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Terms

Antibody – *a protein complex produced by the immune system whose shape is specific for binding to a corresponding protein complex, or antigen. Antibodies serve the role of identifying what they bind.*

Antigen – *a protein complex, often on the outside of a cell, whose identity—or role in a particular pathway—is revealed when bound by an antibody.*

Biomarker – *an item of interest in a biological study, selected to represent a larger function (e.g. virus antigens are a biomarker for virus presence).*

Biosemiotics – *a subfield of biology and rhetoric that interprets biological systems as semiotic systems.*

Downregulation – *in immunology, a reduction in immune response.*

Edema – *excessive buildup of fluid, often due to inflammatory response.*

First messenger – *an enzyme whose shape changes cause the change in shape of a second messenger.*

Immunocompetence – *a measure of immune function. More effective immune systems are considered to have greater immunocompetence.*

Kuhnian paradigm – *a term coined by Thomas Kuhn; an era of predominant scientific thinking. The succession of Kuhnian paradigms result from scientific breakthroughs that are so influential to scientific thinking, they rapidly change the principal pedagogy in science.*

Mechanism– *a series of direct influences that result in a particular event (synonymous with* stepwise mechanism *and* pathway*).*

Pathophysiology – *the responses of the body to a pathogen, or threatening foreign entity.*

Pathway – *a series of direct influences that result in a particular event (synonymous with mechanism).*

Second messenger – *an enzyme whose shape changes cause the production of signal molecules.*

Semiotics – *the study of sign systems.*

Semiotic systems – *multi-dimensional systems in which meaning is granted through interactions that involve interpretation.*

Semiotic triad – *a semiotic model in which interpretant-sign transitions, objects, and forms map the interactions between signs, interpretants, and objects.*

T cell – *immune cells who respond to foreign threats of the body.*

Virus particle – *a single entire infection unit of virus.*

Abstract

Biological systems are dynamic, but predominant reductionist approaches in biology model these systems with little context of other related systems. Peircean semiotics is a methodology that models a pathway in reference to other levels of organization. In this study, immune response of deer mice infected with Sin Nombre Virus (SNV) is modeled using Peircean semiotics. Results suggest the immune systems of deer mice adopt the virus as a part of self, ultimately saving the mice from the inappropriately excessive inflammatory response (Hantavirus cardiopulmonary syndrome, HCPS) that kills humans infected with SNV. This work supports Peircean semiotics as a biological methodology when applied to cellular mechanisms and suggests an immunosuppressive vaccine may be effective for preventing HCPS in humans.

Introduction

Biologists study communication

Biological systems are dynamic. They operate on an extensive variety of levels, from less than particles to solar systems and beyond. Although all levels of these systems interact, the scientific method requires researchers to study levels of biological systems in isolation. The knowledge gathered from such studies is represented in static models, illustrating the properties of the isolated system with little to no reference to other levels of organization with which the isolated system interacts. Take, for instance, the immune system.

When studying a disease model, biologists assess the relative abundance of select biomarkers under various circumstances (i.e. in an uninfected individual, in the early stage of

infection, in a later stage of infection, etc.). By experimentally determining what other biomolecules are influenced by the abundance of the biomarker, biologists determine the pathway, or chain of direct molecular interactions, in which the biomarker plays a role. They can then map the pathways to depict how the immune system at large responds to the disease. Comparing these pathways, therefore, is crucial to our understanding of immune function.

This can be seen with the example of one biomarker, C-reactive protein (CRP), in an inflammatory pathway. A biomarker allows researchers to infer whether a pathway is active in the system and to what degree. Correlated with increased inflammation, CRP abundance in mammals is commonly measured to assess the presence of one active inflammatory pathway (Ridker, 2014). The levels of C-reactive protein indicate the degree to which inflammation is occurring, but do not precisely explain what induces this immune response. Therefore, how the immune system functions in study subjects and in general is synthesized from the data of multiple biomarkers (and thus pathways), often compiled into a complex, linear model such as Figure 1.

