# System Dynamics, Optimal Control and Analytic Hierarchy Process applied to the Chemotherapy of Leukemia

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Abstract
The Myelogenous Leukemia (ML) is a neoplastic disease involving hematopoietic cells. A natural way to model its dynamics is by means of capturing cell cycle kinetics. In this work we develop a formal mathematical model where variables capture quantities involved in the cell cycle phases. It is in some of these phases that medications such as killing agents and recruitment agents can intervene to combat the neoplastic cells. Our work combines system dynamics, optimal control theory and Analytic Hierarchy Process to yield a chemotherapy optimized treatment protocol for instances of ML, tackling in a systematic way the subjectivity involved in the choice of the cost function coefficients.

## 1 Introduction

Many mathematical studies related to cancer chemotherapy have been published in recent years (Swierniak 2005, Fister 2000, Swan 1990, Agur et al. 1988, Dibrov et al. 1985). In particular, differential equation modeling and optimal control theory has been applied to design improved treatment schemes. One of the difficulties with this approach is the subjectivity when one is required to choose the performance indices to be adopted. This work concerns the application of Analytic Hierarchy Process (AHP) to help in a systematic way the selection of the weights in performance indexes.

Leukemia is a malignant disease of the blood that has as the main feature the abnormal accumulation of blasts (precursor cells) in the bone marrow. Because the bone marrow is responsible for the development of blood cells from stem cells, several clinical conditions, such as anemia, infection and bleeding, can develop due to leukemia.

The disease can progress rapidly, requiring an intensive intervention. As soon as leukemia diagnostic is available, a treatment scheme must be started. The pace of evolution of the disease defines if it is acute or chronic, and the affected cell type determines if it is myeloid (or myeloblastic) or lymphoid (lymphocytic or lymphoblastic).

In the chronic phase, there is a relative equilibrium between populations of normal and abnormal cells; this situation can last for years. Chronic leukemia progresses slowly, allowing the growth of a large number of differentiated cells which may be able to exert some of their normal functions. However, at some point, this balance may break down, causing instability that leads to an increased number of affected cells.

The acceleration phase corresponds to a transition between the chronic and the acute phase. The system becomes unstable and the affected cells proliferate at a very high rate. Acute leukemia progresses fast and affects most the immature cells. Those immature cells then lose their ability to perform normal tasks, and multiply uncontrollably, preventing the production of normal blood cells.

The basic treatment aims to destroy the leukemia cells so that the bone marrow can return its production of normal cells. The drug intervention is comprised of stages. The first stage aims to achieve complete remission: a state of apparent normality in which examinations show no more leukemia cells. However, there remain many undetectable leukemic cells in the body, which requires further treatment in order to avoid relapses of the disease.

The following stages of the treatments depend on the type of the leukemia and may range from less than one year in myeloid type and more than two years in lymphoid type. But in general there are three more stages. The consolidation phase, in which an intensive treatment is carried out with substances not previously employed. The re-induction phase, in which the treatment with drugs used in the induction of remission is repeated. And the maintenance phase, in which the treatment is milder and continued for several months.

In some cases, bone marrow transplantation may also be a necessary treatment, however, this type of intervention with transplant is not considered in this work, which is focused on the chemotherapy optimization for acute myeloid leukemia. A main problem arising due to treatment is that high doses of drugs cause devastating side effects, whereas small doses are not effective to control the disease. To inform specific drug dosage to be used, quantitative approaches can be of value in the establishment of specific chemotherapy protocols. In this research, we use differential equation modeling (and system dynamics) and optimal control to achieve a compromise between therapeutic impact and its side effects.

We follow medical priorities to balance the relative importance of side effects and clinical results of chemotherapy through the definition of a cost and proper fine tuning of its coefficients. The Analytic Hierarchy Process (AHP) can aid in this balancing process by consistently choosing the weighing factors that respect the preferences suggested by medical priorities.

## 2 Dynamic Model of Leukemia

The Myelogenous Leukemia is a neoplastic disease involving hematopoietic cells. In this study, we develop a mathematical model capturing cell cycle kinetics. The dynamic model requires variables representing the cells in the characteristic cycle phases, specifically G0, G1, S, G2 and M (Swierniak 2005). The cell cycle is a very well understood phenomenon with wide literature about it. The Fig.1 is a schematic summary of the cell cycle. It is in some of these phases that medications can intervene to modify the model dynamics.

