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Mathematical Modeling of an Ingerable Drug

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Abstract: *In the present study a study is made of the incidence in Brazil of different drugs, indicating the most used by age group and region; the metabolism of an ingestible drug in the human body is analyzed, the possibility of its elimination is analyzed, both for a patient that temporarily for consumption and for those who continue to use the drug. A model that simulates this kinetics is presented, a qualitative study of the system of equations presented and conclusions are given regarding the situation that the patient will present in the future.*
Key Words: *Drug, model, organ, patient.*

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I. Introduction

A classic example of a compartment system is the case of the kinetics of a drug in an organism, the situation to be analyzed is that corresponding to the ingestion and subsequent metabolism of a drug in an individual, [14] and [8]. Consider that the intake of the drug is orally and as soon as it enters the gastrointestinal is absorbed by the blood system and distributed throughout the body to be metabolized and finally eliminated. Consider how the compartment is a gastrointestinal tract, compartment two is the blood system and compartment three is given by the fundamental organs of our body, ie lungs, kidneys, heart, liver and brain.

One of the major problems facing humanity today is the indiscriminate consumption of different drugs, with the consequent affectations to health and social relations in general. But if we analyze this situation deeply, if we could reach the following conclusions, the main causes of death are not consumption, but trafficking, because confronting different groups dedicated to this activity those who defend this work support the personalities who support the liberation, as account adjustments would disappear and those who consume it for vanity would also leave consumption. This situation has been treated by different authors with criteria in both directions; [6] , [5], [10], [17], [13], [9] and [7]. Uma pesquisa realizada pelo CEBRID - Centro brasileiro de informações sobre drogas psicotrópicas, o II Levantamento Domiciliar sobre o uso de drogas psicotrópicas mostrou que o maior percentual de usuários de maconha, solvente e mera está na faixa etária entre 18 e 24 anos, os de cocaína e crack, entre 25 e 34 anos, e os de heroína maiores de 35 anos [4].

In [11] and [12] are treated the affections I produces consumption, be it alcol or another drug; in [1] and [2] are modeled the dynamics and impact of drga usage; this indicates the interest in treating the theme historically.

In relation to young people, the National School Health Survey (PENSE), carried out in 2012 by the Brazilian Institute of Geography and Statistics (IBGE) [3], used for the data collection a self-administered structured questionnaire on the smartphone, which included demographic characteristics, behavior of risk and health protection and other factors. Participation in the study was voluntary and anonymous, with possibility of non-response. The research project was approved by the National Commission for Research Ethics - CONEP, No. 16,805. A total of 109,104 students were interviewed in 2,842 schools. Research has shown that 7.3% of young people who are in school already use some illegal drugs, among them: marijuana, cocaine, crack, cola, loló, perfume, ecstasy. The highest percentages were recorded in the Center-West region, with 9.3% and South, with 8.8%. In relation to the municipalities, the capitals that obtained the highest percentages were Florianópolis (17.5%) and Curitiba (14.4%).

Comparing public and private networks, 7.5% of students in the public network have used illicit drugs, compared to 6.5% of private schools. In comparison to the PENSE in 2009, there was an increase of 8.7% to 9.9% of the 9th year students of municipal schools in the capitals that have already used illicit drugs.

Marijuana is the name received in Brazil by the plant Cannabis sativa, which has more than 400 active substances, among them THC (tetrahydrocannabinol), which is mainly responsible for its effects. Its presence in the country dates from the eighteenth century for the production of fibers, but it is believed that it was used before that by the slaves. Its flowers and leaves can be smoked, taking effect in just seconds or ingested, where its absorption is slow, from 30 to 60 minutes.

Hashishe is a concentrated form of marijuana and is much more potent than the leaves and flowers of marijuana. The skunk is nothing more than a variety of the strongest plant that has been selected to produce a much larger amount of THC. The physical effects after use are: eyes become slightly red, mouth dry and heart pounding. But the use for an extended period of time can cause chronic effects, such as: in men the decrease in testosterone and in women hormonal changes reaching up to inhibition of ovulation. It can also affect the lungs, bringing respiratory problems, especially bronchitis and interferes in the learning and memorizing capacity, and can induce a state of diminished motivation.

Marijuana is also used for therapeutic purposes and is recognized as a drug in some clinical conditions: reducing nausea and vomiting produced by cancer drugs, improving epilepsy, and improving the general state of AIDS patients.

