THE EMERGENCE OF MEANING IN BIOLOGICAL SYSTEMS

THESIS SUBMITTED FOR THE DEGREE OF “DOCTOR OF PHILOSOPHY”

BY

URI HERSHEYBERG

SUBMITTED TO THE SENATE OF THE HEBREW UNIVERSITY

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This work was carried out under the supervision of Prof. Sorin Solomon of the Hebrew University and Prof. Irun R. Cohen of the Weizmann institute.
I would like to dedicate this thesis to my parents Dov and Aia Hershebrg and to the person I always look for, who keeps the world at bay when I cannot - Shira Ninio.

“.... I love her and that's the beginning of everything.”
~F. Scott Fitzgerald~
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Summary

‘The time has come,’ the Walrus said,
‘To talk of many things:’

The Walrus and the Carpenter in Alice in Wonderland by Lewis Carroll.

This is a work of interdisciplinary research. It contains concepts from biology, physics and cognitive science. We take principles from cognition and show how attempts to see immune reactions as cognitive reactions radically change our view of how immunity works and what its functions are. Likewise we study the immune system as an example of cognitive perception and find new basic principles of cognitive development and of the environments in which they can develop. In this thesis we present the results of simulations of the T cell repertoire and of HIV dynamics and discuss theoretical insights into cognitive systems in general and the immune system in particular.

The theory of Useful Examples: - We built a theory of cognitive systems and the common strategies of interaction which are at the basis of their capabilities. At the heart of this theory is the concept of Useful Examples. Cognitive systems must learn to be cognitive systems. We present a view of the system's mode of learning which we describe as a direct result of unsupervised interactions with concrete examples of the environment. Such a simple form of learning is sufficient to allow the system an understanding of its environment because the environment is ordered. There are a few examples which are encountered with high frequency while most other examples are encountered less frequently. The high frequency examples are not ubiquitous by chance. Their prevalence reflects a multiplicity of use within the interaction of system and environment. We call such examples of the environment Useful Examples because they are useful for learning the most relevant general properties of the environment.

In a sense we have built up a theory for the common form of environments that cognitive systems interact with. Our theory suggests a new model of research for cognitive systems. The focus, in studying cognitive systems and
their capabilities of interaction in their environment, shifts from attempting to decipher a system’s function to finding the natural distribution of examples in the environment and the identification of the Useful Examples.

*Models of immune cognition:* The theoretical conclusions regarding cognitive systems are utilized to build models of immune dynamics interacting correctly with their environment (T cell repertoire) and when the immune system is fooled by disease (HIV).

Our method is to study how the manipulation of relationships between receptors and the examples that excite them educates the immune system. To do so we employ Microscopic Simulations of immune dynamics and the relations in shape space$^1$ between immune receptors and the antigens that excite them. Presented here are two models:

- A model of T cell repertoire dynamics in health, and following a primary infection.
- A model of HIV short-term and long-term progression.

*A functioning (cognitive) immune system:* - By considering the distribution of examples encountered naturally by the immune system, we can identify the Useful Examples of immune interaction. We described how the study of the natural distribution of examples encountered by the immune system in our body enhances our understanding of the immune system and its capabilities.

We did this with a model of a functioning T cell repertoire in health and following a primary infection. Our simulation was that of a generic scenario of the T cell repertoire that replicates the time course of a response to a primary infection and the return to steady state. Our model closely followed $^1$

$^1$ Shape space is an imaginary space in which entities represent receptors / ligands. Receptors and ligands at nearby points on shape space, to each other, are at high affinity and those at distant points are at low affinity.
the dynamics and shape distribution of T cells and the self and non self antigens in the shape space of T cell and antigen forms. Our ability to replicate known T cell repertoire dynamics shows the need for a reevaluation of several basic principles of immunology. In particular, by suggesting how the immune system treats the self as the background signal of its reactions, we change the place of self-reactivity in immune function. Such a change causes a paradigm shift towards a cognitive view of the immune system.

Self-reactivity is now the basis not the nemesis of immune reaction. More importantly immune function is focused not merely on foreign exclusion but rather on self maintenance in general. These conceptual shifts have one major conclusion for immune research. The immune system is always active and its activity (and reactivity) in disease is based on its activity in health. Therefore the focus of immune research must shift from studying the body in state of distress (i.e. disease). Instead we should study the immune system under conditions of health so as to understand its function in conditions of disease.

_HIV - A (cognitive) immune system’s conceptual mistake:_ As we have said, a cognitive system is tested by the way it interacts with its environment. The interaction is with the system’s conceptual picture of reality and not just directly with the individual signals that form this picture. This dual form of interaction leads to the abilities of a cognitive system but also implies that we should find the system makes conceptual mistakes in the way it interprets its environment. Our model of HIV progression illustrates how a misconception in the immune system’s conceptual picture of its viral invader leads to the long term latency of HIV ending in AIDS. We show how HIV hyper-mutation (i.e. diffusion in shape space) allows HIV to hide form the repeated successes of the immune system against it. The AIDS virus manipulates the immune system into thinking it is dealing with more and more ‘new’ diseases until it is tired out and collapses.
We thus further strengthen the cognitive outlook of immune dynamics in our model of the shape space interaction of the immune system and the AIDS virus. The cognitive outlook not only enables us to describe the working immune system but also works in the case of a duped immune system, as we succeed in connecting between the known progression of normal viral infection and the long-term latency and progression of HIV.

*Coda:* Our final conclusions have to do with the study of cognitive systems in general. Our interest in shape space raises new questions as to the kinds of environment in which cognitive systems develop. It also leads us to some novel conclusions, namely that for a naïve cognitive system to develop its capabilities, the environment it encounters needs to have some internal order. This order is naturally existent for our cognitive systems because we have evolved to certain niches. We are blinkered by our history from the infinite possibilities of creation towards specific parts of reality. However, in these limitations lie our abilities to reach cognitive perception.

We have shown how this concept of Useful Examples is central to the study of cognitive systems, and suggest that it especially pertains to the design of artificial systems. We offer a new formulation of the design question for building artificial cognitive systems. Rather than asking how to create artificial systems that function as cognitive systems, we ask how to define Useful Examples in the environment so that through interaction with them the system creates itself. This is especially pertinent in complex environments where no natural cognitive system exists, such as for instance the information space of the Internet. Following the theory of Useful Examples, we are no longer aiming to create agents which function intelligently in the net. Rather, we ask how can we divide the net into niches in which different agents, by their interaction with these niches, will find Useful Examples. The new question is an improvement since it acknowledges the interconnectedness of the system, its development and its environment.
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1. Introduction

Not everything that can be counted counts,
and not everything that counts can be counted.
Albert Einstein

Emergence of immune meaning and cognition

We suggest a novel theoretical framework to study immune dynamics. In this framework the interaction of chemical signals to which the immune system reacts builds a conceptual picture of the immune environment. The immune system like other cognitive perceptual systems reacts to the overall picture and not to any one of the individual signals from which it is built.

We built several computer simulations showing how the conceptual picture is built and how it is sometimes subverted by disease.

In building these models we use the immune system as a specific example of the general mechanisms that allow meaning to emerge from the natural interaction of biological systems and their environment. The immune system is a very interesting system to study in this context. This is true not only because of the general dividends to our survival that understanding of immunity gives us, but also because the immune system is a system whose definition of self is a cognitive one (Cohen 2000).

Meaning and information

To explain this point let us start by differentiating between meaning and information. Biological systems and the immune system among them deal with meanings, not with information (Atlan & Cohen 1999). For a definition of information we go back to Shannon’s theory of information. This model is extremely robust since it holds true regardless of the form of the information borne by the message or its eventual result. Whether we analyze the transference of a phone message or the transcription of DNA to mRNA we can
find the loss of ‘Shannon’ information due to noise. However, this very impartiality to the ‘form’ of the message is a weakness when dealing with biological and cognitive systems. In such systems practically all signals are context dependent. For instance, two sentences may have the exact same amount of Shannon information but, through differences in order, convey completely different different meaning. Information, as discussed above, is a property of the intrinsic organization of the message in the form of a frequency distribution of its elements. The meaning of the message, in contrast, is the relationship of the message to some reference point outside of the information borne by the message. Meaning is referential and contingent.

A further point lacking in Shannon’s theory is the neglect of the creation of new information. Self-organizing systems like the brain, the immune system and even uni-cellular organisms create new information and are not merely transmitters of pre-existing information. To solve this second problem H. Atlan developed a formal theory to resolve the paradoxical loss of information which is necessary for diversification or ‘Complexity from noise’ (Atlan 1983).

In principle this theory states that the effect of noise in a channel is different when appreciated at the output of a channel or on a system which contains the channel as one of its parts. For example, a mutation in an antibody gene, which disorganizes the gene’s original string of nucleic acids, could produce a new gene encoding a new antibody that could add information to the organism as a whole. In order that this diversification does not come at the expense of prior information, there is a need of redundancy. However, successful diversification reduces the initial redundancy. Systems that want to continue to diversify must replenish their redundancy. For instance the existence of set learning periods in development is a function of the inability of the brain to replenish its redundancy of neurons.

**Autopoiesis**

This outlook on meaning fits in well with the definition of living entities as autopoietic machines (Maturana and Varela 1980). This definition demands an
auto-catalytic capacity along with a clear differentiation between the entity and its outside world. In other words every living thing has its own point of view and sense of self, even if this is just mechanically defined by a membrane. In the case of second order autopoetic entities such as ourselves, which are themselves built of multiple autopoietic machines, the sense of self - the differentiation from the world, can never be defined in a purely mechanistic way.

This is obviously true in the case of our consciousness and the cognitive modalities that form it. The personal point of view does not have strictly physical constraints and can only be defined in terms of the general working of the system in its environment and the context of its interactions. In a sense the autopoietic nature of life implies the emergence of cognition (Stewart 1996).

**The cognitive paradigm of immune dynamics**

The cognitive view of immune dynamics is less widely accepted. It is that, as stated above for other cognitive systems, the self is not defined by molecular-structural properties. It is defined by a protocol of behavior, whose observance by the agents of the immune system (cells, antibodies, etc.) defines a normal mode of communication between these agents and the rest of the body, encompassing the immune system as a whole. This communication is based on a string of signals that accompany the presentation of antigens to the immune system (Cohen 2000).

**The immune system**

Like the brain the immune system is a dispersed system that has many types of cells as well as effector and signaling substances. The main populations of cells, which constitute the immune system, are known as lymphocytes. The two most important groups of lymphocytes are called B cells and T cells. Both of these cell families have a unique ability to create receptors which use different combinations of the same genetic material to create an immense
variety in their final form. The shape of the receptor, which like all proteins is based on the DNA sequence of a certain gene, implies the shape and type of molecule that will activate the receptor. The genetic variability gives the immune system the potential ability to have receptors that can identify an astronomical number of molecular shapes. The molecules which immune receptors identify are commonly known as antigens. The immune system’s identification of and reaction to a pathogen, or other immune events, is dependent on mutual reaction by both T cells and B cells to that event (Langman & Cohn 2000).

**The clonal selection theory**

Despite this receptor diversity and the essential need for cooperative receptivity, as far as the immune system is concerned, the common view of researchers has been a mechanistic non-cognitive one. Most theories of immune dynamics are still based on the clonal selection paradigm, which claims that the immune system relies on the existence of a receptor that can preferentially select between our chemical self and the outside world (Burrnet 1957, Langman & Cohn 2000).

However when we look at the actual interaction of immune receptors and their molecular environments we encounter two major problems. First, due to our common ancestry and eons of co-evolution there exists an essential similarity between our cellular biology and that of our ‘invaders’ (Gupta 1998). Second, the existence of a necessary benign level of self affinity exists in healthy immune receptor repertoires (Lacroix-Desmazes et al 1998, Goldrath and Bevan 1999). These problems have created doubts as to the validity of the clonal view, and led to the cognitive paradigm of immune reaction (Varela 1994, Cohen 2000).

**A cognitive view of the immune system**

The major difference between the cognitive paradigm and other paradigms of immune research lies in its view of how the immune system reaches its
specificity of reaction. Other paradigms put the emphasis on single receptors and the process that allow the system to acquire highly tuned specific receptors of a given type (Cohn and Langman 2000). This causes several internal problems as immune receptors are actually very widely tuned in their reactivity and highly cross reactive (Borras et al. 2002). The Cognitive paradigm solves this problem by viewing immune decisions as being on a level above the single cell, at the level of the system. The immune system is reacting not to any one signal, but to the overall pattern of signals (Atlan & Cohen 1999). When viewed in such a fashion the degeneracy and cross reactivity stop being a hindrance. The immune system, like other cognitive systems such as vision, is building a very precise picture from very imprecisely tuned receptors. We suggest that Immune reaction is to the overall concepts which are built of many separate but interacting signals. Immune cells and receptors may react very widely, however the overall reaction of the immune system from the pattern of these reactions will be specific.

**Shape space**

In our study of the forming of patterns that influence immune dynamics we decided that more informative representations could be found by studying the shape space of such dynamics.

Shape space is an imaginary space in which every point represents the shapes of receptor/ ligands that are reactive to each other (Perelson & Oster 1979). Entities which are close in shape space are similar and those that are distant are dissimilar. This makes modeling and measuring reactions in shape space a useful representation of the relationship between different patterns and their reactions. The dimensionality of the space and the connectivity of the points depend on the specificity, redundancy and degeneracy of reaction between receptors and ligands of the given system.

The representation of the hypothetical space of examples and the receptors that react to them is a very powerful tool for the study of the general principles of the emergence of meaning common to various cognitive
systems. The dimensionality and connectivity of a given shape space represent aspects of degeneracy and redundancy of the receptive capabilities. We can now focus on these factors and their relationship in cognitive systems without having to deal with their different physiological and physical underpinnings in each system.

Models of the shape space of different receptor systems have been used to study various systems such as the olfactory system (Lancet, Sadovsky & Seidemann 1993) and also the diversity and size of the immune receptor repertoire (Perelson & Wesibuch 1997). However, in most previous instances the models of shape pace were essentially static in their representation of the population of entities in shape space. The element studied where overall levels of cross reactivity or, at best, the strength of points in shape space were seen as weights in an immune network (Burns & Ruskin 2002). This outlook misses two aspects of importance to modeling of biological phenomena. First, the importance of discrete occurrences (Shnerb et al. 2000, Louzoun et al. 2003) and second, the ability of the receptor repertoire to change. The shape space of a young visual system is not the same as the shape space of an old visual system. As vaccines tell us this is also true for the immune system.

**Microscopic Simulations of shape space**

Our simulations of immune dynamics in shape space, using Microscopic Simulation techniques, have dealt with the two points mentioned above. In our shape space model we take into consideration the specific clone population sizes at specific times and the existence of diffusion (mutation) in shape space. This dynamical outlook on the evolution of receptor/ ligand populations in shape space allows us to ask questions about the development of the immune system and cognitive systems in general:

- What are the population dynamics of the (immune) receptor repertoire in terms of their types of affinities?
How are these dynamics influenced by the types of naturally occurring examples (antigens) in the (immune) environment (our body)?

In the results we will start by presenting our theory of Useful Examples, in which we have made a general theoretical suggestion as to the distribution in shape space of examples (ligands) that enables naïve systems to acquire cognitive capabilities. We will show the relevance of this theory to the way cognitive systems in general, and the immune system in particular develop and maintain their capabilities. In section two, we show the ramification of this theory to immunology explicitly, with the aid of a computer model. We show a new model of T cell repertoire dynamics at rest and following a primary infection. With this model we will show how self antigens create for the T cell repertoire a conceptual image of self. In the last section of the results we will present our model of HIV proliferation. With a simpler model of shape space we modeled HIV’s capability of fooling the immune system by changing its conceptual image in the immune system’s ‘eyes’: Appearing again and again as a new invader.
2. Methods

What’s a beast without an algorithm?  

