# ENGINEERING SCIENCES: PHARMACOKINETICS AND PHARMACODYNAMICS AS AN INTER- AND MULTIDISCIPLINARY FIELD

# ESTUDOS DE ENGENHARIAS: FARMACOCINÉTICA E FARMACODINÂMICA COMO UM CAMPO INTER- E MULTI-DISCIPLINAR

# ESTUDIOS DE INGENIERÍAS: FARMACOCINÉTICA Y FARMACODINÁMICA COMO UN CAMPO INTER- Y MULTI-DISCIPLINARIO

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## ABSTRACT

Amongst the entire potential spectrum of expansion of the engineering sciences as an omnipresent field, we might point out the studies of drugs, applied pharmacology, as a good candidate for receiving attention. The common problematic encountered in the literature faced by the industry of drugs is the high cost for drug development and systematic approaches are demanded. On the hope to bring the discussions to engineering's territory, we borrow several insights from mathematical modeling; it is presented a simple case study, tumor treatment using optimal control, we shall see that it is possible with simple tools already standard in engineering to design an optimal regimen for the tumor therapy, given that the tumor respects our model. On the example presented, we shall see that tools already part of (industrial) production engineering, with exception of optimal control theory, is enough for getting insights. The ideas discussed herein could diminish the cost of drug development if properly extended. As any endeavor, we have challenges, such as to gain the credibility necessary for really using those models in the academy and industry.

**Key words**: Computer Models, Pharmacology, Drug Therapy, Neoplasms.

## RESUMO

Entre todo o espectro de expansão das engenharias como um campo onipresente, é possível citar o estudo de medicamentos, de forma mais específica farmacologia aplicada, como um campo interessante em ser considerado. A problemática encontrada na literatura enfrentada pela indústria de fármacos jaz no alto custo no desenvolvimento de novos medicamentos, o que torna necessário o desenvolvimento de procedimentos científicos. Baseando-se no ponto de vista dos autores, de forma alguma a proposta considerada feri a busca da engenharia de produção como campo bem definido. Na tentativa de trazer a discussão para o território da engenharia, usa-se algumas ideias da área de modelagem matemática; um estudo simples de tratamento de câncer. Mostra-se que com ferramentas já presentes na engenharia de produção, com exceção de controle ótimo e biomatemática, novas ideias podem ser

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geradas. A discussão apresentada pode ser usada para diminuir o custo do desenvolvimento de medicamentos se aplicado de forma apropriada. Como toda teoria, uma busca de consolidar a aplicação é necessária, tanto na academia quanto na indústria.
**Descritores**. Simulação por Computador, Farmacologia, Quimioterapia, Neoplasias.

**RESUMEN**

Entre todo el espectro potencial de expansión de la ingeniería como un campo omnipresente, podría señalarse los estudios de medicamentos. La problemática común encontrada en la literatura científica a la que se enfrenta la industria es el alto costo para el desarrollo de medicamentos y existe la necesidad de implementar enfoques sistemáticos. En la esperanza de llevar las discusiones al territorio de la ingeniería, tomamos prestados conceptos de la modelización matemática; se presenta un estudio de caso simple, el tratamiento de tumores mediante un control óptimo, veremos que es posible con herramientas sencillas ya estándar en la ingeniería para diseñar un régimen óptimo para la terapia de tumores. En el ejemplo presentado, veremos que las herramientas que ya forman parte de la ingeniería industrial, con excepción de la teoría de control óptimo, son suficientes para conseguir nuevas perspectivas. Las ideas discutidas en este documento podrían disminuir el costo de desarrollo de nuevos medicamentos. Como en cualquier investigacion, tenemos desafíos, como obtener la credibilidad necesaria en la academia y la industria.
**Descriptores**. Simulación por Computador, Farmacología, Quimioterapia, Neoplasias.