In relation to Marijuana, PENSE was made observing the use in the 30 days before the survey, and the result obtained when considering the total number of students surveyed in the country was 2.5%. Regarding gender, the rate was 3.1% for boys and 2.0% for girls. Of the students who used illicit drugs, 34.5% used marijuana and 6.4% used crack cocaine. Schoolchildren living in the South Region had the highest marijuana consumption of 3.6%. The lowest percentage was observed in the Northeast Region, 0.9%. Considering the municipalities of Capitais, Florianópolis presented the highe

Crack is the crystalline form of cocaine and is considered its most potent form, and also the most dangerous form. It is between 75% and 100% pure, much stronger and potent than regular cocaine, which usually comes in the form of powder. It comes in solid blocks or crystals, ranging in color from yellow to pale pink or white. The drug can be heated or smoked, and gets its name because it makes the sound of a small pop or pop when heated.

Smoking crack allows the drug to reach the brain very quickly and thus brings an intense and immediate euphoria - but of short duration - that lasts about fifteen minutes. A consumer may become addicted after their first time experiencing crack because the effect is more intense when the drug is smoked rather than inhaled.

The President of the Republic, on May 20, 2010, issued Decree No. 7,179, which established the Integrated Plan to Combat Crack and Other Drugs. Some initiatives were adopted due to the expansion of crack in the country and its seriousness for the population. Thus, the National Secretariat for Drug Policy (SENAD), in partnership with Fiocruz, conducted an unprecedented research in 2012, which generated the book "National Survey on the use of crack." The study looked at data from 21,500 people over the age of 18 who had used crack or similar at least 25 days in the 6 months prior to the survey. The estimate is that there are approximately 370,000 users in the 26 capitals plus the federal district, which corresponds to 0.8% of the population of the capitals; this figure represents 35% of illicit drug users in Brazil.

Among the main results, the research showed the profile of the crack user: they have a mean age of 28 to 30 years, male 78.68%, non-white 79.15%, unmarried individuals 60.64%, between 5th and 9th year of elementary school 57.60%, live in the streets 40%, have sporadic or autonomous work 65%, also consume alcohol 77.07% and also consume 85.06% tobacco.Em relação aos menores de idade, a pesquisa aproximadamente 50 mil crianças e adolescentes usam regularmente essa substância nas capitais do país, o que representa 14% da população do crack no Brasil. A maior parte deles 56%, também estão concentrados nas capitais do Nordeste, onde foram identificados 28 mil menores nesta situação.

Cocaine has been consumed for at least 5,000 years; is a natural substance extracted from the plant Erythroxylon coca, which occurs in South America. It can be consumed in the form of powder, stone (crack) or paste. The effects of the powder occur between 10 to 15 minutes and its effect lasts, approximately 45 minutes.

According to a study by the United Nations Office on Drugs and Crime (UNODC), the World Drug Report of 2015 indicates that coca cultivation continued to decline in 2013, reaching the lowest level since 1990. With the prevalence of 0.4 % in the global adult population, cocaine use remains high in Western and Central Europe, North America and Oceania (Australia), although recent data show an overall declining trend. In Brazil, between 2004 and 2010, there was an increase in cocaine use among students. The changes were not uniform among the 27 capitals.

With less crime due to their release can include the case of alcoholic beverages, which are consumed by citizens of different ages and sex including children and adolescents, but in this case there is no problem of trafficking which greatly limits deaths by this activity. Ramos, Sérgio de Paula (2008).

The treatment that we will make in this case corresponds to other models presented in the researches of other diseases, especially the case of sicklemia, quite treated and with a large number of already developed models, we will only mention some of these works, where three papers are presented referring to polymerization and crystallization of hemoglobin. In [15] and [16] are treated the qualitative study of different models in an autonomous and non-autonomous form of polymer formation.

II. Formulation Of The Model.

Initially we will give some basic principles that we will take into account in the writing of the model; let us consider as compartment one the gastrointestinal system, the two the blood system and the three main organs; let's denote by $\overline{x_1}$, $\overline{x_2}$ and $\overline{x_3}$ the permissible values of the drug concentration in compartments one, two and three respectively; we will indicate the following other variables to consider:

- $\tilde{x}_1(t)$ represents the concentration of the drug in compartment one at the moment t.
- $\tilde{x}_2(t)$ represents the concentration of the drug in compartment two at the moment t.
- $\tilde{x}_3(t)$ represents the concentration of the drug in compartment three at the moment t.

In the system we will consider the variables x_1, x_2 and x_3 defined as follows $x_1 = \tilde{x}_1(t) - \overline{x_1}$, $x_2 = \tilde{x}_2(t) - \overline{x_2}$ and $x_3 = \tilde{x}_3(t) - \overline{x_3}$ so when $(x_1, x_2, x_3) \to (0,0,0)$ so $\tilde{x}_1(t) \to \overline{x_1}$, $\tilde{x}_2(t) \to \overline{x_2}$ and $\tilde{x}\ (t) \to \overline{x_3}$.

