Steven Frank's new book continues his lifelong work on conceptual unity. In *Microbial Life History: The Fundamental Forces of Biological Design* (2022), he looks into recent biochemical data on microbial core metabolism. Novel measurement techniques provide clues about the electron redox flows and thermodynamic driving forces that power life. Of course, everyone knows that natural selection and processes of evolution have shaped every aspect of metabolic biochemistry. Yet very few works actually make the link between evolutionary processes and how metabolic systems are designed.

What Frank shows is that we can link the great evolutionary life history questions with biochemical thermodynamics. For example, how would changes in the genetic structure of populations alter the favored characteristics of electron transport cytochromes? How do changes in temporal and spatial resource flows alter microbial demography, changing the reproductive valuation of different fitness components that determine favored biochemical fluxes? This work provides the first comprehensive link between the forces that shape biological design and cellular energetics.

Frank's prior contributions separate into syntheses, original insights into natural history, and other broad themes that emphasize conceptual unification. The following provides a sample for each category.

Broad Syntheses

Natural Selection: series of seven articles (2011-2013). Frank's earlier work on natural selection developed novel insights and fundamental concepts. In this series, he provided a widely accessible synthesis along with several advances in unification. This series remains the standard against which new developments in the study of natural selection are measured. To mention just a few highlights, the first article revisits Frank and Slatkin's (1990) hierarchical approach to dissecting the ways in which variability in performance and reproductive success influence fitness. Many subsequent studies of evolution in variable environments derive from this foundation. The second article provides a succinct way to link phenotypic variability to the origins of evolutionary novelty and the rate of evolutionary advance, an extension of the Baldwin effect. The fourth article is the widely accepted primary source for a full understanding of the Price equation, one of the most influential conceptual and technical advances in the study of natural selection. Other articles develop novel links between information theory, causal modeling, and kin selection.

Dynamics of Cancer: Incidence, Inheritance, and Evolution (2007 book). This book remains the only comprehensive synthesis of age-specific cancer incidence patterns with theory for the causes of cancer progression dynamics. To achieve that synthesis, Frank developed novel quantitative approaches to analyze epidemiological data. For example, his focus on the acceleration of cancer with age naturally develops the duality between acceleration and force, allowing direct study of biological causes. To develop testable theories about cause, Frank built a comprehensive mathematical framework for the dynamics of cancer progression. To set the basis for future work, Frank integrated the epidemiology and mathematical theory of causation

with the molecular details of regulatory controls and how those controls break down in cancer. Frank also linked the study of cancer to his own primary research interest, the study of organismal design. The first paragraphs of the book state:

Through failure we understand biological design. Geneticists discover the role of a gene by studying how a mutation causes a system to fail. Neuroscientists discover mental modules for face recognition or language by observing how particular brain lesions cause cognitive failure.

Cancer is the failure of controls over cellular birth and death. Through cancer, we discover the design of cellular controls that protect against tumors and the architecture of tissue restraints that slow the progress of disease.

Immunology and Evolution of Infectious Disease (2002 book). Adaptive vertebrate immunity refines molecular recognition of pathogen antigenic molecules. That recognition and defense strongly favors pathogens to diversity their antigens. As molecular tools advanced to measure molecular diversity and evolution, many new opportunities arose to study how evolutionary processes shaped the interaction between hosts and pathogens. This book unified the advancing fields of immunology and molecular evolution to provide a new synthesis for the study of pathogen antigenic diversity. Although now 20 years old, it remains the most comprehensive summary of how natural selection shapes molecular specificity and diversity. Once again, Frank combined his fascination of natural selection as the primary force of biological design with the latest emerging frontiers in the biological sciences.

Foundations of Social Evolution (1998 book). This unifying synthesis clarified the key forces of conflict and cooperation. For example, Hamilton himself was never able to use kin selection theory in a simple way to solve basic problems such as sex ratio or dispersal. Instead, Hamilton and others resorted to various complex modeling methods, and then interpreted the results in a post hoc or intuitive way in light of inclusive fitness. Frank cleared up many conceptual issues and then devised simple tools to solve problems of natural history. That unification remains the primary theoretical approach favored by people directly studying natural systems. In addition, work jointly with Peter Taylor established the formal link between demographic life history modeling and kin selection, unifying for the first time the two primary conceptual approaches to understanding how natural selection shapes key traits closely associated with fitness. The book also reformulated the theory of sex allocation at a much deeper level, allowing extension to a wide variety of new applications in natural history and clearing up much conceptual misunderstanding about prior theories.

