Why the first glass of wine is better than the seventh

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Abstract. The response to the title would simply be that the state of the organism has changed between the first and the seventh glass and that, before the seventh, this state was much closer to some kind of "homeostatic limit". Although the external impact i.e. the glass of wine is identical in both cases, the reaction of the receptive organism might be different, depending on its current state: accept the first glass then reject the seventh. It is the couple "wine and current state of the organism" which is important here and not just the wine. Introducing this paper, I will attempt to clarify the famous self-nonself controversy by referring attentively to the debate which took place in 1997 between more traditional immunologists (Langman) and less ones (Dembic, Coutinho), and by proposing a very simple and illustrative computer simulation allowing a beginning of "formalization" of the self-assertion perspective. I will conclude by discussing the practical impact that such a perspective should have on the conception of "intrusion detectors" for vulnerable systems such as computers, and why a growing number of immunologists, like Varela twenty years ago, plead for going beyond this too narrow vision of immune system as "intrusions detector" to rather privilege its "homeostatic character".

1 Introduction: the self-nonself debate

The response to the title would simply be that the state of the organism has changed between the first and the seventh glass and that, before the seventh, this state was much closer to some kind of "homeostatic limit". Obviously, among other things, the swallowing of all precedent glasses i.e. the history of the drinking organism must be taken into account in order to assess the effect of this last glass. Although the external impact i.e. the glass of wine is identical in both cases, the reaction of the receptive organism might be different, depending on its current state: accept then reject. It is the couple "wine and current state of the organism" which is important here and not just the wine. The wine is neither self nor non-self, dangerous or inoffensive as such, but rather pleases or disturbs the drinker as a function of his stomach. An important question logically follows: "would you prevent yourself from drinking a first glass of wine, aware that the seventh could be much more harmful". What a pity and what an enormous "false positive" this would be. Such a rejection would be useless in the first

place. But even worse, this rejected impact (rejected because it can be hurtful in some particular context), could in other circumstances play a positive curing effect (wine is famous for that). Not taking the state into account can lead to too conservative protection policy, up until missing some curing opportunities.

In 1997, a very interesting, long and vivid debate took place among immunologists, some more classical and others proposing alternative views such as the "danger" model (Matzinger [14]), the "integrity" one (Dembic [10]), together with models around the idiotypic networks (Varela, Coutinho, Stewart [21][24]) (this debate is available on the Web at http://www.cig.salk.edu/BICD_140_W99/debate/). Among other issues, one very warmly discussed was the classical self-nonself distinction and the importance given by immunologists to "detection and recognition" processes. To quote this debate moderator Kenneth Schaffner: "All postings thus far accept a major role for the immune system in detecting and eliminating pathogens, while not attacking the body or the immune system. In recognizing some things as "to be eliminated" and others as not, is this tantamount to an implicit definition of the self-nonself distinction?". Even stronger, the following claim of Rod Langman (an immunologist more on the classical side): "I see no escape from the conclusion that all biodestructive protective mechanisms will have to do something that can be described as a self-nonself or dangerous-nondangerous or integrate-nonintegrate, etc. discrimination based on specific recognition and exercise of the biodestructive consequence of recognition". According to him, all the debate boils down to a simple wordy issue, a semantic game, that provides no better way to construe the immune functions. Since many years, I have tried to encourage researchers in AIS, above all if interested in "intrusions detection", to watch more attentively for these alternative views yet having a marginal impact [4] [6]. It is time now to attempt a more pedagogical effort to help to better understand the differences between these positions and above all the impact these differences could have further on their practical developments. Exactly as it is for the immune system, the state of our research community might be today more mature to better receive and echo these once marginal voices.

