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Perspective

# Challenges in cybersecurity: Lessons from biological defense systems

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ABSTRACT

Defending against novel, repeated, or unpredictable attacks, while avoiding attacks on the 'self', are the central problems of both mammalian immune systems and computer systems. Both systems have been studied in great detail, but with little exchange of information across the different disciplines. Here, we present a conceptual framework for structured comparisons across the fields of biological immunity and cybersecurity, by framing the context of defense, considering different (combinations of) defensive strategies, and evaluating defensive performance. Throughout this paper, we pose open questions for further exploration. We hope to spark the interdisciplinary discovery of general principles of optimal defense, which can be understood and applied in biological immunity, cybersecurity, and other defensive realms.

## 0. Introduction

Securing cyber-systems is one of the central challenges of the 21st century. Within the past five years, cyber attacks have disrupted U.S. oil supplies, leaked personal data of 50 million cell phone users, and rerouted Ukrainian Internet traffic through Russian communication infrastructure, just to name a few examples. Future consequences could be even more catastrophic, from severe disruption of financial markets to the demise of democratic governments to inadvertent nuclear war. Although cybersecurity experts have made tremendous progress enhancing the security of computers and networks over the course of decades (e.g. [1]), attackers often appear to be one step ahead, rapidly deploying innovative methods to overcome the latest defensive strategies, and we are still devising piecemeal solutions [2]. Continued creative inspiration for new principles and designs of defensive systems is both timely and likely to be valuable.

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A promising source of this inspiration is the study of biological immune systems. As National Medalist of Technology Carver Mead notes, "As engineers, we would be foolish to ignore the lessons of a billion years of evolution". Indeed, the deep history of coevolution between parasites and vertebrate hosts produced a fully distributed immune system that deploys a remarkable diversity of defenses against an equally remarkable diversity of parasitic attackers, from viruses less than 10 nm long to tapeworms exceeding 10 m [3]. Although the immune systems of other organisms – even plants and single-celled organisms – also have deep coevolutionary histories with parasites [4,5], examples in this paper are restricted to vertebrate immune systems, reflecting the particularly well-developed knowledge base in the field of vertebrate immunology. The challenges faced by the vertebrate immune system share many key similarities with those faced in cybersecurity: both systems must recognize attackers that are diverse, dynamic, and evolving; both must root out these attackers without excessive waste or damage to self; both must handle uncertainties about when, where, and how attacks will occur; and both must be effective at the scales ranging from individuals (e.g. a single human or a single computer) to populations (groups of humans, networks of computers).

Both biological immunity and cybersecurity are examples of complex adaptive systems (CASs), in which patterns at high levels of organization emerge from localized interactions and selection processes operating on diverse agents at lower levels of organization, and feed back to affect those lower-level processes [6]. In immunity, it is the self-organized interactions of numerous cells and molecules that collectively dictate organism- and population-scale infection outcomes [7]. In cybersecurity, analogous interactions of hardware, code, and human users collectively dictate security successes and failures, even at national and global scales [8]. Moreover, while the ability to freely engineer computer systems appears to contrast with the constraints of evolutionary processes that occur across generations, engineering and evolution may ultimately share more similar dynamics and outcomes than most observers would expect [Box I]. This suggests that strategies for defense that have been optimized by billions of years of evolution may also succeed in the engineered context of cybersecurity.

Looking to immunology for insights into computing security is not a new idea [13–20]. For example, intrusion detection systems (IDSs) originally monitored computers for malicious activity using a process called signature detection, in which patterns of system activity were compared to a database of known intrusive patterns. In 1996 an anomaly-detection system inspired by vertebrate immunity [15] was created to instead automatically learn normal system behavior via direct observation and to respond adaptively to unfamiliar patterns, eliminating reliance on a database of predetermined patterns. Subsequently, to further lower the rate of damaging false positives, process Homeostasis (pH) was invented [21] which mimics T cell costimulation—an important mechanism to prevent false-positive immune responses. As IDS were designed for entire networks, further immune-inspired features were incorporated, such as negative selection of detectors (for flexible distributed execution), a secondary response (to respond to previously seen attacks more quickly), diversity of pattern presentation (to avoid single points of failure), and avidity (to further control false positives) [16].

Nonetheless, these success stories are decades old: the many developments in both computing and biotechnology since then warrant a fresh look at how insights from immunology could be leveraged to better protect computer systems. For example, cloud-based computing applications are increasingly built from self-sufficient containers, which can interact, reproduce, and be destroyed, just like biological immune cells [22]. This suggests that other aspects of the evolved immune system could be replicated in cybersecurity settings. Furthermore, the medical utility of burgeoning biotechnologies from CRISPR/Cas9 [23] to mRNA vaccines [24] are revealing new principles of immune action and suggest new interventions more generally in CASs.

Therefore, our goal is to renew interest in the following question: How can biological immunity reveal general principles of optimal defense, which might be applied to provide CASs, including cybersecurity systems, an upper hand against attackers? In the subsequent sections, we provide a framework for studying connections between cyber and immune defense. Each section contains several topics to guide cross-system comparisons, along with related questions to spur future research. While these questions are only a few examples of the many rich and overlapping areas for future research, they are

The most glaring difference between biological defense systems and cyber systems is how they have arisen: One system was produced by a natural evolutionary process and the other by human ingenuity. We argue that the division between these two processes is ambiguous, that modern engineering processes have more in common with evolutionary processes than is commonly believed, and that inadvertent evolutionary dynamics are particularly relevant in computer security.

