A Model on Controlled Evolution of Malignant Cells and on Drug Balance between Blood and Tumor

Quartieri* J., Steri** S., Volzone** G., Guarnaccia* C.

Abstract— A theoretical model for the evolution of a colony of tumoral cells is presented. From a bio-physical point of view, we improve the Dubin model in its form of a Kolmogorov system of equations by adding the action of an external control (e.g. drug therapy), and we write a stochastic system able to give us mean and variance of the random variable (r.v.) describing the number of tumoral cells in the colony.

In the second part of the paper, a suitable model for the evolution of drug concentration both in blood and in tumor, is presented. Therefore this last system is coupled to the first one, which means, from a mathematical point of view, the mixing of a stochastic process (generally non-linear and non-autonomous evolutionary equations) with a deterministic one (drug balance equations). The linkage between these two sections is given by the stochastic parameter *E(X)*, the mean value of the r.v. .

The solution of the final system allows us to find the time history of the drug control factor which could be used in order to develop a strategy for its optimization.

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

I. Introduction

ROUGHLY speaking malignancy is a process in which an imbalance exists between relatively few losses and much more new births in a cellular colony with an almost certain bad epilog for the host. Controlled evolution happens when therapist attempts either to equilibrate those two moments in the colony life or to extinguish colony, e.g. using a certain remedy administered to the host or, more effectively, a cocktail of drugs.

In a previous paper, [1], we discussed some biological foundations of our mathematical representation of the attempt to invert that balance by means of drug therapy. In it we cast some ideas for the acquirement of the experimental data to be utilized in a computer program for practical use. In particular, in [2], we discussed an integration method, due to Gröbner, and only improved by us, which, by Lie series of the generalized type, allows the representation of the solution components.

Similarly to Dubin's one [3], the model representing controlled malignancy may be described by the following controlled stochastic process (forward Kolmogorov equations) supposing a sole controller factor *h(t)* for the random variable (r.v.) *X(t)=n* (number of cells in the colony):

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

λ, μ, k are parameters of the biology of the process, representing the growth, the spontaneous death and the immunological response of the host.

In (1) a procedure of "symmetrization of variables" has been operated by adding the last equation and the corresponding initial condition. This procedure turns the process into an autonomous one, i.e. with no explicit dependence on *t*. In [4] we already found the solution of problem (1), for an assigned *h(t)*.

In the present paper we suppose the controller depends on the concentration in tumor of the drug administered. We have to face the following tasks:

1) writing an initial value problem equivalent to the above (1) concerning with functions linked to the moments of the *X* variable, which, in its turn, represents the number of malignant cells. This equivalent representation will be also useful to determine the mean and variance of the process, in drug presence or in spontaneous evolution (Dubin's model [3]);

Manuscript received June 30, 2007. Revised received November 28, 2007.

*Department of Physics "E. Caianiello" and Faculty of Engineering, University of Salerno, Via Ponte don Melillo, Fisciano (SA), Italy. (corresponding authors QUARTIERI J.: 0039 089 969356; e-mail: quartieri@unisa.it; GUARNACCIA C.: 0039 089 969356; e-mail: guarnaccia@sa.infn.it).

**Department of Mathematics "R. Caccioppoli", University of Naples.

2) writing the balance equations of the drug in the host (only announced in [1]);

3) assembling the stochastic process with the drug balance equations. So obtaining a nonlinear model which will be integrated, by Gröbner's method, in order to constitute the basis for a suitable answer to the following problem of optimization: what is the drug intake which ensures the mean to be stationary and minimum at an assigned instant *T* from the beginning of therapy, compatibly with the necessity to minimize toxicity on noble parenchymal organs?

In a forthcoming paper we will give an appropriate answer to this question, based on Pontryagin's principle.

II. Equivalent Cauchy Problem, Mean and Variance for the Random Variable

The evolution of a tumoral colony in drug absence is described by the above initial value problem (1) when the controller is missing: *h(t)* = 0.

