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SIMULATION OF OPTIMAL INFUSION RATE INPUT: PART I

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Abstract: In previous author's papers some problems of individualization and also some optimization problems related with the individual therapy of a patient were considered. A two compartment pharmacokinetic model was used to solve the following problem: First, a problem of identification was formulated and solved – this means to determine on the basis of experimental data the parameters of the two-compartment model. After this, the drug administration by infusion is considered and a control law which keeps the plasma concentration in the first compartment at a level prescribed by the therapist is found. Some optimization problems were solved. In the present paper we continue these investigations, and replacing control laws which keep the plasma concentration in the main compartment in given limits, are proposed.

AMS Subject Classification: 92C45
Key Words: pharmacokinetics, compartment models

1. Introduction

Pharmacokinetics is the science which quantities, as a function of time, the absorption, distribution and excretion of chemicals by the body. That is, it studies the behavior of drugs in the human body [1], [2], [3]. Pharmacological responses and toxicity are governed by the time-related concentration of drug and their interactions with receptors. The magnitude of the response depends on the pharmacokinetic characteristics of the chemical involved. The intensity of pharmacological or toxic effect is a function of the plasma concentration of

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active substance that reaches the receptors sites of action.

The knowledge of the pharmacokinetic profile of drug or toxic agent within an individual should allow the clinician to choose a dosage schedule that will produce and maintain a desired pharmacotherapeutical effect and yet allows toxicity to be kept under control.

In the previous author's papers (see [4], [5]) some problems of individualization and also some optimization problems related with the individual therapy of a patient were considered. A two compartment pharmacokinetic model was used to solve the following problem: At first, a problem of identification was formulated and solved – this means to determine on the basis of experimental data the parameters of the two-compartment model. After this, the drug administration is considered. It covers two stages - in the first one the drug is submitted by infusion into the main compartment until the plasma concentration reaches the prescribed by the therapist value in a moment of time t_0. In the following (the second stage) an appropriate control is determined in order to keep the plasma concentration in some sense "near" to this prescribed value (in an given interval of time $[t_0, t_m]$). Because the practical realization of the so determined control is very difficult, an approach to replace it with a suitable easy to implement administration is proposed. Two criteria to evaluate the different ways of drug administration were formulated. Related with this, some optimization problems were solved. In the present paper we continue this investigations partly changing the problem formulation. We seek such replacing control which keeps the plasma concentration in the main compartment in a given borders.

2. Problem Formulation

The behavior of the human body under drug administration modeled by a two-compartment model 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 sought control. This division - concentration for the first compartment and quantity for the second compartment is compelled because of the special features of the problem - we can measure the plasma concentration in the first compartment , while in the second one this is impossible. Our investigation starts at the moment t_0, when after the initial drug administration by infusion (with value D_0), the prescribed plasma concentration C_0 is already reached, and in the following interval $(t_0, t_m]$ we shall seek such control $D(t)$ which keeps the plasma concentration in the first compartment $x_1(t), t \in [t_0, t_m]$ in guaranteed borders - $C_0 - \delta \leq x_1(t) \leq C_0 + \delta$ (δ is a parameter which determines these borders).

In [4] a control $D(t)$ which keeps the plasma concentration $x_1(t), t \in [t_0, t_m]$ on the level C_0. It has the form

$$D(t) = V_1 k_{10} C_0 + (C_0 V_1 k_{12} - M_{20} k_{21}) e^{-k_{21}(t-t_0)}, \quad t \in (t_0, t_m], \tag{2}$$

where M_{20} is the quantity of drug in the second compartment in the moment t_0.

In Figure 1 a graph of this control is shown and at Figure 2 a graph of the plasma concentration $x_1(t)$ is demonstrated. From Figure 1 it is clear that after a constant control D_0 follows a jump and the control law (2).

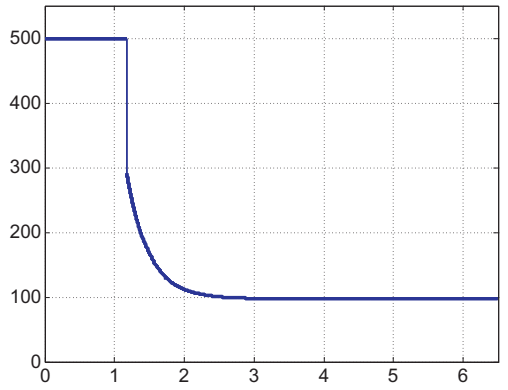

Figure 1

In [5] several laws of control which replace the law (2) and lead $x_1(t)$ very near to C_0 are proposed.

