

QnAs with Terence Hwa

Farooq Ahmed, Science Writer

Over the past two decades, molecular biologists have developed tools to investigate and manipulate cells in an unprecedented and fine-grained manner. Yet fundamental questions about cell behavior, such as how cells perceive and control growth rates, remain unanswered. Terry Hwa, a statistical physicist and a champion of interdisciplinary research at the University of California, San Diego (UCSD), thrives on challenges posed by basic questions about life. A key to Hwa's success is his ability to take a top-down approach: one that views organisms such as *Escherichia coli* as a whole entity rather than as a sum of its molecular parts. This approach, which combines theoretical modeling with quantitative experimentation, has enabled a predictive understanding of bacterial physiology. Hwa serves as the presidential chair and distinguished professor of physics at UCSD with a joint appointment in the division of biological sciences. He was elected to the National Academy of Sciences in 2020. PNAS recently spoke to him about his current research.

PNAS: Your Inaugural Article reveals a strategy by which bacteria sense and control their growth rate in response to changing conditions in the environment (1). Why is it important to understand bacterial growth?

Hwa: Many bacterial behaviors are organized by how fast they grow. For example, they coordinate much of their metabolism according to how fast they grow, with little dependence on the specific substrates they're growing on. As their growth rate varies, they utilize their molecular machinery differently. Growth affects what genes they activate and how they conserve when nutrient conditions are not favorable. Thus, to understand bacterial behaviors and responses, a prerequisite is to understand the context of their growth.

For us, however, there is a broader intellectual question: How does a cell like a bacterium, which comprises individual molecules and compartments of molecules, know how fast it is growing? Molecular biology focuses on the interaction of the components, but growth is about the whole. How does a cell know about the whole through the interacting components? That's the crux of what this study addresses.

PNAS: What did you discover about how bacteria sense growth rate?

Hwa: The molecule guanosine tetraphosphate (ppGpp) has long been known to inhibit ribosome biogenesis by controlling the transcription of ribosomal RNA synthesis. Without ribosomes, of course, proteins cannot be synthesized and growth stops. Therefore, growth rate decreases with increased concentrations of ppGpp, and this mechanism seems to be conserved across bacterial species. But



Terence Hwa. Image credit: Joyce Hwa (photographer).

what sets the concentration of ppGpp? It is known that ppGpp is sensitive to the presence of uncharged transfer RNAs, tRNAs that are not bound to amino acids. Upon nutrient depletion, the concentrations of uncharged tRNAs increase, and ppGpp shoots up. But there are more than 60 species of tRNAs in *E. coli*, any one of which, if depleted, will stop growth. How does ppGpp weigh contributions from different tRNAs so that it senses how fast the cell grows regardless of which tRNA may be limiting growth?

We measured ppGpp levels and the rate of ribosome elongation in *E. coli* under several conditions: during steady-state growth; during a period of diauxic growth, when bacteria shift from one carbon source to another; and during perturbations by antibiotics. We discovered that they always mirror each other with the same inverse relation. ppGpp appears to be listening to the activity of the ribosome, with ppGpp concentration doubling if the rate of elongation is halved.

This is a QnAs with a member of the National Academy of Sciences to accompany the member's Inaugural Article, e2201585119, in vol. 119, issue 20.

This article is distributed under [Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 \(CC BY-NC-ND\)](https://creativecommons.org/licenses/by-nc-nd/4.0/).

Published June 23, 2022.

This relationship immediately reveals a strategy by which ppGpp can simultaneously sense and control the rate of cell growth. On the one hand, ppGpp is spying on the elongation rate of ribosomes. On the other, it controls the concentration of translating ribosomes by controlling their synthesis and activity. Since the growth rate is given by the rate of protein synthesis, which is the product of the concentration of translating ribosomes and their rate of elongation, a unique relation is established between ppGpp concentration and the growth rate.

This relationship also explains how cells can keep track of all the disparate factors that affect their growth rate. Rather than auditing all the molecules—the uncharged tRNAs and their upstream amino acid synthesis pathways, etc., which would get very complicated—they do it in a single stroke by measuring the average rate of ribosome elongation, which itself integrates all these upstream factors and is limited by the slowest component. It's a very clever statistical scheme, a form of dimensional reduction, performed by bacteria. Protein synthesis is a prime example of where the whole emerges from the parts.

PNAS: You started working on biological systems after training in statistical physics. Why did you make the transition?

Hwa: I have always been interested in complex systems, and what's more complex than life? Biology intrigued me since I was an undergrad, but I didn't know how to integrate my interest in biology with physics and engineering, which were the focus of my attention then.

Statistical physics taught me that complexity often depends on how one views a system. A gas, for example,

can seem complex if one tries to keep track of the large number of colliding molecules, but simple in terms of characteristics such as pressure and temperature, which are related by the ideal gas law. I thought that, maybe, one day, the same could be done for biology. It is satisfying to see that the bacterial cell has also developed a simplistic view of itself, through ribosome concentration and activity.

PNAS: How has your background in physics informed your research?

Hwa: Physics has a successful track record of understanding completely new classes of phenomena, including thermodynamics and quantum mechanics. After looking carefully and quantitatively at related phenomena, physicists begin to see patterns, laws, which leads eventually to a deeper, predictive understanding.

This approach—relying on quantitative phenomenology—is rarely employed in modern biology, which has been very successful with a molecular or granular approach. Our quantitative, physiological approach has led my laboratory to establish a number of simple relationships between key physiological characteristics and has helped instill the view that behaviors of biological systems may also be governed by simple laws like those of physical systems.

It is through the work on ppGpp that we realized such simplicity reflects the cell's ability to extract a coarse-grained representation of its own state from complex molecular interactions. I hope this view may inspire others to discover additional strategies that bacteria and higher cells employ to extract important wholistic characteristics out of the zoo of interacting molecules.

1. C. Wu *et al*, Cellular perception of growth rate and the mechanistic origin of bacterial growth law. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2201585119 (2022).