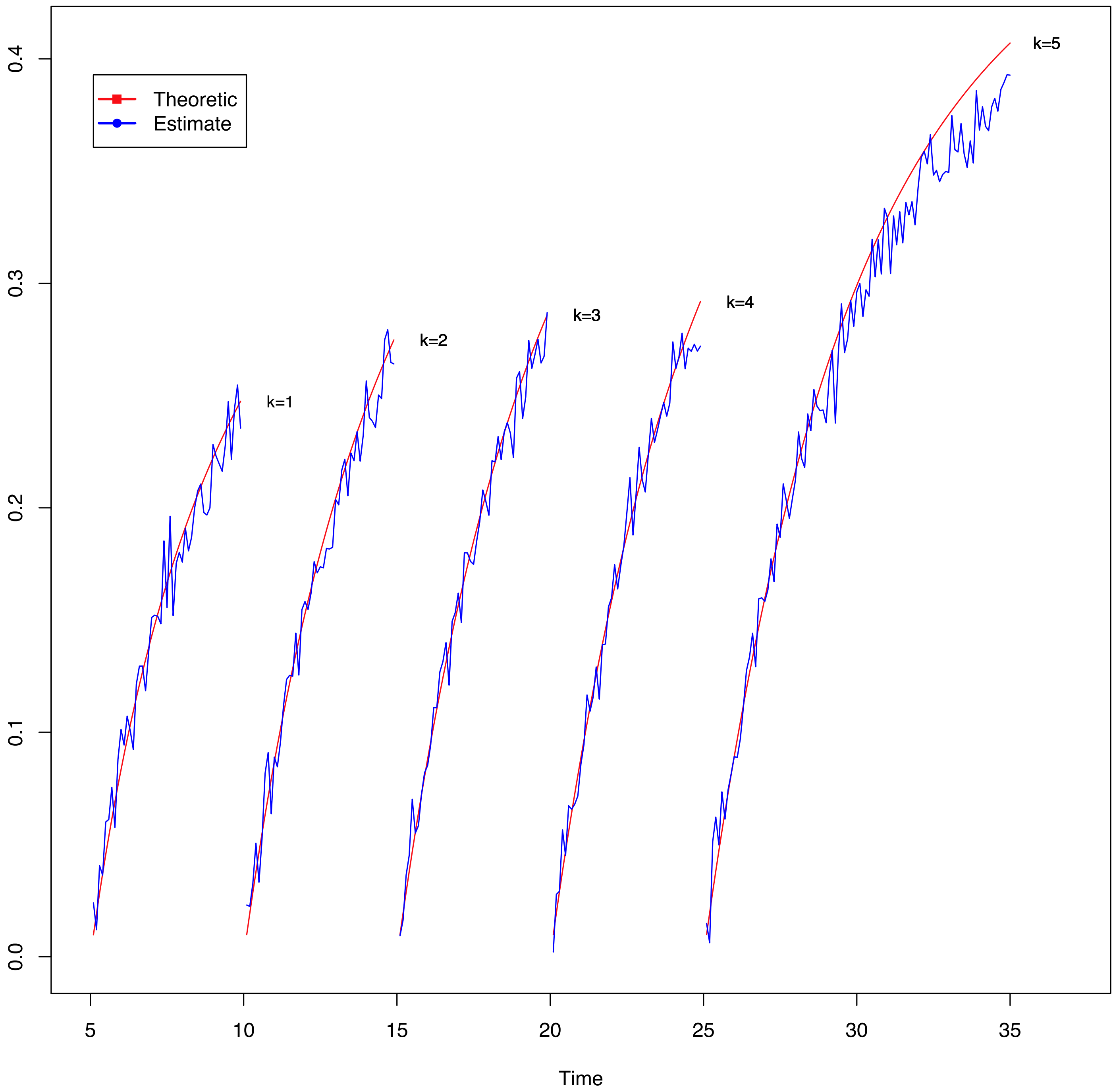

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Figure

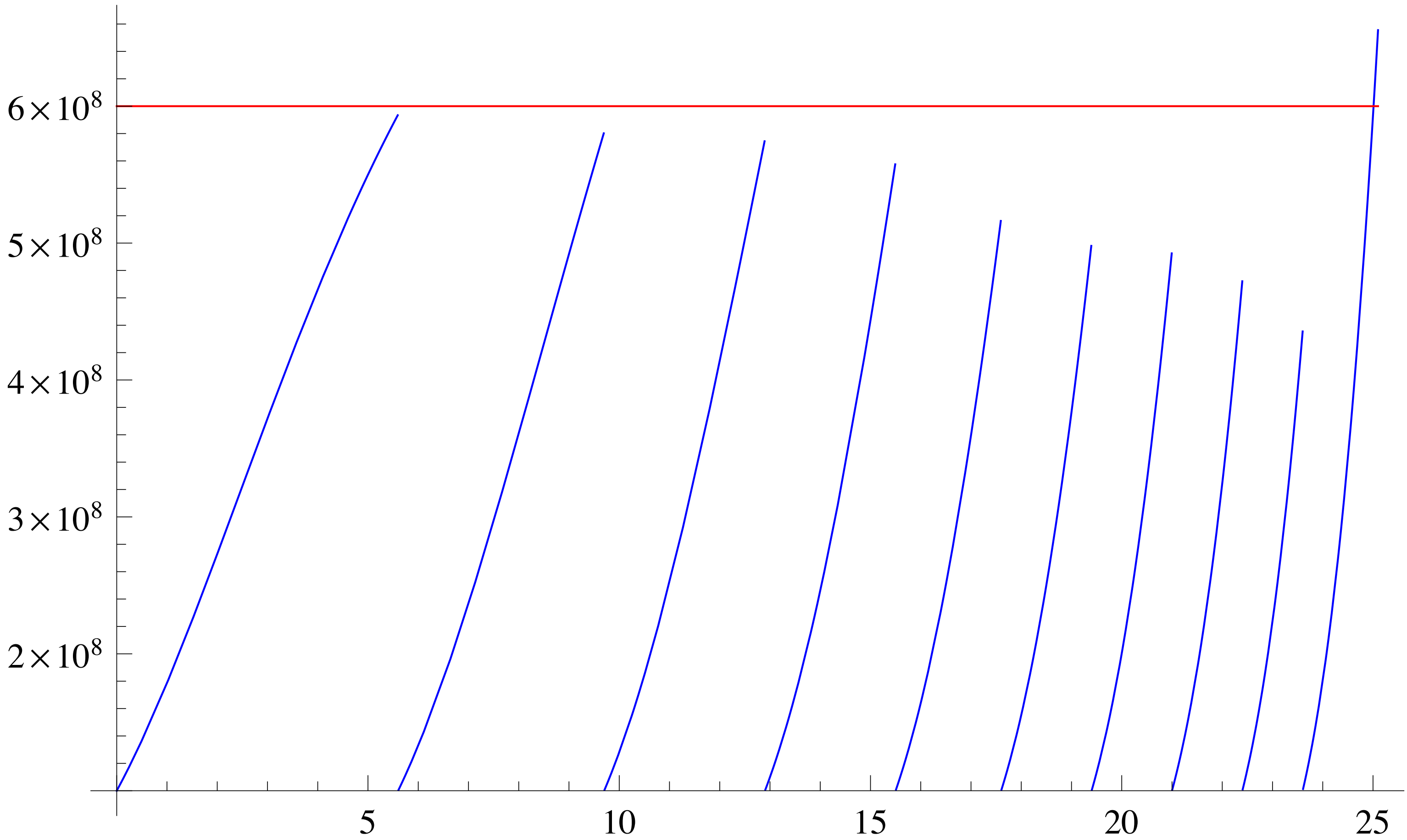

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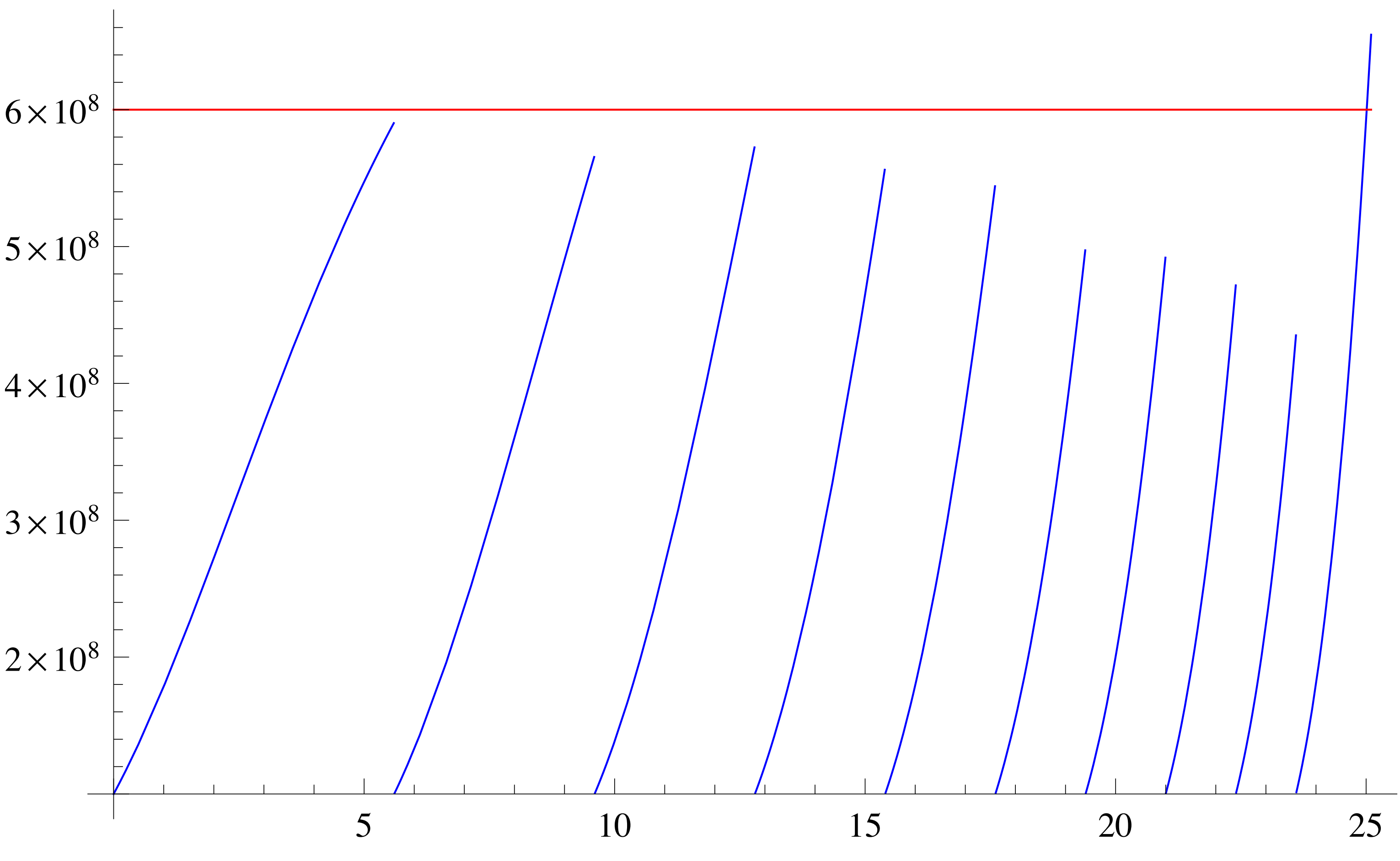