Here, at first, we shall assume control D_{11}, which is a constant in the whole interval $(t_0, t_m]$. It is natural to accept its value as a mean integral of the

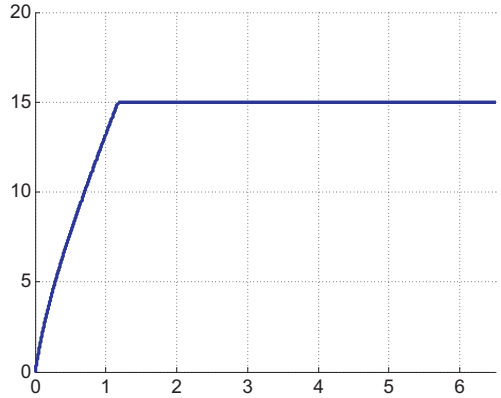

Figure 2

function $D(t)$ in the interval $[t_0, t_m]$, i.e.,

$$D_{11} = \frac{1}{t_m - t_o} \int_{t_0}^{t_m} D(t)dt. \tag{3}$$

After the corresponding calculation one obtains

$$D_{11} = V_1 k_{10} C_0 + \frac{1}{t_m - t_0} \left(M_{20} - \frac{k_{12} C_0 V_1}{k_{21}} \right) \left(e^{-k_{21}(t_m - t_0)} - 1 \right),$$

where M_{20} is the quantity drug in the second compartment in the moment t_0.

The reason to assume such approach is that these both controls - D_{11} and $D(t)$ - get in the human body equal quantities of drug.

Under the control (3) the plasma concentration $x_1(t)$ and the quantity $M_2(t)$ have the following form:

$$\begin{aligned} x_1(t) =& e^{\alpha(t-t_0)} C_1 + e^{\beta(t-t_0)} C_2 + \frac{D_{11}}{k_{10} V_1}, \\ M_2(t) =& \frac{k_{12} V_1 e^{\alpha(t-t_0)}}{\alpha + k_{21}} C_1 + \frac{k_{12} V_1 e^{\beta(t-t_0)}}{\beta + k_{21}} C_2 + \frac{D_{11} k_{12}}{k_{10} k_{21}}, \end{aligned} \tag{4}$$

where the constants of integration (and the above given M_{20}) are

$$C_1 = \left(C_0 - x_{20}\frac{\beta + k_{21}}{k_{12}V_1} + \frac{D_{11}\beta}{k_{10}k_{21}V_1} \right) \frac{\alpha + k_{21}}{\alpha - \beta},$$
$$C_2 = \left(x_{20}\frac{\alpha + k_{21}}{k_{12}V_1} - C_0 - \frac{D_{11}\alpha}{k_{10}k_{21}V_1} \right) \frac{\beta + k_{21}}{\alpha - \beta}$$
$$M_{20} = \frac{D_0\beta(\alpha + k_{21})}{k_{10}k_{21}(\alpha - \beta)} \frac{k_{12}e^{\alpha t_0}}{\alpha + k_{21}} - \frac{D_0\alpha(\beta + k_{21})}{k_{10}k_{21}(\alpha - \beta)} \frac{k_{12}e^{\beta t_0}}{\beta + k_{21}} + \frac{D_0 k_{12}}{k_{10}k_{21}},$$

and α, β are the roots of the characteristic equation of (1) -

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

The graphs shown in Figure 1 and Figure 2 are obtained for the following data: $k_{10} = 0.3134[hr^{-1}]$; $k_{12} = 2.7549[hr^{-1}]$; $k_{21} = 3.1326[hr^{-1}]$; $V_1 = 20.7322[1]$; $C_0 = 15[\mu g]$; $D_0 = 500[\mu g.hr^{-1}]$ (evaluated in [4]). For the same data in Figure 3 is shown the plasma concentration $x_1(t)$ achieved under the control D_{11} which is $D_{11} = 109.1\ [\mu g.hr^{-1}]$. From Figure 3 it is clear that