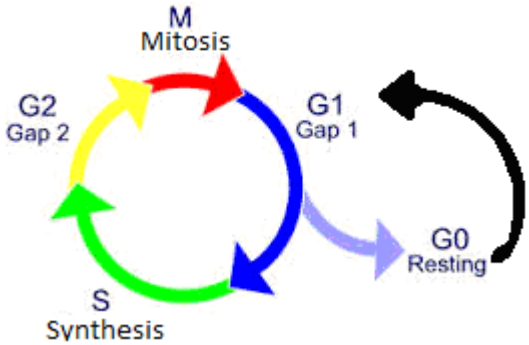

Figure 1: Outline of the cell cycle.

In the mitosis, one mother cell originates to two daughter cells. A cell prepares for mitosis (M phase) through three primary phases: G1, S and G2. After the M phase, the cell can return to G1, thus preparing another mitosis, or can stay at G0 a resting phase in which there is no mitosis-related activity. These phases comprise the basic cell cycle.

In the G1 phase, the cells produce proteins that are essential to the synthesis of DNA. In the S phase, the parent cell replicates its DNA so that each cell will have its genetic material. Afterward, in the G2 phase, proteins that are necessary to the M phase are produced. Then, with two copies of DNA separated on opposite sides of the mother cell, it divides itself in a half yielding two daughter cells and the cycle is complete. After mitosis, the daughter cells can reenter the G1 phase, preparing for another division, or may stay resting in the G0 phase.

Let $N=(N_1,N_2,N_3)^T$ be a state-vector in which $N_1$ is the number of cancer cells in the G0 phase, $N_2$ is the amount of cancer cells in the G1 phase and $N_3$ is the quantity of cancer cells in the phases S, G2 and M, which are lumped into a single stock for the sake of simplicity. With these definitions it is possible to characterize the stocks-and-flows as well as the equations describing the cell cycle dynamics, which are important to describe the optimal control problem. The stock and flows diagram is shown in Fig.2.

