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Mathematical Notes on Malignancy. I-: Data Collection for Controlled Malignancy

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Abstract

In this note we deal with experimental data collection in order to build a model, which is useful in medical therapy of tumors. That includes balance equations for the administered drug, the controller to be optimized, and controlled birth and death process which describes malignancy. Work sponsored by CNR Italy. Grant C004890_002.

1 Balance equations of the drug and controlled tumor evolution

t,temporal variable;
$X(t)$,random variable: number of malignant cells in tumor;
V_1, constant drug distribution apparent volume in blood;
V_2, actual tumor volume;
V_{cell} = constant cellular volume;
Q'_{in}, rate of drug intake;
α_{12}, constant difusion coefcient of the drug from blood versus tumor;
$\alpha_{21}(t)$, time depending difusion coefcient of the drug from tumor
versus the blood stream;
C_1,drug concentration in blood;
$C_{2,n}$,drug concentration in tumor, if X = n;
$[V'_{cl}]_{met}$, 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;
$E(X)$,mean of X;
λ, constant stochastic parameter expressing a new birth in tumoral colony;
μ, constant stochastic parameter expressing a spontaneous death in tumoral colony;
κ, constant stochastic parameter expressing a death by immunological feed-back;
$h(t)$, stochastic parameter expressing a death due to the drug activity;
ζ, coefficient of proportionality in equation which expresses the controller, stochastic parameter of chemical death, $h(t)$:

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

ρ, dissociation constant in drug linkage with cellular receptors at the
equilibrium;
ν, constant concentration of receptors per cell;
κ_{el}, drug elimination constant including kidney, liver and tumor drainage, i.e.:

$$k_{el} = \frac{1}{V_1}([V'_{cl}]_{met} + [V'_{cl}]_{tum} + [V'_{cl}]_{kid}); \quad (1)$$

α_{12}, constant transfer rate per unity of volume from blood to tumor,
such that:

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

α_{21}, constant transfer rate per unity of volume from tumor to blood,
such that:

$$\alpha_{21} = V_2 \times a_{21}.$$

If we want to represent tumoral evolution subjected to a drug action, as we shall dimostrate in a next note in every details, we must consider a controlled process like the following one:

$$\begin{aligned} \frac{dC_1}{dt} &= \frac{Q'_{in}}{V_1} - \left(\frac{\frac{a_{12}V_1C_1 - a_{21}V_{cell}E(X)C_{2,n}}{V_1} + \frac{[V'_{cl}]_{met} + [V'_{cl}]_{tum}}{V_1} C_1 + \frac{[V'_{cl}]_{kid}}{V_1} C_1 \right) \\ \frac{dC_{2,n}}{dt} &= \frac{1}{E(X)V_{cell}} \begin{pmatrix} a_{12}V_1C_1 - a_{21}V_{cell}E(X)C_{2,n} \\ -C_{2,n}V_{cell}\frac{dE(X)}{dt} \end{pmatrix} \\ C_1(0) &= \frac{\text{initial bolus}}{V_1}; C_{2,n}(0) = 0 \end{aligned} \quad (2)$$

which are the balance equations for the drug in the host and:

$$\begin{aligned} \frac{d\eta_n}{dt} &= \beta_{n-1}\eta_{n-1} + \overset{\circ}{\alpha}_n\eta_n + \gamma_{n+1}\eta_{n+1}; n \geqslant 1 \\ \eta_1(0) &= n_o; \eta_i(0) = [E(X(X-1)...(X-(i-1))]_{t=0} \\ \text{with } [E(X^i)]_{t-0} &= n_o^i, \forall i > 1; \text{while } \eta_i(0) = 0, \text{if } n_o = 1. \\ \beta_{n-1} &= n(n-1)\lambda; \\ \overset{\circ}{\alpha}_n &= n\lambda - n\mu(t) - n^2k; \\ \gamma_{n+1} &= -nk; \\ \mu(t) &= \mu + h(t). \end{aligned}$$

which is the stochastic process which represents controlled malignancy, where:

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

if $P(t, z)$, $z \in [0, 1]$ is the generating probability function of the process of birth and death which represents tumoral evolution.