Figure



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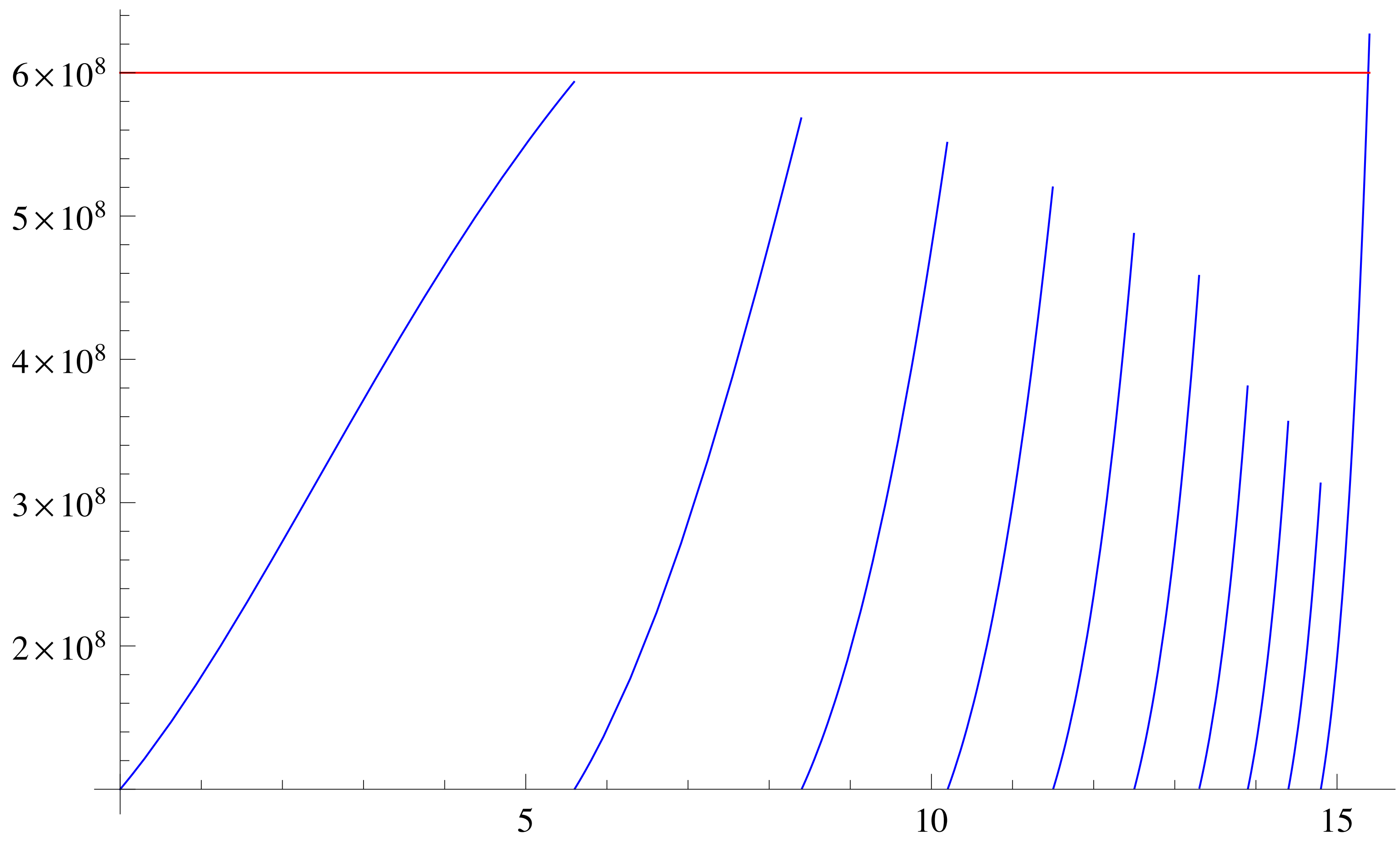

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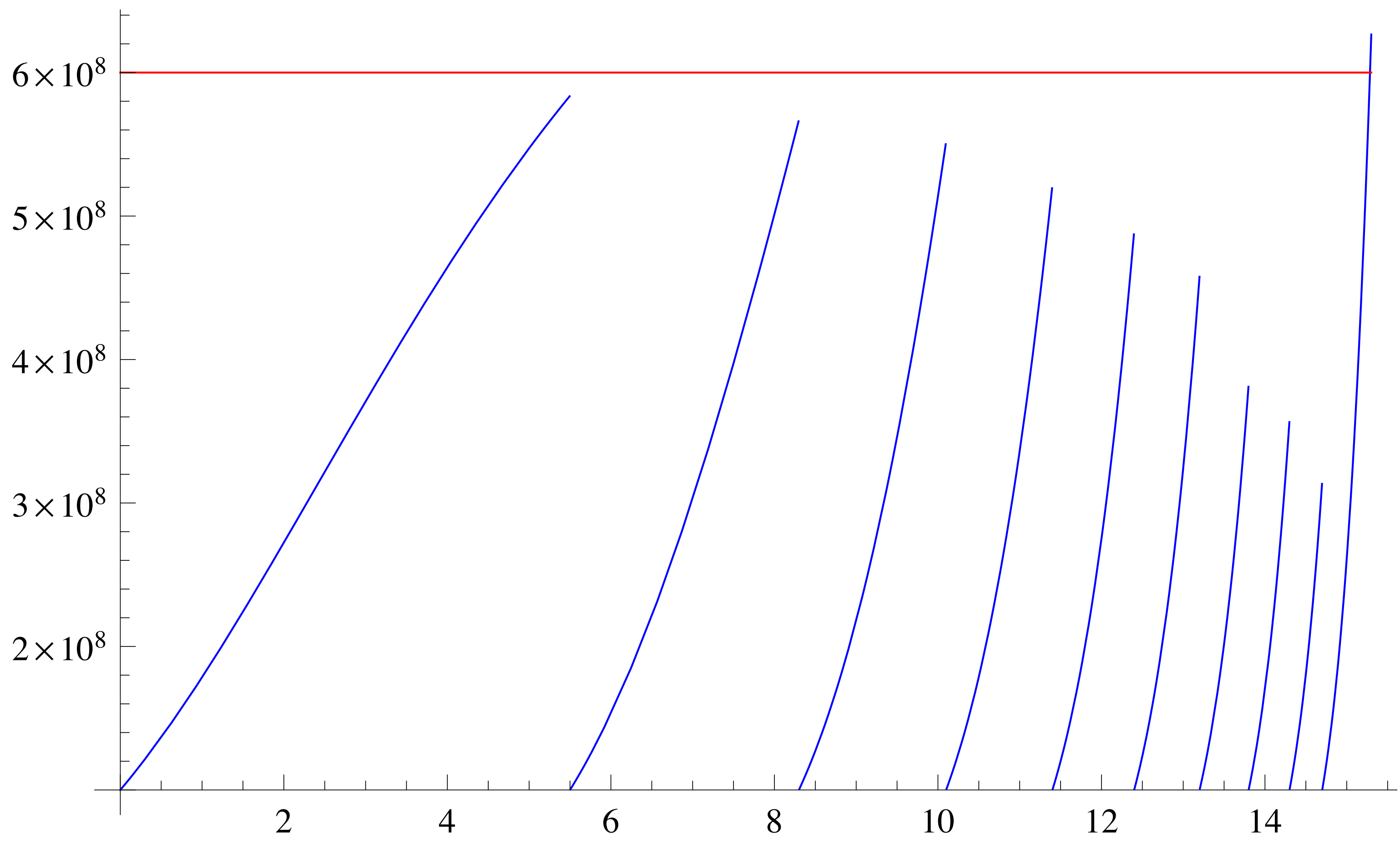

