Nonlinear Evolutionary Process in Biophysics: an Hamiltonian Representation

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Abstract: - The behaviour of a cellular colony in controlled growth is here exploited by means of new mathematical models. The first aim of the paper is to introduce the Hamiltonian function in an analytic nonlinear evolutionary process. In analogy with the finite optimal processes theory, this study leads to the introduction of a canonical representation of the process by means of two sequences of equations. This means that one has to introduce "adjoint variables", namely "generalized momenta", which play the role of classical momenta and have to be considered together with the "positional variables". A correct explanation of the physical meaning of these new variables gives the possibility to extend the analogy with classical mechanics. In this scenario, a biological problem can be considered and used as a case study for this analogy. The authors have already studied the controlled evolution of a cellular colony in some recent papers. Now the application of an Hamiltonian representation to the stochastic process of a tumoral cells colony is approached by means of the introduction of the canonical variables.
This hopefully could lead to the begin of a new optimal control of drug therapy in the evolution of a tumoral colony.

Key-Words: - Hamiltonian Function, Optimal Control, Cellular Colony

1 Introduction

The primary aim of this paper is to introduce, à la Pontryagin [10], the Hamiltonian function in the representation of an evolutionary linear or nonlinear Cauchy problem, either autonomous or not. That is tantamount to introduce a canonical representation of the process starting from the initial configuration occupied by the physical system at the zero instant.

The problem to be considered is the following one, e.g. autonomous, i.e. with a time independent evolutionary operator:

$$ECP: \begin{cases} \frac{d}{dt}P = A(P) \\ P(x,0) = P_0(x) \\ x \in [0,1[, \ t \in [0,+\infty[\end{cases} \quad (1)$$

A is a differential operator which analytically depends on P, its first μ derivatives and x, i.e. $\mu + 1$ arguments.

The initial function $P_o(x)$ is supposed to be analytical in a disk of complex variable x, containing the origin as non singular point, enclosed in the μ + 1 – disk in which $A(P)$ is analytical, i.e. a function developable in a multiple power series of its arguments.

In order to solve problems like (1), (*ECP*), we consider an equivalent initial value problem, (*IVP*) ⇔ (*ECP*), for an open normal first order differential system, [4, 5, 6, 11, 12, 13]. Putting:

$$p_n = \frac{1}{n!}\left[\frac{d^n}{dx^n}P\right]_{x=0}, \; P = \sum_{n=0}^{+\infty} p_n\, x^n \equiv p \bullet \zeta \,,$$
$$if\;\; p = (p_n)_{n=0}^{+\infty},\;\; \zeta = (x^n)_{n=0}^{+\infty} \qquad (1b)$$
$$\Theta_n(p_0, p_1, ..., p_{\mu+n}) = \frac{1}{n!}\left[\frac{d^n}{dx^n}A(P)\right]_{x=0}, \; n \in N_0$$

We obtain (*IVP*):

$$IVP: \begin{cases} \frac{d}{dt}p_n = \Theta_n(p_0, p_1, ..., p_{\mu+n}) \\ a_n = \frac{1}{n!}[\frac{d^n}{dx^n}P_0(x)]_{x=0},\; n \in N_0 \\ initial\, conditions, assigned\; as\; P_0(x) \\ Taylor\;\; coordinates. \end{cases} \qquad (2)$$

IVP integration is allowed in the space of Cauchy sequences on $\mathbb{C}$, in which *IVP* may be written as an *ODE*:

$$\frac{dp}{dt} = D\, p \qquad (2b)$$
$$p(0) = (a_n)_{n=0}^{+\infty} = a$$

where D is the Groebner-Lie operator:

$$D = \sum_{n=0}^{+\infty} \Theta_n(\pi_0, \pi_1, ..., \pi_{\mu+n})\frac{\partial}{\partial \pi_n},$$

with $\pi = (\pi_n)_{n=0}^{+\infty}$ a sequence of parameters.

Since $(\Theta_n)_{n=0}^{+\infty}$ sequence is infinitesimal, we are allowed to introduce D and the correlated Lie operator e^{tD}. Thereby:

$$p = \left((e^{tD}\pi_n)_{\pi=a}\right)_{n=0}^{+\infty}$$

is the solution of the above ODE.

After the integration, we can introduce a Hamiltonian function which allows us to write the canonical representation of the assigned nonlinear autonomous problem; the same may also be pointed out for the non autonomous case.

In order to illustrate in details this procedure, in this paper we consider a particular application, relevant in the fight against tumors. In fact, in the frame of our biomathematical investigations on tumors, the final aim of our work will be the optimization of drug therapy. Therefore, for the controlled birth and death process which, in our case, describes the malignant behaviour of cells colony subject to a suitable remedy by physicians, we shall write a canonical representation of malignancy, in the dynamics sense [9], supposing the process to be either *conservative* or not, namely subjected to a controller constant or variable in time.

