20

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1. What are the most important problems in evolutionary theory?

The most important problems regard the evolutionary origins of innovation and the origins of cooperation. The first problem is very close to my research. A relatively small community of researchers work on it, perhaps because it is a very difficult problem. The key question is how biological systems are able to produce novel things, evolutionary innovations. This is one of the most important unsolved problems in (evolutionary) biology. Darwin's theory has essentially left it untouched. Although Darwin was aware of its importance, his theory was fundamentally unable to explain how genuine novelty can arise from the minor variants that natural selection acts upon. The importance of this question becomes clear by considering the political dimension it has taken in intelligent design (ID) creationism. This pseudoscientific current views evolutionary innovations as beyond the grasp of natural explanations. As I write these lines, its advocates have been quite successful in changing high school curricula in the United States to include teachings that evolutionary biology may be fundamentally unable to understand evolutionary innovation. I call ID pseudoscientific, because its fundamental tenet implies that we should stop trying to understand how evolutionary innovations arose.

In my group's work, we take the ability of biological systems to evolve innovations as a given, and ask a more specific question: Do living things have any special properties that allow them to innovate? Are these properties different from the principles on which systems engineered by humans are built? In this work, we focus on molecular systems, molecules such as proteins and RNA, regulatory systems such as transcription factor networks, and metabolic networks. There are two main reasons. First, ultimately, most evolutionary innovations can be understood as a sequence of small molecular changes in these systems. Second, to understand innovation, we need to understand the relationship between genotype (the genetic material of an organism) and phenotype (any observable feature of the organism). This understanding is easiest to come by in molecular systems. What we have learned from studying such systems is quite striking. Biological systems have an amazing internal flexibility or robustness. They can dramatically change their interior make-up, their genotype, while preserving their functional properties and phenotype. This robustness is crucial for their ability to evolve a wide variety of new features, features that are ultimately responsible for life's success on this planet.

Cooperation, the second paramount problem, I will discuss only briefly. Others in this volume will undoubtedly say much more about it. The origin of cooperation is important to all areas of biology. Take the evolution of multicellularity. How did cells, unthinking lumps of protoplasm "learn" to sacrifice life itself? Without this sacrifice, multicellular life would never have evolved. It arose more than a billion years ago, for reasons that we still do not fully understand. What we do understand, however, is that the cooperation of cells in the interest of a greater good has been important to life's phenomenal success. Another example involves societies, from insect colonies to human organizations. To understand how cooperation arises in them is key to understand their fabric, how conflicts are resolved in them, why conflicts sometime fail to be resolved, and how cooperation can be promoted. When applied to human societies, the problem also acquires a moral component.

2. What does your work reveal about biological evolution that other academics, citizens, philosophers, or biologists typically fail to appreciate?

My work touches upon many questions in evolutionary biology. I will merely speak to one class of problems that has occupied my group recently, the problem of evolutionary innovation. Let me first draw an analogy to politics, where we can distinguish two broad political philosophies: Conservatism, which attempts to preserve time-tested ways of living; and liberalism, which is more open to the new, and to changing the *status quo*. Liberalism and conservatism are opposite extremes of a spectrum, and on any one issue, it may be impossible to be both a liberal and conservative.

