A Biomathematical Study of a Controlled Birth and Death Process Describing Malignancy

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***Abstract*—** In this paper we deal with a mathematical model which describes the malignancy of a cellular clone controlled by drugs or radiant therapy. We first discuss some general ideas which led us to the choice of this model. Furthermore we emphasize the integration method, which uses generalized Lie series to represent the components of the solution, also in sight of possible extensions to similar cases in the theory of stochastic processes

***Keywords*—**Birth and Death processes, Lie series, Stochastic process.

I. Introduction

THIS paper deals with the integration of the problem of tumoral evolution controlled by drugs or by radiant therapy. The control will be introduced in the forward Kolmogorov's difference differential equations, which describes malignancy, by a time dependent parameter *h(t)*, here supposed known. The process is analogous to the one described in the Dubin model of 1976 [1], describing the spontaneous evolution of a malignant colony. Here we shall solve in details only the problem of the integration of such initial-value problem, represented by an open differential system, i.e. with a non-finite number of equations. The model in its completeness, including the equations of the drug behavior in the host, will be presented and discussed in all its implications in a forthcoming paper.

The Gröbner's method here sketched has been already described in some of our previous papers [2-11]. It must be underlined that this method solves the problem even though the control term introduces a nonlinearity in the process. The controlled process, in fact, may be nonlinear, while the spontaneous one is, in general, described by a linear model, according to Dubin [1]. If the global system, including also the physiological behavior of the drug in the host organism, is considered, it may be proved that the loss of linearity is due to the interaction between drug molecules and cellular receptors. In this work we put aside the link between drug in the tumor and in the blood stream of the host, expressed by suitable balance equations, and we assume that the controller *h(t)* is known. This led us to remain in the linearity field. Our aim is also to show that the approach here described is crucial to handle similar questions, both linear or not, in stochastic process theory, and that generalized Lie series, representing the solution components, is the answer we are looking for. For such a reason from a mathematical point of view, this note can be seen as an example close to the interests of scholars in stochastic process, queues theory and correlated questions. In fact generalized Lie series are the components of the true solution and are not just representative of an approximate solution. Therefore they represent a very suitable tool in handling this kind of problems, normally dealt with integration of an approaching initial value problem.

In other words, even if other future extensions are foreseen, we limit our study to the integration of a particular process. This choice is not restrictive and it is useful in the malignancy study. In fact this process describes the controlled evolution supposing that the natural evolution of malignant tumor is perturbed by a known cause, which modifies the representative stochastic process. In order to take into account the therapeutic action, for example of a drug, we introduced some changing in the original Dubin model [1]. This is a review of the historical attempts in malignancy representation and precisely concerns with the difficulties encountered in the integration of the representative evolution equation, equivalent to Kolmogorov's equations, since it concerns the probability generation function of the distribution. Starting from the critical considerations of the author, our attention dropped on Lie series method. This method, in fact, skips the consideration of evolution equation equivalent to the forward Kolmogorov's difference differential system representative of the stochastic process and, in our extension, integrates that initial value problem directly (see below for details). We stress indeed the possibility of integrating similar evolution equations both linear or not, but with analytical operator, by the same improved method. In other words, our method changes the usual procedure which consists in solving the equivalent Cauchy problem for the corresponding evolution equation, in a suitable functional space. In fact the generalized Lie series method solves directly the initial value problem for the birth and death process, spontaneous or controlled. More in general, if we have a Cauchy problem, given for an evolution equation

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$$\frac{dP}{dt} = AP,$$
$$P(x,0) = P_0(x)$$

which is linear, with unknown eigenvalues and eigenfunctions of *A*, or non linear but with *AP* as an analytical function respect to its arguments, the method can represent a suitable tool, as we proved in our recent studies, [2-11]. Every time that the representation with series of the evolution problem solution is convenient, it must be fixed the convergence radius of the series and the truncation error. Here we will present the results concerning the particular case we are dealing with, see below paragraphs 8 and 9.

After having exposed our starting points and having foreseen possible extensions of our study we now refer in details our results.

