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A LINEAR KINETIC THEORY FOR CHEMICALLY INTERACTING BIO-MOLECULES WITH HYPERLIPEMIC DIET AND DRUG ADMINISTERED TO LIVING SYSTEMS

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Abstract. To highlight the role of inappropriate diet and drug administration in living systems a linear kinetic model is discussed taking into account the chemical coupling among the bio-molecules involved and the interaction of these with the corresponding molecules of supplied external factors.

Key works: kinetic theory, diet, drug, metabolism, disease, concentration, living systems.

1. INTRODUCTION

At present, the role of molecular physics is generally accepted in understanding the chemical and biological phenomena. Both in chemistry and biology we have to do with chemical reactions in which some molecules (as reactants) give rise to other (new or "old") molecules (as products).

Among the mentioned chemical reactions are also and those involved in the metabolism of living systems. It is well known that metabolism is one of the basic processes of the cell and is due to the exchange of substance and energy between the living subject and the environment. The main way to have that exchange is to supply the cell with "food" *i.e.*, by diet. However depending on the molecular composition ("normal", "rich" or "poor"), the diet can be one of the major risk factors for many diseases like coronary heart disease (CHD), stroke, diabetes, cancer, etc.

For example atherosclerosis is the major cause of morbidity and mortality throughout the world. A hyperlipemic diet can give rise to atherosclerotic lesions, to increase triglycerides (TG), total cholesterol (TC), LDL-cholesterol (LDL-C) and to form peroxides, etc [1–6].

Once a disease is installed to restore the living systems to a normal state it is necessary to administer efficient drugs. For the treatment of hypercholesterolemia are statins, both for reducing the progression and inducing the regression of

atherosclerosis. Manly the statins act as inhibitors and in this way the synthesis of cholesterol in the cell is limited [7–9].

In many experiments done in biology people measure the concentration of different biomolecules like total cholesterol (TC), low density lipo-proteins (LDL), high density lipo-proteins (HDL), lipid peroxides expressed as total peroxyl radical trapping potential (TRAP), thiobarbituric acid reactive substances (TBARS), angiotensin converting enzyme (ACE) etc. at different stages of hyperlipemic diet and drug administration. From this kind of measurements on important results is revealed, namely, there are interactions among all measured parameters which cannot be neglected in accurate studies [10–12] Also the measured concentrations of bio-molecules were different at various stages of administered diet and treatment showing maxima and minima [1, 2–16].

Since in many cases the experimental parameters (serum concentration of different bio-molecules) are slowly varying with respect to time, it is considered that a linear kinetic description, for these kinds of phenomena, could be appropriate.

In line with this motivation, in a previous paper, [17], we proposed a linear kinetic approach taking into account the coupling both among different bio-molecules on the system and of these with the administered diet and drug.

The aim of this paper is to highlight the strength and weakness of such a model.

2. THE LINEAR KINETIC APPROACH

As has been mentioned above many bio-logical phenomena are rather dynamic, near or far away of thermodynamic equilibrium, the coupling among different parameters (bio-molecules) exists and a kinetic description could be seen as a step for understanding the living processes as a results of diet and drug action. So our whole system consists of the living subject (some bio-molecules of this), diet and drug, all together interacting.

To formulate the kinetic theory, we resume shortly, the bio-chemical model described in [17] as follows:

If at time $t = 0$ (initial time) a diet D is administered to a living subject we suppose that there are bio-chemical reactions of the type:

$$\sum_i A_i + D \Leftrightarrow \sum_i A_i^{(1)} \tag{1}$$

where A_i represents the symbol of i involved bio-molecule, D is the symbol for the diet and A_i is the symbol for the same i bio-molecule with its concentration modified due to the diet D.

At another time $t_0 > 0$ if the same diet D is administered (as a continuation) to a control group the reaction is:

$$\sum A_i^{(1)} + D \Leftrightarrow \sum A_i^{(2)} \tag{2}$$

Also at $t = t_0$, to a second group (the treated group) is administered a drug M along the diet D and the reaction is:

$$\sum A_i^{(1)} + D + M \Leftrightarrow \sum A_i^{(3)} \tag{3}$$

The corresponding concentration values of $A_i^{(1)}$, $A_i^{(2)}$ depends of the action of diet D and $A_i^{(3)}$ is a function both of D and M.

In the reactions (1), (2), (3) the necessary enzyme in the process of metabolism is not explicitly written because it is supposed that the concentration of enzyme is not modified. The role of this is only to catalyze the reactions. Also in writing the reactions (2) and (3) the two groups (the control group and the treated one) are supposed to be, as much as possible, to be homogeneous which is a strong and necessary condition in biological experiments.