By introducing the probability generating function (p.g.f.):

$$P(z,t)=\sum_{n=0}^{+\infty} p_n(t)\, z^n\ ,\quad p_n(t)=\frac{1}{n!}\left[\frac{\partial^n P(t,z)}{\partial z^n}\right]_{z=0} \qquad (2)$$

We can rewrite the birth and death process as an equivalent Cauchy problem:

$$\frac{\partial u}{\partial t}=[\lambda(z^2-z)+(\mu+k)(1-z)]\frac{\partial u}{\partial z}+k(z-z^2)\frac{\partial^2 u}{\partial z^2} \qquad (3)$$

$$\Leftrightarrow \frac{\partial u}{\partial t}=Au \qquad (4)$$

$$u=1-P\ ;\ u^{(n_o)}(0,z)=1-z$$

$$0\le t<\infty\ ,\ z\in[0,1[$$

if n_o is the initial number of cells in the colony.

Integrating problem (1) is tantamount to integrating the corresponding Cauchy problem (3-4). Making it possible is also one of our contributions to the Gröbner's method of Lie series [5], [6].

When a factor limiting the neoplasm growth is present, the evolution may be described by an equation like the following:

$$\frac{\partial u}{\partial t}=[\lambda(z^2-z)+(\mu+k)(1-z)]\frac{\partial u}{\partial z}+k(z-z^2)\frac{\partial^2 u}{\partial z^2}+F(t,z) \qquad (5)$$

where *F(t,z)* is the controller. In this case the integration method reported in our note [6] is applicable.

But the controlled process may also depend by a perturbing operator:

$$\frac{\partial u}{\partial t}=[\lambda(z^2-z)+(\mu+k)(1-z)]\frac{\partial u}{\partial z}+k(z-z^2)\frac{\partial^2 u}{\partial z^2}+$$
$$+[h(t)(1-z)]\frac{\partial u}{\partial z} \qquad (6)$$

as in our current model (1). In fact we suppose the existence of a killer agent, which supplies a chemical death to the spontaneous cellular loss or to the one due to immunological response of the host. In other words in our controlled process the natural evolution is perturbed by a differential operator like:

$$h(t)(1-z)\frac{\partial}{\partial z}\ , \qquad (7)$$

and not by a finite addend represented by an analytic function like *F(t,z)*. Furthermore if *h(t)* is a small perturbing factor then the perturbative Poincaré method is available [6]. It consists, roughly speaking, in expanding the solution in terms of a power series of *h(t)*, with the possibility of retaining only the first few addends according to the *h(t)* weight.

Therefore the above Cauchy problem describing controlled or spontaneous evolution ($h(t)\neq 0$ and $h(t)=0$ respectively) will have its unique solution as the following double series:

$$P(z,t)=\sum_{n=0}^{+\infty} p_n(t)\, z^n=\sum_{n=0}^{+\infty} z^n[e^{tD}\pi_n]_{\pi_{n_o}=1;\,\pi_j=0,\ \forall j\neq n_o} \qquad (8)$$

where the components of the solution of (1) have the meaning of derivatives of the p.g.f., i.e. the probabilities that the random variable *X* takes its possible values: 0, 1, … .

In the above formula e^{tD} is the Lie operator, [7]-[9], [5] with a generalized Gröbner differential operator *D*, i.e. a symbolic series of first order differential addends, which in the present case reads:

$$D=\frac{\partial}{\partial\pi_{-1}}+\Theta_o(\pi_{-1},\pi_1)\frac{\partial}{\partial\pi_o}+$$
$$+\sum_{j=1}^{+\infty}\Theta_j(\pi_{-1},\pi_{j-1},\pi_j,\pi_{j+1})\frac{\partial}{\partial\pi_j}$$

where the coefficients are given by the r.h.s. of the forward Kolmogorov equation (1), whose arguments have been now transformed into parameters.

Since the evolutionary operator *A* is linear and the coefficients of the differential terms are polynomials,

P(z,t) is continuously differentiable at z=1.

So, for example, problem (1) with *h(t)*=0 is equivalent to the following one:

$$\frac{\partial \eta_n}{\partial t} = \beta_{n-1}\eta_{n-1} + \alpha_n \eta_n + \gamma_{n+1}\eta_{n+1} \ ; \ n \geq 1 \qquad (9)$$
$$\eta_1(0) = n_o = 1 \ ; \ \eta_j(0) = 0 \ , \ \forall j \neq 1 \ ;$$

where :

