A mathematical view for ordinary differential equation models
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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Qian Wang et al. have written an interesting article to propose a modeling framework named epiGame in this issue of Physics of Life Reviews [1]. The epiGame framework models how the methylation state of paternal and maternal genomes regulates the embryogenesis 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. Qian Wang et al. also provide solid simulation studies and real data analysis to validate the correctness of their epiGame framework. The importance of embryo development and fertility mechanism cannot be overemphasized, hence, I think that the present review by Qian Wang et al. will stand as a useful modeling guide for practicing biologists or researchers in fertility health to quantify how sperms and oocytes interact through epigenetic process to determine embryo development. In addition, it will serve as a source of many important references to work in the reproductive biology field.

As the authors introduce a very broad topic, it is expected that one paper would not be sufficient to cover all aspects of relevant discussion. In their assessment of the evolutionary interactions between DNA methylation of the parental and maternal genomes, the authors of present review proposed two promising ordinary differential equations (Equations (2) and (6) in their review article [1]). It is true that ordinary differential equations (ODEs) have great power to model the dynamic trajectories of multiple variables changing over time while

maintaining cooperation, interaction, or competition between these multiple variables. However, the dynamics of multiple variables are more than calculations of numerical solutions and estimates of parameters. Based on the mathematical aspects, some questions arise: will an ODE give a good fit? Will the dynamic relationship of parental and maternal genomes be thoroughly captured if the numerical solutions of the ODE are achieved? Central to such questions are actually the theoretical properties of ODEs. An ODE must be stable to guarantee that its biological application is meaningful. Specifically, it will be impossible to quantify how exactly different parties compete or cooperate to regulate embryogenesis for an unstable differential equation system.

Take the ODE, $\frac{dy}{dt} = f(y)$, as an example. Its equilibrium point (or steady state) is defined as the roots of $f(y)$, say $y(t) = c$ [2–6]. Equilibrium is a steady state in which parental and maternal genomes gain a balance through their mutual coordination (either cooperation or competition, or both) and maximizing the fitness of embryos in the end. The existence of an equilibrium indicates that the parental and maternal genomes intersect (i.e., epigenetic modification). The equilibrium solution $y(t) = c$ is stable if all solutions with initial conditions y_0 near $y = c$ approach c as $t \rightarrow \infty$ [2–6]. It means that these multiple variables remain unchanged from a steady state after the balanced is achieved, in the absence of all other external influences outside of the factors considered in the ODE modeling. On the contrary, if the system never returns back to its equilibrium after small disturbances, then the equilibrium is unstable. For an unstable ODE, the regulation of the embryogenesis by the methylation states of the paternal and maternal genomes will differ drastically over time. As a result, the stability of an ODE model will be investigated in the future work to capture the long-term behavior of the trajectories.

In conclusion, Qian Wang et al. present an interesting and new modeling direction. My emphasis on this does not seek to invalidate the ODEs proposed by Qian Wang et al., instead it serves as a complementary note. I hope that my mathematical view, coupled with the epiGame framework that Qian Wang et al. proposed, will eventually make it possible to better model and interpret the interplay between parental and maternal genome.

Acknowledgements This work was supported by National Science Foundation

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