## 1. INTRODUCTION

In engineering sciences, the concept of ‘model’ can signify model in the sense of mathematics, or even a ‘virtual reality,’ such as it can be built in Arena®, something somehow more flexible[5]; it is worth noting that in *pharmacokinetics* we have several models extremely similar in methodological procedures, see[(1)] for more details; as an example see the software Modelica® or COPASI®[6]. However, nowadays, we have models in medicines quite similar to those models applied in engineering for decades; an interesting accounting for the most important moments of medicine and biology can be found in the documentaries by Nye[(2-3)]. We will discuss this on the sphere of pharmacokinetics and *pharmacodynamics;* in general referred to as pharmacokinetic/pharmacodynamic modeling, PK/PD models for short. For instance, this is a common practice in operations research to observe an industrial plant for months, collecting data, and then building a replica of this for studies, this is done in pharmacokinetics for studying drugs on the so called compartmental and noncompartmental models, see discussions in[(4-5)].

In essence, in this paper we demonstrate the branch of applied medicine and pharmacology that was born in the exact sciences, but it is so important in this day and age to the medical sciences that it seems it had been developed on this ramification of sciences[7]. We dissert on the “dynamics

[5] Attention must be taken regarding model and sample; sample can be used to test a model. Further, model here is different from model in that sense of "an ideal material", which is predominant in biology and medicine, but also present in engineering sciences.

[6] The authors are using as reference a summer school attended by the first author and the last one, in Como Lake (Italy, 2014), Systems Biology and Systems Medicine, http://ucbf.lakecomoschool.org/, where several models were presented, either using those softwares or other means of simulation and modeling.

[7] Usually, this is given the credibility to T. Teorell due to works published in 1937, Kinetics of distribution of substances administered to the body.

of drugs," namely, pharmacodynamics, and on the "kinetics of drug," namely, pharmacokinetics, and implicitly, on the "genomics of drug," namely, *pharmacogenomics*[8]. We shall see that pharmacokinetics and pharmacodynamics joined suppose to give a complete picture of the drug workings inside the body, from administration to effects. Pharmacogenomics is recent, mainly due to technology limitations in the past, pharmacogenetics, which is considered inside pharmacogenomics, is older, but had been limited by the difficult experiments it requires, such as to study twins.

On this paper we defend the thesis that amongst the spectrum for expansion in the engineering science, especially industrial (production) engineering, is applied pharmacology. This is clearly an important bridge to important endeavors in the biomedical sciences. Here we are not including the participation of those professionals on the supply chain, for example, which is something already somehow common, we mean an active participation on the development of new drugs using models, systematic approaches such as it is already done in studies of industrial plants. For the reader interested, see[(6)] for several discussions on the importance of biology to engineering sciences, which include this paper as special case.

The discovery of drugs was one of the most important steps in science, it gave us a weapon against situations that before certainly would culminate on deaths; however it came at a price, see for instance[(15-16)] . According to[(7)], the pharmaceutical industry is amongst the most lucrative, and this demonstrate surely the importance of the discovery. Still in accordance with[(7)], besides all the development, we still need quantitative and precise approaches to drug development. In harmony with[(8)], pharmacokinetic/pharmacodynamic models are important for giving us the opportunity for getting the answers for questions such as *How much*? *How long*? *How often?* Further, empirical studies had contributed a lot for our understanding of drugs, but they had not increased our knowledge about drugs in a general sense, what is common to group of drugs and what is peculiar to a smaller group or even a specific drug; new ideias such as P4 medicine hold the promise to revolutionize on these directions. From the viewpoint of new products development, this is an extremely complex case[9].

The most important problematic in the studies of drugs is how to develop them efficiently, in cost and delivery in time[(5)10]. The difficulties faced by the pharmaceutical industry boils down to the high costs on developing drugs for new diseases, or even some well-known, but still to be understood in a level to nullify it using drugs. The referred problem increases the cost of the final product, making it difficult the access by whom really needs them, especially the people with low monthly incomings. On this paper we do not consider the problematic of legislation and ethical issues, something that on its own could take a full paper, or even more.

The case study herein considers a drug interaction case. Drug interaction can be either pharmacokinetic-like or pharmacodynamic-like. With

[8]It is of opinion of the authors that those studies could be important on the chase of cure of several diseases such as AIDS, especially pharmacogenomics. Viruses such as HIV (Human Immunodeficiency Virus) had been so difficult to defeat mainly due to their peculiarities to attack the body, HIV attaches our genome; their host cells are one of the most important cells for our defense, called T-cells.

