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SIMULATION OF OPTIMAL INFUSION RATE INPUT: PART II

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Abstract: In some previous author's papers [15], [16], [17], the following problems are solved. In [15] on the basis of measured plasma concentrations after an intravenous injection a problem of identification of two-compartment model is stated. The distribution of theophylline in the body is investigated and stochastic estimates of the parameters of the model are found. Further, the loading dose and the maintenance dose are traced in [16], [17]. This is carried out in two stages. In the first one, the drug is supplied by infusion untill the concentration in the first compartment reaches a prescribed by the therapist. In the second stage an appropriate drug administration is sought in order to keep the plasma concentration at the already reached level. The control law is determined. Because this theoretically determined drug administration is very difficult for practical implementation, some substituting control laws, easy to implement, are proposed. In connection with these substituting control laws, some optimization problems are stated and solved. Criteria which evaluate the different drug administrations are formulated. In all this investigation the intravenous injection and the parameter's identification, and the followed drug administration by infusion and the maintenance of the reached concentration, are fully separated. This is valid under the assumption that the infusion is accomplished after such interval of time after the injection that the plasma concentration in the first compartment could be neglected. In the present paper, we consider similar problems like in [15], [16], [17] but we assume that the infusion is accomplished immediately after the injection and the initial plasma

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concentration for the infusion process can not be neglected. Thus, a more realistic model and more accurate results of simulation are achieved.

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1. Introduction

Asthma is a complex disease that, when left untreated, can be life-threatening. It is alarming that such a large percentage of older people with asthma are letting their disease go untreated, especially since this can lead to other health problems [14]. Theophylline is the cornerstone in the management of both the acute and chronic phases of reversible airway obstruction. However, it has a narrow therapeutic index. Fortunately, theophylline serum levels correlate well with both therapeutic and toxic effects. Concentrations of 10-20 mg/l are needed to produce bronchodilation with a minimum of side effects. Serum levels exceeding 20 mg/l are associated with an unacceptable incidence of adverse reactions. Theophylline levels above 35 mg/l increase the incidence of seizures and cardiac arrythmias. The plasma levels of theophylline is affected by phrmacokinetics variables which necessitate carefully individualized dosage. Age, smoking, congestive heart failure, other diseases and drug interactions all contribute to a change in the metabolism of theophylline. These factors all necessitate dosage adjustments in order to achieve and maintain therapeutic serum levels and avoid toxicity [1]-[14]. That is why in [15] on the basis of measured plasma concentrations after an intravenous injection a problem of identification of a two-compartment model is stated. The distribution of theophylline in the body is investigated and stochastic estimates of the parameters of the model are found. Further, the loading dose and the maintenance dose are traced [16], [17]. This is carried out in two stages. In the first one, the drug is supplied by infusion untill the concentration in the first compartment reaches a prescribed by the therapist value. In the second stage an appropriate drug administration is sought in order to keep the plasma concentration at the reached level. For drug of the Theophylline group this problem is very important (see [1]-[14]) from therapeutic point of view because the plasma concentrations are heavy influenced by the individual pharmacokinetic patient's parameters. The control law (this means the way of drug administration) which realized the above mentioned property is determined. Because this theoretically determined drug administration is very difficult for practical implementation some substituting control laws, easy to implement, are proposed. In connection with these

substituting control laws, some optimization problems are stated and solved. Criteria which evaluate the different drug administrations are formulated. In all this investigation the intravenous injection and the parameter's identification, and the followed drug administration by infusion and the maintenance of the reached concentration, are fully separated. This is valid under the assumption that the infusion is accomplished after such interval of time after the injection that the plasma concentration in the first compartment could be neglected. In the present paper we consider similar problems like in [16], [17] but we assume that the infusion is accomplished immediately after the injection and the initial plasma concentration for the infusion process can not be neglected. Thus, a more realistic model and more accurate results of simulation are achieved.