I believe with many others (Varela, Coutinho, Stewart, Tauber, Cohen, Dembic) that the self-nonself debate largely goes beyond a simple labeling issue and that the real focus is not so much on defining what is "self", which clearly, as Langman rightly pointed, can be substituted by "non-dangerous" or any synonymous for a homeostatic viable entity. The problem resides much more in the nature and the characterization of the "yes/no" dichotomy. How does it arise? Is this dichotomy just dependent on some proper features of the external impact, like accepted by the whole AIS community (who majoritarily engeneerizes his immune knowledge in a classification system separating data distributed in a space bounded by axis corresponding to external features) or, like I rather defend, is it dependent also on the state of the impacted system at the moment of the impact (making this classification much more problematic)? Is an impact dangerous per se or dangerous because the system at the moment of the impact is much more vulnerable than it usually is? I believe the second interpretation to be a more correct way to see things, both for living organisms but equally so for computers. To quote Tauber [22,23] (a very convincing advocate of the alternative views): "The meaning of a given antigen is governed by the complex interplay of the endogenous and exogenous factors in which it appears" and Cohen

[8]: “Rejection of infectious agents depends more on the site and circumstances of the infected tissue than it does on the identity of the infectious agent”

Polly Matzinger, today one of the best known critics of the self-nonself dichotomy of immunology, and exerting a recent influence on some AIS developments [1] [7], remains quite ambiguous on this specific issue. It is clear that the problem with self and nonself lies in the determination, namely the nature and the location, of the frontier. What she proposes is to maintain the duality, i.e. the immune system keeps two ways of being in response to external impact: defensive and tolerant, but no more depending on a physical evasive frontier to cross. She insists in getting rid of the self-nonself discrimination as such but to substitute it with an alternative dichotomy: dangerous/inoffensive. The fact that this move at first simply consists of a semantic substitution makes a lot of immunologist very skeptic against Matzinger’s position. According to Janeway (another famous classical immunologist): “The problem with this model is its inherent tautology … The immune response is induced by a danger signal but the danger signal is defined as just about anything that can induce an immune response” [15]

To clarify the issue, there is no better way than taking advantage of the metaphor exploited by Matzinger herself in an interview she gave to advocate her position (in http://www.info-implants.com/Walt/01.html): “Let me use an analogy to explain it. Imagine a community in which the police accept anyone they met during elementary school and kill any new migrant. That’s the self-nonself model. In the danger model, tourists and immigrants are accepted, until they start breaking windows. Only then do the police move to eliminate them. In fact, it doesn’t matter if the window breaker is a foreigner or a member of the community…. In the danger model, the police wander around, waiting for an alarm signaling that something is doing damage. If an immigrant enters without doing damage, the white cells simply continue to wander, and after a while, the harmless immigrant becomes part of the community”. Taking that metaphor literally, it is obvious that what she presents as an alternative view is not really so since the familiar/foreign dichotomy just gives place to the gentle/nasty one, the invader’s feature “country of origin” being simply replaced by the feature “basic personal psychology”. A real departure from the classical dichotomy would be for the migrant to make the choice between adopting a gentle or a nasty attitude depending also and perhaps essentially on the internal state of the community at the time he comes in. Such a state will obviously depend on the presence of the previous migrants and thus on the whole flux of them since the origin of this community. However, it will also depend on other internal aspects of this community: the lodging capacity, the social welfare, economical inequalities and the usual police attitude, comprised the one adopted when encountering the migrants. A migrant, usually nice in many circumstances, might turn out to be angry and destructive in very specific contexts.

Presented as she presents it, this Matzinger’s vision of what is dangerous or not is not such an exciting one, because it still demands from the system the ability to discriminate and to defend. The self-nonself frontier is simply re-designed but is maintained outside the system to protect. With such a view, the recognition ability of the immune system still plays the leading role in separating the dangerous impact from the non-dangerous one. A more interesting perspective, which would make Matzinger to integrate the circle of the radical immunologists, instigated by Varela, Coutinho

