

standard WF:  $G_u(x) = \frac{1}{2} \delta(x-x) u'(x)$   
 $\mathcal{D}(G) = C^2[0,1] \Rightarrow d\Omega_x = \delta_x$

$d\Omega_x^\pm(y) = \lim_{N \rightarrow \infty} dF_{N,Lx}^* = \delta_{0,1}(y)$

minimal & maximal processes:

$d\Omega_x^-(y) = \lim_{N \rightarrow \infty} dF_{N,Lx}^* \quad (y) = \delta_0(y)$   
 $d\Omega_x^+(y) = \lim_{N \rightarrow \infty} dF_{N,Lx}^* \quad (y) = \delta_1(y)$

Thus these GWF operators

$G_- u(x) = \frac{1-x}{2} [u(x) + xu'(x)]$ ,  
 $G_+ u(x) = \frac{x}{2} [u(x) + xu'(x)]$ .



By  $\Delta$  inequality

SLP  $\frac{1}{N}$   
 $i \in K_N$

$\| \cdot \| \left( \frac{1}{N} + \frac{\max(\delta, 1)}{N^4} \right) + \frac{2\|f\|}{\sqrt{N}}$

$F(z) = \int \dots$   
 $F(x) = \int \dots$   
 $\int_0^\infty \frac{\phi(x)}{v(x)} \pi(x,y) dx$   
 $\int_0^\infty \frac{\phi(x)}{v(x)} dx = \int_0^\infty \int_0^\infty \phi(x) \pi(x,y) dy dx$   
 $\int_0^\infty \phi(x) \pi(x) dx = \int_0^\infty \phi(x) \pi(x) dx$

# BIOLOGIST AT THE BLACKBOARD

## JOSHUA PLOTKIN AT PLAY WITH THE IMPOSSIBLE PUZZLE OF LIFE

BY MARK WOLVERTON

PHOTOGRAPHY BY SHIRA YUDKOFF

**“I stick out like a sore thumb in the biology department,” admits Joshua Plotkin. That’s because he’s a theoretician in a field that’s traditionally relied on fieldwork and laboratory experiments. Most of his work is done with a piece of chalk and a blackboard or even just pencil and paper. Yet with those simple tools, he’s trailblazing an entirely new direction in biology: applying mathematics to understand and explain the molecular workings of evolution, the guiding principle of all life.**

Plotkin always liked puzzles—the more complex and convoluted, the better. He started out as a pure mathematician, the type who works on ephemeral questions far removed from the real world. “I wanted to work on the most abstract and esoteric puzzles that we could think of,” he says, “and it was exciting to me that they were intangible.” But while finishing his undergraduate work at Harvard, he had what he calls, quite seriously and without exaggeration, “an epiphany.”

It was sparked by a course on evolution. “I’d had very little biology in college,” he recalls. “I didn’t really even know the details of the molecular basis of life, that there’s a DNA code and that strings of A’s, C’s, G’s and T’s encode proteins and that proteins are the building blocks of all life. It just struck me as completely impossible. How could all of life be encoded in such a simple way

and still be stable enough to function properly?”

To Plotkin, it was the most fascinating puzzle imaginable. “The question of how all this diversity of life arose seemed to me such an obvious and interesting question, almost the central enigma that faces us as living organisms,” he says, excitement and wonder still catching in his voice. “So why not work on that?” A year abroad at Oxford, where he had the chance to meet some of the leading researchers in evolutionary biology, cemented his new direction. “I never had a second thought. I just realized that’s what I wanted to do.”

After earning a Ph.D. at Princeton, Plotkin returned to Harvard for postdoctoral work, then joined Penn’s faculty in 2007 to take up posts in both biology and computer science. He’s the Martin Meyerson Assistant Professor in Interdisciplinary Studies, an appointment

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very much in keeping with his untraditional background and the eclectic nature of his work.