2. Problem Statement

The investigated process is described by the following system of differential equations

$$\begin{aligned} \frac{dx_1}{dt} =& -(k_{10}+k_{12})x_1 + \frac{k_{21}}{V_1}M_2 + \frac{1}{V_1}D(t), \\ \frac{dM_2}{dt} =& k_{12}x_1V_1 - k_{21}M_2, \end{aligned} \tag{1}$$

where x_1 is the plasma concentration in the main first compartment, M_2 – the quantity of drug in the second compartment, k_{ij} – are the parameters of the two-compartment model which are already determined, V_1 is the volume of the first compartment and $D(t)$ – is the is the control law. The initial conditions for (1) when one carries out the parameter's identification are:

$$t = 0,\ x_1(0) = \frac{D_{i.v.}}{V_1},\ M_2(0) = 0, \tag{2}$$

where $D_{i.v.}$ is the injection dose. The solution of the system (1) (for $D(t) \equiv 0$) is given by

$$\begin{aligned} x_1(t) =& C_1e^{\alpha t} + C_2e^{\beta t}, \\ M_2(t) =& C_1\frac{k_{12}V_1}{\alpha + k_{21}}e^{\alpha t} + C_2\frac{k_{12}V_1}{\beta + k_{21}}e^{\beta t}, \end{aligned} \tag{3}$$

where C_1, C_2 are the constants of integration which are determined by the initial conditions (2), and α, β are the roots of the characteristic equation of

the system (1): $r^2 + (k_{10} + k_{12} + k_{21})r + k_{10}k_{21} = 0$, and they are:

$$\alpha = r_1 = \frac{1}{2}\left[-(k_{10} + k_{12} + k_{21} + \sqrt{(k_{10} + k_{12} + k_{21})^2 - 4k_{10}k_{21}}\right],$$
$$\beta = r_2 = \frac{1}{2}\left[-(k_{10} + k_{12} + k_{21} + \sqrt{(k_{10} + k_{12} + k_{21})^2 - 4k_{10}k_{21}}\right].$$

After the constants of integration are determined, one obtains

$$\begin{aligned} x_1(t) =& \frac{D_{i.v.}}{V_1(\alpha - \beta)}\left((\alpha + k_{21})e^{\alpha t} - (\beta + k_{21})e^{\beta t}\right), \\ M_2(t) =& \frac{D_{i.v.}k_{12}}{(\alpha - \beta)}(e^{\alpha t} - e^{\beta t}). \end{aligned} \tag{4}$$

In the first of the equations (4) there are four unknown parameters – α, β, k_{21}, V_1. Their statistic estimates are evaluated on the base of 8 observations in the points $(t_i, x_1(t_i))$, $i = 1, 2, ..., 8$ (see [15]).

Our investigation starts at the moment $t_8 = t_s$, in which the observations needed for the statistic analysis are already completed and one begins a drug administration by infusion with dose D_0. Now one have to solve the system (1) for $t \geq t_s$, $D(t) = D_0$, and with initial conditions

$$t = t_s,\ x_{1s} = x_1(t_s),\ M_{2s} = M_2(t_s), \tag{5}$$

where $x_1(t_s)$, $M_2(t_s)$ are determined by (3). The solution is

$$\begin{aligned} x_1(t) =& e^{\alpha(t-t_s)}C_1 + e^{\beta(t-t_s)}C_2 + \frac{D_0}{k_{10}V_1}, \\ M_2(t) =& \frac{k_{12}V_1e^{\alpha(t-t_s)}}{\alpha + k_{21}}C_1 + \frac{k_{12}V_1e^{\beta(t-t_s)}}{\beta + k_{21}}C_2 + \frac{D_0k_{12}}{k_{10}k_{21}}, \end{aligned} \tag{6}$$

where the constants of integration C_1, C_2 are

$$C_1 = \left(x_{1s} - M_{2s}\frac{\beta + k_{21}}{k_{12}V_1} + \frac{D_0\beta}{k_{10}k_{21}V_1}\right)\frac{\alpha + k_{21}}{\alpha - \beta},$$
$$C_2 = \left(M_{2s}\frac{\alpha + k_{21}}{k_{12}V_1} - x_{1s} - \frac{D_0\alpha}{k_{10}k_{21}V_1}\right)\frac{\beta + k_{21}}{\alpha - \beta}.$$

Now one can determine the moment t_0 in which the plasma concentration in the first compartment will reach the value C_0 prescribed by the therapist.

