The Immune System and Its Ecology*

Alfred I. Tauber†‡

In biology, the 'ecological orientation' rests on a commitment to examining systems, and the conceptual challenge of defining that system now employs techniques and concepts adapted from diverse disciplines (i.e., systems philosophy, cybernetics, information theory, computer science) that are applied to biological simulations and model building. Immunology has joined these efforts, and the question posed here is whether the discipline will remain committed to its theoretical concerns framed by the notions of protecting an insular self, an entity demarcated from its environment, or will shift its focus of interest to a wider context. An ecological perspective emphasizes the interchange between the organism and its environment, the processing of information, and the regulation arising from responses to this larger context. Moving from the first attempts at modeling the immune system as a closed network, immunologists have joined the general interest in systems analysis, and that move might portend a significant shift to an open, more holistic consideration of immune regulation.

1. Introduction. How might immunology be regarded from an ecological perspective? Indeed, why consider such a framework? At one level, this project would appear to be an exercise already well traversed. After all, the immune system is generally regarded as responsible for host defense against invading pathogens. Immunology thus presents a primal example of the interactions of species juxtaposed with each other and depicts how either struggle or cooperation is enacted. From this perspective, how animals respond to insult and what comprises the mechanisms of defense or silence seem fundamentally ecological in character. Yet the historical development of the discipline reflects a deep-seated conceptual orientation

*Received December 2006; revised August 2007.

†To contact the author, please write to: Center for Philosophy and History of Science, Boston University, 745 Commonwealth Ave., Boston, MA 02215; e-mail: ait@bu.edu.

‡I am indebted to Andrea Grignolio for assistance in researching the history of immune models and information theory in immunology, a subject he is preparing for publication. I thank Richard Gunderman of Indiana University for alerting me to the term 'ecotone' and its meanings, as well as critical comments offered by Eshel ben Jacob and Zvi Grossman. Portions of this paper have been modified from a previous publication (Tauber 2005).

Philosophy of Science 75 (April 2008) pp. 224–245. 0031-8248/2008/7502-0006$10.00
Copyright 2008 by the Philosophy of Science Association. All rights reserved.

https://doi.org/10.1086/590200 Published online by Cambridge University Press

to an individual-based biology developed at the expense of a more comprehensive interactive ecology. The gains and losses of that approach are becoming evident as immunology is belatedly directing itself towards a systems-based understanding of immune regulation, which regards immune function as part of, and thereby regulated by, its broader context.

This shift has been slow in arriving, for the organizing model of immune function for the last half century has been cast as the discrimination of a 'self' from the 'other' (Tauber 1994; 1999; Podolsky and Tauber 1997). Plainly, immunity is the mechanism by which a self, conceived as having borders, defends itself. Indeed, immunology is often described as the science of discrimination between self and non-self, and it has fulfilled that agenda by following a reductive exercise: defining the components of immunity and their regulation as a *self-contained* system (Moulin 1991). Accordingly, the self as a distinct, circumscribed *entity* could not have been more divorced from its environment in this formulation.

This conceptual structure is hardly surprising. Since immunology was born during the decipherment of infectious diseases at the end of the nineteenth century, immunologists have generally adopted an insular perspective, where an entity is *defended*. Indeed, when elucidating reactions against pathogens dominated immunology, a military metaphor of an 'army' of immune factors fighting to 'protect' the organism became standard currency. Not until the 1930s was the immune system considered as part of a complex ecology, and then, only tangentially. Macfarlane Burnet, a virologist by training, adopted "ecology" as part of a grand view of biology in which he hoped to situate immunology beyond the narrow confines of immunochemistry (Tauber 1994, 94–98; Crist and Tauber 2000). Inspired by the *Science of Life,* co-authored by H. G. Wells and Julian Huxley, Burnet began to fashion a comprehensive view of biology that would include ecology, developmental biology (with genetics), and immunology (Wells, Huxley, and Wells 1929). With an emphasis on ecological succession and the plant community as a complex organism undergoing a life-cycle and evolutionary history, he appreciated, analogous to the individual organism, parallels with the psychological self. Specifically, he regarded the triad—climax community (ecology), human body (organism), and self (psychology)—as analogous constructions and thereby affirmed a deep organic connection at three different levels of organization: ecological, cellular, and individual organism, each of which were structurally analogous and interconnected in a chain of being.

A profound irony then developed: In 1949, Burnet built upon the vague notion of selfhood he developed from his reading of *Science of Life* (Burnet and Fenner 1949) and formally introduced the notion of the immune *self*. According to his theory, the immune system discerned host elements to which it did not react, and those it failed to recognize as 'self' stimulated

https://doi.org/10.1086/590200 Published online by Cambridge University Press

an immune reaction. (The self was thus conceived as a 'negative' image, i.e., that which elicited no response). The Burnetian self, introduced as a metaphor of human personal identity, was consequently construed as requiring defense, and the immune system assumed its original task of protecting the host (the self) against pathogens.

So what began with a vague, metaphorical intuition about how immunity might function as a participant within a larger context, specifically an ecological one, quickly was submerged by the dominant concern of defining the immune self in molecular terms. Indeed, the immune self became a powerful epistemological focus of defining biological individuality.

The first serious challenge to this theoretical formulation was offered by Niels Jerne in 1974 with his proposed "idiotypic" immune system (Jerne 1974, 1985). Basically, Jerne postulated that the immune system consists of antibodies recognizing other antibodies and lymphocytes recognizing other lymphocytes through unique (*idiotypic*) domains. These distinguishing structures purportedly provide specific docking sites for the various elements, which through these interconnections, self-organize into a vastly complex interlocking system of joined antibodies and lymphocytes. The 'network' then rested in a stable state in its ongoing self-recognizing activity, but when a disturbance causes the lattice-like structure to readjust its normal valenced connections, an immune reaction ensues.

The notion of idiotypes remains an eccentric contribution, and its final status is still unresolved, but the main theoretical thrust of Jerne's highly integrated and self-sensing system posed a radical alternative to the self-non-self Burnetian formulation: In Jerne's theory, self and non-self dissolved as useful parameters of immune organization, because the idiotypic network *only saw itself*. Self and other were no longer classes in this theory, and thus immune reactivity became the parameter of interest, not selfhood per se. Essentially, Jerne argued that the perturbation of intricately balanced feedback loops would trigger immune responsiveness. His theory is characterized by the organizational principle of an inner driven, self-organizational model. If there is a self in Jerne's theory, it is the entire immune system as it 'senses' itself, but the distinction between self and non-self has no standing. Jerne's theory thus appears radically different from the dominant theories of immune function built from Burnet's dichotomy between self and non-self. Moving beyond the self, the issue became 'reactivity'—its initiation, its effector mechanisms, its controls.

The challenge posed by the network theory was twofold. Most generally, it demanded a functional theory of immunity, one based on the cardinal principle of an inward-directed self-seeking process; its critical weakness was lacking a stable reference for defining its basis for reactivity. In the older model, selfness served as the foundation of immune reactivity. Jerne

https://doi.org/10.1086/590200 Published online by Cambridge University Press

substituted 'perturbation' to account for immune reactivity, leaving the immune system to know only itself and thus both disqualifying and abdicating any responsibility for discriminating 'self' and 'other'.

