COMMENTARY

Homologous biological structures: Design by natural selection and principle of Pareto optimality

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Biological structures are ubiquitous in nature, including the morphological (external) and anatomical (internal) structures of organisms. Biological structures are subject to trade-offs between different fitness-related objectives, such as mechanical stability, energy efficiency, and environmental adaptability, and thus are shaped by natural selection. According to the theory of evolution (the seminal contribution by Charles Darwin), natural selection is the driving force of evolution, favoring phenotypes that increase organisms' survival and reproductive success. Over millions of years of evolution, phenotypes with low fitness were eliminated due to lack of efficiency and effectiveness, while phenotypes with high fitness were retained and evolved. As such, biological structures are shaped by natural selection acting on heritable phenotypic variations: phenotypes that confer fitness advantages become more prevalent in subsequent generations, gradually optimizing their fitness for specific functional needs over time, ultimately leading to the evolutionary emergence of homologous structures (Figure 1A).

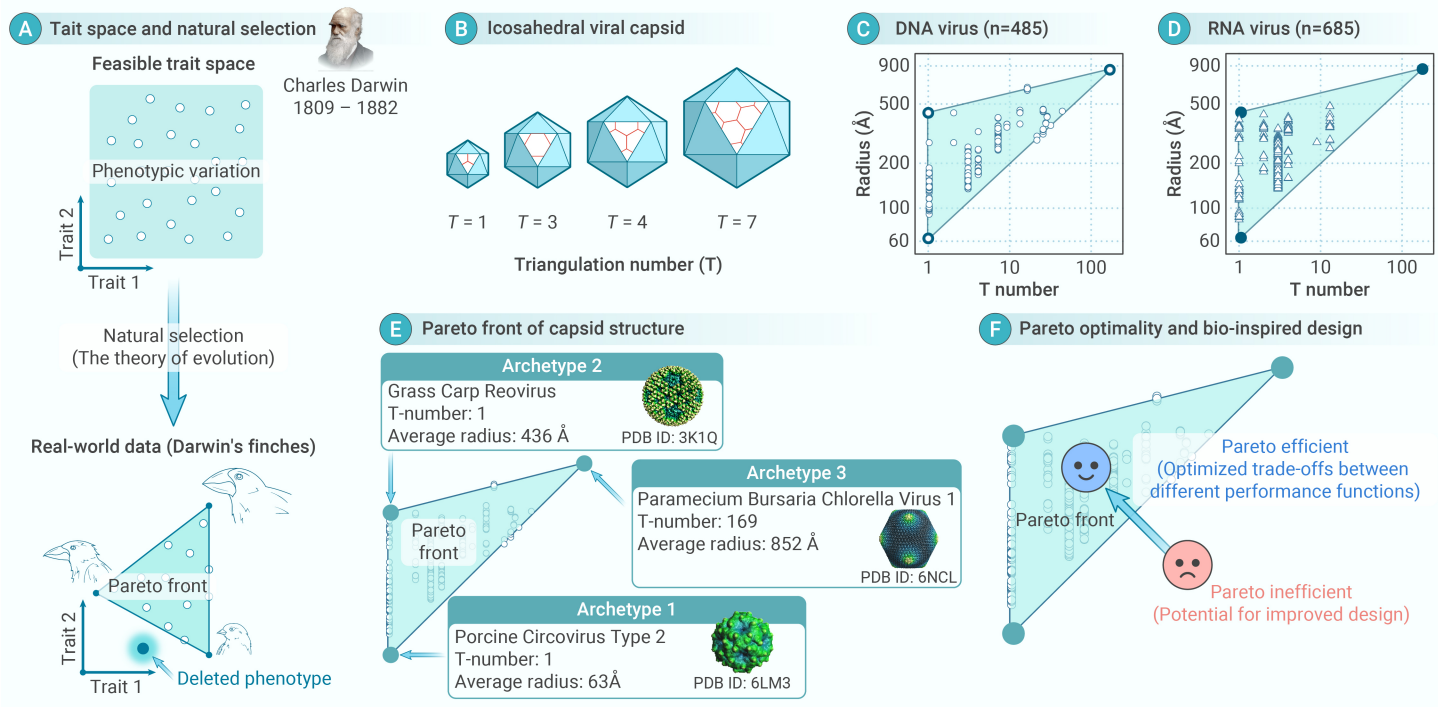

Figure 1. Homologous structures, natural selection, and Pareto optimality (A) Natural selection sculpts the shape of trait space. (B) Icosahedral viral capsid defined by triangulation number (*T*). (C-D) Capsid structures of DNA and RNA viruses. Å, angstrom. (E) Pareto front and archetypes. (F) Pareto optimality in bio-inspired design.