Our results can be generalized and extended to similar stochastic processes, as well as to an analytic evolutionary problem, like the above (1).

Then an interesting analogy with classical mechanics may be found in the formulation of a principle similar to the Hamilton's one and characterizing evolution in Gibbs' space.

After having underlined the aim and foreseen possible extensions of the present study, as a brief introduction to the problem, let us now put in evidence all our starting points, which represent the subjects of previous investigations, both ours and of other authors.

We shall proceed from the following results:

a) the stochastic process describing tumor evolution is integrable via generalized Lie series, according to an improvement of Gröbner's method; this author solved initial values problems for finite normal differential systems by similar series [1, 2], whilst we extended the method to non finite initial value problems and to the integration of an equivalent Cauchy problem for an evolutionary equation [4, 5, 6, 11, 12, 13];

b) by introducing the probabilities generating function $P(t, z)$, with $t \in [0, +\infty[$, $z \in [0,1[$, a Cauchy problem for an evolutionary equation equivalent to the stochastic process may be formulated: solving the latter means to solve the former, [4, 5, 6, 11, 12, 13];

c) by demonstrating the continuously differentiability of P at $z = 1$, we can introduce an equivalent representation for malignancy involving those derivatives, which are linked to the moments of the distribution random variable (r.v.) $X(t)$, number of malignant cells in the colony.

2 First description of the model

In this section, we briefly exploit the above points a), b), c); more details can be found in the references.

Let us consider the following birth and death process involving probabilities (forward Kolmogorov's equations) describing controlled evolution of a malignant tumor, whose random variable is $X(t)$, number of tumoral cells, while $p_n(t)$ is the probability of having n cells at t in tumoral colony. λ, μ, k are constants related to the biology of the spontaneous process, $h(t)$ is a function of time describing drug action on colony cells:

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

or in compact form:

$$
\begin{aligned}
&\frac{dp_0}{dt} = \Theta_0(p_{-1}, p_1) \\
&\frac{dp_n}{dt} = \Theta_n(p_{-1}, p_{n-1}, p_n, p_{n+1}), \qquad n \geq 1 \\
&\frac{dp_{-1}}{dt} = 1 \\
&p_{n_0}(0) = 1; \ p_j(0) = 0, \ \forall j \neq n_0; \ p_{-1}(0) = 0 \ ;
\end{aligned}
\tag{4}
$$

where the last equation and the relative initial condition are added in order to transform the problem in an autonomous or time independent one. In fact in the improved Gröbner method [4, 5, 6, 11, 12, 13] in this way, i.e. by the symmetrization of variables, it is possible to integrate (1-2) through the following steps:

a) the introduction of the Gröbner-Lie differential operator:

$$
\begin{aligned}
D = &\frac{\partial}{\partial \pi_{-1}} + \Theta_o(\pi_{-1}, \pi_1) \frac{\partial}{\partial \pi_o} + \\
&+ \sum_{j=1}^{+\infty} \Theta_j(\pi_{-1}, \pi_{j-1}, \pi_j, \pi_{j+1}) \frac{\partial}{\partial \pi_j}
\end{aligned}
\tag{5}
$$

in which functions $\Theta_0, \Theta_n, n \in N$, are just the r.h.s. of (4) but depending on parameters π_i.

Its existence is ensured by the infinitesimal nature of sequence $(\Theta_n)_{n=0}^{+\infty}$.

b) Afterwards we are able to introduce also the Lie operator:

$$
e^{tD} = \sum_{\nu=0}^{\infty} \frac{t^\nu}{\nu!} D^\nu . \tag{6}
$$

It exists as a consequence of D existence. Then (3)-(4) can be written on the space of Cauchy sequences as (see (1b)):

$$
\begin{aligned}
&\frac{dp}{dt} = D\, p \\
&p_{n_0}(0) = 1
\end{aligned}
$$

every other initial value being null.

Then a unique solution of (3) exists, whose components are:

$$
p_i(t) = [e^{tD} \pi_i]_{\pi_{-1}=0,\ \pi_k = p_k(0),\ k \in N_0} \tag{7}
$$

The forward difference Kolmogorov's differential equations (3) are our improvement of those proposed in 1976 by Dubin, [3], and the time independent parameters linked to the biology of the process have the same meaning: λ expresses the spontaneous birth of a new cell, μ the death of an old cell, k the death of one cell due to immunological reaction of the host. Moreover we introduced the controller $h(t)$ because we admit that the death can be also due to the action of drug. We require this action to be optimal, e.g. it ensures colony extinction after a fixed time T from the beginning of therapy. This achievement is the final goal of this and forthcoming studies, focused on a possible extension of Pontryagin principle.