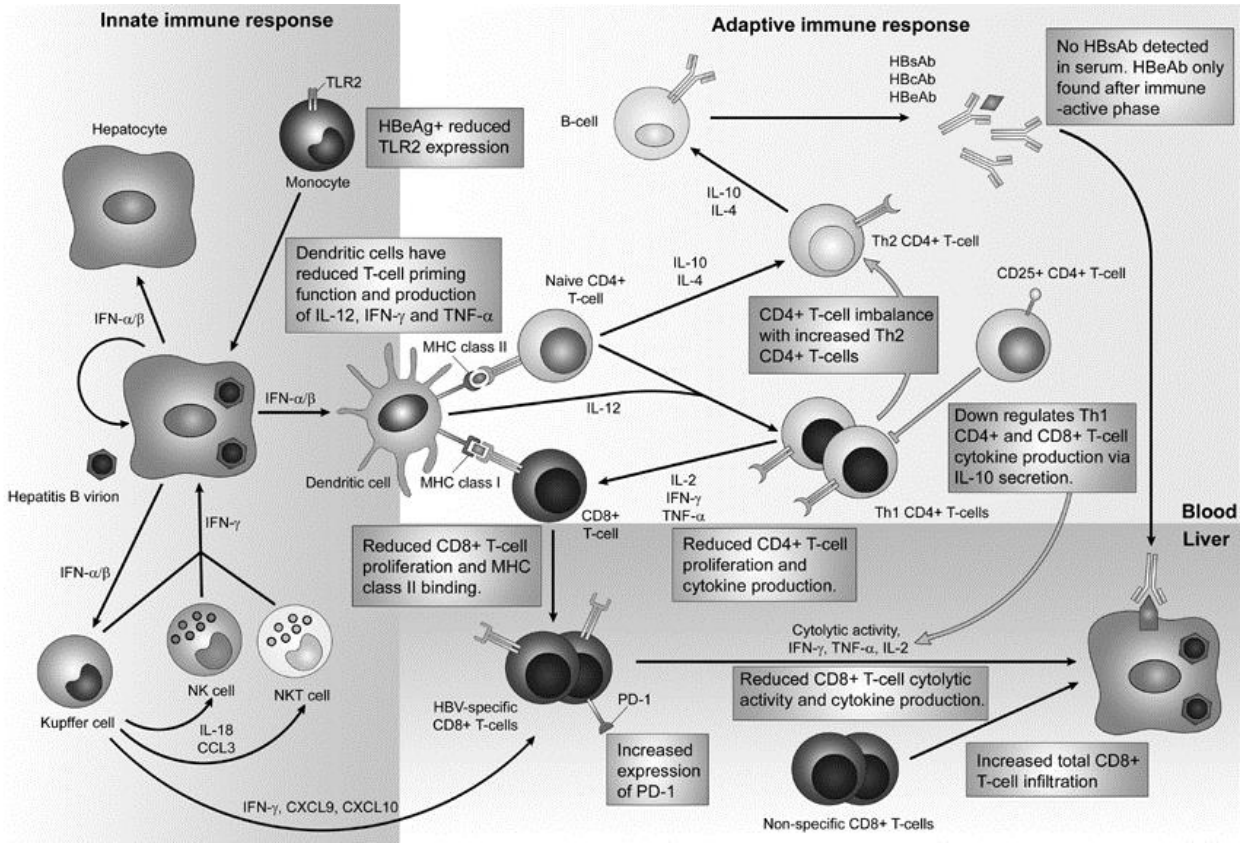

Figure 1. A linear model of immune pathways involved in immune response to viral infection. (Chang & Lewin, 2006)

As demonstrated by the map of immune response to a virus, pathways (represented by arrows connecting biomarkers) suggest little about the immune system as a whole; pathways represent the immune system at large implicitly and only through their interrelations. This model is static because it implies that these pathways are always active or inactive in the disease models—even though the immune responses to diseases generally change through the course of disease development. If a simple pathway (say, with only a few arrows connecting factors) could also explicitly demonstrate its significance to the immune system at large over time, this model could be as insightful as a complex model like Figure 1.

The predominant methodology in biology, the scientific method, is a reductionist approach that attempts to isolate systems and thus nullify the context in which pathways occur. Yet biologists often use metaphors, anecdotes, and personification to explain complex biological processes. *Signal, message, interpretation,* etc. are common terms in biological literature used to articulate processes at every level of organization. *Communication* is something all humans can understand, and may be an ideal metaphor for biology already being heavily used. Every spoken sentence or physical gesture can effectively communicate a message, even though the sentence or gesture can be interpreted differently. Applying various contexts to these actions provides different knowledge about the action as well as the context. Explaining biological processes as communication represents these events in a comprehendible manner, explained simply without undermining the dynamic complexity. How to represent this communication, however, is not uniformly practiced.

