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Uri Hershberg

The researcher whom we have had the pleasure to interview is a representative of a new and comprehensive approach to the biology of cognition. This new trend seeks to establish a new theoretical plane of research on the cognizing organism, accounted for not in a reductionist, but in a holistic and complementary manner. Such a multi-disciplinary sphere is now immunology, combining the achievements of microbiology, organic chemistry, physics and genetics, along with all the evolutionary baggage and philosophical context.

Uri Hershberg is a theoretical biologist, occupying the position of Assistant Professor in the School of Biomedical Engineering, Science & Health Systems at Drexel University (Philadelphia, USA). He received his doctorate in the field of computational biology (bioinformatics) at the Interdisciplinary Center for Neural Computation in Hebrew University in Jerusalem. He also has philosophical and psychological training. He is associated with a number of laboratories and international research projects (Yale School of Medicine, PRIME and others). He is a student of the eminent immunologist Irun Cohen, with whom he worked on the theory of homuncular antigens. In his research he deals primarily with immunology in terms of systems biology, the concepts of gene stability and transcription, mathematical modeling and computational bioinformatics. He has published in various scientific journals: *Proceedings of the National Academy of Sciences*, *Immunity*, *Journal of Immunology*, *Molecular Immunology* (co-author: Irun Cohen) and others.

System Immuology Lab: *http://simlab.biomed.drexel.edu*

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Life as a meshwork of selves
Interview with Uri Hershberg

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It seems that the most fundamental question in philosophy of immunology is the matter of the essence of the immune system. In many handbooks this essence has been defined by "self" – a term introduced by Frank Macfarlane Burnet. Could you tell our readers in your own words, in short, what this is? How can 'self' be characterized most adequately for non-specialists?

I think that self is a temporal definition and highly context dependent. It is a set of living cells or systems that compiles your body in a healthy state. I think it is something which is always in the process of being defined. I gave a talk on this topic recently. There was a meeting in Paris this summer (August 2011), the European Congress on Artificial Life. We were talking about *autopoiesis*. One of its characteristic of this theory is what is a unit, what is a biological unit. In those systems they define the picture as Varela drew it – unit is a sort of Oroboros – the snake that bites itself. This is Francisco Varela's definition of self – closed loop - and they (Varela and Maturana) always try to use this definition to describe self, in cognitive sense. This is the system that allows you to make closure of self.

My suggestion was that the system is totally dynamic. It never reaches ultimate conclusion. The system, according to me, when I think about it, is some sort of temporary definition, of me, right now, of my current context. What happened is that you try to reach this (Uri points at border of the drawing with closed loop), but the definition of self changes. Then you reach the next one and the next one, and so on. It is cycle that never stops. Constantly, your immune system is coming to grips with the definition of self. It is like your identity – it is not something static. Like, *who you are now* is not *who you were years ago*, even though you feel a lot of sympathy to this person, maybe. An immune self in a given time is a collection of molecular characteristics that allows you to maintain health. The exact characteristics though, in fact you can measure the chemical set of self, it would not be the same as ten years before. The same has to do with the bacteria that you live with, which change and due to the fact that you develop, you are different, If you are a child, you are different. And the extreme case is that when you are an infant in the womb – both you and your mother are undergoing lots of changes. The reality is that it is hard to make a static claim *what is self*. Self is a changing phenomenon.

Is 'self' a notion rather philosophical, or rather scientific?

I think 'self' is a philosophical concept that stands on individuality and what individuality means or how important it is. It recalls on what you do in science. So I think it is a philosophical concept but it has direct implication on the way you ask the question. Self is a very ill-defined parameter. Its borders are not so clear-cut as we would like. It is very context dependent.

What has changed in your approach since the article "The Immune System and Other Cognitive Systems", namely in the last 10 years? Who was the most remarkable of your co-workers in the meantime?