The corresponding evolution equation, obtained by the introduction of the probability generating function $P(t, z)$, when putting $u = 1 - P$:

$$
\begin{aligned}
&\frac{\partial u}{\partial t} = [\lambda(z^2 - z) + (\mu + k)(1-z)] \frac{\partial u}{\partial z} + k(z - z^2) \frac{\partial^2 u}{\partial z^2} + \\
&+ [h(t)(1-z)] \frac{\partial u}{\partial z} \\
&z \in [0, 1[, \ u^{(n_0)}(0, z) = 1 - z, \ n_0 = X(0).
\end{aligned}
\tag{8}
$$

in which time dependent control, the $h(t)$ function, makes non autonomous the evolution operator. On the contrary, in the spontaneous (non controlled) process, the evolution operator is autonomous, according to the Dubin model, [3].

The above Cauchy problem (8) may be easily solved by our improved Gröbner method, [4, 5, 6, 11, 12, 13]. In fact a Taylor transformation links the above problem (8) to the initial value problem (3-4), and integrating the latter, one can obtain the unique solution of the former, represented by the double series:

$$P = \sum_{k=0}^{+\infty} p_k z^k .$$

It can be also demonstrated that P is continuously differentiable at z = 1, then if:

$$\left[\frac{\partial^i P}{\partial z^i}\right]_{z=1} = \eta_i ;$$

$$\beta_{n-1} = n(n-1)\lambda;$$
$$\alpha_n = n\lambda - n(\mu + h(t)) - n^2 k;$$
$$\gamma_{n+1} = -nk;$$

the stochastic process which describes the controlled evolution is equivalent to the following one:

$$\frac{d\eta_n}{dt} = \beta_{n-1}\eta_{n-1} + \alpha_n \eta_n + \gamma_{n+1}\eta_{n+1} \; ; \quad (9)$$

(9) can be written in a more compact and general form as follow:

$$\frac{d\eta_n}{dt} = \vartheta_n(\eta_{n-1}, \eta_n, \eta_{n+1}) \; ; \; n \geq 1 \qquad (10)$$

$$\eta_1(0) = n_0 \; ; \; \eta_j(0) = n_0(n_0 - 1)...(n_0 - (j-1)) \, , \; \forall j \neq n_0 ;$$

where:

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

represents the mean of distribution, while the variance is given by:

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

In other words we find that the derivatives of $P(t, z)$ at z = 1 are linked to the other moments of the random variable $X(t)$:

$$\eta_n = E\left(X(X-1)...(X-(n-1))\right).$$

We remark that every function η_n may be known, following Gröbner ideas, by applying operators analogue to (5) and (6), and by suitable definition of parameters into the initial values, as the peculiarity of the method demands.

That can be obtained by considering the new unknown functions $\eta_j * = \frac{\eta_j}{j!}$, being by this way ensured the existence of Groebner-Lie operator. Obviously reduction to autonomy from the time is demanded and may be obtained by symmetrization of variables.

3 Hamiltonian function and canonical representation of malignant process

Now let us demonstrate the following fundamental statement which will be useful to extend the Pontryagin principle to our stochastic process, in order to optimize the controller, and will allow analogies with classical mechanics:

Theorem 1: *Every stochastic process like (3-4) if conservative, i.e. h(t) =constant, admits a unique canonical representation (see below) by means of the Hamiltonian function*

$$H = \sum_{j=0}^{+\infty} \Phi_j \Theta_j \; ,$$

existing at every instant, and in which Φ_j*, the* ***adjoint variables****, are functions suitably defined. If the process is not conservative, the canonical representation is again available, then Hamiltonian function exists at every instant dropping within the convergence disk of h(t), supposing adjoint variables* Φ_j *suitably bounded, in every case concerning integrating Groebner-Lie operator existence.*

Proof:
There are different cases that here we analyze.

1) This point is in particular useful dealing with an extension of the Pontryagin principle, namely for a special aim and represents the starting point also in the other instances 2), 3).

We proceed first by introducing the Hamiltonian function for any problem approaching the stochastic process (3-4).