Therefore, a new field called biosemiotics has emerged to produce a common methodology that can be used to assess and model the communication systems that occur on every scale, from molecules to ecosystems. Currently, the most widely-adopted biosemiotic methodology utilizes Peircean semiotics (explained later in this essay), which has been used to map complex biological systems from mimicry across species to canine communication with humans, extended even to the interactions of cells (respectively: Maran, 2010; Mancini, van der Linden, Bryan, & Stuart, 2012; Mian & Rose, 2011). The extent to which Peircean semiotics can effectively be applied to biological systems remains debated.

Although some biosemiotic authorities question whether Peircean semiotics should be applied to cellular processes, even some of the most critical biosemioticians are recognizing the potential for doing so. In 2009, Editor in Chief of the journal *Biosemiotics*, Marcello Barbieri, published an article entitled "Three Types of Semiosis." In his essay, he asserts that Peircean

semiotics cannot be applied to cellular systems since they do not demonstrate interpretation, but rather operate under the consistent rules of genetics. Three years later, Barbieri published an article in his manuscript *Information and living systems: philosophical and scientific perspectives* that well justifies the interpretative processes of the genetic regulation in cells (which will be discussed throughout the paper; Queiroz, Emmeche, Kull, & El-Hani, 2011). Peircean semiotic models offer an alternative methodology to the current static diagrams of biological systems that has been well supported in almost every biological context in which it is exercised. However, as a new methodology, justifying its usefulness requires further testing of its operations.

In this study, I apply Peircean semiotics to a molecular system, the immune response of deer mice to Sin Nombre Virus (SNV), to assess Peircean semiotics as an effective methodology for modeling communication events that dictate immune response. I begin with a discussion on the fundamental theories of immunology followed by an introduction to the field of biosemiotics, then provide an overview of Peircean semiotic methodology. Finally, Peircean semiotics is applied to the biological model of antibody response in deer mice infected with SNV. Exploring concepts of the emerging field of biosemiotics, the primary findings include 1) Peircean semiotics models the dynamics of the antibody response pathway of SNV infection in deer mice within the context of the immune system at large, and 2) Jerne's immune network theory accounts for the dynamics in which the immune self is continuously redefined.

Sin Nombre Virus: a disease without a vaccine

Sin Nombre Virus (SNV) is a type of hantavirus found only in North America, most prevalent in its primary host reservoir, the deer mouse (*Peromyscus maniculatus*) (Schountz et al., 2007). The mice shed the virus through saliva, urine, excrement, etc. to the ground, where it is kicked up in dust and becomes aerosolized and inhaled by humans (Easterbrook & Klein, 2008). This often results in edema—excessive fluid build-up as an inflammatory response—of the lungs and heart that characterize the hantavirus cardiopulmonary syndrome (HCPS) that kills about 35% of humans infected with SNV in the US (Terajima & Ennis, 2011). While there is a high probability that infected humans will become debilitated or fatally ill, SNV-infected deer mice are able to live long lives with almost no symptoms (Botten et al., 2002).

No biological methodology yet has produced an FDA-approved vaccine for preventing SNV infection in humans (Hooper, Josleyn, Ballantyne, & Brocato, 2013). This is likely due to a lack of fundamental understanding of immune function, both in the disease models and in general.

In infected deer mice, SNV-specific antibodies tend to be present in the highest quantities during the acute (i.e. early) stage of infection (Lehmer et al., 2010; pending publication by Lehmer et al., 2014). After this period, both antibody and inflammatory responses lessen, allowing the mice to tolerate the virus (Schountz et al., 2007). This is not what happens when humans are infected; the human immune system produces such a strong and nonspecific response to the virus that excessive inflammation develops in the areas with the highest prevalence of the virus: the heart and lungs.

A simple systematic modeling of how the mice accomplish this downregulation could offer a new perspective to approaching medical prevention and treatment of human SNV infection. The ability of mice to downregulate their inflammatory response saves them from the excessive and inappropriate immune response that causes the disease HCPS humans often develop when

infected. The immune system is too dynamic to represent in a static map of pathways since context changes which pathways are active. Therefore, an alternative methodology to modeling biological systems is worth testing. As we will see, some authors argue that a better methodology in biology is long overdue.

The call for a Kuhnian paradigm shift

Thomas Kuhn's *The Structure of Scientific Revolutions* introduced the concepts of paradigms and paradigm shifts—terms now staple to the study of scientific advancement (Kuhn, 1962). Kuhn taught that every so often, science produces new knowledge so influential that it revolutionizes how entire generations fundamentally understand how the world works. This revolution is the Kuhnian paradigm shift, transitioning the society from one paradigm (i.e. period of understanding) to another.