BIOLOGICAL STRUCTURES, TRAIT SPACE, AND PARETO OPTIMALITY

The process of natural selection and evolution leads to the development of a set of biological traits, which are optimized for the trade-offs between specific functional requirements, thereby achieving Pareto optimality.[1] The shape of trait space (morphospace) is referred to as Pareto front, which depicts the phenotypic variation of Pareto-optimal solutions (Figure 1A). Pareto optimality has found successful application in the morphological study of various organisms, including Darwin's finches, leaf-cutter ants, bats, and shells.[1]

In addition, biological structures also encompass anatomical structures, indicating how different types of cells constitute the spatial organization of tissue. Using Pareto optimality, single-cell RNA sequencing and spatial transcriptomics analyses reveal the trade-offs between the functions of specialized cells, as well as the homologous spatial organization of specialized cells within tissues.[2]

Overall, Pareto optimality provides a framework for trait space analysis to uncover the Pareto front of homologous biological structures. Moreover, Pareto optimality offers evolutionary insights into complex biological traits, indicating how selective pressures shape the evolution of biological traits and the underlying functional performance involved.

CONVERGENT EVOLUTION OF VIRAL CAPSID STRUCTURES

One prominent example of biological structures is viral capsids. Viral capsids are protein shells surrounding viral genomes, designed to store and protect genetic materials. Viral capsid needs to maintain stability against the high internal pressure of the tightly packaged genome that induces mechanical stress inside the capsid, while it also needs to survive the hostile external environment outside the capsid. The discovery of an ancient virus named *Pithovirus sibericum* found that viral capsid could preserve encapsulated genome over millennia.

After more than half a century of hunting viruses, viral capsid structures have been intensively studied, and most of them exhibit an overall structure of icosahedron—the fact itself highlights the evolution of homologous biological structures. Geometrically, these icosahedral structures can be defined by triangulation number (*T*) (Figure 1B). The capsid T number can be modified by minor alterations in the capsid protein sequence through simple

point mutations.[3] Based on this mechanism, the evolutionary barrier for altering capsid structure is relatively low. Such alteration of capsid structure has important ramifications for viral fitness, because it is a major contributor to the complexity and stability of viral capsids, and thus is vital for viral survival and adaptation to the hostile environment before successful infection.[4]

The morphologies of most viral capsids are well-defined by the icosahedrons' capacities and geometrical complexities, which can be parameterized by their radius and T number. By mapping each capsid as a point in the trait space of capsid radius and T number, all the DNA viruses fill within a small fraction of the trait space, showing a Pareto front of triangular shape (Figure 1C). Outside the Pareto front, most part of the trait space is empty, indicating that those theoretically possible phenotypes are not found in nature. This may be attributed to the natural selection that eliminates inefficient phenotypes, and the surviving phenotypes continuously evolve to reach optimized solutions on the Pareto front.

Notably, RNA viruses occupy the same Pareto front of DNA viruses, and no outlier was observed (Figure 1D). Considering that DNA and RNA viruses evolved independently, the recurrence of phenotypic similarity probably suggests a common evolutionary constraint, where different species converge toward similar phenotypes independently, commonly referred to as convergent evolution. Convergent evolution can be viewed as the evolutionary trend of quantitative traits. These traits are independently pushed by natural selection to evolve toward a common selective optimum, leading to the reduction of their distance in the trait space.

The phenotypic variation of capsid morphologies offers a textbook example of Pareto front, characterized by sharp vertices called archetypes (Figure 1E). These archetypes represent extreme phenotypes, and by connecting these archetypes, the Pareto front can be inferred to reveal a restricted area that encompasses convergent phenotypes favored by natural selection.

PATHOGEN-ASSOCIATED GEOMETRIC PATTERNS (PAMP)

All forms of life are infected by viruses, which continually evolve to infect their hosts. This, in turn, drives their hosts to co-evolve in defense mechanisms against infections. This process creates a perpetual cycle of co-evolution: the evolution of one side imposes selective pressure on the other side to co-evolve. This iterative cycle has persisted for billions of years, resulting in an infinite war between viruses and their hosts. As a result, the hosts have developed effective strategies to recognize and respond to the conserved properties of invading pathogens, such as pathogen-associated molecular patterns (PAMP) and pathogen-associated geometric patterns (PAGP).

Together with PAMP, PAGP—the highly organized and repetitive patterns of pathogens' shapes and structures—is equally important for inducing protective immune responses, involving several steps: antigen uptake and presentation by antigen-presenting cells (APC), activation of APCs for T-cell priming, and activation of B cells, all of which involve PAGPs. For example, the uptake of antigens by APCs relies on the appropriate size and repetitive geometric shape of viral particles. The size range of 10-500 nm facilitates effective antigen uptake by APCs, while the size of 20-200 nm allows efficient antigen trafficking to lymphoid tissues via initial lymphatic vessels, which allows pathogens to be directly processed by the lymphatic system.