Let us introduce the “truncated” Hamiltonian function :

$$H_m = \sum_{j=0}^{m} \Phi_j \Theta_j \qquad (11)$$

in which the *adjoint* variables Φ_j are analytic functions such that:

i)

$$\frac{dp_i}{dt} = \frac{\partial H_m}{\partial \Phi_i} = \Theta_i \; ; i \in \{0, 1, 2, ..., m\} \qquad (12)$$

which is the representation of the normal differential system of the first $m + 1$ equations of our controlled process. This system, together with its relative initial conditions, represents an initial value problem asymptotically approaching the stochastic process (1-2) as $m \rightarrow +\infty$.

ii) In addition, by requiring that holds the fundamental identity:

$$\frac{dH_m}{dt} = \frac{\partial H_m}{\partial t} ,$$

we obtain the (linear) system involving the adjoint variables. In fact:

$$\frac{dH_m}{dt} = \sum_{j=0}^{m} \left(\frac{\partial H_m}{\partial \Phi_j} \times \frac{d\Phi_j}{dt} + \frac{\partial H_m}{\partial p_j} \times \frac{dp_j}{dt} \right) + \frac{\partial H_m}{\partial t} \quad (13)$$

so we obtain the following linear system involving adjoint variables:

$$\frac{d\Phi_i}{dt} \equiv -\frac{\partial H_m}{\partial p_i} = -\sum_{j=0}^{m} \Phi_j \frac{\partial \Theta_j}{\partial p_i} =$$
$$-(\Phi_{i-1} \frac{\partial \Theta_{i-1}}{\partial p_i} + \Phi_i \frac{\partial \Theta_i}{\partial p_i} + \Phi_{i+1} \frac{\partial \Theta_{i+1}}{\partial p_i}); i \in \{1, 2, ..., m\}; \quad (14)$$
$$\frac{d\Phi_0}{dt} \equiv -\frac{\partial H_m}{\partial p_0} = -\Phi_1 \frac{\partial \Theta_1}{\partial p_0} .$$

iii) As a third condition, we require that:

$$\Phi_j(T) = j , \qquad (15)$$

where $(j)_{j \in \{0,1,2,...,m\}}$ is the sequence of the first $m+1$ values of the random variable $X(t)$.

At the following step, H_{m+1} is such that:

$$\frac{\partial H_{m+1}}{\partial \Phi_0} \equiv \frac{\partial H_m}{\partial \Phi_0} \qquad (16)$$

$$\frac{\partial H_{m+1}}{\partial \Phi_i} \equiv \frac{\partial H_m}{\partial \Phi_i} , i \in \{1, 2, ..., m\} \qquad (17)$$

$$\frac{\partial H_{m+1}}{\partial \Phi_{m+1}} = \frac{dp_{m+1}}{dt} = \Theta_{m+1} \qquad (18)$$

Then, if the sequence of partial sums:

$$\{H_m\}_{m \in N_0} \qquad (19)$$

converges, it defines:

$$H = \sum_{j=0}^{+\infty} \Phi_j \Theta_j \qquad (20)$$

the Hamiltonian function of the controlled process, as the limit:

$$\lim_{m \to \infty} H_m = H .$$

as we are going to prove.

The consequence will be that, since:

$$\frac{\partial H_{m+n}}{\partial \Phi_n} = \frac{dp_n}{dt} , \forall m, n \in N_0 ,$$

then:

$$\lim_{m \to +\infty} \frac{\partial H_{m+n}}{\partial \Phi_n} = \frac{\partial H}{\partial \Phi_n}$$
$$\frac{\partial p_n}{\partial t} = \frac{\partial H}{\partial \Phi_n} , n \in N_0 .$$

Similarly:

$$\frac{d\Phi_n}{dt} = -\frac{\partial H}{\partial p_n} , n \in N_0 .$$

In order to prove the convergence of (20), we observe that in every point $t \leq T$ the above sequence:

$$\{H_m\}_{m \in N_0}$$

is uniformly convergent and it defines at least a C^1 function, if $h(t)$ is in C^1 .

In fact at T, within $domh(t)$ we can prove that:

being: $$H_m(T) = \sum_{j=0}^{m} \Phi_j(T) [\Theta_j]_{t=T}$$

it is: $$H_m(T) = \sum_{j=0}^{m} j \left[\frac{dp_j}{dt} \right]_{t=T} \rightarrow \qquad (21)$$
$$\rightarrow \left[\frac{dE(X(t))}{dt} \right]_{t=T} as \;\; m \rightarrow +\infty$$

That is true provided that $E(X(t))$ is a series of functions differentiable term by term. That statement holds. In fact:

being: $P(x,t)=\sum_{i=0}^{+\infty} p_i z^i$

with $p_i(t)=[e^{tD}\pi_i]_{\pi_{-1}=0,\ \pi_k=p_k(0),\ k\in N_0}$,

it is: $\left[\frac{\partial P}{\partial z}\right]_{z=1}=\sum_{i=0}^{+\infty} ip_i=E[X]$ *and*

$$\sum_{i=0}^{+\infty} i[e^{tD}\pi_i]_{\pi_{-1}=0,\ \pi_k=p_k(0),\ k\in N_0}=\left[\sum_{i=0}^{+\infty} ie^{tD}\pi_i\right]_{\pi_{-1}=0,\ \pi_k=p_k(0),\ k\in N_0}=$$