Jerne's theory appeared as growing perplexity about autoimmunity drove some immunologists to ponder the utility of the self versus non-self discriminatory model as the basis for immune function. They have long understood that the beneficial effects of immunity carries costs, since the immune system is capable of apparently capricious assault on its host. So called autoimmune reactions were described at the turn of the last century, and later determined as cause of autoimmune disease, but because the entire orientation of the science was to see immunity as a mediator of host defense, these findings were viewed as a pathological aberrancy. Arising from an unregulated killer system gone awry, autoimmunity, on this view, could hardly be regarded as part of an expected continuum of normal immune function (Tauber 1994). 'Ideal' immunity was the agent of the self, and although there might be inconsistencies in behavior regarding that mandate, the basic structure of immunology demanded articulation of a model of identification and the protection of organismal identity. However, autoimmunity is now regarded as a normal physiological function of the immune system, not so much in the Jernian sense, but rather because immunocytes and their products survey and contribute to normal body economy. From the clearing away of senescent, damaged or dead cells to surveillance for malignancies, the immune system has a robust immune profile of activity directed at host elements, normal and abnormal. This understanding of immunity has served as a springboard of criticism directed at the polarization between self and non-self (e.g., Coutinho and Kazatchkine 1994; Podolsky and Tauber 1997, 326ff.).

The major difficulty, however, is to define "the immune self," which has been notoriously difficult to do. There are at least half a dozen different conceptions (Matzinger 1994) that might be situated by where one places the model on a continuum between a severe genetic reductionism and a complex construct employing different principles of organization. With so much dispute surrounding the definition of self, a growing counter position suggests that the 'self' might be better regarded as only a metaphor for a 'figure' outlined by the immune system's silence, that is, its non-reactivity. That figure is inconstant and modified upon certain conditions. (For instance, pregnancy, where a fetus, clearly different genetically from its maternal host, enjoys immunological indifference.) A second aspect of this imbroglio concerns immune reactivity where certain foreign elements are ignored, for example, cooperative relationships, such as the inactivity against symbionts that coexist in all organisms. (In humans, the best studied case is the vitamin K producing bacteria of the intestine (Ivanov, Diehl, and Littman 2006) that provide the cofactor required for

https://doi.org/10.1086/590200 Published online by Cambridge University Press

components of the blood coagulation and energy metabolism). Because immunology developed in the context of defensive functions, this cooperative biology and its complex teleology have remained obscured by the dominant concerns generated by the threat of pathogens. Indeed, the biomedical model has so dominated immunology that comparative immunology represents a small portion of the literature, and the specific ways in which the immune system tolerates, or even fosters cooperative relationships is smaller yet.

More to the point, the theory built upon 'the self' now appears to have many ad hoc caveats and paradoxes. Perhaps the evolution of the original metaphor to theory has begun to yield to another metaphorical construction (Tauber 1994). Here, we are putting aside this much discussed older debate about the character of the dichotomy between self and non-self that has framed immunology's theoretical structure for the past half century to consider instead a complementary way of addressing these same basic issues by focusing instead on an ecological orientation. That perspective already assumes a subordination of the individual to a collective picture of biological function, and in place of differentiation, integration and coordination serve as organizing principles. To this matter we now turn.

2. Immunology and Ecology: Historical Considerations. An ecological perspective now seems to be asserting its own claims more effectively, largely under the guise of systems biology. This development seems overdue. Beyond the tacit connections between immunology proper and its kindred disciplines of pathology, infectious diseases (human and veterinary medicine), and public health, the immune system as regulated by a larger context demands an accounting. That context still remains undefined, but the challenge of understanding autoimmunity and tolerance suggest that immune regulation arises from complex dynamics, possibly from outside the immune system itself as traditionally conceived. To broaden immunology's conceptual framework, immunologists have joined the general shift towards systems analysis that began to move the discipline from an almost exclusive reductive strategy to a more holistic one. That history is now briefly reviewed.

Immunology and ecology as modern disciplines were born almost simultaneously. Elie Metchnikoff formulated immunology's first active theory of immunity within a Darwinian construct (Tauber and Chernyak 1991; Gourko et al. 2000; Tauber 2003). He was the first to accurately regard phagocytic cells as engaged in a competitive struggle with invading microbes, and in that formulation, we might say he adopted the 'red in tooth and claw' attitude of the era. These initial immunological observations began at about the same time one of his competitors, Ernst

https://doi.org/10.1086/590200 Published online by Cambridge University Press

Haeckel coined the term 'ecology'. Haeckel, like Metchnikoff, was caught up in the Darwinian fever of the 1860s, and Haeckel thought a term was needed to refer to the study of the multifaceted struggle for existence, which Darwin's theory so clearly articulated. In 1866, Haeckel casually mentioned *ecology* as the study of "the interrelationships of living beings among themselves" and in 1870 elaborated this definition:

> By ecology we mean the body of knowledge concerning the economy of nature—the investigation of the total relations of the animal both to its inorganic and organic environment; including, above all, its friendly and inimical relations with those animals and plants with which it comes directly or indirectly into contact—in a word, ecology is the study of all those complex interrelations referred to by Darwin as the conditions of the struggle for existence (cited by McIntosh 1985, 7–8).

Haeckel and many nineteenth century biologists considered ecology simply a branch of physiology. Indeed, two founders of the discipline, the American botanists F. E. Clements and H. C. Cowles, described it as identical to physiology (McIntosh 1985, 3), and by the 1890s, they and others had initiated physiological studies of the relationships between organisms and their environment. They were guided by the theoretical supposition that nature was self-regulating and that balance, despite environmental changes of various kinds, remained operative in stable communities. Yet evolution ceaselessly exhibited how new challenges and opportunities required adaptation and so specific studies to comprehend those dynamics were finally recognized as crucial for understanding Darwinism. Especially in the United States, a dynamic, experimental approach to the study of adaptation, community succession, and population interactions made the early ecologist an "outdoor physiologist" (Kingsland 1991, 2). Despite the 'physiological' approach, ecology remained a distinct discipline quite divorced from those life sciences focused on the organism. Immunology clearly aligned itself with the biology of individuals, and indeed, one might easily argue it became the science of *individuality* at the expense of *community*.

Metchnikoff and Haeckel competed with each other in a number of research areas, including the definition of embryonic germ layers and hypothetical models of the first multicellular organism (Tauber and Chernyak 1991; Gourko et al. 2000). From those research interests, Metchnikoff went on to characterize the dynamics of the struggle between phagocytic cells and pathogens, while Haeckel remained within developmental biology with notorious excursions into eugenics, race theory, and philosophy. Their respective stories are not directly germane to our present concerns, other than to note that neither seemed to appreciate how eco-

https://doi.org/10.1086/590200 Published online by Cambridge University Press

logical relationships might be formally characterized. They, like Darwin, understood 'struggle for survival' in broad descriptive metaphors, and being so focused on the response of the host organism against pathogens, these zoologists never peered seriously beyond the individual to situate the animal within its greater environment—that development awaited the twentieth century.