II. Review of Main Symbols

t, temporal variable;

X(t), random variable: number of malignant cells in tumor;

λ, constant stochastic parameter expressing a new birth in tumoral colony;

μ, constant stochastic parameter expressing a spontaneous death in tumoral colony;

k, constant stochastic parameter expressing a death by immunological feed-back;

h(t), stochastic parameter expressing a death due, e. g., to the drug activity

III. Modified Dubin Model

Let us now consider, with some suitable changes, the Dubin model [1] which describes tumoral growth, in order to obtain some results for our own, for example a pharmacological controlled process. Our attention has dropped on it, because a suitable change may be introduced in order to take into account the fundamental observation that malignancy is due to an imbalance between birth and death of cells. A drug killing cells increases the cellular loss and its administration may be optimized. This may be the final aim of our studies on malignancy: let the malignant tissue behave as much as possible in the manner of a normal one, in which the birth and the death of new cells are balanced.

Let us denote with *X(t)* the random variable, number of malignant cells, at time *t*, with initial size $X(0) = n_0$, being $n_0 = 1$ if the beginning of the phenomenon is described, otherwise 10^9 cells at least, in order to have a macroscopic clinical evidence.

In $[t,\ t+\Delta t]$ let us assume $o(\Delta t)$ the probability of more than one change in tumor colony and the following conditional probabilities for the appearance and disappearance of one new or old tumor cell respectively:

$$P(\{\Delta X(t) = +1, \text{due to reproduction} / X(t) = n\}) =$$
$$= \lambda n \Delta t + o(\Delta t);$$
$$P(\{\Delta X(t) = -1, \text{due to spontaneous and chemical death} / X(t) = n\}) =$$
$$= (\mu n + h(t)n + kn^2)\Delta t + o(\Delta t);$$

where: $\Delta X(t) = X(t+\Delta t) - X(t)$; λ, μ, *k*, indicate known positive constants expressing respectively a new birth, the spontaneous death and the death due to immunological reaction of the host.

Then the probability of no change is:

$$P(\{\Delta X(t) = 0 \ / X(t) = n\}) =$$
$$= 1 - (\lambda n + \mu n + kn^2)\Delta t + o(\Delta t)$$

and if $p_n(t) = P(\{X(t) = n\})$,

$$p_n(t+\Delta t) = p_n(t)[1 - (\lambda n + \mu n + h(t)n + kn^2)\Delta t] +$$
$$+ p_{n-1}(t)\lambda(n-1)\Delta t +$$
$$+ p_{n+1}(t)(\mu + h(t) + k(n+1))(n+1)\Delta t +$$
$$+ o(\Delta t)$$

Then according to Dubin we can write the following forward Kolmogorov's difference equations, with initial conditions:

$$\frac{dp_0}{dt} = (\mu + k + h(t))p_1$$
$$\frac{dp_n}{dt} = -(\lambda + \mu + h(t) + kn)np_n +$$
$$+ \lambda(n-1)p_{n-1} +$$
$$+ (\mu + h(t) + k(n+1))(n+1)p_{n+1}; \qquad n \geq 1$$
$$p_{n_0}(0) = 1; \quad p_j(0) = 0, \forall j \neq n_0; \quad p_{-1}(0) = 0. \qquad (2)$$

If the process is perturbed, for example by some pharmacological action, we can use the above representation. The action starts when the tumoral population has reached a size critical enough to become clinically evident, while no positivity could have been registered with suitable tumor-markers. Viceversa we may assume $n_0 = 1$ only in a preventive therapy, e.g. after surgical eradication of the primitive neoplasm. Of course, we assume *h(t)* = 0 for natural or spontaneous process, non-drug perturbed, i.e. describing malignant process before remedy or cocktails of drugs administration.

As it is well known, a unique solution such as

$$\sum_{k=0}^{+\infty} p_k(t) = 1$$

for the above problem is guaranteed by Feller's condition, which is:

$$\sum_{n=1}^{+\infty} \frac{1}{\lambda n} = +\infty$$

So, how can we determine the solution, after having verified the existence?