That is a tough one. I would say that for me as a scientist I am focusing on more specific biological questions so I was less philosophical in these last years, I have been doing things at least for me based on data, asking specific questions on biology and this has led me to study more on immunity than on cognition because some of the things I thought about in cognition were very hard to test experimentally. It is funny for me now, because over the last 10 years I have spent a lot of my time in medical schools. And medical schools are not very philosophical places, because they involve their time to save people's lives, so it is not a very philosophical place. But recently I started a position in a medical bioengineering department and it is a more entrepreneurial place; there is some leeway to allow you to do other things, so I started such things again. So in last ten years I would say I started looking at more basic phenomena, but recently I started to go back and look at things I stopped ten years ago. Maybe because you guys emailed me, I don't know. One thing that I realized by myself is that in the paper from 2001 I was speaking mostly on the beginnings, and how things form and how cognition starts and begins to be amazing, essentially. Maybe because I am getting older in this second round I started to think of limits why cognition stops working. As to the second half of your question, it is a very hard question to answer. I would say that one person that mostly it was people I already talked a lot with at that time, people who inspired me to write this paper. These were people who I was acting with then and they stayed with me to some degree, so my two PhD supervisors Irun Cohen and Sorin Solomon and in this context I would say especially Irun Cohen. When you do a PhD, you don't realize if you do something that is very strange or not, because you think that everybody does what you do for your PhD. And what I have been realizing since my PhD is that they gave me a very strange outlook on the world and sometimes really what I had to do to make things different it is just bring that outlook. I learnt this outlook from Solomon and Cohen. So these are two people I would say. Another person who inspired me was Prof. Anat Nino, who studies language development in infants and who gave me both insight (and courage) to make a connection between immunology and language (and talk about it out loud). Finally, the last person without whom this would not have come about is Evelyn Andreewsky, who taught me many things about the society of science. In another context of more practical research and the way I later continued – this paper talks about cognition and cognitive systems and even then I already thought in my head that this line between biological systems and cognitive systems is a fake one. What cognition does that is different from biology – it is not categorical difference, it is a mental extension. Even a single cell that needs to act in the world does not do it like a machine. It acts with signals, with meanings. I am not saying that cells have abstract thoughts the way we do. They do not have high cognitive potential. But the way we manage to manipulate those is that we have senses. Even a single cell organism does not really have sensors. They have senses. And I think that trying to think about that biology is what I have been doing since then, even though I think my papers were on different things. But it is really about the fact that whenever you look at the biology context it is what is important. In this sense I think that a lot of interesting things I learnt from Gunter Wagner (Professor of Ecology and Evolutionary Biology at Yale University), who is a professor at Yale, and also from Mark Shlomchik (Professor of Laboratory Medicine and of Immunobiology at Yale School of Medicine, Yale University), with whom I did my post-doc. I don't know if he agreed with my 'philosophizing or if he thinks about cells like this. He is more practical or at least gives that impression. But he thinks very deeply on how immune systems work. And actually there is another person, but the list is too big! Still I would say also Phil Hodgkin (Professor of Immunology at The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia). He is, I would say, the most important immunologist in Australia (a country that likes immunology). We know that Australia is the source of clonal selection theory. What Phil Hodgkin has done which I think is amazing is that he has added some physics to his lab and what he is trying to show is that stochasticity is an essential part of how eventually you get your robust behavior. What is interesting in what he has shown is that it is not noise. So the fact that each cell behaves slightly differently and nearly every parameter you can think of proliferation and differentiation is not hard coded. He has essentially shown experimentally that this competition of stochastic things leads to the immune phenomenon you can see at the end. He is also a guy who is really easy to talk to, which is always nice. He has managed to convince them to do a set of experiments, he is essentially growing individual immune selves in separation so you can really see which population is the source of which cell and then you separate them again, so it is a very difficult experiment to do and very time consuming. But they have shown this amazing thing which only people who care about systems biology would care about and usually people would not do, because most immunologists unfortunately are not system biologists other than Phil Hodgkin. It is very hard to pick one name. Let us go on to the next question.

The theory submitted by you and your colleagues seems to be one of the most timely alternatives for studying the essence of the immune system. It has become famous, and has provoked new discussions among immunologists

(Cohn, Coutinho etc.). Could you briefly characterize this theory? To what extent does your approach differ from the classic notion of immunity?

The idea of this theory is essentially based on Irun Cohen's theories, my PhD supervisor. So the idea is that immune system does not make a hard coded self – non-self discrimination. Rather, it uses the self as kind a background signal to educate self about molecular biological systems. And then it contrasts dynamics of the system – things that it sees - it makes decisions for action. So to take an example from the visual system – we don't make light and dark illuminations, we use patterns of light and dark and the phenomenon of what is background light in whenever we are and we see the specific content. So this is the essence – something that I realized. And this is very different from Melvin Cohn's view and even Danger Theory. Because we know that there is no signal for any one characteristic. Everything has to be context dependent. And context is mostly based on self. Another aspect – we called it cognitive. And it was also used by Francisco Varela and Antonio Coutinho has also used this in his book, but what we also realized years after we published this is that our definition of the cognitive is more radical. When we say "cognitive", we don't mean that we need a multi-cell definition of border – we mean that there is no hard coded vision of border. Your define identity through acting with the fragments. This is most essential thing and what we said in the paper[2] and what I think about now is that all of the systems, you can't make them otherwise. If you try to make them hardcoded it would not work. And it would not be adaptive. So this is our theory in one short description.