An analogous dichotomy can be found in the evolution of organisms, human or otherwise. Their features or phenotypes are often extremely well adapted to the world around them. However, this phenotype is constantly perturbed, either through mutations in the genotype, or through changes in the internal or external environment of the organism. We learned in recent years that phenotypes can be highly robust to such changes (e.g., Wagner, *Robustness and Evolvability in Living Systems*, Princeton University Press, 2005). But at the same time, it may be necessary for organisms to change evolutionarily and to innovate. Some such innovation may require entire new ways of making a living, such as the ability to use new food sources, or the ability to catalyze new chemical reactions. How do organisms preserve what works in the face of mutation, while at the same time being able to innovate? The axis liberalism-conservatism in the political analogy above corresponds to the axis robustness-innovation in the biological realm. It may seem that you cannot do both: You cannot be good at preserving the status quo, while being an innovator. But appearances can deceive. We and others have shown that organisms may accomplish an amazing feat. They may have found a way to avoid this dichotomy. Some systems we study show that the greater their robustness to change is, the greater is their ability to produce evolutionary innovation. For example, we have demonstrated this property for enzymes (e.g., Ferrada and Wagner, Proc. Roy. Soc. London Ser. B, 2008). We examined many different protein structures that differ in their robustness to genetic (amino acid) change, and analyzed the diversity of enzymatic reactions catalyzed by enzymes with a given structure. Such functional diversity is a past record of evolutionary innovation. We showed that proteins with highly robust structures – the phenotypes of proteins – have experienced more functional innovation in their evolutionary history then less robust proteins. It thus seems that phenotypic robustness facilitates evolutionary innovation. Others, including Jesse Bloom and Dan Tawfik, have demonstrated a similar phenomenon in the laboratory. They showed experimentally that protein folds more tolerant against amino acid changes also evolve new enzymatic functions more readily. Briefly, the reason is that highly robust systems can have many alternative genotypes with the same phenotype. This increases the likelihood that a mutation of any one such genotype produces a new phenotype that is the solution to a biological problem (in this case a problem of chemical catalysis). In the submicroscopic world of molecules and molecular networks, "conservatism" and "liberalism" are no contradictions.

3. What practical implications follow from your work on evolution?

Human engineers need to pay even more attention to how biological systems innovate than they do now. The usage of evolutionary principles in engineering is of course not new. Protein engineers mutagenize large populations of proteins in order to produce new functions. Metabolic engineers subject microbial populations to specific nutrient environments in order to evolve new metabolic abilities. And computer scientists employ evolutionary principles to solve difficult optimization problems or optimal design challenges. However, especially computational approaches are still too far from biological reality to mimic the success of biological systems. The key issue is how to represent genotypes and phenotypes computationally: In living systems from molecules to networks, genotypes relate to phenotypes in specific ways that facilitate innovation. For example, the sets of genotypes with the same phenotype are typically very large, and random changes in mutations of two different genotypes that have the same phenotype may yield completely different novel phenotypes. These two ingredients are important for the ability of biological systems to innovate, and our current engineering approaches take insufficient advantages of it.

4. What do you see as the most interesting criticism against your position in the biological or philosophical discussion of evolution?

The first point to highlight is not so much a criticism of my work, but the curious indifference of many biological researchers – in particular biomedical researchers – to evolution in general. We cannot make sense of the origins of disease, of genome architecture, of the workings of organisms, and of virtually any aspect of biological systems without taking an evolutionary perspective. The "why" is key to the "what" in biology. Yet many researchers have only the most naïve and rudimentary understanding of evolution. More generally, I have always been very curious about why different kinds of questions attract different individuals. Many of the scientific questions that might keep me awake at night would leave some of my molecular biology colleagues completely cold, and vice versa. What drives one's scientific interests? The likely cause is a complex mix of personal pre-disposition, access to good senior scientific role models, and social reward systems. This mix and its consequences might be worth studying further.

An issue closer to my personal research agenda is "hard selectionism". It is a view based on the (accurate) observation that most genetic variants occurring in populations affect the fitness of organisms at some point in their history. Their fate is thus determined by natural selection. From this view, a hard selectionist would conclude that neutral mutations, mutations that affect fitness not at all or too little to be visible to selection, do not matter in the evolutionary process. Hard selectionism is an old and established view, and perhaps the dominant view among evolutionary geneticists. It can be contrasted with neutralism, the view – largely refuted by whole-genome data – that most such variation does not affect fitness. Neutralism and selectionism have broad implications on our understanding of how evolutionary innovations arise.