Finding an answer is the aim of this paper.

IV. Integration by Lie Series

In order to integrate (2) let us rewrite the above initial value problem (2) in the following manner:

$$\begin{aligned}
&\frac{dp_0}{dt} = (\mu + k + h(p_{-1}))p_1 = \Theta_0(p_{-1}, p_1)\\
&\frac{dp_n}{dt} = -(\lambda + \mu + h(p_{-1}) + kn)np_n +\\
&+ \lambda(n-1)p_{n-1} +\\
&+ (\mu + h(p_{-1}) + k(n+1))(n+1)p_{n+1} =\\
&= \Theta_n(p_{-1}, p_{n-1}, p_n, p_{n+1}); \qquad n \geq 1\\
&\frac{dp_{-1}}{dt} = 1\\
&p_{n_0}(0) = 1; \quad p_j(0) = 0, \forall j \neq n_0; \quad p_{-1}(0) = 0.
\end{aligned} \tag{3}$$

which we now name: the original problem. Please, note that the time dependent problem has been transformed in a time independent one by adding one more equation, the last one. We now rewrite the problem, this time with parametric initial conditions, as reported in (4) and we call it: the *operative* problem.

$$\begin{aligned}
&\frac{d\chi_0}{dt} = \Theta_0(\chi_{-1}, \chi_1)\\
&\frac{d\chi_n}{dt} = \Theta_n(\chi_{-1}, \chi_{n-1}, \chi_n, \chi_{n+1}); \quad n \geq 1\\
&\frac{d\chi_{-1}}{dt} = 1\\
&\chi_{-1}(0) = 0; \chi_0(0) = \pi_0; \chi_n(0) = \pi_n \; n \geq 1
\end{aligned} \tag{4}$$

In this way, if we write down the solution of the operative problem, we can also write the solution of the original one: we must only specialize, at the end, the initial conditions of the operative problem just into the values of the original problem.

Let us introduce the following two sequences of differential operators: the so-called Gröbner's operator sequence

$$\begin{aligned}
D_m &= \frac{\partial}{\partial \pi_{-1}} + \Theta_0(\pi_{-1}, \pi_1)\frac{\partial}{\partial \pi_0} +\\
&+ \sum_{n=1}^{m} \Theta_n(\pi_{-1}, \pi_{n-1}, \pi_n, \pi_{n+1})\frac{\partial}{\partial \pi_n}, \quad m \in N,
\end{aligned} \tag{5}$$

whose coefficients are the same functions which are present in the r.h.s. of (3) (but now depending on parameters), and the so-called Lie-operators sequence:

$$Exp(tD_m) = \sum_{\nu=0}^{+\infty} \frac{t^\nu}{\nu!} D_m^\nu \qquad \mathrm{m} \in \mathrm{N} \tag{6}$$

We want to stress that the above two sequences, (5) and (6), enable us to define, formally, two analogue operators: the Gröbner's one as an infinite sum of differential first order operators:

$$\begin{aligned}
D &= \frac{\partial}{\partial \pi_{-1}} + \Theta_0(\pi_{-1}, \pi_1)\frac{\partial}{\partial \pi_0} +\\
&+ \sum_{n=1}^{+\infty} \Theta_n(\pi_{-1}, \pi_{n-1}, \pi_n, \pi_{n+1})\frac{\partial}{\partial \pi_n},
\end{aligned} \tag{7}$$

and the Lie's one:

$$\exp(tD) = \sum_{\nu=0}^{+\infty} \frac{t^\nu}{\nu!} D^\nu. \tag{8}$$

Remark *In order to write the solution of an initial value problem concerning finite differential systems, Gröbner has considered the same operator (7) and the analogue Lie operator (8) corresponding to it, but as a finite sum. We can think of our problem (3) as the limit of an asymptotic sequence of analogous problems, all with a finite number of terms, and remaining so in the exact conditions of the Gröbner's approach. This point of view is peculiar to our answer to the problem.*

The foundation of the generalized Lie series method rests on the existence of D and e^{tD} as linear operators.