The Cyberiad by Stanislaw Lem

This thesis describes a theoretical study of biological dynamics and interactions with the environment. We have used computer simulations to elucidate the various theoretical suggestions this work makes.

During the last decade Professor Solomon's group has developed techniques through which one can systematically follow the birth of complex macroscopic phenomenology out of simple fundamental microscopic laws (Solomon 1995). In the field of fundamental physics such understanding was obtained for a wide range of phenomena, using theories based on Microscopic Representation and Universal Dynamics paradigms.

These paradigms deduce the macroscopic objects (Macros) and their phenomenological complex ad-hoc laws in terms of a multitude of elementary microscopic objects (Micros) interacting by simple fundamental laws. The Macros and their laws then emerge naturally from the collective dynamics of the Micros as their effective global large-scale features. However, the mere microscopic representation of a system cannot lead to satisfactory and complete understanding of the macroscopic phenomena.

Indeed, the mere copying on the computer of a real-life system with all its problems does not, by itself, constitute a solution to those problems.

It is clear that a satisfactory representation of complex systems, like the immune system, has to recognize the relevant objects and laws, which describe effectively the system at each scale, and to establish the relations between the different scales. Therefore, our approach is not to try to substitute the study of one scale for the study of another scale (a strategy of "reduction"); rather we attempt to unify into a coherent picture the complementary descriptions of one and the same reality. The main goal is to build the intermediate stages between the meaning we observe in the global network and the microscopic molecular interactions.
We describe the state of the system using an ad-hoc top-down description to find out which are the components taking an important part in the system's evolution. We then try to define the interactions between the components, using the bottom-up description, starting at the molecular level. The size and complexity of the immune system prevents us from building a direct link between the two scales, so that we have to build intermediate levels. These levels should contain rules that are based upon the 'lower' level applications, but their results should be in agreement with the global description. Despite the fact that the fundamental interactions act locally between individual neighbors, the resulting dynamics of the system are such that the effects of acting on the system at a particular point are significantly felt globally.

The emergence of this sort of a multi-scale operational way of acquiring and expressing knowledge has a very far-reaching methodological potential. This is even more evident when coupled with modern computer simulation, visualization and animation capabilities.

The following research routine has been the basis for previous experiments that were conducted in other domains:

1. Modeling the system as a composite of many Micros.

2. Computer simulation and visualization of the resulting model.

3. Identification of the Macros.

4. Modeling the system at the macroscopic level using the macros as building stones.

5. Predictions based on the 'Macro'-scopic behavior of the model.

6. Return to microscopic level to tune the type and amplitude of the local interactions.

7. Comparison with experimental macroscopic behavior.
8. Confirming or correcting the microscopic model in view of the comparison.

9. Starting new experiments based on the results both in the micro and macro level.

The use of this dialogue, inside an artificial system created in the computer in order to understand natural properties, extends to systems away from equilibrium and to complex systems such as the immune system which are not characterized by energy functionals or by asymptotic probability distributions.

**Microscopic Simulations of the immune system**

Generally accepted knowledge about the Immune System can be summarized by specifying:

1. The Microscopic Elementary Objects (Molecules) which compose the Immune System (e.g. B-cells, antibodies, T-cells, cytokines, NK cells, macrophages etc.)

2. Microscopic interactions between these objects (e.g. macrophages may swallow molecules or cells that are covered by antibodies, killer-T-cells may kill cells when presented with certain molecular complexes etc.)

3. The Emergent Macroscopic Objects and Processes composing the Immune System: FUNCTIONS, (e.g. foreign invaders are identified and attacked.) MALFUNCTIONS, (e.g. sometimes the Immune System attacks the self), KINETICS, (e.g. It takes seven days to heal a bout of the flu.)

The form of Microscopic Simulation we have used in the work presented here is a hybrid of the two major methods hitherto used to simulate biological dynamics. These are differential equations and Monte-Carlo simulations:

(1) Ordinary differential equations - The results of such equations simulate the evolution of the average population under the assumption of spatial
homogeneity. With partial differential equations we divide the population into points in space. At each point we consider the population to be homogenous

(2) Monte-Carlo simulations - Work in our group has previously shown the importance of using microscopic Monte-Carlo simulations to describe the dynamics of auto catalytic entities. (Shnerb et al. 2000, Louzoun et al. 2003, Solomon 1995). The importance lies in the discretization of the population levels on the one hand while treating time as a continuous parameter on the other. This auto-catalytic situation is almost universally prevalent when simulating biological and especially immune dynamics. These types of simulations can be divided into two types: asynchronous and synchronous.

(2a) Asynchronous simulations

An asynchronous simulation is built over a lattice of a given dimensionality. Each lattice point contains a potentially unlimited number of reactants. In asynchronous simulations at every time step one and only one reaction between a number of individual entities will happen. The reaction, which may include diffusion, and the entities are selected at random, at a rate proportional to their rates of reaction and concentrations. The size of the time-step which passes after every reaction is not constant. It is also proportional to the chance of the reactions occurrence. This in a sense turns time into a continuous parameter of the simulation.

(2b) Synchronous simulations

The main difference between the two Monte-Carlo simulation types is that in synchronous simulations more than one reaction can happen at every time step. In this type of simulation each time step (dt) is constant. We computed the probability of each reaction at each spot. We then chose the number of reactions
taking place according to a Poisson random generator with the appropriate mean. The Poisson random generator was used as we supposed that each reaction was independent of the others.

If simulating interactions between large amounts of entities of the same type the differences in results between a-synchronous simulations and synchronous simulations become negligible.

When there are big differences in the population levels of entities, over short periods of time, or in different regions in space, Monte-Carlo simulations are very costly in computer run time, we have therefore used in the works shown here:

(3) Hybrid models (Microscopic Simulation) - These computer simulations move fluidly from using synchronous Monte-Carlo simulation to differential equation based cellular automata. Which system is used depends on the population levels at a given point on the lattice. As shape space need not be constrained to real space dimensionality we built lattice structures of N-dimensionality or of random connections, depending on the kinds of similarity in shape we were trying to model. At each point in shape space the reactions were computed by ordinary differential equations when concentration was high and by synchronous Monte-Carlo simulation when concentrations where low. Diffusion was treated as another reaction which removed entities from one point and randomly distributed them to its neighbors. As with the other reactions the amount of diffusion was calculated either by synchronous Monte-Carlo or by ordinary differential equations, depending on the concentrations at the point from which the diffusion started. Note that the use of hybrid models is justified when the average local density is relatively low, and the average number of reactions per time step is limited.
3. Results

Ask me a riddle and I reply – coddelstone, coddelstone, coddelstone pie
Winnie the Pooh by A.A. Milne

The theory of Useful Examples and optimal exemplar learning in cognitive systems


The two papers in this section deal with a theory we built which shows a common criterion of all cognitive systems. This criterion is the essential adaptive stage in the formation of the capabilities of any cognitive system. We further suggested that the adaptive strategy used by naïve cognitive systems has similar general principles among different systems and that the outward representation of these principles can be seen in the distribution of examples in the environment. Certain examples are at a relatively high frequency in the environment, furthermore these high frequency examples are generic of the rules of interaction of the system in the environment. In other words, the shape space of cognitive systems is not regular. A few nodes will be highly populated and will also be highly connected compared to the rest of the shape space which will be relatively empty. We called the important nodes – Useful Examples as they are very useful for the cognitive system in its attempt to learn the rules of interaction with the various signals in the shape space. The first paper describes, in general, the theory of Useful Examples using vision, language and immunity as examples. The second paper explicitly deals with the adaptive method used by naïve cognitive systems, which we called optimal exemplar learning, and its relation to the form of their environments. In this paper only the acquisition of syntax and the forming of immune specificity are used as examples.
The Immune System and Other Cognitive Systems

In the following pages we propose a theory on cognitive systems and the common strategies of perception, which are at the basis of their function. We demonstrate that these strategies are easily seen to be in place in known cognitive systems such as vision and language. Furthermore we show that taking these strategies into consideration implies a new outlook on immune function calling for a new appraisal of the immune system as a cognitive system.

It is becoming clear that the field of immunology is approaching a paradigm shift. It is agreed by most researchers that the immune system is a complex system both in its composition and its behavior. However, the most popular ideas of immune function treat the immune system in a mechanistic and reductionist manner. According to the clonal selection theory the immune system’s function is to defeat pathogens. The immune system identifies foreign antigens and destroys them. The identification of the foreign is made possible by removing, in the immune system’s prenatal development, all receptors that recognize self. Anything that an immune receptor identifies “must be the enemy” [1]. Countering this mainstream view are a growing number of voices that state the need to change the clonal selection theory or discard it, claiming that such a simplistic appraisal of the immune system’s function and mode of action is untenable because, at the molecular level, we are closely related to the pathogens that invade us. There is a need to consider the immune system as a integrative system with the ability to see patterns and understand context [2,3]. It is in the context of this argument about the immune system that we present our theory of cognitive systems and claim that the immune system should be seen as such a cognitive system.

The phrase “cognitive system” is used in many fields to describe the various faculties that we and other organisms use to perceive and interact with the world. Despite its widespread use, the phrase “cognitive systems” has not yet been defined in a way that can be applied to all of the cases in which it is used.

We suggest the following criterion to differ between cognitive and noncognitive systems: In cognitive systems the perceptual sensitivities of the system are not preordained only by the plan of the system but need an interaction with their environment to define the system’s exact sensitivities.
We propose a theory of the general underlying principles of cognitive systems, their perception regarding the environment, and the way in which they deal with the complex patterns their environments present. This is essentially divided into two phases—a phase of priming (top of Figure 1), in which the system defines the general properties of its environment that it knows and a phase of specific interaction (bottom of Figure 1), in which the cognitive system utilizes its knowledge of the general properties to interact with specific encounters with its environment. These phases are not necessarily chronological by nature and happen with each interaction of the cognitive system with its environment.

Cognitive systems are innately built with a tendency toward perceiving certain aspects of the environment. These tendencies are such that they cause the cognitive systems to be receptive toward seeing certain general properties of the environment and examples that embody them. However, the cognitive system will only acquire general properties that are corroborated in its initial interactions with the environment. The definition of general properties by cognitive systems is something that is not completely predetermined but rather defined through interaction with the environment; the environment’s reinforcement is what defines the final set of general properties that the cognitive system uses to know its environment. The general properties are an important aspect of the shape space,¹ and so they are encountered often in meaningful interactions with the shape space. Examples of such properties which are both generic for and

¹Protein shape space is an analogy commonly used to describe a vector space, in which every point describes a configuration of the protein [4]. We will use this in a more general way to describe the vector space of the various cognitive modalities.
ubiquitous to the relevant environment, are extremely beneficial in learning the environment. As such we will call them “useful examples.”

Through specific interactions and based on the previous tendencies of the system certain general properties are corroborated by “useful examples” of these properties appearing in the environment. This corroboration leads to the formation of an achieved set of representations in the system. Specific encounters with the environment start with a deconstruction via a detection of similarities to the useful examples, embodied in the achieved set. After this detection there is a refitting and fine tuning to the specific elements of the event. Having identified the specific elements of the event, there is now a reconstruction of the event together with an association to other contextual factors to a functional/meaningful event that can be appropriately reacted to and added to the memory of the system. (The two phase are chronologically mingled; both happen simultaneously. Every encounter is a specific encounter even while the cognitive system is still building its understanding of the general properties. Also in many cognitive systems it is not clear if the process of defining new general properties ever comes to a complete stop. “Young” cognitive systems are less fluent in working with the general properties, and it is harder to teach an “old” cognitive system new tricks, but all interactions with the environment have elements of both phases.)

In this discussion of cognitive systems, we will start with the visual system. Visual systems are built according to the niche in which they are used. A bee’s view of flowers is different from ours. The limits of sensitivity to wavelength and contrast are to a great extent built in. However, seeing is not merely a matter of light sensitivity. We see because we have learned how to do so; we know what things to “look” for and what they mean. This knowledge is an understanding of the natural context of vision and the general properties of the visual stimulus that we encounter. As an example, take a look at Figure 2 where our knowledge will not help us.

A painting from the brush of Salvador Dali, this picture shows how complicated it is to know what we are looking at when we do not have the natural context to tell us what we should look for. The title may give you a hint, “Apparition of a Face and Fruit Dish on a Beach.” Once we reveal that the “apparition” hides the figure of a dog, it is doubtful if you could ever again look at this picture without seeing man’s best friend. Our preknowledge is not of specific aspects of every stimulus but rather of their general properties. The knowledge of the general properties of visual stimuli is not something that we are born with; rather, it is acquired through the natural exposure to the environment. The process starts with the natural visual tendencies of the visual apparatus and the innate bias that we are born with toward certain things, such as complex stimuli and movement; however, these innate aspects are not enough. Given this tendency, the visual system, in its first stages of development, builds up the tools that later will allow the act of vision.

The need for this priming stage and the existence of a critical period for its occurrence is easily seen in people who have had blocked corneas from infancy. Such people, if their cornea is removed too late, will remain functionally blind; for although they can react to light, they cannot resolve the images they see [5] (much like living in a painting by Dali). In those of us free to see the world, the process of learning the general properties is unsupervised and is based on the existence of useful examples for the general properties of naturally encountered visual stimuli.

The general properties are those things that are both ubiquitous to the different stimuli and appear in many different meaningful contexts. In vision these would be things such as edges or regularities of scale [6]. Their high frequency and usefulness very naturally cause their corroboration, until eventually we have a visual system with an achieved set of representations based on the “useful examples” (stage 1 in Figure 1). This “achieved set” is what enables, from then on, the resolution of visual stimuli: the deconstruction and reconstruction of the second stage, which allows the acquiring of the proper functional understanding of the image and memory.

Vision starts with the general properties of the image rather than its particulars. In our representation this is the phase of detection (second half of Figure 1). Sight, as opposed to taking a picture,
is done while knowing what the important things in the image are. Edges, movement, and other “eye catching” things tell the visual system where to look. Once this phase of *detection* and *deconstruction* is done, the visual system can refit to the particular image it is dealing with and can associate it to the current context. This gives the stimulus meaning and achieves a functional image, while widening the knowledge of the visual world via memory.

The fact that our visual ability is based on and inseparable from our perception of the general properties of visual stimuli can easily be seen in the kinds of illusions that fool us. Movies, animation, and paintings are all only good copies of natural images in the sense that they capture the general properties of the visual world.

Note the different scales involved in the two phases that we have discussed so far regarding vision. The first stage, the stage of priming and obtaining the achieved set, is a stage that responds to some external input, but does so in a duration orders of magnitude longer than the time needed to process new input once the system is fully functional. Moreover, the second stage, specific interaction, is a continuous process going on all the time, whereas the first stage is a once in a lifetime opportunity. It takes a long time to put together an organism, but, once it exists, the organism has to use its mechanisms immediately.

One cognitive system where this separation in time is clearly seen is in the development of language in children. As infants and children, we learn to speak, and it is a long and laborious process. However, once language is acquired, when we add new words to our vocabulary, learning them and their correct use is something that we can do almost instantaneously. We will deal with only one aspect of the acquisition of language—the learning of correct syntactic combinations—how we know the correct order of words that make a meaningful sentence. This step is made possible by the previous stages of auditory and cognitive development, which are influenced by various innate and learned biases. The exact amount of learned and innate influence is the scene of many an argument in the cognitive sciences that we will not go into [7]. In any case, it is obvious that at the stage of syntactic development the language system already has a “tendency” that sets the stage for the learning of syntactic combination. This can be seen in the fact that the learning of sentence formation is always preceded, in children, by a stage of rapid growth in vocabulary or “vocabulary explosion,” that brings about the creation of the vocabulary necessary for syntactic combinations [8].