This is done by the equation

$$x_1(t_0) = C_0 = e^{\alpha(t_0-t_s)}\left(x_{1s} - M_{2s}\frac{\beta+k_{21}}{k_{12}V_1} + \frac{D_0\beta}{k_{10}k_{21}V_1}\right)\frac{\alpha+k_{21}}{\alpha-\beta},$$
$$+ e^{\beta(t_0-t_s)}\left(M_{2s}\frac{\alpha+k_{21}}{k_{12}V_1} - x_{1s} - \frac{D_0\alpha}{k_{10}k_{21}V_1}\right)\frac{\beta+k_{21}}{\alpha-\beta} + \frac{D_0}{k_{10}V_1}. \quad (7)$$

The solution of this equation for the concrete data is obtained in [15], namely

$$k_{10} = 0.3134[\mathrm{hr}^{-1}];\ k_{12} = 2.7549[\mathrm{hr}^{-1}];\ k_{21} = 3.1326[\mathrm{hr}^{-1}];$$

$$V_1 = 20.7322[1];\ C_0 = 15[\mu\mathrm{g}];\ D_0 = 500[\mu\mathrm{g.hr}^{-1}];> t_8 = t_s = 6[\mathrm{hr}],$$

is $t_0 = 6.7861[\mathrm{hr}]$. In [15] the denoted by the same letter time is $t_0 = 1.1738[\mathrm{hr}]$. Here one has to take into account that the counting of the time for drug administration by infusion starts at the moment t_s, i.e., the corresponding to this time now is $t_0 - t_s = 0.7861[\mathrm{hr}]$.

After the prescribed plasma concentration C_0 is already reached, the problem is to keep it at this level. Analogously to [16], [17], one can prove that this will be achieved by the control law

$$D(t) = V_1k_{10}C_0 + (C_0V_1k_{12} - M_{20}k_{21})e^{-k_{21}(t-t_0)}, \quad t \in (t_0, t_m], \quad (8)$$

where

$$M_{20} = \frac{k_{12}V_1e^{\alpha(t_0-t_s)}}{\alpha+k_{21}}\left(x_{1s} - M_{2s}\frac{\beta+k_{21}}{k_{12}V_1}(\beta+k_{21}) + \frac{D_0\beta}{k_{10}k_{21}V_1}\right)$$
$$\times\frac{\alpha+k_{21}}{\alpha-\beta} + \frac{k_{12}V_1e^{\beta(t_0-t_s)}}{\beta+k_{21}}\left(M_{2s}\frac{\alpha+k_{21}}{k_{12}V_1} - x_{1s} - \frac{D_0\alpha}{k_{10}k_{21}V_1}\right)$$
$$\times\frac{\beta+k_{21}}{\alpha-\beta} + \frac{D_0k_{12}}{k_{10}k_{21}},$$

and t_m is the end of the drug administration by infusion and hence the end of the planed therapy. In order to compare the results of the present investigation and the corresponding results of [17], one assumes the interval $[t_0, t_m]$ to be equal to the same interval of [17]. This means that the value of t_m should be chosen as $t_m = t_0 + 6.5 - 1.1738 = 12.1123[\mathrm{hr}]$.

It is clear that at the moment t_0 the control law $D(t)$ is discontinuous with a jump. We assume that at the moment t_0 it has the value D_0 and then for $t_0 + \varepsilon$, it will be $D(t_0 + \varepsilon) = (k_{10} + k_{12})C_0V - 1 - k_{21}M_{20}$. For the concrete numerical data of the parameters one obtains $D(t_0 + \varepsilon) = 289.082[\mu\mathrm{g.hr}^{-1}]$.

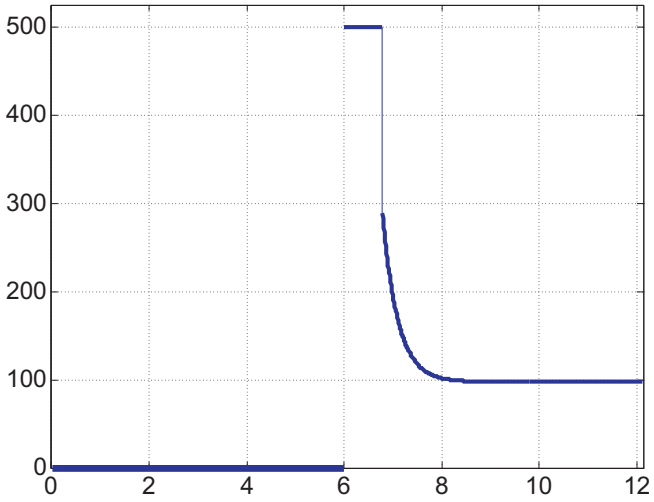

Figure 1

On Figure 1 a graph of the control law $D(t)$ is shown, and on Figure 2 the corresponding plasma concentration $x_1(t)$ is presented. Figure 1 very distinctly demonstrates how after the constant infusion with value D_0, there follows the jump to the control law $D(t)$.