The dynamics of the process are related to: $a_{ij}x_i(t)$ is the drug flow from the magazine to the magazine j; and $f_i(t, x_1, x_2, x_3)$, $(i = 1,2,3)$ is related to the elimination of the drug through the compartment i. Assuming that the $a_{ij}x_i$ proportional to the quantities x_i present in each compartment, the mathematical model that describes the process is given by the following system:

$$\begin{cases} \dfrac{dx_1}{dt} = (a_{11} - a_{12} - a_{13})x_1 + a_{31}x_3 + f_1(t, x_1, x_2, x_3) \\ \dfrac{dx_2}{dt} = a_{12}x_1 - a_{23}x_2 + a_{32}x_3 + f_3(t, x_1, x_2, x_3) \\ \dfrac{dx_3}{dt} = a_{13}x_1 + a_{23}x_2 + (-a_{31} - a_{32})x_3 + f_3(t, x_1, x_2, x_3) \end{cases} \quad \textbf{(1)}$$

At where $a_{11} \geq 0$, $a_{11} = 0$ if the patient stopped taking the drug and $a_{11} > 0$ if you still continue to use the drug.

At the initial moment $t = 0$, the initial conditions of each compartment are given by:

- $x_1(0) = D_0$ (amount of drug ingested)
- $x_2(0) = 0$ (the drug has not started to circulate in the body),
- $x_3(0) = 0$ (the drug has not yet begun to act).

Here it is being considered that the drug of the gastrointestinal system passes into the blood and some organ, and that after a certain time of the organs can pass back to the gastrointestinal system to be eliminated, but it is considered that the blood does not return directly to the gastrointestinal system .

There is thus a Cauchy problem given by the system (1) with the initial conditions: $x_1(0) = D_0$, $x_2(0) = 0$, $x_3(0) = 0$.

III. Qualitative Analysis.

In order to arrive at conclusions regarding the conditions to be fulfilled to achieve the elimination of the drug from the organism, we will assume that the system is autonomous, and, in addition, that $a_{11} = 0$; in this case the system can be written as follows,

$$\begin{cases} x_1' = -a_1x_1 + a_3x_3 + X_1(x_1, x_2, x_3) \\ x_2' = b_1x_1 - b_2x_2 + b_3x_3 + X_2(x_1, x_2, x_3) \\ x_3' = c_1x_1 + c_2x_2 - c_3x_3 + X_3(x_3, x_2, x_3) \end{cases} \quad \textbf{(2)}$$

In accordance with the characteristics of the system, the behavior of the trajectories in many cases can be determined using the system of first approximation, for this we determine the eigenvalues of the matrix of the linear part of the system, that is, the roots of the following characteristic equation,

$$\begin{vmatrix} -a_1-\lambda & 0 & a_3 \\ b_1 & -b_2-\lambda & b_3 \\ c_1 & c_2 & -c_3-\lambda \end{vmatrix} = 0 \Leftrightarrow \lambda^3 + n_1\lambda^2 + n_2\lambda + n_3 = 0.$$

At where,
$n_1 = b_2 + c_3$, $n_2 = b_2c_3 - b_3c_2 + a_3c_1 + a_1b_2 + a_1c_3$,
$n_3 = a_2b_3c_2 - a_3b_1c_2 - a_3b_2c_1 + a_1b_2c_3$

If the conditions of Hurwitz are satisfied,
$n_i > 0$, $i = 1,2,3$ e $n_1n_2 > n_3$.

Then the real part of the roots of the characteristic equation has a negative real part, and by the criterion of first approximation the linear system associated to the system (2) and the same system (2) is asymptotically stable and, thus, drug concentrations will converge to the admissible concentrations, which leads to the conclusion that;

Conclusion: If the conditions, $n_i > 0$, $i = 1,2,3$ e $n_1n_2 > n_3$ the concentrations of the drug will tend to the admissible concentrations, and therefore the patient will have no complications. Otherwise, it is to say if these conditions are not satisfied one must take the prophylactic measures to prevent any type of complication.

IV. Quasi-Normal Form.

If in the characteristic equation one has to, $n_3 = 0$, but $n_i > 0$, $i = 1,2,$ then the matrix of the linear part of the system has a unique null value and two with a real negative part, that is to say we are in the presence of a critical case, for which it is necessary to simplify the system and apply the Qualitative Theory of Differential Equations.

