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The Generic Sensory Automaton (GENSA) for modeling affinity-based dynamics and interactions in biology

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Abstract. Mathematics and computer science play a pivotal role in modern biology. Dynamical models based on differential equations are particularly adapted to describe dynamic behaviors of many biological processes. However, traditional dynamical system theory face limitations to capture nonlinear behaviors of biological systems such as the immune system. Also, dynamical system theory does not always make it possible to model stochastic rare events that biological systems face and process.

To overcome such limitations, we introduce the GENSA (GENeric Sensory Automaton), a new mathematical framework aimed at modeling biological systems, like the immune system, as computational and reactive systems. Unlike conventional approaches that rely on object-based descriptions and differential equations, the GENSA emphasizes the sensory properties of the immune system, framing it as an automaton capable of detecting and responding to environmental changes, so as to maintain or evolve toward homeostasis. As such, the GENSA can function either as a discretized model of differential equations or as an agent, offering a robust alternative to traditional dynamical systems.

The capacity of the GENSA to detect events in its environment and modify its state in response to environmental cues is formalized through mathematical notions of specificity and sensitivity. Two fundamental instances of the GENSA are provided: the Neyman-Pearson GENSA (NP-GENSA) and the Random Distortion Testing GENSA (RDT-GENSA). These two GENSAs embed distinct decision types and satisfy functional redundancy and we say that they are de-generate.

1 Introduction

Mathematics and computer science have become indispensable in biology in many aspects: mathematics models biological processes, from epidemiology to dynamics of ecological systems, typically via differential equations describing population evolutions; mathematical models help also make precise predictions, test hypotheses, and design experiments; computer science provides tools and methods to store, analyze, and interpret biological datasets. Also, mathematics and computer science enable to integrate data across the various scales of biological systems, from molecules to ecosystems, to reveal emergent properties.

Conversely, mathematicians and computer scientists have much to learn from biology, by integrating key features of biological systems in their theoretical frameworks. In this regard, the immune system (IS) is particularly appealing because it is "*a complex adaptive system whose richness makes it an excellent model for nonlinear dynamics and biological complexity*" [1]. As emphasized in [2, 3] among many others, the IS is a cellular system with a time-dependent "*[. . .] dynamic evolution in terms of structure and biological causality*" [4]. Thence the huge literature, among which [1, 5–10], proposing systems of (ordinary, partial, or even stochastic) differential equations to capture the IS dynamic behavior.

Although the theory of dynamical systems has proved its relevance in various aspects to model the IS [9], it suffers however from some limitations and drawbacks [11–15]. At this stage, we retain the following two limitations: 1) Dynamical systems do not easily capture nonlinear behaviors of living systems such as the IS; 2) Dynamical systems may overlook stochastic rare events that can play an important tole in the time evolution of the system. We argue that these limitations are possibly due to the fact that most current dynamical models do not take into account that, as emphasized in [2, 3, 6, 16–23] among many others, a biological system as the IS actively detects and responds to environmental cues "*[. . .] composed of inputs coming from different sensory channels*" [16]. It can thus adapt constantly its state to a changing environment, so as to maintain or evolve to homeostasis, and protect the organism [24–27]. We thus agree with [19] and [3] that "*[. . .] change-detection may also be a basic organizing princi-*

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ple underlying the workings of the immune system" [3]. Therefore, as these authors, our approach aims to capture the capacity of the IS and, more generally, living systems, to modify their state in function of changes they detect in their environment. However, in contrast to Pradeu and co-authors, we do not encapsulate this feature in an ODE system, but embed it instead in an automaton called GENSA, for GENeric Sensory Automaton. In this respect, we align with Efroni and Cohen in that, "*[. . .] if we define computation as the ordered transformation of input into output, we can perceive the immune system to be a computational, living reactive system; the system gathers input about the state of the body, locally, and generally, and reacts to arrange an output of appropriate inflammatory procedures that feedback on the body to maintain, heal, regenerate and protect it*" [28]. The GENSA is thus a formal model capturing the sensor-actuator behavior of living systems. In this respect, it is proposed here in parallel and consistency with the biological framework (GenSA) discussed in our companion paper [29].

The GENSA is generic because of the huge number of its possible instances. It is said to be sensory because, as mentioned above and in contrast with traditional approaches in systems biology and omics that have predominantly concentrated on object-based descriptions — molecular entities, cellular components, interactions — analyzed through descriptive statistics, the GENSA aims to model the sensory properties of the immune system. In addition, as an automaton, the GENSA is expected to serve either as a discretized model of differential equations or as an agent. This versatility is of interest since agent-based modeling is an alternative to overcome limitations of dynamical systems-based approaches [9, 30, 31].

The GENSA approach is introduced in the next section. We begin with a rationale to put in place all the theoretical constituents. We formalize the outcome of this rationale in Definition 2.6 of Section 2.3. In Section 3, we randomize the GENSA to model its decision-making formalized via Definitions 3.2 and 3.4. These definitions incorporate mathematical notions of specificity and sensitivity, in the vein of [32], as counterparts of the biological notions of specificity and sensitivity. In Section 4, we present two fundamental GENSAs, namely, the Neyman-Pearson GENSA (NP-GENSA) and the Random Distortion Testing GENSA (RDT-GENSA). These GENSAs embed two different types of decision. They satisfy functional redundancy (de-generacy) in a sense we formalize. We conclude this work in Section 5 by itemizing prospects of this research.

2 The GENSA

We begin by recalling the definition of an automaton (a dynamical system in discrete time) before presenting our rationale leading to the definition of the GENSA.

2.1 Automata

As recalled above, an automaton is a dynamical system in discrete time. In this respect, we recall that the state of a dynamical system is an n-tuple whose components are called the **state variables**. These state variables are the physical quantities required to fully describe the system at a given time and predict its future evolution by applying the rules governing the system. These state variables can be, for instance and among others, the position, the velocity, the temperature of the system, or concentrations of different components of the system. The **state space** or **phase space** is the set of all possible values that the state variables can take. Each single point of this set represents a possible state of the system. The state space is often a vector space; hence the name. In the general theory of dynamical systems, the *temporal evolution* of a dynamical system is ruled by differential equations; for an automaton, the discrete-time transition rule is provided by the update function f^{updt}.