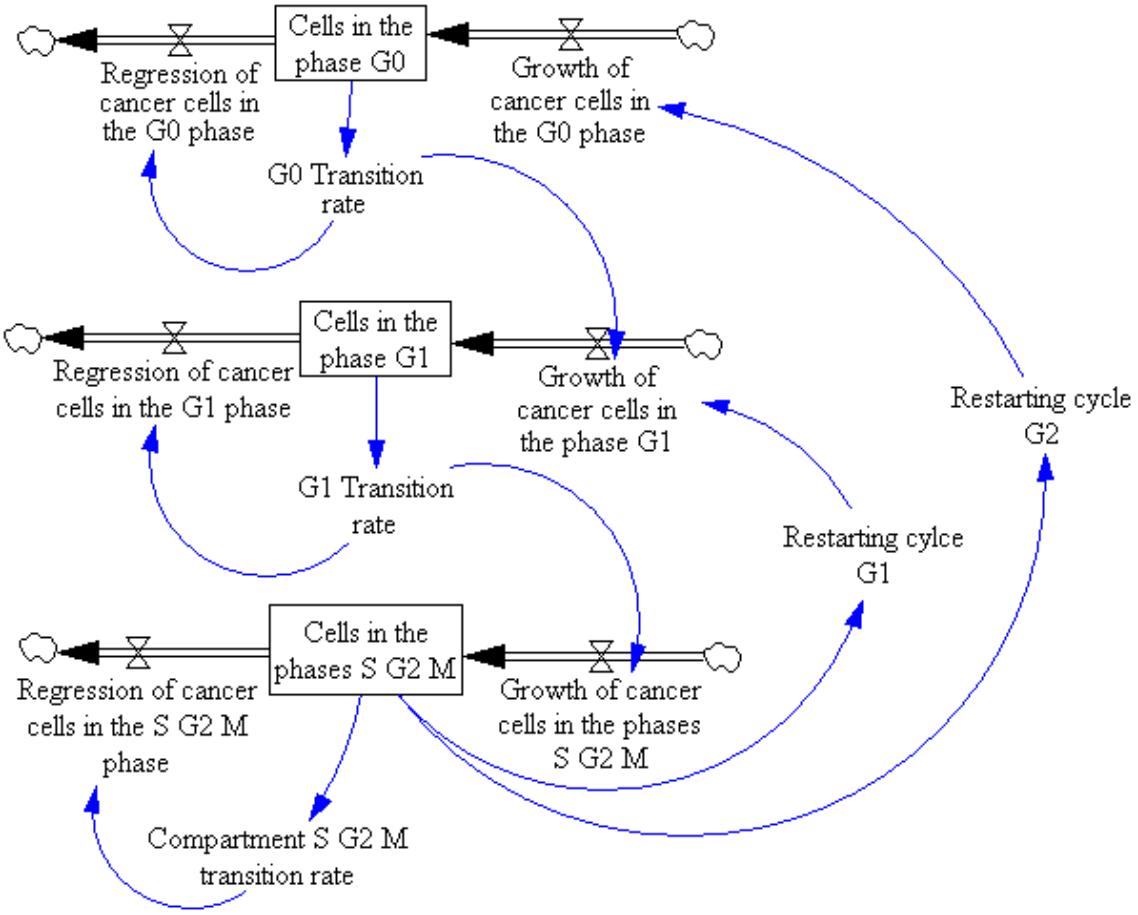


Figure 2: Stock Flow diagram of leukemia.

The cells in the phase G0 can remain in this situation or can move to the phase G1, according to transition rate $\beta$. Similarly, the cells in the phase G1 can turn into cells in the phase S, G2 or M, with transitions that occurs at rate $\alpha$. Finally, the cells which end the mitosis process leave this phase at rate $\gamma$, becoming cells in the phase G0 with probability $P_0$ or restarting the cycle in the phase G1 with probability $P_0=1-P_1$. Let the control vector be $u=(u_1,u_2,u_3)^T$, in which, each component represent the drug dosages of the killing, the blocking and the recruitment agents, respectively. One can see in Figure 3, the new stock flow diagram, now with inputs *u*. The state equation is, therefore, of form

$$\dot{N}(t) = (A + u_1(t)B_1 + u_2(t)B_2 + u_3(t)B_3)N(t) \tag{1}$$

for $0 \le t \le T$, with

$$A = \begin{bmatrix} -\beta & 0 & 2P_0\gamma \\ \beta & -\alpha & 2P_1\gamma \\ 0 & \alpha & -\gamma \end{bmatrix} \tag{2}$$

$$B_1 = \begin{bmatrix} 0 & 0 & -2\gamma P_0 \\ 0 & 0 & -2\gamma P_1 \\ 0 & 0 & 0 \end{bmatrix}, \; B_2 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & \alpha & 0 \\ 0 & -\alpha & 0 \end{bmatrix} \text{ and } B_3 = \begin{bmatrix} -\beta & 0 & 0 \\ \beta & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \tag{3}$$

