Understanding the Mechanisms of Biological Events by Using Mathematical Modeling

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Although biological events proceed according to mathematical rules, it is not easy to bring these two disciplines, biology and mathematics, together in actual research. In my lecture, I would like to present some examples showing how mathematics is important to understand the basic mechanism of biological events.

Our group has been analyzing the mechanism of the somite segmentation clock, which regulates the periodic formation of somites. Somites are metameric structures, which later give rise to the vertebral column, ribs, skeletal muscles and subcutaneous tissues. In mouse embryos, a total of ~65 pairs of somites are formed sequentially from the rostral to caudal orientation, and each pair is formed every two hours under the control of the segmentation clock. We found that the transcriptional repressor Hes7 is expressed in an oscillatory manner with a period of two hours during this process. Both the loss of expression and sustained expression of Hes7 lead to fusion of somites and somite-derived tissues, indicating that oscillatory expression of Hes7 is required for somite segmentation. Hes7 oscillation is regulated by negative feedback with delayed timing, and this dynamic expression has been mathematically simulated by differential-delay equations. We found that reducing the number of introns within the Hes7 gene shortens the delay and results in abolishment or a more rapid tempo of Hes7 oscillation and somite segmentation, as predicted by mathematical modeling.

We also found that Hes1, a Hes7-related transcriptional repressor, is expressed in an oscillatory manner by many cell types, including neural stem cells. In these cells, Hes1 oscillation drives cyclic expression of other factors, and oscillatory expression of these factors is very important for proliferation of neural stem cells. Interestingly, gene expression oscillates in phase between neighboring cells during somite segmentation but out of phase between neighboring neural stem cells. These different oscillatory dynamics can be explained by a unified mathematical model.