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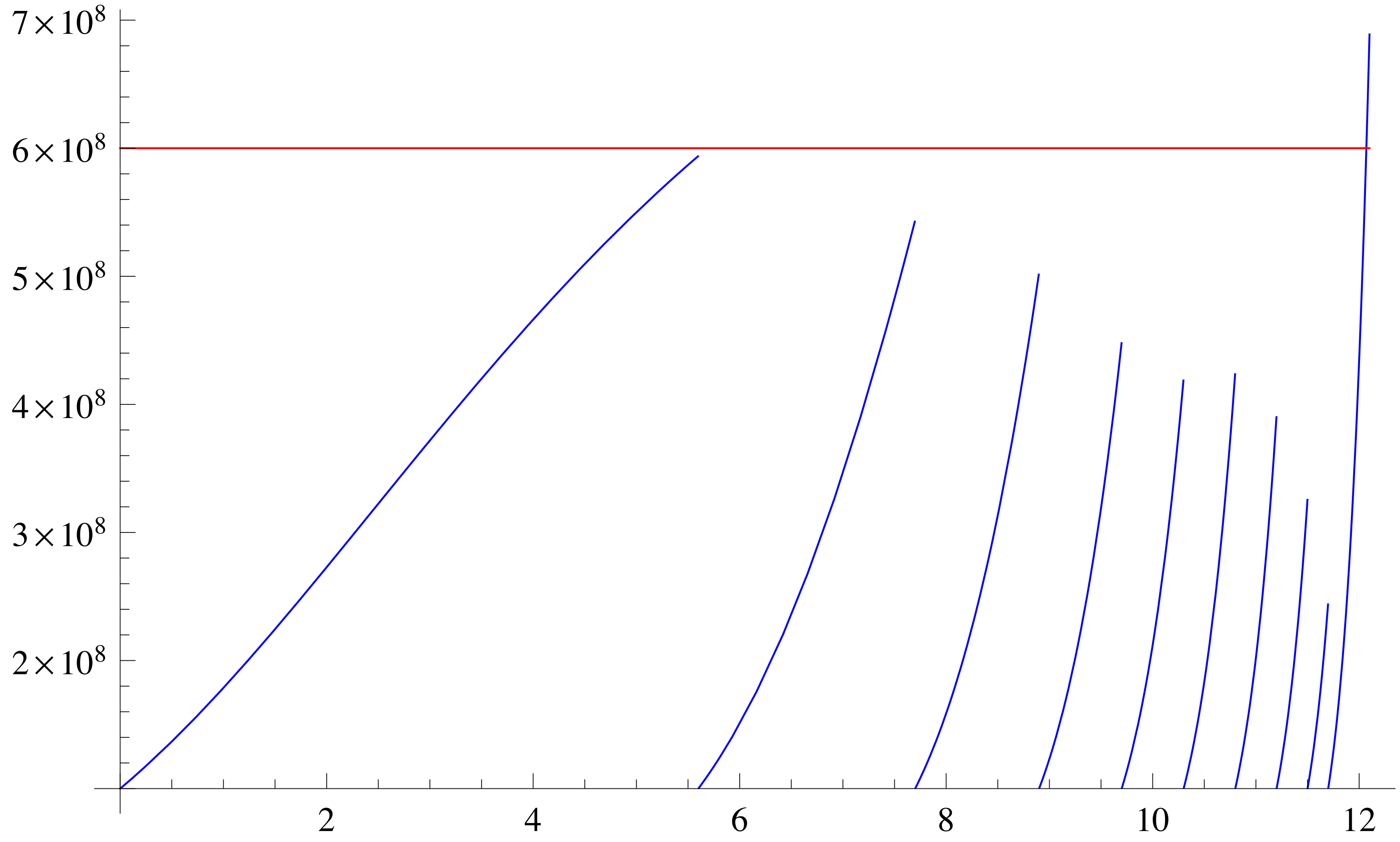

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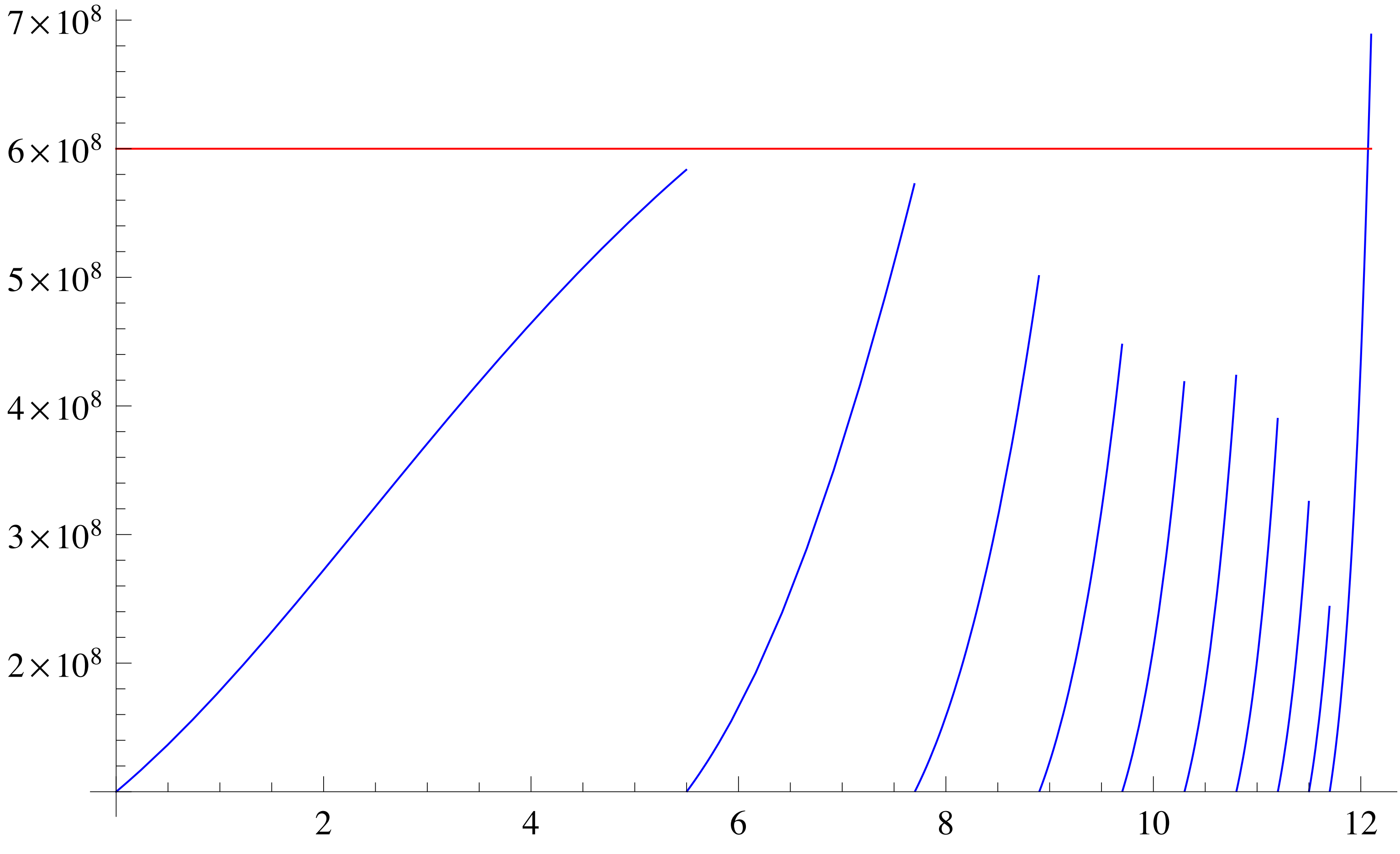

