

## Time for Chronomics?

**E**ver since the derivation of the theory of relativity, physicists have done reasonably well in understanding time; however, biologists are still waiting for a comprehensive theory of timing in living systems: a corpus of “laws” describing how cells and organisms can precisely initiate and terminate processes at specified times. This deficiency is particularly acute in developmental biology, where complex mechanisms of various paces and durations must be orchestrated to solve huge developmental problems such as the one faced by the fertilized egg: how to become an organism.

Animal development is, in fact, nothing but time. From the cell cycle to the beating of the heart, our own lives are composed of a multitude of microscopic and molecular oscillations. For developmental biology, the study of causal relationships implies the examination of two time points: inducing the cause and looking at the effect. We are generally ignorant of the temporal rules governing this transformation. Whereas the rules of a Swiss watch involve a timing mechanism that uses a uniform unvarying tempo to translate rapid oscillations (seconds) into longer periods of time (hours), the rules

of the developmental clock of animals are much more complex. The animal clock is made up of a variety of counting mechanisms that follow varied temporal rules at different frequencies and often run in parallel without any apparent interaction with each other. The goal of the developmental clock is not simply to mark off time, but to integrate and unify the myriad temporal signals received from throughout the organism.

However, the frequencies and amplitudes of most, if not all, developmental clocks are robustly determined within the same species, suggesting that these are genetically encoded devices instead of being produced by the system itself, as an emerging feature. But if time is encoded in our DNA, what are the genetic balance wheel, hairspring, and gears, and what are the specialized tools that are needed to elucidate the intricate workings of the genome? There are two possibilities to consider here. The first one concerns clocks generated by mechanisms in *trans*, generally based on the postulate made in the early 1950s by Alan Turing (mathematician, philosopher, and inventor of the concept of the computer), who argued that the diffusion of substances with activation, repression, and retroactive potentials can generate intrinsic oscillations in space and time. We are beginning to decipher some of these (see the articles in this special issue) and more are likely to come in the near future. The second possibility involves mechanisms in *cis*, using the linearity of our genetic material itself, our chromosomes, to measure time; an admittedly elegant solution, but one that severely lacks both experimental and theoretical support.

Can we expect some help from genome sequencing and related high-throughput technologies? There is little doubt that the mechanisms in *trans* will be advantageously studied in this context. Time-lapse proteomics, adapted to minute amounts of material such as cohorts of less than a thousand cells, would certainly show significant recurrences and, perhaps, allow the temporal algorithms underlying developmental clocks to be uncovered. For example, the tightly regulated timing in the successive appearance of whiskers on the nose of a rodent would likely be deciphered if we could microdissect the whisker field like a chess grid, and submit each square to full protein content analysis.

On the other hand, the challenge in identifying *cis* processes would be to use several species showing graded variations in clock parameters, such as in the frequencies of the same clock, and to find correlations with the *cis* organization of DNA segments through a large-scale approach. Such correlations, if any, could reflect the existence of linear time-measuring devices, from the mere duration of transcription to more complex processes such as progressive transitions in the chromatin state. However, that is easier to say than to do; a genuine “casse-tête” for bioinformaticians.

It might appear a bit pretentious to try to extract the fourth dimension out of our DNA when we still lack complete understanding of the other three dimensions. But this is the privilege and the difficulty of working with embryos: The spatial construction can be understood only in the light of time. Similarly, evolutionary genomics will likely teach us what happened during phylogenetic times, and our ontogenic clocks may be revealed by global comparative analyses. Chronomics is on the way.

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