MATHEMATICAL BIOLOGY

Master Class in Evolutionary Modeling

Steven A. Frank

How does one identify a significant idea? From the purely intellectual perspective, the great mathematician G. H. Hardy gave perhaps the best answer: "We may say, roughly, that a mathematical idea is 'significant' if it can be connected, in a natural and illuminating way, with a large complex of other mathematical ideas. Thus a serious mathematical theorem, a theorem which connects significant ideas, is likely to lead to important advances in mathematics itself and even in other sciences" (*1*). Hardy's definition of significance applies not just to mathematics but to any discipline.

Evolutionary Dynamics
Exploring the Equations of Life

by Martin A. Nowak

Harvard University Press, Cambridge, MA, 2006. 377 pp. $35, £22.95, €32.30. ISBN 0-674-02338-2.

Martin Nowak is certainly not alone when he argues, in *Evolutionary Dynamics*, that evolution is the single most significant idea in biology. But almost all major mathematical syntheses of evolution have been confined to population genetics—the study of gene frequency changes in populations. By contrast, Nowak (a professor of biology and mathematics at Harvard) follows up on Hardy's last qualification for a great idea by showing the many ways in which the mathematics of evolution lead to advances in diverse subjects, including cancer, game theory, and language.

Nowak's way of linking classical population genetics to the somatic evolution of cancer illustrates his approach. In one chapter, he gives a clear, step-by-step introduction to how sampling in small populations causes frequencies to fluctuate and how the directionality of selection balances against the randomness induced by sampling. Simple figures and basic equations lead the reader along to intuition and some classical results. The text emphasizes getting a start on the logic and translating the logic into basic mathematics.

With simple mathematical tools for finite populations in hand, Nowak turns in a later chapter to cancer. In many organs prone to cancer, such as the colon or skin, the tissue separates its cells into many small compartments. Each compartment renews continuously throughout life from a few long-lived stem cell lineages. Nowak develops the population genetics of these numerous isolated compartments to explore how somatic mutations accumulate over time in these populations. Using simple figures that match the biology of cancer genetics to the fundamental processes of population genetics, he shows how to write basic equations for the rate at which cancer progresses under different assumptions about how tissue architecture controls the size of local populations of cells and how particular genetic loci affect the processes of cellular birth and death.

The book does not emphasize new results; most of the theory Nowak discusses has been published previously. Nonetheless, the lucid presentation, drawing frequently on the author's own research, provides a uniquely compelling introduction to mathematical biology. Nowak aims to demonstrate the power of simple mathematics to illuminate diverse aspects of evolutionary analysis. He comments, "I will start with the basics and in a few steps lead you to some of the most interesting and unanswered research questions in the field. Having read the book, you will know what you need to embark on your own journey and make your own discoveries."

I have often wondered how to teach theoretical biology. There does not seem to be any decisive piece of knowledge or method. I know superb mathematicians who have written many mathematically elaborate papers about biology, each one missing the essence of the biological problem and so consigned to be neither good mathematics nor good biology. I know biologists with a vast knowledge of their subject who could never let go of the idea that mathematical models must incorporate every known fact of biology, rendering their models incomprehensibly complex expressions of biological fact forced into the austerely unforgiving language of mathematics.

Learning from the masters. An art student copying an oil painting in the Louvre, Paris.

When my own research on the sex ratios of fig wasps led me to some very abstract but powerful models on the evolution of sex ratios, I set out my own course for learning how to understand biological theory and how to make models. I decided to find a master work and to copy from it each day until the strokes seemed natural, and I could then modulate the technique to my own ends. Each day, I started with a blank piece of paper and tried to recreate the master work. I chose as my target W. D. Hamilton's famous model on sex ratio evolution in which males competed against their brothers in the mating arena (*2*). This was, perhaps, a lucky choice, because Hamilton's work easily satisfies Hardy's dictum for significance: no model has taught us more about the evolution of cooperation and competition and about how to formulate models that illuminate evolutionary process and can be tested empirically.

Evolutionary Dynamics provides a new generation with an

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opportunity to draw from the masters. To begin, read a chapter and get a feeling for the picture. Close the book. On a blank sheet, recreate the mathematical models. The math is very simple, but Nowak has nicely chosen significant problems that run deeply. At first, the task may seem impossible. But after numerous failures, each followed by a check against the book, you will start to feel the way of construction. Soon enough, you will be able to recreate the models. Then the fun begins. You will not like some of Nowak's assumptions about, say, how to model the evolution of language, or you will have your own ideas about how HIV evolves over the many years of an infection. The master becomes your foil rather than your target; you have started on your own research.

