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► **To cite this version:**

Dominique Pastor, Véronique Thomas-Vaslin. Degeneracy models of receptors in biological immune systems. 8èmes journées “ Complexité-Désordre ”, Université Paris Diderot, Oct 2021, Paris, France. hal-03329345

**HAL Id: hal-03329345**

**<https://imt-atlantique.hal.science/hal-03329345>**

Submitted on 30 Aug 2021

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# Degeneracy models of receptors in biological immune systems

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The immune system (IS) is a complex system of  $10^{12}$  somatically diversified and communicating cells in the human body. Each cell is able to adapt its decision to collectively tolerate or reject the  $10^{13}$  cells of our microbiota and detect other infections among the  $10^{31}$  virus surrounding us, to insure our organism integrity. Harnessing the interactions of the IS with its environment is crucial for the understanding of the organization of the IS during development and its disorganization through aging, and to propose personalized medicine and immunotherapy. The most popular disorders are the overreactions of the IS caused by an exponential augmentation of allergens and chemical antigens leading to allergies and inflammatory diseases, as well as infections such as those provoked by the Covid-19 agent that can destruct the host itself. It is then desirable to propose theoretical frameworks and computational models to develop in-silico biology on which research in biology and immunotherapy can rely. In this respect, we address the notion of “immunoreceptor”, which is central to understand the behaviour and performance of the vertebrate IS. Indeed, each lymphocyte acquires an identity at the somatic level through stochastic processes, by generating new genes encoding a unique type of protein immunoreceptor for antigens. An immunoreceptor is thus specific in that a unique variable sequence of amino acids composes it to achieve interaction, perception and adaptive reaction to the lymphocyte environment. In this sense, an immunoreceptor can be modeled as an adaptive holon capable of self-assertion and integration [1]. Albeit made up of a specific sequence, an immunoreceptor is not adapted to a unique antigen since it can actually react to a wide range of signals emanating from various antigens through “degeneracy”. Degeneracy is introduced by Edelman & Gally [2] as “. . . the ability of elements that are structurally different to perform the same function or yield the same output”. The question is then whether populations of lymphocytes through their repertoire diversity of immunoreceptors (theoretical repertoire diversity estimated to  $10^{61}$ ) could be optimal in some sense compatible with the trade-off these basic receptors achieve.

We address this question by modeling an immunoreceptor as a dynamical system, which can also be regarded as an automaton. Collectively, the membrane receptors on a lymphocyte can integrate successive input signals and discriminate them by exceeding a threshold. Then, if the intracellular transduction of signals is correctly provided the cell can update its functions and change its state. The individual receptor is memoryless in that the new state is computed regardless of the former one. Albeit very simple, this stimulus-response model can however be used, in a first stage, to pinpoint the existence of at least two families of update functions satisfying the Multiplicity Principle (MP). The Multiplicity Principle (MP) is a mathematical formalization of degeneracy [3] and extensively studied in [4]. In brief, the multiplicity of these update functions induces their complementary to achieve a better resilience [5] of the whole system composed by the corresponding dynamical systems.

More specifically, we have Neyman-Pearson (NP) update functions. An NP update function is adjusted to a specific signal and triggers a state change in an optimal way to reveal the presence of this signal. Therefore, NP update functions are good candidates to model receptors of cells from the innate IS. However, an NP update function cannot guarantee optimality when the input signal differs from the model to which it is adapted. On the other hand, a Random Distortion Testing (RDT) [6] update function is optimal to detect that an input signal drifts away by too much from a model to which the update function is attuned. As such, RDT update functions are appropriate to model lymphocyte immunoreceptors to detect input signals in interferences resulting from the disorder due to the multiplicity of antigens in the environment. RDT tests are thus robust to disorder and better candidates than NP update functions to model immunoreceptors of lymphocytes from the adaptive IS.

On-going work involves the design of experiments to assess the relevance of the approach and extending the model to dynamical systems or automata with memory.

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