At first glance, the goal-directed nature of engineering, with designs produced by intelligent beings, is quite different from biological evolution, where natural selection responds to undirected random variations and drift. For example, Jacob et al. [9] argues that evolution through natural selection is akin to tinkering and fundamentally different from the work of the master craftsman: "The engineer works according to a preconceived plan in that he foresees the product of his efforts," and "The objects produced by the engineer approach the level of perfection made possible by the technology of the time." But no one would argue that today's computer systems approach perfection, nor that our software infrastructure, which is so vulnerable to attack, was produced according to a preconceived plan, even if, as humans, we can indeed foresee some futures.

In practice, engineering and evolution share many features, and it is often challenging to distinguish between the two. Many of today's engineered systems were produced at least in part by natural evolutionary processes. An obvious example is Arnold's Nobel Prize winning work using directed mutation in chemistry to optimize protein function [10]. Similarly, in computing, tinkering is the norm, and clean slate design is unusual. That is, we rarely get to go back in time and redesign systems from scratch. Why? Many systems are required to maintain backward compatibility, both for communication and networking and also for user experience; it is more expensive and error-prone to redesign from scratch than to reuse existing components. This is similar to evolutionary processes, which can only "work" (evolve) with components and processes already in place, the very arguments that underlie Jacob's thesis. Despite these constraints, evolutionary processes sometimes create large shifts that can be seen on the macro scale in punctuated equilibrium [11] and on the micro scale in microbes that evolve the ability to digest new carbon sources [12]—more akin to the large-scale shifts we might associate with foresight and design, but that require neither.

We hypothesize that simple inspection of an artifact cannot always reveal the process that produced it and that at best we can make a probabilistic guess, which prompts us to ask: What are the distinct properties of engineered and evolved systems that are reflected in the designs they produce? One can even imagine a kind of Turing test that asks how one could distinguish between a product of an evolutionary process versus an engineered process. What are the hallmarks of each? Suppose, for example, that you were presented with an immune system, a cryptography system, and a modern enterprise software system with all of its defenses, would you be able to distinguish whether each was evolved or engineered?

**Box I.** Engineered vs. Evolved Systems.

intended to transcend mere comparisons of systems and inspire general principles, in pursuit of a unified and broadly applicable theory of defense across biological and computing systems.

## 1. Framing the context of defense

When drawing analogies between the defensive systems of biological immunity and cybersecurity, the context in which defense occurs must be carefully considered. This context includes the goals of defense, the goals of attack, and the environment in which attacks and defense occur.

**The Goals of Defense.** Here we primarily consider the vertebrate immune system as a model of biological defense. Having evolved by natural selection, the vertebrate immune system has only one "goal" in the broadest sense: to enhance the lifetime reproductive output of the host organism. There is no direct selection towards other goals. This explains several seemingly disadvantageous aspects of biological immunity. For example, the lack of selection for post-reproductive survival may explain immunosenescence, i.e. the gradual dysregulation and dysfunction of immunity in old age [25]. The lack of selection for host comfort may explain why some parasites are tolerated, i.e. allowed to persist as chronic infections with their negative impacts only partially mitigated [26,27].

At face value, cybersecurity defenses appear to address a broader array of goals. The devices and software that protect both individual computers as well as entire networks must not only prevent infection, but also limit costs on several other fronts. For example, the monetary expense of installation, upgrades, and operation must not be too high, and efficient run-times of legitimate applications must not be sacrificed.

However, in reality, the apparent contrast in the breadth of goals between cyber and biological defenses is not nearly so sharp. By limiting costs to individual and institutional users, cyber defense systems are ultimately designed to attract more users and/or to enable an institution to persist successfully through time. In other words, a cybersecurity system's broad array of proximate goals largely serves the ultimate goal of ensuring continued representation in the future, analogous to natural selection. Following the same logic in the opposite direction, in order to maximize lifetime reproductive output, immune systems must meet a wide variety of proximate goals. Just as cybersecurity systems must limit costs, immune systems must not consume too much caloric energy or limiting nutrients. Just as cybersecurity systems must not hinder legitimate applications, immune systems must not interfere with other crucial biological functions. Indeed, the vertebrate immune system not only defends against parasites but participates in other biological functions, including wound repair [28], cognitive behavior [29], and more. Thus, we argue that the structure of goals is quite similar between biological and cyber defense.

*Open Questions: Can the parallels between the ultimate and proximate goals of cyber and immune defenses be measured to suggest the relative utility of analogies in specific cases?*

**The Goals of Attack.** As with defense, evolution by natural selection in biological systems ultimately selects for the reproductive capacity of attackers. We consider as biological attackers all parasites and pathogens that infect vertebrate hosts, encompassing an enormous diversity of viruses, bacteria, fungi, protozoa, nematodes, and other organisms. Once again, the ultimate determinants of fitness (e.g. growth in the current host and transmission to new hosts) are served by a variety of proximate goals, which vary from parasite to parasite: stealing host resources (e.g. hookworm consumption of host blood [30]); triggering host physiological mechanisms that facilitate transmission (e.g. induction of coughing by rhinoviruses [31] or induction of vomiting by noroviruses [32]); manipulating host behavior (e.g. rabies driving host aggression and biting [33]); or even killing the host (e.g. Ebola causing hemorrhaging and death [34]).