While these shifts are difficult to predict, many scholars believe we're overdue for one right about now. One such scholar, Michelle Sidler, professor of rhetoric at Auburn University, asserts that we are still stuck in a Kuhnian paradigm dating back largely to the discovery of DNA's molecular structure (Sidler, 2013). Crediting Erwin Schrödinger for coining the metaphor for DNA as the "genetic code" of life, Sidler encourages readers to move beyond this simplistic thinking: "Though Schrödinger catalyzed the field of molecular biology, he also sent it down a misleading path by emphasizing a 'one-to-one correspondence' between the code and life development" (Sidler, 2006). Sidler's pleas are being addressed as academics continue to discuss how this potentially overly-simplistic emphasis of "one-to-one correspondence" is hindering scientific advancement. Likeminded scholars created a new field of study—called biosemiotics—to

explore alternative methodologies in biology. As Marcello Barbieri considered, even genetics is an adaptive system in which genetic expression depends on contexts. This weighs heavily on what immune systems are and how they function.

Jerne's immune network theory: the immune self is defined post hoc

Biologists do not fully understand what the immune system is and how it functions. Yair Neuman, an interdisciplinary academic who has published works related to fields from linguistics to neurobiology, explained this in his article "The immune self code: From correspondence to complexity." This article raised a fundamental question integral to biology: how does the immune system distinguish its own cells and necessary components from foreign, potentially harmful ones? In fact, Neuman defines immunology as "the science of self and nonself discrimination" (Neuman, 2008). He discusses the concept of "immune self," in which the body is comprised of all components that the immune system tolerates and thus identifies as "self." To assess biosemiotics' capacity to illustrate such a complex function, he synthesized biological theories for how the immune system "knows itself" with semiotic models for representing systems as a whole.

The immune system is not defined genetically. One biological theory Neuman evaluates, the genetic reduction approach (GRA), asserts that there is a genetic code common among all host cells that indicates to the immune system that a cell is a part of the "self." This approach, however, does not explain autoimmune disorders (i.e. when the responses of the immune system themselves harm the host) or tolerance of such cells as enterobacteria in intestines (i.e. "gut" bacteria that aid in digestion) (252). Thus, neither biological nor semiotic perspectives agree that the immune self is defined as including everything the system explicitly identifies and excluding anything the system

does not explicitly identify in the same way, further complicating what comprises the immune system and the body.

Another theory to address this complication, clonal selection theory (CST), suggests that the immune system produces antibodies that bind to foreign entities—thus identifying them—but do not bind or recognize host cells. The self, according to the CST, includes everything that the immune system does not recognize as foreign, yet this theory also fails to explain how the immune system of a female will not attack a male's sperm cell in her fallopian tubes (253). Here, Neuman's synthesis proposes that the "self" must follow a more lenient system of rules, one in which the concept of "self" can change as the context changes.

Neuman's study finds the most reasonably comprehensive explanation of immune regulation to be Jerne's immune network theory, a theory that proclaims that as the demands on the immune system change (i.e. due to disease, old age, etc.), the processes of the immune system change (Jerne, 1974). In other words, the processes that carry out immune function determine how future processes will carry out immune function. If Neuman's conclusion is valid, the immune self of deer mice must be capable of changing as the course of SNV infection changes. Studying this type of change is what biologists underemphasize, a problem biosemiotics aims to revise.

Defining biosemiotics: communication defines the immune self

Biosemiotics studies biological systems as macrocosms and microcosms, interpreting the meaning of a system through its interactions with other systems. Biosemioticians worry that by using some methodologies, we overemphasize certain components of nature and overlook others. Thus, biosemiotics was born to actively pursue alternative methodologies for biology, applying semiotics to biological systems.

Semiotics is the study of sign systems. That is, semiotics studies all systems by modeling how individual components of the system (considered "signs") interact to create the pathways, or stepwise mechanisms, that characterize the complex operations of a system. Biosemiotics, therefore, assumes that any data indicative of a pathway are also indicative of a larger system in which the pathway plays some role. By adding another dimension to models that emphasize the role of a biological pathway to some larger system, biosemioticians believe that researchers can get many more layers of understanding from the same data. For example, Yair Neuman's analysis of the "immune self" demonstrates how assessing the physical changes *over time* in a dynamic system produces a more coherent understanding than considering one or the other. Considering as many levels of operation within the system as possible produces the most comprehensive representation of the system, promoting an understanding that spans situational context.