$$=\left[e^{tD}\sum_{i=0}^{+\infty} i\pi_i\right]_{\pi_{-1}=0,\ \pi_k=p_k(0),\ k\in N_0} \quad \textit{if}\ \sum_{i=0}^{+\infty} i\pi_i<\infty$$

$$\Rightarrow$$

$$\frac{d}{dt}\left[\frac{\partial P(z,t)}{\partial z}\right]_{z=1}=\frac{d}{dt}E[X(t)]$$

$$=\left[e^{tD}D\sum_{i=0}^{+\infty} i\pi_i\right]_{\pi_{-1}=0,\ \pi_k=p_k(0),\ k\in N_0}$$

$$\sum_{i=0}^{+\infty} i[e^{tD}D\pi_i]_{\pi_{-1}=0,\ \pi_k=p_k(0),\ k\in N_0}=\sum_{i=0}^{+\infty} i\frac{dp_i}{dt},$$

derivation term by term of the series which defines the mean E(X).

Furthermore:

$$\frac{dH_m}{dt}=\frac{\partial H_m}{\partial t}\ \Rightarrow$$

$$\sum_{j=0}^{m}\Phi_j\frac{\partial\Theta_j}{\partial h}\frac{dh}{dt}=\left(\sum_{j=0}^{m}\Phi_j\times(-j\times p_j+(j+1)p_{j+1}\right)\times\frac{dh}{dt}\ \Rightarrow$$

$$\left[\frac{dH_m}{dt}\right]_{t=T}=$$

$$=\left(\sum_{j=0}^{m}[-j^2\times p_j(T)+(j+1-1)(j+1)p_{j+1}(T)]\right)\times\left[\frac{dh}{dt}\right]_{t=T}= \qquad (22)$$

$$=\left(\sum_{j=0}^{m}[-j^2\times p_j(T)+(j+1)^2p_{j+1}(T)-(j+1)p_{j+1}(T)]\right)\times\left[\frac{dh}{dt}\right]_{t=T}$$

$$\to -E(X(T))\times\left[\frac{dh}{dt}\right]_{t=T}\ \text{as}\ m\to+\infty\,. \qquad (23)$$

In fact $E(X)$ is the sum of a Lie series absolutely convergent at $t = T$.

In conclusion there are two power series (of the Lie type) which define H and its derivative, which converge at $t = T$ absolutely, and at $t < T$, i.e. within the circle of convergence of $h(t)$.

Note that $H\in C^1$ only within the domain, *domh*(t) of $h(t)$, whilst, if e.g. $h(t)$ is a constant or a polynomial in t, that happens for every t.

In fact T is any instant in the domain of existence of $h(t)$ and $\frac{dh}{dt}$, in particular any instant if $h(t)$ is a constant, i.e. the process is conservative, or a polynomial, inasmuch in that hypothesis $E(X)$ and $\frac{dE(X)}{dt}$ exist for every T.

Now having introduced the Hamiltonian H, and considered the instances in which its definition may be prolonged to every instant of the domain of $h(t)$, we can integrate, regarding t as a complex variable, the following initial value problem:

$$\frac{d\Phi_i}{dt}=-\frac{\partial H}{\partial p_i};\ i\in N_0 \qquad (24)$$

$$\Phi_j(T)=j,\ \text{conditions at}\ t=T\,. \qquad (25)$$

$$\frac{dp_i}{dt}=\frac{\partial H_m}{\partial\Phi_i}=\Theta_i\ ;\ i\in\{0,1,2,...,m\}$$

In fact we can know the functions Φ_j, which at T represent all possible values of the random variable $X(t)$. This is possible through the usual method of generalized Lie series [4, 5, 6, 11, 12, 13].

To do that we can refer to the new variables $\Phi_i^*=\frac{\Phi_i}{i!}$ and, by this way, consider these equations:

$$\frac{d\Phi_i^*}{dt}=-\left(\frac{\Phi_{i-1}^*}{i}\frac{\partial\Theta_{i-1}}{\partial p_i}+\Phi_i^*\frac{\partial\Theta_i}{\partial p_i}+(i+1)\Phi_{i+1}^*\frac{\partial\Theta_{i+1}}{\partial p_i}\right).$$

The right hand side is wanted infinitesimal as $i\to+\infty$. This happens certainly if, as in the sequel (see below, point 3), the adjoint variables are so upper bounded:

$$|\Phi_i| \leq i + \Delta .$$

Such variables fit our request.