and Cohen, sees the danger as a consequence of the interaction between the external impact and the current state of the immune system. In such a case, a stimulus is no more dangerous per se, but is dangerous in the current context of the immune system. An outside separation in two classes, making the immune system behaves in two ways, simply collapses. No discriminative recognition is at play any more. We remain with an immune system behaving in one only way but, depending on its current state and the nature of the impact, proposing different responses to it. For instance, a same external impact could drive the system to react differently at different times. The internal perturbation caused by the external impact, i.e. the way the internal dynamics "digests" it, is what really counts in order to locate this impact on one side or the other of the immune system. The set of the antigenic attributes is one part of the problem, the state and the history of the system since its appearance is the other key part and definitely not something easy to discriminate upon. At the end of the debate, Langman still remains skeptic and claims "My challenge is to ask whether you would consider the possibility of a set of mechanistic details and boundary conditions that offer a way of establishing a set of criteria that amount to a workable self-nonself discrimination that does not require nonself markers such as "danger", "disintegration", "inflammation", "toxicity"", whereas Dembic rightly answers that we all need to move from a discriminatory process taking place in some feature spaces whatever it is, to a new space, yet to define, that would simultaneously incorporate time and the regulatory dynamics of the system.

In the following section, a more formal reading will be proposed to support and clarify this alternative vision. I'll show that the main difference between the classical view and the new one (designated as "the self-assertion perspective" in previous works [24] [6]) asks to replace a "linear causality", where the whole immune reaction just starts from and is only conditioned by the antigenic impact, with a "circular causality", maintaining some autonomy in the immune behavior, now simply perturbed but no longer initiated from and only conditioned by the antigenic impacts. The third section will briefly recall why the well-known idiotypic network, popularized by Jerne some thirty years ago [12], was an essential but still very preliminary step on the way to this alternative vision. Since "intrusion detection" remains the main engineering use and perhaps abuse of the immune metaphor, the fourth section will describe a little computer simulation in which a complex system is being impacted from outside. A defensive mechanism built around it and aiming at preserving it inside a viability domain will be gradually learned. The simulation will show the need for the adaptive defensive mechanism to take into account not only the nature of the impact but also the state of the system at the moment of the impact. Many false positives are avoided and a finer curing attitude becomes possible. The final section will emphasize again the same shift in perspective as the one advocated many years ago. The internal homeostasis of a system to be protected goes beyond the severity of its frontiers. One needs to re-concentrate the attention on the inside of the system to the detriment of the outside, and to understand better its internal regulatory mechanisms both while isolated and in response to an impact.

2 Linear causality vs circular causality

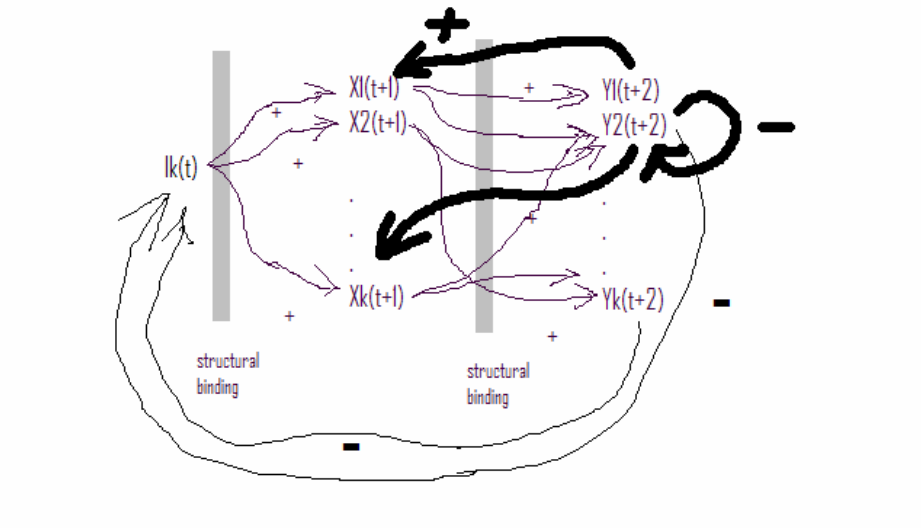

Fig.1 Linear vs Circular causality

In figure 1, a very intuitive mathematical formulation will help to differentiate the two perspectives. We suppose on the left an antigenic intrusion Ik(t) occurring at time t and impacting a first stage of immune cells Xk(t+1). We suppose that the interaction occurs by means of some kind of structural binding between the antigen and these cells, inducing a stimulatory effect on the cells. In the right part of the figure, these latter cells Xk, in their turn, stimulate by structural binding a second stage of immune cells Yk(t+2). Finally these latter have the possibility to inhibit the antigen by decreasing its concentration. Without accounting for the thicker feedback arrows, this figure depicts a linear causation in which the antigen is the initiator of the whole sequence of interaction. Everything happens in reaction to the antigen intrusion and the precise effect will depend on the nature of the antigen, from that the classical self-nonself distinction. Now by adding the feedback thicker arrows, a circular causality is induced, driving the system to manifest a dynamical behavior on its own, perturbed but now longer impelled and impressed by the antigens.

