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In silico analysis of the system determining the morphogenesis of *Drosophila* mechanoreceptors

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Motivation and Aim: Identification of the mechanisms underlying the genetic control of spatial structure formation is among the relevant tasks of developmental biology. Both experimental and theoretical approaches and methods are used for this purpose, including gene network methodology [1], as well as mathematical and computer modeling. Reconstruction and analysis of the gene networks that provide the formation of traits allow us to integrate the existing experimental data and to identify the key links and intra-network connections that ensure the function of networks. Mathematical and computer modeling is used to obtain the dynamic characteristics of the studied systems and to predict their state and behavior. The numerical experiments conducted with the help of mathematical models allow the potential operation modes of a system to be examined, its future states to be forecasted, and its new functions to be predicted by changing parameters or adding new assumptions. In many cases, modeling is the only way to clarify the processes taking place in a system when their characteristics cannot be directly measured in a biological experiment.

An example of the spatial morphological structure is the *Drosophila* bristle pattern with a strictly defined arrangement of its components, mechanoreceptors. The mechanoreceptor develops from a single sensory organ parental cell (SOPC), which is isolated from the ectoderm cells of the imaginal disk. It is distinguished from its surroundings by the highest content of proneural proteins (ASC), the products of the *achaete-scute* proneural gene complex (*AS-C*). The SOPC status is determined by the gene network we earlier reconstructed and the *AS-C* is the key component of this network. *AS-C* activity is controlled by its subnetwork – the central regulatory circuit (CRC), comprising seven genes: *AS-C*, *hairy*, *senseless* (*sens*), *charlatan* (*chn*), *scratch* (*scrt*), *phyllopod* (*phyl*), and *extramacrochaete* (*emc*), as well as the corresponding proteins. In addition, the CRC includes the accessory proteins Daughterless (DA), Groucho (GRO), Ubiquitin (UB), and Seven-in-absentia (SINA) [2].

Although the morphogenesis of mechanoreceptors has been long studied, it is still far from an exhaustive description. It is only qualitatively characterized: the players in this process (genes and proteins) are known and the general concept of their interaction is formed; however, most of the quantitative parameters as well as a relative contribution of the involved genes have not been experimentally determined. The goal of this work was to construct a mathematical model of CRC operation taking into account the roles of the constituent genes that would comprehensively describe the intracellular events in

presumptive SOPC determining the dynamics of ASC content and to perform the computer experiments for verifying the model stability and its compliance with experimental data.

Methods and Algorithms: The proposed dynamical model of *AS-C* activity is described with a system of seven ordinary differential equations (ODE) [3]. The variables in this system are the concentrations of CRC proteins in the cell: $x(t)$ is the content of ASC; $y(t)$, of Hairy; $E(t)$, of Extramacrochaete; and $z(t)$, $u(t)$, $w(t)$, and $p(t)$, the concentrations of Senseless, Scratch, Charlatan, and Phyllopod, respectively. To take into account the mutations of the genes that compose the CRC, the model contains non-negative coefficients k_x, k_y, k_e, and so on reflecting the degrees of the effect of mutations on the synthesis of the corresponding proteins. The values of these coefficients do not exceed unity; $k = 1$ corresponds to the normal operation of a gene; and $k = 0$ denotes a complete inactivation of a gene and the absence of the corresponding protein.

The specially developed web application (https://gene-nets-simulation.shinyapps.io/crc-asc-modeler/) allows the CRC operation modes to be simulated for different values of the ODE system parameters and the results of these numerical experiments to be visualized as plots [4].

Results: The proposed model allowed us to advance from a purely qualitative description of the system controlling the content of ASC proteins and to clarify some of its quantitative characteristics unknown earlier.

In particular, our numerical experiments suggest that the cell is determined as an SOPC when the ASC content increases approximately 2.5-fold relative to the initial level in the cells of proneural cluster. Individual elements of the circuit have different effects on the content of ASC proteins in the presumptive cell of mechanoreceptor. *AS-C*, the key CRC component, and the mutations that decrease the ASC content by more than 40 % have the most significant effect and cause the prohibition of SOPC segregation. As for the mutations in the remaining genes of the circuit, they change the level of ASC proteins to different degrees, with the most pronounced effects of mutations in *emc* and *hairy* genes. Thus, the model demonstrates that the CRC as a system is sensitive to the changes in internal interactions and its robust operation, providing a certain dynamics of the level of ASC proteins, requires a concerted work of all components constituting the regulatory circuit.

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