It is easy to prove that differential operators D_m have a finite norms on the space Π of the Cauchy sequences π, considered on the complex field. The linear space Π is *sup*-normed. Furthermore we regard every D_m, which is defined on a finite sequence:

$$(p_{-1}, p_0, ..., p_m), m \in N,$$

as:

$$D_m = D_m\left(p_{-1}, p_0, ..., p_m, 0, ..., 0, ...\right).$$

defined on a vector of Π. Now the Lie operator e^{tD}, analytic in *D*, satisfies a Lipschitz's condition as *D* runs the sequence $\left(D_m\right)_{m=0}^{+\infty}$:

$$\left\| e^{tD_m} - e^{tD_n} \right\| < K \left\| D_m - D_n \right\|.$$

In fact $\Theta(\pi) = (\Theta_m(\pi_{-1}, \pi_{m-1}, \pi_m, \pi_{m+1}))_{m=0}^{+\infty}$ is a Cauchy sequence, then such as $\left(D_m\right)_{m=0}^{+\infty}$, and

$$D_m \to D \text{ as } m \to +\infty.$$

Then

$$\left(e^{tD_m}\right)_{m=0}^{+\infty}$$

is a Cauchy sequence whose limit is:

$$e^{tD}.$$

From which it can be concluded that *D* and e^{tD} are well defined linear operators on Π.

V. Properties of Lie operators (ordinary or generalized)

Now we review the properties of the Lie operator both associated to a Gröbner finite operator or to a infinite one, in the above sense (refer to: [12,13] for details).

If *z* is a vectorial variable, Γ a differential operator such as:

$$\Gamma = \sum_j \vartheta_j(z) \frac{\partial}{\partial z_j} \qquad (9)$$

where z_j is the *j—th* component of vector *z* and the sum $\sum_j$ is finite or infinite, the following results hold if we consider the Lie operator in any variable *t*, in general complex:

$$e^{t\Gamma} = \sum_{\nu=0}^{+\infty} \frac{t^\nu}{\nu!} \Gamma^\nu \qquad (10)$$

$$e^{t\Gamma}(h_1 g_1(z) + h_2 g_2(z)) = h_1 e^{t\Gamma} g_1(z) + h_2 e^{t\Gamma} g_2(z),$$

where h_1 and h_2 are constants (linearity).

$$e^{t\Gamma}(g_1(z) \times g_2(z)) = e^{t\Gamma} g_1(z) \times e^{t\Gamma} g_2(z),$$

(product preservation)

$$e^{t\Gamma} g(z) = g(e^{t\Gamma} z),$$

if *g* is analytical w.r.t. *z* components (commutation or exchange theorem).

Furthermore when Lie operator (10) works on a function such as $k(\pi_{-1})$, and Γ is of inhomogeneous type, it is not different from the translation operator:

$$\exp(t \frac{d}{d\pi_{-1}})$$

so:

$$\exp(t\Gamma) k(\pi_{-1}) = k(\pi_{-1} + t).$$

VI. Existence of the Solution

The special functions, Lie series:

$$\chi_{-1} = [e^{tD} \pi_{-1}]_{\pi_{-1}=0} = t;$$
$$\chi_0 = [e^{tD} \pi_0]_{\pi_{-1}=0};$$
$$\chi_n = [e^{tD} \pi_n]_{\pi_{-1}=0}; n \geq 1,$$

are the components of the sequence, solution of the operative system (4); and the following:

$$p_0 = [e^{tD} \pi_0]_{\pi_{-1}=0; \pi_{n_0}=1; \pi_j=0, \forall j \neq n_0};$$
$$p_n = [e^{tD} \pi_n]_{\pi_{-1}=0; \pi_{n_0}=1; \pi_j=0, \forall j \neq n_0}; n \geq 1,$$

are the components of the solution of the original system (1)-(2).

