



Comment

A new concept: Epigenetic game theory
Comment on: “Epigenetic game theory: How to compute the
epigenetic control of maternal-to-zygotic transition”
by Qian Wang et al.

Xiu-Deng Zheng^a, Yi Tao^{a,b,*}

^a Key Lab of Animal Ecology and Conservation Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing, China

^b International College, University of Chinese Academy of Sciences, Beijing, China

Received 13 January 2017; accepted 16 January 2017

Available online 17 January 2017

Communicated by E. Di Mauro

The evolutionary significance of the interaction between paternal and maternal genomes in fertilized zygotes is a very interesting and challenging question. Wang et al. developed the concept of epigenetic game theory, and they try to use this concept to explain the interaction between paternal and maternal genomes in fertilized zygotes [1]. They emphasize that the embryogenesis can be considered as an ecological system in which two highly distinct and specialized gametes coordinate through either cooperation or competition, or both, to maximize the fitness of embryos under Darwinian selection. More specifically, they integrate game theory to model the pattern of coordination of paternal genome and maternal genomes mediated by DNA methylation dynamics, and they called this epigenetic game theory.

Epigenetic game theory assumes that each sex tends to maximize its fitness under Darwinian selection using a cooperative (C), or spite (S), strategy. According to this assumption, there are four possible interactions between the male genome and female genome for both sexes’ methylation-dependent fitness in fertilized zygotes. These interactions can be represented by the matrix

$$\begin{array}{cc}
 & \begin{array}{cc} \text{Female} \\ C & S \end{array} \\
 \begin{array}{c} \text{Male} \\ C \\ S \end{array} & \left(\begin{array}{cc} \text{mutualism} & \text{predation on male} \\ \text{predation on female} & \text{antagonism} \end{array} \right), \tag{1}
 \end{array}$$

where the term “mutualism” means the mutually beneficial relationship between two sexes; “predation on male” and “predation on female” means the predation-prey relationship between two sexes; and “antagonism” means the antagonistic relationship between two sexes. Based on this definition, a differential equation is used to describe the

DOI of original article: <http://dx.doi.org/10.1016/j.plrev.2016.11.001>.

* Corresponding author at: Key Lab of Animal Ecology and Conservation Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing, China.

E-mail addresses: zhengxd@ioz.ac.cn (X.-D. Zheng), yitao@ioz.ac.cn (Y. Tao).

time evolution of the expected methylation levels of both paternal and maternal pronuclei in zygotes, which is given by

$$\begin{aligned} \frac{dg_P}{dt} &= F(g_P : \Theta_P) + H(g_M : \gamma_{P \leftarrow M}), \\ \frac{dg_M}{dt} &= F(g_M : \Theta_M) + H(g_P : \gamma_{M \leftarrow P}). \end{aligned} \tag{2}$$

Here g_P and g_M represent the expected methylation levels of paternal and maternal pronuclei, respectively; the terms $F(g_P : \Theta_P)$ and $H(g_M : \gamma_{P \leftarrow M})$ denote how the change rate of g_P depends on g_P (with parameter set Θ_P) and g_M (with parameter $\gamma_{P \leftarrow M}$), respectively; and, similarly, the terms $F(g_M : \Theta_M)$ and $H(g_P : \gamma_{M \leftarrow P})$ denote how the change rate of g_M depends on g_M (with parameter set Θ_M) and g_P (with parameter $\gamma_{M \leftarrow P}$).

As a special case that fits the observed methylation data well, the dynamics (2) is rewritten as

$$\begin{aligned} \frac{dg_P}{dt} &= a_P g_P^{-b_P} + \gamma_{P \leftarrow M} g_M^{-\lambda_{P \leftarrow M}}, \\ \frac{dg_M}{dt} &= a_M g_M^{-b_M} + \gamma_{M \leftarrow P} g_P^{-\lambda_{M \leftarrow P}}, \end{aligned} \tag{3}$$

where the authors show that the parameters in this equation can be estimated well using the observed methylation data. On the other hand, according to this equation, matrix (1) can also be equivalently expressed as

$$\begin{matrix} & & & \gamma_{P \leftarrow M} \\ & & \text{Positive} & \text{Negative} \\ \gamma_{M \leftarrow P} & \begin{matrix} \text{Positive} \\ \text{Negative} \end{matrix} & \begin{pmatrix} \text{mutualism} & \text{predation on male} \\ \text{predation on female} & \text{antagonism} \end{pmatrix} \end{matrix} \tag{4}$$

Thus, the signs of the parameters $\gamma_{P \leftarrow M}$ and $\gamma_{M \leftarrow P}$ denote the interrelation between male and female genomes for their expected methylation levels. These then provide the fundamental framework of epigenetic game theory.