Similarly to the followers of psychoneuroimmunology, you aim to study the complexity of the body – with one exception: for you the relation between the immune system and the neural system is essential, whereas for PNI the key relation is between the immune system and mind. Is there a possibility to describe such an extensive structure and effects of its activity by means of a relatively simple explanation based on cause-result?

I think that essentially the answer is "yes". But we have many technical issues before we can do that. One is that we understand little of these systems, so we don't know how these systems works. And especially neural system is very segregated. So the reality is when a body functions, it functions as a single unit. The system has a set of definitions that we make – well up to a point. The reason why it is not so easy to do this, especially with the neural system, is that it is so segregated. But the reality is that a lot of signals are not so clear. I will get to the immune system later, but first I want to emphasize something about the whole idea of separating and then trying to combine them. When you think of many automatic functions like

[2] Hershberg, U. and Efroni, S. 2001. *Układ odpornościowy a inne systemy poznawcze*. Avant, T/2011: 129-145, http://avant.edu.pl/wp-content/uploads/UHSE_Uklad_Avant_T_20111.pdf

walking. You walk because your brain tells your feet to move. But when you are walking in standardized ways, you are getting input through a pattern generating system. And people realized that this patterns are generated not only in the brain. You can use it even if your brain is disconnected from your spine. And there is also a pattern generated in your brain. They collaborate with each other. But the point I am trying to make is that there is a feeling that we have that everything neural happens in the brain. The brain does more complicated functions. But neural system is everywhere and to some degree it is in a state of flux and feedback. Today I heard example about the heart. The heart is also a huge neural system. It is highly innervated and generates complex electrical patterns. And apparently it is capable of making many complex calculations. So if you transplant heart to a person, you don't innervate it to the local neural system. The heart is autonomous. Despite this it starts to acquire the pattern the person had before. So it somehow calculates what it is meant to do and it becomes more like a heart that the person had before. So the point is that this was another aspect of what I said about self and non-self. If we understood it correctly this way, is that these systems communicate with each other, we would automatically understand it as a single system. The systems you ask about in your question are a false form of division, because if you want to study a simple movement, you don't need to look at the whole brain, you look at a cerebellum. If you want to study an inflammatory response to a vaccine, then you can look in a lymph now. There are very many things happening in the brain. Maybe there is no point to look at them. If you look at the interface, once we do this question, you will see that the interface is very fluid. I will give you an example I am sure you probably know about. Cytokines are probably very good neurotransmitters. It is not only used in immunity. It is also used in neural system. The problem is that anything I can give you will be anecdotal. We still don't know much about these systems and how they communicate with each other. So until we find this out and the way they combine there will be more confusion than useful research. Not because it can't be done. The immune system does communicate with the neural system. Whenever you are sick, one of the main things that happens is that you have a fever, controlled by your neural system, and you feel like going home and not talking to anyone. All of these things are phenomena created by your brain, acted by immune system. So it is not the question: if the neural system talks to your immune system and vice versa – that definitely happens. But going beyond that and doing research on it. There are many questions before that. There is a lot to do before we get to that.

What practical means does your theory offer to scientists?

I don't know. That is not why I did it. I wrote some things I thought came out of it and I have seen people write about it and what happens to me, is that I am surprised when I see what they actually think it means. In general I think "practical" means different things to different scientists. Generally in biology and also in the creation of robots and artificial life it is demanded that scientists ask questions that are usually hard for them to ask. Sometimes it pushes scientists to things that are difficult to do. This is how things move forward into the unknown. I think that what I tried to write in these papers is that if you really want to understand how a specific dynamic works, you have to look at the environment in which it is working. And we have to contrast similar dynamics in different environments. Only then we can really understand what happens. I am not, in this paper, saying how to do it, because I did not think I needed to. The main point in the paper for those doing research on artificial life, was to say – if you go another path, ignoring the environment and its influence on dynamics, you will waste a lot of time and it won't work. And I think of examples of that, people who try to do expert systems in a kind of a subset in the environment. I think that generally this has to be a failure. In immunology, there was a lot of arguments about self and non-self but one of this funny things that happened is that all immunologists now agree that for a specific kind of response for the self part of MHC that this regulation of self and non self is not absolute. So claiming a fluid border of self and non self has become much more mainstream in the realm of immunology. So experimental immunologists today are much less likely to argue my paper then they were when it came out in 2001.

Some time ago I read a study and I found some papers about artificial immune systems that are applied in antivirus programs. And this research programme is very big. I was very astounded. Have you heard about that?