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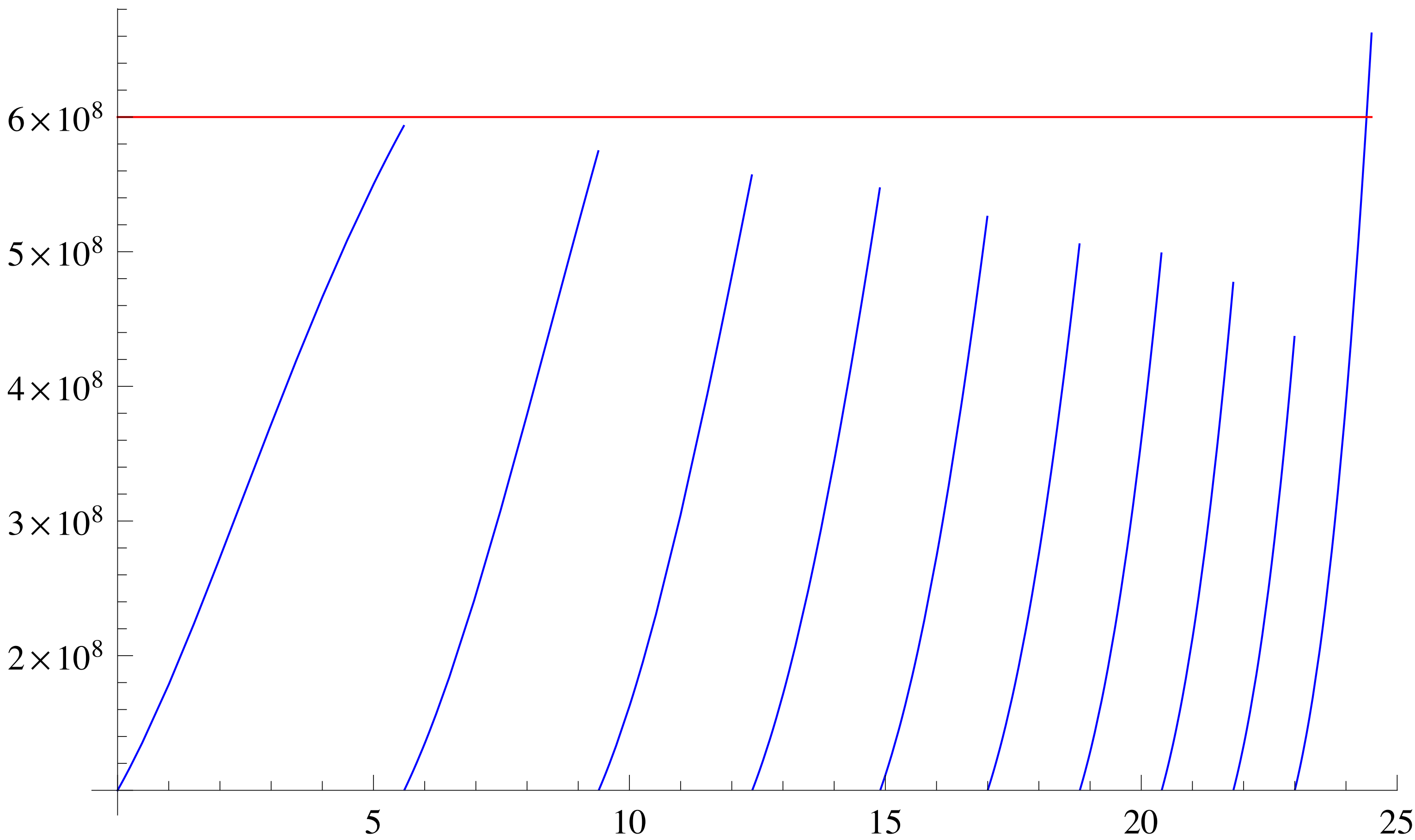

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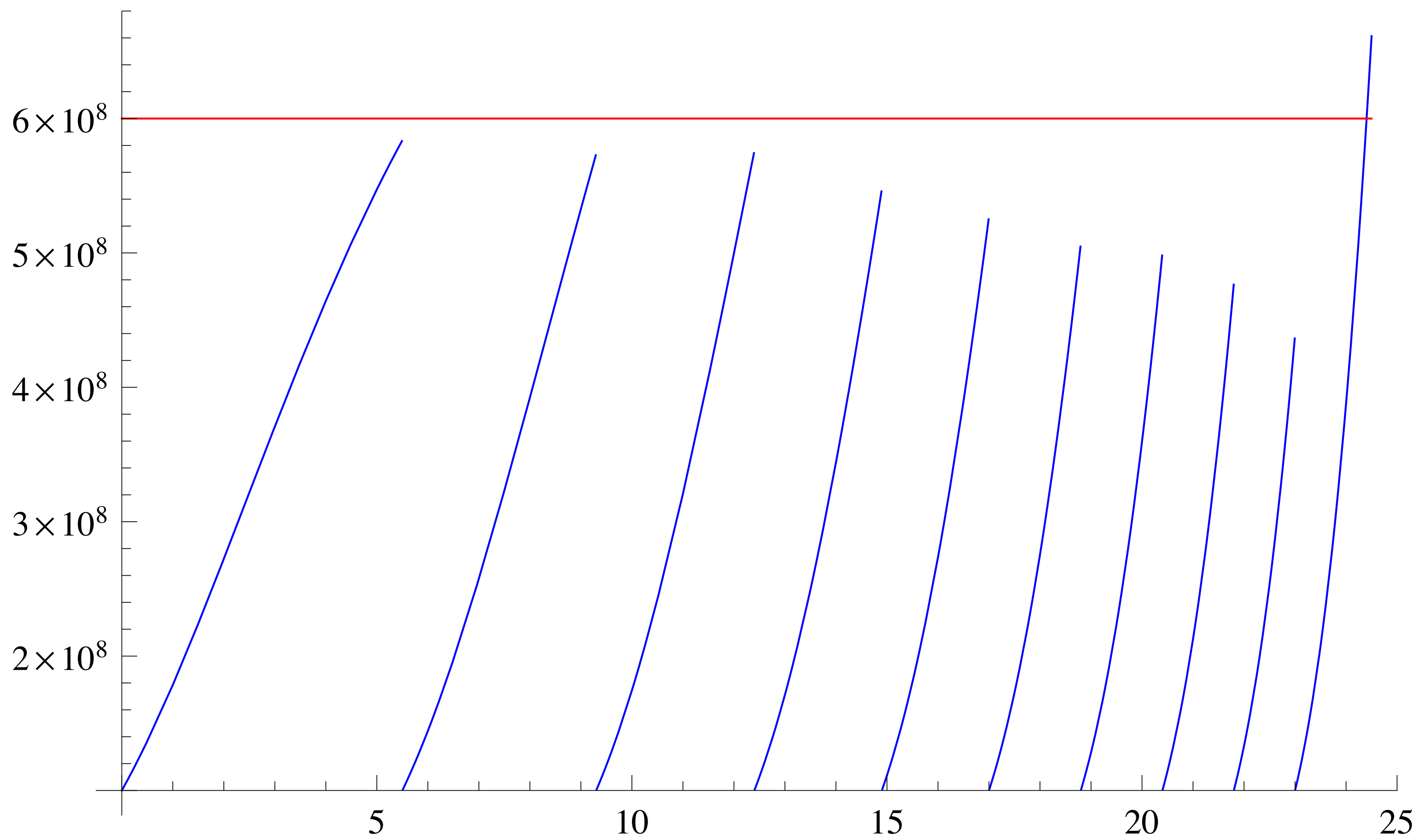

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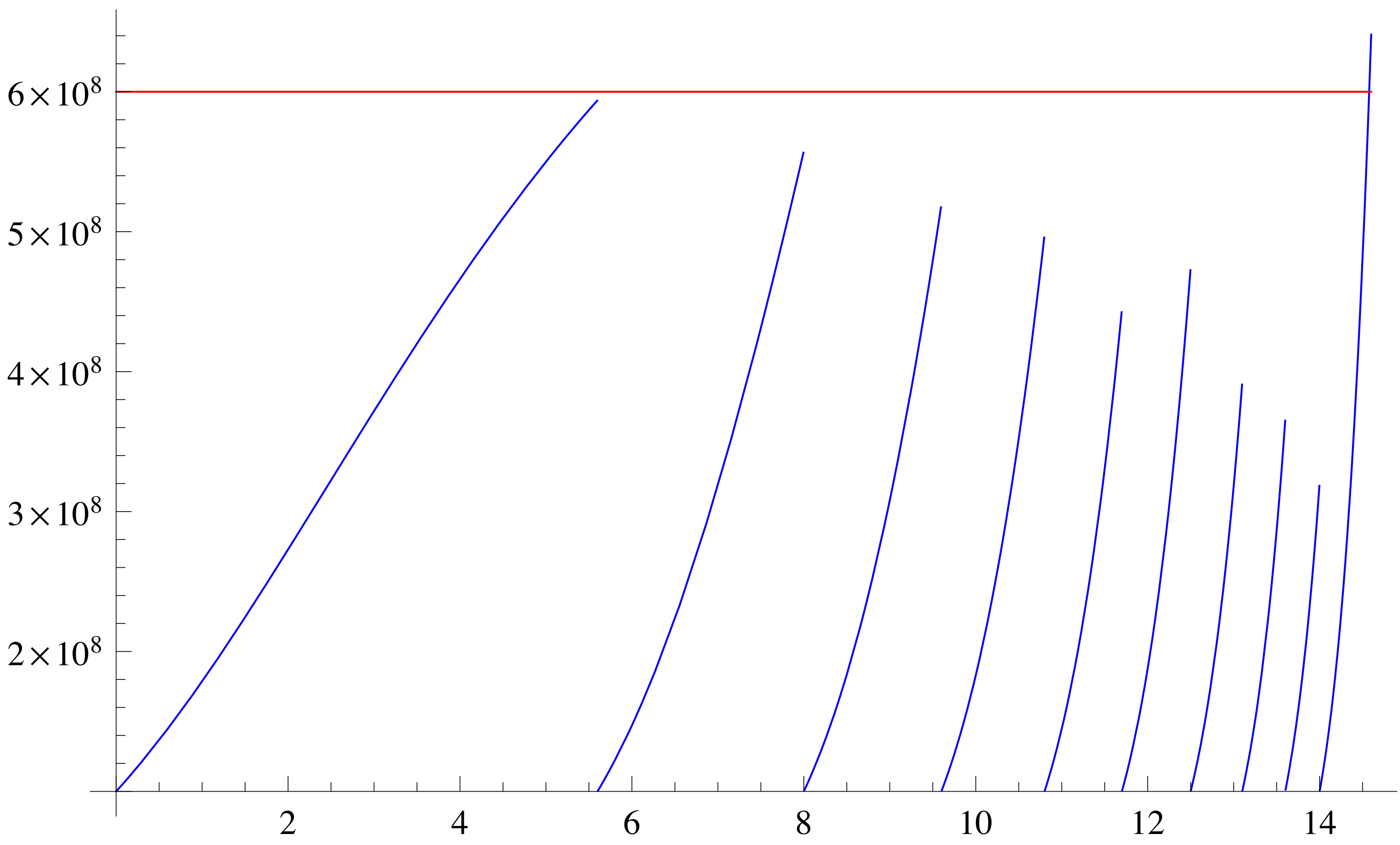