Proof:

$$\frac{d}{dt} e^{tD} \pi_n = e^{tD} D \pi_n =$$
$$= e^{tD} \Theta_n(\pi_{-1}, \pi_{n-1}, \pi_n, \pi_{n+1}) =$$
$$= \Theta_n(e^{tD} \pi_{-1}, e^{tD} \pi_{n-1}, e^{tD} \pi_n, e^{tD} \pi_{n+1} =$$
$$= \Theta_n(t, \chi_{n-1}, \chi_n, \chi_{n+1})$$
$$\Rightarrow$$
$$\frac{d}{dt} \chi_n = \Theta_n(t, \chi_{n-1}, \chi_n, \chi_{n+1}).$$

Similarly, we can prove that:

$$\chi_0 = [e^{tD} \pi_0]_{\pi_{-1}=0};$$

is the first component of solution for (6), while trivially:

$$\frac{d}{dt} e^{tD} \pi_{-1} = e^{tD} D \pi_{-1} = 1$$

Q.E.D.

VII. Guidelines in Lie Series Handling

Now it is fundamental to ask ourselves how a Lie series

works. We conclude that the complexity of the algorithm is only apparent and a Lie series may be easily handled disposing of a suitable computer help.

We have, for example, the case of spontaneous evolution:

$$p_j(t) = \sum_{\nu=0}^{+\infty} \frac{t^\nu}{\nu!} [D^\nu_{j+\nu-1} \pi_j]_{\pi_{n_0}=1;\pi_j=0,\forall j\neq n_0} ;$$

$$D^\nu_{j+\nu-1} = \Theta_0(\pi_1)\frac{\partial}{\partial \pi_0} + \sum_{n=1}^{j+\nu-1} \Theta_n(\pi_{n-1},\pi_n,\pi_{n+1})\frac{\partial}{\partial \pi_n}$$

At each step: ν , *D* works on π_j as well as *D* stopped to its $j+\nu-1$ addendum, i.e. as the partial finite operator $D_{j+\nu-1}$ does.

In particular let us write $\chi_0(t)$, the component which corresponds in the operative problem to $p_0(t)$,the extinction probability of the spontaneous process. We can calculate the sequence of the partial sums which define the Lie series representing $\chi_0(t)$:

$$\pi_0 + tD_0\pi_0 = \pi_0 + tD_1\pi_0 = \pi_0 + tD_2\pi_0 =$$
$$= ... = \pi_0 + tD_k\pi_0 = ...$$

$$\pi_0 + tD_1\pi_0 + \frac{1}{2}t^2 D_1^2\pi_0 = \pi_0 + tD_2\pi_0 + \frac{1}{2}t^2 D_2^2\pi_0 =$$
$$= ... = \pi_0 + tD_k\pi_0 + \frac{1}{2}t^2 D_k^2\pi_0 = ...$$

$$\pi_0 + tD_2\pi_0 + \frac{1}{2}t^2 D_2^2\pi_0 + \frac{1}{3!}t^3 D_2^3\pi_0 =$$
$$= ... = \pi_0 + tD_k\pi_0 + \frac{1}{2}t^2 D_k^2\pi_0 + \frac{1}{3!}t^3 D_k^3\pi_0 = ...$$

...

$$\pi_0 + tD_k\pi_0 + \frac{1}{2}t^2 D_k^2\pi_0 + ... + \frac{1}{(k+1)!}t^{k+1} D_k^{k+1}\pi_0 =$$
$$= \pi_0 + tD_{k+1}\pi_0 + \frac{1}{2}t^2 D_{k+1}^2\pi_0 + ... +$$
$$+ \frac{1}{(k+1)!}t^{k+1} D_{k+1}^{k+1}\pi_0 = ...$$

...

where D_k indicates the *k-th* term of the sequence defining *D*. Therefore, every partial finite Gröbner system co-works in building the sequence of partial sums, defining $e^{tD}\pi_0$:

$$\pi_0 + tD_0\pi_0 = ... \equiv \pi_0 + tD\pi_0$$

$$\pi_0 + tD_1\pi_0 + \frac{1}{2}t^2 D_1^2\pi_0 =$$
$$= ... \equiv \pi_0 + tD\pi_0 + \frac{1}{2}t^2 D^2\pi_0$$

$$\pi_0 + tD_2\pi_0 + \frac{1}{2}t^2 D_2^2\pi_0 + \frac{1}{3!}t^3 D_2^3\pi_0 =$$
$$= ... \equiv \pi_0 + tD\pi_0 + \frac{1}{2}t^2 D^2\pi_0 + \frac{1}{3!}t^3 D^3\pi_0$$