Definition 2.1 (Automaton)**.** *Given two sets $\mathcal{X}^{in}$ and $\mathcal{X}^{out}$, a triple $\mathbf{S} = (\mathcal{S}, f^{updt}, f^{rdout})$ is called an automaton with input (resp. output) signals in $\mathcal{X}^{in}$ (resp. $\mathcal{X}^{out}$) if :*

(i) *$\mathcal{S}$ is a set called the state space of $\mathcal{X}$;*

(ii) *$f^{updt} : \mathcal{X}^{in} \times \mathcal{S} \to \mathcal{S}$ is a function called the update function of $\mathcal{X}$;*

(iii) *$f^{rdout} : \mathcal{S} \to \mathcal{X}^{out}$ is a function called the readout function of $\mathcal{X}$.*

For completeness, Figure 1 summarizes the functioning of an automaton in time, which is useful for an implementation on a computer. Throughout the rest of the paper, the time dependence plays no role and will be omitted to alleviate notation.

2.2 Rationale

Let us consider two automata $\mathbf{S}$ and $\mathbf{S}^{\text{ext}}$: in a biological context, $\mathbf{S}$ models a biological dynamic system such as the immune system and $\mathbf{S}^{\text{ext}}$ models the external environment of $\mathbf{S}$. The state space of $\mathbf{S}$ will be denoted by $\mathcal{S}$ and the state space of $\mathbf{S}^{\text{ext}}$ by $\mathcal{S}^{\text{ext}}$. In what follows, we focus on how the state of $\mathbf{S}$ evolves in function of the state of its environment. This is the reason why the state space $\mathcal{S}^{\text{ext}}$ of $\mathbf{S}^{\text{ext}}$ plays a key role below. On the other hand, we do not address the impact on $\mathbf{S}^{\text{ext}}$ of a change of state of $\mathbf{S}$ and we do not model $\mathbf{S}^{\text{ext}}$.

We hereafter assume that $\mathcal{S}^{\text{ext}}$ is a vector space. In the same way, the observation space $\mathcal{X}^{\text{obs}}$ and the noise space $\mathcal{N}^{\text{int}}$ introduced in the next paragraph will be assumed to be topological vector spaces. The reader will notice that these assumptions are absolutely not needed to state the definitions introduced in this rationale. In Definition 2.4, the zero vector of $\mathcal{N}^{\text{int}}$ does intervene, indeed, not to perform any computation, but rather to formalize the idea that noise can be null and, a bit further, to address the case of a negligible noise. These assumptions are kept in Definition 2.6 and could thus be relaxed. However, in practice, if only to introduce the NP-GENSA and the RDT-GENSA in Section 4, it is rather convenient to suppose that $\mathcal{S}$ and $\mathcal{S}^{\text{ext}}$ are vector spaces, and even that $\mathcal{X}^{\text{obs}}$ and $\mathcal{N}^{\text{int}}$ are topological vector spaces.

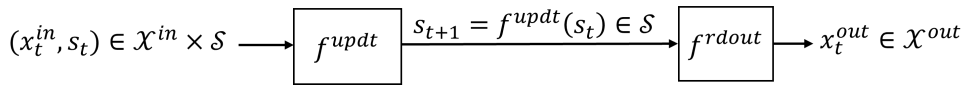

Figure 1. The evolution in time of an automaton $\mathbf{S} = (\mathcal{S}, f^{\text{updt}}, f^{\text{rdout}})$ is iterative. Specifically, at time t, consider the triple $(x_t^{\text{in}}, s_t, x_t^{\text{out}})$. At time t, the input signal is x_t^{in} and the current state of $\mathbf{S}$ is s_t. The updated state of $\mathbf{S}$ is $s_{t+1} = f^{\text{updt}}(x_t^{\text{in}}, s_t)$ and will be the state of $\mathbf{S}$ at time $t+1$. The signal output by $\mathbf{S}$ is calculated as $x_t^{\text{out}} = f^{\text{rdout}}(s_{t+1})$. At time $t+1$, we have a new input signal x_{t+1}^{in} and the current state of $\mathbf{S}$ is now s_{t+1}. We update the state of $\mathbf{S}$ iteratively by calculating $s_{t+2} = f^{\text{updt}}(x_{t+1}^{\text{in}}, x_{t+1}^{\text{in}})$ and the automaton outputs now $x_{t+1}^{\text{out}} = f^{\text{rdout}}(s_{t+2})$.

Observation function. Suppose that $\mathbf{S}$ performs a measurement or **observation** of $s^{\text{ext}} \in \mathcal{S}^{\text{ext}}$. The issue is that $\mathbf{S}$ cannot perfectly observe s^{ext} for two reasons: first, the observation cannot generally be achieved without modifying — we prefer to say "distorting" — s^{ext} and second, without introducing some noise. We say that this noise is internal to $\mathbf{S}$ in the sense that it is generated by $\mathbf{S}$, not by $\mathbf{S}^{\text{ext}}$. The observation is thus a distorted and noisy version of s^{ext}. Let $\mathcal{N}^{\text{int}}$ stand for the set of all possible values for the noise. As pinpointed above, we assume that $\mathcal{N}^{\text{int}}$ is a topological vector space. We call it the **noise space**.

The observation of s^{ext} by $\mathbf{S}$ is modeled as the outcome of a function

$$\text{obs} : \mathcal{S}^{\text{ext}} \times \mathcal{N}^{\text{int}} \to \mathcal{X}^{\text{obs}}$$

valued in a topological vector space $\mathcal{X}^{\text{obs}}$ called the **observation space**. We assume that obs is such that:

$$\forall\, (s^{\text{ext}}, x^{\text{obs}}) \in \mathcal{S}^{\text{ext}} \times \mathcal{X}^{\text{obs}}, \exists\, n^{\text{int}} \in \mathcal{N}^{\text{int}}, x^{\text{obs}} = \text{obs}(s^{\text{ext}}, n^{\text{int}})\,. \tag{1}$$

In other words, given $s^{\text{ext}} \in \mathcal{S}^{\text{ext}}$, the function

$$\begin{array}{rccc} \text{obs}(s^{\text{ext}}, \bullet): & \mathcal{N}^{\text{int}} & \to & \mathcal{X}^{\text{obs}} \\ & n^{\text{int}} & \mapsto & \text{obs}(s^{\text{ext}}, n^{\text{int}}) \end{array}$$

is surjective. We will say that $\text{obs} : \mathcal{S}^{\text{ext}} \times \mathcal{N}^{\text{int}} \to \mathcal{X}^{\text{obs}}$ is the **observation function** and that x^{obs} is the **observation** made by $\mathbf{S}$ of s^{ext} in presence of noise n^{int}. As already noticed above, this observation of s^{ext} achieved by obs is intrinsically distorted and noisy. A case of a null distortion occurs when $\mathcal{S}^{\text{ext}} = \mathcal{N}^{\text{int}} = \mathcal{X}^{\text{obs}}$ is a vector space and $\text{obs} : \mathcal{X}^{\text{obs}} \times \mathcal{X}^{\text{obs}} \to \mathcal{X}^{\text{obs}}$ is the sum of two vectors of $\mathcal{S}$. In this case, there will be no distortion on s^{ext}, but the observation will remain noisy with $x^{\text{obs}} = s^{\text{ext}} + n^{\text{int}}$.