$$\left[\frac{\partial^i P}{\partial z^i}\right]_{z=1} = \eta_i = \qquad (10)$$
$$= E(X(X-1)(X-2)...(X-i+1));$$
$$\beta_{n-1} = n(n-1)\lambda;$$
$$\alpha_n = n\lambda - n\mu - n^2 k;$$
$$\gamma_{n+1} = -nk;$$

where η_i represents the mean of r.v. product. In fact the new variables are related to momenta of *X*, so the mean *E(X(t))* and the variance *Var(X(t))* of the random variable (r.v.) *X* are respectively:

$$E(X(t)) = \eta_1(t)$$

and

$$Var(X(t)) = \eta_2(t) + \eta_1(t) - (\eta_1(t))^2 \ .$$

Therefore the solution of (9) allows us to immediately find these two stochastic parameters.

We plan to develop a computer software in order to find these two fundamental stochastic parameters both in the spontaneous and in the controlled (by drugs) evolution.

III. Drug Balance Equations

V_1, (constant) apparent distribution volume of drug in blood;

$V_2(t)$, (variable) tumor volume;

V_{cell}, (constant) single cell volume;

Q'_{in} , (variable) rate of drug intake;

α_{12}, (constant) diffusion coefficient of the drug from blood towards tumor;

$\alpha_{21}(t)$, (variable) diffusion coefficient of the drug from tumor towards the blood stream;

a_{12}, (constant) transfer rate per unit volume from blood to tumor, such that:

$$\alpha_{12} = V_1 \, a_{12} \ ;$$

a_{21}, (constant) transfer rate per unit volume from tumor to blood, such that:

$$\alpha_{21} = V_2 \, a_{21} \ ;$$

C_1, (variable) drug concentration in blood;

$C_{2,n}$, (variable) drug concentration in tumor;

$[V'_{cl}]_{met}$, (constant) drug clearance due to liver metabolism;

$[V'_{cl}]_{tum}$, (constant) drug clearance due to tumor metabolism;

$[V'_{cl}]_{kid}$, (constant) drug clearance due to kidney depuration;

E(X), (variable) mean of r.v. *X*, number of malignant cells.

Now we must add to the above system (9-10) (equivalent to the forward Kolmogorov's equations (1)) the equations of the drug balance in the host. In our previous paper [1] we discussed the biological methods which permit the acquirement of all data, which we assumed known in balance equations. Now we are going to give a biophysical foundation to the writing of those equations. In doing so we shall follow the theory of the two compartments, taking into account the expansion of one of them. At this aim we shall modify the equation of diffusion of the drug in tumor. In the end the presence of a linkage between the controller *h(t)* and the drug concentration in tumor will lead to a nonlinear initial value problem which we will integrate by Lie series [5], [7]-[9].

Let's suppose that after a rapid intravenous injection in bolus, a slow maintenance by infusion of the drug is administered. In order to write the balance equations, which describe the behavior of the drug in the host, let us assume what follows:

1) $V_2(t)$ the current volume of the colony, V_1 the apparent distribution volume of drug in blood, which is supposed to remain constant;

2) the rate of diffusion between the two compartments (1 blood - 2 tumoral colony) depends on two different parameters: α_{12} for diffusion from 1 to 2 and α_{21} in the opposite direction;

3) the drug is removed from V_1 both by renal excretion and chiefly by liver metabolic degradation.

Then if:

$$Q'_{in} = q_0 + q_1(t)$$
$$q_0 = \text{priming dose}$$

is the rate intake by continuous intravenous infusion, we can write the following drug balance equations:

$$V_1 \tfrac{dC_1}{dt} + \alpha_{12} C_1 - \alpha_{21} C_{2,n} + [V'_{cl}]_{met} C_1 + [V'_{cl}]_{tum} C_1 +$$
$$+ [V'_{cl}]_{kid} C_1 = Q'_{in} \ ;$$
$$\frac{dC_{2,n}}{dt} = \frac{d}{dt}\frac{m}{V_2} \ \Rightarrow \ \frac{dC_{2,n}}{dt} = \frac{1}{V_2}\frac{dm}{dt} - \frac{m}{V_2^2}\frac{dV_2}{dt} \ \Rightarrow$$

$$V_2 \frac{dC_{2,n}}{dt} = (\alpha_{12} C_1 - \alpha_{21} C_{2,n}) - C_{2,n} \frac{dV_2}{dt} \qquad (11)$$