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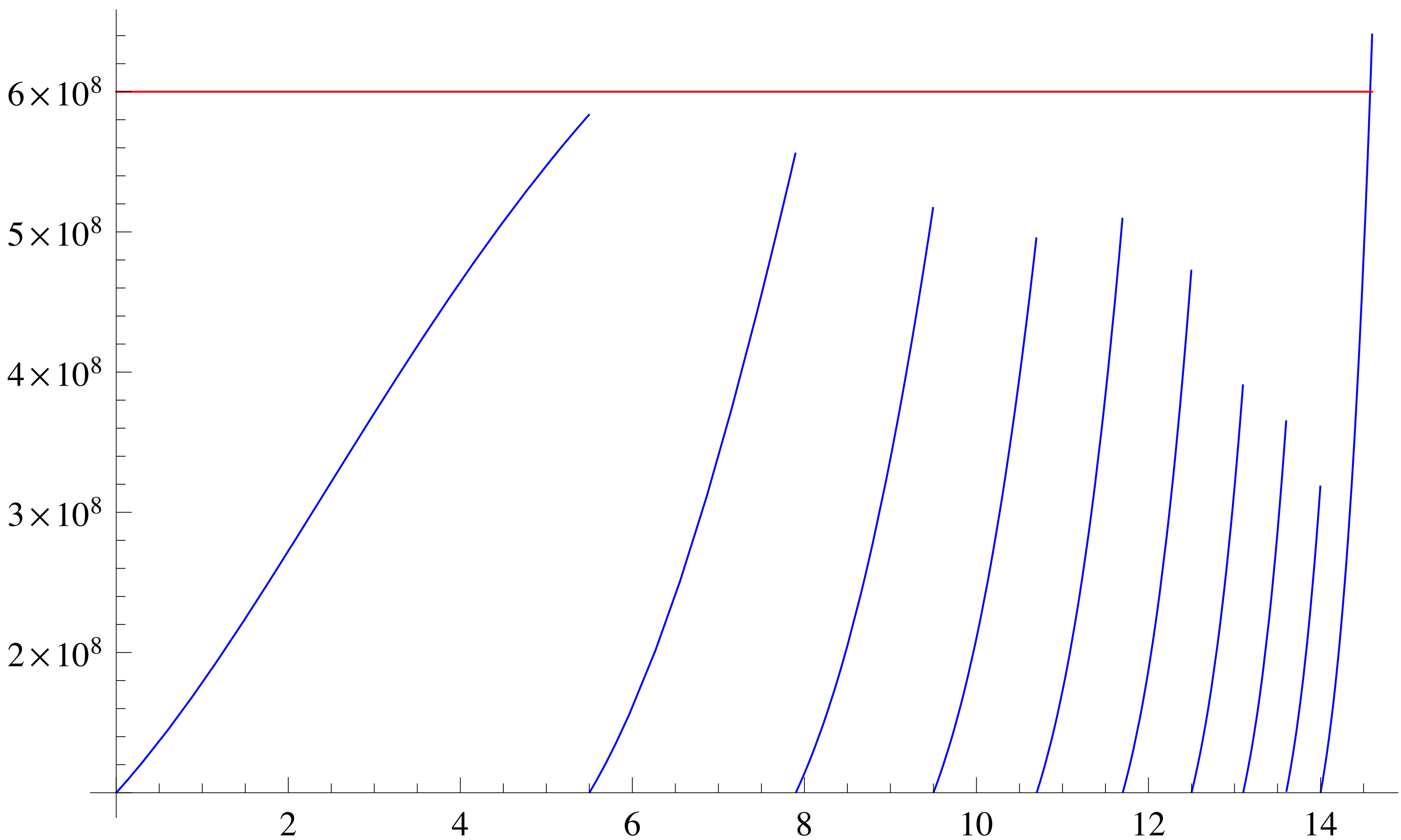

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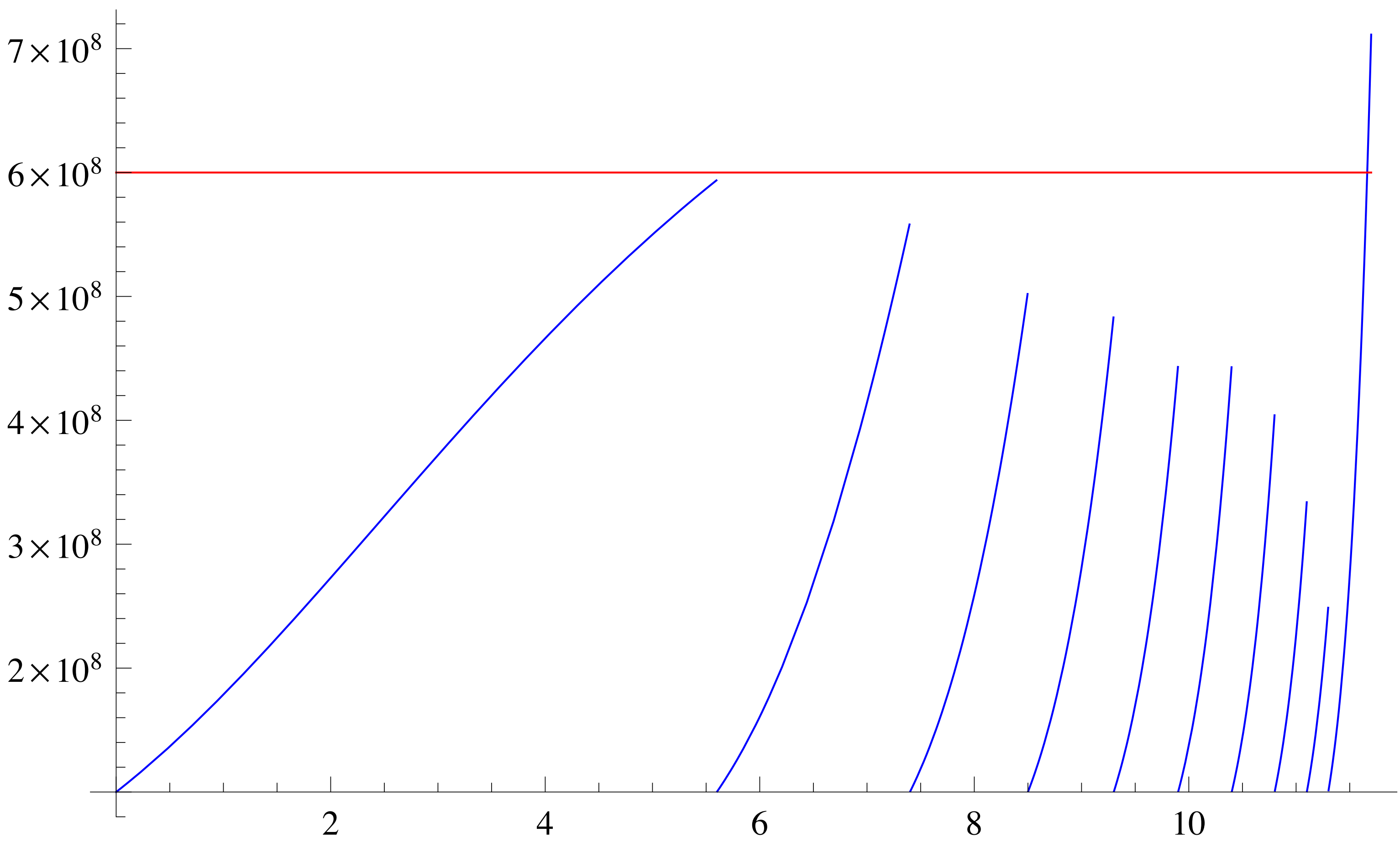

