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Spatiotemporal mechanisms of life

Understanding how organisms measure and respond to space and time at a physical and chemical level is at the heart of a mechanistic understanding of life.

As physical beings, individual cells and whole organisms are bound by the four dimensions occupied by space and time. At a quantum level, the presence of additional dimensions and the so-called strings and black holes that define them has been hotly debated; however, in biological systems a precise mechanistic understanding of how organisms react in four dimensions is only now emerging. Though measuring certain kinetic parameters—such as the order of events in a signaling cascade or individual rate constants for enzymatic reactions—is relatively straightforward, a full understanding comes from knowledge of the interplay between space and time. Organisms and the cells that compose them have finite size and age features, and decisions such as when to stop growing and when to divide are also inherently 'where' questions. A stem cell, for example, has no need to differentiate and divide if it is sitting within an intact tissue, but as the needs of the tissue change or as nearby damaged tissues are encountered, new growth becomes necessary. Continuously monitoring the spatial environment ensures that the mechanisms inherent to cellular processes can be timed appropriately.

We have a limited mechanistic understanding of the timing of events beyond individual enzymatic reactions, yet we understand intuitively how humans and other organisms perceive time. Generally, the activities of humans (as whole organisms) are dictated by the environment, and we set watches to maximize the number of awake hours while the sun is out. These sleep-wake cycles, or circadian rhythms, occur on the timescale of days and months. At the organismal level, daily oscillations come about through coordination of tens of thousands of neurons situated in the suprachiasmatic nucleus. At the cellular level in peripheral tissues, oscillations in gene expression arise due to time delays between activation and repression within coordinated transcriptional loops (reviewed by Kay, p. 630). As described by Buonomano, it becomes difficult to translate this timing mechanism to the level of chemical and molecular interactions occurring on timescales that differ from the circadian rhythms by up to 15 orders of magnitude (Commentary, p. 594). Indeed, there are numerous biological solutions to telling time, and they use divergent mechanisms across the different timescales. For example, Buonomano discusses how neurons are capable of telling time on the scale of tens to hundreds of milliseconds based on their firing dynamics. The molecular clock that is born from this, by virtue of controlling cellular processes, controls the organization of the three spatial dimensions.

On the other hand, in biological systems the fourth dimension, time, can be born from the three dimensions of space. A yeast cell that doubles every two hours does so because its internal measurements and gauges report that a certain DNA and cell volume has been reached. Similarly, the timing of numerous cellular processes such as cell signaling and the immune response are regulated by the isomerization of proline residues (Review, p. 619). The ubiquitous enzyme Pin1 is responsible for the slow proline isomerization and thereby dictates the conformation of various substrates and their ability to perform their dedicated functions or be recognized by their enzymatic counterparts.

Research on telomeres, the specialized ends of chromosomes, reveals another connection between space and time. The length of telomeres is directly related to the age of an organism. Telomeres are shortened at each cellular division because of the inability of DNA polymerase to copy chromosome ends, but these missing ends can be regenerated by the reverse transcriptase telomerase. Because the quantities of telomerase are limited, each cellular division risks a loss of critical pieces of DNA. At the opposite extreme, too much telomerase as a consequence of either mutation or recombinant expression in hopes of extending a cell's or organism's life span can lead to uncontrolled growth and cancer. Blasco reviews the delicate balance of how telomere length is dictated and also how DNA length dictates time (Review, p. 640).

An intriguing feature of zebrafish fin growth lends further credence to the model in which space and time are interrelated. When amputated, fins grow back in the same amount of time whether they are fully amputated or only cut back by a small amount (Perspective, p. 614). Once a final position (in space) is reached, the process stops (in time).

Our understanding of the timing of molecular events in cells will be greatly aided by fluorometric methods such as those described by Miyawaki (Commentary, p. 598). These techniques are based on the different fixed rates of maturation of the chromophores of variant green fluorescent proteins. For instance, E5, a variant of the red fluorescent protein, has been used successfully to determine the timing of gene expression. As an extension in the space dimension, bimolecular fluorescence complementation with its superb sensitivity is predicted to be able to probe the timing and location of molecular events deep within tissues. Such strategies that cause minimal disruption to a living organism will help us to combine the spatial and temporal dimensions to achieve a true four-dimensional picture of life processes, with the ultimate goal being an understanding of how an entire organism builds itself. This goal is shared by Silver, a biologist who has generated yeast that can report their cell division status and therefore count (Elements, p. 603).

In this issue, each of the Commentaries, Reviews and Perspectives demonstrates some aspect of the measurement or control of space and time in biological systems. They also demonstrate that an understanding of the basic measurements made by cells, whether it is the length of a DNA stretch, the length of a zebrafish fin or the number of daylight hours, helps us to restate the fundamental question of how biology works in space and time in specific mechanistic terms. ■