In fact having introduced the suitable Lie operator, this finds all components of the unique solution for every admissible *t*:

$$\Phi_i^*(t) = [e^{(t-T)D^*}\pi_i^*]_{\Phi_i(T)=i} \qquad (26)$$

having operated the final substitution of parameters with initial values and where *D** is the correspondent Gröbner-Lie operator, introduced in the usual manner. Then, in fact, *H* exists in *T* if the $\Phi_j(t)$ have in *T* the same ordered values of *X*(*t*), and the Hamiltonian function exists in every internal point of domain of *h*(*t*) as a C^1 function, such as positional and adjoint variables. In fact solution $\{\Phi_j(t)\}_{i=0}^{+\infty}$ has its components represented by Lie series, whose convergence radius is the radius of analyticity for *h*(*t*), being the problem linear but for *h*(*t*). That because in the integration à la Gröbner we must first proceed to a symmetrization of variables transforming the problem into an autonomous one, procedure that causes the system to lose its linearity, see: [1], [2], depending on $h(p_{-1})$, being the new variable required by the symmetrization of variables procedure.

The following point is useful in looking for analogies with classical mechanics.

2) Now we can observe that if *t* is regarded as a complex variable and the process is in particular conservative, every *t* is admissible and it is:

$$H = constant$$

in fact
$$\frac{dH}{dt} = \frac{\partial H}{\partial t} = 0 .$$

Then if, as we are going to prove, $[H]_{t=0}$ exists, at every other instant stands:

$$H(t) = [H]_{t=0} ,$$

i.e. in complex plane *H* exists for every *t* in which conjugated variables p_j and Φ_j exist, if *H* is existing at *t* = 0. In other words since the conservative problem is linear, p_j and Φ_j are existing at every *t* and so does *H*. This doesn't stand if autonomous problem is nonlinear (see in the sequel point 3).

In fact, supposing process to be conservative, we can think to change the starting conditions, assigned at *T* for the problem (24-25) as initial values, and considered now not any more at time *T* but at the initial instant 0. In the certain configuration the probabilities are:

$$P_r(\{\Phi_{n_0}(0) = n_0\}) = p_{n_0}(0) = 1 ; \qquad (27)$$
$$P_r(\{\Phi_j(0) = j\}) = p_i(0) = 0 \text{ if } i \neq n_0 .$$

Then at *t* = 0,

$$E(X(0)) = n_0, \textit{ and from (9)}$$
$$\left[\frac{dE(X)}{dt}\right]_{t=0} = (\lambda - \mu - h - k)n_0 - kn_0(n_0 - 1)$$

Thereby:

$$H(0) = (\lambda - \mu - h - k)n_0 - kn_0(n_0 - 1)$$

Then *H* exists at *t* = 0, hence for every *t*.

In such a manner we have a complete *canonical representation* of the stochastic process supposed conservative.

Resuming: for a conservative process starting from the initial configuration, supposed known, which the system assumes with certainty at *t* = 0, *H* is defined by the constant assumed at *t* = 0; at every *t* on the real axis, *H*=constant is an integral, i.e. an equality to be satisfied by the solution of the canonical system at every instant.

Then we have the following interpretation of the canonical representation of a conservative system.

This is such that the solution, obtained according to the Gröbner approach by generalized Lie series, of its first part furnishes the distribution of the random variable *X*(*t*), while the components of the solution of its second part, obtained by the same procedure, represent a sequence of functions which at initial instant are the values of *X*(0), non random in this point, whose meaning must be detected (see the sequel), namely:

$$\frac{dp_i}{dt} = -\frac{\partial H}{\partial \Phi_i} = \Theta_i ;\ i \in N$$
$$\frac{dp_0}{dt} = -\frac{\partial H}{\partial \Phi_0} = \Theta_0 , \qquad (28)$$

$$p_{n_0}(0) = 1 ;\ p_j(0) = 0 ,\ \forall j \neq n_0 ; \qquad (29)$$

$$\frac{d\Phi_i}{dt} \equiv -\frac{\partial H}{\partial p_i} = -\sum_{j=0}^{+\infty} \Phi_j \frac{\partial \Theta_j}{\partial p_i} = $$
$$= -(\Phi_{i-1} \frac{\partial \Theta_{i-1}}{\partial p_i} + \Phi_i \frac{\partial \Theta_i}{\partial p_i} + \Phi_{i+1} \frac{\partial \Theta_{i+1}}{\partial p_i}); i \in N, \quad (30)$$
$$\frac{d\Phi_0}{dt} \equiv -\frac{\partial H}{\partial p_0} = -\Phi_1 \frac{\partial \Theta_1}{\partial p_0},$$

$$\begin{aligned} &\Phi_{n_0}(0) = n_0 \text{ with certainty;} \\ &\Phi_i(0) = i \text{ with null probability} \end{aligned} \quad (31)$$

3) Furthermore, if the process is not conservative, we can still observe that a similar canonical representation can be introduced. In fact, like in conservative instance, if the Hamiltonian is directly introduced at $t = 0$, its existence elsewhere is guaranteed on the real axis within the convergence disk of $h(t)$, provided that the Φ_j are under **suitable constraints**. This hypothesis will be suitable also in order to integrate the system involving adjoint variables. In other words the constraints ensuring H existence, also allow the representation of evolution by Lie series.