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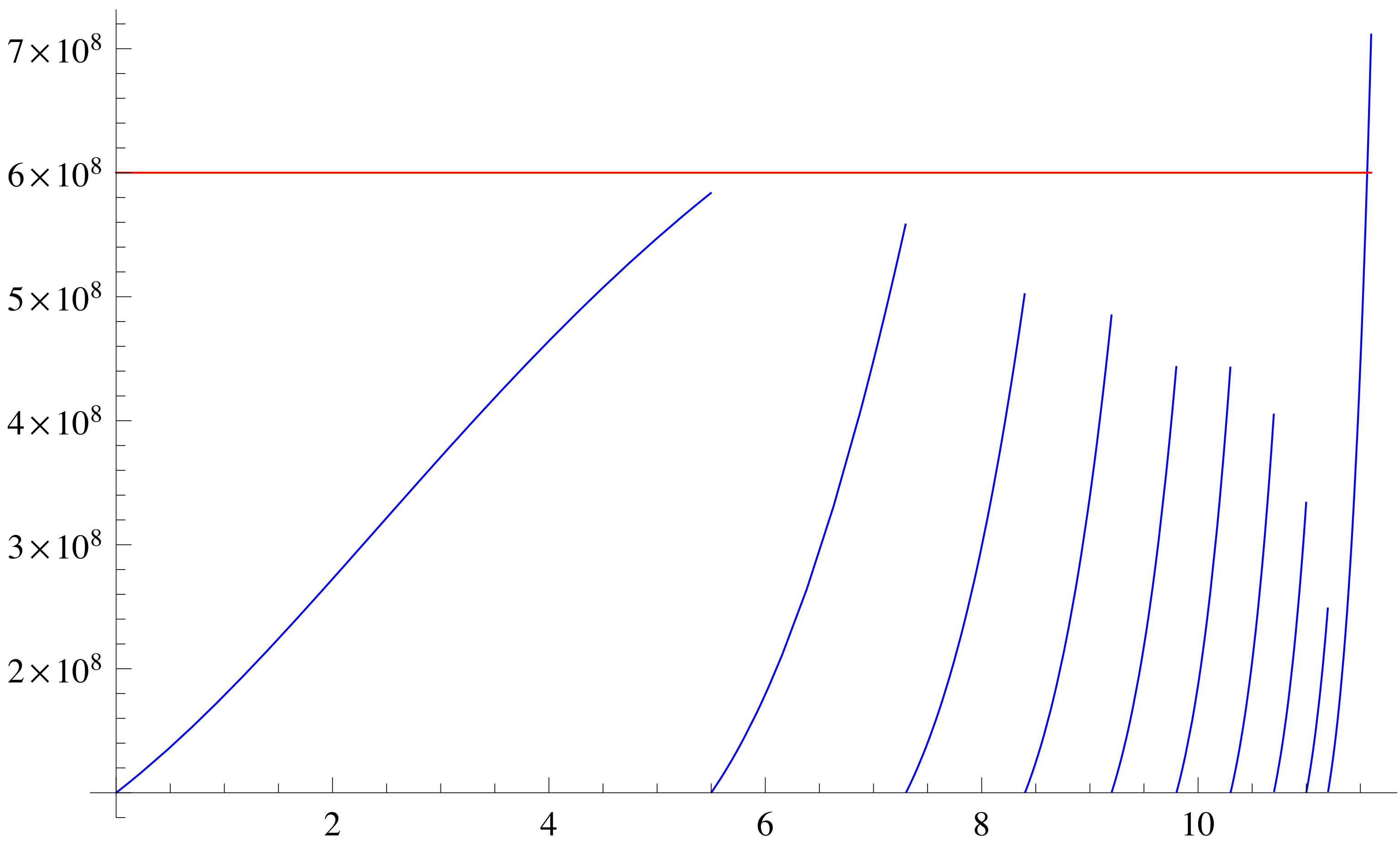

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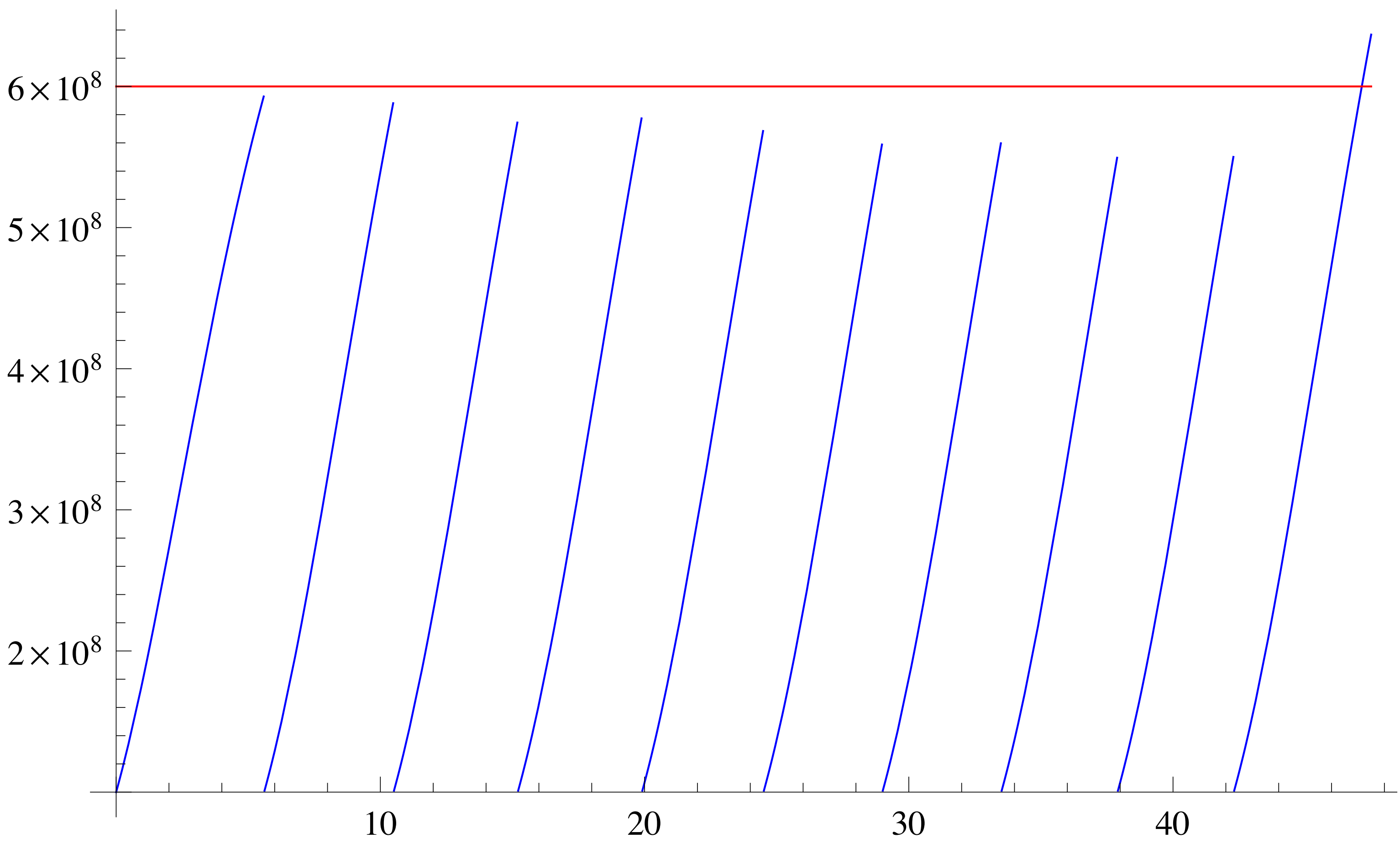