In fact the aim of the present note is quite different from that explaining a procedure building a model. But in sight of necessary numerical studies by suitable software, here we show, beside some critical observations on foundation of hypotheses done in building the model, principally as all constant in play, i.e. involved the representation of biological phenomena, may be determined.
The above stochasic process (4) is equivalent to a birth and death process similar to that proposed by Dubin [6], but including also the chemical death parameter, the controller h(t),which did not consider by that author.

***Conjecture 1**: Assuming a model with deterministic equations to be considered simultaneously to stochastic ones (q.v. above) demands some explicative considerations. Simple physical laws are involved in the former and well describe the behavior of the administered drug in the macroscopic system of the two compartments: blood of host and tumor, while the subsystem tumor must be considered, because of its complexity, non completely predictable in its evolution. Therefore, if the possibility of random variations is wanted to be considered, then it is a purely stochastic system not a deterministic one; therefore being described in terms of probabilities or moments of the random variable, it answers predictably only with expected values.Then the mean of X, E(X), may be the function-linkage between the predictable behavior of the control: the drug, and the controlled system: the tumor, when furthermore to the random variations, which collectively act determining its spontaneous behavior, that perturbing cause is added. In fact E(X) is an asimptotic estimator of the average number of malignant cells in colony.*

Putting a side the problem of integration of (3), process at last will result non linear, which will can be tackled by our improved Gröbner method (q.v. [4]) and also the practically interesting problem of the optimization of the controller h(t), which will demand an extension of Pontryagin principle, the present aim is restrained to the acquirement of all data in order to can utilize them in a final computer package with furnishes answers which can be useful to therapists.
Then we begin specifying what is the linkage of controller *h(t)* with $C_{2,n}$.
At the chemical equilibrium a proportion of cellular receptors is attached to drug molecules and an equal one is free:

rate of detachement = rate of attachement

$$k_{-1}n\nu(1-p) = k_1 C_{2,n} n\nu p \Rightarrow 1-p = \frac{\rho C_{2,n}}{1+\rho C_{2,n}}, \tag{4}$$

where:
ν is the constant number of receptors per cell,
$\rho = \frac{k_1}{k_{-1}}$ is the dissociation constant of chemical equilibrium,
$n\nu$ (1 - *p*) number of receptors attached,
1 - p proportion of occupied receptors,
$n\nu p$ number of free receptors,
p proportion of free receptors;
then:

$$h(t) = \zeta \frac{\rho C_{2,n}}{1+\rho C_{2,n}}. \tag{5}$$

***Conjecture 2:** The above formulation demands some hypotheses or simplifying assumptions: the drug control is due to small rapidly diffusing molecules able to interfere with relatively slow activities of macromolecular species in cells; for the receptors reproduction and the modulation of their concentration in cells, are certainly slower processes, so we can assume:*

ν the same number per cell, the duration of the chemical linkage of cellular receptors combined with drug molecules, by which drug effect, i.e. the cellular death, depends,esteemed by the proportion, in population, of cells attached to drug marked by a radioactive isotope in the same interval of time.

2 Acquirement of data

For the knowledge of all constants in play, pharmacokinetic and cell kinetic studies furnish suitable tools. We only remember some well known ideas in those fields. But the following brief notes want also to stress the fact that the eventual concrete implications of a research like ours must be drawn necessarily in interdisciplinary mode.
1) Balance equations so written:

$$\begin{aligned} &V_1\frac{dC_1}{dt} + \alpha_{12}C_1 - a_{21}V_2C_{2,n} + [V'_{cl}]_{met}C_1 + [V'_{cl}]_{tum}C_1 + [V'_{cl}]_{kid}C_1 = Q'_{in}; \\ &V_2\frac{dC_{2,n}}{dt} = \alpha_{12}C_1 - a_{21}V_2C_{2,n} - C_{2,n}\frac{dV_2}{dt}; \end{aligned} \tag{6}$$

V_1, V_2 are the blood compartment volume and the estimate of neoplasia volume, they are expressed in liters: L; in particular:

$$V_1 = \frac{\text{bolus dose}}{\text{initial plasma conc.}}; \tag{7}$$

$C_1, C_{2,n}$ are the concentration of drug in blood and its estimate in tumor, they are expressed as $\frac{\text{mg}}{\text{L}}$; α_{12} is the proportionality constant which represents the rate of diffusion between the two compartments: bloodtumor, from 1 versus 2, and α_{21} is the analogue coefficient from 2 versus 1; they are expressed as $\frac{\text{L}}{\text{min}}$: $[V'_{cl}]_{met}, [V'_{cl}]_{tum}, [V'_{cl}]_{kid}$, are the clearances of drug by metabolism in the liver and in tumor, by kidney depuration respectively, they are expressed as $\frac{\text{L}}{\text{min}}$;
Q'_{in} is the rate of intravenous administration of the drug and it is expressed as $\frac{\text{mg}}{\text{L}}$.