Now, if we denote the corresponding concentrations X_i, X_D, X_M then in the linear approach (near thermodynamic equilibrium) one can write the following set of coupled kinetic equation for the variation of concentration with respect to time, as a results of mutual interaction of all components including the diet and drug:

$$\frac{\mathrm{d}X_p}{\mathrm{d}t} = \sum_q \alpha_{pq}, \quad p, q = i, D, M \tag{4}$$

where α_{pq} are the coupling coefficients given, for our bio-chemical model, by

$$\alpha_{pp} = -\sum_{q \neq p} k_{pq} \quad \text{(diagonal terms)} \tag{5}$$

$$\alpha_{pq} = k_{qp}, \; p \neq q \quad \text{(off-diagonal terms)} \tag{6}$$

In eqs. (5) and (6) k_{pq} are the chemical rate constants and in general $k_{pq} \neq k_{qp}$.

The set of equations (4) satisfies the Onsager principle as can be easily proved [18].

By using (5) and (6), via (4), one gets:

$$\sum_p \frac{\mathrm{d}X_p}{\mathrm{d}t} = 0 \tag{7}$$

The relation (7) tells us that in the process of interaction among components (two by two) and with the diet and drug, the quantity of matter is conserved such that:

$$\sum_p X_p = C_p = const \tag{8}$$

3. THEORETICAL RESULTS

A. Firstly let us see how eqs. (7) and (8) can be used. Suppose the control group as described by reaction (2) and treated group described by reaction (3) are "identical" or as much as it is possible homogeneous (a compulsory requirement in biological experiments). Also the direct interaction between diet and drug is very weak (a realistic assumption).

Then, by integration of eq. (7) both for the control and treated groups and by using proper initial conditions to determine the corresponding integration constants one obtains an approximate expression for the effective drug concentration actively used during the treatment at a moment $t > t_0$

$$X_M(t) \approx \left[\sum_i X_i^{(0)}(t) - \sum_i X_i^{(D+M)}(t) \right] \tag{9}$$

where X_M is the drug concentration, $X_i^{(D)}$ the concentration of bio-molecule i modified by diet D (control group) and $X_i^{(D+M)}$ the concentration of the same bio-molecule i modified by diet and drug.

Now to use relation (9) there are two possibilities: a) naturally to solve the system of eqs. (4) and the corresponding solutions to be introduced in (9). To do that it is necessary to know coupling constants α_{pq} (respectively the rate constants k_q) which is a tremendous job because are many different bio-molecules in all chemical reactions of metabolism. b) To use the measured values for all relevant concentrations at the "end" of treatment and to compare it with the initial dose of drug to see if it is necessary to increase or decrease the dose in order the treatment to be efficient.

It has to be emphasized that if the homogeneity condition, for the two groups is not fulfilled the results obtained via relation (9) may have no relevance and the relation (12) of [17] is needed to use.

B. The main goal, in our model, is to solve the set of eqs. (4). To do this we are looking for a solution of the form:

$$X_p(t) = A_p e^{rt} \tag{10}$$

where r is obtained from the characteristic determinant:

$$\det \left| r\delta_{pq} - \alpha_{pq} \right| = 0. \tag{11}$$

For some values of α_{pq} coefficients, the roots of eq. (11) may be complex conjugate quantities:

$$r = \alpha + i\beta, \quad r^* = \alpha - i\beta, \quad \alpha = \alpha(\alpha_{pq}), \quad \beta = \beta(\alpha_{pq}). \tag{12}$$

In that case the solution can be written as [19]:

$$X_p(t) = \left[A_p \cos\beta t + B_p \sin\beta t\right] e^{-\alpha t} + \bar{X}_p \tag{13}$$

where the constants A_p, B_p, $\bar{X}_p$ can be determined from the initial conditions. Also, X_p constants are satisfying the relation

$$\sum_q \alpha_{pq} \bar{X}_q = 0 \tag{14}$$

The solution (13) is a good one only if the restriction $\alpha > 0$ is fulfilled.

As has been mentioned before, there are many coupling constants to be known what it makes difficult to use the solution (13). Therefore more approximations are needed. For example a semi-empiric solution.