Three definitions of ecology structure the modern literature: (1) a Haeckelian form—the study of the relationships between organisms and environment; (2) the distribution and abundance of organism—a population-centered ecology; and (3) the study of ecosystems—the most encompassing, moving from an emphasis on organisms to a comprehensive study of the structure and function of nature. One might assume that a holistic attitude dominated ecological thinking from the inception of the discipline, but the concept of the *ecosystem* emerged slowly (Golley 1993). Indeed, since the 1950s, contemporary ecology theory has developed around a core of issues, each of which may be seen as adopting, at least implicitly, a systems orientation: (1) community populations; (2) niche theory; (3) population dynamics of single species; (4) multi-species interactions; (5) population structure, and (6) the implications of individual behavior on population phenomena (Real and Levin 1991, 177).

The first version of general systems theory was presented in the context of multi-species interactions. These were the mathematical models (produced between 1910 and 1920) of Sir Ronald Ross and W. R. Thompson, which were based (ironically!) on host-parasite epidemiology (Kingsland 1985). This work was developed in the 1920s by A. J. Lotka and Vito Valterra, who demonstrated oscillatory predator-prey dynamics (Real and Levin 1991, 187–188). Yet *ecosystem,* as such, awaited another context. Although A. G. Tansley, a British plant ecologist, introduced the term 'ecosystem' in the context of a super-organism plant community, Raymond Lindeman ([1942] 1991) outlined what became ecosystem ecology by (1) emphasizing quantitative relations in determining community patterns through succession; (2) identifying the dynamic process of energy flow, and (3) adopting a theoretical orientation in ecology (McIntosh 1985, 193ff.). Eugene Odum's influential textbook (1953) formally brought this systems-based thinking to modern ecology. Initially organized around the measurement of energy flow through the system (the first example was the study of a lake), this 'new ecology' expanded its horizons quickly to deal with "the structure and function of levels of organization beyond that of the individual and the species" (Odum quoted by McIntosh 1985, 200), which Odum expanded into a new biology: Ecology is "not just a subdivision of biology, but a new discipline that integrates biological, physical, and social science aspects of man-in-nature interdependence" (quoted by McIntosh 1985, 202). The *ethos* of the discipline was now

https://doi.org/10.1086/590200 Published online by Cambridge University Press

guided by a holistic ideal, which would integrate the component parts and consider the ecosystem as a *hierarchical* unit (O'Neill et al. 1986). The influence of this orientation eventually permeated the organism-based sciences, including immunology.

3. A Conceptual Shift? An obvious way of approaching the immune system ecologically is to consider the overall adaptation of the individual, as well as the species-as-a-whole, within its environment. Characterized by population dynamics, the competitive context is traditionally assessed by predator relations, cooperative behaviors, food sources, environmental effects, and so on. Immunity is another important measurement of these relationships. How microbe and host relationships maintain stability, and perhaps just as important, how equilibriums are disrupted, provides a key parameter by which individuals and species competition are defined in the medical, economic, and agricultural disciplines. If one seeks a teleological explanation of immunity, survival and fitness certainly present a rich basis for sorting out immune behavior.

Because the immune system resides at the interface between the organism and its environment, it is fairly regarded as a first line of defense, or more broadly an information processor for the host organism. While immune cells distribute themselves throughout the body, they are particularly conspicuous at the interfaces between host tissues and the environment: within the skin and underlying muscosal surfaces (e.g., the respiratory tract and gastrointestine). These are the sites where the body first encounters chemicals and micro-organisms, and thereby senses toxins and destroys pathogens. Such interfaces are obviously open and dynamic, and they possess a complexity distinct to themselves.

Ecologists refer to such transition sites of adjacent ecological communities, for example, forest and grassland habitats, as an *ecotone*. 'Ecotone' is derived from *eco*-, 'house' or 'household', and the root *tonos*, the source of the word 'tone,' which means 'act of stretching or tension' (i.e., 'tone' is produced from a stringed instrument). The ecotone then is both the 'home' of certain species, but also one in which new tensions, or opportunities, arise. The notion of an ecotone captures the biological richness and diversity of comingled species interacting in the same space, and more to our concerns, the ecotone explicitly frames the reference of study to include both the microbe and the host animal. Because such border areas contain species from each habitat, unique forms of competition may occur, giving rise to unique dynamic relationships. From one perspective, new competition means facing new threats, but from another vantage, new opportunities arise in such an environment. From a quite different point of view, ecotones may be seen as engines of biological innovation. Diversity and dynamism are greatest at the margins

https://doi.org/10.1086/590200 Published online by Cambridge University Press

between habitats, and it is at such interfaces that whole new biological forms probably originated. Far from being places of pure strife, some ecotones are characterized as much by cooperation and synergism as by cutthroat competition. How might immunologists formally utilize this context in which to conduct studies relevant to 'ecological physiology'?

4. Introducing Systems Biology to Immunology. To adequately address the larger dynamics that must account for the coexistence of interacting species, a systems approach is required that is capable of accounting for the behaviors of the immune system—both of individuals and that of the population's collective immunity. Such a study presents the language of a dialogue between individual organisms and their environments in response to the challenges received from diverse encounters. In short, the immune system functions at the interface of host organism and its environment both defensively and cooperatively. Immunity accomplishes that task in a two step process: First, as a cognitive system, one responsible for perceiving the environment, and second, as enacting appropriate responses to that environment. By first framing immunity as perception, regulation becomes a process arising from both internal equilibrium mechanics *and* stimulation from external sources. A systems approach accounts for both, and here I will explore the conceptual resonances between three different organizing orientations: ecological, cognitive, and systems biology.

Cognitive functions are fundamentally *open*, and thus immune theory should describe how immune system design permits, and then responds to, open information flow. Given these general concerns, immunology already has the conceptual infrastructure to assume a fuller ecological orientation—placing immune reactivity (regulation) within an environment of inputs. So beyond understanding how a particular antigen might be regarded as harmful to a particular individual or species (and thus subject to immune destruction), the wider reference of 'ecological immunology' attempts to determine the costs of defensive mechanisms to the community-at-large[1] (Sheldon and Verhulst 1996; Norris and Evans 2000). That understanding requires a systems biology approach firmly

1. Note, 'ecological immunology' is not the same concept as 'immuno-ecology', which Charles Orosz defines as "the study of the immunological principles that permit effective immunologic function within the context of the immensely complex immunologic network" (2001, 125). Orosz is seeking to understand the immune system as an ecology, but he makes no effort to 'open' that system in the way I describe here, i.e., to place the animal within its larger environment and turn immunology into an ecological science. Elling Ulvestad's *Defending Life* (2007; reviewed by Tauber [2008]) qualifies as the most comprehensive treatment to date of the 'ecological consciousness' described here.

https://doi.org/10.1086/590200 Published online by Cambridge University Press

planted in information theory, which then reaches beyond the organism to its placement within it environment: Information theory represents the window by which the organism must be understood as living in an environment it must *know* in order to survive.