Models of parasite virulence (1996). This article made the tragedy of the commons famous in evolutionary biology. Previously, Egbert Leigh had mentioned the fundamental role of the tragedy but his article had little impact. Frank picked up on the idea from George Price's unpublished notes. He then linked that general model of conflict and cooperation to the conditions in which parasites live within hosts. Frank then went much further, connecting the simple tragedy model for conflict to broad aspects of parasite demography, creating the first comprehensive foundation for the study of parasite life history evolution. This widely influential article triggered many new studies of parasites and new theories that linked demography,

ecology, and evolution. Current studies of microbial evolution continue to build on these basic life history principles, which were explained in a direct and comprehensive way for the first time in Frank's article. Frank built on major insights by prior authors, including Anderson, May, Hamilton, Leigh, Levin, Lenski, Bull, Ewald, Herre, and many others. However, it was Frank's conceptual advances and unification that turned those earlier works into a solid foundation, providing the basis for rapid growth in subsequent empirical and theoretical studies. Frank's follow up article in 2008 with Schmid-Hempel cleared up several challenges of linking physiological mechanisms of pathogenesis to evolutionary process and its consequences for the study of virulence.

Novel Insight into Natural History

Sexual antagonism and X-autosome conflict (2020). Males and females have different favored values for some traits. Frank and Crespi (2011) noted that alleles on the X chromosome spend twice as much time in diploid females as in haploid males, possibly favoring X-linked genes to push more strongly toward the female optimum. However, Patten (2019) showed that certain dominance relations cause the X to favor alleles pushing toward the male optimum. These facts suggest that the X may ultimately be mosaic for alleles favoring one sex over the other. Autosomes tend to favor a balance between the optima, causing conflict with the X. The theory is still too new to have convincing empirical support, but the topic is very active and eventually will lead to insight into how these strong forces have shaped both phenotypes and genomes.

Negative immune regulators (2019). Hosts must recognize pathogen invasion and respond rapidly. The need for speed requires a low threshold for triggering a response, causing occasional false alarms. Host immune systems therefore require strong negative regulators to shut down unnecessary responses. The evolutionary consequences of rapid trigger dynamics balanced by negative regulators have received little attention. This article summarizes data and concepts suggesting that the need for speed has significantly influenced four aspects of immunity: diverse gene families of rapidly acting triggers opposed by slower-acting negative regulators, pathogen attack against negative regulators, diversifying selection of negative regulators by pathogen pressure, and heritability of immune-related disease from imbalance between triggers and negative regulators. As the following older ideas show, it takes many years for comprehensive empirical testing of such broadly unifying insights.

Infective dose (2007). The number of pathogens required to start an infection varies widely between species. No general theory explained that wide variation. Frank and Schmid-Hempel suggested that the particular molecular virulence mechanisms during initial pathogen invasion may explain variation in infective dose. They predicted that virulence factors directly injected into neighboring host cells require few initial pathogens to start an infection. By contrast, virulence factors that act distantly on host immune regulation may require many initial pathogens to generate a sufficient concentration of diffusible factors. Local versus global virulence factor action may correspond to small versus large minimum infective dose. That idea is the only theory to explain the widely varying infective dose observed among pathogens. Many follow-up studies have been designed specifically to test the idea. Some strong support

has emerged. More importantly, the idea provides the basis for ongoing advances on a crucial topic.

Somatic mosaicism (2003). A human body has about 100 trillion cells derived from the single zygote. The vast number of cell divisions introduces many mutations, causing widespread somatic mosaicism. Frank and Nowak's theory predicts great diversity in mosaicism between individuals. That mosaic diversity may explain a significant fraction of the variance in predisposition to disease. This article was the first to relate mosaicism to the mathematical population perspective of branching cellular lineages, with emphasis on cancer risk. This theory provided the first clear predictions about the high level of mosaicism expected within individuals and the great variability in mosaicism and the risk of disease between individuals. Frank's (2010) later article on somatic evolutionary genomics provided the first direct connection between neurodegeneration and a fully realized theory of mosaicism. With subsequent advances in single-cell genomics, this topic has developed into a major research field. So far, empirical studies have mostly confirmed the existence of mosaicism. Going forward, Frank (2014) outlined several key problems that have yet to be analyzed empirically. This work once again shows the broad conceptual unification between the population perspective of evolutionary biology and the pressing empirical problems that arise in biomedical research.