Cyber attacks, in contrast, can and do have a broader array of goals. These goals include stealing data or credentials, stealing or extorting money, triggering system failures, manipulating human behavior (e.g. through the spread of misinformation), or even seeking the collapse of corporations or governments. Because the numerous proximate goals of cyber attacks do not always serve an ultimate goal of persistence into the future, analogies with biological systems may break down. Nonetheless, diversity in the nature of cyber attacks does mirror diversity in the strategies of biological parasites, thus posing similar challenges for defense.

Unlike defensive systems, which typically balance many goals, individual attackers often pursue only a small subset of the numerous possible goals. Thus, analogies between cyber and biological attackers must be drawn carefully. For example, a spyware cyber attack, which aims to maximize the amount of data siphoned from a computer over an extended period of time, (where fitness might be measured as the volume of leaked data) would not accurately be compared to Ebola virus. Ebola virus maximizes its total transmission by destroying its host quickly via hemorrhaging [35]. Such fast and obvious harm would undermine the intent of spyware, which cannot continue to gather data from an incapacitated computer. Instead, spyware would be better compared to the human herpesvirus Cytomegalovirus, which maximizes its total reproduction by escaping detection during intermittent periods of latency [36].

*Open Questions: What are the analogues of evolutionary fitness that can be used to understand the success of cyber attacks, or their probability of being observed again in the future?*

**The Role of Third Parties.** Both immune systems and cybersecurity systems are embedded in wider 'ecosystems,' where attackers and defenders are not the only relevant actors. In both arenas, the interplay between attack and defense is often mediated by third parties —those who are unintentionally or unwittingly exploited to benefit one side or the other by enabling, exacerbating, or mitigating the threat of attack. Classic examples of third parties in human immune defense include disease vectors such as mosquitoes and ticks, as well as animal reservoirs where zoonotic infections evolve independently of human immunity (e.g. pigs and birds for new influenza strains, bats for Covid-19). At wider scales of public health, other third parties may include those who manage land use and wildlife, ship biological materials, develop vaccines, etc, as these activities all impact the risk and/or severity of infection. Third parties are equally diverse in cybersecurity, including those who produce and sell hardware, provide network connectivity, manage storage and application servers, become unwitting participants in distributed denial-of-service attacks, or simply use the internet. For example, in the 2016 U.S. election cycle, those who posted minority political opinions on social media became third parties when Russian hackers amplified their posts to distort public perception of the political climate [37].

It often seems that third parties are disproportionately exploited by attackers, particularly to increase the number of victims they can target. As such, a better understanding of third-party influences is an opportunity for major improvements in defensive systems, where insights from biological defense might translate to cybersecurity settings.

Consider malaria (the disease caused by the unicellular protozoan *Plasmodium falciparum*)—a widespread cause of morbidity and mortality in many developing countries [38]. Malaria achieves high rates of transmission among human hosts via the bites of mosquitoes (*Anopheles* species specifically). Here, mosquitoes are arguably a third party exploited by the protozoan attacker of human immune systems.

In direct combat between attack and defense, the human immune system can rarely clear all the infecting *P. falciparum* protozoans from the body. Neither evolution nor drug treatments nor vaccines, even the most promising recent vaccine candidates (e.g. [39,40]) have yet resulted in sterilizing immunity against malaria (though there are some signs that vaccine-induced immunity in combination with drugs may come close; e.g., [41]). Worse yet, mosquito-borne transmission causes widespread infection in areas with temperature, precipitation, and land use conducive to mosquito breeding [42]. However, reliance on

mosquitoes for transmission also presents unique opportunities for a different defense strategy: decreasing infection risk in the first place. Where individuals use insecticide-treated bed nets to prevent mosquito bites, malaria infection risk is significantly reduced [43,44]. Further defenses at levels of organization higher than the individual (e.g. regulating the trade of commodities that harbor mosquito eggs, reduction of mosquito habitat via reforestation, etc.) are also effective, and we discuss considerations of system scale in the next section. But bed nets alone mirror a principle that is already well-appreciated in cybersecurity: avoiding contact with malicious code altogether is the best defense. For example, exposure can be minimized by avoiding interfaces with hardware produced by third parties. One limitation of this analogy is that reducing contact with mosquitoes is desirable even in the absence of malaria infection risk, whereas third-party hardware may provide many advantages in terms of cost and convenience if not for the increased infection risk.

*Open Questions: Does lack of control over third party behavior inherently favor exploitation by attackers? Or can probabilistic descriptions of third party behavior be leveraged to favor defense?*

**System Scale.** As CASs, both biological immunity and cybersecurity span a range of temporal, spatial, and organizational scales. Immune systems comprise molecules that act within seconds (e.g. [45]), produced by cells that interact in local tissue zones over minutes to hours (e.g. [46]), whose interactions lead to emergent outcomes for the whole organism over many days (e.g. [47]). Similarly, cyber outcomes emerge from the action of individual pieces of code operating at multiple levels. For example, low-level assignment of Internet packet headers combined with high-level Completely-Automated-Public-Turing-Tests-to-Tell-Humans-and-Computers-Apart (CAPTCHAs) improve security in large networks [48]. Such cross-scale activities can sometimes interact to create non-linearities in system behavior which can lead to sudden and/or unexpected outcomes, especially when faced with spatially and temporally heterogeneous attacks.