The first step along the path that will decipher this cognitive structure requires a re-formulation of an atomistic conception of immune selfhood, namely that an entity, 'a self', exists to be defended against intruders (Janeway 1989). However, just as important as the offensive weaponry might be, the ability to remain 'silent' (tolerant), to live in a world of others, must also mark immune function. Immune tolerance, the absence of reactivity, also distinguishes the immune system as a cognitive apparatus. Thus, neither indolent innocence nor persistent aggression captures the activity of the immune system, which must function within a changing environment of friend and foe. Defining the off or on status of immune reactivity is not simply a question of identifying the 'other', but involves multiple stages of sensing, adjusting, and configuring immune reactions—positive and negative—in settings that vary in time and space.

Immunity ranges from a 'pre-immune' state, whereby immune cells sense the presence of bacteria well before their formal encounter, to full blown activation (Germain 2001). 'Priming' events signal the sensitive connections of an ecological state—bacteria and immune system—in which a web of molecular links communicate the presence of 'the other'. This ecological orientation brings issues of communication and information theory directly onto notions of immune regulation, where different tiers of bidirectional cognition between pathogens and immune cells set the balance of responses and adaptation. Indeed, 'immune cognition'—replete with metaphorical 'memory', 'perception', and 'recognition'—has already provided a new scientific lexicon for a variety of converging conceptual orientations (Tauber 1997).

Immune cognition has been appropriated by immunologists of widely differing theoretical orientations. On the one hand, it has been used to describe the MHC-lymphocyte encounter as a perception event to be understood by the reductive strategies employed by those descendents of the immunochemists, who sought definition of the immune reaction in terms of the most basic molecular mechanisms. On the other hand are those theorists who seek to model the immune system in terms of its global properties, understanding cognition as analogous to the emergent properties of the mind. These conflicting uses of cognition have long antecedent historical roots, which reflect differing cognitive models (Tauber 1997).

In the 1990s, various theoretical speculations about immune 'dialogue' with the body emerged from this cognitive orientation. Surveillance and autoimmunity framed Irun Cohen's model, in which the immune system

https://doi.org/10.1086/590200 Published online by Cambridge University Press

continuously exchanges molecular signals with its interlocutor, the body (Cohen 1992, 1994). Zvi Grossman placed the reactive lymphocyte in a medium of varying activation states that were set by the larger inflammatory context (Grossman and Heberman 1986; Grossman 1989; Grossman and Paul 1992), an idea further developed by Polly Matzinger, whose contextualist orientation explicitly extended immunity to include an array of physiological functions, each of them now regarded as fully integrated with the organism-as-a-whole (Matzinger 1994; Anderson and Matzinger 2000a, 2000b). She formulated the immune system as interlocked with every compartment of the body, and thereby regulated in response to 'danger' signals that might arise from any tissue subject to injury or insult. The 'meaning' of immunogenicity, that is, reactivity, in this format is situated within a larger functional framework, for example the sense of 'danger' ensuing from inflammation (Matzinger 1994).

These theorists agreed that antigenicity, then, is only a question of degree: healthy host constituents are assessed and ignored; damaged or senescent host elements evoke responses ranging from vary degrees of tolerance to active destruction, and that regarded as 'foreign' suffers full blown assault. These conceptions of the immune system thus highlight immune activity engaged in ongoing sensing of the organism itself as immunocytes constantly survey their jurisdiction (Schwartz and Cohen 2000). This move from a simple on or off switch heralds a decisive shift in immunology's theoretical foundations, one more attuned to the diversity of immune functions, and the various modalities of activation, which contribute to evolutionary fitness (Cohen 1992, 1994; Grossman and Paul 1992; Stewart 1994b; Tauber 2005). Note, however, these models were contextually driven, but still not fully ecological, inasmuch as the host organism formed the boundaries of regulation.

From an ecological perspective, there can be no circumscribed, self defined entity that is designated *the self* (Tauber 2000; alternate views are given in Langman 2000). Rather, the organism adjusts its own identity as it responds along a continuum of behaviors to adapt to the challenges it faces, and, indeed, 'identity' is determined by particular context. Responses are consequently based not on intrinsic foreignness, but rather on how the immune system sees an 'alien' or 'domestic' antigen in the larger context of the body's economy (Grossman and Paul 2000; Horn et al. 2001). So, while host defense is a critical function, it is hardly the *only* one of interest. Indeed, the immune system might be regarded as primarily fulfilling an altogether different autoimmune role if its resting physiology is measured and its phylogeny carefully examined. On this basis, John Stewart has provocatively suggested that the immune system became defensive only after its primordial neuroendocrine communicative capabilities were usurped for 'immunity' (Stewart 1992, 1994b). Accord-

https://doi.org/10.1086/590200 Published online by Cambridge University Press

ingly, immunology becomes part of a more comprehensive psychoneuroimmunology, which defines immunity as a cognitive activity coordinated with other cognitive systems (Ader et al. 2001). To model such complex behavior, a systems approach seems appropriate. Movement toward this goal is evident, but *what* is systems biology?

5. A New Approach? Systems biology applied to ecology, as already reviewed, is not new. And in immunology, early stirrings appeared in the 1950s under the mantle of cybernetics. Indeed, both ecologists and immunologists were intrigued with the promise of cybernetics for their respective disciplines, but the hopes were largely frustrated, inasmuch as direct application of Shannon-Weaver formalisms failed (McIntosh 1985, 210–213; Tauber 1994, 161–165). But frustration ran deeper. The cybernetic movement was actually part of a larger systems approach, one which drew from several sources. As a result, the discipline has had difficulty melding itself into some unity, indeed, some would argue that systems biology has never come to peace with its own definition. No wonder, inasmuch as it is a mosaic of six theoretical programs (Lilienfeld 1978):

1. Systems philosophy (von Bertalanffy 1968; Laszlo 1972; Patten 1975);
2. Cybernetics (Ashby 1956; Weiner 1961);
3. Information theory (Shannon and Weaver 1949);
4. Operations research;
5. Game theory (von Neumann and Morgenstern 1947);
6. Computer simulation of complex systems (e.g., Forrester 1961).

According to this schema, a philosophy underlies the technical enterprise, and cybernetics, coupled to information theory, serve together in various guises in the modeling of complex systems. Which horse will lead the chariot is still unclear. Different systems may require different sorting of the various components, but more fundamentally, systems biology lacks a specific definition and has no specified method, so perhaps proponents follow an intuition, which skeptics regard as a promissory note (at best). Accordingly, systems biology seeks to supplement an older reductionist analysis of complex biological phenomena with an integrative strategy that would combine the various elements into a coherent, dynamic whole (Woese 2004).