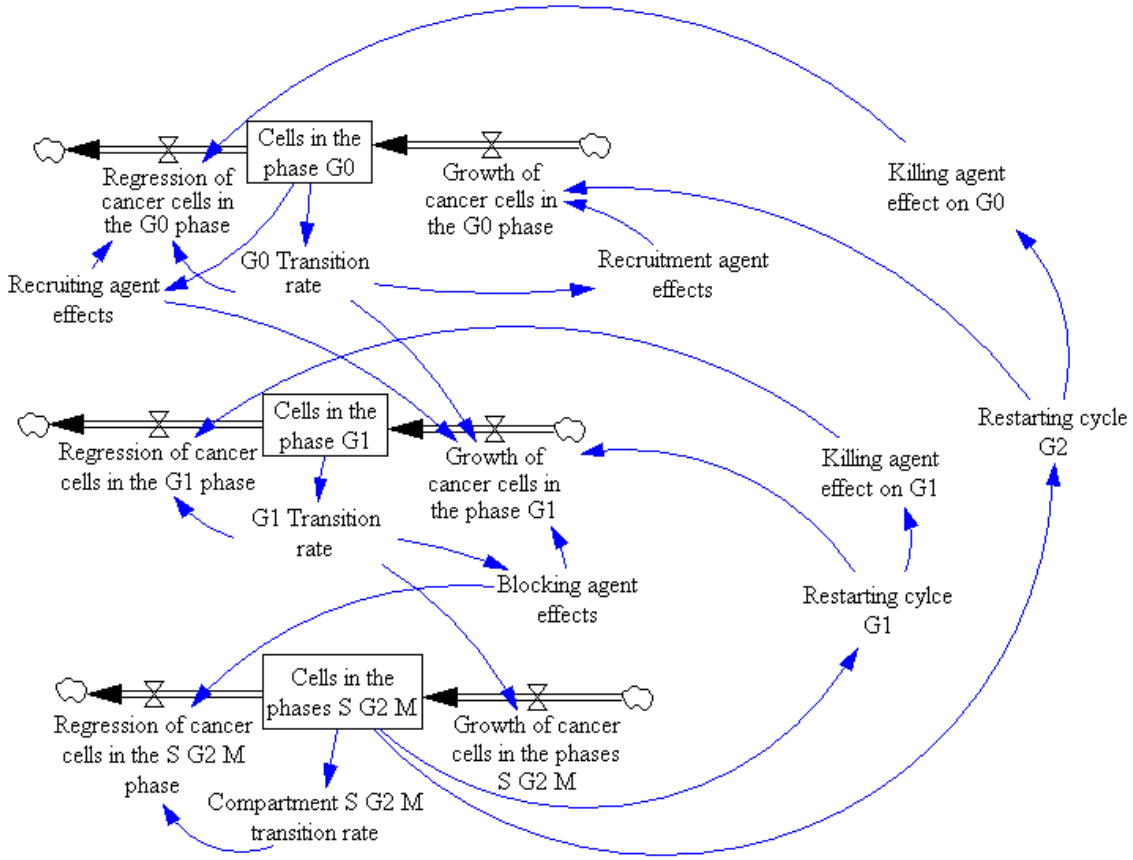


Figure 3: Stock Flow diagram of leukemia under treatment.

The structural validity was checked with the tests of boundary adequacy, structure verification, parameter verification and dimensional consistency (Qudrat-Ullah 2005). These procedures were omitted since this is not the focus of this work.

## 3 Optimization of Drug Administration Schedule

Let the performance index be the same as used in (Swierniak 2005)

$$J = rN(t) + \int_0^T su(t)dt \tag{4}$$

The vectors $r = (r_1, r_2, r_3)$ and $s = (s_1, s_2, s_3)$ contain weights to be chosen with the AHP assistance, since they express subjective preferences about the relative importance of the side effects, and the final therapeutic results.

The coefficient $r_1$ expresses the relevance of the diminution of cancer cells in the G0 phase at the final moment of the treatment. Similarly, $r_2$ and $r_3$ express the importance of the reduction of cancer cells in, respectively, the G1 phase and S, G2, M phases at the final moment of the chemotherapy.

Additionally, the coefficient $s_1$ indicates the relative importance of the side effects, due to the accumulated action of the killing agent. The factor $s_2$ is related to the blocking agent relative relevance, due to its toxicity in the non-cancer cells. Finally, the recruitment agent negative interference on healthy cells is virtually null, since this kind of drug does not kill any healthy cell. Therefore, its relative importance in terms of side effect is also null, which is represented by the coefficient $s_3 = 0$.

It can be shown that for the model adopted here, the optimal controls are not singular on any subinterval contained in the time horizon (Swierniak 2005). Thus the natural candidates are bang-bang controls. The restrictions on non-negativity of the state variables are naturally satisfied due to the structure of the system (Swierniak 2005).

The solution to the optimal control problem can be obtaining by applying the Pontryagin's Maximum Principle, i.e., minimizing the Hamiltonian

$$H(t) = \lambda(t)AN(t) + \sum_{j=1}^{3} u_j(t)(s_j + \lambda(t)B_jN(t)) \tag{5}$$

subject to

$$\dot{\lambda}(t) = -\lambda(t)(A + u_1(t)B_1 + u_2(t)B_2 + u_3(t)B_3) \tag{6}$$
$$\lambda(T) = r$$
$$\dot{N}(t) = (A + u_1(t)B_1 + u_2(t)B_2 + u_3(t)B_3)N(t) \tag{7}$$
$$N(0) = N_0$$

where $\lambda$ is the co-state and $N_0$ is the initial condition.