Molecular engineering and evolutionary genetics work that focuses on phenotypes (molecular structures and functions, gene expression patterns, and metabolic abilities, to name a few) demonstrates a much more subtle relationship between neutral and other mutations. Specifically, recent experimental and computational work shows that robust biological systems – from molecules to networks – that can tolerate many genetic changes without losing their phenotype, have a leg up in producing evolutionary innovations, new phenotypes with new functions beneficial to the organism. Any given genetic change is more likely to be neutral in such robust systems than in less robust systems. However, neutral mutations may only be neutral shortly after they arise, and may become affected by selection later-on, after other genetic changes arise, or in a new and different environment. From this point of view, neutral mutations pave the way for adaptation, and may become beneficial (or deleterious) only later. The role of neutral mutations is analogous to the role exaptations play in morphological evolution.

Selectionism contains an interesting but subtle flaw that is symptomatic of how we like to view natural phenomena, namely in *essentialistic* terms. This means that we seem to have innate difficulties in viewing properties of biological phenomena as depending on the context in which they occur (although we pay much lip-service to such context-dependence). When applied to selectionism, this means that we have difficulty appreciating that a mutation that was neutral at some point in time may become either beneficial or deleterious later on, depending on other genetic or environmental changes. (Problems with essentialism are not new in biology. The problem of how to define biological species properly is another example of how our thinking can be plagued by it.) If, however, we can accept this notion, then we can accept the importance of neutral mutations for evolution, while at the same time embracing the importance of natural selection in explaining genetic variation.

5. Why were you initially drawn to research in evolutionary biology?

I still remember the day in school when we learned that many organisms are diploid, that they have two copies of each gene. I remember asking my high school teacher whether diploidy evolved because it protected against "failure" of genes. He was a competent teacher whose classes where rigorous and engaging, but this question baffled him. He just said evasively that the matter might not be quite that simple. (Unbeknownst to both of us he was right, but I would not learn that until a decade later.) I soon forgot about this question, and it would not re-emerge until many years later when I became interested in why biological systems – from genes to whole organisms – are robust to genetic change.

On a different occasion, our high school teacher introduced the concept of homeostasis in physiology. Our didactic introduction to homeostasis was not a biological system, mind you, but a flushing toilet. This rather lowbrow example illustrates the powerful yet simple principle that feedback regulation can use a sensor (a float connected to a valve) to bring a controlled variable (the water level in the toilet tank) back to a set point (the fully filled tank) after a perturbation (the act of flushing). Since my first exposure to it, I was fascinated by this abstract language, because it is able to subsume a great variety of biological phenomena into a single, generalizing principle. The teacher deserves a great amount of credit for exposing high school biology students to such material.

These two are the earliest occurrences I recall of themes that would later play an important role in my work: Questions about ultimate (evolutionary) causes rather than proximate (mechanistic) causes, and general principles that unify a diverse range of phenomena.

After high school, at the university level, I would train primarily in molecular biology. I was never an avid naturalist, interested in cataloguing and systematizing natural history. Fortunately for me, mine was among the first generations of biologists that could hope to have a career without being naturalists. Molecular biology attracted me, because it seemed to offer explanations about why organisms function they way they do. However, because molecular biology was about mechanistic explanations for cellular processes, it did not satisfy my taste for evolutionary questions. I also eventually tired of absorbing the innumerable details of complicated molecular process, for example, of the complicated networks comprising dozens of proteins that communicate information from the cell surface to DNA. What had seemed like a molecular explanation of biological processes to a beginning student, became a mere description once I had become sufficiently immersed in the literature. It did not help that none of my advisors in molecular biology encouraged me to pursue the questions I was interested in. I thus soon turned away from molecular and to evolutionary biology.

My interest in ultimate causes, combined with a taste for general principles, explains much of the direction my research has taken. To give one example, in recent years my laboratory has been studying the evolution of very different classes of systems, RNA and protein molecules, regulatory gene networks, and metabolic networks. The intent of this work is to identify deep and non-obvious commonalities between these systems that could explain how they produce evolutionary innovations. This is an ambitious goal, and it is not certain that we will be successful (but we will certainly be unsuccessful if we do not try.)

In sum, to me, evolutionary biology is not so much about cataloguing the diversity of life, or about explaining our place in it. Although I greatly respect those who dedicate their life to these problems, I was always drawn to the most general principles of biological organization, those which may hold for all of life. Evolutionary biology has been my access road to them.