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ON SOME STOCHASTIC MODELS FOR PROTEIN BIOSYNTHESIS

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The stability of the solutions of a model proposed by Gibbs et al. to describe the protein biosynthesis is studied in terms of the relative values of the kinetic parameters characterizing the three main steps of the polymerization process, i.e., initiation, elongation and termination. When the rate of initiation is equal to the rate of termination, the stationary state is unstable and depends thus on the perturbations imposed to the system. A comparison with results established by Vassart et al. suggests that initiation could be the rate determining step in protein biosynthesis.

1. Introduction

Theoretical studies of open chemical reaction networks with non-linear kinetics have shown that such systems may become unstable far from equilibrium and evolve to a new regime depending on time and/or space. Non-linear evolution equations may also allow far from equilibrium for multiple stationary states. Such situations have been called by Prigogine *dissipative structures* [1–3].

The object of this paper is to analyze in similar terms a model proposed by Gibbs et al. [4, 5] for the translation process of the protein biosynthesis. This model describes the diffusion of the ribosomes along the messenger RNA and gives the steady state distribution of nascent polypeptide chains.

Further models [6–8] have also been elaborated to simulate the protein biosynthesis. These models deal essentially with the polymerization process which is the basis of the protein biosynthesis. Here, we shall focus on Gibbs' results, which are the only ones to give rise to many possible types of stationary states. Our purpose will be to study the properties of these states in terms of the values of certain characteristic parameters of the system, by simulation on a C.D.C. 6400 computer. As we shall see, this numerical study will permit us to find again results established by Gibbs, to interpret them in terms of a transition between different polymerization states of the system as the parameters vary and to study properties such as the stability of these states.

2. The model

In their model, Gibbs et al. assimilate the diffusion of the ribosomes along the mRNA to the diffusion of segments along a one-dimensional lattice of K sites. Every site of the lattice represents one codon. The segment of length $L (L < K)$, representing the ribosome, may cover one ($L = 1$) or several ($L > 1$) sites of the lattice. This description of the protein biosynthesis is represented schematically on fig. 1.

This complex phenomenon has an irreversible character due to the polarity of the message contained in the mRNA. Moreover, this irreversible process requires continuous flow of tRNA and ribosomes. Thus, the biosynthetic apparatus can be looked upon as an open system operating in the nonlinear domain of thermodynamics of irreversible processes. The protein synthesis includes three main steps: initiation, elongation and termination [9] which are respectively characterized by the kinetic constants $k_f^{(0)}$, k_f and $k_f^{(K)}$.

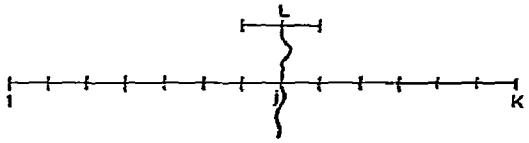

Fig. 1. The ribosome is represented by the segment of length L which diffuses along the lattice of length K representing the mRNA.

The probability $n_j(t)$ that the site j of the lattice be occupied by the polymerization site of the segment at time t is given by the following equation:

$$\frac{dn_j(t)}{dt} = q_{j-1}(t) - q_j(t) \qquad (1)$$

where $q_j(t)$ is the forward flow of the polymerization centre from site j to site $j+1$.

The value of this forward flow is given by the relation:

$$q_j(t) = k_f \frac{n_j(t)\left(1 - \sum_{s=1}^{L} n_{j+s}(t)\right)}{1 - \sum_{s=1}^{L} n_{j+s}(t) - n_{j+L}(t)} \qquad (2)$$

which has been derived by Gibbs et al. by adopting a markovian approximation for the motion of the ribosome. This assumption is perhaps far from biological reality because the motion of the ribosome results from a complex reaction including several chemical factors, most of which are not taken into account in this description*.

The kinetic equation (1) assumes a particular form at the boundaries of the system, where q_j becomes, for the first site:

$$q_0(t) = k_f^{(0)}\left(1 - \sum_{s=1}^{L} n_s(t)\right), \qquad (3)$$

for $1 \leqslant j \leqslant L-1$:

$$q_j(t) = k_f \frac{n_j(t)\left(1 - \sum_{s=1}^{L} n_{j+s}(t)\right)}{1 - \sum_{s=1}^{L} n_{j+s}(t) + n_{j+L}(t)}, \qquad (4)$$

for $K - L + 1 \leqslant j \leqslant K - 1$:

$$q_j(t) = k_f\, n_j(t), \qquad (5)$$

for the last site:

$$q_K(t) = k_f^{(K)}\, n_K(t). \qquad (6)$$

* A well known result in stochastic theory is that a process which is markovian in a certain space may become non-markovian when "projections" to smaller subspaces are made.