Dissimilarity functions. With the idea that the state of $\mathbf{S}$ should evolve in function of that of $\mathbf{S}^{\text{ext}}$, we argue that, in a sense to define, the more similar s and s^{ext}, the closer the next state of $\mathbf{S}$ should be to s; conversely, the more dissimilar s^{ext} and s, the more the next state of $\mathbf{S}$ should drift from s. To formalize this heuristic, we could think of introducing a similarity function. We find it more convenient to use the dual notion of dissimilarity function.

Definition 2.2. *A **dissimilarity function** is any function*

$$\delta : \mathcal{S} \times \mathcal{S}^{ext} \to \mathbb{R}\,.$$

Given $(s, s^{ext}) \in \mathcal{S} \times \mathcal{S}^{ext}$, we will say that the smaller (resp. the larger) $\delta(s, s^{ext})$, the more similar (resp. dissimilar) s and s^{ext}.

For instance, if $\mathcal{S} = \mathcal{S}^{\text{ext}}$ is a real vector space with finite dimension, we easily construct an internal dissimilarity function valued in $[0, \infty[$ by considering any norm N over $\mathcal{S}$ and set $\delta(s, s') = \text{N}(s - s')$ for any $(s, s') \in \mathcal{S} \times \mathcal{S}$. We use the term of dissimilarity because this terminology is usual in pattern recognition and signal processing. However, a dissimilarity function δ can be regarded as a comparison function: it compares s and s^{ext} and the larger $\delta(s, s^{\text{ext}})$, the more s and s^{ext} are reckoned to be different.

The issue with the dissimilarity function, as defined in Definition 2.2, is that it involves $s^{\text{ext}} \in \mathcal{S}^{\text{ext}}$. Basically, s^{ext} is unknown to $\mathbf{S}$; otherwise, there would not be any real issue at stake. Therefore, $\mathbf{S}$ cannot but have a partial knowledge of s^{ext}, via x^{obs} provided by the observation function defined above. Since x^{obs} is the sole means for $\mathbf{S}$ to extract knowledge about s^{ext}, we introduce the notion of observed dissimilarity that makes it possible to construct a dissimilarity function based on x^{obs} only.

Definition 2.3. *An **observed dissimilarity function** is any function:*

$$\delta^{obs} : \mathcal{S} \times \mathcal{X}^{obs} \to \mathbb{R}\,.$$

*Given $(s, x^{obs}) \in \mathcal{S} \times \mathcal{X}^{obs}$, $\delta^{obs}(s, x^{obs})$ is called the **observed dissimilarity** between s and x^{obs} and we say that the smaller (resp. the larger) $\delta^{obs}(s, x^{obs})$, the more similar (resp. dissimilar) s and x^{obs}.*

Given an observed dissimilarity function δ^{obs}, we can define a dissimilarity function in the sense of Definition 2.2 by introducing the following definition.

Definition 2.4. *The estimate $\widehat{s^{ext}} \in \mathcal{S}$ of $s^{ext} \in \mathcal{S}^{ext}$ via the observation obs is defined as*

$$\widehat{s^{ext}} = obs(s^{ext}, 0)\,. \tag{2}$$

We can regard $\widehat{s_t^{\text{ext}}} \in \mathcal{X}^{\text{obs}}$ as the **image S** would have of s^{ext} in absence of noise and thus, as an **estimate** of s^{ext}. The observed dissimilarity function is sufficient to construct the following dissimilarity function.

$$\begin{array}{rccc} \delta: & \mathcal{S} \times \mathcal{S}^{\text{ext}} & \to & \mathbb{R} \\ & (s, s^{\text{ext}}) & \mapsto & \delta^{\text{obs}}(s, \text{obs}(s^{\text{ext}}, 0))\,. \end{array} \tag{3}$$

Given an observed dissimilarity function δ^{obs}, as in Definition 2.3, and the dissimilarity function δ of (3) deriving from δ^{obs}, the definition of δ^{obs} induces that:

$$\delta(s, s^{\text{ext}}) = \delta^{\text{obs}}(s, \text{obs}(s^{\text{ext}}, 0)) = \delta^{\text{obs}}(s, \widehat{s^{\text{ext}}})\,. \tag{4}$$

The dissimilarity $\delta(s, s^{\text{ext}})$ between s and s^{ext} is thus the observed dissimilarity between s and the image $\widehat{s^{\text{ext}}}$ that **S** has of s^{ext}.

Activation function and decision. With the same notation as above, if obs and δ^{obs} are continuous with their second argument and $n^{\text{int}} \approx 0$, then

$$x^{\text{obs}} = \text{obs}(s^{\text{ext}}, n^{\text{int}}) \approx \widehat{s^{\text{ext}}}$$

and

$$\delta^{\text{obs}}(s, x^{\text{obs}}) \approx \delta^{\text{obs}}(s, \widehat{s^{\text{ext}}}) .$$

Therefore, $\delta^{\text{obs}}(s, x^{\text{obs}}) \approx \delta(s, s^{\text{ext}})$ and $\delta^{\text{obs}}(s, x^{\text{obs}})$ can thus be regarded as an estimate of $\delta(s, s^{\text{ext}})$. The observed dissimilarity $\delta^{\text{obs}}(s, x^{\text{obs}})$ is a reasonable estimate of $\delta(s, s^{\text{ext}})$ when noise is negligible. However, in general, n^{int} is not necessarily small and approximating $\delta(s, s^{\text{ext}})$ by $\delta^{\text{obs}}(s, x^{\text{obs}})$ can be erroneous. Therefore, we argue that **S** makes a **decision** on whether $\delta(s, s^{\text{ext}})$ is small (strong similarity between s and s^{ext}) or large (weak similarity between s and s^{ext}), given the observed dissimilarity $\delta^{\text{obs}}(s, x^{\text{obs}})$. In this respect, $\delta^{\text{obs}}(s, x^{\text{obs}})$ plays the role of a statistic to make the decision, as in mathematical inference.

Reformulating the foregoing by using δ^{obs} only, the principle retained for the GENSA is that **S** makes a **decision** on whether $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}})$ is small (strong similarity between s and $\widehat{s^{\text{ext}}}$) or large (weak similarity between s and $\widehat{s^{\text{ext}}}$), given the observed dissimilarity $\delta^{\text{obs}}(s, x^{\text{obs}})$.

To make **S** decide on whether $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}})$ is small or large, given the observed dissimilarity $\delta^{\text{obs}}(s, x^{\text{obs}})$, we introduce the notion of activation function.