[9] In Brazil this is well-known on the issues created since the launched of the "genéricos", cheap drugs, but in theory with the same quality as the conventional ones.

[10] As an example, see the development of the vaccine for the virus that causes the so well-known and feared disease called dengue. See http://agencia.fapesp.br/17988 for more details.

a pharmacokinetic interaction, one drug affects the other's Absorption, Distribution, Metabolism, or Excretion, ADME for short, we shall discuss here these terms. In a pharmacodynamic interaction, two drugs have additive ("positive") or antagonistic ("negative") effects. The model presented here is a case of pharmacokinetic interaction; a pharmacodynamic case can be created by a simple change of the dynamics, but not discussed here. Further, we give a simple example of a pharmacokinetic/pharmacodynamic model, PK/PD models for short. This paper can be decomposed into two boxes: the algorithm for optimal regimen, based upon optimal control theory; and the model for tumor growth[11]. For future improvement, which is really needed, we might improve the boxes isolated, either provide a better model for PD/PK or provide better optimal control methodologies.

On the next section we shall present the basics of applied pharmacology, we intend a writing that could be interesting and easy for beginnings on the area, in special engineers, students for example, looking for new areas for investigation, areas that surely will be important in the future. We try to demonstrate the common challenges to any endeavor on that direction. Then we present a case study, tumor therapy, with the objective to transfer the issues to engineering grounds, the choice is merely the authors' inclinations. And, finally, we finish up the paper with conclusions and final remarks. Following, we present the references, which indeed is a poor list for the readers interested, many more can be found given the importance of the topics nowadays.

## 2. DYNAMICS AND KINETICS OF DRUGS

Dynamics of drugs (*pharmacodynamics*) might be defined as "what the drugs do to the body," whereas the kinetics of drugs (*pharmacokinetics*) can be defined as "what the body does the drugs;" this can be used as thumb rule. The third related field is not discussed here, but pharmacogenomics, which includes pharmacogenetics, can be defined "as what genetics make to the drugs and vise-verse." A way to see it clearly the subtle differences between pharmacokinetics and pharmacodynamics is recollecting that 'kinetics' is related to motions, without wondering the forces that cause it, whereas 'dynamics' is related to interactions, forces that generate motion. It must be pointed that recipes always help, but being aware of limitations of recipes is a good strategy. For instance, the absorption process, in general associated to pharmacokinetics, might be influenced by pharmacodynamics as well, or even pharmacogenomics given that several people has poor absorption to some substances and high absorptions to others, not taking into account this information can end up on inefficient treatment or even toxicity. Divisions within science, namely, "divide and conquer", are always motivated by future unification. The most important models are called *Pharmacokinetics/Pharmacodynamics models*, PK/PD models for short. In theory, PD/PK models should endow us with a complete picture of drug administration, an unification between pharmacokinetic and pharmacodynamic models.

[11] Using as reference the summer school attented by the first author "Mathematical Models and Methods for Living Systems", CIME-Foundation and CIRM, Levico Terme, 2014, Italy, the model discussed here is not the state of the art, it is more didactic than else. For instance, some modern models divide the tumor mass into three regions forming a sphere or circle in 2D: dead tissue (center), normal or low infected tissue (ring), and outer region, which represent the attacking region. Further discussions will be omitted.

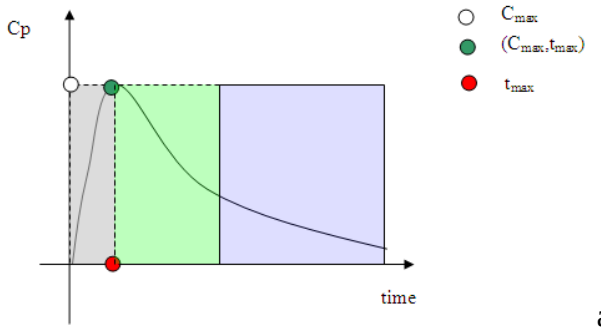
One way to draw the line between the fields is dividing the whole process of drug administration and sojourn inside the body into: Dose (D), Concentration (C), Effect (E); this can be seen as three boxes (state spaces), by mass conservation, the drug can only be on one of the boxes. PK Models strives to comprehend what is happening mathematically from the administration until the drug concentration increase on the site of actions, as we shall see, unfortunately the best we can achieve is measuring the blood plasma concentration, while PD models take over the task from the increase in concentration to effect. Given that we target a single model, we can create the PK/PD models, that is, given an administration profile (for instance, one dose daily), we must have a predictive model; the advantage of those models is that given that we have a reliable model, we can create non-evasive systems for real-time treatments. A typical graph for pharmacokinetics is Time (x-axis) vs. Concentration (y-axis), and for pharmacodynamics, Concentration vs. Effect. Mathematical models are so chased because they make possible automation, standardization, and optimization. A typical equation for PK/PD models is on the template presented below.