Eqs. (1) to (6) define for the K sites of the lattice, a set of coupled non-linear differential equations. Gibbs has shown that the behaviour of their solutions will depend on the relative values of the three parameters $k_f^{(0)}$, k_f and $k_i^{(K)}$. The different types of solutions are presented in the following section. A certain analogy between the occurrence of multiple solutions for those equations and some results obtained in biochemical models giving rise to dissipative structures [10–13] suggest that it is essential to study the stability of these solutions in order to determine the particular regime which will be physically realizable for different ranges of values of the parameters. This will be carried out in the following section.

3. Numerical analysis

We have investigated the evolution of the system towards the stationary state for various initial conditions and various values of the parameters by integrating the system of differential equations [1] which represents the progression of the segments along the lattice by the Runge Kutta method.

3.1. The segment covers only one site of the lattice (L = 1)

As shown by Gibbs et al., at the stationary state, we have three possibles types of solutions according to the boundary conditions and the rate constants.

n_{LD}: uniform low-density solution, which prevails when the initiation is the rate-determining step. This implies that $k_f^{(0)} < k_f^{(K)}$ and $k_f^{(0)} < k_f/(1+\sqrt{L})$.

n_{HD}: uniform high-density solution, which prevails when the termination is the rate-determining step. This implies that $k_f^{(K)} < k_f^{(0)}$ and $k_f^{(K)} < k_f/(1+\sqrt{L})$.

$n_{L/H}$: in this case, the rates of initiation and termination are of comparable magnitude and rate-determining, i.e. $k_f^{(0)} \simeq k_f^{(K)} < k_f/(1+\sqrt{L})$. This solution corresponds to a transition between n_{LD} and n_{HD}. The situation is analogous to a traffic jam in automobile traffic. Fig. 2 shows the three types of solutions.

We have tested the stability of these solutions with respect to small and large fluctuations for various values of the parameters.

(a) $k_f^{(0)} < k_f^{(K)} < k_f/(1+\sqrt{L})$.

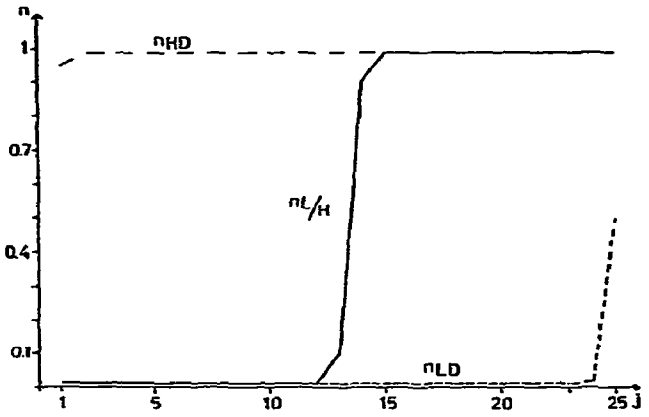

Fig. 2. The probability as a function of j.

If one discards the boundary conditions, two solutions are obtained at the stationary state: n_{LD} and n_{HD}. But the fact that the initiation is the rate-determining step eliminates n_{HD} and leaves us with only one stationary state solution, the low-density one. This solution is stable with respect to all disturbances.

(b) $k_f^{(K)} < k_f^{(0)} < k_f/(1+\sqrt{L})$.

As in the preceding case, the fact that the termination is the rate-determining step restricts us to one solution, the high-density one which is always stable.

(c) $k_f^{(0)} = k_f^{(K)} < k_f/(1+\sqrt{L})$.

The only solution satisfying the boundary conditions is $n_{L/H}$ which corresponds to an accumulation of nascent proteins near the site K of the lattice. This implies that the high-density part of the solution should be unstable at the level of the first sites of the lattice and that the

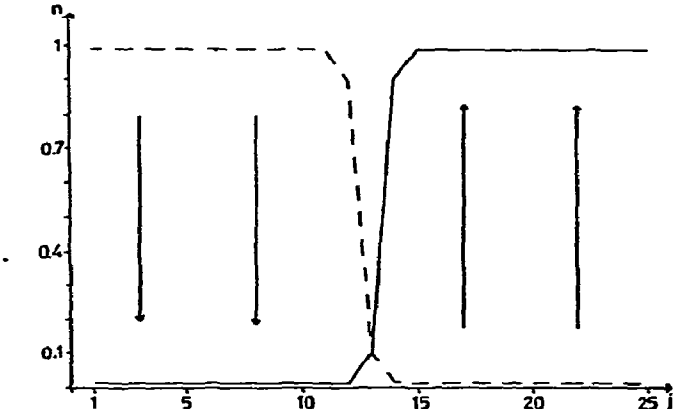

Fig. 3. As initial conditions, one has a "population inversion" (—). The arrows show the evolution of the system to a stationary state which is characterized by an accumulation of segments at the level of the last sites. The numerical values chosen for the parameters are: $K = 25$, $k_f^{(0)} = k_f^{(K)} = 0.1$, $k_f = 10.0$.