In studies concerning the use of intransitive and transitive verbs in syntactic combinations, in parents’ conversations with their children, it was seen that parents use a very small subset of verbs at a very high frequency when talking to their children. Words such as want, come, go, and make account for a high fraction of the verbs used in parental conversation. All these high-frequency verbs are very general, have uses that are almost empty semantically, and can be said to be generic of the verb subcategories to which they belong. In return, all the first verbs used by children are drawn from this group of verbs (though individually each child’s first verb need not be the most commonly said word of his parent). Further, once the first verbs are learned in a certain syntactic construction, the speed of learning other verbs in the same syntactic construction, but not necessarily in other constructions, is greatly enhanced. This could be indicative of a scenario where the child learns the first 2 or 3 examples, after which the others are greatly facilitated (Reference 9 and Figure 3).

In effect, because of the shape space of languages, in the course of normal conversation, children are exposed to the useful example of the different types of syntactic combinations and the correct use of language. The first words are very common and have many uses (they embody various ideas). In this fashion the useful examples of language are corroborated, bringing about the formation of an achieved set of representations that greatly facilitates the latter identification of similarities to the use-

![Figure 3](attachment:figure3.png)

Figure 3. Cumulative number of different verbs in V0 and SVO word combinations produced by a subject as a function of age [9].
ful examples and the formation of correct functional syntactic combinations.

The studies mentioned above deal with the learning of intransitive verb-dependent combinations and of transitive verbs in verb–object (VO) and subject–verb–object (SVO) relations. The view of the first examples as useful examples is further strengthened by the fact that the first words learned are easily seen to be generic of some relation of the speaker to the world. In learning intransitive verbs children deal with animate objects, and the first few verbs spoken in word combinations (i.e., learned) always cover categories both of active (come, go) and passive/static (fall, sleep) relations [9]. VO syntactic combinations are learned before SVO. The improvement in one syntactic combination is separate from the improvement in the other. In 13 of 16 children, the Hebrew verb “raza” (want) was one of the first VO verbs (and if not, it was generally the first SVO verb). In VO, 84.4% of first utterances were requests, whereas in SVO 25.9% were requests and 44.4% were descriptions of creation or consumption of objects. In learning both syntactic combinations what is being learned, along with the correct use of VO and SVO, are useful examples of the child’s relation to alienable objects (things that can be part of me or not part of me). The child is learning to add, remove, or maintain objects in his “personal space” [10] and in essence is acquiring an achieved set of representations to deal with objects and their abstract reflections.

The statistical shape of language is such that when speaking to those who do not speak, we will use those words that are useful examples and enable the cognitive task of learning. Languages are “built” so that when talking in simple language to children, we will corroborate the general properties of correct speech and sentence formation, thus enabling the acquisition of language. Possibly, we have here also evidence for the priming phase of the most cognitive of modalities: our ability to exercise abstract thoughts. Together with the general properties of language, we see here that children learn useful examples of the mental interaction with alienable objects and define some of the general properties of abstract thought.

Having shown how our theory works in systems, commonly agreed upon to be cognitive, we come now, finally, to the immune system. It is in treating the immune system as cognitive that we believe that our theory is most controversial and also of the greatest benefit compared with the present paradigm, the clonal selection theory. We hope to show, citing various sources of contemporary research, that present knowledge of the immune system and its interaction with the antigenic/molecular patterns of our body calls for the treatment of the immune system as a cognitive system.

The immune system has an ability to identify specific events and changes in the body. The immune system’s environment is the body. It interacts on the cellular/molecular level. To do this, it has many types of cells as well as effector and signaling substances, many of which are yet to be identified and understood. However, in general the population of cells that make the immune system can be characterized as the populations of cells known as lymphocytes. The two most important groups of lymphocytes are called B cells and T cells.

Both of these cell families have a unique ability the create receptors, which, though they all originate from the same genetic material, use different combinations of this material to create an immense variability in their final form. The shape of the receptor, which like all proteins is based on the sequence of a certain gene, implies the shape and type of molecule that will activate the receptor. Therefore, this genetic variability gives the immune system the potential ability to have receptors that can identify a near infinite number of molecular shapes. The molecules that immune receptors identify are commonly known as antigens. The region within the antigen to which they attach is known as an epitope. A single antigen may have several different epitopes.

The receptors of B cells identify extracellular substances. The receptors of T cells identify intracellular substances by interacting with specialized antigen-presenting proteins known as major histocompatibility complex (MHC) receptors [11], which are expressed on the surface of every one of the body’s cells. MHCs present fragments of intracellular proteins, in effect mirroring the internal state of the cell. Together, T cells and B cells can identify most intra- and extracellular substances. The immune system’s identification and reaction to a pathogen or other immune events is dependent on mutual reaction by both T cells and B cells to that event [12].

In trying to fit the immune system to our theory of cognitive systems, we are making a remark on the kind of receptor repertoire that the immune system forms out of its potential variability.

The potential repertoire of receptors is immense, between 10^{11} for B cells and 10^{16} for T cells [4]. Because (in mice) the immune system contains only about 10^{6} of each of the types of cells and every single cell has only one type of receptor, it is obvious that the actual repertoire is smaller. If the immune system were to have a repertoire built of every potential receptor it can generate, then in a rat, for example, this would necessitate having a spleen 70 times the size of the rat’s entire body [13]. What kind of repertoire actually exists, and what factors are important in its formation?

As we mentioned above, immunology is in the midst of a paradigm shift. There is an especially widespread debate on the way in which the immune system differentiates between the molecular patterns of the body and foreign pathogens [3]. We will not go into all aspects of this discussion. In plain words, the current textbook outlook on immunity, the clonal selection theory, states that anything that an immune cell receptor identifies is a foreign pathogen. According to the clonal selection theory, this state of affairs is brought about in the following way: During embryonic development immune cells are created randomly, each reactive to a different antigen.
cells bearing receptors that bind to self-antigens at a certain level of affinity or above are eliminated. This is known as negative selection. At the end of this process any receptors that remain can only be activated by foreign pathogens [1,14].

This is a classical reductionist theory that is extremely elegant and simple. It explains how we create a repertoire, which on the one hand can identify pathogens and yet does not react falsely with our body’s molecular patterns. It is also a very mechanistic way of viewing the workings of the immune system. One major implication of this theory is that autoimmunity—the reaction of immune receptors to self antigens—is something that exists only as a pathology and never in a properly functioning immune system or a healthy body. Even if we were not about to show that the immune system works like a cognitive system, there is a major problem with this theory. The elimination of self-repertoire completely ignores other functions of the immune system that are essentially involved with self, such as wound healing and combating cancer [2,15].

Several generally known aspects of immune detection, agreed on even by the most ardent supporters of the clonal selection theory, seem to imply that the immune system is working as a cognitive system: First, the need for costimulation of B cells and T cells for immune reaction [12], and second, the fact that B cells are reacting to extracellular information, whereas T cells react to intracellular information. Together these appear to imply an immune reaction to patterns and context.

Treating the immune system as a cognitive system, the idea of building a repertoire in the way suggested by the clonal selection theory becomes less plausible. The immune system’s environment is built completely of cells both endogenous and exogenous, which at the time of encounter are residing in the body. Also, all of this cellular and viral life is built of similar building blocks. There is no intrinsic molecular signal that differentiates between the organic substances of our body and those of other organisms. Removing all receptors to self amounts to removing all receptors to all of the things that are common to all cellular life. Building a system that needs to recognize the important aspects of this environment but is blind to the general properties (which are those things that are ubiquitous in the environment) is like building a human visual system that can not become aware of edges.

We are suggesting a model of the immune system as a cognitive system. This implies several things about the way the immune system is primed and how it detects its environment (see Figure 1). As we showed for vision and language, the priming of the system and building of the achieved set of representations starts by fulfilling innate systemic biases or tendency. In this case, this would probably be a genetically transferred tendency to present certain protein examples that are used to build the receptor repertoires. These useful examples would, as in vision and language, be examples of the general properties of the living molecular environment. They should, therefore, be examples of self that cause a positive selection of receptors with at least some minimal affinity to these examples.

We would, therefore, expect to find that, from the first randomly generated stock of receptors, the adult repertoire of immune receptors are created by a combination of positive and negative selection using specific molecular examples of self.

Part of the reason that the clonal selection theory is being forced to change is that positive selection is apparently important for the creation of the mature repertoires in both B cells and T cells [16,17]. This is especially evident in T cells. One form of positive selection is agreed on for T cells, even by the clonal selection theory. T cells must have a minimal affinity for at least one self antigen—MHC receptors—if they are to function. However it appears that the recognition of self-MHCs is not the only kind of self-recognition that is necessary for proper T-cell development, in fact the proteins nested in the MHCs, while selection is in process, affect the positive selections outcome [18]. Further, it has been shown, using genetic engineering techniques, that an immune system built with fewer kinds of fragments presented by MHCs, within the context of positive selection, will have a less diverse T-cell repertoire [18].

The selection of T cells within certain boundaries of affinity to MHC receptors and the fact that MHC receptors only present the fragments of certain proteins [11], together show a possible mechanism by which the immune system creates an important bias toward a certain population of examples while creating the repertoire of receptors.

What are the “useful examples” presented by the MHCs bias? The exact types of proteins, fragments of which are presented by MHC, have not yet been characterized. However, let us consider, given a tendency, what would constitute the useful examples that are corroborated, and what is the environment for which they create an achieved set? As we mentioned before, the environment of the immune system is the body’s cellular life. Candidates for “useful examples” would have to have the following properties: they would have to be part of every cell; they would have to have been there all through the history of the development of the immune system for them to be such a major part of its function; they should be relevant in times of stress (or otherwise they cannot serve extreme conditions usually common in immune response).

Indeed, it is possible to find such a set. The set corresponds to a group of antigens Cohen has named “homuncular antigens” [2], and all belong to a group called housekeeping or maintenance proteins. Housekeeping proteins are essential in all cells, because they are responsible for ongoing energy metabolism, protein construction, and basic genetic manipulations.

One group of housekeeping proteins of special interest is called heat shock proteins (HSPs). HSPs are part of a larger group of proteins called chaperones, which are essential in correct protein construction and folding. HSPs help cells maintain the proper form (and function) of proteins in various
states of emergency and stress. The situations when HSPs are most expressed, emergency and stress, are also the ones where you may usually find immune response. That alone suffices to mark HSPs as useful examples to the immune system, but more than that, because states of emergency abound in all environments, HSPs are essential and are expressed in all cells. In fact, these proteins are ubiquitous in cells in times of stress and are highly preserved throughout evolution, from prokaryotes to multicellular organisms [19]. All this suggests HSPs to be part of the useful examples that build the achieved set through which detection is carried out.

Now that we have proposed this possible achieved set (the homuncular antigens), we can go on to the mechanism of detection. If the immune system behaves according to our suggested theory, we would expect several points of immune behavior. We have just shown that housekeeping genes in general and HSPs in particular would be good candidates as “useful examples,” which would imply that the immune system and its receptors would have a bias in its reaction to these proteins when reacting to the environment and performing immune functions. At least in HSPs this appears to be the case. Receptors to different types of endogenous and exogenous HSPs have been shown to be important to immune reaction. In Cohen and Young’s review of the immunological reaction to HSPs, they show that during almost any reaction to bacteria and parasites, the recognized antigen detected is a type of HSP [20]. In other immune activities, T cells reactive to specific self-proteins, for example, HSP60 and MBP (an essential factor in nervous tissue), have been shown to enhance the regeneration of skin and nerve tissue [21–24].

If the immune system is indeed working as a cognitive system, as we have described it, then the immune mechanisms of detection should include a means for the detection of the general properties of the environment along with a mechanism for refitting toward specific encounters. This should allow for the deconstruction and reconstruction of the immune “image.” Therefore, we are expecting an adult repertoire of receptors built to react degenerately, at a median level of affinity, to a few self-antigens. This repertoire will not change much during our lifetime. Along side this, we expect a repertoire of non-self-reactive receptors, which changes and evolves over time as the immune system encounters pathogens and evolves throughout our life.

Both T cells and B cells have adult receptor repertoires that are highly cross-reactive and react degenerately to self-antigens. These repertoires remain at a steady level throughout life [13,25]. B cells have an added ability: when activated by the innate immune repertoire, they start a process of fine tuning, known as affinity maturation [26], by which they create highly specific and accurate receptors that react to a specific antigens. In B cells we find a sharp distinction between a self-reactive repertoire, which remains permanent throughout life, and a changing population of receptors that is a result of the immune system’s interactions with different immune events [25]. B cells, while acquiring a growing repertoire toward specific pathogens, during the lifetime of the organism, maintain a permanent repertoire of cross-reactive receptors, possibly through interaction with the less changeable T-cell repertoire.

The stability of T-cell repertoires and fluidity of B-cell repertoires could very well be a way to allow the process of detection and refitting, while keeping focused on the achieved set of molecular life (homuncular antigens).

The existence of self-reactive receptors does not mean that an autoimmune reaction of the immune system is something that happens in health. It means that such an occurrence is avoided, not through the lack of self-reactive immune receptors, but rather through their heavily controlled existence.

Although we have not described exact cellular mechanisms of detection and interaction, we feel that we have given enough of an argument to justify treating the immune system as a cognitive system.

The immune system’s ability to function is dependent on its understanding the environment in a cognitive manner and its ability to discern the complex patterns it encounters. The world of immune function is the body in which it resides. This is the source of the examples it uses to see the generalities of cellular life. These points imply a new outlook at the receptor repertoire of the immune system, which enables it to react to changing and unexpected patterns.

Our self is the source of examples, and yet in the end the immune system knows not to react to the patterns of self. This could be because the immune system has no receptors for self and so the immune system can not “see” it. We would suggest that this is not so, but rather the immune system has many receptors with a sensitivity for self; however, their interaction is such that it recognizes the patterns of self as what they are—the background on which the picture of immune events are painted. Self-immunity is the basis not the nemesis of immune function.

In closing, although we have used vision and language as examples to explain something about the immune system, still in doing so we have also put together principles that are at the base of all cognitive systems. These three systems are all different in their particular components and in the specific fashion in which they interact with their part of the environment. Still they all share the common traits of dealing with the specifics of their environment through an acquired sensitivity to the general properties of their environment. We would say that this is what makes them all cognitive systems.

Cognitive systems have the common trait of functioning in an existing environment constantly on the brink of change. Noncognitive systems are built with a limited wired perceptual ability capable of reacting to certain stimulants and no others. In cognitive systems, the existence of a built in (genetic) tendency promises the acquisi-
Cognitive understanding deals with specific things and the ability to recognize a great amount of the specific aspects of its environment. However, the ability to deal with all of the varying and changing aspects of the environment starts not from the specifics of the world but from generalities. First are learned the general metaphors, the useful examples of general properties, which are applicable in many different ways to the world. Once they are grasped, it is easy to apply them in many different ways to the world around us. The fact that generalities take on many different aspects is not a drawback to learning them. It is one of the main reasons they are learned first. We have dealt here with only three systems and only in a superficial manner; still, we are sure that studying other cognitive systems will show similar patterns. Furthermore, we believe that in studying cognitive systems discovering the nature of their useful examples and the general properties they represent will tell us much as to those systems basic function and abilities.