$$E = f_{PD}\left(f_{PK}\left(Dose, time\right)\right)$$

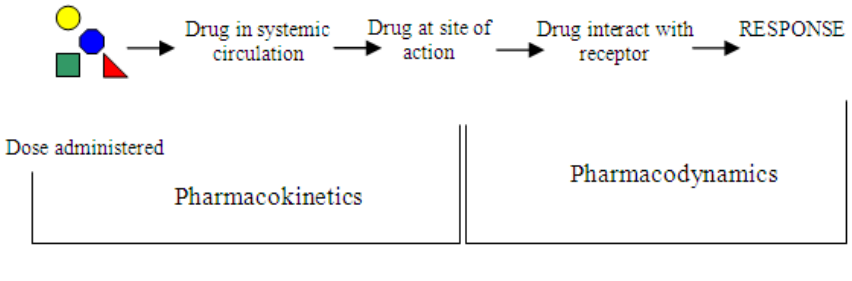
PK models include studies on the steps of: absorption, distribution, metabolism, and elimination, ADME for short. PD models are more recent once they require studies on the level that just with the support of current technologies we could probe such as molecular interactions. Further, example of PD models includes models for drug-receptor interactions, study the receptors interactions, or finding the right receptors for a new drug. See figure 1 for a schematic view.

## 3. CHALLENGES

In simple terms, the following challenges are common in pharmacology, that is, for building up PD/PK models: 1) **Input and Output routes:** bearing in mind that we desire to "control something" such as the number of cancer cells in a patient, we must figure it out the best way to feed the system. Further, in other to build laws for the system, we must understand how the input is processed and eliminated, the routes used to eliminate the introduced substances; 2) **Target not accessible:** on the majority of the cases, the site of action are out of access either for administration or measurements, and we must somehow delivery the drug to the correct place; 3) **Effect Measurements:** given that we have done the treatment properly, we must accompain (monitor), and this might be another challenge, find what to measure; 4) **Side Effects:** given that we cannot have direct access to the site of action and our blood "is in constant movement" due to the circulatory system, we must be aware of side effect, which is not simple to predict.




a)




b)

**FIGURA 1** – "Frontiers" between pharmacokinetics and pharmacodynamics and the phases for the pharmacokinetics. a) depicts the pharmacokinetic phases for the drug administration; b) is the frontiers between pharmacokinetics and pharmacodynamics. 'C' stands for concentration, and the subscripts 'max' for the maximum concentration. In a) the first phase is absorption, the second is distribution and metabolism and the third is elimination. Several parameters used in simulations are estimated from those graphs. The metabolism phase cannot be differentiated from the distribution just using this kind of graphs. Source: own elaboration.

### 3.1 Input and Output Routes

As any system with potential ways to be influence or even control, the human body possesses several input and output routes. Basically, we have two groups of input routes: *intravascular* and *extravascular*. Intravascular signify that the drug were administrated directly on the blood such as veins, whereas extravascular is reserved to routes such as oral, that is, the drug must pass through the absorption process. It is a well-known trick to eliminate the complexity of drug studies to make it in intravascular way for getting ride of the absorption, several parameters is estimated this way, they are the same for extravascular administration.