where, m is the amount of drug molecules in tumor, C_1, $C_{2,n}$ are drug concentrations in blood and in a tumor of $X = n$ cells. Furthermore:

$$(a_{12} V_1 C_1 - a_{21} V_2 C_{2,n}) = \frac{dm}{dt} \qquad (12)$$

is the rate of the exchangeable aliquot of drug between the two compartments blood stream and tumoral colony. Besides

$$[V'_{cl}]_{met} \ , \ [V'_{cl}]_{tum} \ , [V_{cl}]_{kid} \ , \qquad (13)$$

are the constant clearances. The first one is due to metabolism of the drug in liver. The second term takes into account the metabolic degradation of drug due to the tumor itself and the last one is due to renal depuration.

In particular we have assumed that the rate of drug presence in colony: i.e. free molecules and the ones combined to cellular receptors, with these two fractions in chemical equilibrium, through the same coefficients α_{12}, α_{21}, depends from the rates of diffusion from blood to tumor and vice versa.

Note that if V_2 represents the current colony volume, whose evolution is perturbed by the drug, it may be esteemed as follows:

$$V_2 = (\text{ mean of } X) \times (\text{ average cellular volume }) =$$
$$= E(X) \times V_{cell} \ ,$$

where we assumed, for simplicity, an average volume of the cells sample V_{cell} (even though malignancy can be characterized by some variability in the cellular volume). *E(X)*, mean value of the random variable, esteems the current number of cells in the colony, if the mean well resumes the random variable, i.e. in hypothesis of little variance.

Now the balance equations of the drug can be so rewritten:

$$\frac{dC_1}{dt} = \frac{Q'_{in}}{V_1} - \left(\frac{a_{12} V_1 C_1 - a_{21} V_{cell} E(X) C_{2,n}}{V_1} + \frac{[V'_{cl}]_{met} + [V'_{cl}]_{tum}}{V_1} C_1 + \frac{[V'_{cl}]_{kid}}{V_1} C_1 \right)$$

$$\frac{dC_{2,n}}{dt} = \frac{1}{E(X) V_{cell}} \left(a_{12} V_1 C_1 - a_{21} V_{cell} E(X) C_{2,n} - C_{2,n} V_{cell} \frac{dE(X)}{dt} \right)$$

$$C_1(0) = \frac{initial\ bolus}{V_1}; \ C_{2,n}(0) = 0 \qquad (14)$$

Then if we add the above balance equations (14) to the previous system (9-10), and if (as we are going to show in what follow) the controller *h(t)* may be expressed by $C_{2,n}$, we achieve a complete initial value problem describing the controlled malignant process. By means of this system we can reach the important goal to modulate the drug concentration in blood and in tumor so that the maximum positive effect is obtained, i.e. being able to minimize *E(X)* after a suitable limited time interval in order to restrain the toxicity of drug on noble parenchymal organs.

Then if a daily range may be established in order to avoid toxicity, the temporal administration function must be modulated in time in such a way that the drug amount present in tumor increases towards an optimal value. This is one of our major aims we pursue in this research.

IV. Dependence of *H(T)* on Drug Concentration

Let us remember here some our assumptions also present in our previous note [1] in order to link in a simple model cellular death to tumoral concentration of drug $C_{2,n}$, which is supposed in equilibrium with the blood concentration. In fact we can suppose chemical death depends on $(1-q)\Delta t$, the proportion of time in which drug molecules are combined with cellular hypothesized receptors:

$$P(\{\Delta X(t) = -1 \text{ , due to chemical death}$$
$$/ \ X(t) = n\}) = \zeta (1-q) n \Delta t + o(\Delta t) \ .$$

At the chemical equilibrium the same proportion of cellular receptors is such that:

$$\text{rate of detachment = rate of attachment}$$
$$k_{-1} n \nu (1-q) = k_1 C_{2,n} n \nu q \ \Rightarrow$$
$$1 - q = \frac{\rho C_{2,n}}{1 + \rho C_{2,n}} , \qquad (15)$$

where:

ν is the constant (in the interval of the achievement of chemical equilibrium) number of receptors per cell,

$\rho = \frac{k_1}{k_{-1}}$ is the dissociation constant of chemical equilibrium,

$n\nu(1-q)$ receptors attached, $n\nu q$ free receptors,

then:

$$h(t) = \zeta \frac{\rho C_{2,n}}{1 + \rho C_{2,n}} \ . \qquad (16)$$

It is fundamental to recollect the biological foundation of our model.