Importantly, B cell activation is promoted by antigens with repetitive geometric organizations, since highly repetitive surfaces of pathogens effectively cross-link B-cell receptors, delivering strong activation signals to the B cells. The repetitive surface of antigens conjugated to nanoparticles with 60 antigens displayed per particle at a spacing of 5-10 nm were optimal for effective antibody responses. IgM antibodies bind strongly to the PAGP of repetitive surfaces through multivalent high-avidity interactions. Tightly bound antibodies facilitate the trapping of pathogens in lymphoid tissues, as well as stimulate APC-mediated priming of T cells. It might not be a coincidence that other vital components of the immune system, like pattern recognition molecules such as collectins, ficolins, and pentraxins, are multimeric thereby allowing high-avidity interactions with repetitive PAGPs.

In summary, PAGPs include pathogens' size and repetitive geometric patterns. PAGPs are closely related to the size and spacing pattern of viral capsids, which are typically assembled from just one or a few protein subunits (capsomeres), resulting in highly ordered and repetitive structures. It is therefore imperative that the host immune system has evolved to recognize the evolutionary constraints of viral structures as PAGPs.

PARETO FRONT AS BLUEPRINT FOR OPTIMIZED BIO-INSPIRED DESIGN

Pareto front offers a quantitative explanation for the constrained boundary of natural-selected phenotypes, as well as helps interpret the potential for improving man-made bio-inspired design. The performance function of a phenotype decreases with distance from the Pareto front; in other words, the closer to the Pareto front, the better the performance function. Therefore, the position of a bio-inspired design in the trait space, namely its distance to the Pareto front, can indicate design constraints and suggest the relative potential for further improvement towards a Pareto-optimized design (Figure 1F).

Pareto optimality provides a framework for systematically comprehending and scrutinizing the evolution of complex biological structures from macroscopic to microscopic scales. The analysis of icosahedral capsids across virosphere reveals that the design principle for icosahedral architectures has been widely explored by nature. These icosahedrons encompass blueprints for the bionanotechnology design of nanocontainers such as virus-like particles (VLPs). VLPs are made by viral capsids without encapsulating viral genetic material. Serving as molecular cages, VLPs deliver molecular cargoes and can be engineered to display specific antigens on their surface. VLPs emulate PAGPs to induce strong and long-lasting immune responses, and they can elicit higher levels of neutralizing antibody titers 10 to 100-fold compared to soluble antigens or mRNA vaccines.[5]

The concept of Pareto optimality was originally derived from engineering and economics, suggesting that a solution is Pareto optimal if no objective can be made better off without making another objective worse off, thus reflecting the best trade-offs between different requirements of resource allocation. Likewise, trade-offs are inherent for biological phenotypes due to the finite resources available to organisms, such as materials, energy, nutrients, etc., and the multifaceted functional demands for the organism's fitness, including survival, growth, reproduction, and competitive ability. Biological structures need to balance these objectives to maximize overall fitness to environmental conditions. Through the lens of Pareto optimality, Pareto front—a set of optimized phenotypes designed by natural selection—indicates optimized trade-offs between different performance functions.

The utilization of Pareto front streamlines design optimization by transitioning from single optima to multiple optima. Depending on the designer's requirements and priorities, Pareto font can help guide the selection of designs to strike a balance between preferred objectives and key constraints. As such, we can employ the hand of natural selection to develop innovative solutions using bio-inspired design.

REFERENCES

1. Tendler, A., Mayo, A., and Alon, U. (2015). Evolutionary tradeoffs, Pareto optimality and the morphology of ammonite shells. BMC Syst. Biol. **9**: 12. DOI: 10.1186/s12918-015-0149-z.
2. Adler, M., Moriel, N., Goeva, A., et al. (2023). Emergence of division of labor in tissues through cell interactions and spatial cues. Cell Rep. **42**: 112412. DOI: 10.1016/j.celrep.2023.112412.
3. Fiedler, J.D., Higginson, C., Hovlid, M.L., et al. (2012). Engineered mutations change the structure and stability of a virus-like particle. Biomacromolecules **13**: 2339-2348. DOI: 10.1021/bm300590x.
4. Stone, N.P., Demo, G., Agnello, E., et al. (2019). Principles for enhancing virus capsid capacity and stability from a thermophilic virus capsid structure. Nat. Commun. **10**: 4471. DOI: 10.1038/s41467-019-12341-z.
5. Huang, Y., Guo, X., Wu, Y., et al. (2024). Nanotechnology's frontier in combatting infectious and inflammatory diseases: prevention and treatment. Signal Transduct. Target Ther. **9**: 34. DOI: 10.1038/s41392-024-01745-z.

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DECLARATION OF INTERESTS

The author declares no competing interests.