Conceptually, modeling has been divided two distinct strategies. (1) A *holistic* approach treats the system as a black box and considers only inputs and outputs, in contrast to (2) a *mereological* (reductionist) approach, which builds the system from its component parts. Despite their obvious oppositions, these conceptual roots are revealing and potentially important. Integrative, holisitic, contextualist and organicist approaches

https://doi.org/10.1086/590200 Published online by Cambridge University Press

each refract a reaction against analytic atomism and combine to *suggest* a major reorientation in scientific thinking—from Cartesian reductionism to something else. However, at this point, depending on its various applications, systems biology has several personifications, and most would agree, based on projected experimental suggestions or predictive applications, systems biology has yet to 'deliver the goods'.

Levins and Lewontin correctly observed that the computer models of 25 years ago were not holistic, but rather only expressions of large scale reductionism (1985). That criticism still holds among many skeptics as they await a major breakthrough (Mekios 2007). While the contemporary agenda remains holistic in sentiment, the question remains whether system-wide principles may be discerned beyond the assembly of connected discrete elements determined by relationships formed at their own level. Proponents say all the right things: Their approach aims at a "system-level understanding of biological systems," which includes the identification of a system's structure, behavior, control, and design (Kitano 2001, 2–4). Presumably this includes establishing, for various biological systems—cellular (metabolic, genetic), physiological (e.g., immune, neuroendocrine), and ecological—their large-scale organization, regulation, information processing, and integration with other systems.

Immunology's basic theory may well be in a transition period, but it is simply too soon to decide. Without presenting some singular method for immunologists seeking their own recipe to mix these various elements, suffice it to note that as a cognitive system, immune reactivity requires information theory, that is, the means by which the organism *knows* its environment. (Here, I am referring to information theory as the window by which to conceptualize the transition of latent information to some active form, that is, information that is selected and then processed. Or as John Nicolis quipped [1991, viii], "Information is an *a posteriori* measure of an *a priori* uncertainty, i.e., lack of predictability.") By better understanding how information is selected, regulatory mechanisms will be both deepened and broadened. In short, models based on systems analysis presumably will push immunology towards a larger ecological conceptualization for understanding immune regulation.

6. Formalizing Immunology. The applications in ecology of differential equation modeling and computer simulations began in earnest during the 1950s (Neel and Olson 1962), while immunology lagged behind by almost 25 years. Computer modeling, most closely related to Shannon information theory, was first used by Alan Perelson in the mid-1980s (Farmer et al. 1986). This programmatic paper contained no data, only differential equations that sought to formulate an immune system 'learning machine'. The modeled system was based on the self-contained network proposed

https://doi.org/10.1086/590200 Published online by Cambridge University Press

by Jerne (1973, 1974). The development of this approach may be traced to Jerne's suggestion that the immune system was analogous to a translation-reading machine (Jerne 1960), and, indeed, Perelson's paper employed 'bits' and 0–1 nomenclature. Noteworthy, Perelson, and virtually all who followed him, were dependent on an immune system model that was self-contained and self-regulated. They would design a system, but it was a *closed* system, and in that very formulation, a wider systems biology was beyond reach.

Shortly thereafter, Perelson (1988) edited two volumes of papers dedicated to immune modeling and with Tom Schneider's "sequence logos" approach (Schneider and Stephens 1990), the field began to attract some interest and other approaches soon followed (e.g., Atlan and Cohen 1989; Cohen and Atlan 1989; Vertosick and Kelly 1989; Stewart 1994a). Schneider graphically represented an aligned set of binding sites and proteins measured in Shannon bits of information, which threw open the door to artificial immune systems, bioinformatics algorithms and computational biology. Led by advances in connectionism then popular in the neurosciences, these modelers pushed on despite recognizing that the limits of the linear dynamics were insufficiently robust to deal with the complexity of such systems.

The 'systematic' strategy requires high output, comprehensive data from simultaneous measurements of multiple features. For example, to obtain a complete understanding of gene regulatory networks, various simulations and analyses must be performed in order to assess binding constants; rates of transcription and translation; kinetics of chemical reactions, degradation, diffusion; speed of active transport, and so on. Thus simultaneous study at several different levels of cellular organization are required. Drawing strong analogies from engineering, admittedly a big assumption (Kitano 2001, 18; Heinemann and Panke 2006), enthusiasts argue that biological systems achieve robustness and stability through the same principles with which we build machines, namely using system controls (e.g., feedback), redundancy (e.g., gene duplication, alternative metabolic pathways), modular design (to minimize damage to local units), and structural stability. From a systems perspective—perturbation of the dynamics dependent on diverse and multiple causes, coupled to complex controls—result in altered network activities. Nonlinear, probabilistic, mathematics are required to model such behavior, and so the resultant simple mechanical machine models will be replaced by different kinds of formalisms.

Moving from the theoretical to the practical, one strategy calls for the establishment of a 'systeome', an assembly of system profiles for all genetic variations and environmental stimuli responses of a cell. Unlike a cascade map, a systeome would provide active and dynamic simulations of various system statuses, as opposed to a static entity. Hiroaki Kitano has sug-

https://doi.org/10.1086/590200 Published online by Cambridge University Press

gested, analogous to the Human Genome Project, a 'Human Systeome Project', which endeavors to complete a detailed and comprehensive simulation model of the human cell at an estimated error margin of 20 percent by the year 2030, which would include identifying the system profile for all genetic variations, drug responses, and environmental stimuli (Kitano 2001, 25). From such analyses, the argument goes, elucidation of what appears as emergent phenomena of complex systems will have a material basis (Kitano 2001; Hood 2002; Alm and Arkin 2003; Mekios 2007). Those seeking a New Biology might well herald systems biology as an antidote to "molecular biology's obsession with metaphysical reductionism" (Woese 2004, 179), and immunologists seeking the elucidation of complex regulatory mechanisms have joined this new effort.

Indeed, much has changed since the early attempts at immune system analysis, where a simple dichotomy between self and non-self framed simple linear, mechanical model of on or off switches (i.e., 'self' and 'other' reflect the binary decisions of such mechanisms). But in systems based on nonlinear dynamics, where control mechanisms arise from many sources and effects are realized by the summation of signals in a complex calculus, how could such a dichotomous picture survive? If regulation were understood in terms of the fine tuned accession of responses, as opposed to the simplified on or off setting of discrimination between self and non-self, more sophistication would be required. Such a reformulation may develop as a result of the growing understanding of system analyses, and, indeed, the advent of systems biology is beginning to impact on immunology.

'Immunocomputing', or artificial immune systems, has drawn on recent developments in computer science, information processing, pattern recognition, language representation and knowledge based reasoning (e.g., Tarakanov et al. 2003; Cohen 2007), and, in turn, immune based system analysis is regarded by some as a fruitful source for applications to pattern recognition, fault and anomaly detection, data analysis, scheduling, machine learning, autonomous navigation and control, search and optimization methods, artificial life, and security of information systems (de Castro and Timmis 2002). The first textbook devoted to immunological bioinformatics and the goal "to establish an *in silico* immune system" (Lund et al. 2005, ix) has been followed by a surge of interest and speculation (e.g., Bersini and Carneiro 2006; Flower 2007; Flower and Timmis 2007). As one enthusiast opined, "after . . . 100 years of empirical research, immunology is hovering on the brink of reinventing itself as a quantitative, genome-based science . . . whether or not the multitude of practitioners of immunology wish to acknowledge it" (Flower 2007, 2).