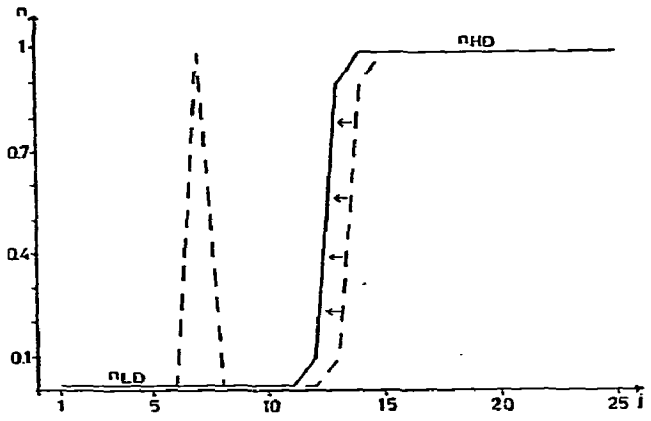

Fig. 4. A perturbation result in a displacement of the transition point. The initial transition point is situated at the level of the sites 13, 14. If one imposed the value of n_{HD} for the site 8, one observes a displacement of the transition point to the sites 11, 12. The numerical values chosen for the parameters are: $k_f^{(0)} = k_f^{(K)} = 0.1$, $k_f = 10.0$, $K = 25$.

low-density one should be unstable at the level of the last sites of the lattice. This is confirmed by the numerical calculations described in fig. 3. An interesting point is that the position of the transition between the two branches depends on the perturbations imposed on the system: any perturbation results in a displacement of the transition as shown in fig. 4.

3.2. The segment covers more than one site of the lattice ($L > 1$)

This case is more realistic, because it is known that a ribosome covers several codons of the mRNA

(a) $k_f^{(0)} < k_f^{(K)} < k_f/(1+\sqrt{L})$.

As in the previous case ($L = 1$), at the stationary state, the only possible solution is the low-density one.

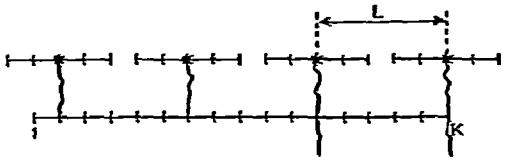

Fig. 5. Spatial periodicity observed when $L > 1$. Here $L = 5$ and $K = 17$.

(b) $k_f^{(K)} < k_f^{(0)} < k_f/(1+\sqrt{L})$.

These values of the parameters correspond to the uniform high-density solution, when $L = 1$. In this case, the uniform high-density solution does not exist at the stationary state. One observes instead spatial oscillations with "period" L around this solution. These oscillations result from the fact that the boundary conditions only concern the polymerization sites. The latter are distant from each other by a length L. Thus, the other "inactive" sites of the segments block the remaining sites of the lattice as shown on fig. 5. Obviously, this spatial periodicity is not a spatial dissipative structure, as it is the only solution available to the system for the given values of the parameters.

Clearly, this situation is a direct consequence of the assumption that the segments cannot overlap.

In this case, the oscillatory solution is unique and stable. Fig. 6 represents this type of solution

(c) $k_f^{(0)} = k_f^{(K)} < k_f/(1+\sqrt{L})$.

One observes a transition from the low-density solution which prevails at the level of the first sites, to the oscillatory one, which prevails at the level of the last sites. As in the previous subsection, the position of the transition appears to depend on the initial conditions and on the type of perturbations imposed on the system. Fig. 7 present such a solution.

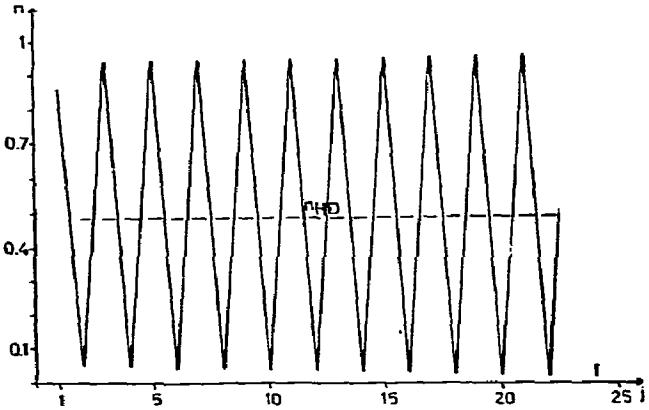

Fig. 6. Oscillations around n_{HD}. The numerical values chosen for the parameters are: $L = 2$, $K = 25$, $k_f^{(0)} = 1.0$, $k_f^{(K)} = 0.1$, $k_f = 10.0$.