C. A semi-empiric approximation of (13). Whenever $\beta t < 1$, by using the expansion in series of $\sin\beta t$ and $\cos\beta t$ from (13) up to second order in t one gets for bio-molecule i:

$$X_i(t) \approx \left(a_i + b_i t + c_i t^2\right) e^{-\alpha_i t} + \bar{X}_i \tag{15}$$

where $a_i = A_i$, $b_i = \beta B_i$, $c_i = -\frac{1}{2}\beta^2 a_i$ and from the initial conditions:

$$X_i(0) = a_i + \bar{X}_i, \quad \text{for} \quad t = 0, \tag{16}$$

$$X_i(\infty) = \bar{X}_i, \quad \text{for} \quad t \to \infty. \tag{17}$$

The advantage of expression (15) is the following: the average value $\bar{X}_i$ of (15) is

$$\bar{X}_i = \lim_{t\to\infty} \frac{1}{t} \int X_i(t) \mathrm{d}t = X_i(\infty) \tag{18}$$

and with a good approximation it is the average value over the corresponding time interval of experimental values (*i.e.*, the duration of treatment) if the stationary state is reached.

Also it was noted above that experimental $\bar{X}_i(t)$ has minima and maxima [1, 12] at a time t_m. Then from the extremum of (15) with respect to time one gets:

$$\alpha_i = \frac{b_i + 2c_i t_m}{a_i + b_i t_m + c_i t_m^2}, \qquad \alpha_i > 0. \tag{19}$$

The value of β can be chosen such that to ensure a good convergence of our series expansion of (13), *i.e.*, the contribution of next term $\propto t^3$ in (15) to be neglected or to be less than 5% (an accepted approximation).

This corresponds to:

$$\beta_i \approx 0.056 \quad \text{and} \quad b_i < \frac{3a_i}{t_m}. \tag{20}$$

By this choice of β_i the constant c_i is:

$$c_i = -\frac{\beta_i^2 a_i}{2}. \tag{21}$$

The coefficient b_i can be determined now by fitting the solution (15) with the experimental data.

Now we have a procedure to describe the time variation of bio-molecules concentration, with minima and maxima and to get the stationary state after a time shorter or longer which will be in fact the duration of treatment with specific medicines. This final statement is in agreement with many experimental observations [1, 12], etc.

From solution (15) it results that the time variation of concentration $X_i(t)$ is much faster at the beginning action of diet and drug than at the end of treatment if the administered drug is adequate. This prediction is confirmed by experience too.

D. The production of entropy S. In the same frame of bio-chemical picture and near thermodynamic equilibrium, the production of entropy can be written as:

$$\frac{\mathrm{d}S_{ext}^{(D)}}{\mathrm{d}t} + \frac{\mathrm{d}S_{\mathrm{int}}^{(i)}}{\mathrm{d}t} \to \frac{\mathrm{d}S_{\mathrm{int},f}^{(D)}}{\mathrm{d}t} \tag{22}$$

for the control group and

$$\frac{\mathrm{d}S_{ext}^{(D)}}{\mathrm{d}t} + \frac{\mathrm{d}S_{ext}^{(M)}}{\mathrm{d}t} + \frac{\mathrm{d}S_{\mathrm{int}}^{(i)}}{\mathrm{d}t} \to \frac{\mathrm{d}S_{\mathrm{int},f}^{(D+M)}}{\mathrm{d}t} \tag{23}$$

for the treated group. The notation "ext" refers to diet D and drug M and "int" to subject parameters while f to the situation when diet and drug was already consumed.

In eqs. (22) and (23) $\frac{\mathrm{d}S_{\mathrm{int}}}{\mathrm{d}t} \geq 0$ (as for isolated systems) while $\frac{\mathrm{d}S_{ext}}{\mathrm{d}t} \gtrless 0$ both for diet and drug.

For us, the most interesting situation is when the production of entropy corresponds to a stationary state (see [20, 21]) because in that case the effect of drug is considered good. But, in that case, due to Prigogine, the production of entropy has to be minimum *i.e.*,

$$\frac{\mathrm{d}}{\mathrm{d}t}\left[\frac{\mathrm{d}S_{\mathrm{int},f}^{(D+M)}}{\mathrm{d}t}\right]_{t=t_s}=0,\quad \frac{\mathrm{d}^2}{\mathrm{d}t^2}\left[\frac{\mathrm{d}S_{\mathrm{int},f}^{(D+M)}}{\mathrm{d}t}\right]_{t=t_s}>0 \tag{24}$$

where t_s is the moment when stationary state is reached.

Indeed, following the references [20, 21] the production of entropy given by eqs. (22) and (23), for our bio-chemical model, can be written as:

$$\frac{\mathrm{d}S_{\mathrm{int},f}}{\mathrm{d}t}=\frac{AJ}{T}=R\left[k_{12}\prod_k (X_k)^{\nu_k}-k_{21}\prod_l (X_l)^{\nu_l}\right]\ln\frac{\prod_k (X_k)^{\nu_k}}{\prod_l (X_l)^{\nu_l}} \tag{25}$$

where A is the chemical affinity, J-the current flux, T-the temperature, R-the ideal gas constant, k-the rate constant, ν_k and ν_l the stoichiometric coefficients for reactants and products, respectively, and K-the constant of chemical equilibrium.

