

# THE PACKAGE STEP+ FOR NUMERICAL STUDY OF AUTONOMOUS SYSTEMS ARISING WHEN MODELING DYNAMICS OF GENETIC-MOLECULAR SYSTEMS

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## SUMMARY

*Motivation:* Development and analysis of mathematical models of genetic-molecular systems is one of the actual problems of molecular biology. For this purpose it is necessary to develop specific algorithms and software.

*Results:* In this paper we present the package STEP+ for numerical study of autonomous systems of differential equations arising when modeling genetic-molecular systems.

*Availability:* This package is available by request.

## INTRODUCTION

Intensive accumulation of data on structure functional organization and dynamics of gene networks put in the forefront the problem of development of tools for computer modeling and visualization of dynamic characteristics of gene networks. In this connection, one of the important problems as the problem of analysis of models under the development emerges. In turn, it requires elaboration of appropriate methods, approaches, and software. In this paper we present the package STEP+ realizing a complex of methods for numerical analysis of autonomous systems of differential equations modeling dynamics of gene networks (Fadeev *et al.*, 2002, 2004). Study of behavior of solutions of the given class of systems in dependence of parameters is one of the important parts of the general problem of constructing mathematical models adequate to experimental data. This package includes algorithms for numerical study of abstract autonomous systems consisting of  $N$  equations of the form

$$dy/dt = f(y,p), \quad (1)$$

where  $p \in R^m$  is a vector of parameters. Among these algorithms there are integration of systems of the form (1) with given initial conditions (Cauchy problem), constructing stationary solutions in dependence of a parameter  $\alpha$ ,  $\alpha \in p$ , i.e., solutions of the system of nonlinear equations

$$f(y,\alpha) = 0, \quad (2)$$

and study of asymptotic stability of the obtained stationary solutions. The first version of the package was published in (Fadeev *et al.*, 2002).

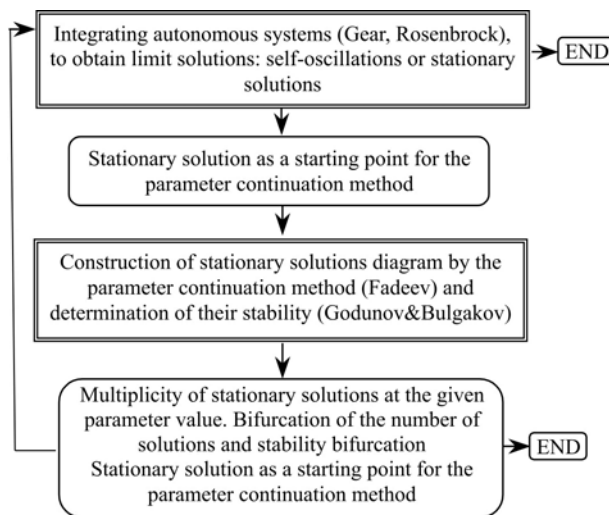


Figure 1. Operating opportunities of the package STEP+.

## RESULTS

The package STEP+ is intended for numerical study of autonomous systems and systems of nonlinear transcendent equations. The present version of the package for Windows is a version of the package STEP (Fadeev *et al.*, 1998) and an update of the previous version (Fadeev *et al.*, 2002). The kernel of STEP+ is universal and allows the user to research numerically arbitrary systems consisting of  $N$  ordinary differential equations of the form (1). The package STEP+ uses original computational algorithms elaborated at the Sobolev Institute of Mathematics SB RAS for study of dynamical systems: a variant of the parameter continuation method, the Godunov-Bulgakov method (so called  $\kappa$ -criterion) for study of stability of solutions. These algorithms make it possible to research systems of arbitrary orders and take into account nonlinear effects (hysteresis, strong parametric sensitivity, self-oscillations and etc.) observed, as a rule, in mathematical models describing dynamics of genetic-molecular systems. In this package we realized also standard methods of numerical integration for stiff problems; in particular, multistep Gear's method of fractional accuracy order (Gear, 1971) and etc. Detailed descriptions of the methods can be found in the textbook (Fadeev *et al.*, 1998). The package STEP+ allows us:

- using the parameter continuation method, to establish numerically dependence of stationary solutions  $y(\alpha)$  of the system (2) on parameter  $\alpha$  and indicate domains of multiple solutions;
- to study stability of the stationary solutions and mark points, on the diagram of the stationary solutions, where an unstable stationary solution passes into a stable limit cycle (Hopf bifurcation);
- integrating autonomous systems, to obtain self-oscillations or start looking for stationary solutions which can be chosen as initial solutions for the continuation method;
- to point out domains of  $\alpha$ , where all stationary solutions are unstable, i.e., self-excitation of self-oscillations for any initial data.

The structure of the package STEP+ is intended for organization of numerical experiments to study mathematical models presented by autonomous systems and systems of nonlinear equations. This package consists of three divisions: "Model development", "Cauchy problem", and "Nonlinear systems". The package STEP+ provides for automatic input right-hand sides of autonomous systems of differential equations by means of a

converter-program. To run any calculated program and input calculated parameters by means of user interface we produced a program for generation of DLL library. Owing to special input form of right-hand sides of systems of differential equations, this generator finds analytically the Jacobi matrix  $df_i/dy_j, i=1, \dots, N, j=1, \dots, N$ , and the matrix consisting of partial derivatives with respect to parameters  $df_i/dp_j, i=1, \dots, N, j=1, \dots, m$ . Admissible order of dynamical systems is equal to 1000. The package contains a series of models among which are mathematical models of gene networks, developed at the Institute of Cytology and Genetics SB RAS, and models from the literature (for example, the Lorentz model). The package STEP+ is realized in the visual programming environment Visual Basic.NET and intended for Windows 2000/XP.

Opportunities of the package STEP+ are demonstrated by a mathematical model describing dynamics of functioning of the genetic system controlling the cholesterol homeostasis in the cell (Ratushny *et al.*, 2003a, b; Ratushny, Likhoshvai, 2006). This model consists of 122 differential equations and contains 414 parameters. For given initial data and parameters we obtain a stationary solution, study its stability and sensibility on the parameters (Ratushny, Likhoshvai, 2006).

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## REFERENCES

- Fadeev S.I., Berezin A.Yu., Gainova I.A., Kogai V.V., Ratushny A.V., Likhoshvai V.A. (2002) Development of the program software for mathematic modelling of the gene network dynamics. In *Proc. III Intern. Conf. on Bioinformatics of Genome Regulation and Structure (BGRS'2002)*, **2**, 93–95.
- Fadeev S.I., Gainova I.A., Berezin A.Yu., Ratushny A.V., Matushkin Yu.G., Likhoshvai V.A. (2004) Study of stationary solutions in gene network models by the homotopy method. *Sib. Electronic Mathematical Reports*, **1**, 64–75.
- Fadeev S.I. Pokrovskaya S.A., Berezin A.Yu., Gainova I.A. (1998) *The Package STEP for Numerical Study of Systems of Nonlinear Equations and Autonomous System of General Form*. Description of work of the package STEP by examples of problems from the course “Engineering chemistry of catalytic processes”. Izdatel'stvo Novosibirskogo universiteta, Novosibirsk.
- Gear G.W. (1971) The automatic integration of ordinary differential equations. *Comm. ACM*, **14**, 76–179.
- Ratushny A.V., Likhoshvai V.A., Ignatieva E.V., Goryanin I.I., Kolchanov N.A. (2003a) Resilience of cholesterol concentration to a wide range of mutations in the cell. *Complexus*, **1**, 142–148.
- Ratushny A.V., Likhoshvai V.A., Ignatieva E.V., Matushkin Yu.G., Goryanin I.I., Kolchanov N.A. (2003b) A computer model of the gene network of the cholesterol biosynthesis regulation in the cell: analysis of the effect of mutations. *Dokl Biochem Biophys.*, **389**, 90–93.
- Ratushny A.V., Likhoshvai V.A. (2006) Mathematical modeling of the gene network controlling homeostasis of intracellular cholesterol. *This issue*.