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Optimal exemplar learning in cognitive systems

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Abstract

The following paper is the fruit of an interdisciplinary discourse between the study of the learning of syntax in infants and the study of the development of immunity. Showing specific examples from these fields, we propose a form of optimal exemplar learning. We suggest that this form of learning is how all cognitive systems reach the "rules" or general properties of their environment.

In such learning, the specific interaction of the system with any example is identical. However, not all examples of the environment are equally encountered in natural interactions with the environment. There is a class of examples that are ubiquitously encountered and generic of the general properties of the environment. This ensures that they will be the first noticed and learned by the system. The very ubiquity of the useful examples also ensures their rapid reinforcement and facilitates the learning of other examples of the same property.

In talking to infants, parents use with high frequency a set of verbs that are almost empty semantically, being generic to the subcategory to which they belong. The first verbs used by the infants in learning syntax belong to the same group of verbs. Once these first examples of a given syntactic combination are learned, the ability to learn further examples is greatly facilitated.

In living cells those proteins that the cells need most in trauma that are most highly conserved throughout evolution. These proteins are ubiquitous in both humans and microbes. The immune system creates the major antibody clones precisely to these proteins when combating diseases.

In summary, we have discovered an underlying similarity between the learning processes of two a priory unrelated systems. This leads us to believe that optimal exemplar learning may be operative in all cognitive systems. This is a strong hypothesis that should now be investigated in other cognitive systems.
1. Introduction.

There are many different cognitive systems, and there exist many descriptions of their characteristics and functioning. In terms of general system theory one trait that is quite clearly common to all such system regardless of their definition, is their self organization through interaction. In all cognitive systems the final capabilities of the system are not fully determined by the plan of the system. To reach these capabilities the system must interact with its environment (Hershberg & Efroni, 2001). In the following pages we present a theory of the common traits and learning strategies of cognitive systems. Specifically we would like to suggest a form of exemplar learning, called Optimal Exemplar Learning, that enables a cognitive system to learn to be a cognitive system. These common strategies do not reflect a similarity between the specific building blocks of each system. They are a result of a common relationship between cognitive systems and their environments. To demonstrate this point we will use two very disparate systems, language and immunity. It is very clear that both systems are very different both in their biological substrate, neurons and lymphocytes, and in their environments, the abstract information space of language and the molecular jungle of our bodies.

However, as we will see in the following pages, both share a common strategy in the manner by which they interact with their diverse environments and acquire their capabilities.

2. Optimal Exemplar Learning: How does a cognitive system learn to be a cognitive system?

The mode of learning by which a cognitive system acquires its capabilities and understanding of the general properties of the environment is by interacting with concrete exemplars of the environment. Learning is the result of unsupervised interactions with exemplars; all interactions with the environment are of the same type.

We think that this mode of learning is extremely efficient in cognitive systems because the environment itself is ordered, and because examples of the general properties of the environment are ubiquitous. We call these optimal exemplars of the environment "useful examples", because they are useful for learning the environment and its relevant general properties by the relevant cognitive systems.

Learning of examples of the general properties of the system does not change the types of interactions with new examples. However, due to the centrality of
Useful Examples in the environment, learning them facilitates the acquiring of, or the correct reaction to, new examples. Useful Examples make for optimal exemplar learning.

The environment is ordered in a specific way which is especially pertinent to a naive unformed system. This order is not a chance occurrence; it is a reflection of the fact that cognitive systems are fitted to certain niches. Based on genetic inheritance and previous development, a cognitive system has certain tendencies, which give it the framework of its environment. This reflects the previous environments in which this system has developed / evolved and not the final capabilities of the system, which are dependent on future interactions with the environment.

It is tempting to speculate that if there were no statistical disparities among the exemplars of the environment, making the central exemplars easiest to assimilate by the learner, learning would be much more difficult, drawn-out and error-ridden than it is in fact. This is why we call exemplar leaning based on Useful Examples of the environment, Optimal Exemplar Learning.

Having given a general description of Optimal Exemplar learning we would like to show how two cognitive systems, language and the immune system fit in with these principles. We will start our examples with language, a more accepted cognitive system, and show how it works within the framework of optimal exemplar learning.

3. Language: The role of central examples in the acquisition of syntax.

We will deal with only one aspect of the acquisition of language - the learning of correct syntactic combinations, namely, how to construct a meaningful sentence from more than one word. However, our points should hold for other stages of language acquisition as well. Learning syntax is made possible by various innate and learned biases whose exact amount of influence is the scene of many an argument in the cognitive sciences which we will not go into. In any case, it is obvious that at the stage of syntactic development the language system already has a "tendency" which sets the stage for the learning of syntactic combination. This can be seen in the fact that the learning of sentence formation is usually preceded in children by a stage of rapid growth in vocabulary or "vocabulary explosion", that brings about the creation of the vocabulary necessary for syntactic combinations (Bates, Bretherton, Snyder & Beeghly, 1988).
It is a fact of long standing that, in general, the statistical shape of language is such that a relatively small subset of words are highly frequent while the rest are used at a lower frequency (Zipf, 1965). According to hypothesis, the highly frequent words have a special role in syntactic development (Ninio 1999a, 1999b).

The studies on the basis of which this hypothesis was formed, compared the order in which children learned to form syntactic combinations with intransitive and transitive verbs, with parents' use of verbs in syntactic combinations in conversations with their children. It was observed that parents use a small subset of verbs with very high frequency when talking to their children. Words like want, come, go and make account for a high fraction of the verbs used in parental conversation. All these high frequency verbs are very general, have uses that are almost empty semantically and can be said to be generic of the verb sub-categories to which they belong, defined by their following a certain set of syntactic rules. In other words, children are presented with high frequency exemplars that have very few irrelevant features as far as their syntactic behavior is concerned. In return, all the first verbs used by children in combination are usually drawn from this group of verbs.

Fig. 1. Cumulative number of different verbs in VO and SVO word-combinations produced by a child acquiring English, as a function of age. Source: Ninio (1999a).
Once the first verbs are learned in a certain syntactic construction, the speed of learning other verbs in the same syntactic construction, but not necessarily in other constructions, is greatly enhanced. This could be indicative of a scenario where the child learns the first examples with a great deal of investment of effort, after which the ability to learn new verbs in the same syntactic combination is greatly facilitated. Figure 1 presents as an example two graphs documenting the development of verb-object and subject-verb-object word-combinations in a child, as a function of age. The dependent measure is the cumulative number of different verbs participating in each type of construction as observed in recorded interaction sessions of child and caregiver. Each verb is counted at the age when it is first produced in the relevant syntactic construction.

It is evident that these graphs have the characteristic shape of typical gradually accelerating learning curves: The time it takes to apply the new rule to yet another verb is much longer at the beginning of acquisition of that rule, and it gets shorter the more verbs the child has already learned to produce in the relevant pattern. Accelerated learning has also been observed with regard to other aspects of language acquisition such as the growth of vocabulary (Dromi 1987, Van Geert & van Dijk, 2002).

The conclusion is that languages are statistically shaped so that when we talk simply to those who are just learning to talk, we are accentuating the general properties of language. The statistical structure is a means of ascertaining that language can be learned through meeting with the concrete exemplars of the linguistic environment. The statistical structure of language, in other words, allows Optimal Exemplar Learning.

4. The Immune System: Learning from similarities.

The definition of the behavior of the immune system as a cognitive system is not new; it has been put forward by Cohen (2000), Varel (1994) and others (Hershberg & Efroni, 2001).

The immune system starts with a large random collection of receptors from which only a subset survives. The receptors of the immune system are selected according to a certain level of affinity to antigen examples from the body, through a process of negative and positive selection in which all receptors of too high or too low an affinity to these antigen examples are killed (along with the cells that produce them). These examples reflect the expression of proteins in the various cells of our bodies. As in other perceptual systems the selection of receptors is competitive. If a receptor spends a long time
inactive, it will be pushed aside by more active receptors (Goldrath & Bevan, 1999). The immune system is left with a repertoire of cells that all share this level of affinity to the antigen examples of the body.

Let us look how this fits in to the principles of optimal exemplar learning. It seems bizarre to emphasize that all examples are concrete in the immune system. Compared to other, more obvious, cognitive systems, where it is apparent that abstraction and general concepts may exist as objects, in the immune system the receptors are all dealing with specific concrete molecular patterns. However, as in the other systems, the environment is ordered, and to reflect this order the receptor repertoire is better served by learning form certain examples and not others. All accumulation of knowledge from previously presented examples is by transference. Cells of the immune system react differently to an antigen or other chemical signals depending on previous experience and reaction to examples. This is true in the thymus where a previous reaction may cause cell death but also in the periphery where activation can cause differentiation of naive immune cells to active and to memory cell subsets.

To show how the immune system fits to the form of Optimal Exemplar Learning, let us start with the statistical distribution of examples. As in language the environment is ordered, the antigens, which select the cells, have a distribution which is similar in shape to that of words in language. In an Antigen Presenting Cell 50% of all antigens presented will belong to 200 of a possible 10^14 antigens (Barton & Rudensky, 1999).

In an attempt not to use too many names and other forms of biological jargon we have left out what exactly are the Useful Examples in the immune system and what are the general properties they embody. The general properties the immune system notices are based on the fact that as cells, both our selves and the pathogens that invade us are not far distant from each other. We all stem from the same evolutionary chain and share many biological mechanisms. Possible candidates as Useful Examples that reflect this fact could be housekeeping proteins (Cohen, 2000). This group of proteins have, as their name implies, essential cellular housekeeping functions that are expressed in times of cellular stress to help the cell maintain its viability in hard conditions. These are good candidates for Useful Examples of cellular status for three reasons: first they are expressed in times of stress which is a good signal to raise the interest of the immune system, second they are necessary in all cells and so are expressed in all the cells of our body and outside it. Third and not least they are so important that they have changed very little over the evolution of life on earth and so are extremely similar in us and in the
bacterial pathogens that invade us (11). Therefore a receptor repertoire built around such examples would have to change little to become efficient identifiers of foreign proteins and their derivatives. Beyond these theoretical considerations such housekeeping proteins and the immune receptors that are sensitive to them have been found to be important for good immune reactions to both foreign invaders, and to other immune functions, such as combating cancer and the repair of damaged tissue (Cohen & Young, 1991; Moalem, Yoles, Leibowitz-Amit, Muller-Gilorr, Mor, Cohen, Schwartz, 2000 Schwartz & Cohen, 2000).

Much like in learning language, when the immune system interacts with its environment it will often encounter the Useful Examples causing the repertoire of receptors to be built around them. A repertoire built around other examples, not ubiquitous to all cells would have receptors that could be irrelevant to some pathogens, or even some cells of our bodies. As it is possible that some cells do not even express these proteins or any proteins similar to them. Even should some of the repertoire be built around other antigens these receptors will be less versatile in dealing with immune events and so over time should die out relative to the repertoire built around the Useful Examples which better reflect the common ground of cellular life and the factors essential to its viability.

5. Conclusions: Differences and unifying principles

Although we have dealt here only with two system, we believe that what we have said here may hold true for other cognitive systems as well. Cognitive systems and their environments differ in their interactions and in their building blocks. General properties and the examples that represent them have different reason for being signaled out by the perceptual tendencies of different cognitive systems. In the immune system it is the co-evolution of pathogens and hosts that defines the general properties. In language it is the fact that language is a cultural artifact, which needs to be passed on between users. For each cognitive system the reason for the singling out of specific Useful Examples is different. It depends on the specific environment and the specific types of interactions that the cognitive system undergoes with its environment. This reflects the fact that cognitive systems are fitted by evolution to specific niches. Therefore this difference basically represents the differences of environment and strengthens the feeling that in many disparate environments different cognitive systems are using the same rules to learn to be cognitive system.
Optimal Exemplar Learning allocates great importance to the statistical structure of the natural environment and in particular, to the identity of its most frequent exemplars. In attempts to study and simulate cognitive systems we must retain the statistical shape of the natural environments in which they develop, as this appears to be one of the essential features in their development. Even before we consider other aspects of cognitive learning implied by the principles of Optimal Exemplar Learning, for example the embodiment of examples in their natural environment; the importance of the behavioral and perceptual tendencies of the system; and so forth, we must consider the statistical distribution of the environments. This distribution by itself may direct us to the essential pieces of information that the systems use to learn their capabilities.

When studying a specific cognitive system and its environment or, for that matter, when trying to create an artificial system with the traits of a cognitive system, we should try and understand what are the Useful Examples they use to learn to be cognitive systems, as knowing what the Useful Examples are, gives a great amount of information about the cognitive system, its environment and the nature of the interactions between them.

References:


Self affinity is the basis not the nemesis of immune reaction


Hershberg U. ( in press) Useful Examples and a new model of the immune system, Revue d'Intelligence Artificielle (11 manuscript pages).

The papers in this section present two versions of a model of T cell and antigen populations in the immune periphery. The various clone types are represented as populations at points in shape space. T cells can react to antigens at the same points as themselves in shape space and also (at less affinity) to those on adjacent points in shape space. The use of this shape space representation allows us to embody the degeneracy and cross-reactivity of T cell receptors along with their essential level of self-affinity. We succeeded in building a stable (i.e. benign) T cell repertoire, around a small set of self-antigens, which reacts to a foreign antigen and returns to its resting state once the foreign antigen is destroyed.

The success of this model radically changes the view of immunity as it shifts the place of self-immunity and degeneracy from being possible faults to being essential assets.

The first paper in this section and its concepts are obviously influenced by the papers in the previous section. However, our wish to emphasize the biological / immunological aspects of our results led us to leave out the more general ideas relevant to cognitive systems. The final paper can be considered to be a summary of the three papers before it. It explicitly connects between the theory of Useful Examples, optimal exemplar
learning, our simulation, and the new view of immunology it entails. The simulation presented in it is similar to the one in the paper before it but it utilizes multiple foreign antigens to represent the pathogen while reaching similar results.

The reason for inserting both papers on the T cell repertoire simulation into the thesis is because it is only through understanding the reasoning and results from both a cognitive science and an immunological point of view, that we gain its full interdisciplinary import.
What is the basis of the immune system’s specificity?

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Abstract. In this paper, we present a model of T cell clonal repertoire dynamics and present a new view of the place of self reactivity in the maintenance of the T cell repertoire, and in the specificity of the immune reaction. Taking into consideration the cross-reactivity and self affinity of T cell receptors, essential to their maintenance in the healthy immune system, we have built a simulation of T cell dynamics in the shape space¹ of T cell and antigen forms. This simulation replicates the time course of a response to a primary infection and the return to a steady state, without requiring receptor affinity exclusively to non self antigens. These results suggest that the self-affinity should be seen not as a confounding paradox but as part of the background physiology of immune reaction, and show the need for a reevaluation of several basic principles of immunology. In order to better understand the place of self-reactivity, the function of the immune system, and how the cross-reactivity of immune receptors enables this function, we suggest that future research should focus on immune reactivates in the healthy body, and not just in disease.

1 Introduction

Immune interactions can be divided into three basic components. Antigens, cells that sense them and effector mechanisms. In this model we wish to focus on the first two components and more specifically to suggest how it is possible to have an effective sensing mechanism built of highly cross-reactive receptors. We present a model of T cell repertoire dynamics in the immune response based on existing knowledge of these dynamics, which aims to illuminate the basis of immune specificity in primary reactions to pathogens.