Definition 2.5. *An **activation function** is any continuous increasing function*

$$act : \mathbb{R} \to [0, 1] .$$

Given an observed dissimilarity function δ^{obs}, $(s, x^{\text{obs}}) \in \mathcal{S} \times \mathcal{X}^{\text{obs}}$, and $s^{\text{ext}} \in \mathcal{S}^{\text{ext}}$, $\text{act}(\delta^{\text{obs}}(s, x^{\text{obs}}))$ is regarded as the decision made by **S** on $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}})$: the closer $\text{act}(\delta^{\text{obs}}(s, x^{\text{obs}}))$ to 1 (resp. 0), the stronger (resp. the weaker) the decision that $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}})$ is likely to be large (resp. small). In case of activation functions valued in $\{0, 1\}$, instead of the whole unit interval, the decision made by **S** by the activation function act is binary.

The increase of the activation function is justified as follows. Suppose that obs and δ^{obs} are continuous with their second argument. When $n^{\text{int}} \approx 0$, we have $x^{\text{obs}} \approx \widehat{s^{\text{ext}}}$ and $\delta^{\text{obs}}(s, x^{\text{obs}}) \approx \delta(s, s^{\text{ext}})$. Next, by continuity of the activation function, $\text{act}(\delta^{\text{obs}}(s, x^{\text{obs}})) \approx \text{act}(\delta(s, s^{\text{ext}}))$. In this case, the larger (resp. the smaller) $\delta(s, s^{\text{ext}})$, the closer $\text{act}(\delta(s, x^{\text{obs}}))$ should be to 1 (resp. 0). Increase of act is a sufficient condition for this function to satisfy this property. Whence our assumption.

Affinity function. In chemistry, affinity is "*the attractive force binding atoms in molecules*"; in immunology, affinity is *the attraction or the stereochemical compatibility between an antibody and an antigen* (see https://www.biologyonline.com/dictionary/affinity). The concept of affinity pervades biology because "*Life is based on specific interactions between biomolecules. The underlying affinities form the basis for molecular recognition events that make up the complex machinery of all living organisms, including man*" [33]. To model the notion of affinity and its role in biology as a means for biological systems to make decisions, we define the affinity function as:

$$\begin{array}{rccl} \text{aff} = 1 - \text{act} \circ \delta^{\text{obs}} : & \mathcal{S} \times \mathcal{X}^{\text{obs}} & \to & [0, 1] \\ & (s, x^{\text{obs}}) & \mapsto & 1 - \text{act}(\delta^{\text{obs}}(s, x^{\text{obs}})) . \end{array}$$

The activation function act increases. Therefore, if we interpret a small dissimilarity as a strong similarity then, for any pair $(s, x^{\text{obs}}) \in \mathcal{S} \times \mathcal{X}^{\text{obs}}$, the larger (resp. the smaller) the similarity between s and x^{obs}, the larger (resp. the smaller) the affinity $\text{aff}(s, x^{\text{obs}})$ between s and x^{obs}.

Updating. The available data to update the state of **S** in function of the outcome of the activation function, seen as the decision made by the automaton about the dissimilarity between s and s^{ext} is thus: the current state s of **S**, the observation $x^{\text{obs}} = \text{obs}(s^{\text{ext}}, n^{\text{int}})$ and $\text{act}(\delta^{\text{obs}}(s, x^{\text{obs}}))$. The update of s is thus a function f^{updt} of s, s^{ext} and n^{int} that we factorize via a function

$$\varphi^{\text{updt}} : \mathcal{S} \times [0, 1] \to \mathcal{S}$$

so that

$$f^{\text{updt}}(x^{\text{in}}, s) = \varphi^{\text{updt}}\left(s, \text{act}(\delta^{\text{obs}}(s, x^{\text{obs}}))\right)$$

with $x^{\text{in}} = (s^{\text{ext}}, n^{\text{int}}) \in \mathcal{S}^{\text{ext}} \times \mathcal{N}^{\text{int}}$ and $x^{\text{obs}} = \text{obs}(s^{\text{ext}}, n^{\text{int}})$. By so proceeding, we put to the fore the role played by the decision to achieve a trade-off between the current state of **S** and the observation captured by **S**. In addition, φ^{updt} relies on the sole available data to the GENSA, namely, s and x^{obs} via $\text{act}(\delta^{\text{obs}}(s, x^{\text{obs}}))$.

Readout. At this stage, we do not propose any kind of readout function. It is when we de-generate the GENSA to exhibit the NP-GENSA and the RDT-GENSA below that we will propound and justify readout functions.

2.3 Definition of the GENSA as an automaton

The following definition formalizes the above rationale. In this definition, we retrieve all the elements and their role introduced and discussed so far. Throughout the paper, given a function g with domain E, $g(E)$ will designate the image of E by g, that is, the set of all values $g(x)$ for all $x \in E$.

Definition 2.6. *(GENSA) Given vector spaces $\mathcal{S}^{ext}$ and $\mathcal{X}^{out}$, and topological vector spaces $\mathcal{N}^{int}$ and $\mathcal{X}^{obs}$, a* 10*-uple*

$$\mathbf{G} = (\mathcal{S}^{ext}, \mathcal{N}^{int}, \mathcal{X}^{obs}, \mathcal{S}, \mathcal{X}^{out}, obs, \delta^{obs}, act, \varphi^{updt}, f^{rdout})$$

is called a GENSA with external state space S^{ext}, internal noise space $\mathcal{N}^{int}$, observation space $\mathcal{X}^{obs}$, state space $\mathcal{S}$,

and output space $\mathcal{X}^{out}$, if:

(i) *$obs : \mathcal{S}^{ext} \times \mathcal{N}^{int} \to \mathcal{X}^{obs}$ is a function, called the observation function of* **G***, continuous with its second argument, and such that $obs(s^{ext}, \bullet)$ is surjective for all $s^{ext} \in \mathcal{S}^{ext}$;*

(ii) *$\delta^{obs} : \mathcal{S} \times \mathcal{X}^{obs} \to \mathbb{R}$ is a function, continuous with its second argument and called the observed dissimilarity function of* **G***;*

(iii) *$act : \delta^{obs}(\mathcal{S} \times \mathcal{X}^{obs}) \to [0, 1]$ is a continuous and increasing function, called the activation function of* **G***;*

(iv) *$\varphi^{updt} : \mathcal{S} \times [0, 1] \to \mathcal{S}$ is a function, called the elementary update function of* **G***;*

(v) *$f^{rdout} : \mathcal{S} \to \mathcal{X}^{out}$ is a function, called the readout function of* **G***;*