Conjecture *We assume that the drug control is due to small rapidly diffusing molecules able to interfere with relatively slow activities of macromolecular species in cells; since the*

receptors reproduction and the modulation of their concentration in cells are certainly slower processes, then:

ν , the number of receptors per cell, can be considered constant; furthermore the duration of the chemical linkage of cellular receptors combined with drug molecules in cellular population can be considered esteemed by the proportion, in the sample, of cells attached to drug, in the same interval Δt . Attached cells are detected in the sample, e.g. by a radioactive isotope.

Then it is founded the introduction, in a single drug administration, i.e. in mono-therapy with a drug killing malignant cells, of the new parameter in Kolmogorov equations (9-10), in the above shape (16) and write:

$$\begin{aligned}
&\frac{d\eta_n}{dt} = \beta_{n-1}\eta_{n-1} + \alpha_n\eta_n + \gamma_{n+1}\eta_{n+1}\ ;\ n \geq 1 \\
&\eta_1(0) = n_o = 1\ ;\ \eta_j(0) = 0\ ,\ \forall j \neq 1\ ; \\
&\beta_{n-1} = n(n-1)\lambda; \\
&\alpha_n = n\lambda - n\mu(t) - n^2 k; \\
&\gamma_{n+1} = -nk; \\
&\mu(t) = \mu + \zeta\frac{\rho C_{2,n}}{1+\rho C_{2,n}}\ .
\end{aligned} \tag{17}$$

Once these equations are associated to the balance equations (14) they constitute a nonlinear initial value problem.

V. Integration by Lie Series of the Controlled Evolution

The integration by Lie series of the control problem is not easy. In previous papers [1], [2], [4]-[6], [10]-[16] we demonstrated the possibility to integrate, by Lie generalized series, a differential system obtained by a Taylor Transform of an evolutionary differential equation having an analytical operator in the r.h.s.. This condition is indeed sufficient for the existence of the generalized Groebner's operator which, in turn, defines the Lie Series. So in order to obtain the solution of system (17) via generalized Lie series we can write a symbolic representation of a slight different problem strictly linked to it which we name "the original system". At this aim we perform a Taylor transformation to both sides of the evolutionary equation with initial point *z* =1, naming the new unknown functions

$$\eta'_n = \frac{\eta_n}{n!}$$

and obtaining:

$$\frac{d\eta'_n}{dt} = \Phi_n(\eta'_{n-1}, \eta'_n, \eta'_{n+1}, C_{2,n}) \qquad n > 0 \tag{18a}$$

to which now we add the drug balance equations in the new unknown functions:

$$\begin{aligned}
&\frac{dC_1}{dt} = \Phi_0(C_1, \eta'_1, C_{2,n}) \\
&\frac{dC_{2,n}}{dt} = \Phi_{-1}(C_1, \eta'_1, \eta'_2, C_{2,n}) \\
&C_1(0) = \frac{initial\ bolus}{V_1};\ C_{2,n}(0) = 0 \\
&\eta_1(0) = n_o\ ; \qquad \eta_j(0) = 0\ , \qquad \forall j \neq 1\ ;
\end{aligned} \tag{18b}$$

Now the "operative" system is reached just rewriting the above system with parametric initial conditions. These parameters are the components of the sequence: $(c_1, c_2, \varepsilon_1, ...)$.

Once having written, by means of Lie Series, the components of the solution of the operative system we obtain the solution to the "original" problem by fixing the parameters to the initial conditions. Lie Series depends on the Groebner's operator:

$$\begin{aligned}
\hat{D} = &\Phi_0(c_1, c_2, \varepsilon_2)\frac{\partial}{\partial c_1} + \Phi_{-1}(c_1, c_2, \varepsilon_1, \varepsilon_2)\frac{\partial}{\partial c_2} + \\
&+ \sum_{n=1}^{\infty}\Phi_n(c_2, \varepsilon_{n-1}, \varepsilon_n, \varepsilon_{n+1})\frac{\partial}{\partial \varepsilon_n}
\end{aligned} \tag{19}$$

and on the Lie operator:

$$e^{t\hat{D}} = \sum_{\nu=1}^{\infty}\frac{t^\nu}{\nu!}\hat{D}^\nu \tag{20}$$

The former operator is represented by a symbolic series. Its coefficients are the same as in the original system but with parametric arguments.