In [17] we give some substituting control laws which in a certain way draw near the plasma concentration $x_1(t)$, $t \in [t_0, t_m]$ to the value C_0. According to the investigations there, one may conclude that the most effective approximation to the theoretical control law (8) is obtained after dividing the interval $[t_0, t_m]$ into two or three subintervals in which the theoretical control law is substituted by partly constant control law which is integral equivalent to it (the theoretical control law) in the subintervals.

In the present paper we accept the same approach. Let us state the problem more generally. Let us divide the interval $[t_0, t_m]$ into N subintervals by the points $t_0 = t_1 < t_2 < ... < t_{N+1} = t_m$. In each of these subintervals we substitute the control law $D(t)$ with constant control law which is integral equivalent to it. The reason for such substitution is that in this case the quantities of the

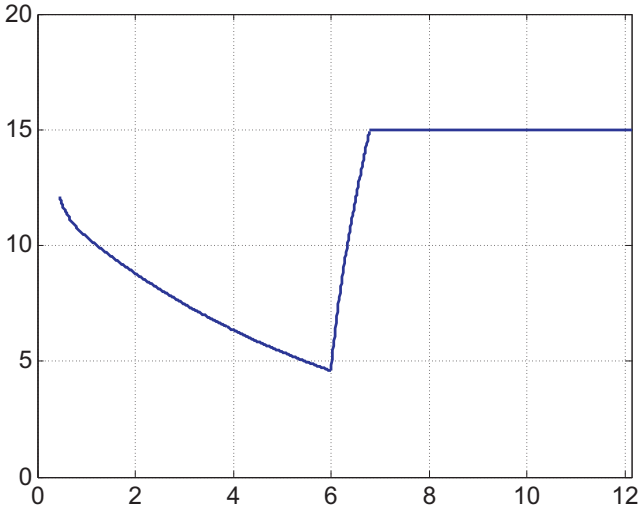

Figure 2

applied drug in these two ways are equal. Thus, one obtains

$$D_{Ni} = V_1 k_{10} C_0 + \frac{1}{t_{i+1} - t_i} \left(M_{20} - \frac{k_{12} C_0 V_1}{k_{21}} \right) \times \left(e^{-k_{21}(t_{i+1} - t_i)} - e^{-k_{21}(t_i - t_1)} \right), \qquad i = 1, 2, ..., N. \quad (9)$$

The solution of the system (1) for this control law is

$$\begin{aligned} x_1^{(i)}(t) =& C_{1i} e^{\alpha(t - t_{i-1})} + C_{2i} e^{\beta(t - t_{i-1})} + \frac{D_{Ni}}{k_{10} V_1}, \\ M_2^{(i)}(t) =& \frac{k_{12} V_1}{\alpha + k_{21}} C_{1i} e^{\alpha(t - t_{i-1})} + \frac{k_{12} V_1}{\beta + k_{21}} C_{2i} e^{\beta(t - t_i)} + \frac{D_{Ni} k_{12}}{k_{10} k_{21}}, \\ & i = 1, 2, ..., N, \end{aligned} \quad (10)$$

where the constants of integration C_{1i}, C_{2i} are

$$C_{1i} = \left(x_1^{(i-1)}(t_{i-1}) + \frac{D_{iN} \beta}{k_{10} k_{21} V_1} - \frac{x_2^{(i-1)}(t_{i-1})(\beta + k_{21})}{k_{12} V_1} \right) \frac{(\alpha + k_{21})}{\alpha - \beta},$$

$$C_{2i} = \left(\frac{x_2^{(i-1)}(t_{i-1})(\alpha + k_{21})}{k_{12} V_1} - x_1^{(i-1)}(t_{i-1}) - \frac{D_{iN} \alpha}{k_{10} k_{21} V_1} \right) \frac{(\beta + k_{21})}{\alpha - \beta}.$$

To evaluate the effectiveness of the substituting control law, we use the criterion introduced in [16]:

$$F_1 = \frac{1}{N}\left(\sum_{i=1}^{N}(X^2_{i\max})\right)^{1/2}, \tag{11}$$

where

$$X_{i\max} = \max|x_1(t) - C_0|,\ t \in [t_i, t_{i+1}].$$

It is clear that this criterion takes into account the maximal deviations of the plasma concentration in the first compartment $x_1(t)$ with respect to the prescribed value C_0.

