



Comment

Epigenetic game theory and its application in plants
Comment on: “Epigenetic game theory: How to compute the
epigenetic control of maternal-to-zygotic transition” by Qian Wang
et al.

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Wang’s et al. article [1] is the first to integrate game theory (especially evolutionary game theory) with epigenetic modification of zygotic genomes. They described and assessed a modeling framework based on evolutionary game theory to quantify, how sperms and oocytes interact through epigenetic processes, to determine embryo development. They also studied the internal mechanisms for normal embryo development: 1) evolutionary interactions between DNA methylation of the paternal and maternal genomes, and 2) the application of game theory to formulate and quantify how different genes compete or cooperate to regulate embryogenesis through methylation. Although it is not very comprehensive and profound regarding game theory modeling, this article bridges the gap between evolutionary game theory and the epigenetic control of embryo development by powerful ordinary differential equations (ODEs). The epiGame framework includes four aspects: 1) characterizing how epigenetic game theory works by the strategy matrix, in which the pattern and relative magnitude of the methylation effects on embryogenesis, are described by the cooperation and competition mechanisms, 2) quantifying the game that the direction and degree of P–M interactions over embryo development can be explained by the sign and magnitude of interaction parameters in model (2), 3) modeling epigenetic interactions within the morula, especially for two coupled nonlinear ODEs, with explicit functions in model (4), which provide a good fit to the observed data for the two sexes (adjusted $R^2 = 0.956$), and 4) revealing multifactorial interactions in embryogenesis from the coupled ODEs in model (2) to triplet ODEs in model (6). Clearly, this article extends game theory from evolutionary game theory to epigenetic game theory.

This comment mainly focuses on potential applications of epigenetic game theory in plants.

1. Origin and development of game theory

Although game theory was developed by Ernst Zermelo and John von Neumann in 1928, it was published for the first time in its entirety by von Neumann and Morgenstern [2] in 1944. Since the publication of its second edition, the literature on this subject has increased very considerably, though this literature mainly involves economic and

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sociological problems and statistical theory, in which subject the most famous works is the Nash equilibrium proposed by John Nash in 1950 [3] and 1951 [4]. Generally, game theory provides a formal language for the representation and analysis of interactive situations, where several players take actions that affect each other.

Game theory mainly has two branches, namely cooperative and non-cooperative game theories. The former assumes that the players can communicate and sign binding agreements, while the latter assumes that the players are either unable to communicate or able to communicate but cannot sign binding contracts. Since Smith and Price [5] introduced game theory to evolutionary and behavioral studies in the 1970s, its application in this area has developed rapidly. In essence, this theory was first developed by RA Fisher in his attempt to explain the approximate equality of the sex ratio in mammals. Clearly, the game theory has proven itself to be a particular use in biological studies [6].

There is no doubt that the confluence between statistical genetics and game theory will open a new direction in the future for genetic research in mathematical biology. In the long term, this will not only advance and promote the general theory of genetic mapping into medical and agricultural genetics, but also increase the application spectrum of game theory. Pfeiffer et al. [7] introduced game theory to investigate how the cooperation and competition of molecules lead to the evolution of ATP-producing pathways. As we know, production of a specific phenotype is a consequence of the trade-off between competition and cooperation among the underlying components pervasively expressed at different levels of organization. Thus, Zhu et al. [8] integrated game theory with genetic mapping of complex traits, and this provides new opportunities to enhance the precision and resolution of quantitative trait locus mapping for complex traits.

2. Potential applications in plants

Potential factor in the application of epigenetic game theory in plants and humans. The cooperation and competition mechanisms in epigenetic game theory are conditional on vigorous sperms and oocytes. If sperms or oocytes have no vigor, it may be necessary to incorporate new parameters in the current epiGame framework. For example, Ma et al. [9] demonstrated a correlation between zika virus and testis infection/damage and suggest that zika virus infection, under certain circumstances, can eventually lead to male infertility. Actually, this situation is more complicated in plants because genes control plant fertility and sexual reproduction requires recognition between the male and female gametes. For example, peptides have been identified as female attractants, while MDIS1–MIK is one receptor in the pollen tube perceiving the female attractants [10].

Genetic analyses of longitudinal datasets. Phenotypic values of traits at one time point, along with genotypic values of individuals, can be used to conduct genetic analysis. If these traits are measured at a series of time, the dataset is longitudinal. Although functional mapping has been developed, individual–individual interactions are not considered and phenotypic formation is not viewed as an evolutionary system. To avoid these shortcomings, Zhu et al. [8] integrated evolutionary game theory and functional mapping to estimate the genetic parameters that specify the dynamic relationship between competition and cooperation and to predict how genes mediate the evolution of this relationship in the formation of traits. These parameters and genes are helpful in the genetic dissection of complex traits. The epiGame framework in Wang et al. [1] is similar to the mathematical equations in Zhu et al. [8] to model the ecological mechanisms that drive the interaction and coordination of phenotype constituent components.

A mechanistic framework to model scion–rootstock interactions in plants. Grafting is an easy and rapid vegetative propagation technique, and it is widely used in horticulture and biology. To investigate the molecular mechanisms of graft-induced phenotypic variation in anatomy, morphology and production, much evidence of macromolecule transportation between scions and rootstocks was found. Wang et al. [11] consider that epigenetic modifications play potential roles in creating heritable phenotypic variation via grafting. Thus, they proposed a conceptual framework that characterizes and quantifies the driving mechanisms of scion–rootstock interactions toward vascular reconnection and regeneration. Of course, how to model graft-induced phenotypic changes needs to be addressed. If this theory is well established, it may be helpful for human organ transplantation and especially the improvement of organ matching efficiency.

Gene–gene interaction network. Gene regulatory networks play an important role in every process of life, including cell differentiation, metabolism, the cell cycle and signal transduction [12]. By understanding the dynamics of these networks, we can shed light on the mechanisms of diseases in human genetics and complex traits in animal and plant genetics. Although genes control complex traits or disease, the relationships among and between genes are

complicated, some genes cooperate and other genes compete. These relationships can be described by ODEs. This is similar to the epiGame framework.

3. Future issue

The epiGame framework is based on ODE. As described by Karlebach and Shamir [12], simple ODE systems can be formulated by an analytical solution, while large or complicated networks always require a numerical solution. When the number of ODEs is not too large, it is not difficult to estimate their parameters. In this situation, many algorithms, such as fourth-order Runge–Kutta algorithm, generalized profiling approach, Bayesian estimation, nonlinear mixed effects model method [1] and continuous optimization approach [13], are available. If the number of ODEs is too large, it is difficult to estimate their parameters. Therefore, this issue should be addressed in the future.

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