While evolution by natural selection is expected to tune cross-scale interactions to minimize sudden negative outcomes in a probabilistic sense, uncertainty in the exact nature of attacks means that catastrophe is always possible [49]. For example, during bacterial infection, immune cells are transported by the bloodstream to sites of local infection, where they secrete inflammatory cytokines to help kill the bacteria. But too many sites of local infection, particularly when targeted against heterogeneous bacterial attackers, can allow these same molecular signals to accrue in the bloodstream. This rapidly expands the spatial scale of a typically beneficial defensive mechanism, unexpectedly causing septic shock and death rather than healthy recovery [50]. In terms of temporal scales, during some respiratory infections, such as Covid-19, immune mechanisms that cause symptoms are evoked after viral shedding has already begun [51]. While this timing leads to successful recovery of the individual host with minimal tissue pathology, it also leaves the host unable to curb transmission to other hosts before it is too late.

As these examples demonstrate, it is crucial to understand the potential for propagation of unanticipated effects and interference between defensive strategies operating at different biological scales [52]. These issues are equally relevant in cybersecurity settings. For example, implementation of two-factor authentication at the institutional level may actually compromise security at the level of individual computers if it lulls individual users into being less vigilant about creating strong passwords [53]. Shutting down an infected computer may prevent the spread of malware but also cause disruptions in routing across a broader network. Progress toward stronger holistic cybersecurity will require improved understanding of how specific strategies affect higher and lower scales of organization.

While mismatched scales can present a challenge for effective defense, they also present opportunities for new defensive strategies. In particular, heterogeneity at one scale of organization can be leveraged to achieve protection at another, by making the particular defenses an attacker will encounter unpredictable. The many billions of B and T lymphocytes of the vertebrate immune system each expresses a unique receptor, generated by randomized DNA somatic recombination [54]. This hinders an evolving parasite population from anticipating which of its peptides is likely visible to immune surveillance. Because such changing or varied defensive structures are not always achievable within the body or lifetime of one host, heterogeneity can also be deployed across a population. Each vertebrate host also expresses several out of hundreds of possible major histocompatibility complex (MHC) alleles, which are responsible for presenting parasite molecular structures to T lymphocytes. As a result of variation across hosts, a mutation which helps a parasite escape detection in one host may actually increase its probability of detection in the next host. Just as heterogeneity among attackers creates uncertainty and makes defense difficult, so too does heterogeneity in defense strategy impose adverse uncertainty on attackers.

The benefits of heterogeneity in defense are appreciated in the realm of cybersecurity as well. Users of uncommon operating systems are serendipitously shielded from attack simply because they are not part of the largest, and therefore most attractive, pools of potential targets [55]. There are several examples of intentionally engineered heterogeneity such as N-variant systems [56], address-space randomization [57], instruction set randomization [58], and platform diversity [59]. All of these strategies leverage unpredictability, sometimes explicitly mimicking biology by 'genetically' altering each code copy or layout. However, biological immunity appears to deploy heterogeneity as a defense more ubiquitously and spanning more organizational layers than does cybersecurity. In the technology market, economic and logistical factors provide strong incentives for standardization, which can curtail the appeal of heterogeneity. This creates a tradeoff in cybersecurity which would be beneficial to break.

*Open Questions: How can unpredictability in defense be generated at multiple organizational scales, and which mechanisms are most effective? What dynamic cross-scale feedbacks are required to stabilize such systems? Should engineered heterogeneity be implemented across a wider range of scales in cybersecurity, and how much heterogeneity is sufficient?*

## 2. Choosing defensive strategies

As CASs, both immunity and cybersecurity comprise many interacting components and mechanisms. While these mechanisms are inextricably linked by their feedbacks and influences on one another, we and others (e.g. [60]) find it useful to assort individual defense mechanisms into 5 general strategic "layers". (Table 1). Which defensive layers are used, how they are implemented, and how they are wired together into a single self-organized system, surely depends on the context of defense, as described above. Here we explore several other crucial factors that influence these choices.

**Resource Costs.** Maintaining and deploying any defensive system has resource costs, i.e. the consumption of time, energy, or materials that could have been used for other purposes. For example, antivirus software can increase the run-time of legitimate software, effectively reducing the computing time available for other tasks. There are also massive costs in terms of energy: the use of cryptography for secure internet browsing alone is estimated to consume more than 3 million kilowatt-hours annually [61], and cryptography is only one component of modern cybersecurity defense. In the biological realm, a large body of research in ecoimmunology quantifies the temporal, energetic, caloric, and protein costs of immune responses (e.g. [62]). For example, secreting antibodies uses amino acids that could have been invested in reproduction (e.g., [63]) and conversely, experimentally resource-limited animals mount weaker B cell and antibody responses to antigenic challenge than do animals fed *ad lib* (e.g., [64]). More recently, immunometabolic research has revealed that organismal metabolic pathways provide energy and substrates for cellular growth and survival while honing immune effector function [65]. For example, bacterial infection induces adipocytes surrounding lymph nodes to

**Table 1**
General layers of defense.

| Layer | Definition | Examples from vertebrate immunity | Examples from cybersecurity |
|---|---|---|---|
| Avoidance | Preventing exposure to attacks | Shunning sick individuals, disgust response toward waste and detritus | Blocking access to blacklisted websites, end-to-end encryption for messages |
| Blockade | Preventing entry of attack upon exposure | Skin, mucous membranes, anti-viral cell states | Firewalls, passwords, cryptography |
| Detection | Recognizing an attack upon entry | Toll-like receptors, T cell receptors, immunoglobulin | Virus scanner, intrusion monitoring, anomaly detection. |
| Alleviation | Reducing the harm caused by an attack | Tissue-repair macrophages, granuloma formation | Slowing down suspicious programs, reinstalling compromised software, changing passwords, replacing infected hardware |
| Counter-attack | Expelling or destroying the attacker | Killer T cells, inflammatory macrophages, neutrophils, B cell antibody secretion, eosinophil toxic granules | Take-down requests for counterfeit websites, censorship, content moderation |

cease lipid metabolism and instead launch a transcriptional response conferring immune effector function [66], and the metabolic profile of the immune cells infiltrating a tumor can determine the fate of cancer patients [67]. In spite of these energetic costs, cybersecurity algorithms derived from immunology may have energetic advantages over cryptography [68].

