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MOBISIM - Package for Simulation in Molecular Biology

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Abstract. A computer program for simulation of protein synthesis regulatory processes is described. A short theoretical background reveals the requirements of a simulation program. Our program, MOBISIM, offers several facilities and a user-friendly interface for molecular biologists. An example illustrates the graphical representation both as time evolution of the system or as phase diagram.

1. Introduction

An important role in gene activity control is played by specific activator and repressor transcription factors which bind to specific regulator DNA sequences Interactions between genes coding such transcription factors should explain the different stable or oscillatory gene activities characteristic for various tissues. A set of models has been built for several systems with interconnected genes. We have published our first model in 1985 [1], which has not been extended due to the scarce experimental support [3]. Meanwhile several new findings [4, 5] made us reconsider and develop the model [6, 7]. An important role in model refinement was brought by a set of computer programs developed in our laboratory [1, 8, 9].

2. Theoretical background

A typical sequences of gene control of protein synthesis comprises three steps (fig.1):
- *transcription:* mRNA structure is copied from the synthesis gene SG of the nuclear DNA, with a rate dependent on the activation degree of the regulatory gene R located uphill
- *translation:* protein P is synthesised with a rate proportional to mRNA concentration
- *regulation:* the regulatory gene R might either promote/enhance or inhibit/repress SG.

The regulatory gene activity might be controlled either by its own protein (selfregulation), or by other proteins, produced by other genes, named interconnected genes (inter-reulation).

Both mRNA and protein have a natural decay.

Using the notations of fig. 1, we can build the general model for a typical "unit of protein synthesis":

$$\begin{cases} \dfrac{dy}{dt} = \varphi \cdot F\left(x, x^{'}, t\right) - \eta y \\ \dfrac{dx}{dt} = \psi \cdot y - \lambda x \end{cases} \qquad (1)$$

The general form cannot be integrated, so the easiest way to analyse such models is to study their simulations.

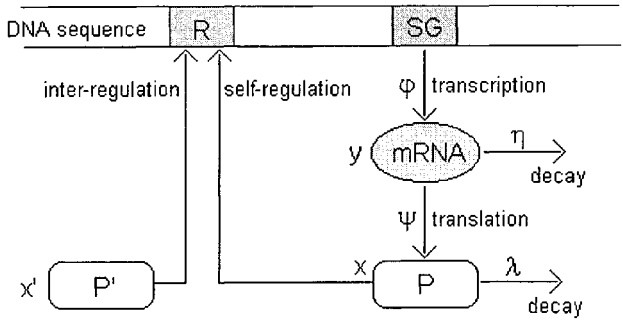

Fig. 1. Scheme of regulatory processes

The particular form of the activation function F is the determinant factor of most peculiarities found in different cases:

a) *self regulated gene* [1, 2]:

$$F(x) = \frac{Ax^n}{K_1 + x^n} + \frac{Bx^n}{K_2 + x^n} \tag{2}$$

Three steady states might be obtained with this model; there is an experimental support for such case [3].

b) *threshold activation of interconnected genes:*

$$F_1(x_1, x_2) = \begin{cases} 0 \text{ for } x_1 < x_A \\ 1 \text{ for } x_1 \geq x_A \end{cases} \tag{3}$$

These discontinuous (stepwise) activation functions with two or three intervals correspond to threshold phenomena. In particular instances the system of differential equations type (1) can be integrated on intervals

c) *delayed activation*:

The real phenomena comprise a delay between the moment of a certain concentration change and the moment of its effect; we have added all the delays of one cycle as a single delay, τ, and attributed it to the longest lasting event, i.e. activation:

$$F(t) = F(x(t - \tau)) \tag{4}$$

which means that we compute the activation function at moment t from the concentration value of the regulatory protein at an earlier moment, $t - \tau$.

This short presentation of the basic theoretical background reveals the main features, which have to be covered by a simulation software dedicated to these phenomena [6, 7].