Simplifying this scheme even further, we can see how the two figures above lead to two different mathematical dependencies. In the first linear case: $X(t+1)=f_+(I(t))$, $Y(t+2)=g_+(X(t+1))$ and $I(t+3)=h_-(Y(t+2))$ which, by concatenating all dependencies, gives $I(t+3)=f_+ (g_+ (h_- (I(t))))$, reducing so the becoming of the antigen to its sole intrinsic nature. In contract, in the second case: $X(t+1)=f_+(I(t),Y(t))$, $Y(t+2)=g_+(X(t+1))$ and $I(t+3)=h_-(Y(t+2))$ which, by concatenating all dependencies, gives $I(t+3)= h_-(g_+(f_+(I(t),Y(t))))$ and making the future of the antigen still dependent on the state of the impacted system at the moment of the impact, here the variable Y. The value of this variable, depending on the previous impacts, the reaction to any antigen depends on the whole evolution of the system, comprised all previous impacts. So the nature of the antigen alone i.e. the structural category it fits in is far from enough to predict what will happen to it. Only a complete knowledge of the couple (antigen, system state) can allow predicting the antigen destiny.

3 Idiotypic networks show this circular causality

In the middle of a Nobel lecture given the 8th December 1984 in France [13], Niels Jerne discoursed on a topic he considered to be a major breakthrough in immunology: "*I shall now turn to some remarkable discoveries, made during the past years, showing that the variable regions of antibody molecules are themselves antigenic and invoke the production of anti-antibodies…. Jacques Oudin and his colleagues in Paris [18, 19], showed that ordinary antibody molecules that arise in an immunized animals are antigenic and invoke the formation of specific anti-antibodies. In other words, the variable region of an antibody molecule constitutes not only its "combining site", but also presents an antigenic profile (named its idiotype) against which anti-idiotypic can be induced in other animals.*" Since Oudin's experimental finding and Jerne's enthusiastic emphasis on the existence of idiotypic network, that antibodies can mutually stimulate themselves in a way very similar to the stimulation antigen exerts on antibody has been convincingly revealed by a large set of experiments [15,16,24]. The Burnetian clonal selection theory, which describes how an antibody is selected to proliferate in response to antigen recognition, extends now to antibodies themselves that turn out to be as much selector as selected. Jerne had many reasons to be so enthusiastic, since this discovery was the first rupture with the classical linear causality, still so vivid among its immunological colleagues.

The circular causality is obvious by watching the simplest scheme below:

An antigen stimulates a first antibody Ab1 which in its turn stimulates and is stimulated (creating the circularity) by a second antibody Ab2. In the self-assertion

simulation presented in [6], the program instructions changing the concentration of any antibody are:

if (low $< \alpha \Sigma_i$ *affinityOfAntibodies*$_i$ $+ \beta \Sigma_i$ *affinityOfAntigen*$_i <$ *high)*
Cj(t) = Cj(t) +1
else
Cj(t) = Cj(t) – 1

indicating that the concentration of any antibody *Cj(t)* changes, not only as a function of the antigens stimulating it, but also of the other antibodies present in the network. We show in the simulation how indeed the evolution of an antigen concentration depends in part on its own characteristics but also on the evolution of the antibodies concentration and the network interactions. Despite the lack of attention and interest for this network in today immunology, many other immunological ways exist to induce this circular causality. It is enough that any cell, lymphocyte or macrophage of any sort, stimulated by the antigen, mutually stimulates themselves, to have feedback loops and memory effects in the system, relaxing the importance of the external stimuli.