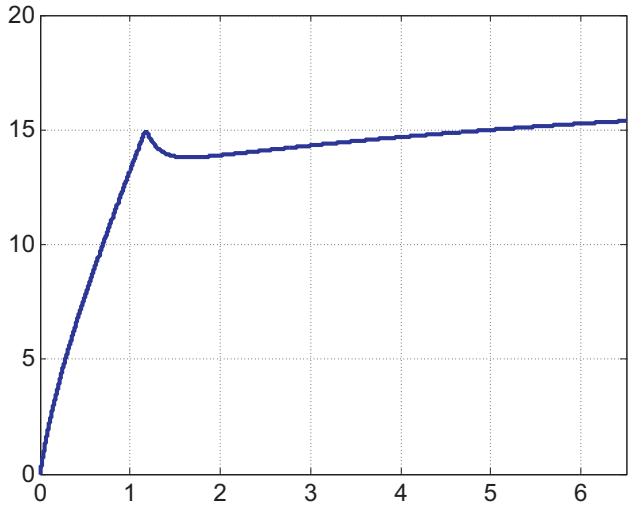

Figure 3

the function $x_1(t)$ possesses one minimum in the interval $[t_0, t_m]$. This minimum determines the maximal deviation of $x_1(t)$ about the prescribed concentration C_0. In [5] this minimum is determined for the more general case when the interval $[t_0, t_m]$ is divided into N equal subintervals (and the minimum in the first subinterval is found). For $N = 1$ (the considered now case) the maximal deviation about C_0 is $\delta_1 = 8.05\%$. Hence, if δ in the condition $C_0 - \delta \leq x_1(t) \leq C_0 + \delta$, $t \in [t_0, t_m]$ is greater than δ_1 the stated problem is already solved - the control $D_{11} = 109.1[\mu g.hr^{-1}]$ keeps the plasma concentration $x_1(t)$ in the prescribed borders.

Let us assume that this is not fulfilled and continue the investigations.

3. Case $N = 2$

After we have not achieved the desired result without dividing the interval $[t_0, t_m]$, it is natural to divide the interval into different subintervals. Let us state the problem more generally. Let us divide the interval $[t_0, t_m]$ into N different 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 a constant control which is mean integral of $D(t)$ in this subinterval. Thus one obtains

$$D_{Ni} = V_1 k_{10} C_0 + \frac{1}{t_{i+1} - t_i} \left(M_{20} - \frac{k_{12} C_0 V_1}{k_{21}} \right) \times \left(e^{-k_{21}(t_{i+1} - t_i)} - e^{-k_{21}(t_i - t_1)} \right), \qquad i = 1, 2, ..., N. \quad (5)$$

The solution of the system (1) for the subinterval $[t_i, t_{i+1}]$ has the form

$$\begin{aligned} x_1^{(i)}(t) =& C_{1i} e^{\alpha(t - t_{i-1})} + C_{2i} e^{\beta(t - t_{i-1})} + \frac{D_{Ni}}{k_{10} V_1}, \\ M_2^{(i)}(t) =& \frac{k_{12} V_1}{\alpha + k_{21}} C_{1i} e^{\alpha(t - t_{i-1})} + \frac{k_{12} V_1}{\beta + k_{21}} C_{2i} e^{\beta(t - t_i)} + \frac{D_{Ni} k_{12}}{k_{10} k_{21}}, \\ & i = 1, 2, ..., N, \end{aligned} \quad (6)$$

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 different divisions of the interval $[t_0, t_m]$, we shall use the criterion introduced already in [5] which takes into account the maximal deviations of $x_1(t)$ with respect to the value C_0:

$$F_1 = \frac{1}{N}\left(\sum_{i=1}^{N}(X_{i\max}^2)\right)^{1/2}, \tag{7}$$

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

For the case $N = 2$ we have one-dimensional minimization - the only variable is t_2 ($t_1 = t_0$, $t_3 = t_m$ are fixed). For the already given numerical data one can obtain the following results. In Figure 4 the graph of the function $F_1(t_2)$

