Jim's View: Analog to Digital Conversion in Biology

One of my many failings is that I am not usually very observant of what is going on around me. For example, as a student, walking daily for months into the Harvard Biological Laboratories, I somehow completely failed to notice the dramatic life-size statues of rhinoceres (Fig. 1) flanking the entrance. Then, one day all of a sudden I saw them! This all-or-none recognition was genuinely shocking, and made me wonder how I could not have seen what I finally saw on that day? Certainly "recognition" is an emergent property of the nervous system, but could it have a more fundamental basis in cellular biology?

Many years later a similar event took place which made me think it could. In addition to animals, I confess to never having paid much attention to plants (bad habits for a biologist, perhaps accounting for why I became a biochemist enthralled with the properties of ground-up extracts of animals and plants, which all look about the same). But there have been rare exceptions. On one particularly memorable occasion, after two decades of annually driving down the same Rocky Mountain road in Colorado returning from Keystone Conferences, I looked up and for the first time noticed that the trees seemed to disappear in an all-or-none fashion. My wife, also a scientist, kindly informed me that my revelation was not entirely original, and was termed the "tree line."

I wondered whether these plants make some sort of virtually all-or-none decision, a recognition really, based on an overall assessment of whether they can thrive. Perhaps they recognize whether they can successfully grow or not – and act accordingly. Presumably, each plant assesses a combination of factors as air, water and light. Each of these factors (signals) is itself quantifiable as a continuous variable. The plant must then measure these and other variables and execute a binary decision based on the combination of them it finds in its environment, essentially converting analog (continuous) signals into a binary (digital) outcome. How could this happen?

In fact, we are immersed in a world of analog-to-digital conversion, for example in the ubiquitous digital cameras in our iPhones. In electronics, an analog-to-digital converter is a system that converts a continuous analog signal into a discrete quantized value. For example, an input analog voltage may be converted into a digital number. Typically, the digital output is a two's complement binary number that is proportional to the input, but there are many other possibilities (from Wikipedia). It seemed to me that some version of analog-to-digital conversion might explain the relative sharpness of a tree line.

In chemistry, phase transitions bear fundamental similarities to analog-to-digital conversion. Phase transitions are an all-or-none, binary behavior in the arrangements of molecules in which a continuous (analog) value such as temperature or solute concentration triggers sharp change at a critical value. For example, we are all familiar with the fact that ice melts to water when it is heated to a critical temperature (whose value is the definition of 0^{o} Centigrade). In more compositionally complex systems, such changes of state (solid, liquid, gas) occur when any of its chemical components reaches a threshold value which varies systematically depending on the overall composition. In systems containing polymers, including proteins, subsets of proteins can separate dramatically from the bulk forming droplets within the mixture that can even have internal organization.

In thermodynamics, a multi-dimensional graph depicting how the threshold varies with the concentration of each component (each axis represents a different component) is termed a phase diagram. If we were to graph the binary outcome of tree growth as a function of the concentrations of relevant components in the environment, wouldn't the result approximate a phase diagram?

In fact, all-or-none behavior is a fundamental property exhibited by nearly all cells. Based on its compositional environment (by which I mean not only the concentrations of nutrients but also the concentrations of social signals in the form of growth factors, cytokines, components of the extracellular matrix, signaling molecules on the surfaces of neighboring cells, and so on) a cell continuously makes all varieties of consequential binary decisions. It can divide or stay in interphase; but it can't do both at the same time. It can differentiate to another cell type, or remain as it is, but not both. It can continue to live or trigger its own death, but not both. It can migrate to another location or it can stay in place. Cancers and no doubt many chronic diseases result when the phase diagrams governing these decisions are shifted, due to mutation or pathological environmental compositions, or both.

We know that cells make these kinds of decisions based on interacting signal transducing pathways involving surface receptors (mainly for the social factors) and intracellular sensors (mostly for nutritional factors). In my view, understanding how these continuous signals combine to result in binary, phase transition-like outcomes is perhaps the single biggest mystery in cell biology.

Recent and remarkable discoveries of actual physical phase transitions involving the components of the signal reception and processing machinery within cells may offer some hints of how this might work. For example, phase separated droplets form in the test tube and in vivo when multicomponent signal transduction networks combining numerous weakly interacting protein scaffolds reach critical concentrations. We now recognize that many prominent, classically described "bodies" within the nucleus (including nucleoli) are in fact dynamic phase-separated liquid-like condensates involving RNA and proteins. There are indications that individual transcriptional units and epigenetic inheritance involve phase separations. Phase separations of critical components have even been found at neuronal and in immunological synapses, suggesting that binary outcomes such as memory and immunological recognition may employ phase transitions.

Droplets have been analogized to "membrane-less organelles" because, like membrane vesicles, they are particulate and have distinct compositions. Certainly droplets differ from membrane-bound compartments in that droplets can form *de novo* while membrane-bound organelles only form from pre-existing membrane templates. But if, like membrane vesicles, droplets can bind motor proteins, then they could presumably transmit digitized signals from one location in the cell to another. For example, a signaling network of proteins assembling at the inner surface of the plasma membrane in response to extracellular signals could form a droplet that desorbs from the surface when it is complete, and then it could motor in to the nucleus, where it could then be adsorbed into a nuclear pore (which itself is filled with droplet-forming proteins), thereby transmitting a binary signal for transcription. This process would be entirely analogous to the budding and fusion of a membrane-bound transport vesicle, except that it would be far more flexible in evolutionary terms because droplets can add new cargo or machinery based on acquisition of a single binding domain, whereas inclusion of a new cargo in a membrane vesicle requires many steps.

Such speculations aside, we know virtually nothing about the detailed phase diagrams governing any of these kinds of intracellular signaling droplets. So there is a whole landscape of cellular biochemistry in front of us awaiting discovery of a fundamental basis of vital analogue-to-digital conversions in biology.

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Figure 1. Entrance to the Harvard Biological Laboratories, from https://dmg5c1valy4me.cloudfront.net/wp-content/uploads/2018/09/19142625/2018_losick_nobel_bl_rhinos.jpg
(NOTE: permission may be required)