The strategy offered is a stepwise approach, where models of discrete immune phenomena (e.g., diseases, immune reactions, vaccines) or per-

https://doi.org/10.1086/590200 Published online by Cambridge University Press

haps more modestly, function of various cell types, might be combined into larger models. Thus quantitative modeling requires an analysis at several levels—comparative genomics and proteomics, co-evolution with pathogens, tissue-specific processes, population dynamics, cell turnover kinetics, and regulation networks. This multidisciplinary approach includes bioinformatics, genomics, proteomics, cellular, molecular, and clinical immunology modeling, and ultimately, mathematical descriptions and computer simulations.

Protein-protein and protein-peptide interactions are key to the recognition process and the overall functionality of the immune response, and thus proteome-wide knowledge of such interactions is essential. Due to novel high throughput techniques, interaction data are quickly developing and the databases have already provided new initiatives for modeling and systems analysis. Once protein-protein interaction networks are better established, these may then be integrated with more sophisticated organizational models of cell-cell interactions and the cytokine network that regulates them. The cellular field has developed in parallel with the protein analysis, but as the system is studied at finer and finer levels of resolution, decreased predictability in the behavior of any particular unit of function (e.g., a gene, a cell) decreases (Germain 2001). Nevertheless, simulation computer graphics have been used to produce and direct an animation of T lymphocytes and other cells moving, interacting, multiplying, differentiating or dying in the course of development in the thymus (Efroni et al. 2003). The simulation allows analysis of individual cells and their component molecules as well as the ability to view thousands of cells interacting in the formation of the thymus. Whether such computational modeling reveals self-regulatory properties of the immune system (Cohen and Harel 2007) remains to be tested experimentally.

7. Conclusion. Despite reasonable skepticism, the systems biology movement with its holistic aspirations has, at the very least, supplemented the present fixation on reductionism. As many intuited during the past decade that older approaches had reached some nebulous limit, a new enthusiasm for a bona fide systems-based biology appeared. With this shift to a global or holistic construct, concomitant with the technology to achieve these ends, biology may be moving towards realizing concepts already evident with Aristotle. Indeed, from *De Anima* to twentieth century physiology, holism has held its position in biology, albeit subordinate to the prevailing reductionist strategy. Now, with the multitudinous generation of data emerging from genetics and cell biology, biologists must seek new means of analyzing their findings, which requires the synthesis of vast amounts of data. The field of bioinformatics was thus born, and with it systems biology. If successful, the current emphasis on reductive analyses will be

https://doi.org/10.1086/590200 Published online by Cambridge University Press

seen as closed and ironically incomplete. Some would argue that such a shift has been overdue.

Modern biology has been committed to the physical and epistemological reductionism originally developed by Hermann Helmholtz and other German physiologists in the mid-nineteenth century (Galaty 1974; Lenoir 1982). This philosophy has focused research efforts at defining the various elements of complex organic processes, and then only as a secondary step, attempting to bring those parts into coherent wholes. Through that strategy, twentieth century biochemistry, cell biology, molecular biology, and immunology have each constructed increasingly complex structures to depict life processes, but the ability to reassemble the elements back into the wholes from which they were partitioned have been stymied, because the simple mechanical models that have been employed for a century (Loeb 1912) cannot account for the regulatory dynamics exhibited by such complex phenomena.

In the case of immunology, the context of immune reactivity has demonstrated that simple on or off responses and feedback loops are insufficient for explaining immune function. The extracellular milieu of the lymphocyte is a critical determinant, and that larger context must be understood as encompassing ever-increasing domains (tissue, organism, external environment). And even at the single cell level, the condition of the local cell surface, the scene of interacting accessory molecules (e.g., cytokines), have long been known to mediate the immune reaction through various modulations (e.g., Grossman and Paul 1992; Banchereau 1994). The cytokines comprise hundreds of mediators and their receptors controlling dozens of functions. They exhibit the same general functional properties of other bioactive peptides: in one setting, an agonist may exhibit stimulatory properties, whereas in another, inhibition (Denny 2001). Indeed, clues from the cytokine system suggest designs for a distributed autonomous control network that must be dynamic, robust to small perturbations, and yet responsive to large disturbances (Forrest and Hofmeyr 2001).

Because the physiological role of any antigen or cytokine is determined by a larger context than simply binding to its receptor, effects cannot be predicted within a narrow domain of inquiry, because (1) signals of different integrated strengths evoke different responses; (2) the mode of response depends on timing of signal events; (3) activation thresholds may be 'tuned' so that some lead to an enhanced state, while others become inhibitory so that molecular agents may operate as an agonist or an antagonist, depending on the adapted state of the cell (Podolsky and Tauber 199, 352ff.). These characteristics must guide models that would address how the discriminatory challenges facing the immune system require balancing immune protection, damage to the host, and physiological

https://doi.org/10.1086/590200 Published online by Cambridge University Press

(normal) autoreactivity (Grossman and Paul 2000, 2001), within the larger context of the organism's place in its ecosystem, where cooperative relationships must also thrive. Coupling these various layers, lines of regulation dramatically multiply. In short, to explain immune reactivity, functions must be placed within larger teleological constructs, and how these are drawn already assumes a limited domain of what must comprise an integration of *all* levels of directed responses.

On this view of immune regulation, the various biochemical cycles of intermediate metabolism drawn in the 1950s appear simple and refreshingly clear, where homeostasis became the sole parameter of assessment. The successes of those depictions now appear as resulting from a smaller scale of detail, the more simplified on or off character of the described reactions (relatively few components integrated by single positive- and negative-feedback connections), and most importantly from our point of view, the singular teleology of homeostatic balance in which biochemical functions were framed. With the advent of contemporary molecular studies, such an approach has become fraught with technical and conceptual difficulties.

Whether we are now witnessing stirrings of an effective alternative approach or only the excitement of a misconceived venture remains for experimentalists to determine. I remain agnostic about the outcome, but as a philosopher, I regard systems biology as an organizing idea supportive to an alternative formulation of the immune system. So beyond systems biology applied to immunology as a technical matter, a fully ecological perspective (supported by systems biology more generally) would alter the basic postulates of immune theory based on an insular self. Instead of a theory grounded on self/non-self distinctions, models of the immune system would be built on an 'open' architecture to fully represent the dynamic and dialectical relationship characterizing an organism engaged in its environment. Note, a systems approach may be applied to either the self/non-self or ecological conception of immunity, and so *conceptually*, the arguments for and against these competing views provide the arena for the philosopher's own discourse, one that has repercussions for philosophy of biology at large.

REFERENCES

Ader, R., D. L. Felten, and N. Cohen, eds. (2001), *Psychoneuroimmunology*. 3rd ed. San Diego: Academic Press.

Alm, E., and A. P. Arkin (2003), "Biological Networks", *Current Opinion in Structural Biology* 13: 193–202.

Anderson, C. C., and P. Matzinger (2000a), "Anderson and Matzinger Round 2", *Seminars in Immunology* 12: 277–291.

