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Reply to Zhang et al.: The critical temperature dependence of developmental rates is in search of a mechanism

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The observation that the rate of development scales with temperature T as $(T - T_C)$ for a broad range of animals is very interesting as it strongly suggests a common mechanism, yet an explanation for it is currently lacking. Zhang et al. (1), in their letter responding to our recent study on developmental timing in *Caenorhabditis elegans* (2), suggest this temperature dependence is due to development taking place near a critical point, with T_C the critical temperature. If correct, it would imply that similar conceptual mechanisms underlie processes as diverse as phase transitions in inanimate matter and development in complex multicellular organisms.

However, an explanation based on similarity to critical phase transitions should account for a number of observations. First, temperature dependence can be more complex than reported by Zhang et al. (1). Recently, Olmedo and coworkers (3) measured temperature dependence of *C. elegans* larval development at high throughput. Interestingly, they also find that the developmental rate scales as $(T - T_C)$, with T_C similar to the value determined by Zhang et al. from our data. The rate of the molts, a developmental substage, shows a similar temperature dependence, however now with a significantly lower T_C. Moreover, when we shifted temperature middevelopment we observed major changes in event order (2). Both observations appear in contrast with the prediction that near a critical point all developmental rates show exactly the same temperature dependence.

Second, we observe temporal scaling also for changes in timing that are independent of temperature, for example for intrinsic variability in timing between individuals (2). It seems unlikely that maintaining temporal scaling relies on distinct mechanisms, depending on whether temperature or other conditions are changed. A theory based on critical points should therefore explain changes in the developmental rate beyond temperature dependence only. We suggest that this could be achieved by taking into account metabolism. Decreasing temperature likely slows developmental rates by lowering the rate of key biochemical reactions. Lower metabolite levels, due to changes in diet or misregulation of metabolic enzymes, probably have a similar impact on biochemical rates.

Zhang et al. (1) speculate that critical behavior could be due to a single transcription factor that therefore must be conserved between widely disparate animals. However, recent theoretical studies have shown that simple behavior, in terms of temperature dependence (4) or recovery dynamics (5), can emerge from complex reaction networks independent of the details of individual interactions. A more parsimonious explanation might thus be that critical temperature dependence arises from general properties of the metabolic or genetic networks that control development, rather than from the action of any specific molecule.

Finally, it was found that the rate of individual developmental substeps often follows the Arrhenius rule, scaling with temperature as $\exp(-\text{const}/T)$ (4, 6, 7). This is qualitatively different from the critical temperature dependence noted by Zhang et al. (1). How these two different temperature relationships can be reconciled and, more generally, how critical temperature dependence emerges from the networks that control development will be important experimental and theoretical questions.

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