The form chosen to administer the drug is vital as well. The most theoretical approach is called bolus administration[12], *bolus dose*. Mathematically this is represented by the Dirac Function, largely applied in mathematics and quantum mechanics for representing pulses. The second way, much more realistic, is the intermittent infusions; in fact this is possible as well to cite multiple bolus administrations. The advantage of intermittent infusions[13] is that the concentration does not rise fast as it happens with bolus doses, further, the concentration starts from zero. Thus, in intermittent infusions, the concentration grows gradually toward a steady state. In the case of bolus doses, in real cases, they are administered using a short time, shorter than intermittent infusions[14].

We have essentially two "output doors", in fact for some cases we have three, the lung might be added up, for elimination of drugs introduced to the body: livers and kidneys[15]. The two output routes make use of the blood to eliminate the drug. Hence, compartment models, see coming sections, just assume elimination on the central compartment, in general the blood and (well perfused tissues) "well-fed" tissues. On the case of a second compartment, we call this second one peripheral compartment.

[12] It gives us some nice mathematical tricks such as convolution, it can be used to estimate cumulative effect of multiple dose in time.

[13] Here we reach a problem, why intermittent infusion? A second option is continuous infusions. Intermittent infusions is more typical for oral administration. Bolus and continuous infusions are more typical of intravascular administration. The choice here was motivated by the fact that intermittent infusion, due to the interval, represents more challenge to program.

[14] Seer, http://www.uri.edu/pharmacy/faculty/rosenbaum/basicmodels for several simulations and discussions. Last access: June, 2014.

[15] This is true for the majority of drugs, except for drug such as for anesthetics, volatile drugs, where the lungs starts to be important on the elimination process.

## 3.2 Inaccessible Target

With rare cases, such as skin diseases, the region affected by the disease is out of access, any access would be considered surgical procedure, something avoided in several cases, or even impossible[16]. Therefore, the problematic in drug administration is how to efficiently treat a disease giving we cannot access the place where it is, in several cases such as AIDS or even cancer, they are impossible to be accessed. See scheme in figure 2. Thus, the omnipresent problem in pharmacokinetics/pharmacodynamics is how to access the site of action of a given drug.

The circulatory system is the commonest way used to overcome the problem of administrating drugs once it runs all of over the body. In the case of oral administration, such as pills, we have the process of absorption before the systemic circulation is reached; see that a drug is considered to be inside the body just after being completely absorbed, in the blood, the absorption process is so complex that even after overcoming the wall of the intestinal tract, the drug still can be "rejected." And on the case of measurements, either samples from the blood or the substances eliminated such in the urine can be used to measure expected results, tests adopted in the majority of companies.

[16] See that the lungs can be directly accessed, or even the liver in some therapies.

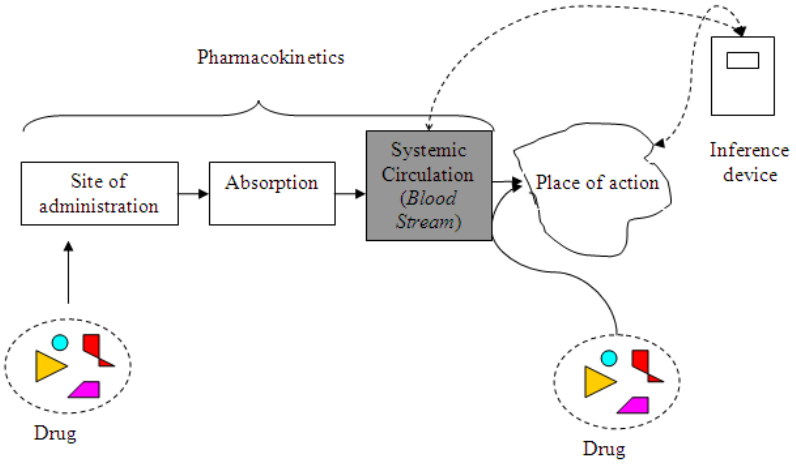



**FIGURE 2 –** Scheme giving emphasis to the problems encountered when we study drugs administered to the body. We show two potential ways: direct on the systemic circulations and by other routes that culminate on the systematic circulation. Source: own elaboration.