Born out of communication studies, semiotics commonly equates interaction with communication, drawing conclusions about the properties of information. Rather than seeing information as a thing that can be obtained, stored and shared, it as a process dependent on characters and events across time. It is important to emphasize how well the view of information as a process coincides with the view of information as a thing. For instance, communication depends on the things involved (e.g. communicators, words, etc.) as well as the processes (e.g. gestures, change in mental states, articulation). To understand all the information about an occurrence to

the best of one's ability, one should utilize both lenses to analyze the characters as well as action involved. Viewing information as a process may seem like a semantic abstraction, but this concept may be more easily coupled with static models of biological pathways than it may appear.

The revolutionary concepts of Jerne's immune network theory and information as a process not only well represents immunology, but also attests to the validity of semiotics as a method of studying how the interpretation of characters of a pathway (signs) determines how other signs can be interpreted, thus using the characters *and processes* of a system to define the system at large. The present study applies Peircean semiotics to the biological model of immune responses to SNV in deer mice to assess the validity of this concept. Two biosemiotic publications introduce an applied Peircean semiotic methodology to cellular systems: "Modeling a Semiotic Process in the Immune System: Signal Transduction in B-cells Activation" (authors 2007) and "The Biosemiotic Approach in Biology: Theoretical Bases and Applied Models" (authors 2011). Synthesizing these works, I follow this methodology to investigate the cellular communication that saves deer mice from SNV.

Methodology

Charles Peirce's Semiotic Triad

The most comprehensive and thorough biosemiotic methodology thus far for producing a model of a system appears in *Information and Living Systems: Philosophical and Scientific Perspectives,* a biosemiotic compilation published in 2011. Well-justified in a chapter entitled "The Biosemiotic Approach in Biology: Theoretical Bases and Applied Models," this methodology was written by semioticians at the Federal University of Bahia, Brazil including João

Queiroz, Claus Emmeche, and Charbel El-Hani in collaboration with Kalevi Kull, a leading author of biosemiotics working from the University of Tartu, Estonia. This research group aspired to create a biosemiotic methodology that can be applied to any sign processes within a biological system.

Queiroz and his team found that current biological understanding best aligns with one semiotic methodology in particular that appears predominant in biosemiotic literature: Peircean semiotics. Proposed by Charles Peirce, this triadic model focuses on three main characters: *sign*, *object*, and *interpretant* (see Figure 2). The *sign* is anything referring to something else when interpreted by the *interpretant*. Queiroz offers the example of the thorn bug, an insect whose physical appearance mimics a thorn of a plant (see Figure 3). When a predator sees the bug, the ridge resembling the thorn (*sign*) causes the predator to think of the thorn in a plant (*object*), thus producing the effect of avoidance (*interpretant*) from the predator. The *object*, in this case the thorn of the plant, is the message being conveyed in this *sign-interpretant* interaction. This interaction is governed through the *form* of similarity— the similarity between the physical appearances of the thorns in the bug and in the plant dictate how the predator will interpret the bug. In this way, the object represents the meaning of the sign in this interaction, causing an effect on multiple levels of other biological systems (e.g. evolution of bug and predator, population ecology of bug and predator) through one particular pathway.

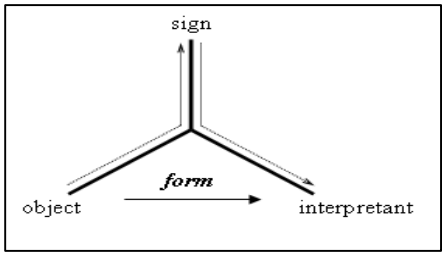

Figure 2. The semiotic relationship (Queiroz, Emmeche, & El-Hani, 2005)

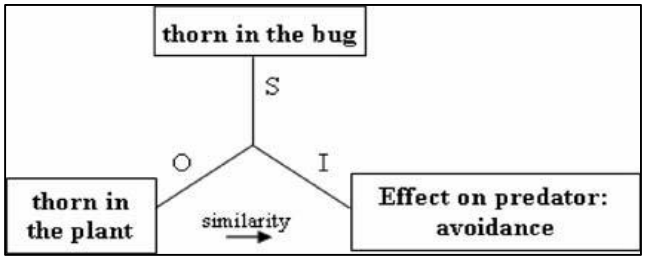

Figure 3. A semiotic interpretation of mimicry in the thorn bug. (Queiroz & El-Hani, 2006)