The details of the solution can be found in (Swierniak 2005) and the optimal solution can be written in a convenient manner by defining the switching functions $\Phi_j(t) = s_j + \lambda B_j N$, $j = 1, 2, 3$:

$$u_j^*(t) = \begin{cases} 0 & if \quad \Phi_j(t) > 0 \\ u_{j\max} & if \quad \Phi_j(t) < 0 \end{cases} \tag{8}$$

## 4 Performance Index Weighting

The values of the five coefficients ($r_1$, $r_2$, $r_3$, $s_1$ and $s_2$) ought to be defined with the appraisals of experts so that the treatment optimization can be well designed. There are several manners to deal with group assessments and decisions (Saaty 2008), but here it is considered that the evaluations are already a final outcome of the potentially collective observations, debate and conclusion about an assessment at the beginning of a treatment.

It is necessary that the variables of interest are in comparable units so that the weighing factors values can indeed express the relative importance of each variable's

behavior. A normalization of the variables is then a solution to put all the variables in some equivalent scale.

Nevertheless, there are many norm measures and manners of normalizing the variables, so that again some subjectivity returns to the problem. For the sake of simplicity, here the normalization adopted is the division of the variables by the arithmetic mean of their uncontrolled trajectory values. In other words, the system is simulated without any control during the defined time horizon, then the arithmetic mean of each variable is calculated and used as denominator for the normalization. The time horizon adopted is the same of the work showed by Swierniak (2005), so that the studies can be directly compared.

Using the initial values $N(0) = (6.50, 0.15, 0.10)^T$ the system response is found, depicted in Fig. 4 and the mean values are $(\bar{N}_1, \bar{N}_2, \bar{N}_3)^T = (6.43, 0.45, 0.19)$.

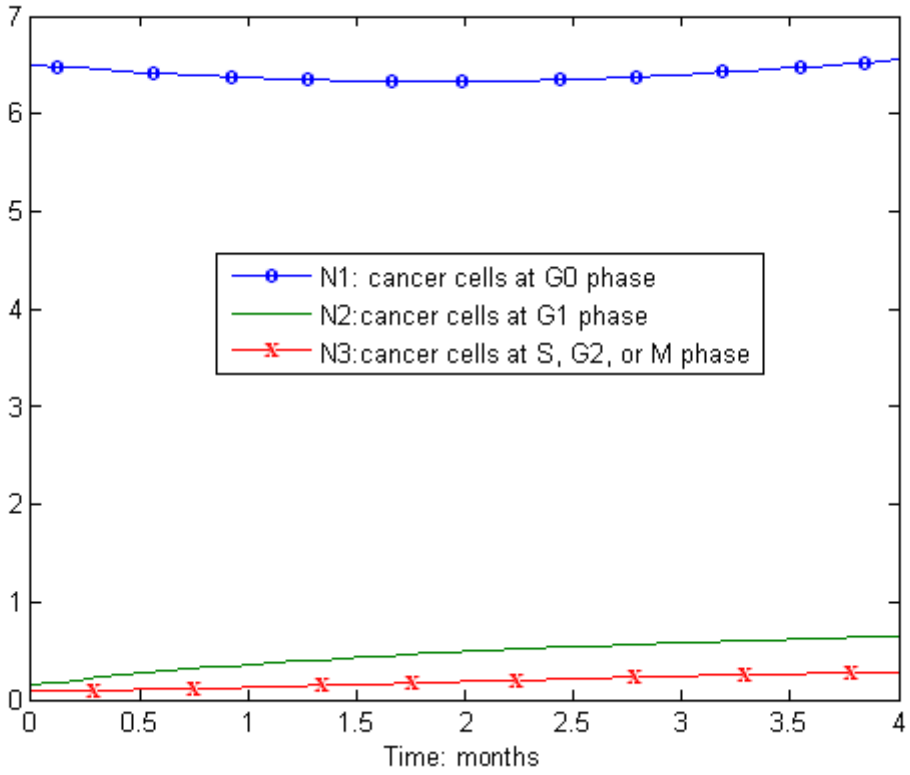


Figure 4: Leukemic cells evolution without treatment.