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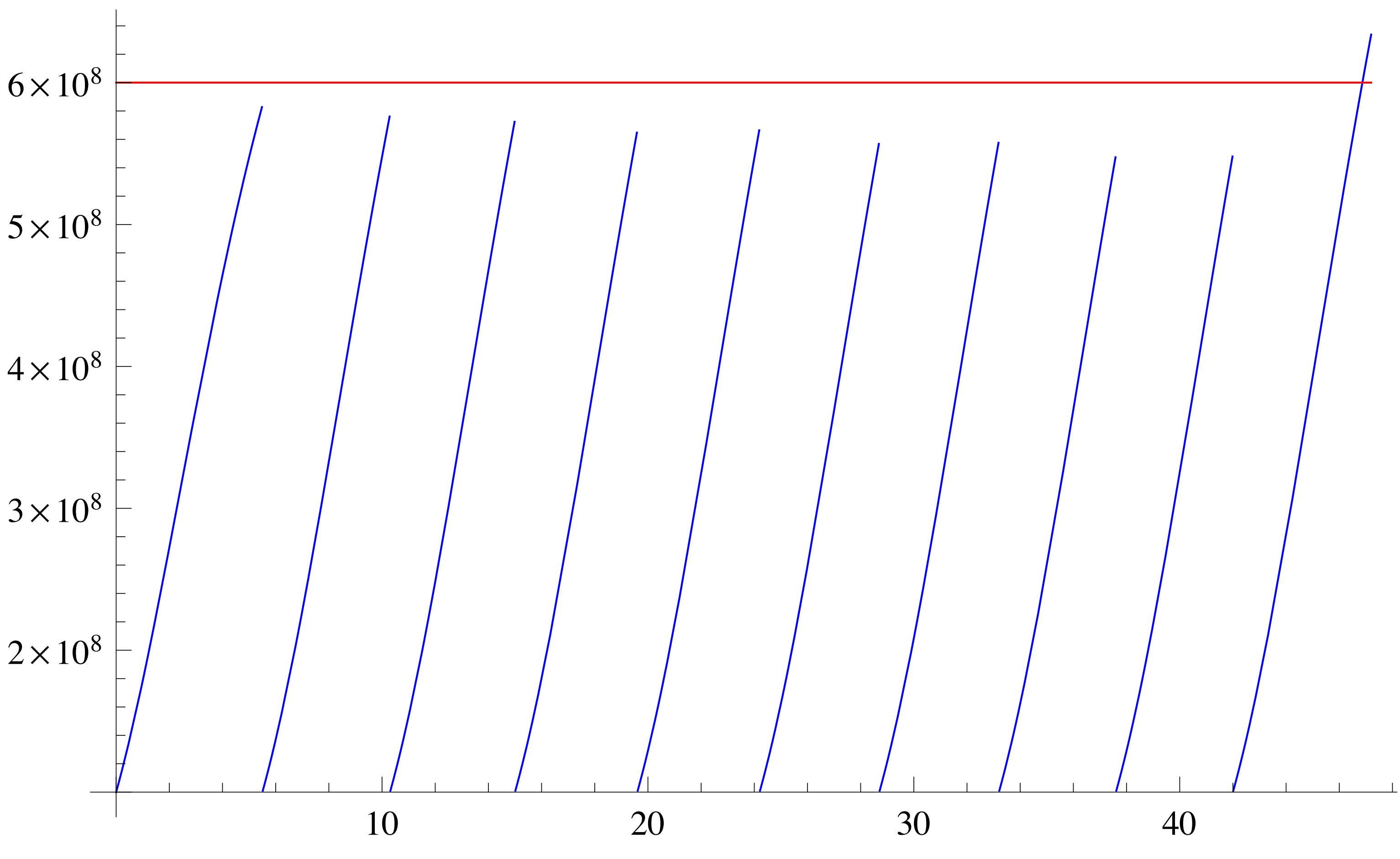

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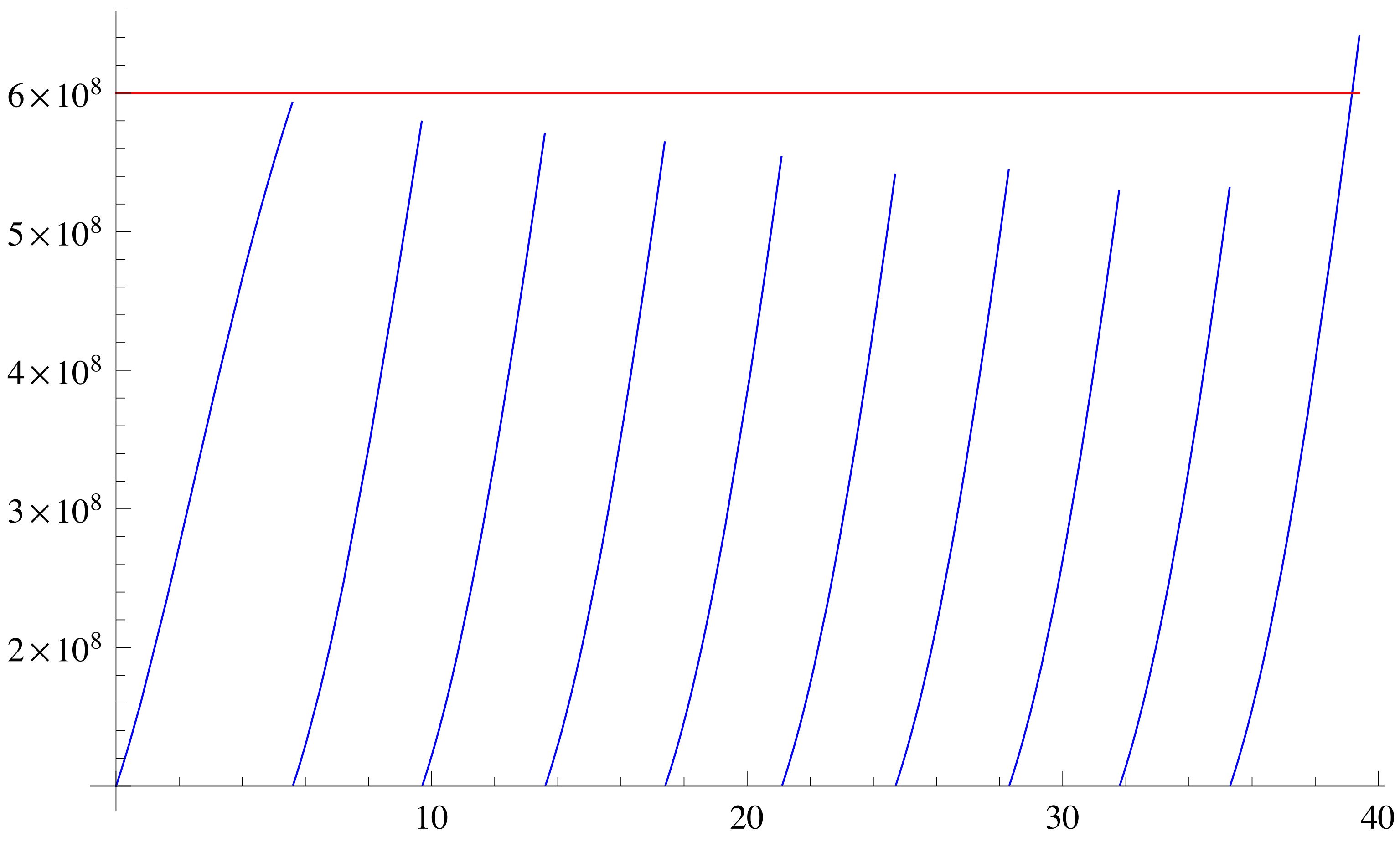

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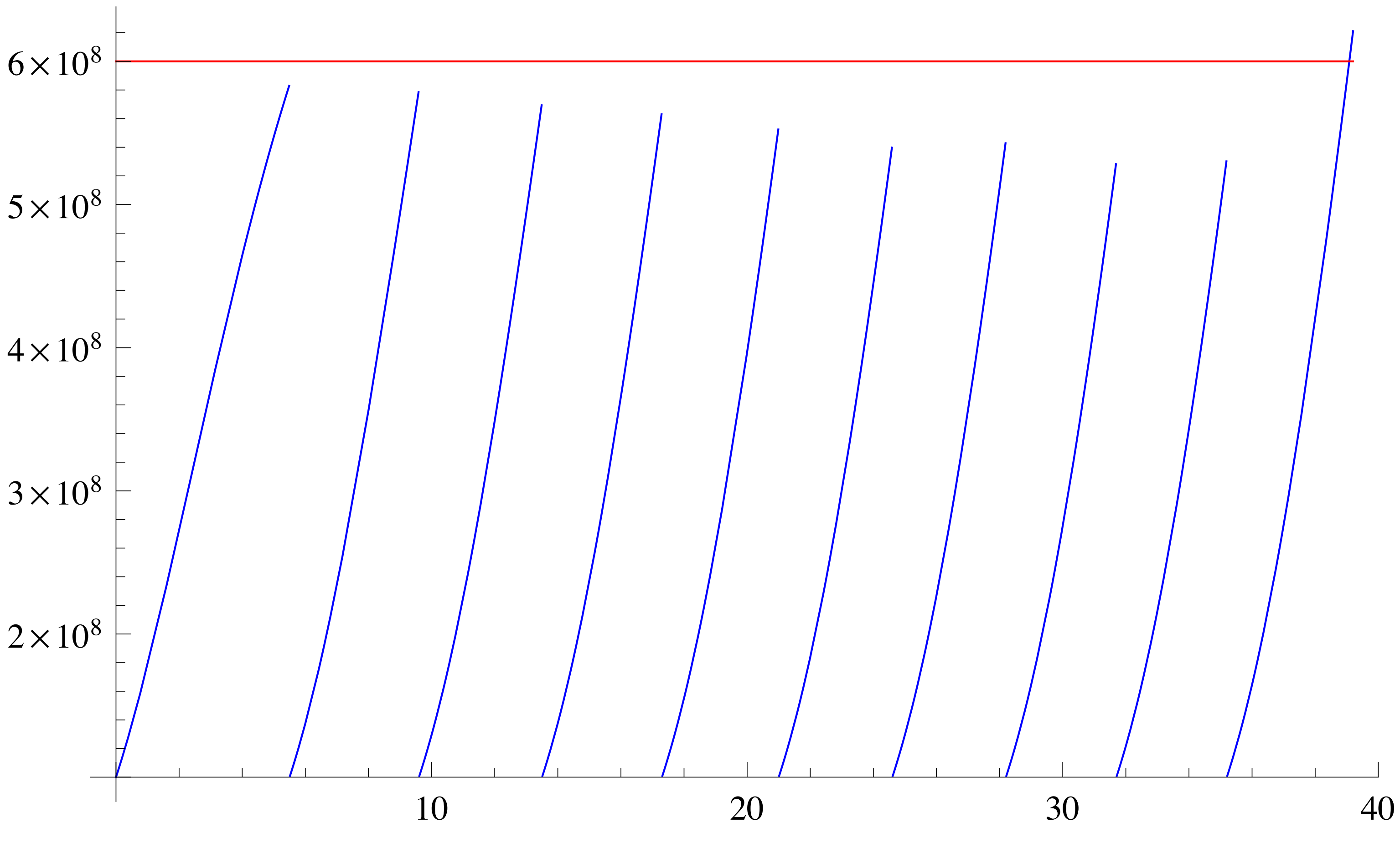