3. Case $N = 2$

In this case the interval $[t_0, t_m]$ is divided into two subintervals by the point t_2 ($t_1 = t_0$, $t_3 = t_m$ are fixed), determined by the condition - the function $F_1(t_2)$ to obtain its minimal value. This minimum is reached for $t_2 = 7.2690$[hr] and the corresponding minimal value is $F_1 = 0.1975$. The corresponding substituting control law $D(t)$ has the form

$$D_2(t) = \begin{cases} D_{12}, & t_0 = t_1 < t \le t_2 \\ D_{22}, & t_2 < t \le t_3 = t_m, \end{cases}$$

where $D_{12} = 196.2$, $D_{22} = 100.2$.

On Figure 3 the plasma concentration $x_1(t)$ of the first compartment in the interval $[0, t_m]$, and on Figure 4 – the corresponding control law, are shown. In addition, the dividing of the interval $[t_0, t_m]$ into two subintervals could be clearly distinguished. The deviation of $x_1(t)$ in the interval is bounded as follows:

$$C_0 - \delta_2 \le x_1(t) \le C_0 + \delta_2, \quad t \in [t_0, t_m],$$

where $\delta_2 = 2.0665\%$. The comparison of these results with the correspondent results in [17] shows a certain closeness (there $t_2 = 1.6557$[hr] and $F_1 = 0.1993$, i.e., now one has a bit smaller value of the criterion F_1). The more profound analysis produces not a simple result's removal but a changed optimization problem.

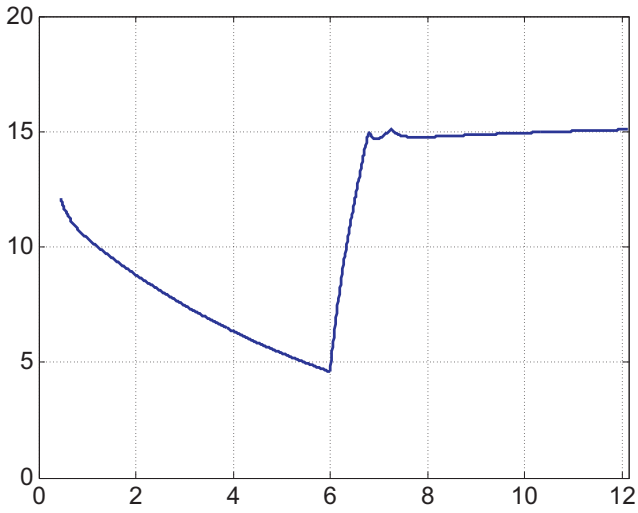

Figure 3

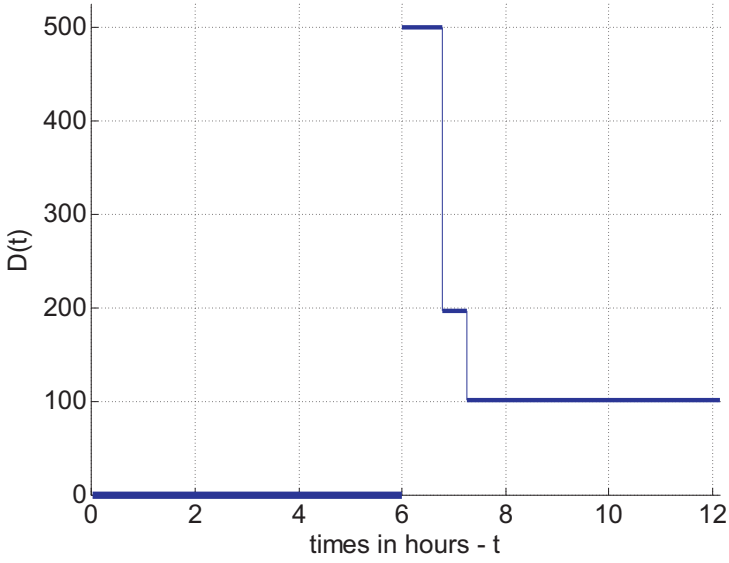

Figure 4

4. Case $N = 3$

In this case the interval $[t_0, t_m]$ is divided into three subintervals and one has two independent variables: t_2, t_3 ($t_1 = t_0$, $t_4 = t_m$ are fixed). The minimum of the function $F_1(t_2, t_3)$ will be sought by the coordinate search method. The following results are obtained:

$$\min F_1(t_2, t_3) = 0.0703,$$

which is reached by the dividing - 6.7861 7.0451 7.5178 12.1360, i.e., the minimal point is $(t_2, t_3) = (7.0451, 7.5178)$. The corresponding substituting control $D(t)$ is

$$D_3(t) = \begin{cases} D_{13}, & t_0 = t_1 < t \le t_2 \\ D_{22}, & t_2 < t \le t_3 \\ D_{33}, & t_3 < t \le t_4 = t_m, \end{cases}$$

where $D_{13} = 228.71$, $D_{23} = 141.87$, $D_{33} = 98.80$.