### 3.3 Effect Measurements

As any area of knowledge, measure effects on the treatment of diseases is not something always straightforward, and something creativity is the best that we can do, that is, a "movement of art." In[9] it is proposed a physical device, non-invasive measurement system, based on the degradation of a electronic polymeric solution for measuring the effectiveness of the phototherapy, mainly for avoiding continuous blood sampling on babies effective by the neonatal jaundice. In[10], it is studied an intelligence based algorithm using fuzzy logic for identifying diabetic patients using the electrocardiogram signal. These surely represent examples where we must make use of alternative techniques for overcoming problems of measuring the state of human body with reference to normal states. Systems for measuring response to treatments are in general called biometers. Even on invasive cases, it might not be obvious what to measure, such on the treatment of diseases that attack the immune system, it might be a good strategy to monitor the number of platelets on the blood.

### 3.4 Side Effects

Several texts discuss on the concept of side affects, toxicity, and undesired effects. Here we assume that undesired effects and side affects are the same. Nonetheless, the concept of toxicity is little more delicate. In several books about pharmacology the topic is treated, nonetheless, toxicity is not expected to be a topic since it is not what we want, it is studied to be avoided. Side affects might emerge even if it is applied the drug properly and in several cases, this is tolerated, such as gaining weight as result of use of several drugs. However, toxicity is never welcome. For avoiding toxicity, but having results on a treatment, the concept of therapeutic window is widely used. It basically endow us with a superior and inferior limits, the former shows where we start to expect toxicity and the latter where we do not expect results at all. A good drug treatment must keep the concentration of drug in the body within this window. For several medications, due to a narrow therapeutic window, just intravascular administration can be used to keep the

concentration on this window, above needed concentration for effect, but below danger concentrations. Each drug possesses a therapeutic window, and it can change even from person to person using the same drug.

## 4. COMPARTMENT MODELS

As other areas in science, studies of drugs are done by several models. One of the most popular due to simplicity and applicability are the ones called compartment models. The name comes from the fact that the body is divided into compartments "seen" by the drug. Some drugs after administration quickly spread out throughout the body, others take time. From the viewpoint of engineering, it does not represent a new methodology once software such Arena®, Umberto®, and others have already been applying these for a while in an industrial framework. In simple language, this is just the famous "divide and conquer." On those models, the body is divided into compartments that communicate among each other. For example, take the study of lead, toxic substance, a heavy metal. See scheme below. The body is divided into blood, bone, and soft tissues. There is movement from the blood to bones, and coming back. Similarly, we have a movement from blood to soft tissues, and the return. From the blood, the metal can be eliminated, thus coming back to environment[17].

## 5. OPTIMAL DRUG ADMINISTRATION: *TUMOR THERAPY*[18]

Tumor is a state of the body where cells divide (*mitosis*, multiply) on an uncoordinated way. This is a type of cancer[18]in some cases. Tumors might be classified as benign, premalignant, or malignant (cancer). Cancer is so feared for spreading out, invading neighboring tissues, tumors (*premalignant cancer*) does not invade neighboring tissues. On this section we present the simplest model possible to build applying the theories presented throughout the papers so far. We have decided to spend time on such section for making the discussions accessible to professional for engineering sciences. Here we make a typical methodological approach in engineering: we have a problem, we model the problem, and we study it with our model. The model presented herein is relatively simple. We apply the theory of optimal control for the treatment of cancer[19]. Using the mentioned theory, we can optimize the behavior of a set of differential equations, on our case, ordinary differential equations.

The model discussed here was published by(11) and studied by(12-13); we try to make it better by adding the dynamic of the drug.

The referred model used on the study of treatment of tumor is as following:

[17] The biggest danger of heavy metals is that they "stick" to the bones, causing problems in the future of the people that had contact with them. A quite common problem used to happen in Brazil in the chase for gold, using mercury, forbidden by law now, what had not necessary stopped completely the problem.

[18] See for example http://en.wikipedia.org/wiki/Neoplasm, last access: June/2014.