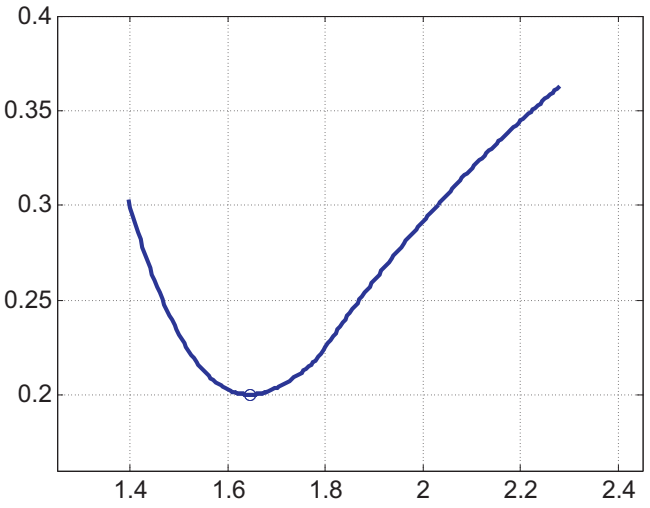

Figure 4

is shown and also its minimum is pointed. The optimal division of the interval $[t_0, t_m]$ is obtained for $t_2 = 1.6557$ [h] and the minimal value of the criterion is $F_1 = 0.1993$. The correspondent optimal control which replaces $D(t)$ 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 $D_{12} = 197.3$, $D_{22} = 100.3$.

In Figure 5 the graph of $x_1(t)$ for this division is presented, while in Figure 6 the graph of $D_2(t)$ is given.

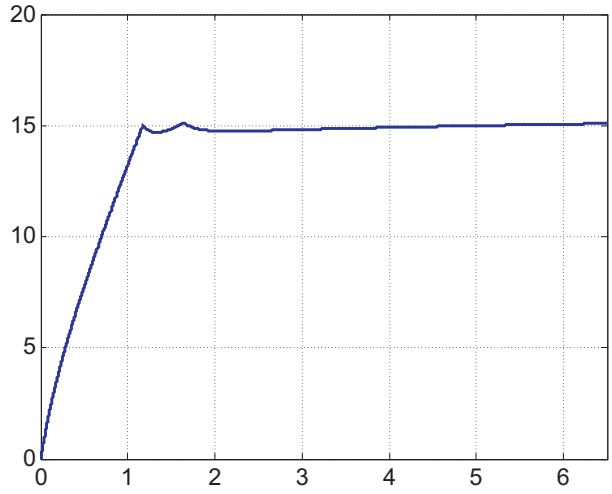

Figure 5

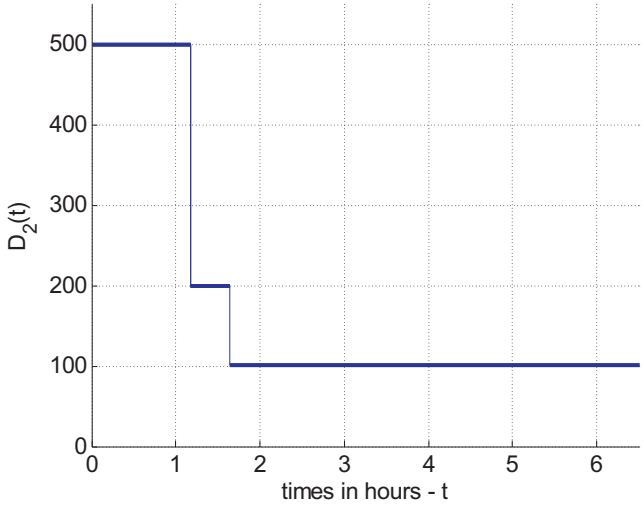

Figure 6

In Figure 7 the graph of $x_1(t)$ in a short band about C_0 in the interval $[t_0, t_m]$, as well as the corresponding subintervals, are shown.

