Journal of Multidisciplinary Engineering Science and Technology (JMEST)
ISSN: 2458-9403
Vol. 7 Issue 2, February - 2020

Combined Normal Form In The Model Of An Injectable Drug

B. Aguilar[a] , L. Leão[c], S. Sánchez[a], K. Oliveira[b], M. Lacort[b], R. Ferreira[b], E. Rodrigues[b], A. I. Ruiz[b]
sandys@csd.uo.edu.cu; lleide.lopes@hotmail.com; lacortt@upf.br; raineynascimento@hotmail.com; erpereira@uea.edu.br; iruiz2005@yahoo.es
a: Faculty of Mathematics and Computation, Universidad de Oriente.
b: University of the State of Amazonas.
c: Federal University of Amazonas.

***Abstract*—In the present work a study of the different tendencies with regard to the release or not of the drug is made; the dynamics of an injectable drug in a human organism is treated, the possibility and its elimination is analyzed, either for a patient that temporarily for consumption or for those who continue to use the drug; the most commonly consumed drugs in Brazil are indicated, as well as their main effects. A model is presented by means of a system of differential equations that simulates said kinetics, the system is reduced to the combined normal form, a qualitative study of the presented system is presented, and conclusions are drawn regarding the situation that the patient will present in the future.**

Keywords—Drug, model, organ, patient.

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 injected and as soon as it enters the blood system is absorbed 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.

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. In relation to minors, the survey approximately 50 thousand children and adolescents regularly use this substance in the country's capitals, which represents 14% of the crack population in Brazil. Most of them 56%, are also concentrated in the capitals of the Northeast, where 28 thousand minors have been identified in this situation.

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 time 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 $(x_1, x_2, x_3) \rightarrow (0,0,0)$ so $\tilde{x}_1(t) \rightarrow \overline{x_1}$, $\tilde{x}_2(t) \rightarrow \overline{x_2}$ and $\tilde{x}_3(t) \rightarrow \overline{x_3}$.

The dynamics of the process are related to: $a_{ij} x_i(t)$ is the drug flow of the compartment i to the compartment j; $f_i(x_1, x_2, x_3)$, $(i = 1,2,3)$ 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:

$$\begin{cases} x_1' = a_{31}x_3 + f_1(x_1, x_2, x_3) \\ x_2' = (a_{22} - a_{23})x_2 + a_{32}x_3 + f_2(x_1, x_2, x_3) \\ x_3' = a_{23}x_2 + (-a_{31} - a_{32})x_3 + f_3(x_3, x_2, x_3) \end{cases} \quad \textbf{(1)}$$

At where $a_{22} \geq 0$, and $a_{22} = 0$ if the patient stopped injecting the drug and $a_{22} > 0$ if you are still consuming the drug.

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

-$x_1(0) = 0$ (the drug has not started to circulate in the body)

-$x_2(0) = A$ (amount of drug that passes into the blood),

-$x_3(0) = 0$ (the drug has not started to circulate in the body).

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: $x_1(0) = A_1$, $x_2(0) = 0$, $x_3(0) = A_3$.

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,

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

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,

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

At where, $n_1 = b_2 - c_3$, $n_2 = b_2c_3 + b_3c_2$.

If the conditions: $n_i > 0$, $i = 1{,}2$and $n_3 = 0$, the characteristic equation has a negative root and two other roots with real part less than or equal to zero, because this is a critical case the Qualitative Theory of Differential Equations will be applied to arrive at conclusions regarding the trajectories of the system (2).

According to the characteristics of the system that models the dynamics of an injectable drug in the organism, a combination of critical cases can be presented, in this case it could be the existence of a null value and a pair of pure imaginary eigenvalues $b_2 = c_3$; thus making use of the Analytical Theory of Differential Equations the system will be transformed to a simpler form that in this case will be the almost normal form combined.