Naturally within the analyticity disk of $h(t)$, according with the general result for every analytic evolutionary process which demands convergence of Lie series inside the domain of the evolutionary operator.

More in details, let us suppose to consider a bounded sequence of non negative numbers $\{\delta_j\}_{j=0}^{+\infty}$ with:

$$\sup\{\delta_j\}_{j=0}^{+\infty} = \Delta \leq 1 \quad .$$

Let us assume that every $|\Phi_j|$ is dropping in a circular neighbourhood of the integer j:

$$\left| |\Phi_j| - j \right| < \delta_j \ ,$$

being:

$$0 \leq |t| < r,$$

with r the radius of the convergence disk $domh(t)$ of the analytical function $h(t)$, or in a non symmetric neighbourhood of every integer j:

$$j - \delta_{j-1} < |\Phi_j| \leq j + \delta_j ; \delta_{j+1} = \delta_j ,$$

being the last equality the condition of contiguity for the assigned intervals.

If the above assumption holds, then:

$$\frac{d}{dt}\left[\frac{\partial P(z,t)}{\partial x}\right]_{x=1} = \sum_{j=1}^{+\infty} j \frac{d}{dt} p_j \Rightarrow$$
$$|H| \leq \sum_{j=0}^{+\infty} \left| \Phi_j \frac{d}{dt} p_j \right| \leq \Delta \frac{dp_0}{dt} + \sum_{j=1}^{+\infty} (j+\Delta) \left| \frac{d}{dt} p_j \right| < \infty$$

being $\sum_{j=1}^{+\infty} j \left| \frac{d}{dt} p_j \right| < \infty$ *within domh*(t),

and $\sum_{j=1}^{+\infty} \Delta \left| \frac{d}{dt} p_j \right| < \sum_{j=1}^{+\infty} j \left| \frac{d}{dt} p_j \right|$

i.e. H exists at every t dropping in $domh(t)$.

Resuming all above points:

we introduce the Hamiltonian H in the stochastic representation of a birth and death process by defining the adjoint variables Φ_j as analytical functions which assume the integers, which are the values of the random variable X, number of entities, i.e. cells of colony, at an instant T which drops within the convergence circle of $h(t)$, the function responsible of non autonomy of evolution. By this way H is defined as a C^1 function.

In order to obtain a canonical representation of the process, having in sight analogies with classical mechanics, it needs that adjoint variables assume the integers, values of X, as the initial values, namely at $t = 0$ from which the process starts. We need first to distinguish the autonomous instance, in which

$$H = constant$$

as an integral equality satisfied by all and only the solutions $\{p_j, \Phi_j\}_{j \in N_0}$ of the canonical representation of the process; H, in this instance, which we can name conservative case, exists at every instant t.

The non autonomous instance demands an additional hypothesis in order to do H existing at every instant $t \neq 0$, dropping in the convergence disk of $h(t)$, i.e. the adjoint variables must be properly bounded:

$$|\Phi_j| \leq j + \Delta; \ \Delta \leq 1.$$

This is a suppletory hypothesis also in conservative instance in order to integrate the system of the adjoint variables; in fact, in every instance, the infinitesimal feature of the right hand side terms in equations involving the new variables

$\Phi_i^* = \frac{\Phi_i}{i!}$ is sufficient to the existence of integrating Groebner-Lie operator. Furthermore it allows an interesting interpretation, see the sequel, of the adjoint variables in every case: the adjoint variables describe trajectories walked in the evolution by the single values of the random variable *X*.

4 More on adjoint variables meaning

In the end we observe that in every instance, i.e. the process being either conservative or not, and starting from initial instant, the set of all configurations of adjoint variables Φ_j, regarded as real valued positive functions, must include the trajectories of the random variable *X*.