The immune system is unique in having a highly diverse variety of receptors like no other system in the body. This great variance is used to identify a near infinite number of antigens. This sensitivity of different antigen receptors is however highly regimented allowing the immune system to react to one type of antigen in a given context while ignoring other antigens. It is as yet an open question how the immune system maintains the specificity of reaction. - The possible answers lie in two camps: Receptor specificity and

¹ Protein shape space is an analogy commonly used to describe a vector space in which every point describes a configuration of the protein (A. S. Perelson and G. Wölbuch 1997).
systemic response specificity. By receptor specificity we mean that antigen receptors themselves are each highly focused and specific. Thus the specificities of an immune response is based on a repertoire built only of certain kinds of receptors. By systemic specificity we mean a mechanism that does not rely on the specificity of the receptors, but rather on some specific global behavior of the system.

The fact that we can find receptors sensitive to practically any substance and the importance of negative selection in the building of the immune repertoire in the thymus have led to the wide acceptance of the clonal selection theory [2], which supports receptor specificity. However, a closer look at the way immune cells are selected in the bone marrow and the thymus indicates that this interpretation is problematic:

- Immune cells are not completely specific; they are degenerate and cross-reactive.
- A certain level of benign affinity to self-antigens exists in all receptors.

These points hold true for all cells of the adaptive immune system, both B cells and T cells, and weaken the claims that the immune system’s specificity is based on either type of receptor specificity. As we wish to present a model of T cells we shall focus on the theoretical problems relevant to T cells, ignoring at present the existing parallel problems relevant to B cells.

The basic tenet of the clonal selection theory is that all receptors with affinity to self are destroyed leaving a repertoire which only reacts to foreign antigens. Most of the varying views on immune specificity, including those that have moved away from this severe view, hold that the cause of specificity is still in some way the result of receptor specificity. This is true whether it is the theory of B and T cell cooperation of Cohn and Lahngman [7], the danger theory of Matzinger [8] or Grossman’s theory of changing receptor excitation [6]. All in the end insist that there must be a greater receptor affinity for foreign antigens among immune receptors. This receptor specificity is what brings about the system’s specificity of reaction to the pathogen and not to the self. Such a view raises immediately the question of self-reactivity. How does the system deal with the self-reactive receptors that are known to exist in healthy immune systems? The answers to this question lead to various mechanisms, from regulatory T cells to anergy of cells, which lead to the cancellation of all self-reactive T cells and a functional blindness to all the information that could be gleaned from such cells. All such theories are incapable of reconciling several facts of immune physiology with the concept of blindness to self-antigens. Most importantly, T cells are highly cross-reactive, each T cell can react to as many as $3 \times 10^7$ different peptide-MAC complexes [1]. Furthermore, although T cells of a high affinity to self antigens are culled by negative selection, all T cells must have some level of affinity to self or they will not pass the positive selection phase and die of neglect [5]. Positive selection appears to be especially important as it is now found to be an essential factor in the maintenance of the T cell repertoire in the periphery. Low level
affinity to self is not only essential as a maintaining signal of T cells but is also causes them to proliferate [4]. We thus find a situation where the actual T cell repertoire is not, as is commonly suggested by clonal selection and the other immune theories, built of specific receptors reactive to foreign antigens. The repertoire is, in point of fact, built of highly cross-reactive receptors that all share some minimal common affinity to self antigens.

These discrepancies between the theoretical and actual characteristics of T cell repertoires lead us to suggest a new role for self affinity which better captures the highly cross reactive nature of T cell receptors and their affinity to self. We do this using the basic components of the known dynamics of T cell repertoire maintenance [5]. These are:

- The maturation of T cells in the thymus, at a steady rate regardless of immune activity.
- The proliferation of peripheral T cells in the presence of antigens (self or non-self) occurs at a rate proportional to their affinity and concentrations.
- The Global competition of T cells among themselves reaches a homeostatic level.

The T cells and the antigens they react to are modeled as points in an abstract shape space. The closer a T cell and an antigen are in shape space, the higher the affinity between them. To model the high cross-reactivity of the T cells, we allow them to react not only to antigens at the same point in shape space but also to neighboring antigens. We further emphasize cross-reactivity by making the points in this shape space highly interconnected. This makes every point a close neighbor of much of the shape space.

2 The model

In this model, we focus on the relationship between similar antigens (be they foreign or self) and the T cells that react to them. To do so, we ignore the physical space of immune interaction and look at the shape space of T cell receptors and antigens. Every point in shape space represents the various similar antigen shapes that a single clone of T cell is reactive to with high affinity; high affinity is that affinity which leads to negative selection in the thymus. First neighbors in shape space are those antigens and T cells that have a high enough affinity to be affected by the positive selection of protein antigens.  

We present a generic scenario that models the immune reaction in terms of the following observed mechanisms:

- The continuous feeding of T cells from the thymus takes place at a steady rate regardless of immune activity. These T cells are positively selected

\[\text{This supposes the existence of a relatively permanent group of self-antigens, similar in the thymus and the periphery.}\]
in the shape space 'around' certain self-antigens. We represent this by a probability rate (A) for an immune cell to randomly appear on a specific lattice site.

- The local (in shape space) proliferation of peripheral T cells is triggered in the presence of antigens of more than minimal affinity. The rate of proliferation is proportional to their affinity and concentration, \( \gamma_T \times (|A_i| + \sum_{ Neighborhood[A_j] \times affinity}) \) i.e. proportional to the number of antigens in its environs in shape space.

- The global down-regulation of the level of T cells represents the fact that the total population of T cell clones maintains a homeostatic level. We represent this by a death rate for T cells that is proportional to the average population of T cells in points in the shape space, \( (\gamma_D \times T_{avg}) \).

These three forces by themselves in synchrony with a steady level of self antigens brings about a steady population of T cell clones of various types with common levels of affinity to the self antigens that maintain them.

To show the feasibility of this model of T cell repertoire maintenance and behavior, we model the reaction to a primary infection by a pathogen. We therefore add a specific effector mechanism to these three basic forces of the T-cell repertoire maintenance. This mechanism is activated at high levels of T cell reactivity and acts to return the antigen pattern to its resting state. As in Grossman’s model [6] this means that the T cells, during an infection, are not reacting to a specific antigen but to a change in antigen concentration. Although it is quite feasible that both a rise and a decrease in concentration could have biological relevance to the immune system our model uses an increase in antigen concentration as a signal for the T cells.

In the present instance of this model, the actual effector arm is not modeled. It is simply something that, at a rate proportional to the population of T cells, annihilates the antigens that caused the T cells to be activated.

The addition of an effector mechanism does not disturb the 'resting' state of the immune system, nor does it cause spurious activation. To cause an immune reaction we add an infection to the simulation. Infection is represented by an auto-catalytic antigen which starts proliferating in an hitherto 'uninhabited' point in the shape space. We emphasize again the lack of a need for T cells that are more highly reactive to foreign antigens. Therefore, the proliferating foreign antigen is placed in a spot in shape space that is no nearer (i.e. not of a higher affinity) to surrounding T cells than to their maintaining self-antigens.

3 Results

The simulation results in a repertoire of varied T cell clones that maintain a steady state without inimical reactivity as long as no pathogen is evident. Figure 1 shows the effect of a primary infection on the T cell repertoire. In these “snapshots” of the T cell repertoire, the system turns it attention
and resources towards a change in the pattern of antigens in shape space progressing in the following stages: (a) Pre-infection day 0 - all the antigens are self-antigens and the repertoire is stable. (b) Six days after infection - the total level of T cells is only slightly higher, but it has become skewed towards those members of the repertoire that are reactive to the pathogen’s antigens. (c) At 8 days, the immune system is completely committed to dealing with the pathogen. The high levels of T cells and pathogens trigger the specific reaction of the immune system that rapidly decimates the pathogen, causing a depletion of its antigens. (d) Day 11 - Without the driving force of the pathogen antigens, the homeostatic forces in the system quickly bring the total population back to pre-infection levels. (e) Even though at 12 days the levels of T cells relevant to the infection are still high, we can see that the rest of the repertoire is more or less at pre-infection levels. (f) As we can see from the last snapshot, the system has returned to its resting state three weeks after infection. The ‘days’ are calibrated according to the rate of T cell arrival from the thymus. T cells mature from the thymus at a rate of ~ 2% of total T cell population (at rest) per day. The general time course of the reaction to the pathogen in silico fits in well with what occurs in vivo.
4 Conclusions

This simulation emphasizes several points that turn on its head the way we view self-reactivity in the immune repertoire and the nature of the immune system's function in general. Based on known dynamics of T cell behavior [5] - positive selection in the immune periphery and T cell homeostasis [4] - we change our view of self affinity. We have taken Grossman's theory or immune reaction to change in activity [6] to its logical extreme and done away with any kind of heightened receptor specificity to non self antigens. By showing, in our simulation, that this does not preclude a normal immune reaction, we have shown that affinity to self need no longer viewed as something to be avoided. Instead the ability to detect novel antigens and maintain a stable repertoire appears to be based on an affinity to self.

The immune system behaves like other perceptual systems [3]. It uses the self as a background signal, which it ignores, while reacting to the changes this background emphasizes. Affinity to self is the basis not the nemesis of immune reactivity.

This upward re-evaluation of the centrality of self-reactivity to immune capabilities, leads to important changes in our general view of immune dynamics. Primarily, it unifies the various functions of the immune system which deal with the self with those that deal with the foreign. Combating cancer and repairing tissue damage obviously requires some affinity to self. Here self-reactivity comes under one umbrella with combating infection. We can now view the immune system as a housekeeper rather than a gatekeeper.

The results using our model emphasize the need to study the dynamics and reactivities of the immune system in healthy states. We believe that further research of the clonal types and affinities found in the healthy body will further strengthen the view we have put forth in this paper. Immunology is unique among the life sciences that the basic state for most research is not the system active in a healthy body, but rather when the body is in distress. Realizing that there is meaningful immune activity when we are healthy should move the science of immunity to redress this basic prejudice.

References

Useful Examples and a New Model of the Immune System

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ABSTRACT: It is central to the development of cognitive systems that they have in their environment certain examples that are both high frequency and generic to some general property of their interaction with the environment. We have called such examples Useful Examples and suggested that in order to understand cognitive systems and their capabilities we must study these examples. In the following pages I will use a model of immune cell repertoire dynamics in the immune response to pathogens as an illustration of this point. This model is based on the application to immunology of the theory of Useful Examples and on existing knowledge of immune dynamics. Its conclusions place self-reactivity at the basis of immune specificity of reaction, causing a paradigm shift in existing conceptions about immune functions and sensitivities. In closing I will go over conclusions about the general importance of Useful Examples in the study of cognitive systems.

KEY WORDS: complex systems, immunology, cognitive systems, learning, development, self organization.
1. Introduction

When talking of analogies and their use in the behaviour and development of cognitive systems we focus mostly on how much the two 'ends' of the analogy are the same. We ask how this sameness is used by cognitive systems to relate and learn about the world. This ignores a basic facet of analogies, which is that by finding things similar we are implicitly saying that they are not the same. What we learn from the analogy are the differences. The similarities are used as framework / scaffold to teach us about the new and the different.

We have previously suggested that cognitive systems share a common strategy of interaction with their environment to acquire their capabilities (Hershberg & Efroni 2001). Cognitive systems must learn to be cognitive systems. We have presented a view of the system's mode of learning in which we described it as a direct result of unsupervised interactions with concrete examples of the environment (see fig. 1 and Hershberg & Ninio 2003).

Such a simple form of learning is sufficient to allow the system an understanding of its environment because the environment is ordered. There are a few examples which are encountered with high frequency while most other examples are encountered less frequently. The high frequency examples are not ubiquitous by chance. Their prevalence reflects a multiplicity of usages for these examples within the interaction of system and environment. Viewed as separate instances, the variety of contexts in which such examples exist appears a deterrent to learning. However, when examined in the light of the complete set of interactions between system and environment, this variety becomes an asset. In effect, these examples embody important properties of the environment for the cognitive system.

These examples are constantly encountered; once acquired, they can greatly enhance the ability to learn new less generic examples by similarity-matching; and finally, both in their own right and due to their similarity to other examples, they will be consistently reinforced by the system's interaction with its environment. We call such ubiquitous and generic examples of the environment Useful Examples because they are useful to the system for learning the environment, and its relevant general properties. The distribution of examples in the environment is not arrived at by chance. For each cognitive system the reason for signalling out of specific Useful Examples is different. It depends on the specific types of interactions which the cognitive system undergoes with its environment. This reflects the fact that cognitive systems are fitted by evolution to specific niches. Based on genetic inheritance and previous cognitive development a cognitive system has certain tendencies, which give it the framework of its environment.

As an example of the application of this theory of Useful Examples to the study of cognitive systems I will in the rest of this paper, deal mostly with the immune system. I will show how studying the Useful Examples, used by a given system to acquire its capabilities, can influence our scientific understanding of that cognitive
system and its function. I will explain how by leading from the theory of Useful Examples we reach a new model of immune reaction and the importance of self reactivity to the proper maintenance of immune capability.

Figure 1. The two phases encompassing cognitive action/perception: Through specific interactions, and based on the previous (innate) tendencies of the system, certain general properties are corroborated by Useful Examples of these properties appearing in the environment. This corrobororation leads to the formation of an achieved set of representations in the system. Specific interactions with the environment start with the deconstruction of the specific patterns encountered via the detection of similarities to the Useful Examples embodied in the achieved set. After detection there is a refitting and fine-tuning of the perception to the specific elements of the event. Having identified the specific elements of the event there is now a reconstruction of the raw event, accompanied by association to contextual factors into a functional or meaningful event, which can be appropriately reacted to and added to the memory of the system. The two phases are chronologically mingled. Every interaction is a specific interaction even while the cognitive system is still building its understanding of the general properties. In addition in many cognitive systems it is not clear if the process of defining new general properties ever comes to a complete stop. 'Young' cognitive systems are less fluent in working with the general properties and it is harder to teach an 'Old' cognitive system new tricks, but all interactions with the environment have elements of both phases. (Adapted from Hershebrg and Efroni 2001).
2. Paradigms of immune specificity.

To show how the theory of Useful Examples changes our view of the immune systems sensitivities we must first go over the existing view. The immune system starts with a large random collection of receptors from which only a subset survives. The receptors of the immune system are selected according to a certain level of affinity to certain molecular shapes from the body, called antigens. The receptors are selected through a process of negative and positive selection in which all receptors of too high or too low affinities to these antigens are killed (along with the cells that produce them).

The resulting immune system is unique among the systems in our body in having an amazingly diverse variety of receptors. This great variance is used to identify a near infinite number of different antigens. The high sensitivity of different antigen receptors is however highly regimented allowing the immune system to react to one type of antigen in a given context while ignoring other antigens. It is as yet an open question how the immune system maintains the specificity of reaction. - The possible answers lie in two camps: Receptor specificity and systemic response specificity. By receptor specificity we mean that antigen receptors themselves are each highly focused and specific. Thus the specificities of an immune response is based on a repertoire built only of certain kinds of receptors. By systemic specificity we mean a mechanism that does not rely on the specificity of the receptors, but rather on some global behaviour of the system.

The mainstream paradigms of immunology answer this question by various mechanisms of receptor specificity (Langman et al 2000) based to some extent on Jerne’s clonal selection theory: The immune systems function is to defeat pathogens. The immune system identifies foreign antigens and destroys them. The identification of the foreign is made possible by removing, in the immune systems prenatal development, all receptors that recognize self. Anything that an immune receptor identifies “must be the enemy” (Burnet 1957).

The fact that we can find receptors sensitive to practically any substance and the importance of negative selection in the building of the immune system’s naïve repertoire have supported this paradigm based on receptor specificity. However, a closer look at the way immune cells are selected in the bone marrow and the thymus indicates that this interpretation is problematic:

- Immune cells are not completely specific; they are degenerate and cross-reactive.
- A certain level of benign affinity to self-antigens exists in all receptors.