References

1. G. H. Hardy, *A Mathematician's Apology* (Cambridge Univ. Press, Cambridge, 1967).
2. W. D. Hamilton, *Science* **156**, 477 (1967).

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HEALTH, GENES, & ENVIRONMENT

Prosperous People, Penurious Genes

Steve Jones

Time, said Hamlet on seeing his father's ghost, is out of joint: he was no longer in the world he knew, but in a strange and alien sphere where the old laws no longer held. And that, according to Peter Gluckman and Mark Hanson in *Mismatch*, is becoming a global predicament: a man-made universe of riches in which man himself no longer feels at home.

Mismatch
Why Our World No Longer Fits Our Bodies

by Peter Gluckman and Mark Hanson

Oxford University Press, Oxford, 2006. 297 pp. $29.95, £16.99. ISBN 0-19-280683-1.

Shakespeare had an old-fashioned view of genetics: of Caliban, in *The Tempest*, he said: "On thy foul nature, nurture shall never stick." Mendel felt much the same, while Lamarck and Lysenko were each certain that the environment had an influence upon the next generation. All were to some degree right, and the boundaries of nature and nurture are far less distinct than once they seemed. Perhaps, developmental biologists Gluckman (University of Auckland, New Zealand) and Hanson (University of Southampton) suggest, today's lifestyle diseases can be traced to the mismatch between our current rich environment and our parsimonious genes—between the way we are and the way we used to be.

Fat runs in families but so do frying pans, which makes it hard to know whether DNA or dripping is more to blame for today's plague of obesity. My own generation—those now in middle age—may be the longest-lived in history, for they gained from the healthy diet of the 1950s while their successors are losing to the pressure to eat more and exercise less.

CREDIT: JOE SUTLIFF

Fat cats tend to have fat owners because of shared lifestyle rather than shared genes. Even so, changes in DNA can cause drastic changes in body weight. The *obese* mouse, with its fault in the satiety hormone leptin, offered the first hint of the complex mechanism of appetite control. The few children born with that mutation can be treated with the missing protein (although a vaccine against another such hormone as a means of weight loss has just been abandoned). Within the normal range, too, genes are involved, for identical twins experimentally gorged or starved tend to gain, or lose, avoirdupois to the same degree.

The search for other molecular culprits has been, if anything, too successful. The Human Obesity Gene Map has swollen to 250 loci, a number that beggars belief. Gluckman and Hanson make a convincing case that the environment and, crucially, the ghost of environments past each play a major role not just in fat but in many other attributes once confidently ascribed to simple Mendelism.

Mothers who smoke, or who have a poor diet, tend to have skinny babies (and the British press has put out scare stories about pregnant women smoking to ensure an easier birth). A tough time in the uterus damages the child in many ways. Underweight babies are at higher risk of adult hypertension and diabetes. They are also more likely to become obese in the modern world of surfeit, which does not match their deprived uterine experience, although in ancient times an impoverished fetus could expect a hard life as an adult and stored up reserves to match. Perhaps the best escape from that dilemma is to concentrate on the health of young women in the hope of helping the next generation

Birth weight has rather a small genetic component, but its effects continue into the next generation. More remarkable, recent studies in Scandinavia hint that even the health of grandfathers influences the well-being of their grandsons. Quite how, in this brave new epigenetic world, their fate is inherited is far from clear, but the discovery is another stake through the heart of Shakespeare's, and Weissman's, dogma that the germ line is kept safe from the thousand natural shocks that flesh is heir to.

Gluckman and Hanson make a good case for a modern mismatch for diet, but there is more to life than cheeseburgers. We often manage the world to fit our lifestyles. Social primates as we are, we flip open mobile phones to ensure that our networks stay in good shape. In the same way, we take the climate of the savannah with us (and pay the price in furs, tropical holidays, and air conditioning). Even so, *Mismatch* is a salutary reminder that the old genetics, with its rigid separation of nature from nurture, is giving way to a murkier model of inheritance in which the environment, almost as much as the DNA, plays a central part as generations succeed one another. In this brave and unexpected new world, it pays us all to—unlike Hamlet—choose our parents, and even our grandparents, well.

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