As the controls are of the bang-bang kind, their maximum values are readily known, and can be used as denominators to normalize the control variables. Finally, using the temporal interval to compensate for the medication time accumulation effect on the magnitude of the integral, the final instant value also ought to be used as divisor to the control variables normalization. Thereby, the normalized performance index can be written:

$$Jnorm = \frac{r_1' N_1(t)}{\hat{N}_1} + \frac{r_2' N_2(t)}{\hat{N}_2} + \frac{r_3' N_3(t)}{\hat{N}_3} + \frac{1}{T_f}\int_0^{T_f}\left(\frac{s_1' u_1(t)}{u_{1\max}} + \frac{s_2' u_2(t)}{u_{2\max}}\right)dt$$

With the variables adjusted to comparable magnitudes now it makes sense to use the Analytic Hierarchy Process to come up with the values of the relative importance of each element involved in the performance index. By virtue of an organizational matter, it is convenient to represent each criterion considered in the performance measure by the factors $F1$ to $F5$.

Aiming at this purpose, it can be written $F1=\frac{N_1(t)}{\hat{N}_1}$, $F2=\frac{N_2(t)}{\hat{N}_2}$, $F3=\frac{N_3(t)}{\hat{N}_3}$, $F4=\frac{1}{T_f}\int_0^{T_f}\frac{u_1(t)}{u_{1\max}}dt$ and $F5=\frac{1}{T_f}\int_0^{T_f}\frac{u_2(t)}{u_{2\max}}dt$. With this simplified letter representation it is easier to carry out the assessments about the relative importance of each element. The values used in the comparisons follow the fundamental scale of Saaty (2008) for pairwise comparisons.

- Comparison between $F1$ and $F2$, $F1$ and $F3$, $F2$ and $F3$: As the effects of the cancer cell on the body are similar, it can be considered that the decrease of the cancer cells in any of the cell phases have the same relative importance.
- Comparison between $F1$ and $F4$, $F2$ and $F4$, $F3$ and $F4$: The killing agent has severe interference with healthy cell of the body. Many tissues can be affected and the clinical picture of a patient can become worst if the dosages of killing agents are too high. Nevertheless, it is not reasonable to allow high cancer cells multiplication while trying to lower doses. Thus, the importance of the cancer cells (whatever the phase they are) reduction can be considered slightly higher, with relation to the reduction of the killing agent's side effect.
- Comparison between $F1$ and $F5$, $F2$ and $F5$, $F3$ and $F5$: The drugs of the kind of blocking agents have, in general, little cytotoxic effect in the non-cancer cells. Therefore, the relevance of the reduction of cancer cells with respect to the reduction of the side effects of the blocking agents can be considered moderately higher.
- Comparison between $F4$ and $F5$: As the killing agents are more aggressive than the blocking agents, then the relevance of the reduction of the killing agents cumulative effect can be considered moderately higher than the importance of the reduction of the side effects due to the blocking agents.

Following the AHP methodology (Saaty 2008) briefly described in the appendix, these comparisons must now be organized in the as pairwise comparison matrix:

$$M=\begin{bmatrix} 1 & 1 & 1 & 3 & 4 \\ 1 & 1 & 1 & 3 & 4 \\ 1 & 1 & 1 & 3 & 4 \\ 1/3 & 1/3 & 1/3 & 1 & 1/2 \\ 1/4 & 1/4 & 1/4 & 2 & 1 \end{bmatrix} \quad (9)$$

Once this matrix is available, the consistency of the judgments about the preferences and the assessments about the relative relevance of each element can be verified. The measure adopted here of how much $M$ deviates from consistency is the Consistency Index, defined as $CI=(\lambda\max-n)/(n-1)$, where $\lambda\max$ is the maximum eigenvalue and $n$ is the order of the matrix. Since $\lambda\max\approx 5.119$ and $n=5$, then $CI\approx 0.0298$.