These points hold true for all cells of the adaptive immune system, and weaken the claims that the immune system’s specificity is based on any type of receptor specificity. The adaptive immune system is usually divided into two main groups of
cells, humoral immunity (B cells) and cellular immunity (T cells). We present a model of T cells, focusing on the theoretical problems relevant to T cells.

All T cells are highly cross-reactive, each T cell can react to $3 \times 10^7$ different antigen types (Borras et al 2002). Furthermore, although T cells of a high affinity to self antigens are culled by negative selection, all T cells must have some level of affinity to self or they will not pass the positive selection phase and die of neglect (Goldrath and Bevan 1999). Positive selection appears to be especially important as it is now found to be an essential factor in the maintenance of the T-cell repertoire in the periphery. Low level affinity to self is not only essential as a maintaining signal of T cells but is also proliferative in its effect (Ernst et al. 1999). We thus find a situation where the actual T cell repertoire is not, as is commonly suggested by immune theory, built of specific receptors reactive to foreign antigens. The repertoire is, in point of fact, built of highly cross-reactive receptors that all share some minimal common affinity to self antigens.

3. Looking at the order of the immune environment.

The answer rests in replacing the mechanistic view of the immune system with a view of the immune system that considers it to be comparable to other cognitive perceptual systems (Varela 1994, Cohen 2001, Hershberg and Efroni 2001). This view leads us, as we suggest from the study of other cognitive systems (Hershberg and Ninio 2003), to study the distribution of examples that are naturally encountered by the immune system. When we do this we see that not all antigens are equally encountered. Much as has been seen in language (Zipf 1935) the distribution is such that a few antigens are highly frequent while most potential antigen types are rare or non-existent. In fact 200 antigens, out of $10^{14}$ potential types, will be presented in 50% of T cell encounters (Barton and Rudensky 1999). This over expression in itself is not enough for us to apply the theory of Useful Examples as it does not suggest any generic trait of immune interaction. However if we add that most, if not all, high frequency antigens are self antigens the picture changes. We would like to suggest that the above inhomogeneity of presentation reflects the fact that certain families of proteins are ubiquitously expressed in all cells while others are only sometimes expressed. The proteins that are most expressed are those which are essential for cellular life, such as chaperones and other housekeeping proteins. Such housekeeping proteins have been suggested as important to immune function and they are expressed in all cells and at high levels (Cohen 2000). Because they are so important these proteins are also the most highly conserved (Gupta 1998).

We share a common heritage with the pathogens that invade us. The points of similarity between invader and host represent the essential factors of cellular life – the manipulation of genetic material and energy production. Those molecules that we share with our pathogens are essential to them and to us. It should therefore be no surprise that antigens derived from such proteins make effective immune signals.
They are older than the immune system, can be counted on to exist in all immune environments and cell types, and are over-expressed in times of stress. In fact, it has been found that antigens derived from certain foreign housekeeping proteins are very immunogenic, and induce better activation of the immune system the more they are similar to self proteins (Cohen & Young, 1991; Schwartz & Cohen, 2000). Considering the wealth of information regarding points of similarity between the self and its pathogen invaders, building an immune system that ignores the self is like constructing an eye without a fovea. In the immune system the general properties of interaction are based on the co-evolution of cellular life. The Useful Examples of such an environment are those proteins essential to cellular viability. Such proteins, due to their importance to all cells, are ubiquitous and highly conserved throughout evolution. Their derivatives are therefore ideal as base signals of cellular stress and change.

4. A model of primary immune reaction based on affinity to self.

We have presented the following model to show how a repertoire of cross reactive T cell receptors with a common affinity to self antigens could function effectively against a foreign pathogen (Hershberg et al 2003). In this model, we focus on the relationship between similar antigens (be they foreign or self) and the T cells that react to them. To do so, we ignore the physical space of immune interaction and look at the multi dimensional shape space of T cells and antigens (for illustration figure 2 shows a two dimensional representation of shape space). Every point in shape space represents the various similar antigen shapes that a single clone of T-cell is reactive to with high affinity (figure 2 (iii)); high affinity is that affinity which leads to negative selection in the thymus (A). First neighbours in shape space are those antigens and T cells that have enough of an affinity to be affected by the positive selection of protein antigens (A’).

We present a generic scenario that models the immune reaction in terms of the following observed mechanisms (Goldrath et al. 1999):

- A steady feeding of T cells from the thymus to the periphery regardless of immune activity (figure 2 (ii)). The T cells will only arrive into points in shape space that are close enough to the high frequency self antigens ((A)) so that they where positively selected in the thymus.

- T cells proliferate at a rate relative to the level of antigen they encounter and to their level of affinity to each other (figure 2 (iii)), regardless of the source of the antigen (self or non self).

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1 This supposes the existence of a relatively permanent group of self-antigens, similar in the thymus and the periphery.
Figure 2. Reactions in shape space – shape space is an imaginary space in which every point represents the shapes of receptor/ligands that are reactive to each other. As represent antigens and Ts represent T cells. (i) If a T cell and an antigen are at the same point (AT) they have high affinity to each other. If they are far away (T a) they have a low affinity to each other.

To represent the homeostatic competition between T cell clone types the T cells die at a rate proportional to the total population of T cells.

To these three reactions of T cell repertoire maintenance we add an effector mechanism to kill pathogens. Based on existing ideas suggesting that the effector mechanism may be activated not merely by antigen activation but rather by changes in T cell activity (Grossman et al 2001), we have built in the model an effector mechanism which is activated against antigens that change the level of T cell activity. In this model only positive changes in activity are considered.
5. Results and conclusions for immunity.

Figure 3. Results of the simulation: Upper panel: Snapshots at progressive days post infection until the height of T cell reaction at approximately eight days post infection. Changes in T cell repertoire activity [a-c] Changes in the antigen repertoire [d-f] of self antigens (blue) and non-self antigens (red). Lower panel: T cell repertoire three days [g] and three weeks [h] after the foreign antigens are cleared.

Built around a permanent set of antigens, representing the high frequency (self) antigens, the above reactions result in a steady homeostatic population of T cells (fig. 3 [a]), without reactivity of the effector mechanism, as long as no pathogen is evident. We therefore add a primary infection in the form of new antigen populations in shape space (fig. 2 (iv) - A’). We place them so that no T cell will have a higher reactivity to them than to the self antigens that maintain them. Therefore there is no possibility of receptor specificity.

The foreign antigens differ in two traits. They are in a new place in shape space causing an imbalance in the T cell competition over antigens; and they have different dynamics from self antigens – they are proliferating rapidly.
Figure 3 shows the effect of a primary infection on the T cell repertoire. In these “snapshots” we see the change of the T cell repertoire [a-c] until the clearance of foreign antigen, and the relative types of antigens [d-f] of self (blue) and non self (red) that push this change. At first when the level of the foreign antigens is low [d] the repertoire is at its stable resting state [a]. The rapid proliferation of pathogens [e] causes the immune system to turn its attention and resources towards the change in the pattern of antigens in shape space [b]. This change in T cell activity activates the effector mechanism, which rapidly decimates the pathogens and the antigens they exhibit [f]. Much as in reality the highest point of T cell activation is shortly after the height of the disease [c]. Those T cell types that are most highly expressed at this stage become the memory cells that allow more rapid reaction to secondary infections. The entire time course of the simulation, from infection to the height of immune reaction takes eight days, much as is seen in actual infections. Once the foreign pathogens are cleared the two final snapshots show the return of the repertoire to its resting state. Within a few days without the drive of foreign antigens the overall level of T cells is close to normal, however some T cell types are still over expressed [g]. Approximately three weeks later [h] the repertoire is once more at its resting state shaped around the self antigens of the body.

Thus without ignoring T cell cross-reactivity we have built a model that uses a small set of self antigens to educate the T cell repertoire. In doing so the simulation successfully recaptures the dynamics of a primary infection without the need for T cell specificity. We have shown a way that the immune system could react to foreign pathogens without the need for a special affinity to non self antigens. This success strengthens the plausibility of the paradigm of cognitive immunity and of systemic specificity in immune reactions. Most importantly it causes a complete reevaluation of the place of self immunity in immune function. Self immunity is no longer viewed as the bane of an over reactive immune system, instead it is seen to be the basis of immune specificity. The ability to detect novel antigens and maintain a stable repertoire is based on a background signal built of the affinity to self.

The re-evaluation of the place of self immunity does not merely change our conceptual view of immune dynamics - it calls for an actual change in the way immunology is studied. Immunology is highly motivated by our wish to combat disease and by our perception of disease. This has lead to a unique scientific situation. Usually in science the system studied is compared at rest to its perturbed states. In immunology the view that when not activated by foreign antigens the immune system is inactive and in dynamical sense non-existent, has lead to a skewed scientific research situation. Most, if not all, immune research is done on the perturbed (disease state) immune system. However, with this new view of self affinity as a calibrating background signal, we see that the immune system is constantly active and that to understand immune disease dynamics we must first study the immune system in healthy states.

A day in the simulation is calculated according to the steady rate of T cell arrival form the Thymus which is known to be ~2% a day of the resting population.
6. Useful Examples and study of other cognitive systems.

In the last sections I have shown how considering the natural distribution of examples encountered by the immune system has suggested a model of immune interaction that radically changed the basic paradigm of immune study. In closing I would like to stress that this is not unique to the immune system. The immune system is brought here as a primitive example of cognitive systems in general. The example is not at the level of the building blocks. There is no claim here that immune cells and neurons are the same. The similarities rest in the common strategies of interaction and in the need to create a fit between system and environment though their natural interaction. This actually strengthens the theories relevance for the creation of artificial systems. It tells us something about the general design principles of a cognitive system regardless of its specific building blocks or function.

If we wish to understand or to recreate cognitive systems we must look at the initial developmental stages that turn a naïve system into a fully functional cognitive one. The outward representation of this process is the skewed distribution of examples in the environment. The networks of analogies are not evenly distributed. Some nodes are far more central and, once learned, give the system a much easier access to the rest of the network. We have called these nodes Useful Examples; by studying them we have an observable handle to study cognitive systems. Such a handle is essential, as cognitive systems are so intuitively known to us as to make it very hard for us to study them objectively. This paper has shown, using the immune system as an example, that our intuitive view of the function of a cognitive system is not a good place to start studying them. We should instead, when attempting to study or emulate a cognitive system, focus on the actual patterns of interaction with the environment and the Useful Examples that embody them.

This form of research has been shown to be relevant to the development of several cognitive systems - language (Ninio 1999, Hershberg & Ninio 2003), and as seen above immunity. Due to its generality we anticipate that it should hold true also for the study of other cognitive perceptual modalities.

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HIV time hierarchy - Winning the war while loosing all the battles


Chronologically this was our first attempt to use a model of dynamics in shape space to model the immune system. The actual view of immunity is very simple and mechanistic. Measuring the changes in relations between populations of immune cell types and populations of virus types resulted in a simple explanation connecting between normal virus dynamics and the special dynamics of HIV. In the wider view of this thesis we see here how the immune system makes a conceptual mistake in identifying the escape mutants of HIV as novel invaders. The use of shape space shows us a potential hiding place for HIV which de-mystifies the diseases insidious dynamics. The virus’s high mutation rate is modeled as diffusion in shape space which allows HIV escape mutants to propagate. Thus, after every immune victory, in which both immune system and virus behave much as in the case of a normal virus, a few strains of HIV are created and escape to adjacent points in shape space where no immune reaction is as yet ready. These grow and are duly identified and destroyed by the immune system, except for a few more escape strains. At every stage the immune system triumphs over a specific strain but the overall number of strain types and the overall population of HIV continues to rise. At some point, the immune system, which is being decimated by global levels of HIV without the need for identification in shape space, is overwhelmed and the HIV population explodes.
HIV time hierarchy: winning the war while, loosing all the battles

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Abstract

AIDS is the pandemic of our era. A disease that scares us not only because it is fatal but also because its insidious time course makes us all potential carriers long before it hands us our heads in a basket. The strange three stage dynamics of aids is also one of the major puzzles while describing the disease theoretically (Pantaleo et al., N. Engl. J. Med. 328 (1993) 327). Aids starts, like most diseases, in a peak of virus expression [R.M. Zorzenon dos Santos, Immune responses: Getting close to experimental results with cellular automata models, in: D. Staufer (Ed.), Annual Review of Computational Physics VI, 1999, pp. 159–202; R.M. Zorzenon dos Santos, S.C. Coutinho, On the dynamics of the evolution of HIV infection, cond-mat/0008081], which is practically wiped out by the immune system. However it then remains in the body at a low level of expression until later (some time years later) when there is an outbreak of the disease which terminally cripples the immune system causing death from various common pathogens. In this paper we show, using a microscopic simulation, that the time course of AIDS is determined by the interactions of the virus and the immune cells in the shape space of antigens and that it is the virus’s ability to move more rapidly in this space (its high mutability) that causes the time course and eventual “victory” of the disease. These results open the way for further experimental and therapeutic conclusions in the ongoing battle with the HIV epidemic. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The natural progression of the human immuno-deficiency virus (HIV) infection varies between individuals, however a general pattern of the progression has been observed (Fig. 1).

- Within weeks of infection, a short transient jump of plasma virema (virion concentration in plasma) is seen together with a marked decrease in immune cell counts (CD4 T helper cells).
- Partial control of the disease by the immune system ensues, causing variable periods of practically, asymptomatic clinical latency, which can last for several years. During this period the immune cell population continues to slowly decline until the immune system is so crippled that it can no longer contain the disease.
- A renewed outbreak of the virus which, together with constitutional symptoms and the onslaught by opportunistic diseases, cause death [1].

The dynamics of HIV was traditionally described using simple homogeneous ODEs [5] (for a review see Perelson [6]). This method was enlarged to models considering the spatial structure mainly by Zorzenon dos Santos and Coutinho [2,3]. Such models consider the importance of the localization of the interactions between the HIV virions

![Fig. 1. The typical three-stage evolution of the HIV illness: according to the experimental data, the HIV illness presents three distinct phases. During the first months after infection, there is an acute phase with a very large increase in the virus population and a corresponding destruction of the immune cells. This ends with the reprise of the immune system to the invasion and the decrease of the virus population to very low values. After the immune systems reprise, comes a long period of slowly increasing virus population and slowly decreasing immune cells population. At some stage, the virus population explodes and the immune system collapses (the AIDS phase) resulting in an onslaught of opportunistic diseases and death. (Adapted from picture, Copyright Dr. R.E. Hurlbert, from the Washington State University Fundamentals of Microbiology 101 course home page: http://www.wsu.edu:8080/~hurlbert/pages/Chap16.html#STD_intro) [4].](image-url)
and immune cells. Taking into consideration the global features of immune response and the high mutation rate of HIV they described the spatial and temporal interactions of infected and healthy cells in lymphoid tissue in the body.

The methodology used in spatially extended models was limited up to now mainly to cellular automata [2,3], or to compartmental models [7]. The main advantage of cellular automata is their capacity to emphasize the emergence and the importance of spatial structures. For example the propagation of waves of infection in the lymph nodes, or the creation of immune cell aggregations [2,3]. Consequently Zorzenon dos Santos and Coutinho, in contradiction with most ODE models, succeeded to reproduce all the stages of HIV evolution, using a single set of rules (see Ref. [3], and Fig. 13 in Ref. [2]).

The present model is inspired by the observed interesting features in the spatially extended model [2,3]. Our model acts in the shape space rather than in the physical space and exploits the dynamical implications of the HIV virus ‘propagation’ in the molecular shape space: The immune system’s need to identify the virus’s form correctly in the shape space of possible viral and immune receptor shapes. The main ingredients in our model are the mutations (represented by propagation of the multiplying virions in the structure-less infinite dimensional shape space) and the confrontation with the immune system cells (resulting in the disappearance of the both cells and virions). Our model does not display any geometrical patterns in either space or shape space. In this model we assume that we can average the spatially distributed reactions (as in the ODE approach).