The systemic implications of such costs are best understood in light of epidemiological risks. While underinvesting in defense leaves a system vulnerable to attacks, overinvesting in defense leaves the user of the system ill-equipped to perform other important tasks. Thus, the cost of a defense strategy should be commensurate with the risks faced. Although this principle is simple, accurately following it is not, due to the difficulty in quantitatively predicting risks posed by inherently unpredictable attacks. Natural selection uses the evolutionary history of attack risk along with resource costs to calibrate investment in defense [69,70]. Even so, ongoing variance or sudden shifts in attack risk often cause hosts to invest incorrectly in specific instances; for example, the mammalian immune system is prone to overproduce inflammatory cytokines, resulting in severe immunopathology [49].

Similarly, attack history can be used to forecast future risk in cybersecurity, but correct calibration of defenses cannot be guaranteed in every case. Infamously, after a period of relative calm and correspondingly low investment in cyber defense, in 2017 Equifax experienced a security breach that leaked the information of 147 million people [71]. If the risk of attack is difficult to predict, then detection and counterattack layers that are rapidly induced after an attack occurs may be favored over a blockade layer that is constitutively active. This is partially because inducible responses consume resources less frequently than constitutive defenses [72,73]. However, it is not clear that this is always the case in cyber realms.

*Open Questions: What (combinations of) defensive layers minimize aggregate resource costs while maximizing protection? How can energy budgets be used to dynamically redistribute resources across multiple defense layers in real time?*

**Sensitivity Tradeoffs.** In both organisms and computers, some ingressions are dangerous, but the majority are not (e.g., food, e-mail messages, most software updates). Fighting innocuous ingressions can be as costly as permitting dangerous ingressions. As a result, the sensitivity of defense must be carefully tuned. False positives occur when the immune system attacks an innocuous substance or its own uninfected cells, or when a cybersecurity program denies a user or authorized code legitimate access to data or other resources. False negatives occur when an immune or cybersecurity system fails to respond to a genuine attack. Reducing false positives often increases false negatives, creating a sensitivity tradeoff that constrains the design of defensive systems [74].

Different defensive contexts call for different sensitivity levels. Users of email spam filters typically prefer never to have legitimate mail withheld, even if it means that they are exposed to some junk mail—a balance tipped in favor of false negatives. Meanwhile, managers of servers containing top secret data might prefer multiple checkpoints that slow legitimate accesses, in order to completely block illegitimate attempts—a balance tipped in favor of false positives. Interestingly, the advancement of medical technology and hygiene to treat or prevent infections (e.g. the rapid development of mRNA vaccines [75]) has outpaced the treatment of autoimmunity, such that false negatives may be relatively less risky than false positives today than during earlier human evolutionary history. The optimal level of sensitivity may determine which defensive layers are chosen and how they are implemented. Generally, the more layers a defensive system uses, the more sensitive it becomes, because there are more opportunities for an ingression to be blocked, regardless of whether the ingression is harmful or benign.

Ideally, the sensitivity tradeoff could be blunted by simultaneously reducing false positives and false negatives. Several features of the vertebrate immune system accomplish this to some degree, suggesting analogous strategies for cybersecurity. Consider T cells as a detection layer. During their generation in the thymus, T cells that either react against self molecules bound to MHC or else cannot recognize any molecules bound to MHC are deleted [76], simultaneously limiting the potential for false positives and false negatives, respectively. After exiting the thymus, multiple "peripheral" checkpoints continue to delete T cells that either respond to self or fail to respond to any invader [77]. This suggests that ongoing learning based on continually updated signatures of self and attack is a key principle of defense. Indeed these and other immune-inspired principles have been translated into many artificial immune systems for intrusion detection [78].

Other immune mechanisms have received less attention from cybersecurity experts. For example, T-regulatory cells are crucial for accurate detection. When T cells that detect a perceived threat begin proliferating, they compete with surrounding T-regulatory cells for secreted growth factors. The outcome of this competition determines whether or not a full immune response is elicited, and it is a required mechanism to prevent spontaneous autoimmunity [79]. We are not aware of explicit attempts to mimic T-regulatory cells in cybersecurity algorithms, but this suggests that majority voting processes among

multiple autonomous detectors, each biased toward different levels of sensitivity, may outperform a single trained detector.

*Open Questions: What cybersecurity analogues of T-regulatory cells can simultaneously reduce false positives and false negatives? Which defensive strategies are best-suited to implement these algorithms?*

**Decentralization.** A fundamental problem in defense is that attackers have many more frequent opportunities to update their strategies than do defenders. Cyber attackers can privately test many attack strategies before launching the best one, and parasites have much shorter generation times and larger effective population sizes than hosts. This imbalance creates a fundamental asymmetry between attacker and defender. By decentralizing the task of defense to numerous distributed autonomous agents, a defensive system can partially close this gap in evolution rate by allowing the agents to evolve as a single defensive response unfolds. Indeed, the vertebrate immune system is composed of hundreds of lymph nodes and trillions of autonomous cells, many of which (specifically B and T lymphocytes) undergo positive selection during the course of a single infection. Given the growth of large networked enterprise systems and trends toward lightweight container-based processes spread across numerous processors, cybersecurity may also begin to realize the advantages of decentralization [16].