(vi) *$(\mathcal{S}, f^{updt}, f^{rdout})$ is an automaton with input signals x^{in} in $\mathcal{X}^{in} = \mathcal{S}^{ext} \times \mathcal{N}^{int}$, output signals in $\mathcal{X}^{out}$, and update function $f^{updt} : \mathcal{X}^{in} \times \mathcal{S} \to \mathcal{S}$ defined by*

$$\forall (x^{in}, s) \in \mathcal{X}^{in} \times \mathcal{S}, f^{updt}(x^{in}, s) = \varphi^{updt}\Big(s, act\left(\delta^{obs}(s, x^{obs})\right)\Big) \tag{5}$$

with $x^{obs} = obs(x^{in})$ and where $act\left(\delta^{obs}(s, x^{obs})\right)$ is called the decision of **G** *given (s, x^{obs}).*

In what follows, when no confusion is possible, we will alleviate the notation of **G** *by designating it as the quintuple*

$$\mathbf{G} = (obs, \delta^{obs}, act, \varphi^{updt}, f^{rdout})$$

of functions specifying the GENSA discrete-time transition rules. Also, we will simply call δ^{obs} a dissimilarity function, dropping the adjective "observed".

3 Randomization and the detection problem

3.1 Motivation

According to Definition 2.6, there exist infinitely many possible observation, similarity and activation functions, and thus a huge amount of parameters to specify a GENSA. Without further refinement of the model, deployment of the GENSA, by fitting omics data to retrieve population dynamics for instance, could raise parameterization issues with significant impact on the accuracy, reliability, and even the plausibility of the resulting model. The GENSA model above is not operational yet and we must identify, among the countless possible GENSAs, those actually suitable for representing dynamic biological systems.

To refine the GENSA model, we hereafter formalize the decision-making achieved by the GENSA. According to our heuristic of Section 2.2, $act\left(\delta^{\text{obs}}(s, x^{\text{obs}})\right)$ is the decision made by the GENSA on whether $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}})$ is large or not, given the observed dissimilarity $\delta^{\text{obs}}(s, x^{\text{obs}})$. To proceed theoretically, we fix some $\tau \in [0, \infty[$ and we say that $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}})$ is large if $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}}) > \tau$, and that $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}})$ is small if $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}}) \leqslant \tau$.

On the other hand, we also enhanced that, in the GENSA model, $\delta^{\text{obs}}(s, x^{\text{obs}})$ plays the role of a statistic as in mathematical statistics. Therefore, to refine the GENSA, we introduce randomness in our framework to actually formalize the activation function as a statistical decision, and $\delta^{\text{obs}}(s, x^{\text{obs}})$ as a statistic to achieve this decision. The introduction of randomness in our framework echoes with the crucial role played by stochasticity in biology [34, 35]. For example, the ability of the immune system to stochastically generate somatic receptors enables it to create diverse receptors, allowing it to explore a broad range of antigens, which is key to respond to unexpected threats [36, 37].

3.2 Randomization of the GENSA

We introduce randomness in our framework by randomizing the inputs, namely, with the notation of Definition 2.6, the environment state s^{ext} and the noise n^{int}.

First, we assume the existence of a set Ω^{ext} of all possible events occurring in the environment of $\mathbf{S}^{\text{ext}}$. We assume that we can equip Ω^{ext} with a σ-algebra $\Sigma_{\Omega^{\text{ext}}}$ and the resulting measurable space $(\Omega^{\text{ext}}, \Sigma_{\Omega^{\text{ext}}})$, with a probability measure $\mathbb{P}^{\text{ext}}$ to construct the probability space $(\Omega^{\text{ext}}, \Sigma_{\Omega^{\text{ext}}}, \mathbb{P}^{\text{ext}})$. Similarly, we introduce the set Ω^{int} of all events that can yield noise. We suppose that this set can be endowed with a σ-algebra for which exists a probability measure $\mathbb{P}^{\text{int}}$ so that we can construct the probability space $(\Omega^{\text{int}}, \Sigma_{\Omega^{\text{int}}}, \mathbb{P}^{\text{int}})$.

The product space $\Omega = \Omega^{\text{ext}} \times \Omega^{\text{int}}$ can be equipped with the σ-algebra $\Sigma_\Omega = \Sigma_{\Omega^{\text{ext}}} \otimes \Sigma_{\Omega^{\text{int}}}$ and we can define the probability measure $\mathbb{P} = \mathbb{P}^{\text{ext}} \otimes \mathbb{P}^{\text{int}}$ to obtain the probability space

$$(\Omega, \Sigma_\Omega, \mathbb{P}) = (\Omega^{\text{ext}} \times \Omega^{\text{int}}, \Sigma_{\Omega^{\text{ext}}} \otimes \Sigma_{\Omega^{\text{int}}}, \mathbb{P}^{\text{ext}} \otimes \mathbb{P}^{\text{int}}) .$$

On the other side, we assume that $\mathcal{S}^{\text{ext}}$ can be endowed with a σ-algebra $\Sigma_{\mathcal{S}^{\text{ext}}}$ to obtain the measurable space $(\mathcal{S}^{\text{ext}}, \Sigma_{\mathcal{S}^{\text{ext}}})$. Similarly, we equip $\mathcal{N}^{\text{int}}$ with a σ-algebra to obtain a measurable space $(\mathcal{N}^{\text{int}}, \Sigma_{\mathcal{N}^{\text{int}}})$. Since $\mathcal{N}^{\text{int}}$ is assumed to be a topological vector space, we can always take $\Sigma_{\mathcal{N}^{\text{int}}}$ as the Borel σ-algebra of all open sets of $\mathcal{N}^{\text{int}}$. We then define the measurable product space $(\mathcal{S}^{\text{ext}} \times \mathcal{N}^{\text{int}}, \Sigma_{\mathcal{S}^{\text{ext}}} \otimes \Sigma_{\mathcal{N}^{\text{int}}})$.