In fact, the following illustration of the process is allowed: all happens in the canonical representation, as the discrete r.v. *X* is substituted by the continuous r.v. with values: $\Phi = \Phi_j$. Every adjoint variable may wander by chance in a neighbourhood of its certain value. In order to do that at every instant *t* the set of all possible determinations of the r.v. Φ, i.e. the totality of its admissible values, drops closely the simultaneous random configuration of r.v. *X*. More particularly the happening determinations of Φ are picked up by chance from the compact ranges of every Φ_j, resulting as component of the solution to the canonical representation of the evolution under constraints. Hence the random choice with probability p_j, is done in the subset which has as upper bound the correspondent value *j* of the random variable *X*, plus δ_j i.e. $(X = j) + \delta_j$ and as lower bound $(X = j) - \delta_{j-1}$. Then every admissible value $\Phi = \Phi_j$ is not greater than $(X = j) + \Delta$, whilst the value *j* may be certain only at initial instant, provided that, in stochastic pattern, colony starts just from the certain configuration:

$$\{\Phi_j(0) = j\},$$
$$p_j(0) = 1\ ;\ p_m(0) = 0\ ,\ m \neq j\ ;$$
and $\Phi(0) = X(0)$ and generally not elsewhere.

Resuming, at last we have:

$$N_0 = rangeX \subset range\Phi \subseteq \bigcup_{j=0}^{+\infty} [\, j - \delta_{j-1},\, j + \delta_j [\, \subset \Re$$
density of $\Phi = \bigcup_j$ *density of* Φ_j, $\forall j \in N_0$.

Furthermore we can conclude that there are two ways in describing evolution of a stochastic process similar to ours: while canonical variables p_j describe it in terms of probabilities the happening of every value of the random variable $\{X = j\}$, the adjoint ones Φ_j do the same in terms of trajectories of all possible random values.

By that point of view, canonical representation of a stochastic process, i.e. its Hamiltonian form, is far to be artificial but needs in complete representation of evolutionary behaviour by probabilities and trajectories, if special purposes are in sight.

In order to justify what said above, we can do the following considerations. Φ may be regarded as a transformation one to one of the random variable *X*, because, given this last variable, a sole Φ exists as the unique solution of the system of adjoint variables and, vice versa, starting from Φ, the sole *X* with associated distribution exists.

We ask ourselves what is the associated distribution. At every instant, for conservation of probability principle:

$$p_j(t) = P_r(X(t) = j) =$$
$$P_r(\{\Phi = \Phi_j(t) \in [\, j - \delta_{j-1},\, j + \delta_j\,]\}) = \int_{\delta_j^*}^{\delta_{j+1}^*} f_j \, d\Phi$$

with obvious meaning of the integration extremes,

$$p_j(t) = \int_{\delta_j^*}^{\delta_{j+1}^*} f_j \, d\Phi$$

where have been introduced any non negative integrable function playing the role of local density, then the above formula gives the probability that, at every instant, $\Phi = \Phi_j$ drops inside $[\delta_j^*, \delta_{j+1}^*]$ and is null elsewhere.
Namely $\forall t$

$$1 = \sum_{j=0}^{+\infty} p_j(t) = \int_0^{+\infty} f \, d\Phi$$

being f a density function, whose restriction to partial subintervals $[\delta_j^*, \delta_{j+1}^*]$ are local density: f_j.

Resuming: the condition of upper bounded adjoint variables, sufficient for *H* existence in non conservative instance, allows their determination by Lie series in every instance either conservative or non.

Furthermore the integers, values of the discrete range of random variable *X*, are the certain determinations at the instant *T* of the adjoint variables dependent on them, and their probabilities to happen are the same to take place of oscillations in time of new variables close to them. Random walks around the values of certainty in the classical mechanics phrase are trajectories for the "dynamical system" representing *X*.

5 Conclusions on biological problem

A birth and death process similar to our (1-2) admits a canonical representation (24-25), (26-27) in the frame of classical Lagrangian dynamics, which may furnish hints in solving the trajectories determination problem of the relative random variable, provided that every adjoint variable Φ_j has as upper bound the integer, say *j*, which is the correspondent value of the random variable, plus a suitable positive number, say δ_j, and, as lower bound, the same integer minus some suitable positive δ_{j-1} (see above), being the sequence $(\delta_j)_{j \in N_0}$ upper bounded by a number $\Delta \le 1$.

The integration is available by an extension of the classical Gröbner method which utilizes more general Lie series with respect to those which have been used by that author in his investigations, e.g. on finite initial value problems for linear or not linear but analytical normal differential systems. In the economy of our mathematical investigations on tumors, the above results will be useful to introduce some interesting analogies with classical mechanics and, in the control of the stochastic process by drugs, to solve the problem of optimization of the controller and so the drug administration if the aim is to extinguish colony. In fact, the controller is linked to the concentration of drug in situ and in the blood stream of the host to which the remedy is administered in daily doses, which are demanded optimal in practical fight against tumors under the necessity to restrain toxicity on noble parenchymal organs.

Those aims will constitute the matter of forthcoming papers. However, it is easy to foresee that the same algorithm of the Hamiltonian may be useful in canonical representation of any evolutionary process. The representation must allow similar analogies with some principle of Lagrangian mechanics as we shall prove forth.

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