4 Defending complex systems

The small computer simulation to be presented in the following aims at illustrating how the self-assertion perspective can lead to some practical advantages (as compared with the self-recognition one) in the construction of effective defenses for complex systems such as computer ones. The complex system to be protected here is a fully connected Hopfield network composed of 8 units:

$$x_i(t+1) = \tanh(\sum_{j=1}^{8} w_{ij}\, xj(t)) \text{ with } w_{ii} = 1 \text{ and } w_{ij} \text{ taken randomly in [-0.5,0.5]}$$

This structure should be construed as a generic metaphor for complex systems since it displays a strong circular causality, each variable influencing all the others. The weights being not symmetric and the diagonal unitary, the network does not stabilize into fixed points but into cyclic attractors instead. After a long transient, we define a viability interval Vi for each variable as the interval in between the boundaries of its range of variation [x_{imin},x_{imax}]. The viability domain of the whole system becomes the union of all these intervals. A viable and "healthy" system has all its variables comprised in their viable intervals. It is no longer the case as soon as one of its units leaves its interval. The mission of the whole defensive process to be described consists in maintaining viable this system.

A deleterious impact here amounts to a perturbation I_j taken randomly in [-2,2] and exerted at time t on one variable x_j(t) randomly chosen:

$$x_i(t+1) = \tanh(\sum_{j=1}^{8} w_{ij}\,(x_j(t) + Ij))$$

As figure 2 illustrates the whole defensive strategy is organized around three types of agent: monitoring, filtering and curing agents.

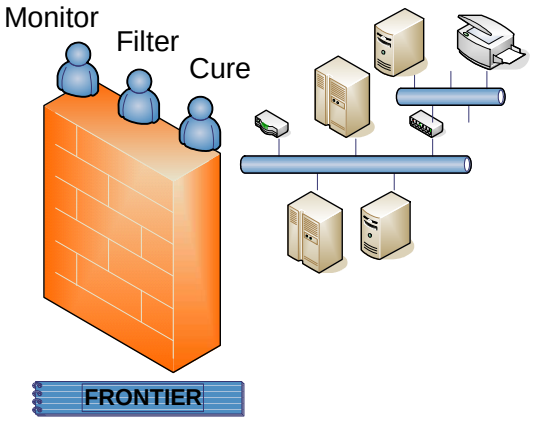

Fig.2 The defense of complex systems organized around three types of agent: monitoring, filtering and curing.

The system is experimented in two phases. During the first phase, the defensive strategy is gradually built in the presence of the monitoring agent whereas this strategy is evaluated in the second phase.

The learning phase and the role of the monitoring agent: During this phase, at each time step, an impact is exerted on the system at time t and, if the system exits its viability domain at time t+1, the couple (I_j, x_j(t)) is memorized in a data base as a bad impact. In the following, any impact will consist in this couple of data. The impacts are memorized with a certain granularity threshold g. Whenever a new impact arrives and makes the system unviable at t+1, this new impact will be memorized only if not similar to an existing impact. The similarity is defined by computing the Euclidean distance with the existing impacts and by checking if the result is inferior to the granularity threshold. Once the system unviable and the impact memorized, the system is reset into its original position and a new impact is tested. The learning terminates as soon as no more deleterious impacts can be memorized.

The evaluation phase and the role of the filtering agent: During this successive phase, every three time steps, an impact is exerted on the system. However, the data base learned previously, composed of the bad impacts, will be the basis of a filtering mechanism. Only if the impact is authorized, it will be allowed to perturb the system. To be authorized, the impact needs to be dissimilar (taking into account the same granularity g) from all impacts included in the learned data base.

In order to compare the self-recognition perspective with the self-assertion one, in a second set of experiments, an impact will now consist in the couple (I_j,$X(t)$). By

X(t), it is intended all the variables and not only the impacted one. It is now the whole state of the system (the eight variables) that is being memorized for each impact. As referred in the previous sections, the alternative vision of the immune system takes the state at the moment of the impact to be as important as the nature of the impact itself. In both cases, following the learning phase, the system is fully safe; none of the authorized impacts can throw the system away from its viability zone. During the evaluation phase, the filtering is playing a perfect role, no false negative occurs. The results are shown in figure 3. In the graph, the number of authorized impacts is shown as a function of the number of impacts memorized in the data base, both for the self-recognition and the self-assertion cases. This data base grows as a function of the granularity. The smaller the granularity, the bigger the number of impacts to be memorized is in order to cover the whole set of possibilities. It resorts clearly that the more precise the learning is (i.e. the smaller the granularity) the more impacts are being authorized.