***Conjecture 3**: In order to illustrate in a short review some standard procedures on determination of the fundamental parameters let us consider the following differential system describing the post-phase of an intravenous bolus administration of the drug, which is considered instantaneously distributed in blood compartment and in tumoral one, then for constant volume of 1 and 2 in the duration of experiment, which is conducted during hours not days, we can write:*

$$\begin{aligned} &\frac{dX_1}{dt} = -k_{el}X_1 - a_{12}X_1 + a_{21}X_2 \\ &\frac{dX_2}{dt} = a_{12}X_1 - a_{21}X_2 \\ &X_1(0) = bolus\ dose; \\ &X_2(0) = 0; \end{aligned} \tag{8}$$

where X1 and X2 are the actual doses in blood and in tumor of the drug, i.e. the number of mg per unity of volume, k_{el} is

the drug elimination constant, which includes kidney, liver and tumor drainage, a_{12} and a_{21} are the constant transfer rate per unity of volume from 1 to 2 and vice versa.

Then using Laplace transform:

$$X_1(t) = Ae^{-\alpha t} + Be^{-\beta t}; \alpha > \beta \tag{9}$$

where α, β are such that:

$$\begin{aligned} \alpha + \beta &= k_{el} + a_{12} + a_{21} \\ \alpha \times \beta &= k_{el} a_{21}. \end{aligned} \tag{10}$$

Now it is possible to determine experimentally all parameters: in fact if t is large enough then:

$$C_{1late} = Be^{-\beta t}$$

because:

$$e^{-\alpha t} \to 0$$

more rapidly as $t \to +\infty$.

Then if the determined blood concentrations are represented in the plane with semilogarithmic scale versus time, the representative points are closely on a straight line, which is determined, with more precision, by the linear trend of the terminal temporal data, and whose slope furnishes – β, and the extrapolated value of B may be read on the vertical axis as the intersection point abscissa of that straight line.

In the early times we can consider:

$$\text{Residual } = X_1 - X_{1late} = Ae^{-\alpha t} \tag{11}$$

and determine in an analogue manner: α and A.

Then

$$\begin{aligned} \alpha_{21} &= \tfrac{A\beta + B\alpha}{A+B} \\ k_{el} &= \tfrac{\alpha \times \beta}{\alpha_{21}} \\ a_{12} &= \alpha + \beta - a_{21} - k_{el} \\ V_1 &= \tfrac{\text{bolus dose}}{A+B} \end{aligned} \tag{12}$$

If we know k_{el} then the sum of the clearances implicated is:

$$[V_{cl}']_{met,kid,tum} = k_{el} \times V_1,$$

and we can apart calculate, as organ clearance, the liver metabolic contribution and also the kidney elimination by specializing ([3]) the general formula here below written, therefore at last we can obtain indirectly the tumor metabolic amount in fact very often it is not possible a direct measure because there is not an evident sole way entering the tumor and leaving it because to disorder of growth often correspond a untidy irroration:

$$\begin{aligned} Organ\ clearence &= Q\frac{C_a - C_v}{C_a} \\ &= Q \times E \end{aligned} \tag{13}$$

C_a =drug concentration in blood entering the organ;
C_v = drug concentration in blood leaving the organ;
Q = perfusion velocity through the organ,
E = steady-state extraction rate.

At last the transfer rate coefficients become:

$$\alpha_{12} = a_{12} \times V_1, \alpha_{21} = a_{21} \times V_2.$$

2) Spontaneous (untreated) tumor evolution:

λ, μ, κ are the stochastic parameters which characterize the cellular growth, spontaneous death, the death by antibody response from immunological system respectively; they are expressed in day^{-1}. The parameters λ and μ are the same which, in deterministic models, are linked to the doubling time in tumoral growth in vitro by the formula:

$$T_d = \frac{\log 2}{\lambda - \mu}, \tag{14}$$

i.e. evaluated in a cultural colony.