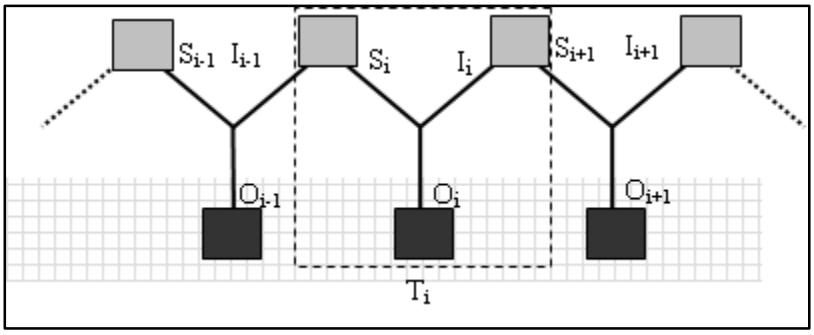

Figure 4. The dynamicism of the triadic relation of sign (S), immediate object (O), and interpretant (I). This figure illustrates how the interpretant (e.g. I_i) of one sign (S_i) becomes the sign (S_{i+1}) of another interpretant (I_{i+1}). (Queiroz, Emmeche, & El-Hani, 2005)

This model detailed in Figure 4 is dynamic because it demonstrates sign-interpretant transitions (S-I transitions) in which the interpretant of a sign becomes the sign of the next object (Queiroz, Emmeche, Kull, & El-Hani, 2011). This is the process by which all communication occurs, and Peirce demonstrates the significance of the triad by distinguishing the *immediate object* from the *dynamical object*: "the immediate object is the dynamical object as the sign represents it" (Queiroz, Emmeche, Kull, & El-Hani, 2011, pp. 101). Thus, Peirce's semiotic triad models how the purpose of a pathway is maintained even though the messengers transform and translate the message as they themselves transform across time. So what purpose can be revealed by modeling the immune response of deer mice to SNV infection using Peircean semiotics?

Results

Both Figures 5 and 6 model the immune pathway in the deer mice to suppress immune response. When regulatory T lymphocytes [immune cells] bind to the antigen [surface protein] of the virus, they initiate a cascade of molecular responses that cause gene expression to produce

TGFβ1, a molecule that inhibits other lymphocytes from attacking the virus (Vaheri et al., 2013). Figure 5 is a linear model of this pathway, demonstrating the common approach in biology. Figure 6 is a Peircean semiotic model of the same pathway, emphasizing the Sign-Interpretant transitions and their corresponding immediate objects.

SNV Antigen → Regulatory T Lymphocyte Antibody → Unknown Gene --x TGFβ1 Innate lymphocytes

Figure 5. Linear, static model representing the interacting characters in the pathway for deactivating innate immune response to SNV infection in deer mice. Arrows indicate activation while the last symbol indicated inhibition.

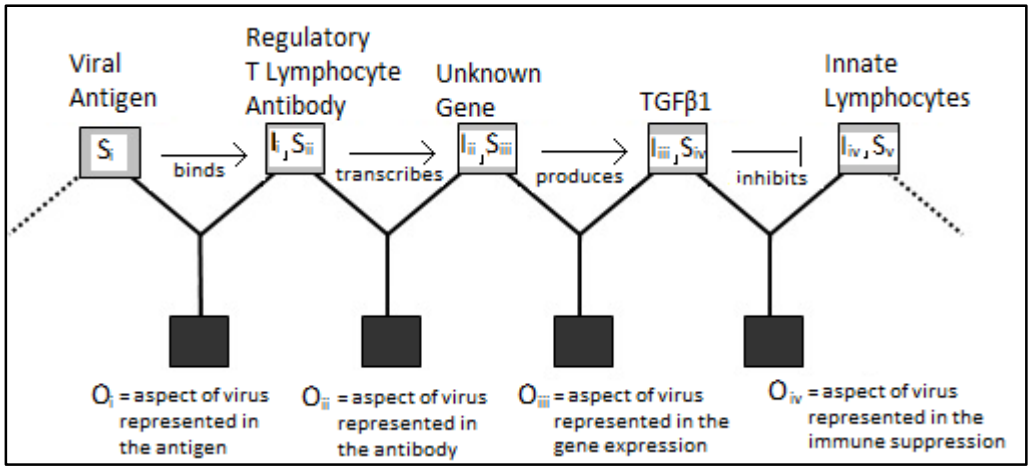

Figure 6. Peircean semiotic triad of the pathway of immunosuppression mediated by regulatory T lymphocyte binding to the viral antigen (adapted from El-Hani, Arnellos, & Queiroza, 2007). S = sign, I = interpretant, and O = immediate object.