The model presented in the following pages relies on the basic known facts on the immune defense system. The viruses (antigens) have various characteristic geometrical shapes. In order to act against them, the immune system has to ‘identify’ them by producing cells which contain shapes complementary to the geometry of (parts of) these antigens. Since the immune system does not know a priori what is the characteristic shape of every new invading virus, the immune system generates randomly cells with various shapes. If a cell encounters (by chance) an antigen (virion) with complementary shape, then more cells with characteristic shapes identical to it are produced and a mechanism is triggered for the destruction of all the individuals (virions) belonging to this virus strain (and sharing the same shape) [8].

Usually the destruction mechanism is quite efficient and once a virion is “identified” by the above random search in the shape space, its fate and the fate of all the virions in the same strain is sealed: they are wiped out by the immune system within days.

With HIV however, the issue is more complicated [2,3]: Since the virus’s replication mechanism is relatively imprecise, as it multiplies, it undergoes a large amount of mutations/changes in shape compared to those found in other kinds of virus [9–11]. Based on empirical and theoretical results in the research of HIV we propose the following scenario. The immune system cells that are complementary to the old shape are ineffective in dealing with the new mutant virus strain. The virions belonging to the strain with the new shape can multiply with impunity until a strain of immune cells which fits the
new shape is generated by the immune system. Once the immune system’s shape generation process succeeds to produce by chance a immune cell carrying a complementary shape to the new virus strain and this cell encounters (by chance) a virion belonging to the new strain, the new strain is wiped out too (with the exception of the eventual new mutants that again can multiply freely until their new shape is detected by the immune system). The process continues indefinitely with the virus loosing every battle but succeeding to produce increasingly many small populations of new shapes (Fig. 2) [8,12–16].

The process is compounded by the additional fact that virions can kill directly and indirectly immune cells (whether or not they are of complementary shape) [17].

The immune system continues to win every battle until the increase in production of immune cells with shape complementary to a virus strain is overcome by the rate at which the immune cells are destroyed by various other HIV strains. At this point the immune system has effectively lost the war.

In the rest of the paper we provide a detailed microscopic simulation model [18–21] which supports this scenario and that fits quite well the known phenomenological data on HIV in terms of the following basic mechanisms:

- The local (in shape space) destruction of HIV by the immune system [15].
- The fast mobility of HIV in shape space (high mutation rate) [9,10].
- The global destruction of immune system cells by HIV [17].
2. The model

We represent the shape space of the virus by a random lattice in which each site \((i)\) has a fixed number of neighbors. Neighboring sites represent shapes that can be reached from one to the other by a single base mutation of the virus. The occupation number on each site \((N_V)\) represents the number of virions existing with that shape in the organism. The immune system cells that recognize that shape are also represented through an occupation number on the same site \((N_C)\). Note that the existence of a virus and an immune cell on same lattice site does not imply their proximity in real space: Quite to the contrary they might be located in very distant locations in the organism. However, there is a small probability that the virus and the corresponding cell might meet and react in real space. Therefore, each pair of virion and immune cell located on the same lattice site has a small, but finite probability to react (according to the rules described in detail below).

One represents the eventual mutations of the virus and the immune cells by their rate of diffusion in the shape space \((D_V, D_C)\). More precisely both viruses and immune cells have a certain probability for jumping between neighboring sites.\(^1\)

HIV can replicate in and destroy immune cells. This is irrespective of the cell’s characteristic shape. That is, the virus can destroy immune cells located on sites arbitrarily far away from the site of the virus). In our model we represent this by:

- A virus proliferation rate proportional to the total immune cells population \((C_{tot})\).
- An immune cell death rate proportional to the total viral population \((V_{tot})\).

We list bellow the reactions taking place in the model:

1. When an HIV virion and an immune cell reside on the same site the immune cell duplicates with a rate of \(\tau_C\). However, following realistic biological data, we limit the multiplication rate of the immune cells (to a factor of 3 per day).
2. When an HIV virion and an immune cell reside on the same site the virion is destroyed with a probability rate of \(d_V\).
3. Each HIV virion replicates with a rate \((\tau_VC_{tot})\) proportional to the total number of immune cells.
4. Each immune cell is destroyed with a probability rate \((d_VC_{tot})\) proportional to the total number of virions.
5. New immune cells, with various shapes are created continuously. We represent this by a probability rate \((\lambda)\) for an immune cell to appear on a random lattice site.
6. Both the immune cells and the HIV virus diffuse slowly in the shape space with rates \(D_V\) and \(D_C\).

3. Results

The reactions listed in the previous section lead to the following scenario for the evolution of the HIV infection. The virus enters the body in a high concentration

\(^1\)The diffusion rate, and the neighborhood structure implied by the node’s connectivity can be different for the virus and for the immune cells.
Fig. 3. The acute phase analyzed by strains. The simulation of the acute phase provides an explanation to the very large peak in the virus population: as opposed to an infection by a single strain, the organism has to discover a multitude of strains. The height of the virus population peak is dominated not by the average strain population but by the population of the strain which is discovered last by the immune system (and has the longest time to exponentiate). The acute phase starts with a constant concentration of HIV distributed between 20 strains (upper-right drawing). Each one of these strains activates an immune response and is then destroyed (upper-left drawing). The observed average HIV and immune cell concentration is the average over all strains (lower drawing).

limited to a restricted number of strains. As long as there is no immune cell in the site corresponding to a certain strain, the virions located in this strain site proliferate exponentially. The rise in virus concentration is accompanied by a destruction of random T cells hosting the virus (according to item (4)). These T cells can be located anywhere in the lattice. Eventually, one of the immune cells generated by the immune system will fall by chance on the site of this strain (according to item (5)). This immune cell will proliferate very fast, since, according to item (1), the proliferation rate increases with the local viral concentration. The resulting high local immune cells concentration will destroy all the virions of this strain (item (2)). As a result, after a short period (1–2 month) all the initial strains will be discovered by the immune system and will be destroyed ending the acute phase of the disease. In the absence of virus diffusion in shape space (i.e., mutations), this would stop the disease (Fig. 3).

It is the diffusion rate of the virus in shape space (item (6)) which is responsible for the continuation of the infection. Before all the initial strains are destroyed, some of the virions have a chance to mutate and escape to lattice points containing no immune cells.
Each of these new lattice points in the shape space will contain a lower concentration of virus than the original infection. Since the probability for the discovery of a virus strain by the immune cells is proportional to the virus strain concentration (according to item (1)), the time it will take for the immune system to discover, and destroy these new strains (item (2)) will be longer than it is in the acute phase. By the time these new strains are destroyed some virions from these strains will have diffused to neighboring sites (undergo mutations), and constitute the germs for a new generation of emerging strains. These strains in turn will have the fate of their predecessors in the previous generation. One sees now that one can describe the long-term evolution of the HIV infection as an iterative process. More precisely, the long-term evolution will consist of a chain of small infections, each of which is easily defeated by the organism. However, after each such infection the number of strains will grow. Therefore, even though the number of virions in each strain is always kept under control by the organism, the total amount of virions will slowly increase stochastically. The increase is stochastic, since it depends on the random time it takes the immune system to discover and destroy each new strain. As the number of virions increases, the death rate of the immune cells also increases (item (4)). At a certain stage the death rate will be high enough to impair the capacity of the immune system to react locally to new strains. This constitutes the last stage of the disease (Fig. 4).

This typical scenario can vary from person to person:

1. The typical case observed in most hosts is a disease composed of three stages (Fig. 4). The first acute stage is due to the fast proliferation of the original strains before the appropriate immune response is set. This stage ends when the appropriate immune response to each and every original strains is completed. This stage takes approximately \( \lambda \ln(\text{number of original strains}) \) days (see below). This gives an expected number of virions at the peak, which is much higher than in a usual disease (Appendix A). The latent stage is the stage in which the number of virion strains is limited, and the number of virions in each strain is low. This stage will last as long as the number of strains is much smaller than \( \tau_C / d_C \) (Appendix B). When the number of strains grows above \( \tau_C / d_C \) the last stage of the disease occurs. This is the regime in which the local (in shape space) activation of the immune system by the local virus strain (item (2)) becomes lower than the global destruction rate of immune cells by the virions (item (4)), and the immune system fails to destroy locally (item (4)) the existing strains. At this stage many old strains that were kept under control during the previous stages can reappear.

2. If the efficiency of immune reaction to HIV (items (1) and (2)) is high enough, the immune system will manage to defeat the new virus strains fast enough. Thus, the average number of strains will stay constant or slowly decrease. In this case, the total number of virions will vary around a fixed number, or slowly decrease to 0. This fate can be one of the long-time carriers [22,23]. In reality, the total number of virions never decreases to zero, since there are other sources (macrophages, neuronal cells, etc.) that contribute a small number of new virions [22,24] (Fig. 5).
Fig. 4. Typical HIV evolution in our simulation: in the top part of the figure we see that with our simulation, we capture the dynamics found in the empirical data. By comparing with the Fig. 1, one sees that our model reproduces correctly the three stages of the disease. The acute phase (A), a phase of chronic latency (B) and finally a renewed outbreak of HIV coupled with the destruction of the immune system (C). Note that the first 100 days are plotted at a different scale. In the other two figures we see, over the progression of the disease, the number of different HIV strains (middle) and the average concentration of virions per strain (bottom). Together these two graphs strengthen our explanation that the time course of HIV is based on the contradiction in local and globals concentration of HIV – locally the levels of HIV are kept by the immune system at a minimum far below the level found in the primary infection. Globally, through the rise in the number of strain types, the virus is spreading stochastically through shape space and increasing its numbers by avoiding the local immune attacks.

(3) When, on the other hand, the efficacy of immune reaction is low a large number of new strains will be created before the immune cells finish destroying the virions from the strains of the first infection. In this case, the acute phase will directly lead to the death of the host (Fig. 6) [22,25].

The results of our simulations show that although each new strain that emerges is destroyed within a few weeks (like any ordinary disease), the long-term evolution of the infection takes several years. The time scale that determines the long-term evolution scale is the diffusion (mutation) rate of the virus. A number of new strains grows exponentially with time, but the unit of time in this exponential is the time it takes for a new strain to establish itself i.e., weeks.

One might ask how the scale hierarchy between the cellular interactions (hours) and the evolution of the infection (years) emerges in this model. The answer is the following. The single strain lifetime is determined by an exponential rate proportional to the local interaction rate (h). This exponent rises to macroscopic virus concentration within weeks. Only when the value of this exponent is high enough does the long-term
Fig. 5. Merely by raising the efficiency of immune cell reaction to HIV at the different sites we can bring about a time course suggesting the progression of HIV in long-term latents [23].

Fig. 6. By decreasing the efficiency of immune cells we arrive at a scenario where already in the first acute phase we witness a full-fledged outbreak of AIDS. This is reminiscent of empirical evidence to the fact that quick progressors of HIV have a less flexible immune system and thus succumb to the disease with less strains of the virus in their bloodstream [25]. (Note that since death is so rapid the time course is only measured until the collapse of the immune system around day 400).
mechanism of virus mutation becomes operative. Thus, the time unit for one interaction in the shape space is the time needed for a single strain to establish itself. The time scale of the entire disease is the time necessary for evolving a macroscopic number of strains. Therefore, we expect that the time scale of the entire disease will relate to the time scale of new strain creation as the time scale of the strains relate to the individual virion division time. The actual numbers are indeed \((13 \text{ years}/2 \text{ weeks}) = (2 \text{ weeks}/\text{hours})\).

4. Conclusions

The main success of the present model is the natural emergence of a hierarchy of very different dynamical time scales. The very long-term decrease in immune (CD4+T) cells count cannot be explained by a simple dynamic system. The transition from the microscopic time scales (hours) to the macroscopic time scales (years) requires a profound explanation. A simple dynamical system would require extreme fine tuning of its parameters in order to achieve such a transition [2,3]. We propose a mechanism that can bridge between the microscopic and macroscopic time scales, which does not need fine tuning. The transition can be expressed best by representing the evolution of the system in the shape space (the strain of the virus), rather than the real space (the location of the virus in the organism). The relevant unit of time step for the operations in shape space is the time it takes for a strain to reach a macroscopic concentration and therefore have a significant probability to generate a mutant. This time step is of the order of weeks and not of hours. The evolution of the disease takes a few hundred time steps. i.e., a few hundreds of weeks.

The mechanisms operating at the short times and at the long times are completely different. At the microscopic level the mechanism is the recognition and the destruction of the virions by the immune cells. The short-time scale evolution of the disease is similar to any other disease. The long-scale evolution of HIV infection is based on the competition between localized (in shape space) processes and global processes. To be precise the evolution is due to the spread of the virus strains across the shape space. In the initial acute phase most of the viral load is distributed between a small number of localized virus strains. At the last stages of the disease the viral load is distributed between a large variety of many strains. The immune cells manage to destroy locally every particular virus strain within a couple of weeks from its emergence. However, as the number of strains at each given moment increases, the virus succeeds in destroying an increasing amount of immune cells. Thus, locally the virus looses every battle. Yet in the end, the shape space is filled with a multitude of small but numerous strain populations. At that point, the virus wins the war by killing more immune cells than it activates.

In short, during the latent stage every virus strain looses every battle since it is activating the cells that can destroy it. Transition to AIDS occurs when the combined contemporary virus population wins the war by killing in total more immune cells than the sum of cells it activates.
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Appendix A. Acute phase

Imagine one has a lattice containing $V$ nodes out of which $N$ are occupied by the strains that constitutes the initial infection. We assume that the population of each initial infection strain is large enough that if the immune system generates randomly an immune cell in this site (a cell with a complementary shape to that virus strain) then that cell will discover this strain with probability 1. The probability rate for generating in a given lattice site an immune cell is $\lambda$. Therefore, the probability rate for discovering one of the strains is $N\lambda$. Thus, the average time it takes the immune system to detect the first strain in the initial infection is $1/N\lambda$. Once this strain was discovered the probability rate to discover one of the remaining $(N-1)$ strains is $(N-1)\lambda$. This means that the time it takes to discover a second strain is $1/(N-1)\lambda$ and so on. Thus, the average time it will take for the immune system to discover the $N$ strains is: $1/\lambda + 1/(N\lambda) + 1/((N-1)\lambda) + \cdots = \ln(N)/\lambda$. As long as the virus strain is undetected by the immune system, it can proliferate freely. Therefore, the strain discovered last had the most time to proliferate. The factor by which it grew more than a single strain infection is

$$e^{\ln(N)-1/\lambda+1/C_{\text{total}}} \approx N^{\tau_V/C_{\text{total}}}/\lambda. \tag{A1}$$

Appendix B. Transition to AIDS

In this appendix we estimate the conditions for the final collapse of the immune system, when it fails to react appropriately to local virus strains. The dynamics of the population of the immune cells in a given site in the shape space is dominated by two parallel processes:

- Proliferation due to the activation of the immune cells by the interaction with the local (in shape space) virus strain ($\tau_C V_i$) (item (1)).
- Random global destruction by arbitrarily shaped virus strains ($d_C V_{\text{tot}}$) (item (4)).