[19] This is worth to pinpoint that the same authors had submitted a second paper to this same edition of the periodic where optimal control is discussed on the domains of operations research. The algorithms and methodological procedures are the same, then the reader interested might want to consult this paper.

$$N'(t) = rN(t)\ln\left(\frac{1}{N(t)}\right) - u(t)\delta N(t), \qquad N(t) \in (0,1]$$

Where: $N'(t)$ is the growth rate, derivative of the unknown function for the tumor cells; $N(t)$ is the density of tumor cells at time 't', this variable is normalized, minimum value close to '0', small amount of tumor cells, and maximum equal 1, maximum tumor cells; $r$ is the "aggressiveness" of the tumor; $\delta$ is the "efficacy" of our treatment, "responsiveness" to the treatment; $u(t)$ is the control variable. The log on the growth term is justified bearing in mind that the tumor growth is nonlinear.

See that the first term of the differential equation represents a 'growth', a natural process, using a dynamics called Gompertz model[20], and the second represent our control by means of the treatment. It should be pointed out that we can use just this equation on the study of optimal control applied to tumor therapy and this is what is done on[12], but we can do better! What about the dynamics of the drug? This is what we add here. This is motivated by the discussions on this paper, in the last sections. Drugs might exhibit peculiar behavior and assuming that we can control the amount exactly of drug that reaches the site might be a mistake. As[12] highlights studies of drugs is a rich and state of the art field, and one of the models lacking are the ones that studies multiple drugs taken at the same time. That is, models that takes into account interactions between different drugs; see that the model presented here is limited in the sense that it is still kinetics, not dynamics, models for dynamics are much complicate, we skip them. Just to provoke these studies on the literature, let's consider an ideal case of two drugs taken for eliminating this tumor. We consider a simple case, the second drug just increase the absorption of the first, the drug one is the one that really can eliminate the tumor. This can increase the possibility to maintain the plasma concentration within the therapeutic window; see that the second drug is increasing the absorption, then it should eventually increase the concentration above the therapeutic window of the drug we need to monitor, and this exactly the trick of optimal control, the optimal control policy will just use what is needed given a goal (therapeutic window). This is known as bioavailability; this is similar when you are suggested to take a drug together with milk, milk is not a drug, just increase the bioavailability of the take drug, or even when you are asked to use a drug with empty stomach. This type of analysis is concern of noncompartmental models. Noncompartmental models are considered easier to use due to several reasons such as it does not change from individual to individual so much as compartment models. See[5] for more details.

We should not let it stay unmentioned that the model presented here for tumor treatment is merely illustrative, we have not conducted experiments for creating the model, this is a theoretical model. We are motivated to apply optimal control for finding the best optimal policy for the cancer treatment, given that our model is correct or at least not too far away from what happen in living systems, we omit the methodological procedures; see second paper submitted to this event by the same authors. In simple terms, we apply the theory of optimal control, we arrive to a system of differential equations, and then we apply numerical

[20] The growth is slow in the beginning and end. With the L'Hospital's Rule, limit theory, and some patience, we can show those proprieties, or just plot the graph.

schemes for integrating differential equations for finding the optimal control and optimal trajectory for the function of the cancer cells. It is not redundant to mention that drug only on the site of action is wanted, before it can achieve the site of action, this must achieve the circulatory system. Here for simplicity we assume a single-compartment for the individual-drug profile, that is, the concentration of drug in the blood stream is instantaneous transmitted to the site of action. The model is composed of three differential equations: drug 1, drug 2, and cancer dynamics. The first equation is for the drug one, the one that really matters for the tumor treatment: administration minus elimination. The second equation is similar, but remember that it just effects the drug 1 dynamics, alone it is meaningless. The third equation is the one for cancer cell, just the drug 1 matters for this dynamics. For modeling the interaction of drug 1 and drug 2 we make use of the famous Michaelis-Menten Equation, widely used in biochemistry. We apply the treatment on the style of intermittent infusions, we apply for a while and than we give a break. This is repeated for a time determined period of time. Below is the graph that results from the simulations, figure 3.