With the advantages of decentralization come several challenges, which impact the holistic design of a defense system. For example, coordinated action of distributed autonomous agents requires communication among these agents. The nodes comprising modern computer networks continually exchange packets of information, and immune cells constantly secrete signaling molecules called cytokines that modulate the behavior of surrounding cells. Decentralization vastly increases the number of signaling events, and every signaling event is an opportunity for subversion [80], such as spoofing or man-in-the-middle attacks. Defensive systems must expect and preempt such attacks. One approach is to base strategic decisions on the time-integrated sum of many agents' signals, where high stochastic variability is added to the signaling output of each individual agent. As a result, subversion of any individual signaling event is swamped by group-level noise and is less likely to affect the downstream decision. Indeed, parasites often spoof or sequester cytokine signals to promote ineffective immune counterattacks, but high variability in cytokine secretion rates of individual T cells can prevent such mistakes [81]. Even if an attacker does successfully subvert an entire signaling axis, other approaches can mitigate the consequences. By increasing the number of signaling axes used and the complexity with which they are integrated, defensive systems can create signaling logics that are much more challenging for attackers to manipulate toward a desired outcome [82]. This might partially explain the vast complexity of cytokine signaling networks [83].

If successful adaptations by decentralized agents are retained after an attack has been cleared and used to improve performance in the future, then the defense system is said to have learned. Whenever a defensive system persists on a longer timescale than the duration of an attack, as in both vertebrate immunity and cybersecurity, learning is desirable [84]. But the optimal dynamics of learning can vary according to the attack landscape and the goals of defense, among other factors. For example, receptor repertoire updating in the vertebrate immune system follows a Bayesian scheme which optimally balances the weights it assigns to new vs. past attacks according to the sparsity of parasite molecular signatures and the expected host lifespan [85]. It is not clear how the current gold standard in machine learning – neural networks – should be optimized for cybersecurity, given the diversity of adversarial strategies that can be used to sabotage performance. For example, in a phenomenon called "catastrophic forgetting", manipulating the order in which training samples are fed to a neural network can cause predictable downstream failures. Some progress has been made toward overcoming catastrophic forgetting by condensing individual memories into small independent units and then entrenching these units [86]. These strategies inadvertently mimic B and T cells, which are the small independent units of immune memory that become entrenched via clonal expansion and differentiation into long-lived subtypes. Further analogies should be explored to improve other facets of adversarial learning in cybersecurity.

Importantly, the examples discussed here are constrained to single layers of defense. Noisy cytokine signaling precipitates a choice between different varieties of alleviation or counterattack layers. Neural network learning has been used in detection of genuine attacks vs. innocuous activity [87]. However, the benefits and challenges of decentralized defense certainly span across defensive layers. For example, a memory formed during the detection of a bizarre attack that bears no resemblance to normal activity might be translated into an avoidance heuristic that prevents future contact with such an attack altogether, allowing it to be deleted from the detection memory to free more space for future learning. The amount of damage caused by different attacks might drive learning to tune the balance between alleviation and counterattack in the future.

*Open Questions: How can communication across different layers of defense enable holistically optimal decentralized learning? What signaling logics are needed to protect this communication from sabotage?*

**Complexity.** As CASs, it is no surprise that immune and cybersecurity systems are themselves complex: they contain many intricately interacting mechanisms. The vertebrate immune system includes multiple mechanisms within each of the five broad layers of defense (Table 1), and even the immune systems of much simpler organisms such as corals and bacteria achieve at least four of these layers [73,88]. The repeated evolution of multi-layer defense systems suggests an advantage of complexity in defense. This is echoed by the cyber principle of defense-in-depth, which says more layers and mechanisms lead to fewer successful attacks. The common intuition for this principle is independent redundancy: if one defensive mechanism fails, another can compensate for it. But pure redundancy is rarely an evolutionarily stable outcome, and must be complemented by features like diversity and modularity that provide adaptive capacity [89]; hence immune mechanisms that appear redundant in any given infection may have partially overlapping but not completely identical uses, more broadly [90]. This suggests that multifaceted defense systems could evolve simply because no single mechanism can prevent all attacks, and redundancies across different mechanisms in specific cases are merely serendipitous side effects, rather than adaptative drivers.

In fact, complex interactions among multiple layers of defense could even evolve with no benefits whatsoever. The theory of constructive neutral evolution explains complexity in cell biology as the result of a ratchet: given multiple proteins, there are more possible mutations that increase than decrease their interdependence, and the former mutations are less likely to be reversible, so random chance inevitably leads to higher degrees of interdependence [91]. Scaling this argument up, the addition of each new layer or mechanism of defense means that existing layers or mechanisms are underutilized, reducing the selective pressure for their continued independent functioning. Thus, sophisticated multilayer defense systems could arise by natural selection without providing long-term advantages over simpler defenses, and perhaps even proving more costly in terms of resources [52]. Because the engineering of cybersecurity systems may follow similar patterns as biological evolution, deliberately or inadvertently (Box I), it is important to understand whether defensive complexity evolves due to inherent optimality, constraints on otherwise preferable simpler systems, or the inevitability of runaway complexity.