An immune strain can increase its population if its proliferation rate is higher than its destruction rate, $\tau_C V_i > d_C V_{\text{tot}}$. In other words we need the ratio between local virus concentration and global virus concentration to be: $V_{\text{tot}}/V_i < \tau_C/d_C$. If we have $N$ virus strains proliferating in the system, we can assume that their population are of the same order of magnitude, and estimate $V_{\text{tot}}/V_i = N_{\text{strains}}$. Thus, in order for an immune strain to be able to rise its concentration and react appropriately against the corresponding virus strain, one needs the number of virus strains not to exceed: $N_{\text{strains}} = \tau_C/d_C$. If one assumes that the virus population is not equally divided between strains then the inequality is even more stringent.
Appendix C. Discretization vs. continuous differential equations

The evolution of a dynamical system can be expressed by two types of models:
(1) Ordinary differential equations (ODE) that simulate the evolution of the average population under the assumption of spatial homogeneity.
(2) Microscopic simulation (MS) models, that compute each reaction separately.

The ODEs have the advantage of being cheap in CPU time. They enable us to simulate precisely the system when its concentration is very high, but fail to describe the stochastic aspects of the system. The MS takes into account the stochastic effects and describes precisely the discrete aspects of the agents and of the strains. However, MS is very inefficient if the number of agents and the probability for reaction are high.

In the present model, most of the sites are basically empty. However, there is a relatively small number of sites occupied by a macroscopic number of virions and immune cells. This special situation invalidates both the possibility to use continuity assumption (ODE), and discrete operations (MS).

We solved this problem by using a hybrid model. This model computes the probability for interaction between every two agents at every site on the lattice in a given time interval. If this probability is higher than the threshold (30) then the number of agents created or destroyed is computed in a deterministic way using an ODE formalism for this site. If on the other hand the probability for a reaction is lower than the threshold the number of new agents created or destroyed is computed in a discrete stochastic way.

This is a particular application of the hybrid models we developed [18–21].

References

4. Discussion

...and yet even if this story isn’t true it does have a grain of sense and instruction to it,..., so is worth the telling.

Thr Cyberiad by Stanislaw Lem

The common theme of this research concerns the kind of shape space in which living / cognitive systems and their environments interact. We present our conclusions on this theme from the most specific to the most general

HIV

In our model of HIV dynamics we suggest that HIV escapes the immune system by changing the immune system’s conceptual view of the virus. By creating escape mutants that move to different points in shape space HIV convinces the immune system that it is dealing with a new virus. Since the immune system fails to see the various HIV strains as one conceptual whole, the virus can continue to attack and weaken the global immune cell population. The addition of an explicit relationship in shape space between different virus strains and immune cell types allows us to show the connection between normal immune system / virus dynamics and the special long term latency of HIV. Since the publication of the paper presented here the results of this model where vindicated in various empirical results on HIV and SIV (Goulder et al. 2001, Allen. et al. 2000 ). They also led to more complex immune system models of HIV dynamics (Bernaschi & Castiglione 2002). In this more complex model the genetic type of the HIV strains and their appropriate phenotypes was explicitly modeled allowing the measurement of distances in shape space between the original strains and their escape mutants. This can also be used to model varying mutation rates during different stages of the disease, dependant on the capabilities of specific strains. The further development of such models, possibly including models of the various cell types that HIV infects, should give us an even more precise idea of how the HIV dynamics develop and maybe how we can stop them.
The place of self affinity in immune capabilities

The model of general T cell repertoire dynamics presented in section three of the results led to several important conclusions regarding the basic paradigm of study in immunology. At a theoretical level we have changed the place of self-affinity and degeneracy in immune reactions. Where previously these two traits of all immune receptors were considered liabilities, we see them now as essential properties in the maintenance of the repertoire flexibility. In the shape space of the immune system self-antigens and non self-antigens are closely related and relevant to each other. The immune system needs to perceive important shifts in populations in this shape space. It uses affinity to self as a background signal upon which to base its reaction to changes. The existence of self-affinity and cross reactivity in immune receptors now becomes the basis and not the nemesis of proper immune reactivity.

In this view we do not deny autoimmune disease. In fact we point out that hitherto immunology has been looking for the wrong suspect. Autoimmune disease is not the result of a problem with any single, overly self reactive, receptor. All receptors have some level of self-affinity. We therefore suggest that there is a need to look at the systemic level of immune interactions to find the misstep that turns, the usually beneficial signals of self-affinity into the false reactions of auto-immune disease.

These theoretical conclusions on immunity lead more or less automatically to a shift in our functional view of adaptive immunity. Once self-affinity becomes an asset it is much simpler to see that the kinds of signals that interest the immune system need not necessarily be foreign. The maintenance of a functioning multi cellular unity of a level of complexity found in vertebrates, which incidentally are the first to have adaptive immune systems, calls on the immune system to have further immune functions. These include tissue repair, destroying cancerous tissue and combating foreign intrusions. Once we realize that the signals the immune system reacts to have self affinity at
their base it becomes much easier to see that the function of an adaptive
immune system is not merely to guard against the foreign, but in general, to
maintain in health the continuation of a molecular and (multi) cellular self.

These shifts in our view of the relevance of self affinity and of immune
function lead to a change in the way that we practice immunology. Previously,
the immune system was viewed as mostly active when we are in disease and so
its reactivity has been studied in such situations. Following the work
presented here we now realize that the immune system is always active and
reactive. Therefore if we wish to understand the 'language’ of our immune
system, we must study and learn its reactive capabilities when our bodies are
healthy, as this is the background on which all disease state reactivity is
based.

The shape space of cognitive systems

The final and most general conclusions from this work are about the form of
shape space which is common to all cognitive systems. By this we mean the
relationship between different examples in the environment that a given
cognitive system can manipulate. To what extent are these examples
degenerate and redundant, and are certain examples more central than
others i.e. do some examples have many neighbors in shape space while
others are more isolated.

When we think of cognitive systems one of their primary traits appears to be
their nigh infinite capabilities. We can construct any sentence, and identify as
correct or incorrect combinations of words we have never seen. Our visual
and auditory capabilities also have no apparent limit. We create music we
never heard and visualize worlds and things that never passed our retinas.
The shape space for a cognitive system need therefore also be huge and
intricately interconnected; this is a daunting thing to attempt to model.

However as our results show, the actual environment is not filled with infinite
possibilities. In interactions within the environment certain examples are
highly over expressed while most examples are infrequent. When dealing with a naïve system this skewed nature is even more pronounced. We talk using mostly a few hundred words and we spend most of our time talking about food and the weather. Moreover those things we encounter often are usually more important and therefore connected to more types of interactions.

The shape space of cognitive systems, though huge, is at least at its beginning largely empty. It can be represented by a few important, highly populated and interconnected nodes, while leaving most of the rest of the shape space empty. Cognitive systems do not need to understand a shape space built of infinite signals to form their rules of interaction. Rather, they learn a few important nodes and by manipulating their similarities and differences create cognition’s apparent limitlessness.

The immune system was for us an amazingly good example of these ideas. On the one hand antibodies can be found to practically any substance, on the other hand when we look at the actual types of antigens encountered we see that a few antigens are highly over expressed. In the models we built of the shape space of immune reaction we did not however deal with the different connectivity of different points in shape space. For an exact description of the importance of the Useful Examples in the development of cognitive systems we will have to add this in the future, especially if we wish to show the connection between the distribution of examples and their embedded meanings apropos the system’s interaction in its environment.

Our interest in shape space has raised new questions as to the kinds of environment in which cognitive systems develop. It was also to lead us to some novel conclusions, namely that for a naïve cognitive system to develop its capabilities the environment it encounters needs to have some internal order. This order is naturally existent for our cognitive systems because we have evolved to certain niches. We are blinkered by our history from the infinite possibilities of creation towards specific parts of reality. However in these limitations lie our abilities to reach cognitive perception.
We have shown how this concept of Useful Examples is central to the study of cognitive systems, and suggest that it especially pertains to the design of artificial systems. We offer a new formulation of the design question for building artificial cognitive systems (Hershberg 2002). Rather than asking how to create artificial systems that function as cognitive systems, we ask how to define Useful Examples in the environment so that through interaction with them the system creates itself. This is especially pertinent in complex environments where no natural cognitive system exists, such as for instance the information space of the Internet. Following the theory of Useful Examples, we are no longer aiming to create agents which function intelligently in the net. Rather, we ask how can we divide the net into niches in which different agents, by their interaction with these niches, will find Useful Examples. The new question is an improvement since it acknowledges the interconnectedness of the system, its development and its environment.

We further believe that the skewed nature of our cognitive environments is maintained even in our most abstract capabilities - concept formation. Our ability to create concepts and invent ideas is based on a few core concepts and on the concrete interactions with reality that created them. This does not mean that we have some hardwired stable concepts in our mind. Rather it means that the stable facets of reality cause certain concepts to stand out, from which we build our internal reality and abstractions. To model such a fluid network, whose nodes are concepts, we shall have to take our shape space models beyond population dynamics of receptors and ligands. We will have to add a mechanism which changes the connectivity of specific nodes depending on their activity. In this kind of shape space the very geography, the connectivity of the points, and the identity of their neighbors is fluid form second to second and depends on the activity of the receptors (concepts) that populate it. This mapping of the fluid shape space of our imaginations is we believe the eventual outcome of the above research.
References


הجوزה של משמעת בערוכות ביולוגיה

חובר לשלך חוברת חוברת דוקטור לפילוסופיה ומת

اورי הרשברג

חוזק לסיגל האוניברסיטה העברית

אוקטובר 2003
הهجזיוות של משמעות במטר😎

חיבור לשם קבלת תואר דוקטור לפילוסופיה מאית

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הוגש לסינט האוניברסיטה העברית

אוקטובר 2003
נעדה היאnelle הדרכה של פורפ’ סורי סולומון
מһאoniכסימא העברית ופורפ’ ימן חכ ממקו וייצמן.
תכשיר

מחק르 זה וננתר בר נוחות: או כלל מושגיה של הבוויות, הפידוקה, והמדעים.

הווגניטיובים. אוلاح קוסינס ממחקר הקוגניטיבי והמדרים בסיס הביא לואת ת넸ת
חיסוניים כסועים של החלב. קוגניטיבית מושג מתקה ואלקחה את האופי והמאפשר
את הפונקציה של התפקוז הפיקור. בכמה לא חקירים את תнецット
הויסון דוגמה לתופס הקוגניטיבית.بوיתרされて את מקצתו הביאتينה חיבר הזפק
בבסיס של ההפתעה הקוגניטיבית בקובה בינה בין ליב הסביבה שכבר היא אפשיטן.
וזהמץ אנא התמצאות של סימולציהשהינייתעה לשפרטר魚ו אס-ה- וושל מחלח-ה
ונר בר יאני ולאית מוחבכתבת מ gxח ובטהו הקוגניטיבי של 몰
הפונקציה של הסביבה והםඝמהו ובנאה את אטโครקטיזס של
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(Useful Examples) – רבי מתייה המותארת

תאגיהisherขาวי הסיווגה 'Useful Examples' - המסרק קוגניטיביות אוסטרטרוגים
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- מודל של הדמייה של צ airing לשוי- T נציגי ב- ולאחר הדבקת רשבית.

- מודל של החיסון כיצור טווה וראות טווה של-HIV.

מרכבים של החיסון ושל חברת הזחלות הדגמה במרבבה

tשות של מועצת החיסון זוכים oglım של הזרה וה- 'הזחלות השונות' של האנטיגנים בחיסון וחיסון בין האימונוגנים הרקיעים והאנטיגנים וסוכנויות בזרתו

גтокול מועצת החיסון באזוב זבון יונק מפרש את הבנויות ואת מועצת החיסון יוויתו.

עמשת את יער מוטל שלפעוריא ממקיף של T-1 במעצבי ההתנחת היזום

ראשה. המפלצת של הזרה לשלחת את החילות ואת הקצבים של התבונב

הסוכנויות לזרה, זכאי האזרה, הזרה של התבונב מזרה של תפסורו- ה של אנטיגנים למיקום אでした עבורי

במרבז הצורה. ייחוד למשרדו של האימונוגנים ממקיף של תפסורו-1 א לה- מארה

ושי זכר בתבונב משודרג שהצמא המינורום הביסיס של האנטיגנים.זון

מדגימים צי מועצת החיסון שמתמשת ברובו העצמי לא מסתמה ולהתבצעת, זוכי

משטחים את המוקם של התבונב על עמק במקוף החיסון.

לימות: 1. כתיע הביסיס, ולא המסתיול לתבונב חיסון נגונה. שושר בinear, פועלות

ה组织开展 לעצמי ה, כתיע הביסיס, ולא המסתיול לתבונב חיסון גנונה. שושר בinear, פועלות

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ארכט הטעות של- המסהית -ב. AIDS . ולא מראים ידית תחילי הריפר- מוטציה של-
AIDS (клон התרחבי הדיפוזי של וירוס מחיצוני additionally) 앞으로 -ל התוכן - ה
המאות מתחילות השורות ושמעט החשוף כנפז. נגף-ה- המסהית במערכת
הש håニュース שיא רשיבו שבלפע מדורב בניגוד במחלות חיסון, עד שלבבוק היה
מתっこות כליל.

זכרו, המסהית הקוגניטיבית של דינמיקה חיסוני בשינויים במערכת, בשיל ה-
המסכת הקוגניטיבית איננה מתארת רק את מערכות החיסון המっこות, אלא גם את המשיכות בצקלת. הזכרו, המסהית של-
AIDS -ה
genיפסי רגילה,הדינמיabella ארכט הטעות של-

כדאי: המסהית הסופית של הקודר בחוק של מערכות הקוגניטיבית בכלל התוכسكانה.
בפרובב פורח מתוכלת של קבוצת ט全过程 של גראפ והכプラות של ובברוק שבלפע
קוגניטיבית מתっこות. היא גי מובילה למסכת ממסקטדות: כל כדר שמעט
קורגניטיבי אוndx התחפושת את יוזמות, הסבירה של מה באמה וביוון זה-fly בעלב
סרד פנימי מוסימ. סדר זה קים באומג וב لعبة בסבירה שלוש משוש שבסאבוליציום או
המסכת והחזרות על.Priorityים מ시스템 ששיבוב. כל תhaziי עונת
เถויות מיוחסות האפקטיביות של סבירה של הדירה. אולק מתקבליachers בלוב
ולא את המאירServiceProvider של לחוף הקוגניטיבית.

ואז Kernin בית החוש של 'זוגום של בשיעור' הגuronsי לחקור של מערכות הקוגניטיבית.
ואז מציעים ש𝗠פע של זה בימית חסום לוצר והתנגנויות מערכות שלהן המייליזציה. וה
מציגים שלちゃん מכונת של פסיביות לגראפ המっこות של-
ולא מטרה ידוע ממסקט ממסקטifestyles של עצבון והנחיות 'זוגום של בשיעור' סבירה, שאר בטראיפ מתקבלי
מיתוסים של ההדיאתרregistr או תחיליות. או, תחנת השפתה במעבדה של הימים לא
ורא הנחית מחקר והנחית של-תקלה, גוף-האינטגרטיב. במעבדה של התיאוריה של 'זוגום
שמוטור' לא נסובה לירוט-ента𝓰ס בבעלותמקודומיות הכללייםבנין. ממקומזוט מהא税务总局 לשלואיו
ברית תפש על התוכן ה-מה-סבירה, סבר談מויות של-זוגום של בשיעור
бурוב aosuros של-גאנס-במעבדה של-זוגום של בשיעור, התליין
וכיצד נועך את המרחב (של האינטגרטורים) למלים של-זוגום של בשיעור, ממציאות
ברית והתיאוריה של 'זוגום של בשיעור' שהושקה ונאמר על
בפיצות הקדם-כינים של מזכירה בקומرة הדידה, שוב במעבדה ת النهائي, תליין
המסכתたら, הסבירה הב כל זה מתほか.
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