

Analytical and numerical modeling of a pluripotency gene network

Golubyatnikov V.P.*, Tatarinova E.A.

Novosibirsk State University, Novosibirsk, Russia

*v.golubiatnikov@g.nsu.ru

Key words: gene network models; positive and negative feedbacks; equilibrium points; stability

Motivation and Aim: We study two 10-dimensional systems of differential equations proposed in [1] as mathematical models of pluripotency gene network functioning. Its main components are the proteins Oct4, Sox2, and Nanog. A simplified version of one of these systems was considered in [2]. Equations of all these systems depend on 62 parameters which were assumed to be fixed in all numerical experiments described in these publications; their values are listed in the Table 1 in [1], see also [3]. In order to extend results of [1] to more general situations, we consider here all these dynamical systems in the cases when the value of all their parameters can vary. For such variable parameters and coefficients of these dynamical systems, we find conditions of non-uniqueness of their equilibrium points, and formulate a criterion of their stability.

Methods and Algorithms: Using methods of qualitative theory of ordinary differential equations, we have fulfilled parametric analysis of these dynamical systems in order to describe these equilibriums, and stability of these equilibriums. We have obtained also a criterion of existence of periodic trajectories near these points, and we have localized these oscillations.

Results: On the basis of these analytical studies, we have realized series of numerical experiments with these dynamical systems for non-fixed values of their parameters described in [1]. Following [4–6], two special cloud programming complexes were elaborated for numerical experiments with these two mathematical models: https://colab.research.google.com/drive/1BKX9KUrgxhOLPkl_WwbCn1EYppu1lu5K?usp=sharing https://colab.research.google.com/drive/13-pjMCF2SE-v_PxQ6b5ejMFvKM5nUui4

Here, we start with detection and analysis of equilibrium points of these models. The libraries numpy and math were used here for work with data set, and with mathematical functions, the library Matplotlib was used for visualization of the results. In contrast with the previous studies [1, 2], one can vary here all the parameters of these models within some prescribed intervals. The access to these cloud sources is possible from any google account, the values of the current parameters of the systems, and the equilibrium points are demonstrated here as well.

All calculations are performed in the clouds, and presentation of the results is available in a browser. In preparation of similar numerical experiments, it is useful to give a qualitative description of solutions to corresponding differential equations, in order to get their clear presentation. The elaborated interface allows to assign the values of all 62 parameters of the models.

Figures 1 and 2 show results of some numerical experiments with the system (1) described in [1]. On Figure 1, parameters of this system are chosen so that the system has one unstable equilibrium point and two stable equilibriums, the points 1 and 3. On

the Figure 2, these parameters correspond to the case of unique stable equilibrium. Similar variations of multistability of the equilibriums is observed in mathematical analysis and in numerical experiments with the system (4) where following [2], an additional positive feedback loops between Oct4-Sox2-Nanog factors have been taken into account.

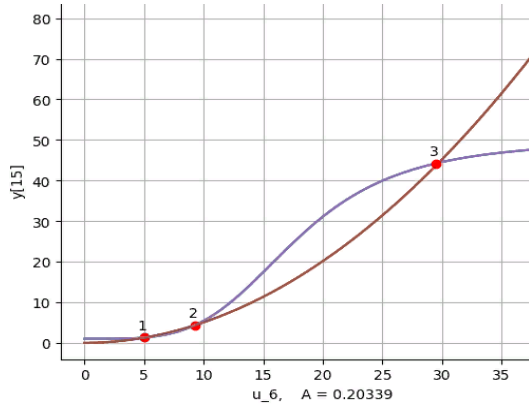


Fig. 1. Three equilibrium points

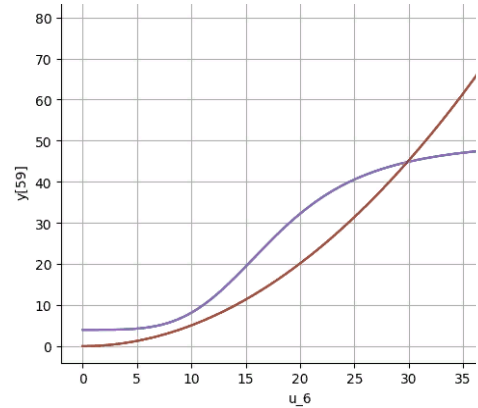


Fig. 2. One equilibrium of the model

Conclusion: The phase portraits of both models under consideration have similar structure; this mathematical observation corresponds to that of [3]: Nanog protein has minimal influence on Oct4 and Sox2 expression.

Funding: The study is supported by RSCF (No. 23-21-00019), <https://rscf.ru/project/23-21-00019/>.

References

1. Akberdin I.R., Omelyanchuk N.A., Fadeev S.I. et al. Pluripotency gene network dynamics: System views from parametric analysis. *PLoS One*. 2018;13(3):e0194464. doi 10.1371/journal.pone.0194464
2. Chickarmane V., Troein C., Nuber U.A., Sauro H.M., Peterson C. Transcriptional dynamics of the embryonic stem cell switch. *PLoS Comput Biol*. 2006;2(9):e123. doi 10.1371/journal.pcbi.0020123
3. Navarro P., Festuccia N., Colby D. et al OCT4/SOX2-independent Nanog autorepression modulates heterogeneous Nanog gene expression in mouse ES cells. *EMBO J*. 2012;31(24):4547-4562. doi 10.1038/emboj.2012.321
4. Akinshin A.A., Ayupova N.B., Golubyatnikov V.P. et al. On a numerical model of a circadian oscillator. *Numer Anal Appl*. 2022;15(3):187-196. doi 10.1134/S1995423922030016
5. Bukharina T.A., Akinshin A.A., Golubyatnikov V.P., Furman D.P. Numerical models of the central regulatory circuit of the morphogenesis system of drosophila. *J Appl Ind Math*. 2020;14(2):249-255. doi 10.33048/SIBJIM.2020.23.203
6. Akinshin A.A., Ayupova N.B., Golubyatnikov V.P., Minushkina L.S. Stratifications and foliations in phase portraits of gene network models. *Vavilov J Genet Breed*. 2022;26(8):758-764. doi 10.18699/VJGB-22-91