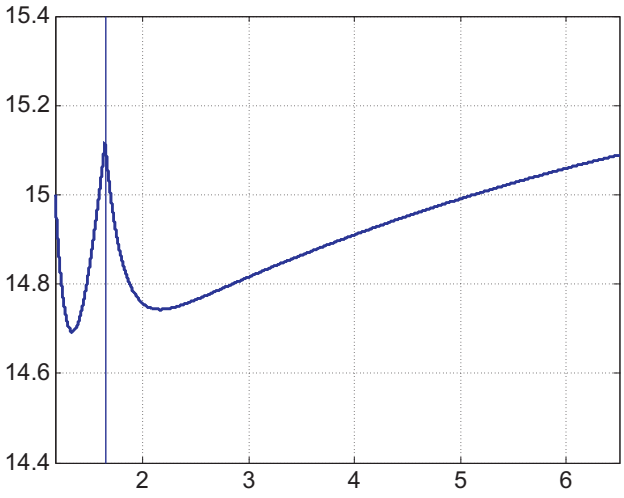

Figure 7

The maximal deviation of $x_1(t)$ about in the interval $[t_0, t_m]$ (with respect to C_0) is $\delta_2 = 2.0822\%$. This means that if δ in the condition $C_0 - \delta \leq x_1(t) \leq C_0 + \delta$, $[t_0, t_m]$. is greater than δ_2 the stated problem is already solved - the control $D_2(t)$ keeps the plasma concentration $x_1(t)$ in the prescribed borders.

Here we shall continue our investigations in order to obtain better results.

4. Case $N = 3$

In this case we divide the interval $[t_0, t_m]$ into three subintervals and have two independent variables $-t_2, t_3$ ($t_1 = t_0$, $t_4 = t_m$ are fixed). The minimum of the function $F_1(t_2, t_3)$ we seek employing coordinate search. For starting point we divide the interval the $[t_0, t_m]$ into three equal parts. As a result of the carried out optimization the following minimal value of the objective function is obtained – $\min F_1(t_2, t_3) = 0.0710$, and it is achieved for the division:

$$1.1738 \quad 1.4327 \quad 1.9051 \quad 6.5000,$$

i.e., the minimal point is $(t_2, t_3) = (1.4327 \quad 1.9051)$.

In Figure 8 the graph of for this division is presented.

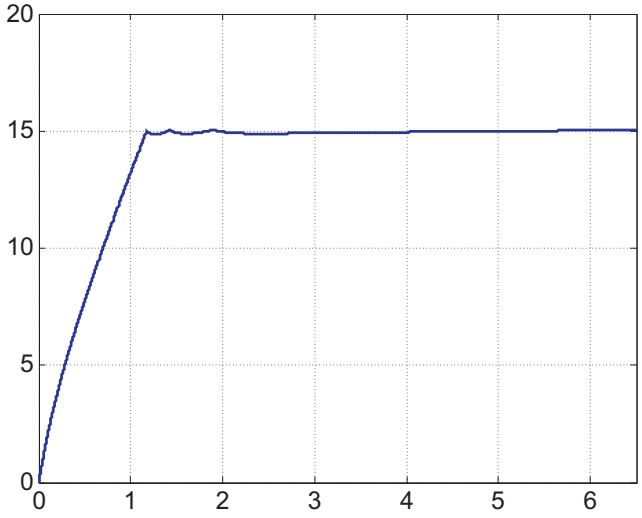

Figure 8

The corresponding optimal control replacing $D(t)$ has the form

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

where $D_{13} = 230.02$, $D_{23} = 142.34$, $D_{33} = 98.82$. A graph of this optimal control is given in Figure 9. In Figure 10 the graph of $x_1(t)$ in a short band about C_0 in the interval $[t_0, t_m]$, as well as the corresponding subintervals, are shown.

The maximal deviation of $x_1(t)$ about C_0 in the interval $[t_0, t_m]$ is $\delta_3 = 0.9180\%$. This means that the control $D_3(t)$ keeps the plasma concentration $x_1(t)$ in less than one percent about the prescribed value C_0.

In Figure 11 and Figure 12 the graph of the function $F_1(t_2, t_3)$ is presented (by 3D graphic and iso-lines). The pictures show a very good defined minimum of the function which supported the efforts for its finding.