...

$$\pi_0 + tD_k\pi_0 + \frac{1}{2}t^2 D_k^2\pi_0 + ... + \frac{1}{(k+1)!}t^{k+1} D_k^{k+1}\pi_0 =$$
$$= ... \equiv \pi_0 + tD\pi_0 + \frac{1}{2}t^2 D^{k+1}\pi_0 + ... +$$
$$+ \frac{1}{(k+1)!}t^{k+1} D^{k+1}\pi_0$$

...

We can write these functions explicitly down by means of suitable machine program (that we shall furnish in a forthcoming paper in order to allow numerical experiments). In the following picture, S_{1o} is the first partial sum generated by D_0 ; S_{21} is the second partial sum generated by D_1 and so on; the columns indicate the sequences of partial sum of the approximating problems, each one involving only one, two, three, four, ...equations. We are particularly interested in determining the terms of the diagonal (bold typed) in the following matrix, which represent the sequence defining $e^{tD}\pi_0$, because this is the path we shall follow in the computer algorithm to approach $e^{tD}\pi_0$:

$$\begin{array}{lllll}
\boldsymbol{S_{1o}} & (=)S_{11} & (=)S_{12} & (=)S_{13} & \dots \equiv S_1 \\
\dots & \boldsymbol{S_{21}} & (=)S_{22} & (=)S_{23} & \dots \equiv S_1 \\
 & \dots & \boldsymbol{S_{32}} & (=)S_{33} & \dots \equiv S_1 \\
 & & \dots & \boldsymbol{S_{43}} & \dots \equiv S_1 \\
 & & & \dots & \dots \quad \dots \\
\downarrow & \downarrow & \downarrow & \downarrow & \dots \searrow \downarrow \\
e^{tD_0}\pi_0 & e^{tD_1}\pi_0 & e^{tD_2}\pi_0 & e^{tD_3}\pi_0 & \dots \rightarrow e^{tD}\pi_0
\end{array}$$

where:

$$S_{jk} = \sum_{h=0}^{j} \frac{t^h}{h!}(D_k)^h \pi_0 , \qquad k \in \{j-1, j, j+1, ...\} \quad (11)$$

Now the sequence

$$S_k \to \exp(tD)\pi_0 \qquad (12)$$

uniformly converges.
In fact

$$\left|S_{n+k} - S_k\right| = \left|S_{n+k,h_2} - S_{k,h_1}\right|, \qquad (13)$$

where:

$$\begin{aligned} &h_1 \in \{k-1, k, k+1, \ldots\}, \\ &h_2 \in \{n+k-1, n+k, n+k+1, \ldots\}, \end{aligned} \qquad (14)$$

therefore:

$$\left|S_{n+k} - S_k\right| = \left|S_{n+k,h_2} - S_{k,h_2}\right|, \qquad (15)$$

with the r.h.s. definitively constant starting from $h_2 = n+k$

Due to convergence of all the Lie series :

$$\exp(tD_{h_2})\pi_0, \qquad (16)$$

which is uniform within its convergence domain, assigned $\varepsilon > 0$,it is possible to find $k > \nu_\varepsilon$ such as:

$$\left|S_{n+k,h_2} - S_{k,h_2}\right| < \varepsilon, \qquad \forall n \geq 0 \qquad (17)$$

and to choose $h_2(n)$ in such a manner that the sums S_{n+k,h_2}, S_{k,h_2} , belong to the above superior triangular matrix for every $n \in N_0$.

Remark *Roughly speaking we have two different paths to approach* $e^{tD}\pi_0$ *: one, based on the definition, the last row in the above matrix, but we will not follow it, as the single steps are unknown sums of series of the same type; the other, from the computation: the diagonal of that matrix. In fact this way can be run in a computer suitable programming and provides the component searched of the true solution with the desired precision.*

VIII. Convergence Radius

Convergence: *The Lie series representing the components of the solution of (4) converges for every t.*

Proof:
For an ordinary Lie series the convergence radius may be determined by the ratio test applied to the majorant series in the Cauchy sense [12, 13].