When the antibody of a T cell binds to the antigen of the SNV virus particle, the *sign* is the antigen and the *interpretant* is the antibody (Queiroz, Emmeche, Kull, & El-Hani, 2011). This in turn changes the shape of the antibody, activating an enzyme (i.e. first messenger) on the inside of the T cell by causing its shape to change. The antibody—initially an interpretant of the antigen—is

now the sign, and the first messenger is the interpretant. The first messenger then changes shape (I-S transition), morphing and thus activating a second messenger (a sign that transitions into an interpretant when activated). The *object,* in this case, is the threat of SNV, and the *form* would be any response that changes the shape of an interpretant into becoming a sign itself for another interpretant. The second messenger ultimately induces genetic expression, producing signaling molecules that are secreted by the cell as signs to be interpreted by other cells they recruit.

Discussion

Deer mice adopt SNV as a part of the self

SNV infection resides in the same regions of tissue in both deer mice and humans and the stages of infection in these two species begin the same way—with an increased inflammatory and antibody response to identify the virus. This process continually progresses in humans until either the host clears itself of the virus or the inflammatory response becomes so great that it develops into HCPS. In deer mice, however, inflammatory response decreases as the infection progresses, and thus they can live with the virus inside them with almost no obvious symptoms. Both being mammals, the immune mechanisms through which humans and deer mice detect and evade pathogens are similar, and the differences that lead to the different consequences are not well understood. (Easterbrook & Klein, 2008)

The immune system is comprised of two divisions: innate immunity and adaptive immunity. Innate immunity includes genetically predetermined responses, such as production of specific lymphocytes and antibodies (Hoebe, Janssen, & Beutler, 2004, 971). Adaptive immunity includes the lymphocytes and antibodies that identify new materials previously unknown to the

body, and replicate to amplify the defense against these materials (971-972). Figures 5 and 6 illustrate an adaptive immunity pathway in deer mice that suppresses innate immunity. In other words, when the regulatory T lymphocytes in the mouse find SNV particles, they initiate a series of signal molecules that eventually dictate to the already-existing immune cells not to respond.

In order to recognize how information is presented both as a thing and a process, compare the semiotics model of Figure 6 to traditional linear model of Figure 5. The linear model maps the physical changes (I-S transitions) occurring through this chain of events. The triadic model also maps the changes, but also maps what remains constant through the chain of events (the objects). In other words, the triad forces its creator to account for the significance of the pathway to the larger system in equal emphasis to the signs and interpretants that compose the pathway itself.

After explaining their methods and the concepts they are built upon, Queiroz and his team apply these methods to genetics, asking what sort of information genes entail and how this information materializes. They found that, within the context of a larger network (i.e. the cell),

> what is being communicated is only potential information, that is, the potentiality of a process called "information." It is only this potentiality that can be said... to be carried by stretches of DNA. Signs in DNA will become elements in effective information only when interpreted by the cell. Effective information itself cannot be carried from one system to another; only potential information can be carried by the [signs]. (Queiroz, Emmeche, Kull, & El-Hani, 2011, pp. 113)

We can thus say that in the case of SNV infection in deer mice, the DNA of a mouse has the potential for information that becomes activated, producing information only when "interpreted by the cell" (113). This agrees with modern immunological thinking in how the cell identifies the virus particle by producing an infinite variety of antibodies designed to target specific antigens that are not present, breaking these antibodies down over a period of time and producing new randomized antibodies (Dasgupta, 1999).

Therefore, the DNA encodes the potential to identify SNV along with the potential to identify any foreign entity. When SNV is present, then one of these randomized antibodies will bind to the virus and signal for other cells to generate identical antibodies. This is the process of information that can only take place within the larger contexts of the cell and the body. Without a physiological response from other characters, DNA alone would have potential for a response without being able to respond at all, and thus the potential would not be for information at all. Much like how semiotic triads rely on objects and interpretants to make a form from a sign, physiological responses rely on messengers and signals to make a response to an imbalance.