Let us suppose the existence of a measurable function

$$S^{\text{ext}} : (\Omega^{\text{ext}}, \Sigma_{\Omega^{\text{ext}}}) \to (\mathcal{S}^{\text{ext}}, \Sigma_{\mathcal{S}^{\text{ext}}}) \tag{6}$$

such that, for any $s^{\text{ext}} \in \mathcal{S}^{\text{ext}}$, there exists $\omega^{\text{ext}} \in \Omega^{\text{ext}}$ such that $s^{\text{ext}} = S^{\text{ext}}(\omega^{\text{ext}})$. Similarly, we also assume the existence of

$$N^{\text{int}} : (\Omega^{\text{int}}, \Sigma_{\Omega^{\text{int}}}) \to (\mathcal{N}^{\text{int}}, \Sigma_{\mathcal{N}^{\text{int}}}) \tag{7}$$

such that, for any $n^{\text{int}} \in \mathcal{N}^{\text{int}}$, there exists $\omega^{\text{int}} \in \Omega^{\text{int}}$ such that $n^{\text{int}} = N^{\text{int}}(\omega^{\text{int}})$. With the help of the projections

$$\begin{cases} \pi^{\text{ext}} : & \Omega^{\text{ext}} \times \Omega^{\text{int}} & \to & \Omega^{\text{ext}} \\ & (\omega^{\text{ext}}, \omega^{\text{int}}) & \mapsto & \omega^{\text{ext}} \\ \pi^{\text{int}} : & \Omega^{\text{ext}} \times \Omega^{\text{int}} & \to & \Omega^{\text{int}} \\ & (\omega^{\text{ext}}, \omega^{\text{int}}) & \mapsto & \omega^{\text{int}} \end{cases} \tag{8}$$

we can define the measurable function

$$\begin{array}{rcl}(S^{\text{ext}} \circ \pi^{\text{ext}}, N^{\text{int}} \circ \pi^{\text{int}}) : & & \\ (\Omega^{\text{ext}} \times \Omega^{\text{int}}, \Sigma_{\Omega^{\text{ext}}} \otimes \Sigma_{\Omega^{\text{int}}}) & \to & (\mathcal{S}^{\text{ext}} \times \mathcal{N}^{\text{int}}, \Sigma_{\mathcal{S}^{\text{ext}}} \otimes \Sigma_{\mathcal{N}^{\text{int}}}) \\ (\omega^{\text{ext}}, \omega^{\text{int}}) & \mapsto & \left(S^{\text{ext}}(\omega^{\text{ext}}), N^{\text{int}}(\omega^{\text{int}})\right) .\end{array}$$

The two random vectors $S^{\text{ext}} \circ \pi^{\text{ext}}$ and $N^{\text{int}} \circ \pi^{\text{int}}$ are independent. Therefore, in what follows, we directly assume the existence of a probability space $(\Omega, \Sigma_\Omega, \mathbb{P})$ and that of two measurable functions $S^{\text{ext}} : (\Omega, \Sigma_\Omega) \to (\mathcal{S}^{\text{ext}}, \Sigma_{\mathcal{S}^{\text{ext}}})$ and $N^{\text{int}} : (\Omega, \Sigma_\Omega) \to (\mathcal{N}^{\text{int}}, \Sigma_{\mathcal{N}^{\text{int}}})$ that are independent. Thence the following definition.

Definition 3.1. [Randomization of GENSAs] *Given a probability space $(\Omega, \Sigma_\Omega, \mathbb{P})$, a $(\Omega, \Sigma_\Omega, \mathbb{P})$-randomization of all GENSAs with same external state space $\mathcal{S}^{ext}$ and same internal noise set $\mathcal{N}^{int}$, is the data of*

- *a measurable space $\overline{\mathcal{S}^{ext}} = (\mathcal{S}^{ext}, \Sigma_{\mathcal{S}^{ext}})$,*
- *a measurable space $\overline{\mathcal{N}^{int}} = (\mathcal{N}^{int}, \Sigma_{\mathcal{N}^{int}})$,*
- *a pair*

$$\left(S^{ext} : \overline{\Omega} \to \overline{\mathcal{S}^{ext}}, N^{int} : \overline{\Omega} \to \overline{\mathcal{N}^{int}}\right)$$

of independent measurable functions, with $\overline{\Omega} = (\Omega, \Sigma_\Omega)$.

Such a $(\Omega, \Sigma_\Omega, \mathbb{P})$-randomization will be denoted $\left(S^{ext} : \overline{\Omega} \to \overline{\mathcal{S}^{ext}}, N^{int} : \overline{\Omega} \to \overline{\mathcal{N}^{int}}\right)$. The set of $(\Omega, \Sigma_\Omega, \mathbb{P})$-randomizations of GENSAs with external state space $\mathcal{S}^{ext}$ and internal noise set $\mathcal{N}^{int}$ will be denoted as $(\overline{\mathcal{S}^{ext}}, \overline{\mathcal{N}^{int}})_{(\Omega, \Sigma_\Omega, \mathbb{P})}$, so that

$$(\overline{\mathcal{S}^{ext}}, \overline{\mathcal{N}^{int}})_{(\Omega, \Sigma_\Omega, \mathbb{P})} = \left\{ (S^{ext}, N^{int}) \,\middle|\, \begin{cases} S^{ext} : \overline{\Omega} \to \overline{\mathcal{S}^{ext}}, N^{int} : \overline{\Omega} \to \overline{\mathcal{N}^{int}}, \\ S^{ext} \text{ and } N^{int} \text{ independent} \end{cases} \right\}.$$

Given a GENSA

$$\mathbf{G} = (\mathcal{S}^{\text{ext}}, \mathcal{N}^{\text{int}}, \mathcal{X}^{\text{obs}}, \mathcal{S}, \mathcal{X}^{\text{out}}, \text{obs}, \delta^{\text{obs}}, \text{act}, \varphi^{\text{updt}}, f^{\text{rdout}})$$

and a randomization $\left(S^{\text{ext}} : \overline{\Omega} \to \overline{\mathcal{S}^{\text{ext}}}, N^{\text{int}} : \overline{\Omega} \to \overline{\mathcal{N}^{\text{int}}}\right)$ applied to $\mathbf{G}$, we can always endow $\mathcal{X}^{\text{obs}}$ with a σ-algebra $\Sigma_{\mathcal{X}^{\text{obs}}}$ and thus construct the measurable space $\overline{\mathcal{X}^{\text{obs}}} = (\mathcal{X}^{\text{obs}}, \Sigma_{\mathcal{X}^{\text{obs}}})$. For instance, since $\mathcal{X}^{\text{obs}}$ is supposed to be a topological vector space as $\mathcal{N}^{\text{int}}$, $\Sigma_{\mathcal{X}^{\text{obs}}}$ can be chosen as the Borel σ-algebra generated by the open sets of $\mathcal{X}^{\text{obs}}$. We can then define the **randomized observation**

$$\begin{array}{rcl}X^{\text{obs}} = \text{obs}(S^{\text{ext}}, N^{\text{int}}) : & \overline{\Omega} & \to & \overline{\mathcal{X}^{\text{obs}}} \\ & \omega & \mapsto & \text{obs}(S^{\text{ext}}(\omega), N^{\text{int}}(\omega)) .\end{array} \tag{9}$$