The Consistency Ratio is defined as $CR=CI/RI$, where $RI$ is the Random Index. Thereby, $CR=0.0269<0.1$. Consequently, the judgments are consistent and the next step of calculating the eigenvector relative to the maximum eigenvalue can be carried out. The eigenvector is normalized to sum to unity and represents the priority of the variables:

$$P=[0.2778 \quad 0.2778 \quad 0.2778 \quad 0.0782 \quad 0.0885] \quad (10)$$

The relative importance of the elements $F1, F2$, $F3$, $F4$ and $F5$ in the cost function is indicated by the weighs, $r_1'=27.78\%$, $r_2'=27.78\%$, $r_3'=27.78\%$, $s_1'=7.82\%$

and $s_2' = 8.85\%$. Unlike the original AHP methodology, here the stage of choosing one single option among the alternatives is substituted by the usage of all elements with their respective relevancies.

## 5 Simulations

The values adopted for the parameters here are the same as the found in the literature (Swierniak 2005): $\beta = 0.05$ month$^{-1}$; $\alpha = 0.5$ month$^{-1}$; $\gamma = 1$ month$^{-1}$; $u_{1\max} = u_{2\max} = 1$; $u_{3\max} = 6$; $P_0 = 0.9$; and $P_1 = 0.1$. The matrix $A$ has eigenvalues 0.0456, -0.50 and -1.0956, thus the system has an unstable mode since one eigenvalue is located outside the unitary circle. This is in accordance with the strong cancer growth associated with the unstable stage of the acute myelogenous leukemia. Besides, as all the eigenvalues are real, the first candidates to check as optimal control are extremal controls with one transition per state variable (Kirk 1970).

The switching optimal instant of each control is to be calculated, as well as the type of transition, i.e., a beginning or a suspension of a drug application. The optimal treatment protocol with the AHP aid was found by heuristic search and is summarized in the Table 1. The control applications are compared with the optimal control presented by Swierniak et al. (2005).

Table 1. Instants and type of transitions of two optimal treatments.

| Adapted AHP scheme | | Swierniak et al. (2005) | |
|---|---|---|---|
| Switching time | Transition | Switching time | Transition |
| $t_1 = 0.0087$ | $u_1 = 0$ to $u_{1\max} = 1$ | $t_1 = 1.96$ | $u_1 = 0$ to $u_{1\max} = 1$ |
| $t_2 = 3.4259$ | $u_2 = 0$ to $u_{2\max} = 1$ | $t_2 = 4.00$ | $u_2 = 0$ to $u_{2\max} = 1$ |
| $t_3 = 0.0359$ | $u_{3\max} = 6$ to $u_3 = 0$ | $t_3 = 0.28$ | $u_{3\max} = 0$ to $u_3 = 6$ |

With regards to the cell results and the side effects the data is shown in summarized in the Table 2.

Table 2. Cell results and the side effects of two optimal treatments.

| Initial state | Adapted AHP scheme | | Swierniak et al. (2005) | |
|---|---|---|---|---|
| | Final state | Side effect | Final state | Side effect |
| $N1 = 6.50$ | $N1 = 5.262$ | $\frac{s_1'}{T_f}\int_0^{T_f}\frac{u_1(t)}{u_{1\max}}dt = 0.078$ | $N1 = 2.277$ | $\frac{s_1'}{T_f}\int_0^{T_f}\frac{u_1(t)}{u_{1\max}}dt = 0.040$ |
| $N2 = 0.15$ | $N2 = 0.708$ | $\frac{s_2'}{T_f}\int_0^{T_f}\frac{u_2(t)}{u_{2\max}}dt = 0.013$ | $N2 = 2.252$ | $\frac{s_2'}{T_f}\int_0^{T_f}\frac{u_2(t)}{u_{2\max}}dt = 0$ |
| $N3 = 0.10$ | $N3 = 0.156$ | - | $N3 = 1.139$ | - |
| | $Jnorm = 0.976$ | | $Jnorm = 3.193$ | |

The cancer cells in the G1 phase (represented by $N2$) increased 372%, from the beginning to the final state, with the AHP relative importance of $r_1' = 27.78\%$, whereas with the protocol presented by Swierniak et al. (2005) the rise in the cancer cell in the G1 phase was 1401%. This result is due to the weighting factor in the cost function used by Swierniak

et al. (2005), in which no normalization is taken into account. The mean value $\bar{N}_1 = 6.43$ heavily impacts the relative importance of the cancer cell in the G0 phase.