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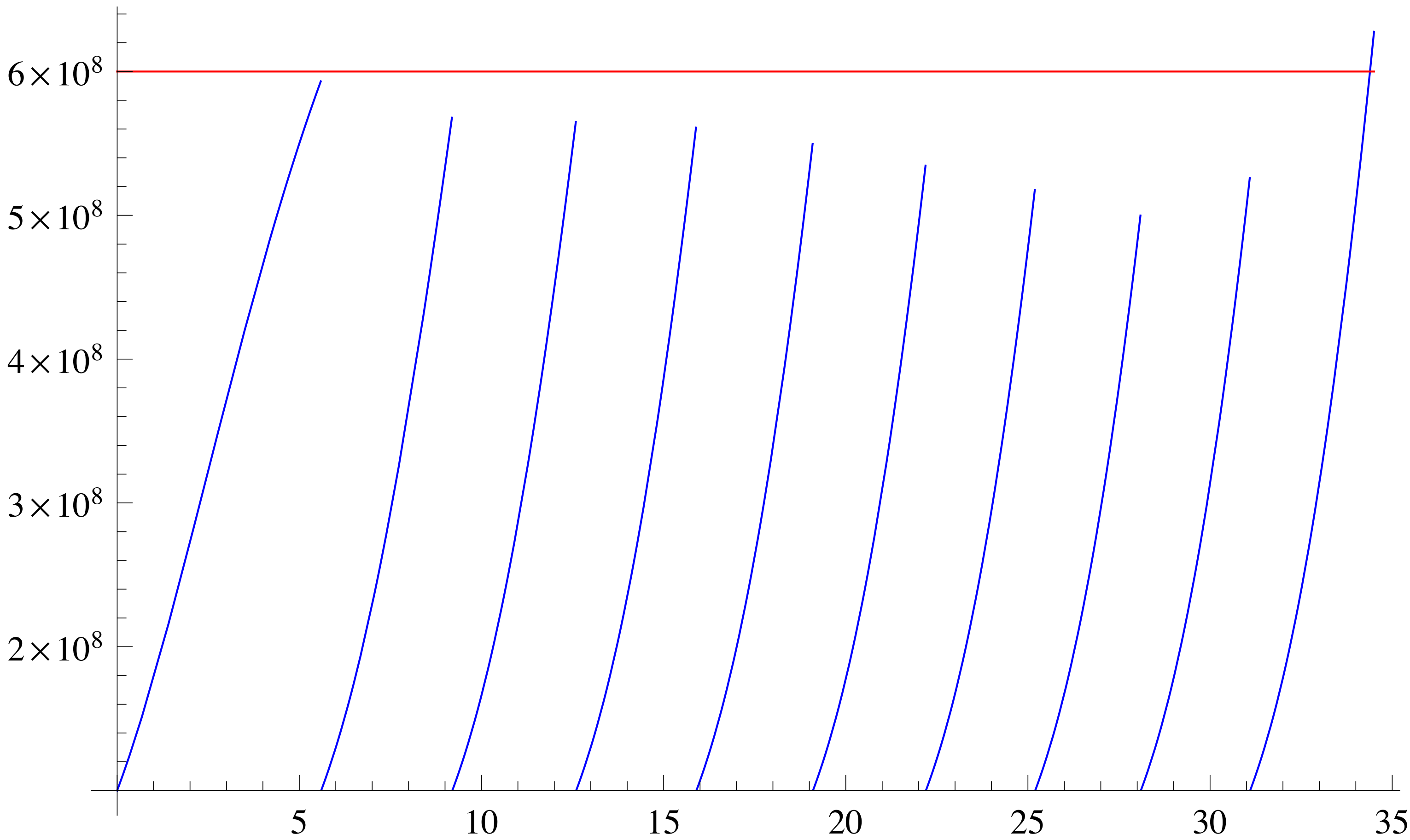

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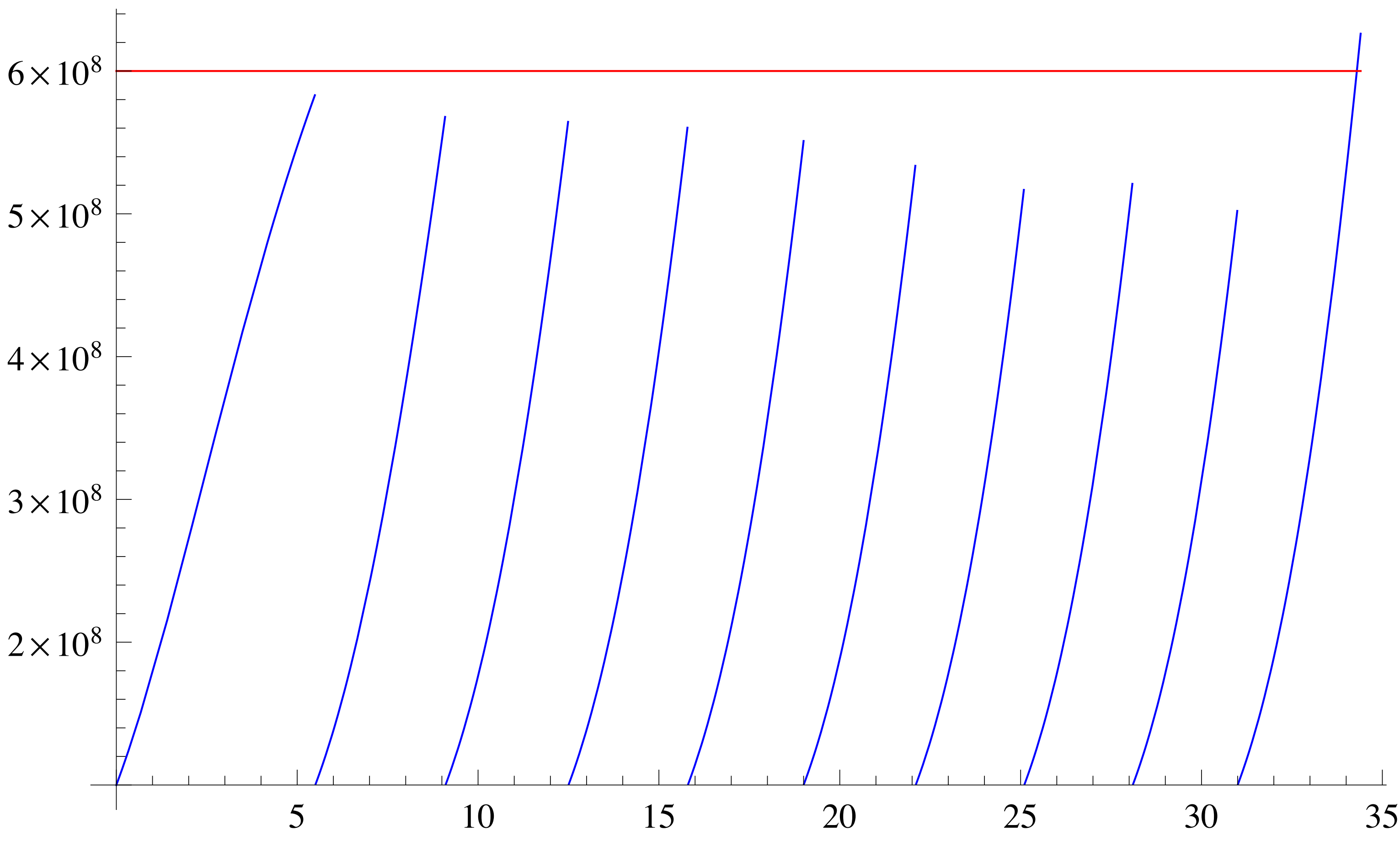

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Potential reviewers

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- **Luigi Ferrante,** Dipartimento di Scienze Biomediche e Sanità Pubblica, Università Politecnica delle Marche, Ancona, Italy. E-mail: l.ferrante@univpm.it

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