For much of its history, biology has been largely a descriptive science, relying mostly on observations of

**“I WOULD LOVE TO BE TOLD THE ANSWER, BUT EVEN BETTER, I’D LOVE TO FIGURE IT OUT FOR MYSELF.”**

living organisms and whatever experiments could be done in the laboratory. It lacked the mathematical rigor and predictability of the “harder” physical sciences. Plotkin observes, “I think the central problem for modern biologists, especially evolutionary biologists, is to be able to quantify our understanding, not of how life works in a mechanistic way, but more interestingly for me, how it evolves and how life forms change over time.” After the discovery of DNA and the subsequent

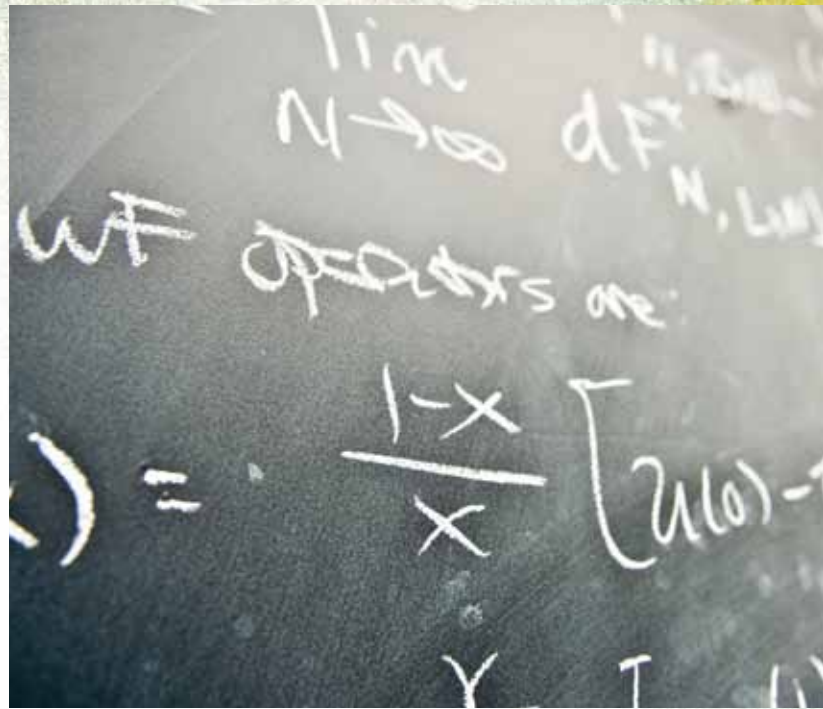
ability to sequence genomes and read the genetic blueprint of a particular organism, he explains, “we had finally the ability to quantify the rates at which changes are occurring at the molecular level that are in the end responsible for the kinds of evolutionary changes that Darwin was describing in the 19th century on a more macroscopic level.” Plotkin was in the ideal place to join this renaissance in biology because his mathematics background is perfectly suited to exploring this new frontier of evolutionary science.

The main subjects of his work are microorganisms, particularly viruses, because their generation times and mutation rates are far higher than larger, more complex organisms. “That gives us the practical advantage of actually being able to observe the changes that occur over 10 years as opposed to over 10,000 years,” he notes. By tracking the changes that occur in the genome of a virus or a bacterium over generations, Plotkin can study the factors that affect its evolutionary path. The processes revealed govern the evolution not just of microbes but ultimately all life, because as Plotkin

explains, “The rules of physics apply to a viral protein just as they do to a human protein.”

Because thousands of its genomes have been sequenced in recent years, the influenza virus is especially useful for such research, as is the *E. coli* organism. But the work can have more immediate payoffs. Better understanding of the evolution of the flu genome, for example, could allow some educated guesses about what mutations might arise next—leading to more effective vaccines targeted to those specific strains.

Much of the mathematical study of evolution involves probability theory, since randomness is an inherent element of the process. Just how random, however, is an open question and one of Plotkin’s chief interests. Part of what drives evolution involves how a particular mutation affects an organism’s “fitness,” or its ability to survive and prosper in its environment—more



## “HOW COULD ALL OF LIFE BE ENCODED IN SUCH A SIMPLE WAY AND STILL BE STABLE ENOUGH TO FUNCTION PROPERLY?”

fit organisms survive and multiply; less fit ones don’t, which is the essential idea that Darwin described in his theory of natural selection.

But some mutations persist even without any obvious enhancement of fitness. “Separating out the random processes from the Darwinian processes is the principal challenge,” Plotkin says. “I think it’s still unknown, for the most part, the degree to which genetic changes observed in natural populations are driven by randomness. That is an underlying and fundamentally important question to resolve. I would love to be told the answer, but even better, I’d love to figure it out for myself.”

Although Plotkin is doubtful that biologists will ever achieve the sort of deterministic certainty that allows astronomers to predict eclipses or calculate orbits with painstaking precision, he believes that the marriage of mathematics and evolutionary biology could eventually lead to some ability to predict evolutionary outcomes. “Statistical physicists can’t predict where every single one of a billion particles is going to be, but they can tell you

something about the likelihood of different outcomes,” he observes. “We can do the same thing in evolutionary theory, and people have started to develop such theories. We can’t tell you which exact mutations will occur next in a population, but we can tell you what types of outcomes are likely and what types of outcomes are unlikely.”