In general an operator as the first one introduced with a symbolic series is an effective differential operator if the original initial value problem, which it is related to, comes from a Cauchy problem with an analytical evolutionary operator "*A*" obtained by a Taylor Transform in a non singular point of *domA*.

In fact it has been demonstrated [15] that the symbolic series "*W*", in a Groebner's operator such as $\hat{D}$, defines a linear operator on the *S* space of the Cauchy's sequences (normed with the *Sup-norm*) provided that the coefficients Φ_n form an infinitesimal sequence. This condition is sufficient to ensure that the sequence of the partial sums of the *W* series converges in norm on *S* space.

Let's now observe that if the sequence of the coefficients of *W* is infinitesimal, it doesn't change if we add a finite number of terms such as the ones corresponding to the first two addends in $\hat{D}$, so $\hat{D}$ is effectively a differential operator on *S*. In the case under study the two more addends come from the drug balance equations (18b).

The second operator (20) is analytic in $\hat{D}$ and in general it exists for every *t* belonging to *domA*. In particular if the evolutionary operator *A* (4) does not depend explicitly from *t* (i.e. it is an autonomous operator), then the Lie operator (20) exists for every value of *t*.

Therefore the components of the solution of the original problem are:

$$C_1 = [e^{t\hat{D}} c_1]_{c_1 = C_1(0), c_2 = C_{2,n}(0), \varepsilon_n = \eta'_n(0)\ 1 \le n \le \infty}$$

$$C_2 = [e^{t\hat{D}} c_2]_{c_1 = C_1(0), c_2 = C_{2,n}(0), \varepsilon_n = \eta'_n(0)\ 1 \le n \le \infty}$$

$$\eta'_n = [e^{t\hat{D}} \varepsilon_n]_{c_1 = C_1(0), c_2 = C_{2,n}(0), \varepsilon_n = \eta'_n(0)\ 1 \le n \le \infty}$$

Consequently

$$P(z,t) = \sum_{n=1}^{\infty} \eta'_n (z-1)^n$$

We stress that from a general point of view Lie series converge, as a power series of *t*, in *DomA*. In the case we just presented we have an autonomous system, so convergence is found for every time. On the contrary, in a model where *h(t)* were a known function, we would have convergence only in the domain of analyticity of *h(t)*.

VI. Conclusions

In this paper we wrote and integrated, by Gröbner's method, the nonlinear controlled process describing malignancy if control is due to the action of a sole remedy. This study may constitute the matter basis for similar more complicated studies when one wants to use more than one remedy, as the practice suggests, in the fight against tumors. But this model is also a starting point for an optimal control problem. In fact we must ask ourselves which is the best choice of the controller *h(t)* that optimizes drug therapy, optimal control being the minimization of the mean of the random variable at any instant *T*, after the beginning of therapy. We shall study the questions in a forthcoming paper.

References

[1] J.Quartieri, S.Steri, G.Volzone, *Int. J. Nonlin. Sci. and Num. Simul.* 2001.V. 2

[2] 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.

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

[4] J. Quartieri, S. Steri, M. Guida, C. Guarnaccia, S. D'Ambrosio, A Biomathematical Study of a Controlled Birth and Death Process Describing Malignancy, *Advanced Topics on Mathematical Biology and Ecology*, 4th WSEAS Int. Conf. (MABE'08). Acapulco, Mexico, January 25-27, 2008. ISBN: 978-960-6766-32-9 / ISSN: 1790-2769

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

[6] 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

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

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

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

[10] 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

[11] 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

[12] 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

[13] 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

[14] 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.

[15] S. Steri, J. Quartieri, G. Volzone, C. Guarnaccia, On Picard Iteration and Lie Series in Analytic Evolutionary Problems of Physics, Proceeding of the 9th WSEAS *International Conference on Mathematics & Computers in Biology & Chemistry* (MCBC '08), Bucharest (Romania), 24-26 June 2008. ISBN: 978-960-6766-75-6 / ISSN: 1790-5125, pp 157-163.

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

[17] B.C. Goodwin, Temporal organization in cells, *Accademic Press, London and New York, 1963*.

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

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