*Open Questions: Is defensive complexity ever advantageous? If so, under what circumstances, and how much is optimal?*

## 3. Evaluating the performance of defense

However well designed and adapted a defense system may be, the unpredictability and continual evolution of new attacks means that

monitoring and updating defense will always be necessary. In both cybersecurity and immunity, new defenses inspire new attacks and vice versa. Below we consider specific factors that are particularly useful for evaluating defensive systems and predicting their future performance.

**Co-evolutionary Patterns.** The invention of new attack strategies in response to new defensive strategies and vice versa is a coevolutionary process called an arms race. Both attacks and defense systems gradually become more sophisticated and potent. Arms races can follow a range of trajectories, several extreme cases of which are useful to consider. Improved defensive capability may become so deterrent that the threat of attack largely vanishes. Conversely, attackers may unleash a catastrophic assault that leaves the defensive system overrun and unable to make future updates. Between these extremes, investment in attack and defense may escalate so far that both parties pay wastefully high resource costs that exceed the actual risk and reduce overall fitness. Or attack severity may plateau at a low enough level that alleviation is more cost-effective than counterattack, leading to chronic infections that are simply tolerated by the defender.

The ability to predict which trajectory an arms race is following in real time would be extremely beneficial in the evaluation and preemptive improvement of defensive strategies. Such prediction is sometimes possible using data from vertebrate immunity, thanks to the genomic signatures left by evolving facets of attack and defense. For example, time series of viral and antibody sequences in chronic HIV infections can be used in time-shifted neutralization assays to characterize how well the immune system tracks the evolving virus, which in turn may predict patient prognosis [92]. Similarly detailed data documenting gradual and reciprocal changes in attack and defense strategy are available in cybersecurity settings such as vulnerability databases, records of software updates, and Internet measurement. Analogous to HIV sequencing data, records of which sites are queried, blocked, and accessed from within China have been used to quantify the performance of the Great Firewall of China, ultimately predicting whether this strategy for national censorship is likely to remain effective [93,94].

*Open Questions: Can coevolutionary patterns predict likely outcomes in cybersecurity: catastrophic attacks, unnecessary expenditure on defense, or prudent tolerance of low-risk ingressions?*

**Cost–Benefit Analyses.** As discussed earlier, operating a defensive system is costly in terms of resources. Energy, materials, and time spent on immunity are no longer available for other purposes, such as foraging or reproduction [95]. Therefore, maximizing resource investment in defense is rarely an optimal strategy [96,97]. Instead, mathematical cost–benefit analyses can reveal the optimal investment in defense, by balancing the resource costs paid with the benefits reaped. Cost–benefit analyses can reveal non-intuitive results; for example, short-lived hosts might not seem to require immune defenses, because the time window for any given host to become infected is small. However, a rigorous epidemiological model reveals that if these same short-lived hosts also reproduce at a high rate, then there is a sufficient supply of susceptible hosts to sustain an endemic parasite population, raising the risk for each host and warranting investment in immunity after all [98].

Another population-scale process that can non-intuitively modulate optimal defense investment is herd immunity. If enough threshold fraction of hosts are sufficiently defended against a parasite, then transmission among hosts is limited, and a parasite population cannot be sustained. As a result, rare undefended hosts are unlikely to be exposed to the parasite, and they reap the benefits of immunity without paying the costs [99]. Thus, immunity is a public good that suffers from the classic game-theoretic problem of free-riders. An identical problem exists in cybersecurity settings where infections spread on a network. For centrally controlled networks, network managers can strategically tune the defenses of each computer using analogues to network models that are well-developed in epidemiology (e.g. [100]). However, in distributed autonomous networks, defense systems of individual computers may need to implement cost–benefit analyses to determine optimal defense levels—a practice which is gaining traction (e.g. [101]).

Cost–benefit analyses are complicated by uncertainty. Measuring the benefits provided by defense is tricky, due to estimation of the severity of attacks that did not succeed, discounting of future benefits, and the nonlinearity of utility curves. Moreover, measuring costs of infection is also tricky, because the magnitude of the average attack may be far less important than the magnitude of the worst-case scenario. A 1% probability of contracting a common cold or of receiving a spam email may be acceptable, but a 1% probability of fatal systemic infection or of a compromised control system in a nuclear reactor is not. In other words, investment in defense ought to be tailored to the attack risk profile, i.e. the probability distribution across the range of possible attack severities. Experimental evolution studies in the model nematode organism *Caenorhabditis elegans* reveal that prevalent mild infection is not sufficient to warrant hosts paying high costs for defense, but deadly infection does drive the evolution of high-cost defense [102]. This suggests that the most important part of a risk profile for deciding defense investment is the rightmost tail: how severe are the worst-case attacks, and how probable? Unfortunately, both measures are notoriously difficult to estimate in cybersecurity, and the calculus can change over time.