To demonstrate this, it is convenient to explicitly present the values and relations between the weighting factors for the non-normalized cost function used by Swierniak et al (2005). It can be written that $\bar{N}_1 r_1 /(r_1 + r_2 + r_3 + s_1 + s_2)$ = 6.43*1/(1+0.5+1+1+0) = 1.837. Similarly, $\bar{N}_2 r_2 /(r_1 + r_2 + r_3 + s_1 + s_2)$ = 0.45*0.5/3.5 = 0.064, and $\bar{N}_3 r_3 /(r_1 + r_2 + r_3 + s_1 + s_2)$= 0.19*1/3.5 = 0.054. Thus, it is evident that the relative importance given by Swierniak et al. (2005) to the cancer cells in the G1 phase was much smaller than the relative importance given to the cells in the G0 phase. This is the reason why it is observed that the cancer cells in the G0 phase are reduced in 20% of the initial value with the AHP, while with the scheme presented in the literature the reduction was around 65% of the initial value.

A similar situation is observed with regards to the S, M and G2 phase cancer cells. The rise of the cancer cells in these phases with the AHP treatment scheme was 56%, while the rise reported by Swierniak et al. (2005) was 1039% due to the small relative importance of these cells with respect to the cells in the G0 phase.

These results show a superiority of the proposed AHP scheme, since the decision maker can be aware of his preferences in the optimization process. Although the elicitation and preferences standpoint are best address with the AHP scheme, both treatments are optimal solutions, so one treatment can not Pareto dominate the other treatment in all the criteria $F1$ to $F5$, situation observed regarding to the drug usage.

As shown in the "Side Effect" columns of Table 2, the AHP proposal has slightly worst side effects on the patient than the treatment proposed by Swierniak et al. (2005). It is important to recapitulate that there is always a tradeoff between cell results and drug side effects as also analyzed by Swierniak et al. (1996).

## 6 Conclusion

The systematic scheme proposed improves the understanding about the problem question, since the System Dynamics approach helps to think about the relationship among the variables and the parts of the system. A model based on the cell cycle was built so that the leukemia could be addressed. Then, the differential equations were written down so that an optimal problem could be posed.

Time behavior of leukemia without treatment is shown and used for normalization purposes. The relative weights in a cost function that involves multiple objectives in the optimization of drug usage for the chemotherapy treatment of leukemia were assigned using an adaptation of the AHP methodology.

As expected by theory, the numerical results show that the proposed AHP scheme surpassed the results of another optimal solution only in some criteria. Nevertheless, the main advantage of the proposed method is the elicitation of the preferences of the stakeholders in the optimal control problem.

As future research, it is intended to develop dynamic assessments which will allow obtaining continuous functions as the cost functions coefficients. This study has also potential to include real clinical data in order to experimentally check the use of different treatment protocols.

## Appendix

The Analytic Hierarchy Process (AHP) is a decision tool based on mathematics and psychology. The name of the method is related to structuring a decision problem as a

hierarchy of sub-problems, namely the goal at the top, the criteria at the middle, and the alternatives at the bottom of the hierarchy.

Once the decision hierarchy is structured, a set of pairwise comparison must be defined following the fundamental scale (Saaty 2008). These judgments are values related to each node of the hierarchical structure and are used to construct a correspondent matrix. In any pairwise comparision matrix, the diagonal is unitary and each remaining input is the reciprocal of its transpose input.

The next step is to calculate the matrix´s principal right eigenvector. (A right eigenvector is defined as a vector $X$ satisfying $MX = \psi X$, where $M$ is a matrix and $\psi$ is a scalar called eigenvalue.)

Then the consistency of the appraisals must be checked in order to guarantee that the judgments are coherent. If the degree of consistency is not acceptable the pairwise evaluations must be redone. If consistency is plausible then one can proceed to choose the best alternative in accordance with the priority criteria.

As the AHP is not the focus of this work, we provide only this brief appendix and suggest the interested reader to study specific articles on the method, such as the seminal Saaty´s article of 1977, or one of the several ones in the AHP literature, as the one cited in the references.

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