We recall that a Cauchy majorant is a power convergent series in some variable ,with real and positive coefficients, such as

$$\sum_{\nu=0}^{+\infty} \tau^\nu c_{\nu k} \ ; \text{ if } \ \frac{b_{\nu k}}{\nu!} = c_{\nu k} \ ; \text{ it is } b_{\nu k} \geq \left|a_{\nu k}\right|; \qquad (18)$$

if the Lie series considered is:

$$e^{tD}\pi_0 = \sum_{\nu=0}^{+\infty} \frac{t^\nu}{\nu!} D_k^\nu \pi_0 = \sum_{\nu=0}^{+\infty} \frac{t^\nu}{\nu!} a_{\nu k}, \qquad (19)$$

i.e. the $k+1-th$ approaching series of the generalized one: $e^{tD}\pi_0$.

The ratio test [12, 13] takes one to the limit

$$\frac{b_{n+1,k}}{b_{nk}} \frac{1}{n+1} \to 0, \qquad (20)$$

according to the result of an infinite radius of every approaching ordinary Lie series with associated initial value problem of the linear type.

Then we can write:

$$\frac{\left|a_{n+1,k}\right|}{\left|a_{nk}\right|} \frac{\left|a_{nk}\right|}{b_{nk}} \frac{1}{n+1} \leq \frac{b_{n+1,k}}{b_{nk}} \frac{1}{n+1} = y_{nk} \frac{\left|a_{nk}\right|}{b_{nk}},$$

where $\dfrac{\left|a_{nk}\right|}{b_{nk}}$ is a bounded sequence as $n \to +\infty$ and

$$y_{nk} \to 0 \text{ as } \ n \to +\infty. \qquad (21)$$

Then

$$\frac{\left|a_{n+1,k}\right|}{\left|a_{nk}\right|} \frac{1}{n+1} \to 0, \text{ as } \ n \to +\infty, \forall k \in N_0. \qquad (22)$$

and assigned $\varepsilon > 0$,it is

$$\frac{\left|a_{n+1,k}\right|}{\left|a_{nk}\right|} \frac{1}{n+1} < \varepsilon, \forall n > \nu_k(\varepsilon). \qquad (23)$$

Then if $\nu^* = \min\{\nu_0, \nu_1, \ldots\}$,it is

$$\frac{|a_{n+1,k}|}{|a_{nk}|}\frac{1}{n+1}<\varepsilon,\forall n>\nu^*,\forall k\in N_0. \qquad (24)$$

Now the ratio

$$\frac{|a_{n+1,k}|}{|a_{nk}|}\frac{1}{n+1} \qquad (25)$$

is definitely always the same, starting from k=n, and defines

$$\frac{|a_{n+1}|}{|a_n|}\frac{1}{n+1} \qquad (26)$$

the ratio of the $n+2-th$ term and the n+2-th one in the generalized Lie series $e^{tD}\pi_0$, therefore it is:

$$\frac{|a_{n+1}|}{|a_n|}\frac{1}{n+1}<\varepsilon \qquad \forall n>\nu^* \qquad (27)$$

and the convergence radius of generalized Lie series $e^{tD}\pi_0$ is infinite.

The same happens to every other generalized Lie series, associated to the assigned linear problem.