This is the autonomous case, the non-autonomous case can be treated as it does in Sánchez, S., Fernández, G. A. A., Ruiz. A. I., & Carvalho, E. F (2015), where the case in which time dependence is periodic is specifically treated. We will consider the combined critical case, when the eigenvalues of the matrix of the linear part of the system are $\lambda_1 = 0$, $\lambda_2 = \sigma i$ and $\lambda_3 = -\sigma i$. By means of a non-degenerate linear transformation $X = QY$, o system (2) can be reduced to the shape,

$$\begin{cases} \dfrac{dy_1}{dt} = Y_1(y_1, y_2, y_3) \\ \dfrac{dy_2}{dt} = \sigma i y_2 + Y_3(y_1, y_2, y_3) \\ \dfrac{dy_3}{dt} = -\sigma i y_2 + Y_3(y_1, y_2, y_3) \end{cases} \quad \textbf{(3)}$$

Theorem 1: 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) into the system,

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

at where $z_3 = \bar{z}_2$, P and $\bar{P}$ are conjugated, in addition Z_2, Z_3 and h^0 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,

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

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 $p=(p_1,0,0)$ the system

,

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

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, and the remaining series are determined in a unique way.

Case II) This is the case when $z_2\neq 0$ and $z_3\neq 0$ of the system (6),

$$\begin{cases}\boldsymbol{(p_1-p_2)h^0=Y_1(z_1+h_1+h^0,z_2+h_2,z_3+h_3)}\\ \qquad\boldsymbol{-\frac{\partial h^0}{\partial z_1}Z_1-\frac{\partial h^0}{\partial z_2}Z_2-\frac{\partial h^0}{\partial z_3}Z_3}\\ \boldsymbol{Z_2=Y_2(z_1+h_1+h^0,z_2+h_2,z_3+h_3)}\\ \boldsymbol{Z_3=Y_3(z_1+h_1+h^0,z_2+h_2,z_3+h_3)}\end{cases} \quad (8)$$

Because the series of the system (5) are known expressions, the system (8) allows to calculate the series h^0, Z_2 and This proves the existence of the exchange of variables.

Theorem 2: The transformation of coordinates,

$$\begin{cases}z_1=u_1\\ z_2=u_2+\overline{h}_2(u_2,u_3)\\ z_3=u_3+\overline{h}_3(u_2,u_3)\end{cases} \quad \textbf{(9)}$$

reduces the system (5) to the combined normal form,

$$\begin{cases}u_1'=U_1(u_1)\\ u_2'=i\sigma z_1+u_1P(u_1u_2)\\ u_3'=-i\sigma u_2+u_2\overline{P}(u_1u_2)\end{cases} \quad \textbf{(10)}$$

Demonstration: Deriving the transformation (9) to the logo of the trajectories of systems (5) and (10) we obtain the system of equations,

$$\begin{cases}U_1(u_1)=Z_1(z_1)\\ (p_1-p_2-1)i\sigma\bar{h}_2+u_2P=Z_2-\frac{\eth\bar{h}_2}{\eth u_2}u_2P-\frac{\eth\bar{h}_2}{\eth u_3}u_3\bar{P}\\ (p_1-p_2-1)i\sigma\bar{h}_3+u_3\bar{P}=Z_3-\frac{\eth\bar{h}_3}{\eth u_2}u_2P-\frac{\eth\bar{h}_3}{\eth u_3}u_3\bar{P}\end{cases} \quad \textbf{(11)}$$

The system (11) allows the series $\overline{h}_2$, $\overline{h}_3$, P and $\overline{P}$ thus the theorem being proved. Because P and $\overline{P}$ are different from zero in the resonant case, ie when satisfying equations $p_1-p_2-1=0$ and $p_1-p_2+1=0$ isso garante a forma antes indicadas para essas séries; entretanto $\overline{h}_2$ e $\overline{h}_3$ por ser não ressonantes são determinados de forma única.

In the system (10) the functions P and U_1 admit the following development in series of powers:

$$P(u_2u_3)=\sum_{n=k}^{\infty}a_n(u_2u_3)^n+i\sum_{n=l}^{\infty}b_n(u_2u_3)$$

and

$$U_1(u_1)=\alpha u_1^s+\dots$$

Theorem 3: If $\alpha<0$, s odd and $a_k<0$, then the trajectories of the system (10) are asymptotically stable, otherwise they are unstable.