Mitochondria and male disease (1996). Mitochondria typically transmit through the female line. Mutations drift in frequency if they cause disease in males but are nearly neutral in females. By contrast, selection removes mutations that are deleterious in females. That sex-biased selective sieve predicts a widespread association between mitochondria and male disease. Frank and Hurst identified this puzzle, which had not previously been noted.
This topic has become its own distinct discipline, sometimes known as *Mother's curse*. Several empirical studies designed to test this idea found support, with potentially widespread consequences for understanding male infertility, sex differences in aging, and speciation. Numerous theoretical articles have developed the mathematical biology of this topic.

Host-symbiont conflict (1996). Host and symbiont often conflict over patterns of symbiont transmission. Symbionts favor dispersal out of the host to avoid competition with close relatives. Migration leads to competition among different symbiotic lineages, with potentially virulent side-effects on the host. The hosts are favored to restrict symbiont migration and reduce the virulent tendencies of the symbionts. Reduced mixing of symbionts would, in many cases, lower symbiont virulence and increase the mean fitness of the host population. This prediction led to numerous empirical studies and has become a foundational principle in analyses of how fungal farming termites and ants manage their symbionts. Conceptually, this work broadens the perspective on parasite virulence to a wider view of the tragedy of the commons and its consequences in nature.

Meiotic drive, Haldane's rule, speciation (1991). The first step in hybrid species incompatibility is typically sterility of the heterogametic sex, a pattern known as Haldane's rule. Frank suggested that genomic conflict arising from sex-chromosome meiotic drive may explain this

sex-biased pattern of hybrid sterility. Conflicts often associate with rapid evolutionary change. Meiotic drive within species would likely lead to rapid divergence between species (see also Hurst and Pomiankowski 1991). This idea founded a new discipline of genomic conflict and speciation. Several labs now devote their research to this topic. Although the idea was originally controversial, it is now widely accepted as one of the important competing theories for the genetics of speciation. In Frank's work, the idea first arose by the unification of studies of plant cytoplasmic male sterility with studies of animal speciation, illustrating once again the strong emphasis on conceptual unity in Frank's approach.

Other Major Themes

Robustness: precise phenotypes from sloppy components. Biological traits often seem remarkably precise given that biological components tend to be stochastic or a bit sloppy. How does system precision arise from component sloppiness? The most obvious answer is error-correcting feedback, perhaps the single greatest principle of system design. If a system can detect drift from a target and correct itself, then a system can remain precise even with fluctuating components. Frank's primary research interest is organismal design. So he has pursued this fundamental problem of systems and components in a variety of ways, a primary focus of his current work.

His first major contribution was in *Maladaptation and the paradox of robustness* (2007). The better a system is at correcting errors, the more that system can tolerate mistakes made by its components. Because the mistakes by components of a robust error-correcting system do not matter so much, such systems tend to accumulate variable components that decay in performance. Better error correction begets more errors, the paradox of robustness.
The tendency for robustness to cause the accumulation of mutations had been discussed previously. However, Frank's paradox of robustness applies much more broadly because greater robustness at the system level reduces the pressure of natural selection on the performance of the system's components. That change in the intensity of natural selection alters the costs and benefits of component design. System-level error correction tends to favor the evolution of cheaper lower performing components.

Frank has developed these ideas in many ways, including a pair of papers in 2019 on the evolutionary design of regulatory control and a new preprint *Precise traits from sloppy components. I. Perception and the origin of phenotypic response* that begins a series extending the topic to broader issues of system precision and component sloppiness. Frank also published a small book on engineering control theory in 2018 to bring the key ideas of that discipline into the biological sciences.

The paradox of robustness seems like it could be a fundamental principle that shapes the evolutionary design of organisms. The long-term impact of the idea remains an open problem. Several labs are pursuing applications. For example, in a PNAS article in 2012, Michael Lynch said: "As pointed out by Frank, an appreciation for the internal evolutionary dynamics of redundant systems provides an alternative perspective on the origin and maintenance of the

myriad of molecular attributes often interpreted as acquired enhancements of cellular robustness.''