On Figure 5 the plasma concentration $x_1(t)$ in the first compartment for the interval $[0, t_m]$ is shown, and on Figure 6 – the corresponding control law. It could be seen also the division of the interval $[t_0, t_m]$ into three subintervals. The deviation of $x_1(t)$ in the interval $[t_0, t_m]$ is bounded as follows:

$$C_0 - \delta_3 \le x_1(t) \le C_0 + \delta_3, \quad t \in [t_0, t_m],$$

where $\delta_3 = 0.9024\%$.

The comparison of these results with the corresponding results in [17] demonstrates the same above mentioned tendency (the value of the criterion F_1 is again a bit less than the value in [17] – there $F_1 = 0.071$).

5. Conclusion

The investigations carried out demonstrate what is the situation when the drug administration by infusion follows immediately after the initial intravenous injection and the identification of the model's parameters. Analogous optimization problem like in [17] is stated and solved but its treatment does not allow any direct transferring of the results from [17]. As a general tendency here, a slight improvement of the optimization criterion could be observed.

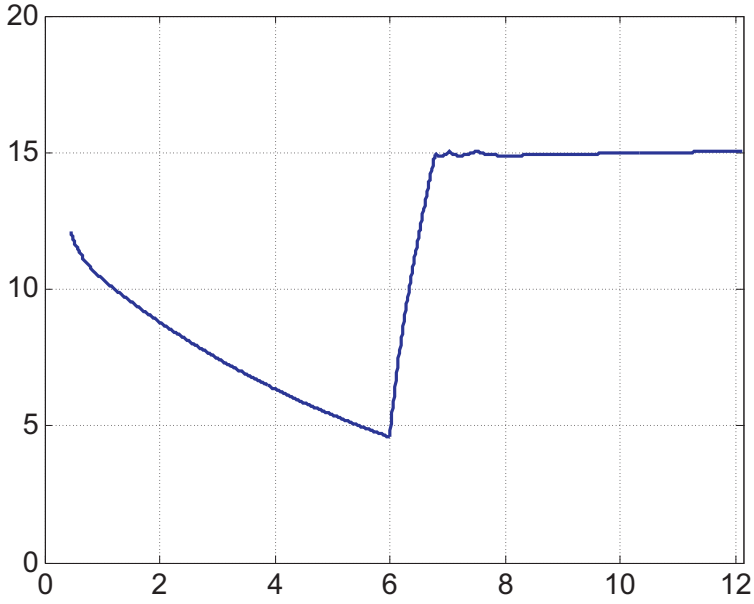

Figure 5

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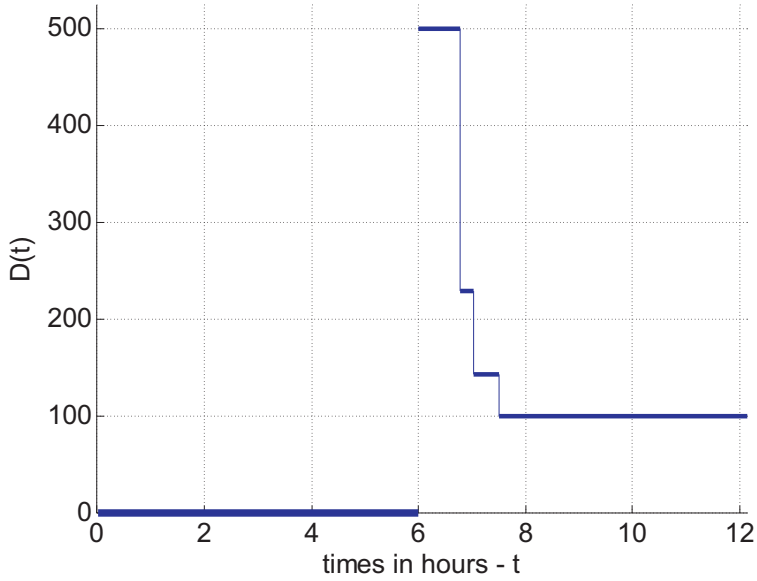

Figure 6

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