Aside from the role of randomness in evolution, another unanswered question involves what biologists call an organism’s “fitness landscape.” Plotkin explains, “It tells you for any possible genome how fast will that organism replicate, what will its fitness be. It’s a lot like an energy function in physics that tells you which of many different states is more likely to be observed. The fitness function for even a very simple biological organism is completely unknown.” That’s because the only way to truly define it would be to synthesize and study every possible genome of the organism and observe how it replicates, an impossible task. The only possibility is to look at the evolutionary pattern and extrapolate backward in time for clues about what sort of fitness landscape might have produced the observed traits, taking into account the specifics of the environment in which the organism evolved.

Plotkin is not so much a descendant of Darwin as of theoretical physicists like Albert Einstein and Niels Bohr. He works in a different field but uses similar



ISTOCKPHOTO / SZE FEI WONG

## FOREST GENEALOGY

Most of the time, biologist Josh Plotkin works at a chalkboard calculating the workings of life at the smallest scale, but sometimes his work leads into the field and to the larger view. “Nowhere is it more apparent that there’s a question about the source and origin of all the diverse life in front of you than when you’re sitting in the middle of a tropical forest,” he muses. “You can’t look anywhere without seeing some new life form you’ve never even observed before. It’s a place where it becomes a pressing question to you of how this arose.” How does such an incredible diversity of species, all competing for the same limited resources, evolve and coexist in the same environment?

To find out, Plotkin has ventured to Malaysia, Thailand and Indonesia, where despite steady deforestation, there are still large tracts of ancient tropical forest with intact ecosystems that have been exhaustively studied and catalogued. “As a result, we know the exact spatial arrangement and species identification of everything that’s coexisting in these little slices of forest,” he says, which ties directly into his work at the molecular level. “That kind of information coupled now with what’s emerging in molecular data, where we actually sequence the individual characteristics of individual trees and thereby can reconstruct which tree is the parent of another tree, allows us to understand how a forest was specifically assembled. That kind of information gives you an incredible view on the ecological question of diversification in tropical forests.”

There’s also a personal element to his tropical work. “It gave me a lot of inspiration to work in biology.” And perhaps even more important, he adds, “I got engaged to my wife in Borneo.”

—Mark Wolverton

techniques—analyzing, interpreting and building on data obtained by experimentalists to find new truths and develop new theories. “Most of my time’s spent at the chalkboard, I’d say 80 percent of my time,” he guesses. “Ten percent of the time is at the computer and maybe once in a while the lab bench, but very seldom. We have to use a computer, of course, when we try to reconcile a theory with data because massive amounts of data are generated. But computers are not used to actually develop the theory or to develop our expectations for how the data should look. That’s mostly pencil-and-paper work.”

As for the evolution of his own career, Plotkin considers himself a late bloomer who’s followed a rather unconventional path as a scientist: starting college intending to major in the classics, switching to advanced mathematics and now working as an evolutionary biologist. “But it’s fun to be at the beginning of a new field,” he says. “I think the circuitous route is more enjoyable. It gives you a different perspective.”

A trim, dark-haired man who looks more boyish than his 34 years, Plotkin is happily settled in at Penn. “Penn Biology is a very broad but fairly small department, and they’ve therefore been welcoming of a theorist in their midst,” he says. Although he’s a fairly new addition to the Penn family, he’s no stranger to the University. “My father actually attended Penn for college, and I recently found some old diary or something from my childhood. My dad had taken me to a reunion event at Penn,” he recalls, “and I wrote in this journal, ‘I definitely want to go to college at Penn.’ I didn’t actually attend Penn for college, but I ended up here as a faculty member—close enough.”

Finding new and original ways to explore and explain the basic mysteries of life will continue to be Plotkin’s abiding passion. “I do think that some of the neatest topics in biology border on the subjects of philosophy of biology and philosophy of life,” he says. “That’s something I think a lot of people can immediately appreciate. Physics and astronomy have amazingly vast questions to ask about the entire cosmos, and it can be exciting to think of those things, but somehow the fact that life is all around us and visible in front of us and completely unexplained seems to be an issue that everyone must face every day.” ♦

*Mark Wolverton is a science writer based in Bryn Mawr, Penna., and the author of A Life in Twilight: The Final Years of J. Robert Oppenheimer.*