Remark 1: *The why stochastic coefficients are equal to deterministic ones may have the following justification: the first equation of stochastic spontaneous process with h(t) = 0 which involves the mean of random variable number of neoplastic cell, has the same shape of that describing the colony growth in a deterministic model, then the variance is null and no difference exists between them.*

Namely:

$$\begin{aligned} \frac{dE(X)}{dt} &= (\lambda - \mu - k)E(X) - kE(X(X-1)) \\ &= \lambda E(X) - \mu E(X) - kE(X^2) \end{aligned}$$

and

$$\begin{aligned} &\frac{dx(t)}{dt} = \lambda x(t) - (\mu + kx(t))x(t) \\ &x(0) = n_o = 1 \Rightarrow \\ &x = \frac{\lambda - \mu}{k + (\lambda - \mu - k)\exp(-(\lambda - \mu)t)} \end{aligned} \tag{15}$$

x(t) is the function which has in its range the integers which represent the number of cells in each instant.

But the above formula (14) does not involve the antibodies response, however κ must be take in consideration although sensibly less than λ and μ,because the immunological system dully answers to the tumoral presence in an organism which has tolerated the survival of anomalous cells. More in details the cellular loss factor μ is obtained from:

$$\frac{\mu}{\lambda} = 1 - \frac{T_{pot}}{T_d} \tag{16}$$

if λ was obtained from

$$T_{pot} = \frac{\log 2}{\lambda}, \tag{17}$$

which is the potential doubling time in cellular loss absence i.e. in pure birth, and it can be determined by valuing the labeling index

$$LI = \Lambda \frac{T_s}{T_{pot}}, \tag{18}$$

which is the proportion of marked cells in a tissue culture measured by autoradiography technique, with T_s the mitosis interval, Λ a constant which depends by the position in cellular cycle of the *S*-phase, the interval of time in which there is the intake in the DNA molecule of the marker, e.g. H^3-thymidine. While k may be valued in vivo starting from solution of (15) if λ, μ are already determined. After, e.g. marked thymidine administration to the subject and successive biopsies of the neoplasia or a metastasis and incubation of the specimens with the patient serum which contains growth factors and antibodies too, the T_d is measured and so k may be found.

3) Controlled (treated) tumor evolution:

$h(t) = \zeta \frac{\rho C_{2,n}}{1+\rho C_{2,n}}$ is the stochastic parameter which represents the rate of the chemical death, it is expressed in day^{-1} if $C_{2,n}$ estimates the actual drug concentration in tumor: $C_{2,n}$ expressed as $\frac{\text{mole}}{\text{L}}$; ρ is the equilibrium dissociation constant depending upon the affinity between the active molecules and cellular receptors, which may be expressed as $\frac{\text{mole}}{\text{L}}$; the factor of proportionality ζ is expressed as $\frac{\text{L}}{\text{mole} \times \text{day}}$.
The datum may be acquired by a preliminary Scatchard's analysis [5] concerning the interaction drug-receptor, by incubating the tumoral cells membrane, which contains receptors, with a range of concentration of the ligand (drug) if a radioactive isotope has been attached to drug molecules; ζ may be measured as the per cent variation by chemical death per day in cells number in a tissue culture during the drug exposure if the drug concentration is kept constant.
Furthermore since every drug therapy attempt must be keep in account toxicity, the marrow of the host may be cultivated in the same experiment in order to evaluate drug toxicity and to be able to fixe an upper bound to the drug daily dose.
Therefore integration of the model (3)-(5) becomes, if we must consider also toxicity, a problem with constraints, but we speak about that in a forthcoming note.

3 Conclusions

Having drawn the pathway for the achievement of all data, our aim remains to be able to write a forthcoming computer program, by which, entered the numerical data, the output furnishes the optimal nursing conduct in drug tumor care, expressed by suitable temporal functions of the drugs intake. At last we adfirm, although in the fight against tumors a mathematical approach can seem to add some complexity to a just complex problem, that no doubt it is worthy to be put beside theoretical considerations which guide the experimental laboratory searches and those on clinical field. But also we hope that an interdisciplinary effort may continue a similar investigation, which seems to promise practical implications.

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