One important observation has to be revealed: the production of entropy satisfies the condition (24) only if there is interaction between different components which is in accord with the kinetic approach described above via eqs. (4) and also with the most of experimental observations which show that there is correlation effects among different bio-molecules of the living cell.

Again, to see if (24) is satisfied there are two possibilities: a) to use for $X_i(t)$ the solution (13) or (15) and b) to use the experimental values whenever the stationary state can be obtained by treatment. As a matter of fact from (24) the shortest time (critical time t_s) can be determined to getting the stationary state.

A simple example. Since in many cases the administered diet and drug doses are constant, it can be supposed that:

$$\frac{\mathrm{d}S_D}{\mathrm{d}t}=C_D=const,\quad \frac{\mathrm{d}S_M}{\mathrm{d}t}=C_M=const. \tag{26}$$

Also, for simplicity, we consider $\frac{\mathrm{d}S_{\mathrm{int}}}{\mathrm{d}t}=0$ on the left side of (22) and (23) which may or may not be true. Then, by integration, from (26) one gets:

$$S_{\mathrm{int},f}^{(D+M)}-S_{\mathrm{int},f}^{(D)}=(t-t_0)C_M \tag{27}$$

because

$$C_M=-C_D \quad \text{for} \quad t>0 \tag{28}$$

where t_0 is the starting moment of treatment. The condition (28) is necessary in order to get the stationary state.

The important result contained in (27) is that the entropy, after treatment, is smaller, for $C_D>0$, than of the control group which is a desire in medical care, *i.e.*, the order is higher in normal subjects.

E. Some concluding remarks

1. In order to explain the time variation of many experimental serum parameters (concentrations) of living systems a set of coupled kinetic equations is written taking into account the interaction among bio-molecules (two by two) and also the interaction of these with administered diet and drug.
2. The solutions of eqs. (4) are found: a) in general, under the form (13) which requires that the coupling coefficients (the chemical rate constants) to be known and b) a semi-empiric solution (15) with parameters. A simple procedure to determine the corresponding parameters is done.
3. From the solution (13) and (15) the complete description of time dependence, of interested concentrations, is obtained including the observed minima and maxima, which are due to the interaction between bio-molecules. Also the stationary state can be foreseen.
4. Using the conservation condition of matter (equation (7), relation (9), for the effective drug concentration actively used during the treatment of subject with drugs, is obtained. Two points are important to be noted here: a) the relation (9) is valid only for homogeneous groups and b) both the diet and drug are time varying in the process of metabolism even if a fixed dose is administered in the initial phase.
5. If the production of entropy is analyzed (in the same bio-chemical picture) it results that to satisfy the Onsager and Prigogine principles it is necessary to have interactions among in valued bio-molecules which is the case in our model. Also, the living systems to have higher order after treatment with drugs the effect of these has to be contrary to the action of "rich" (or wrong) diet.

The model discussed here and in (17) has and some deficiencies:

a) Because there are a lot of important bio-molecules and many chemical reactions (more than 100!) in the process of metabolism it is almost impossible to know and take into account all coupling coefficients which enter in equation of type (4). Of course there is a way to eliminate a part of these by using the experimental data, *i.e.* to calculate the correlation coefficients and then to apply the F-test in order to see which are important.
b) There is in practice a real problem of homogeneity group's (the control and treated groups) during of the medical experiments what means that the relation (9) gives us just an idea how things happen.
c) Many biological phenomena are not near but rather far away of thermodynamic equilibrium such that the non-linear effects are important and the instabilities can arise. The linear kinetic approach is unable to describe the instabilities and the corresponding critical concentrations hence the non-linear theories are necessary. A first step, in this direction, has been done, recently in [22] with promising results.

Between the two approaches developed here, as an extension of [17], and that proposed by us in [22] there is a natural connection. Firstly, both are based on a

bio-chemical picture. Secondly, *via* eqs. (4), (8), (9), (13) and (15) the diet and drug concentrations can be obtained as function of time. Then the corresponding solutions could be used in the eq. (3) of [22] in a trial to find numerical results for instability problems.

Anyway, the model discussed in this paper is a satisfactory description for some biological processes that take place inside living systems (in the presence of external factors) and can be used for a large category of bio-molecules and diseases like atherosclerosis, diabetes, cancer etc.

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