Similarly, we have the **randomized estimate of the environment state**

$$\begin{array}{rcl}\widehat{S^{\text{ext}}} = \text{obs}(S^{\text{ext}}, 0) : & \overline{\Omega} & \to & \overline{\mathcal{X}^{\text{obs}}} \\ & \omega & \mapsto & \text{obs}(S^{\text{ext}}(\omega), 0) .\end{array} \tag{10}$$

3.3 Embedding statistical testing in the GENSA

The randomization of GENSAs makes it possible to formalize the important biological notions of specificity and sensitivity in connection with affinity. We recall that biological specificity refers to the tendency of a biological molecule (such as an enzyme, antibody, or receptor) to bind or interact with a single type of molecule, or a limited group of closely related molecules, so as to limit unwanted cross-reactions. Biological sensitivity is the ability of an organism, organ, tissue, or cell, to detect and respond to internal or external stimuli. Sensitivity enables organisms to perceive and react to changes in their environment (e.g., light, temperature, chemicals, pressure). A good balance between sensitivity and specificity is critical in biological interactions because systems must detect true signals (such as pathogens or target ligands) as accurately as possible, while minimizing false positives (such as self-attack or non-target binding) [38, 39].

The decision made by the GENSA on the dissimilarity between the current state s of the GENSA and s^{ext}, the current state of the environment, is made by computing the decision $\text{act}(\delta^{\text{obs}}(s, x^{\text{obs}}))$. This decision, by its definition itself, is a level of activation induced by the dissimilarity between the observation x^{obs} and state s. It is desirable that a small dissimilarity between s and s^{ext} should thus induce a limited level of activation $\text{act}(\delta^{\text{obs}}(s, x^{\text{obs}}))$, whereas a high dissimilarity between s and s^{ext} should trigger a significant level of activation. Yet another way to interpret the foregoing rationale is to introduce the affinity function $\text{aff} = 1 - \text{act} \circ \delta^{\text{obs}}$. In this case, the lower (resp. the higher) the dissimilarity between s and s^{ext}, the higher (the lower) the affinity.

In the same way as a high (resp. low) dissimilarity is mathematically formalized above by the inequality $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}}) > \tau$ (resp. $\delta^{\text{obs}}(s, \widehat{s^{\text{ext}}}) \leqslant \tau$), we formalize a strong decision — or high level of activation — by the inequality

$$\text{act}(\delta^{\text{obs}}(s, x^{\text{obs}})) > \lambda$$

for some threshold $\lambda \in \mathbb{R}$. On the other hand, a weak decision — or low level of activation — will be formalized by the inequality

$$\text{act}(\delta^{\text{obs}}(s, x^{\text{obs}})) \leqslant \lambda .$$

We thus propose a probabilistic formalization of the notions of specificity and sensitivity by resorting to randomizations. Any randomization $\left(S^{\text{ext}} : \overline{\Omega} \to \overline{\mathcal{S}^{\text{ext}}}, N^{\text{int}} : \overline{\Omega} \to \overline{\mathcal{N}^{\text{int}}}\right)$ yields a randomized observation X^{obs} and a randomized estimate $\widehat{S^{\text{ext}}}$. Specificity will thus be the probability guaranteed by the GENSA that $\text{act}(\delta^{\text{obs}}(s, X^{\text{obs}})) \leqslant \lambda$ for all S^{ext} such that $\delta^{\text{obs}}(s, \widehat{S^{\text{ext}}}) \leqslant \tau$. Hence, specificity will be a global performance measurement of the GENSA. In contrast, sensitivity will be a function assigning to each given $(S^{\text{ext}}, N^{\text{int}})$ the probability that $\text{act}(\delta^{\text{obs}}(s, X^{\text{obs}})) > \lambda$ conditionally to $\delta^{\text{obs}}(s, \widehat{S^{\text{ext}}}) > \tau$. The sensitivity thus quantifies how strongly the GENSA is sensitive to a high dissimilarity between its state s and the randomized estimate $\widehat{S^{\text{ext}}}$ of the environment state. The activation function thus plays the role of a statistical test, the observation that of the statistic used by the test to make the decision, and the notions of specificity and sensitivity relate to the

notions of size[1] and power[2] encountered in mathematical statistics, with specificity = 1 − size and sensitivity = power. Thereby, we hereafter formalize the foregoing considerations via the next definition in the vein of those made in mathematical statistics. However, note that we define specificity and sensitivity as probability values whereas, in statistics, they are usually empirical rates calculated over a data set. In preparation of the results stated in Section 4, we henceforth consider the case of a subset rand $\subset (\overline{\mathcal{S}^{\mathrm{ext}}}, \overline{\mathcal{N}^{\mathrm{int}}})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$ of randomizations.

Definition 3.2. [Specificity and sensitivity] *Given a probability space $(\Omega, \Sigma_\Omega, \mathbb{P})$, consider the set $(\overline{\mathcal{S}^{ext}}, \overline{\mathcal{N}^{int}})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$ of all $(\Omega, \Sigma_\Omega, \mathbb{P})$-randomizations of GENSAs with external state space $\mathcal{S}^{ext}$ and internal noise set $\mathcal{N}^{int}$, and rand $\subset (\overline{\mathcal{S}^{ext}}, \overline{\mathcal{N}^{int}})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$.*

Given a GENSA

$$\mathbf{G} = (\mathcal{S}^{ext}, \mathcal{N}^{int}, \mathcal{X}^{obs}, \mathcal{S}, \mathcal{X}^{out}, obs, \delta^{obs}, act, \varphi^{updt}, f^{rdout})$$

and a pair

$$(\tau, \lambda) \in \delta^{obs}(\mathcal{S} \times \mathcal{X}^{obs}) \times act\,(\mathcal{S} \times \mathcal{X}^{obs}),$$

(i) the (τ, λ)-specificity with respect to rand of $\mathbf{G}$ given state $s \in \mathcal{S}$, is defined as

$$\Upsilon^{rand}_{(\tau,\lambda)}(\mathbf{G}, s) = \inf_{\substack{(S^{ext}, N^{int}) \in\ rand,\, s.t. \\ \mathbb{P}[\delta^{obs}(s, \widehat{S^{ext}}) \leqslant \tau] \neq 0}} \mathbb{P}\Big[act\,(\delta^{obs}(s, X^{obs})) \leqslant \lambda \,|\, \delta^{obs}(s, \widehat{S^{ext}}) \leqslant \tau)\Big];$$

(ii) the (τ, λ)-sensitivity of $\mathbf{G}$, given state $s \in \mathcal{S}$, is the function defined for each $(S^{ext}, N^{int}) \in$ rand such that

$$\mathbb{P}[\delta^{obs}(s, \widehat{S^{ext}}) > \tau] \neq 0$$

by setting:

$$\beta^{(S^{ext},N^{int})}_{(\tau,\lambda)}(\mathbf{G}, s) = \mathbb{P}\Big[act\,(\delta^{obs}(s, X^{obs})) > \lambda \,|\, \delta^{obs}(s, \widehat{S^{ext}}) > \tau)\Big]$$

In what follows, τ is called tolerance.