There is no doubt that this is a very interesting study, and it provides a new possibility for us to understand the evolution of epigenetics. However, some fundamental questions are still not very clear:

- (1) Although it seems reasonable to take the interaction between male and female genomes in fertilized zygotes as a game, the question is whether there is the conflict of interest between male and female genomes in a fertilized zygote. If we are unable to define clearly what are the benefits of male and female genomes in fertilized zygotes, why do we need to use game theory to characterize the interaction between male and female genomes? On the other hand, the authors say that the interaction between male and female genomes maximizes the fitness of embryos under Darwinian selection, but do not say how to define the fitness of embryos. So, the definitions of the basic concepts involved in epigenetic game theory should be made clear first.
- (2) The matrix (1) is key to how epigenetic game theory can be used to understand the interaction between male and female genomes in fertilized zygotes, in which there two possible strategies for both sexes, called “cooperation” and “spite”. A natural question is what this matrix tells us. For example, for standard evolutionary game theory, the payoff matrix is used to find a Nash equilibrium strategy [2–4], or an evolutionarily stable strategy (ESS). On the other hand, as a game, “player”, “game rule”, “strategy” and “payoff” are the four most basic elements. For epigenetic game theory, even if we accept male and female genome as two types of players, and “cooperation” and “spite” as two possible strategies, it is still unclear how the “game rule” and “payoff” are defined in this game.
- (3) From the game-theoretic perspective, methylation-dependent fitness is a very important concept. However, Eq. (2) only shows how the interaction between male and female genomes affects their expected methylation levels but does not show how methylation-dependent fitness is affected by the expected methylation levels of the two sexes. Specifically, even if we assume that Eq. (3) can correctly characterize the dynamics of expected methylation levels of male and female genomes (for example, the authors said that the parameters in Eq. (3) can be estimated well using observed methylation data), matrix (4) based on the signs of parameters $\gamma_{P \leftarrow M}$ and $\gamma_{M \leftarrow P}$ is still unable to give an appropriate game analysis because it cannot provide a logical judgment for which one of the interaction

pairs (or strategy pairs) $(\gamma_{M \leftarrow P}, \gamma_{P \leftarrow M}) = (+, +), (+, -), (-, +), (-, -)$ will be favored by Darwinian selection. That is, Eq. (2) (and Eq. (3)) is a model based on biochemical reaction dynamics rather than a game model. Of course, the statistical analysis of the observed methylation data may help us to understand the interrelation of paternal and maternal pronuclei in a fertilized zygote.

- (4) Finally, we also notice that the mathematics of epigenetic game theory seems exactly the same as Zhu et al.'s [5] model called “Integrating Evolutionary Game Theory into Mechanistic Genotype–Phenotype Mapping”. Although we do not think that Zhu et al.'s model is a good example of evolutionary game theory, we would still like to know the connection between epigenetic game theory and Zhu et al.'s model.

Acknowledgement

This work was supported by the Natural Science Foundation of China (11401562 and 11471311).

References

- [1] Wang Q, Gosik K, Xing SJ, Jiang LB, Sun LD, Chincbilli VM, et al. Epigenetic game theory: how to compute the epigenetic control of maternal-to-zygotic transition. *Phys Life Rev* 2017;20:126–37. <http://dx.doi.org/10.1016/j.plrev.2016.11.001> [in this issue].
- [2] Maynard Smith J. *Evolution and the theory of games*. Cambridge: Cambridge University Press; 1982.
- [3] Hofbauer J, Sigmund K. *Evolutionary games and population dynamics*. Cambridge, England: Cambridge University Press; 1998.
- [4] Nowak MA. *Evolutionary dynamics*. Cambridge: Belknap Press; 2006.
- [5] Zhu XL, Jiang LB, Ye MX, Sun LD, Gragnoli C, Wu RL. Integrating evolutionary game theory into mechanistic genotype–phenotype mapping. *Trends Genet* 2016;32:256–68.