3. Requirements for a simulation program in molecular biology

a) Variables. The most common output of a simulation program modelling a process, is a graphical plot representing the evolution of one or more variables.

b) Iteration refinement. Classical methods (Runge-Kutta) are used for differential equation systems. The iteration step (dt) should be extremely small, especially for fast variations. The program should accept its adjustment.

c) Scaling: an automatic choice of the appropriate scale for each variable is advisable. However, one may prefer changing the scales for a better comparison.

d) Parameters. A set of default values for all the parameters is customary used but an important feature of a simulation program is to offer simple facilities for changing their values. These values should always be displayed aside the graph.

e) Parameter influence on graphical representation. A common procedure in simulation studies is to estimate the influence of (some of) the parameters on the evolution of a certain variable. In this case one would rather prefer to have a set of curves representing the evolution of only one variable for the set of different values of that parameter.

f) Phase diagram. The behaviour of systems comprising several regulatory mechanisms require a graphical plot having any (chosen) pair of variables on the axes, called phase diagram. One can better see the trends of the system towards steady states (attractors), or towards oscillations.

g) Operation facilities like adding a text for the graph, saving the parameters used for a graphical representation, reading parameters from a file, changing colours etc. - should also be available.

4. Description of MOBISIM

Our program is a Pascal application fulfilling the requirements. It has three modules:

- the **main module** comprising the variables and constants sections. The set of differential equations type (1) and the set of analytical equations type (2) or (3) or (4). The description of these equations is not automated, they have to be introduced as Pascal lines, specifying the parameters used. Actually all manual operations are included in this module. The core procedure computes the elements of the matrix corresponding to time evolution of the variables (and activation functions), calling the Runge-Kutta procedure for each iteration. After these computations, the graphical representation module is called.
- the **Runge-Kutta module,** (fourth order) in a general form (for any number of differential equations type (1)); this procedure is called in each iterative step.
- the **graphical representation module,** carries the tasks of scaling and representing the evolution of the desired variables or the phase diagram. One can change the variables to be represented, the limits of scales or the graph type (evolution or phase diagram).

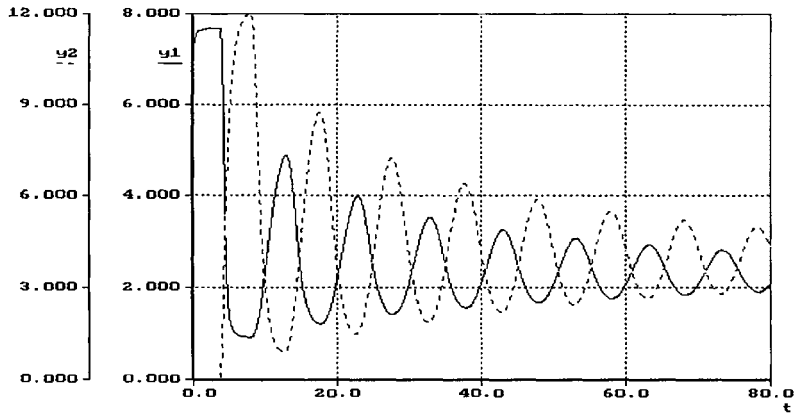

Fig.2. Time evolution of a system of two interrelated genes for a model with delay

5. Results and conclusions

An application of MOBISIM on a biosystem of two interrelated genes, p53 and mdm2, [4, 5] is presented below. Depending on the values of the parameters, the biosystem can evoluate either towards a steady state showing damped oscillations (fig. 2), or towards permanent oscillations. The corresponding phase diagram is presented in fig. 3.

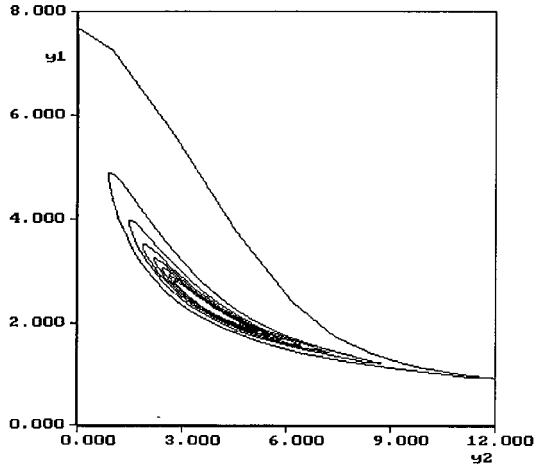

Fig. 3. The phase diagram for a system of interrelated genes with damped oscillations

Even the program was designed for molecular biology, it is quite general and it has also been applied to immunology [8] and physiology [9].

Acknowledgements

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