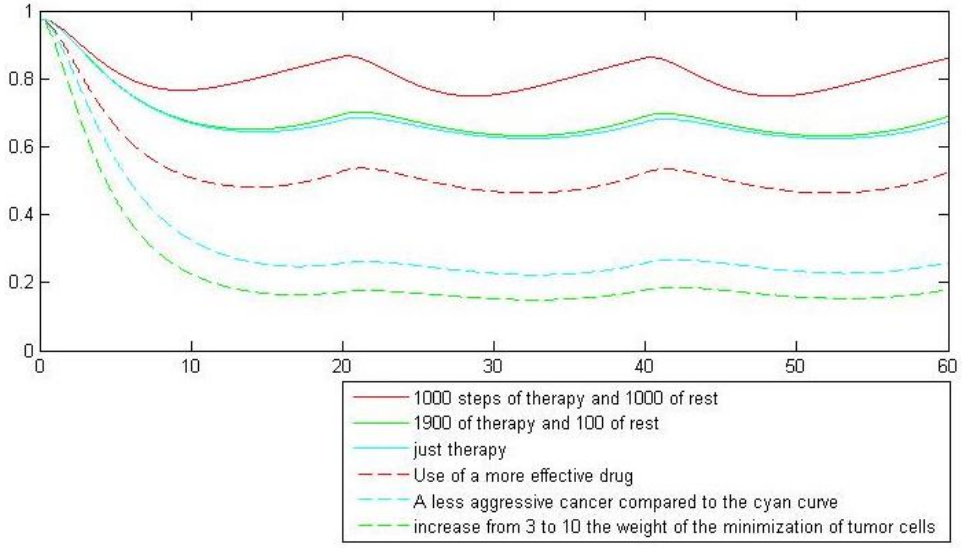



**FIGURE 3** – Simulations for the discontinuous treatment of tumor. The dashed and continuous line simulates the treatment in several scenarios. The continuous lines represent variations on the therapy, drug infusion, compared to the breaks, non drug at all. On the dashed green line we simulate the case of increasing the importance of minimizing the cancer cells compared to the costs and side effects, weight here is similar to problems in operations research where preferences are entered the model, or even penalty values. We have used the same weight – impact for using – in the minimization process for the drugs. We have used a very bad case 0.975/1 – initial value/maximum possible tumor mass – well-advanced. The x-axis was discretized for numerical simulations, 'step' means one unit of this discretization. 2000 steps (20 units of time) comprise a whole treatment (therapy plus rest). y-axis is the tumor cell density 'Rest' means that all the control is "turned off" and we let the dynamics of the cancer to evolve free. An interesting improvement would be to model the body response to the lack of medication after the treatment had started. By 'just therapy' it is meant that we do not stop from one infusion to another, the wave-like behavior is a result of the tumor "trying to come back." Source: own elaboration.

On the case just presented, we have showed that we can calculate the optimal therapy for the treatment of an ideal tumor, given that we have found a proper dynamical model. We know that real cases are full of surprises, contra-reactions is quite common. Some models for control that has been gaining certain respect are the ones that comes form computational intelligence[14], something sadly we must skip.

## 6. CONCLUSIONS AND FINAL REMARKS

On this paper, we have discussed on the possible impact of studies on drugs in engineering sciences. Furthermore, this works might be faced as extension of[6], but now on

the domain of pharmacology instead of biology.

On the hope to bring the studies to engineering grounds, we have used mathematical modeling. We have analyzed the case of studying (designing) the therapy of an ideal tumor using a dynamics taken from the literature and mathematical models derived from optimal control theory for chasing a best policy given a set of information of an ideal cancer. On the discussed case we have showed that with tools already present in engineering sciences, such as industrial engineering, we can gain insights regarding the problem. We have used an external methodology from production called optimal control, but discussed on a second paper by the same authors on the context of industrial (production) engineering[17]. This can be seen from reality and from the literature that the pharmaceutical industry are one of the most complex, lucrative, and high costs for developing and designing new products. Take as example the problem with cheap drugs in Brazil, several programs had started, but it had not been easy to keep up the promises.

Regarding the simulations, caution must be placed, the dynamic used is ideal, better models are being proposed everyday, the same way in statistics a good inference model can give wrong results if applied in bad sampling, even the best optimal control technique cannot yields something correct if not fed with a proper dynamic.

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Sources of funding:
CAPES Foundation, Ministry of Education of Brazil
Conflict of interest: No
Date of first submission: 2015-03-16
Last received: 2015-03-16
Accepted: 2015-03-17
Publishing: 2015-04-30

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