*Open Questions: What factors are most crucial to include in cost–benefit analyses to inform cybersecurity designs? How should the uncertain right tail of a risk profile be conservatively estimated to best balance costs with prevention of worst-case scenarios?*

**Changes in the Context of Defense.** If a defense system is carefully designed for a specific context, then unanticipated changes to that context may cause catastrophe. Thus, vigilance in monitoring not only defensive performance but also potential changes to the context of defense is essential. Contextual changes can be externally driven. For example, shifting political alliances among nations may change the origin, and thus the resources and techniques available, for cyber attacks. Contextual changes can also be driven by the defense system itself, in the form of unintended consequences. Antibodies generated during infection with one strain of Dengue or Zika virus actually prevent *de novo* generation of antibodies during an infection with a second Dengue strain, eliminating one of the key layers of defense and typically leading to more severe disease [103]. In another example, imagine that avoidance of malaria-carrying mosquitoes via bed nets were not only to succeed, but also to impose strong selective pressure for the *Plasmodium falciparum* protozoan to survive in other biting insects, perhaps with much wider geographic ranges. The context of defense would have changed drastically—a new third actor is involved, the spatial scale of attack has changed, and many new populations of people are at risk.

Unfortunately, changes to the context of defense appear difficult or impossible to predict, especially if they are not direct feedbacks of defensive action itself. While both biological immunity and cybersecurity are CASs with many components that span spatial and temporal scales, any predictive model of their behavior must nonetheless specify relevant components, their interactions, other aspects of their context, in advance. Unknown external forces that alter these assumptions cannot be fully accounted for in model predictions.

However, some approaches may aid in the evaluation and updating of defensive systems. A purely data-driven approach is to observe the time and trajectory taken by the defensive system to return to a stable, protected state after each attack. This may reveal critical slowing down: a phenomenon in which slower and slower returns to equilibrium predict that the system dynamics are gradually approaching a tipping point, where outcomes will suddenly become drastically different [104]. For example, chronic inflammation during old age markedly slows the rate at which cellular debris can be cleared from tissues after infection or injury, increasing the risk of tissue degeneracy and ultimate mortality [105]. More generally, the cause of a gradual shift in system dynamics – perhaps external forces changing the context of defense – can remain entirely unknown, and yet an impending catastrophe can be

predicted. In cybersecurity, early detection of critical slowing down can spur periods of greater investment in explicitly researching the context of defense, to adaptively modulate efforts.

Theoretical approaches are also available, in the form of sensitivity analyses. By identifying which (combinations of) parameters exert the strongest influences on model behavior and prediction uncertainty, sensitivity analyses can highlight which components and interactions in a defensive system are likely to be least robust against external forcing from contextual changes. Knowing such vulnerabilities, even without knowing which specific contextual changes to anticipate, could suggest further safeguards to prevent sudden failures in defense.

*Open questions: What design features of defensive systems make them least susceptible not only to unpredictable attacks, but even to unpredictable changes in context?*

## Conclusion

Across evolved biological immunity and engineered cybersecurity, we find meaningful parallels in how the defensive contexts are framed, strategies chosen, and performance evaluated. Especially as technological advances allow these two defensive systems to resemble one another more closely, we believe that carefully drawn analogies between these systems can reveal general principles of defensive design to protect against unpredictable attacks. Lists of proposed principles already exist in some fields (e.g., [106], [7]), but their generality across systems has not been examined in depth, either theoretically or practically. We hope the open questions articulated above will spark collaborative study, whether by sharing data and analytical techniques or constructing theoretical models. Finally, as general defensive design principles emerge, we hope to see them vetted and successfully deployed in other realms, such as national defense against domestic and international terrorism, and public health defense against zooneses and epidemics.

## Declaration of competing interest

None.

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## Glossary

*B Cell/Lymphocyte:* an abundant cell type in the mammalian immune system that is largely responsible for antibody production upon parasitic intrusion

*Complex adaptive system:* any system of interacting autonomous agents in which patterns at high levels of organization emerge from localized interactions and selection processes at lower levels of organization, and feed back to affect those lower-level processes

*Computer:* any device that stores or processes data and/or executes programs, including laptops and desktops, routers, servers, smartphones, etc.

*Container:* a software program that bundles together all necessary components to run in any computing environment, without any external requirements

*Cytokine:* a class of signaling molecules secreted by immune cells to coordinate their behavior and functioning

*False Negative:* the failure of a defense system to detect or respond to an attack

*False Positive:* the erroneous deployment of a defensive response in the absence of an attack

*Herd Immunity:* a phenomenon in which a small fraction of susceptible hosts are protected from infection because a large enough fraction of hosts are well-defended, preventing any appreciable parasite circulation in the host population

*Immunopathology:* damage incurred by a host organism that results directly from the action of its own immune system

*Immunosenescence:* the gradual decline in immune function and increase in immunopathology experienced with aging in many species

*Infection:* any attack that causes harm, whether referring to a parasite in/on a host organism or a cyber attack on a computing system.

*Intrusion Detection System:* a program that monitors a single computer or a network to find and report abnormal or potentially harmful activity

*Major Histocompatibility Complex:* a cell-surface molecule in vertebrates that is responsible for displaying molecular fragments to the immune system, playing a crucial role in discriminating self from non-self

*Network:* any set of computers that can exchange data and/or instructions

*Operating System:* the software platform on a computer that coordinates all tasks and programs that the computer executes

*T Cell/Lymphocyte:* an abundant cell type in the mammalian immune system that is largely responsible for detecting parasitic intrusion and coordinating the subsequent immune response

*T-Regulatory Cell/Lymphocyte:* a T cell variant that reduces rather than amplifies the immune response upon detection of parasitic intrusion

*Third Party:* an entity that unintentionally modulates the risk or harm of an attack

*Tolerance:* a strategy by which a host's immune system fully or partially mitigates the harm caused by a parasite while allowing it to remain in the body

*Transmission:* the transfer of parasites from one host organism to another, thereby facilitating long-term parasite reproduction