Peircean semiotics supports Jerne's immune network theory

These pathways operate by maintaining some reference to the imbalance they respond to, but how they maintain this reference is not well understood. Queiroz's research team also analyzed a specific messenger pathway, the *Syk* messenger pathway, to explore this phenomena. What they found was that, by referring to a "non-self entity" (e.g. the antigen of a pathogen), an organism is able to produce changes in self (e.g. the abundance of specific antibodies) that would not exist if the information was not present and activated.

This supports the biosemiotic understanding of the "immune self" that Yair Neuman discusses in his biosemiotic review of the immune system. Indeed, the physiological changes in immune response of deer mice to SNV infection suggests that *tolerance* seems to be the key to the immune self, and the immunes system constructs itself "post hoc" (Neuman, 2008). But what does this imply about SNV in deer mice?

HCPS in humans may be prevented with an immunosuppressive vaccine

In the five cases known in 1999 of humans who were infected with SNV but did not develop HCPS, their inflammatory responses were significantly lower than in those who developed the syndrome (Kitsutani et al., 1999). Deer mice have coevolved with the Sin Nombre Virus to suppress immune response to a level that keeps both the mouse and the virus alive. The immune systems of those who develop the syndrome misdiagnose the virus as excessively harmful because it is foreign and alters cellular functions, and in doing so produces an immune identity that destroys itself. Maybe humans can learn from this example of coevolution and create an immunosuppressive vaccine that produces the same result without the long period of evolution by including genetic tools for maintaining immune response at tolerable levels.

As demonstrated in Figures 5 and 6, the genetic expression of TGFβ is present. The signal molecule is known to be present in deer mice infected with SNV, but not infected humans (Vaheri et al., 2013). While this signal molecule has been identified, the gene that encodes its expression has not. If we can identify this gene, and if it is also found in humans, we may be able to inhibit its expressions similar to how coevolution of virus and mouse has produced this effect in the mice. In this way, we could communicate with our immune systems that a virus like SNV can be a part of

our own bodies, then there is potential for the virus to actually be a part of our bodies. If the virus does end up becoming harmful to us through its replication mechanisms, then our immune system will be better able to recognize what aspects of the process are problematic and attack those particular pathways.

Peircean semiotics models the conformation changes of proteins

In Figure 6, the arrows indicating S-I transitions represent the direct interaction between molecules that physically change the signs into interpretants. In biology, this is called a *conformation change*, the physical change in protein or complex of proteins that "activates" them. In Figure 1, there is no reference to the physical events that mediate the pathway. Peircean semiotics directly refers to these events as S-I transitions. This property makes Peircean semiotic models more effective at illustrating the dynamics of a pathway than linear, static biological models. These static models are easily conformed into Peircean semiotic models, and thus biology can easily adopt Peircean semiotic methodology.

Conclusion

The Peircean semiotic model produces a more insightful representation of the molecular interactions that mediate immune response to the virus as opposed to a linear model. This triadic representation explicitly accounts for the significance of the pathway to the larger system—the self-nonself discriminating immune system—and suggests that deer mice survive with chronic SNV infection because they elicit an immune response similar to how they respond to their own mice

cells: they allow these cells to reproduce within acceptable limits that are not threatening to the host. Recognizing the virus as a part of the self prevents the host from expressing an autoimmune deficiency like HCPS. These findings support an approach to producing a vaccine to SNV and other hantaviruses by suppressing immune response to the virus within tolerable limits. These finding also have implications for how information is expressed and can be represented.

Information can only manifest through its transmission; it is a form of communication in which the significance of the words only have meaning when influencing an interpreter. When applied to the case of immunological response of deer mice to SNV infection, it becomes apparent the mice tolerate the virus in the same manner they tolerate their own cells: only attack when quantities become harmful. This is the only means through which the virus can replicate—by hijacking the host's cellular machinery to replicate the viral genome while replicating the host's genome. Deer mice seem to survive SNV infection by accepting the message of the virus and recognizing it as a part of itself. Human immune systems, on the other hand, reject this message and, in an effort to eradicate the virus genome within its own cells, produce immune responses that can and will kill the human.

Communication, then, is the means through which the virus is identified by itself and by a host, through which the rodent host combats or tolerates the virus, and through which the human host makes a mistake and eventually kills itself. Tolerance is the means through the body identifies itself, and tolerance is how the body adopts the nonmammalian components such as helpful bacteria. In the case of Sin Nombre Virus, the only hosts that can survive are those that can tolerate it forever, adopting it as a part of itself. Tolerance may therefore be the key to symbiosis—living together as one.

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