Here is the case where, $\lambda_1 = 0$ and $\operatorname{Re}\lambda_i < 0$ for $i = 2,3$. By means of a non-degenerate linear transformation $X = QY$, the system 2 can be reduced to the form,

$$\begin{cases} y_1' = Y_1(y_1, y_2, y_3) \\ y_2' = \lambda_2 y_2 + Y_2(y_1, y_2, y_3) \\ y_3' = \lambda_3 y_3 + Y_3(y_1, y_2, y_3) \end{cases} \quad \textbf{(3)}$$

Theorem1: The exchange of variables,

$$\begin{cases} y_1 = z_1 + h_1(z_1) + h^0(z_1, z_2, z_3) \\ y_2 = z_2 + h_2(z_1) \\ y_3 = z_3 + h_3(z_1) \end{cases} \quad \textbf{(4)}$$

transforms the system (3) in the following quasi-normal form,

$$\begin{cases} z_1' = Z_1(z_1) \\ z_2' = \lambda_2 z_2 + Z_2(z_1, z_2, z_3) \\ z_3' = \lambda_3 z_3 + Z_3(z_1, z_2, z_3) \end{cases} \quad \textbf{(5)}$$

At where h^0, Z_2, Z_3 annul for $z_2 = z_3 = 0$.

Demonstration: By deriving the transformation (4) along the trajectories of systems (3) and (5) we obtain the system of equations,

$$\begin{cases} (p_2\lambda_2 + p_3\lambda_3)h^0 + Z_1(z_1) = Y_1 - \dfrac{dh_1}{dz_1}Z_1 - \dfrac{\partial h^0}{\partial z_1}Z_1 - \dfrac{\partial h^0}{\partial z_2}Z_2 - \dfrac{\partial h^0}{\partial z_3}Z_3 \\ \lambda_2 h_2 + Z_2 = Y_2 - \dfrac{dh_2}{dz_1}Z_1 \\ \lambda_3 h_3 + Z_3 = Y_3 - \dfrac{dh_3}{dz_1}Z_1 \end{cases} \quad \textbf{(6)}$$

To determine the series that intervene in the systems and the transformation, we will separate the coefficients of the power of degree $p = (p_1, p_2, p_3)$ in the following two cases:

Case I: Making in the system (6) $z_2 = z_3 = 0$, is to say to the vector $p = (p_1, 0, 0)$ results the system,

$$\begin{cases} Z_1(z_1) = Y_1(z_1 + h_1, h_2, h_3) - \dfrac{dh_1}{dz_1}Z_1 \\ \lambda_2 h_2 = Y_2 - \dfrac{dh_2}{dz_1}Z_1 \\ \lambda_3 h_3 = Y_3 - \dfrac{dh_3}{dz_1}Z_1 \end{cases} \quad \textbf{(7)}$$

The system (7) allows to determine the coefficients of the series, Z_1, h_1, h_2 and h_3, where for being the resonant case $h_1 = 0$, and the remaining series are determined uniquely.
Case II: In the case When $z_2 \neq 0$ and $z_3 \neq 0$ of the system (6) it follows that,

$$\begin{cases} (p_2\lambda_2 + p_3\lambda_3)h^0 = Y_1 - \dfrac{\partial h^0}{\partial z_1}Z_1 - \dfrac{\partial h^0}{\partial z_2}Z_2 - \dfrac{\partial h^0}{\partial z_3}Z_3 \\ Z_2 = Y_2(z_1 + h_1 + h^0, z_2 + h_2, z_3 + h_3) \\ Z_3 = Y_3(z_1 + h_1 + h^0, z_2 + h_2, z_3 + h_3) \end{cases} \quad \textbf{(8)}$$

Because the series of the system (5) are known expressions, the system (8) allows to calculate the series h^0, Z_2 and Z_3. This proves the existence of the exchange of variables.
In the system (5) the function Z_1 admits the following development in series of powers:

$$Z_1(z_1) = \alpha z_1^s + \dots$$

At where α is the first non-zero coefficient and s is the corresponding power.

Theorem2: If $\alpha < 0$ and s is odd, then the trajectories of the system (5) are asymptotically stable, otherwise they are unstable.
Demonstration: Consider the positive defined Lyapunov function,

$$V(z_1, z_2, z_3) = \frac{1}{2}(z_1^2 + z_2^2 + z_3^2)$$

The function V is such that its derivative along the trajectories of the system (5) has the following expression,

$$V^{'}(z_1, z_2, z_3) = \alpha z_1^2 + \lambda_1 z_2^2 + \lambda_2 z_3^2 + R(z_1, z_2 + z_3)$$

This function is defined as negative because in R potencies of degrees higher than those indicated in the initial part of the expression of the derivative of V, this allows us to state that the equilibrium position is asymptotically stable.

V. Conclusions

1. For the characteristics of the problem considered it is natural for the critical case analyzed to appear.
2. The almost normal form combined allows for great difficulties to make a qualitative study of the trajectories of the system.

3. The theorems one of the methodology to follow so that the original system is simplified, transforming it in almost normal form, in order to find a better treatment to the process studied.
4. If $\alpha < 0$ and s is odd, the patient will remain in the basal state at a later time than the time at which the analysis is performed.
5. If the above conditions are not met, the prophylactic measures necessary to change the clinical picture and prevent a fatal outcome as a consequence of excessive drug concentration should be taken.

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