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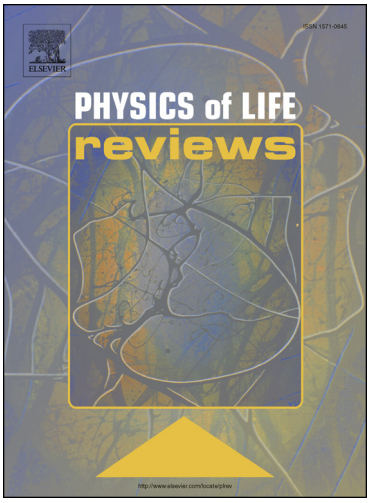


Game theory in epigenetic reprogramming

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**Title**

Game theory in epigenetic reprogramming: Comment on “Epigenetic game theory: How to compute the epigenetic control of maternal-to-zygotic transition” by Q. Wang, K. Gosik, S. Xing, L. Jiang, L. Sun, V.M. Chinchilli, and R. Wu

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**Article**

Von Neumann and Morgenstern published the “Theory of games and economic behavior” in 1944, describing game theory as a model in which intelligent rational decision-makers manage to find their best strategies in conflict, cooperative or other mutualistic relationships to acquire the greatest benefit [1]. This model was subsequently incorporated in ecology to simulate the “fitness” of a species during natural selection, designated evolutionary game theory (EGT) [2]. Wang *et al*. proposed “epiGame”, taking paternal and maternal genomes as “intelligent” players that compete, cooperate or both during embryogenesis to maximize the fitness of the embryo [3]. They further extended game theory to an individual or single cell environment. During early zygote development, DNA methylation is reprogrammed such that the paternal genome is demethylated before the maternal genome. After the reset, the blastocyst is re-methylated during embryogenesis. At that time, the paternal and maternal genomes have a conflict of interest related to the expression of their own genes. The proposed epiGame models such interactive regulation between the parental genomes to reach a balance for embryo development (equation (2)).

To demonstrate epigenetic regulation, Wang *et al.* formulated ordinary differential equations (ODE) to link sex-specific DNA methylation with expression of the corresponding genes (equation (6)). During pre-implantation epigenetic reprogramming, imprinted genes escape DNA demethylation [4] to retain the parental epigenetic memory. They are expressed in a parent-of-origin-specific manner in that they do not follow the rule of inheritance in which both alleles in a heterozygote are equally expressed, and a normal level of DNA methylation is required to control paternal and maternal allelic expression [5]. Therefore, known imprinted genes may serve as a benchmark dataset for validating the parental effect from DNA methylation; *i.e.*, parameters $\gamma_{k\leftarrow P}$ and $\gamma_{k\leftarrow M}$ that specify a sex-specific DNA methylation effect on gene expression in equation (6).