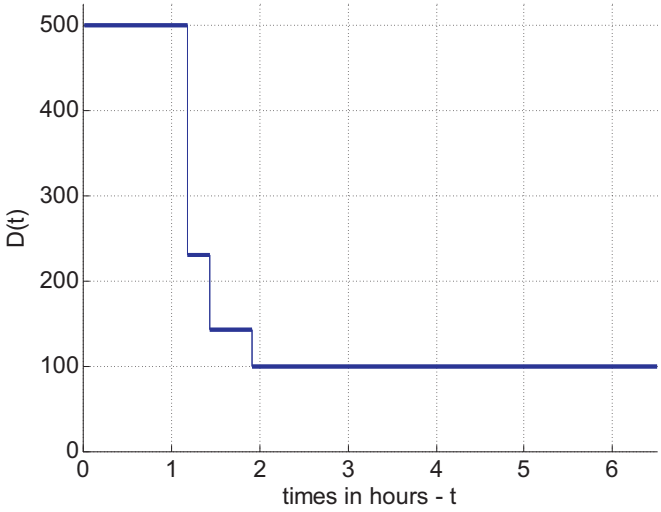

Figure 9

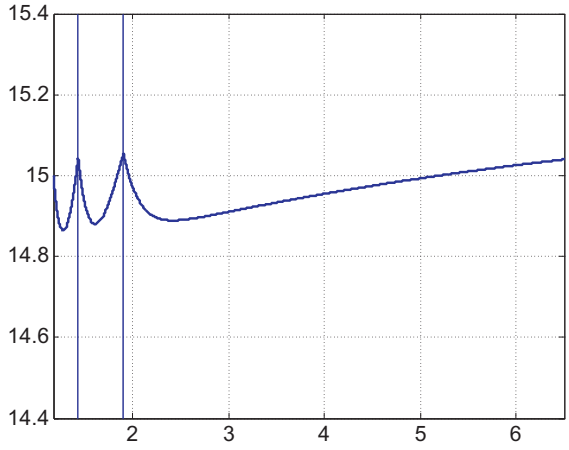

Figure 10

5. Conclusion

The considered investigations show how employing some optimization methods, a very useful approach for drug administration can be realized. The optimal

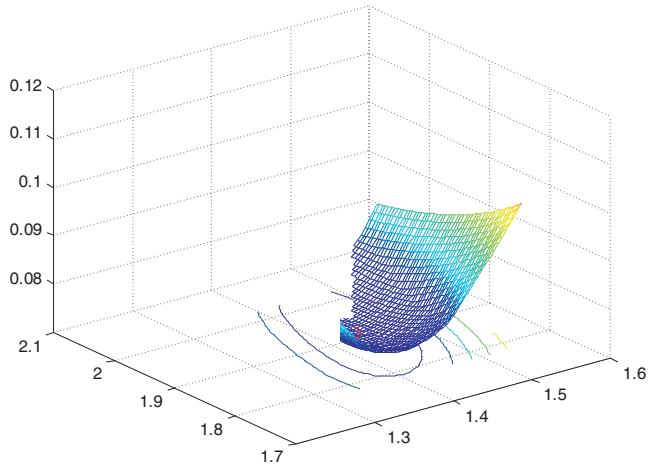

Figure 11

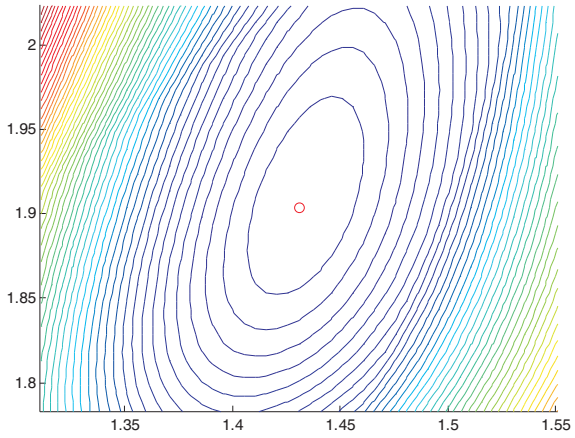

Figure 12

law theoretically found in [4] can be replaced by a control which is constant in the divided subintervals. The main result is the optimal division of the given interval into subintervals. It should be pointed the very sharp improvement for the results from one to two subintervals. The next improvement (from two to

three subintervals) is more moderate.

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