So I know about it and I have to say I have not seen one that I found theoretically sound. If I ever did, I would talk about it a lot. I often have two issues with them. One is that they often use immunology as a metaphor, some immunological model that nobody believes anymore which is fine if it helps, but it is not immunology. And the other thing that I sometimes see is that they overdo it, in terms of claiming the utility of adaptive immunity. One of the reasons we need immune system is that environment is very complicated. It would be maybe cheaper if we could as living systems do it, somehow tag all bad things with a sign saying "you are bad". It would be better than to have all this cognition but we can't do it. It is not viable. And sometimes I feel that all this anti viral immune models are not clear to me as they should, we could do it with a simpler tool – this is two. So if you are going to do things in a very complicated way, you have to really show that it is necessary, if you are making something. So I have to say that I haven't looked at this recently, maybe because of these two reasons but the last time I looked at this direction of research and it was full of things that were very… I wish it was better – let us leave it at that. Do you like cyberpunk?

Yes.

So you know William Gibson and Bruce Sterling. William Gibson is really super cool. But he is a fantasist. This is magic. The way he describes a computer is the way like someone who has never seen a computer. Bruce Sterling shows things that will happen in fifteen of fifty years and it shows you how information structure will change and what you think about the world. And I think that people who do immune system antivirus, they think that this cyber structure is much more complicated than it is. It would be a good environment to make living things, but right now I am not sure if it is complex enough.

What tool is the most useful in your research? To what extent do computational modelling and visualization determine the results of this research?

Everything I do is based on computational model. And these days a lot of statistics and analysis goes on in my research. But I have to admit that I am actually doing a lot of reasoning thinking, about phrasing the questions so most of the time, things I do are based on coding and programming are not very complicated. This may change a little bit cause I have a lab. And some of my students are really good in programs usage. Everything I do is based on visual thinking and visualisation, but it is usually simple visualisation. I have never done a 3D map of the thymus. The closest I would say to have, the visualisation that really made me think of the idea was in paper I published in 2006. I made this small networks that represented codons and Amino acids. The whole paper came about because I was obsessed with making this visual things and then I found some other things and I did some small physical analysis, but I would not think about those things if I didn't try to get the visual. I was obsessed with the idea that the genetic code really limits to some degree what you do next – so if I am already one amino acid, I can't really go to another. And this is again a context thing, so that was the visualisation that I really used one time. So I think very much visually, but my visualisation at the end tends to be very simple. It is something that you can do on a piece of paper if you wanted.

It seems that the key point of cognitive immunology is auto-aggression. What happens when an organism starts to attack itself? And more generally: what is the position of auto-aggression in your research? In your doctoral thesis you wrote about HIV as "a (cognitive) immune system's conceptual mistake".

By auto-aggression you mean self reflectiveness or self attack?

Self attack.

What I am going to tell you know is a thing I was thinking about last month, but some of these is older. So in general my feelings on autoimmunity as you call it – auto-aggression is a cognitive mistake. The reason why my thesis didn't talk about it and the example I gave was HIV is that I was trying to shy away from it. I think that to some degree we are over obsessed with it.

So the point I am trying to make is the fact that we have biological cases of autoimmunity is not surprising. What is surprising is that we have very few of them. The problem in immunology is that we focus on pathological cases, but when we really want to see how immune systems functions when it is not pathological. I guess that it is another aspect of theory which I also think it is held by others but I think it is definitely not in Melvin Cohn's and Frank Burnet's theory, so it is a immune system that is always active. So if you think of immune system as it is always active and you see how seldom we have autoimmunity, then you see the way it is – it is a mistake. If you think about a speech. Even when we talk on Skype, when we speak in language which is second to both of us, we make very few mistakes. And information comes to us, even though we make some mistakes. Let us say - The system is busy and the likelihood of having autoimmunity is zero. We can't build system that way. The immune system as a system is trying to minimize autoimmunity. So it is top – down. The idea that segregating cells move all kinds of thing, but it is a self police but in case when you have a police, this police is getting against the police itself and then you get autoimmunity. But it really is only one example of cognitive mistakes that immune system can make and I think is relatively rare and pathological. I mean that it is very important to study for medical reasons, and also because it tells us about limits of the immune system, but I would like to study healthy immune systems.

Now there are many ongoing studies in the world related to the notion of group immunity or collective immunity (for example: research on malaria). Is this an object of your science interests, and if so, to what extent?