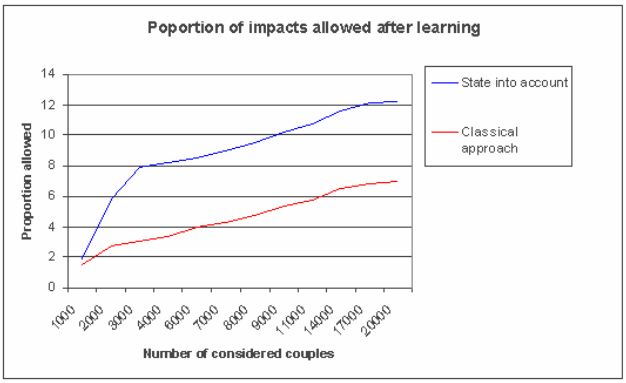

Fig. 3 The proportion of authorized impacts as a function of the number of memorized impacts during the learning phase. This figure compares the self-recognition approach (with no account for the state) and the self-assertion one (where the state is taken into account).

However, the most interesting result lies in the comparison of the two curves. The self-assertion curve remains always above the self-recognition one, meaning that the first strategy avoids many false positive. The explanation is obvious. By ignoring the state, it is enough for one impact to make the system unviable, independently on its current state, to prevent any similar impact. Whereas by adding the state information, only for specific value of the state will a same *Ij* be prevented from entering the system again. It is the simulation replica of the story of the glass of wine. Taking the state into account allows the defensive strategy to be much less conservative, some glasses are allowed others not.

Beyond the avoidance of many false positives, taking the state into account allows some impacts to play an extra curing role. This curing part, once again, takes place in two successive phases: the learning and the evaluation phases.

The learning phase and the role of the monitoring agent: At each time step, the system is set in a random but non-viable state. Thus an impact is exerted on it. If that impact makes the system viable in the next time step, this impact is memorized as a curing impact and the couple $(I_j,X(t))$ is added in the data base. The learning terminates when no more curing impact can be added in the data base.

The evaluation phase and the role of the curing agent: We have supposed a first very intuitive default curing strategy in the case the system exits out of its viability zone. It just consists in inverting the previous impact and impacting the same variable again but now in this "inverse" way. The intuition behind is that in systems not knowing anything about the potential cure coming from the precedent learning phase, there must always exist a "safety procedure" that can take very urgent but not accurate recovery action. However, as the figure 4 shows, this rough recovery strategy works for only 70% of the cases. An additional cure can be tried that consists in searching in the data base an impact which, for such state condition of the system, was able during the learning phase to bring the system back to a viable situation. In the best case, 19000 memorized impacts, the figure shows that an improvement of 13% is possible with respect to the sole "inversion strategy".

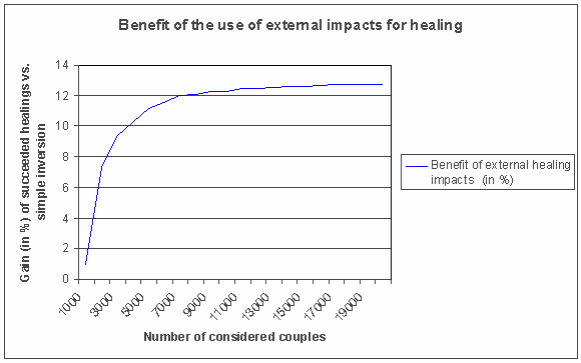

Fig.4 This graph shows the percentage of time that the application of a curing impact, retrieved from the learned date base, can compensate for the failure of the "inversion strategy"

The cure can consist in fact in regulating some internal variables of the system, included the ones not directly impacted. An impact exerted on one connected unit can re-equilibrate the system after the perturbation exerted on another specific unit. The graph also shows that the bigger the data base the more successful is the curing strategy since more and more information is obtained on the curing potentialities.