——— (2000b), "Danger: The View from the Bottom of the Cliff", *Seminars in Immunology* 12: 231–238.

https://doi.org/10.1086/590200 Published online by Cambridge University Press

Ashby, W. R. (1956), *An Introduction to Cybernetics*. New York: Wiley.
Atlan, H., and I. R. Cohen, eds. (1989), *Theories of Immune Networks*. Berlin: Springer-Verlag.
Banchereau, J., et al. (1994), "The CD40 Antigen and Its Ligand", *Annual Review of Immunology* 12: 881–922.
Bersini, H., and J. Carneiro, eds. (2006), *Artificial Immune Systems*. Berlin: Springer-Verlag.
Burnet, F. M., and F. Fenner (1949), *The Production of Antibodies*. 2nd ed. Melbourne: Macmillan.
Cohen, I. R. (1992), "The Cognitive Paradigm and the Immunological Homunculus", *Immunology Today* 13: 490–494.
——— (1994), "Kadishman's Tree, Escher's Angels, and the Immunological Homunculus", in A. Coutinho and M. D. Kazatchkine (eds.), *Autoimmunity: Physiology and Disease*. New York: Wiley-Liss, 7–18.
——— (2007), "Real and Artificial Immune Systems: Computing the State of the Body", *Nature Reviews/Immunology* 7: 569–574.
Cohen, I. R., and H. Atlan (1989), "Network Regulation of Autoimmunity: An Automaton Model", *Journal of Autoimmunity* 2: 613–625.
Cohen, I. R., and D. Harel (2007), "Explaining a Complex Living System: Dynamics, Multi-scaling and Emergence", *Journal of the Royal Society Interface* 4: 175–182.
Coutinho, A., and Kazatchkine, M. (1994), "Autoimmunity Today", in A. Coutinho and M. Kazatchkine (eds.), *Autoimmunity: Physiology and Disease*. New York: Wiley-Liss, 3–6.
Crist, E., and A. I. Tauber (2000), "Selfhood, Immunity, and the Biological Imagination: The Thought of Frank Macfarlane Burnet", *Biology and Philosophy* 15: 509–533.
de Castro, L. N., and J. Timmis (2002), *Artificial Immune Systems: A New Conceptual Intelligence Approach*. London: Springer-Verlag.
Denny, T. N. (2001), "Cytokines: A Common Signaling System for Cell Growth, Inflammation, Immunity, and Differentiation", in L. A. Segel and I. R. Cohen (eds.), *Design Principles for the Immune System and Other Distributed Autonomous Systems*. New York: Oxford University Press, 29–77.
Efroni, S., D. Harel, and I. R. Cohen (2003), "Toward Rigorous Comprehension of Biological Complexity: Modeling, Execution, and Visualization of Thymic T-Cell Maturation", *Genome Research* 13: 2485–2497.
Farmer, J. D., N. H. Packard, and A. S. Perelson (1986), "The Immune System, Adaptation, and Machine Learning", *Physica* 22: 187–204.
Flower, D., ed. (2007), *Immunoinformatics: Predicting Immunogenicity in Silico*. Totowa, NJ: Humana.
Flower, D., and J. Timmis, eds. (2007), *In Silico Immunology*. New York: Springer.
Forrest, S., and S. A. Hofmeyr (2001), "Immunology as Information Processing", in L. A. Segel and I. R. Cohen (eds.), *Design Principles for the Immune System and Other Distributed Autonomous Systems*. New York: Oxford University Press, 361–387.
Forrester, J. W. (1961), *Industrial Dynamics*. Cambridge, MA: MIT Press.
Galaty, D. H. (1974), "The Philosophical Basis of Mid–Nineteenth Century German Reductionism", *Journal of the History of Medicine and Allied Sciences* 29: 295–316.
Germain, R. N. (2001), "The Art of the Probable: System Control in the Adaptive Immune System", *Science* 293: 240–245.
Golley, F. B. (1993), A History of the Ecosystem Concept: More than the Sum of the Parts. New Haven, CT: Yale University Press.
Gourko, H., D. I. Williamson, and A. I. Tauber, eds. (2000), *The Evolutionary Biology Papers of Elie Metchnikoff*. Dordrecht: Kluwer Academic.
Grossman, Z. (1989), "The Concept of Idiotypic Network: Deficient, or Premature?", in H. Atlan and I. R. Cohen (eds.), *Theories of Immune Networks*. Berlin: Springer-Verlag, 38–52.
Grossman, Z., and R. B. Herberman (1986), "Immune Surveillance without Immunogenicity", *Immunology Today* 7: 129–131.
Grossman, Z., and W. E. Paul (1992), "Adaptive Cellular Interactions in the Immune System:

https://doi.org/10.1086/590200 Published online by Cambridge University Press

The Tunable Activation Threshold and the Significance of Subthreshold Responses", *Proceedings of the National Academy of Science (U.S.A.)* 89: 10365–10369.
——— (2000), "Self-Tolerance: Context Dependent Tuning of T Cell Antigen Recognition", *Seminars in Immunology* 12: 197–203.
——— (2001), "Autoreactivity, Dynamic Tuning and Selectivity", *Current Opinion in Immunology* 13: 687–698.
Heinemann, M., and S. Panke (2006), "Synthetic Biology—Putting Engineering into Biology", *Bioinformatics* 22: 2790–2799.
Hood, L. (2002), "My Life and Adventures Integrating Biology and Technology", Commemorative Lecture for the 2002 Kyoto Prize in Advanced Technologies. http://www.systemsbiology.org/extra/2002kyoto.pdf.end-break-point
Horn, M. P., et al. (2001), "Natural Antibodies—Benefits of Recognizing 'Self'", *Modern Aspects of Immunobiology* 1: 267–270.
Ivanov, I. I., G. E. Diehl, and D. R. Littmann (2006), "Lymphoid Tissue Inducer Cells in Intestinal Immunity", *Current Topics in Microbiology and Immunology* 308: 59–82.
Janeway, C. A., Jr. (1989), "Approaching the Asymptote? Evolution and Revolution in Immunology", *Cold Spring Harbor Symposia of Quantitative Biology* 1: 1–13.
Jerne, N. K. (1960), "Immunological Speculations", *Annual Review of Microbiology* 14: 341–358.
——— (1973), "The Immune System", *Scientific American* 229: 52–60.
——— (1974), "Towards a Network Theory of the Immune System", *Annals of Institute Pasteur/Immunology* (Paris) 125C: 373–389.
——— (1985), "The Generative Grammar of the Immune System", *EMBO Journal* 4: 847–852.
Kingsland, S. A. (1985), *Modeling Nature: Episodes in the History of Population Ecology*. Chicago: University of Chicago Press.
——— (1991), "Defining Ecology as a Science", in L. A. Real and J. H. Brown (eds.), *Foundations of Ecology: Classic Papers and Commentaries*. Cambridge, MA: MIT Press, 1–13.
Kitano, H. (2001), "Systems Biology: Toward System-Level Understanding of Biological Systems", in H. Kitano (ed.), *Foundations of Systems Biology.* Cambridge, MA: MIT Press, 1–36.
Langman, R., ed. (2000), *Self-Non-self Discrimination Revisited*, *Seminars in Immunology* 12, no 3.
Laszlo, E. (1972), *Introduction to Systems Philosophy: Toward a New Paradigm of Contemporary Thought*. New York: Harper Torchbooks.
Lenoir, T. (1982), *The Strategy of Life: Teleology and Mechanism in Nineteenth-Century German Biology*. Dordrecht: Reidel.
Levins, R., and R. Lewontin (1985), *The Dialectical Biologist*. Cambridge, MA: Harvard University Press.
Lilienfeld, R. (1978), *The Rise of Systems Theory: An Ideological Analysis*. New York: Wiley.
Lindeman R. L. ([1942] 1991), "The Trophic-Dynamic Aspect of Ecology". Reprint. In L. A. Real and J. H. Brown (eds.), *Foundations of Ecology: Classic Papers and Commentaries*. Originally published in *Ecology* 23: 399–418. Cambridge, MA: MIT Press, 157–176.
Loeb, J. ([1912] 1965), *The Mechanistic Conception of Life*. Cambridge, MA: Harvard University Press.
Lund, O., et al. (2005), *Immunological Bioinformatics*. Cambridge, MA: MIT Press.
Matzinger, P. (1994), "Tolerance, Danger, and the Extended Family", *Annual Review of Immunology* 12: 991–1045.
McIntosh, R. P. (1985), *The Background of Ecology: Concept and Theory*. Cambridge: Cambridge University Press.
Mekios, C. (2007), *Approaching Organisms as Systems: A Critical Study of the Method of "Systems Biology"*. PhD Dissertation, Department of Philosophy. Boston: Boston University.
Moulin, A. M. (1991), *Le dernier langage de la médicine: Histoire de l'immunologie de Pasteur au Sida*. Paris: Presses Universitaires de France.