Demonstration: Consider the positive defined Lyapunov function,

$$V(u_1,u_2,u_3)=\frac{u_1^2}{2}+u_2u_3$$

The function V is such that its derivative along the trajectories of the system (10) has the following expression,

$$V'(u_1,u_2,u_3)=\alpha u_1^{s+1}+a_k(u_2u_3)^{k+1}+R(u_1,u_2,u_3)$$

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; in this case, it follows that $\tilde{x}_1(t)\to\overline{x_1}$, $\tilde{x}_2(t)\to\overline{x_2}$ and $\tilde{x}_3(t)\to\overline{x_3}$.

IV. CONCLUSION

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. Theorems one and two give the methodology to follow so that the original system is simplified in order to find a better treatment to the process studied.

4. If $\alpha < 0$, s odd and $a_k < 0$, the patient will remain in the basal state at a later time than the analysis performed, since the concentrations of the drug per compartments converge to the values admissible by the organism.

5. If the above conditions are not met, they should take the prophylactic measures necessary to change the clinical picture and prevent a fatal outcome as a consequence of drug concentration, as an overdose could result.

REFERENCES

[1]. Behrens, D. A., Caulkins, J. P., Tragler, G., Haunschmied, J. L., & Feichtinger, G. . A dynamic model of drug initiation: implications for treatment and drug control. Mathematical Biosciences, 159 (1), 1-20. 1999.

[2]. Borack, J. I. An estimate of the impact of drug testing on the deterrence of drug use.Military Psychology, 10 (1), 17-25. 1998.

[3]. Brazilian Institute of Geography and Statistics (IBGE),(2012)

[4]. Disponível em: http://200.144.91.102/sitenovo/download.aspx?cd=54 . Acesso em 09. Junho. 2016.

[5]. Castro, Élcio Pinheiro. The New Traffic Law: Misuse of Drugs and Special Courts. Criminal Law and Criminal Procedure. Porto Alegre: Magister Magazine, p. 5-13, Aug / Sep, 2006.

[6]. Dionê, Debora; MUTTINI, Rúbia. Drugs, only school does not want to see. New school. São Paulo, SP, Year XXII, n. 205, September 2007.

[7]. Hartmann, Arlete. Drug use crime or exercise a right? Porto Alegre: Editora Síntese, 1999.

[8]. Martinez, M.N. Article I: Nonocompartmental Methods of Drug Characterization: Statistical moment Theory. *JAVMA*, 213. 974-980. (1998).

[9]. Mendonça, Andrey Borges de; CARVALHO, Paulo Roberto Galvão de. Law of Drugs: Law 11,343,

of August 23, 2006 - Commented article by article. São Paulo: Editora Method, 2007.

[10]. Oliveira, Pedro Ribeiro. No drug is much better. Young world. Porto Alegre, RS, n 313, Feb 2001.

[11]. Pineda-Ortiz, J., & Torrecilla-Sesma, M. Neurobiological mechanisms of drug addiction.

Addictive, 1 (1), 1-12. (1999)

[12]. Ramos, Sérgio de Paula. Alcohol: who pays the bill is us. Young world. Porto Alegre, RS, Ano 46, n 383, Fev 2008.

[13]. Rangel, Paulo. Criminal Procedural Law. 12.ed. Rio de Janeiro: Editora Lumen Juris, 2007.

[14]. Rodney Carlos Bassanezi. “Mathematical Modeling”. São Paulo.2004.

[15]. Sánchez, Sandy; Ruiz, Antonio I.; Fernández, Adolfo. "A model of the molecular processes of the

polymerization and crystallization of Hemoglobin S", Rev. Mathematical Sciences. 26 (2012), No.

1, pp 53 -- 57.

[16]. Sánchez, S., Fernández, G. A. A., Ruiz. A. I., & Carvalho, E. F "Model of the periodic

coefficients in the polymerization function ". Tecnica Vitivinicola Journal, (2016).

[17]. Silva, Edevaldo Alves. Toxic in Brazilian Criminal Law. São Paulo: Editor José Bushatsky, 1973.