I think it is very, very interesting, and unfortunately I have never done any research on something like that. I am now talking with collaborators looking at how different people in different biomes… how that relates to the immunity. In ten years or so when the technology of doing sequencing of DNA will have become much cheaper we will be able to actually do studies like that. Right now, like several years ago, we would never do a study like that - in terms of immune system you could not really sample diversity in any meaningful way. Now I can determine diversity of few people. So instead of starting looking at one, which is really weak, I can look at many people and identify things that are relevant to immune system. If I was to study this, I would need to sequence and I would not do it on humans, because no one would give me all of their immune system. If I sequence a million cells. So first I would need to million of them, if not more, and then would need to, I would only be able to see things existing in a thousand cells. So answering these questions is right now practically impossible But I would study if it becomes possible.

The language of immunologists is rather figurative and full of metaphors. For example: Ilya Ilyich Mechnikov used military metaphors, Claude Bernard – economic metaphors; among contemporary scientists, Polly Matzinger used the metaphor of being threatened, Irun Cohen - the metaphor of immunologi-

cal homunculus. To what extent is this metaphorical language adequate, and to what extent can it darken the point of the matter?

I think that this is a good question for any discussion on science, not just immunology. I met a lot of people who like metaphors. I think that you have to be careful using them but I think that to some degree everything we say is a metaphor. Everything except a specific level of something is a metaphor. Even if we make a small extrapolation, it is to some degree a metaphor. So I think metaphorical language is not adequate on its own, but it is very hard to say anything without using metaphors. So I like metaphors. And people who say they hate them – I think they just use boring metaphors instead of being more careful with that.

Continuing the subject of science metaphors: some people point out the predominant language of aggression and war in the medical and science descriptions. In their opinion this fact can have negative resonance for e.g. social relations. Do you see any alternative language acceptable both for scientists and for critics?

I think it is a very bad thing and it also goes to other things. People say things like when they sell you a yoghurt and they tell you: these are good bacteria. This is good, because they found significant good result. This kind of situation which are bringing good and evil into biology I think they are very bad. The problem is that it is much easier to think like that and also this is catchy. We need to be more careful about the language we use, which is a more context dependent language. One way that I like to do it, especially when talking about bacteria or the immune system is by using examples to show what things are good or bad for you. So when you get one type of bacteria from yoghurt and you bring it to the blood system, you will have septic shock immediately. The fact that your immune system rejects some things is good, but not when you have an organ transplant. These are signifying words – it is not so much about a wall between things, it is about saying this guy is a good guy and this guy is a bad guy. The reality is that it depends. Sometimes we can use viruses for good reasons. A lot of genetic things for living systems are transferred by virus. So it is not good or bad. In that context people are very happy to have something statistically significant. If it is not statistically significant, they are sad. People are very focused on finding good or bad. Significant – not significant.

Are the questions concerning immunity still underestimated?

There are many, many unquestioned theories. I will give you the worst one: we don't know why vaccines work. Most of vaccines we have we know they work, because they are proven effective over billions of people and multiple generations. We don't know how cells cooperate. We know the influences, but we don't know accurately how it happens. How the signal allows your cells to protect your body and retain memory. We don't know how the cognate immune signal works. It is a really surprising phenomenon – you have two cells and they are reacting with different antigens and they associate with each other. You observe things that temporarily happen in the same time and your brain is very interconnected so you associate it. How it is actually physically done – we don't know. And there are many questions like that – we have theory and we have many incidental evidences showing that this theory is probably correct, but when we try to explain how it result to action – how multiple cells cooperate together without being controlled by third one – we don't know.

Ten years ago you and Sol Efroni wrote : "It is in treating the immune system as cognitive that we believe that our theory is most controversial (...)". For many philosophers and for some scientists the notion of the immune system being a cognitive system is still notional abuse. Is there any one non-functional argument worth using before orthodox approaches? You suggested the following criterion of system difference: "cognitive systems need an interaction with their environment to define the system's exact sensitivities".

I wanted to explain why I said that there is no functional definition, and I am not alone in this. It is about cognition and active process. So I don't think we have a priori a function. Eyes do have a function, the immune system does have a function. But what the immune system does – it acts (it functions). All cognitive systems are active things. So you can't make a definition that does not involve an action.

Is science immune against philosophy? Is philosophy defenceless in the face of science?

Only in the minds of bad scientists [laughing]. There is no such things like "science" without "philosophy". Why I chose my PhD supervisor was that the other ones thought that you can make a science without a philosophy. And I thought that they were lying to themselves. I think that philosophy is the status of what we think about the world, to inform how we ask the questions and to inform what questions mean. I don't think that these things are disconnected. The greatest scientists are those who are willing to philosophize. And the philosophers I like the most from 21st century were philosophers who were talking about science, so I think these are very interconnected things.