4. Discussion

We have studied in some detail the transitions between polymerization states occuring in a model proposed by Gibbs et al. for the protein biosynthesis. Our results show that the nature of the steady states depends on the boundary conditions imposed on the system and, in certain cases, on the initial conditions.

Three domains can be determined, depending on the relative values of the kinetic constants.

The first domain corresponds to $k_f^{(0)} < k_f^{(K)} < k_f/(1+\sqrt{L})$. The uniform low-density solution is the only possible one. Biologically, this situation would correspond to a fast reading of the mRNA when the initiation is the rate-determining step.

The second domain correspond to $k_f^{(0)} = k_f^{(K)} < k_f/(1+\sqrt{L})$ a transition between the low- and the high-density solutions is observed. It is the only case in which we observe multistationarity: this results from the fact the position of the transition is undetermined since it depends on the initial conditions and on the perturbations imposed on the system. Thus, in this case, various solutions coexist for given values of the parameters. Experimentally, this domain would correspond to the accumulation of nascent proteins at variable positions near the 3 end of the mRNA.

The third domain corresponds to $k_f^{(K)} < k_f^{(0)} < k_f/(1+\sqrt{L})$. When $L = 1$, the high-density solution is stable. When $L > 1$, as shown by Gibbs et al., oscillations occur around the high-density solution. This situation would correspond to an accumulation of nascent proteins along a mRNA which is slowly read.

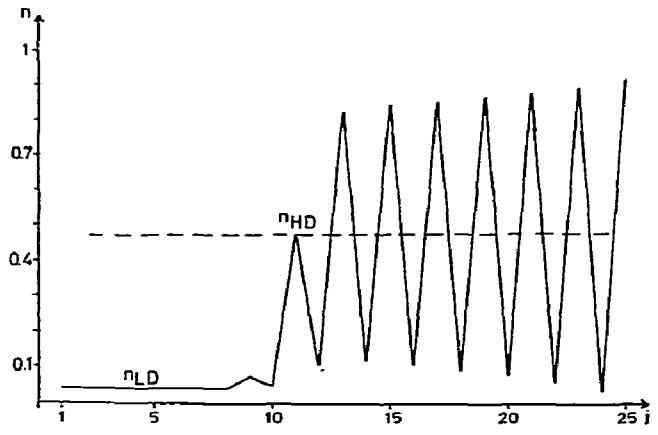

Fig. 7. Solution with transition. The numerical values chosen for the parameters are: $L = 2$, $K = 25$, $k_f^{(0)} = k_f^{(K)} = 0.1$, $k_f = 10.0$.

Summarizing, the only region of existence of multiple stationary states for given values of the parameters is $k_f^{(0)} = k_f^{(K)} < k_f$. In this case, each point at the interior of the lattice may occur at the high density as well as the low density state, depending on the initial conditions. This behavior corresponds therefore entirely to the one analyzed by Prigogine et al. for systems exhibiting dissipative structures.

In the other regions of values of the parameters the solution are unique and therefore cannot be regarded as dissipative structures. Still, a certain analogy exists with multiple solutions and dissipative structures owing to the fact that the variation of the different parameters induces transitions between different types of steady state solutions. In a sense, one can say that we have "parametrical" transitions inducing qualitative changes in the character of the solution.

The purpose of our stability analysis was to establish a relation between the value of the parameters and the physicaliy realizable situations. Next, we must compare these stable solutions provided by the model with the situations observed in living cells.

The model discussed in this paper describes protein biosynthesis in a rather simplified way. It is therefore difficult to establish a tangible link between such a model and the biological reality. However, one can compare the number of ribosomes which constitute a polysome and the number of segments which are moving along the lattice. Vassart et al. [8] have evaluated that the mRNA of hemoglobin is composed of 150 codons, that a ribosome covers 10 codons and that a polysome is formed of 5 ribosomes. In our treatment, for $L = 2$, and $K = 25$ which have the same ratio as $L = 10$ and $K = 150$, we have indeed obtained five ribosomes when the initiation and the termination are of comparable magnitude and rate-determining, we have obtained between seven and nine ribosomes. When the termination is the rate-determining step, we have obtained eleven ribosomes. Similar results were also obtained by Vassart et al. [8], who have concluded that the initiation is the rate-determining step of the protein biosynthesis.

In order to better approach the biological reality, which is probably far from the rather restrictive approximation for the polymerization flow (eq. 2), it

would be interesting to develop a nonmarkovian stochastic model to represent the protein biosynthesis.

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