IX. Truncation Error

In order to estimate the truncation error in a generalized Lie series we recall the following useful statement:

If in a numeric series with positive terms, $\sum_{\nu=0}^{+\infty}\alpha_\nu$, it happens that

$$\frac{\alpha_{n+1}}{\alpha_n}\le r_2;\quad r_2<1 \qquad (28)$$

(definitively from n^*), then the truncation error turns out to be:

$$R_{n^*}=\sum_{\nu=n^*}^{+\infty}\alpha_\nu\le\alpha_{n^*}\frac{r_2}{1-r_2}.$$

So, if for a generalized Lie series, e.g. $e^{tD}\pi_0$, we determine the index, such as, starting from it,

$$\frac{|a_{n^*+1}|}{|a_{n^*}|}\frac{t_0}{n^*+1}\le r_2<1 \qquad (29)$$

we are sure that the truncation error is not greater than

$$\frac{|a_{n^*}|}{n^*}t_0^{n^*}\frac{r_2}{1-r_2}. \qquad (30)$$

X. Conclusion

In the present paper we approached the controlled behavior of a malignant process by means of a strategy inspired to Groebner's mathematical ideas. This study is our starting point for future investigations in order to optimize the controller action and to obtain hopefully some practical applications in the fight against tumors. In particular we introduced a modified Dubin model describing malignancy and controlled by a drug and we integrated the open system of the relative differential equations by introducing Lie series of a generalized type.

In addition we want also to emphasize the possibility of using this method in order to integrate general birth and death processes occurring in the theory of stochastic processes.

References

[1] N. Dubin, A stochastic model for immunological feedback in carcinogenesis, Springer Verlag Berlin 1976.

[2] J.Quartieri, S.Steri, G.Volzone, *Int. J. Nonlin. Scien. And Num. Simul.* 2001.V. 2.

[3] Guida M., Quartieri J., Steri S., Groebner's integration of a special class of nonlinear Cauchy problems, *Int. J. Nonlin. Sci. Num. Sim.*, 4 (2003), 99-102.

[4] Quartieri J., Steri S., Volzone G., Lie series and nonlinear evolution problems. *Int. J. Nonlin. Sci. Num. Sim.*, 2 (2001), 167-168.

[5] Di Bartolomeo A., Quartieri J., Steri,S., Perturbed non-linear evolution problem solved by a generalized Lie series method. *Int. J. Nonlin. Sci. Num. Sim*., 1, 3 (2002), 75-76.

[6] Di Bartolomeo A., Quartieri J., Steri S., A class of non-linear implicit Cauchy problems integrated by Groebner method. *Int. J. Nonlin. Sci. Num. Sim.*, 4 (2003), 103-104.

[7] Di Bartolomeo A., Quartieri J., Steri S., Lie and Lagrange series in nonlinear equations with controlled evolution, *Int. J. Nonlin. Sci. Num. Sim*., 4 (2003), 95-97.

[8] Di Bartolomeo A., Quartieri J., Steri S., Second order nonlinear Cauchy problem in a four dimensional space. *Nonlinear Oscillations*, Vol.6, N.2 (2003), 166-170.

[9] Quartieri J., Steri S., A New Method for Solving 2D Nonlinear PDEs Relevant in Physics, *Int. J. Nonlin. Sci. Num. Sim.*, 4, n.4 (2003), 423-427.

[10] Quartieri J., Steri S., G.Volzone, Picard Method in Analytic Evolutionary Problems Describing the Behaviour of Complex Systems of Physics (*in press*).

[11] Guida D., Quartieri J., Steri S., A Procedure for Calculating an Approximate Analytical Response in a Large Class of Mechanical Systems. *WSEAS International Conference on Non-Linear Analysis*, Tenerife 2006.

[12] W. Gröbner, Gruppi anelli e algebre di Lie, *Cremonese,Roma 1975*.

[13] W. Gröbner, Serie di Lie e loro applicazioni, *Cremonese,Roma 1973*.

[14] W. Gröbner, H. Knapp, Contribution to the method of Lie series, *Bibliographisches Institut, Univ. Mannheim 1967*.

[15] I. F. Tannock, R. P. Hill, The basic science of oncology, McGraw-Hill 1992.

[16] V. T. De Vita Jr., S. Hellman, S. A. Rosemberg, Cancer, J.B. Lippincott Co. 1993.

[17] M. Guida, J. Quartieri, E. Quarto, S. Steri, G. Volzone, Feedback control with delay in biological problems: a new approach. WSEAS Transactions on Mathematics Issue 5, Volume 6, p. 688, May 2007.