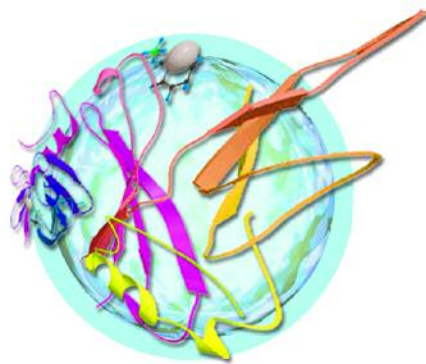


Analyzing networks in embryos



Biological processes, such as development, are built on complex networks of chemical reactions. Rustem Ismagilov at the University of Chicago explains his fascination for studying these networks. “I’m very interested in chemical networks, especially those that have spatial and temporal components,” he says. “Certainly, development is a fantastic example of such a process because dozens, even hundreds, of different processes take place exactly at the right place at the right time.”

Ismagilov teamed up with Elena Lucchetta, a graduate student in his lab; Nipam Patel, a professor of integrative biology at the University of California, Berkeley; and other colleagues to investigate the mechanism that compensates for variation during the embryonic development of *Drosophila melanogaster*. The investigators exposed the fruit fly embryos to an unnatural environment in a microfluidic device and discovered that the embryos could compensate for environmental perturbations and still develop normally (*Nature* **2005**, *434*, 1134–1138). According to Shuichi Takayama at the University of Michigan, the investigators did “a really good job of using microfluidics to ask a significant biological question.”

In their experimental approach, Ismagilov and colleagues created a PDMS microfluidic device that could be constructed around a live embryo in 1 min. The device was built as interlocking top and bottom halves. A piece of double-sided tape was stuck on the bottom half of the device, and the embryo was placed on the tape. The second half snapped on top of the first, like two Lego blocks, to complete the device.

While in the device, the embryos were exposed to temperature differences that they wouldn’t normally encounter in the wild. The investigators created a temperature step across an embryo by introducing two streams of solutions into the device by laminar flow. One stream was

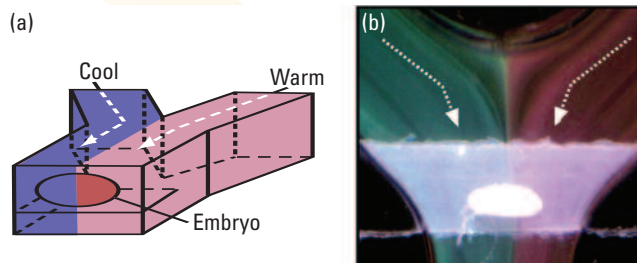
assumed that the temperature perturbation would disrupt the embryos’ growth into larvae. Although the halves that were exposed to warmer temperatures developed faster than their cooler counterparts, the embryos ultimately grew into normal larvae.

Ismagilov and colleagues concluded that compensatory networks in the embryos counteracted the effects of the environmental perturbations. By applying time-specific reversals of the temperature step, they found that the compensatory networks were activated within 65–100 min after the start of embryonic development. This time period could provide a clue about the nature of the compensatory networks.

These days, the researchers are analyzing the compensatory networks in greater detail by combining their microfluidic approach with a genetic approach in which a particular gene is removed to form mutant embryos. “If you combine the two [methods], it might be really powerful,” says Lucchetta. “You [could] see individual molecular interactions but also [observe] how they function in the network in space and time.”

Experts say that the method used by Ismagilov and colleagues to tackle the analysis of chemical reaction networks is particularly noteworthy. “The work represented in this paper is one of the most impressive examples of chemists, engineers, and biologists getting together to use cutting-edge tools from each of their systems,” says David Bilder at the University of California, Berkeley. “This [work] is a real harbinger of a future trend.”

—Rajendrani Mukhopadhyay



(a) A schematic drawing of a fruit fly embryo developing inside a PDMS microfluidic device. (b) Thermo-chromic liquid crystals show a temperature step inside a microfluidic device. The green stream is at 21 °C, and the red stream is at 24 °C. (Adapted with permission. Copyright 2005 Nature Publishing Group.)

heated and the other was cooled so that the half of the embryo along the anterior–posterior axis was exposed to a warmer temperature than the other half.

Creating a temperature step by laminar flow was easier said than done. “Fluids are quite thermally conductive,” explains Ismagilov. “You have to fight thermal diffusion, which is rapid. For example, if you were using proteins to create a step in concentration, that [would be] a lot easier because diffusion is much slower.” Ismagilov also points out that, in contrast to chemicals, heat can be lost to the walls of the device or tubing.

Embryos were exposed to the temperature step (17 °C/27 °C or 20 °C/27 °C) for 150 min and then returned to room temperature. The densities of nuclei in the two halves of the embryo were monitored to track the rates of development. The investigators originally