5 Conclusions and still open perspectives

At one point of the debate referred previously, Ephraim Fuchs, a close colleague of Matzinger, pertinently says: "It is easy to see how the self-nonself distinction was important during an era in which the major challenges to human health were viral and bacterial infections. Now, however, we have to deal with problems like autoimmune disease, cancer, and transplants … It is difficult to see how a self-nonself paradigm would be of much assistance in understanding these phenomena". And Rod Langman, although the most attached at this distinction, surprisingly concludes by: "The organism is a complicated thing with lots of different activities going on inside. We assume that a normal organism is in a state of homeostasis, under the control of many regulators. These regulators have to know when the system is becoming disordered, and these regulators then attempt to restore the old order"

For many years, Varela, Coutinho and Cohen have plead for a radically different understanding of autoimmunity that could give rational to other forms of successful treatment such as the injection of antibody serum (coming from healthy subject [16]) or the T-cell vaccination [9], where the vaccine is composed of a key member of the immune system itself. They expect immunologists to be less obsessed by characterizing what comes from outside the system and how it gets in but instead to have them more concentrated on what happens inside, autonomously. They encourage them to pay more attention on the very sophisticated self-regulation mechanisms which allow such a complicated system, characterized by so many different dynamical actors, to still maintain a viable organization. It appears that while an increasing number of biological disciplines are becoming more and more influenced by the "network or systemic thinking", immunologists are still very reluctant in sympathizing with these views. Nevertheless, this thinking seems inescapable if one wants to tackle with diseases more logically imputable to network deregulation than to the presence of an undesirable foreigner. Beyond the prevention of impacts, how these impacts influence the whole system might be more precious as knowledge to have and to gain that just their intrinsic characteristics.

15 years ago, together with Francisco Varela, we tried in a succession of papers to propose new principles for distributed control of complex processes based on our understanding of the immune functions [2-5]. Nothing has changed from that time expect the sad premature disappearance of the instigator. Among these principles, we proposed to control the process by a set of small operators distributed in time and space and organized into a network structure represented by an affinity matrix. The aim of the controller was to maintain the viability of the process to control. The controller learned to maintain this viability despite perturbations affecting this process. The learning was based on mechanisms of reinforcement type, by modifying some parameters associated with the controller but also by adding some fresh new ones. The homeostatic maintain was the main mission of these controllers and the whole methodology was tested and illustrated in part for robotic and non-linear control toy applications. For process control application, such as the cart-pole, the aim of the control was to keep the pole balancing the longest period of time. In a robot control, the aim of the control was to find viable path preventing the robot to bump obstacles.

In the control of chaotic systems, the aim was to control the chaotic trajectory about fixed points that are embedded in the attractor but are unstable.

Very similar principles could have interesting roles to play in the conception of protective systems for computer while it is again the recognition ability of the immune system which is set to work in order to distinguish bad invading programs from inoffensive ones. Interestingly enough, it seems that computer engineers are encountering exactly the same kind of conceptual difficulties immunologist encounter when trying to separate a priori the good files from the bad files. Roughly said, what is self and nonself for computer systems? It would not be surprising that the computer engineers had to step back a pace and envisage this problem under the new lights presented in this paper. What is safe and non-safe for a computer has to be seen by the computer itself in its current state and in the context of its current operations. It might be possible to first identify a set of characteristic variables of the computer operations which should remain in between decent values, let's say to define what could be the viable operational zone or data for a computer, and thus to teach the computer how to organize its own defense (i.e. which program to tolerate and which to reject) in order to maintain this viability.

More recently, Somayaji and Forrest [11][20] proposed a very exciting work, totally in line with the view we defended for all these years. They design defensive mechanisms in which the computer autonomously monitors its own activities, routinely making small corrections to remain in a viable state. They pertinently write that what they work on supposes a move to recognize that immune systems should be more properly thought of as homeostatic mechanisms than pure defense mechanisms. This time, I can't agree more with them.

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