Common patterns of nature. D'Arcy Thompson emphasized that morphology must always be understood by the duality of physical laws that constrain form and biological processes that mold form within physical constraint. It can never be just one or the other. In the same way, Frank has emphasized that patterns in data always arise by joint action of statistical processes that constrain the forms in data and the particular biological forces under study. Of course, that duality is very well known, for example, in the central limit theorem and the Gaussian or Normal distribution. However, beyond the central limit theorem, the constraining statistical forces are not well understood, and so interpretations of patterns in data often mislead. Frank has devoted much work to enhance our understanding of how the constraining statistical forces shape patterns in data. Few topics can be more important with regard to how we study and unify our understanding of nature.

Frank's (2009) article *The common patterns of nature* is perhaps his most readable outline of the problems. Following that, he developed a novel framework based on measurement and symmetry to unify understanding of the commonly observed probability distributions. For example, his 2016 article *Common probability patterns arise from simple invariances* lays out how we can understand the morphology of data. He has applied the mathematical insights to real examples in his articles *The invariances of power law size distributions* (2016), *Invariant death* (2016), and *Invariance in ecological pattern* (2019). Through his mathematical study of symmetry and invariance, he has also discovered a shared form in the basic mathematical equations of natural selection and the basic fundamental equations in other scientific disciplines in his *Simple unity among the fundamental equations of science* (2020).

The mathematics of this work is challenging, and so it will take a while for further studies to clarify how much impact Frank's ideas will actually have on the study of natural pattern. However, we can say that that he is intensely pursuing conceptual unification of the sciences in novel and creative ways.

Metapopulation dynamics of conflict. Frank's 1989 article on cytoplasmic male sterility in plants provided the first comprehensive unification of genomic conflict with metapopulation dynamics. He started by assuming that a population harbors many different mitochondrial genetic variants that cause male sterility, each factor with its own matching complement of nuclear genes that can restore pollen fertility. He then showed that, in theory, such multiple matching specificities would lead to spatial colonization-extinction processes that would lead to continual non-equilibrium local genetic sweeps. Such sweeps would cause low diversity within local patches but, by asynchrony between patches, would maintain high global genetic diversity.

This idea of metapopulation dynamics depends on the high potential diversity of molecular specificity assumed in the analysis. Frank argued that molecular recognition is by its nature highly specific and with a natural tendency for diversification. Subsequent empirical work on

the molecular basis of male sterility has supported this idea, showing high specificity and diversity. And, at the population level, several empirical studies have demonstrated the kind of colonization-extinction dynamics and spatial asynchrony emphasized by Frank's original theory.

A couple of years after Frank's male sterility work, similar empirical problems and ideas began to develop in the study of plant pathogens, for example, by Burdon and Thompson. Frank developed and extended that work by creating a unified vision of attack and defense. At bottom, the mechanistic basis by which defenders recognize and repel attack and by which attackers evade defense determines the broad features of diversity and evolutionary dynamics. Through a series of articles, Frank developed these ideas, ranging from the classic "matching alleles" model that was subsequently used in many theoretical studies to a broad analysis of quantitative genetic variability in attack and defense. This early work through the 1990s on plants and simple animal systems eventually led to the 2002 book mentioned above on vertebrate immunology and antigenic variation, the final piece in the broad unification of attack and defense.

Symbiosis and mutualism. Compared with attack and defense, symbiosis and mutualism define the complementary side of coevolutionary analysis. Symbiosis and mutualism also expanded Frank's long interest in conflict, cooperation, and social evolution. Frank's classic 1994 genetics of mutualism article developed the first fully realized theory of how mutualism may arise via favored genetic changes in partner species. Genetic associations between species may arise by codispersal or by the intrinsic dynamics of ecological and genetic processes. In either case, such associations between species create an extended concept of linkage disequilibrium, broadening the standard Mendelian view of population genetics.

And, Frank realized, the correlations between species that drive interspecies cooperation have exactly the same mathematical form as the coefficients of relatedness in classical kin selection theory. That insight became the basis for Frank's later reformulation of kin selection theory to a much broader and more general understanding how genetic and phenotypic associations create pathways of causation in the evolution of cooperation.

Frank's later articles on synergistic symbiosis (1995) and models of symbiosis (1997) generalized these insights and provided links to empirical study. In many ways, this topic remains an open problem with regard to empirical application. Perhaps the great recent developments in the study of microbial ecology and evolution provide the most promising ways of linking the theoretical insights to natural history. In particular, much of microbial metabolism is distributed, that is, the biochemical processing of food passes through the metabolic pathways of multiple species. Unification is an ongoing process, and Frank's recent interest in microbial life history connects back to this earlier work and may eventually lead to broader understanding.