https://doi.org/10.1086/590200 Published online by Cambridge University Press

Neel, R. B., and J. S. Olson (1962), *Use of Analog Computers for Simulating the Movements of Isotopes in Ecological Systems*. Publication no. 3172. Oak Ridge, TN: Oak Ridge National Laboratory.
Nicolis, J. S. (1991), *Chaos and Information Processing: A Heuristic Outline*. Singapore: World Scientific.
Norris, K., and M. R. Evans (2000), "Ecological Immunology: Life History Trade-offs and Immune Defense in Birds", *Behavioral Ecology* 11: 19–26.
Odum, Eugene P. (1953), *Fundamentals of Ecology*. Philadelphia: Saunders.
O'Neill, R. V., et al. (1986), *A Hierarchical Concept of Ecosystems*. Princeton, NJ: Princeton University Press.
Orosz, C. (2001), "An Introduction to Immuno-ecology and Immuno-informatics", in L. A. Segel and I. R. Cohen (eds.), *Design Principles for the Immune System and Other Distributed Autonomous Systems*. New York: Oxford University Press, 125–149.
Patten, B. C., ed. (1975), *Systems Analysis and Simulation in Ecology*. New York: Academic Press.
Perelson, A. S., ed. (1988), *Theoretical Immunology*. 2 vols. Redwood City, CA: Addison-Wesley.
Podolsky, S. H., and A. I. Tauber (1997), *The Generation of Diversity: Clonal Selection Theory and the Rise of Molecular Immunology*. Cambridge, MA: Harvard University Press.
Real, L. A., and S. A. Levin (1991), "The Role of Theory in the Rise of Modern Ecology", in L. A. Real and J. H. Brown (eds.), *Foundations of Ecology: Classic Papers and Commentaries*. Cambridge, MA: MIT Press, 177–191.
Schneider, T. D., and R. M. Stephens (1990), "Sequence Logos: A New Way to Display Consensus Sequences", *Nucleic Acid Research* 18: 6097–6100.
Schwartz, M., and I. R. Cohen (2000), "Autoimmunity Can Benefit Self-Maintenance", *Immunology Today* 21: 265–268.
Shannon, C. E., and W. Weaver (1949), *The Mathematical Theory of Communication*. Urbana: University of Illinois Press.
Sheldon, B., and S. Verhulst (1996), "Ecological Immunity: Costly Parasite Defenses and Trade-offs in Evolutionary Ecology", *Trends in Ecological Evolution* 11: 317–321.
Stewart, J. (1992), "Immunoglobulins Did Not Arise in Evolution to Fight Infection", *Immunology Today* 13: 396–399.
——— (1994a), "Cognition without Neurons: Adaptation, Learning and Memory in the Immune System", *Communication and Cognition in Artificial Intelligence Journal (CC-AI)* 11: 7–30.
——— (1994b), *The Primordial VRM System and the Evolution of Vertebrate Immunity*. Austin, TX: Landes.
Tarakanov, A. O., V. A. Skormin, and S. P. Sokolova (2003), *Immunocomputing: Principles and Applications*. London: Springer-Verlag.
Tauber, A. I. (1994), *The Immune Self: Theory or Metaphor?* New York: Cambridge University Press.
——— (1997), "Historical and Philosophical Perspectives on Immune Cognition", *Journal of the History of Biology* 30: 419–440.
——— (1999), "The Elusive Self: A Case of Category Errors", *Perspectives in Biology and Medicine* 42: 459–474.
——— (2000), "Moving beyond the Immune Self?", *Seminars in Immunology* 12: 241–248.
——— (2003), "Metchnikoff and the Phagocytosis Theory", *Nature Reviews, Cell Biology* 4: 897–901.
——— (2005), "The Biological Notion of Self and Non-self", *Stanford Encyclopedia of Science*, http://plato.stanford.edu/entries/biology-self/.end-break-point
——— (2008), "Expanding Immunology: Defensive versus Ecological Perspectives", *Perspectives in Biology and Medicine* 51 (2): 270–284.
Tauber, A. I., and L. Chernyak (1991), *Metchnikoff and the Origins of Immunology: From Metaphor to Theory*. New York: Oxford University Press.
Ulvestad, E. (2007), *Defending Life: The Nature of Host-Parasite Relations*. Dordrecht: Springer.

https://doi.org/10.1086/590200 Published online by Cambridge University Press

Vertosick, F. T., and R. H. Kelly (1989), "Immune Network Theory: A Role for Parallel Distributed Processing?", *Immunology* 66: 1–7.
von Bertalanffy, L. (1968), *General Systems Theory*. New York: Braziller.
von Neumann, J., and O. Morgenstern (1947), *Theories of Games and Economic Behavior*. Princeton, NJ: Princeton University Press.
Weiner, N. (1961), *Cybernetics*. 2nd ed. Cambridge, MA: MIT Press.
Wells, H. G., J. Huxley, and G. Wells (1929), *The Science of Life*. New York: Literary Guild.
Woese, C. R. (2004), "A New Biology for a New Century", *Microbiology and Molecular Biology Reviews* 68: 173–186.

https://doi.org/10.1086/590200 Published online by Cambridge University Press