Remark 3.1. *With the same notation as in the definition above, the connection between the (τ, λ)-sensitivity of $\mathbf{G}$ and the notion of size in statistical inference is made by noticing that*

$$1 - \Upsilon^{rand}_{(\tau,\lambda)}(\mathbf{G}, s) = \sup_{\substack{(S^{ext}, N^{int}) \in\ rand\ s.t. \\ \mathbb{P}[\delta^{obs}(s, \widehat{S^{ext}}) \leqslant \tau] \neq 0}} \mathbb{P}\Big[act(\delta^{obs}(s, X^{obs})) > \lambda \,|\, \delta^{obs}(s, \widehat{S^{ext}}) \leqslant \tau\Big]\,.$$

The right hand side to this equality is the size of the statistical test

$$\mathcal{T}(X^{obs}) = \begin{cases} 1 & \text{if } act(\delta^{obs}(s, X^{obs})) > \lambda \\ 0 & \text{otherwise} \end{cases}$$

for testing the null hypothesis $\mathcal{H}_0$ that $\delta^{obs}(s, \widehat{S^{ext}}) \leqslant \tau$, when we observe $X^{obs} = obs(S^{ext}, N^{int})$ and $(S^{ext}, N^{int}) \in$ rand. Similarly, the (τ, λ)-sensitivity of $\mathbf{G}$ to $S^{ext} : \overline{\Omega} \to \overline{\mathcal{S}^{ext}}$ can be regarded as the power of the test defined above when the alternative hypothesis $\mathcal{H}_1$ to $\mathcal{H}_0$ is that $\delta^{obs}(s, \widehat{S^{ext}}) > \tau$.

To guarantee a certain specificity, it suffices to introduce a lower bound for the (τ, λ)-specificity of $\mathbf{G}$. Thence the next definition.

Definition 3.3. *Given sets $\mathcal{S}^{ext}$, $\mathcal{N}^{int}$, $\mathcal{X}^{obs}$, $\mathcal{S}$, and $\mathcal{X}^{out}$, and functions*

$$\begin{cases} obs : \mathcal{S}^{ext} \times \mathcal{N}^{int} \to \mathcal{X}^{obs} \\ \delta^{obs} : \mathcal{S} \times \mathcal{X}^{obs} \to \mathbb{R} \end{cases}$$

let

$$\mathcal{G} = \left\{ \mathbf{G} = (obs, \delta^{obs}, act_{\mathbf{G}}, \varphi^{updt}_{\mathbf{G}}, f^{rdout}_{\mathbf{G}}) \,\middle|\, \begin{cases} act_{\mathbf{G}} : \delta^{obs}(\mathcal{S} \times \mathcal{X}^{obs}) \to [0,1], \\ \varphi^{updt}_{\mathbf{G}} : \mathcal{S} \times [0,1] \to \mathcal{S}, \\ f^{rdout}_{\mathbf{G}} : \mathcal{S} \to \mathcal{X}^{out} \end{cases} \right\}$$

be the class of all GENSAs with observation function obs, dissimilarity function δ^{obs} and arbitrary activation, readout and elementary update functions $act_{\mathbf{G}}$, $f^{rdout}_{\mathbf{G}}$ and $\varphi^{updt}_{\mathbf{G}}$.

Given a probability space $(\Omega, \Sigma_\Omega, \mathbb{P})$, consider

$$rand \subset (\overline{\mathcal{S}^{ext}}, \overline{\mathcal{N}^{int}})_{(\Omega,\Sigma_\Omega,\mathbb{P})}.$$

(i) Given $\tau \in \delta^{obs}(\mathcal{S} \times \mathcal{X}^{obs})$ and $\gamma \in]0,1[$, we define $\mathcal{K}^{rand}_{\gamma,\tau}(\mathcal{G})$ as the set of all $\mathbf{G} \in \mathcal{G}$ with tolerance τ for which

$$\left\{ \lambda \in [0,1] : \forall s \in \mathcal{S}, \Upsilon^{rand}_{(\tau,\lambda)}(\mathbf{G}, s) \geqslant \gamma \right\}$$

is non-empty and has a minimum $\lambda_{\mathbf{G}}(\gamma, \tau) \in [0,1]$.

(ii) Given $\tau \in \delta^{obs}(\mathcal{S} \times \mathcal{X}^{obs})$, we define

$$\mathcal{K}^{rand}_{\tau}(\mathcal{G}) = \bigcap_{\gamma \in]0,1[} \mathcal{K}^{rand}_{\gamma,\tau}(\mathcal{G})\,.$$

as the set of elements of $\mathcal{K}^{rand}_{\tau}(\mathcal{G})$ that are τ-specific in $\mathcal{G}$ with respect to rand.

Statement (i) in the definition above is motivated by the fact that, for any fixed s, $\Upsilon^{\mathrm{rand}}_{(\tau,\lambda)}(\mathbf{G}, s)$ increases with λ. In Section 4, the minimum $\lambda_{\mathbf{G}}(\gamma, \tau)$ will always exists.

To model the balance between sensitivity and specificity of biological interactions, it is thus important to exhibit activation functions that are τ-specific and, at the same time, able to achieve a good sensitivity to external states that are significantly dissimilar from the GENSA internal state. In this respect, we make the following definition.

Definition 3.4. *With the same notation as in Definition 3.3, a GENSA*

$$\mathbf{G}^* = (obs, \delta^{obs}, act_{\mathbf{G}^*}, \varphi^{updt}_{\mathbf{G}^*}, f^{rdout}_{\mathbf{G}^*}) \in \mathcal{G}$$

[1] Type-I error probability
[2] Complementary to 1 of the Type-II error

is Uniformly Most Sensitive (UMS) in $\mathcal{K}_\tau^{rand}(\mathcal{G})$ with respect to rand if:

(i) $\mathbf{G}^*$ is τ-specific in $\mathcal{G}$: $\mathbf{G}^* \in \mathcal{K}_\tau^{rand}(\mathcal{G})$;

(ii) for all $\mathbf{G} \in \mathcal{K}_\tau^{rand}(\mathcal{G})$, all $s \in \mathcal{S}$, all $(S^{ext}, N^{int}) \in rand$ such that $\mathbb{P}[\delta^{obs}(s, \widehat{S^{ext}}) > \tau] \neq 0$,

$$\forall \gamma \in]0,1[, \beta^{(S^{ext},N^{int})}_{(\tau,\lambda_{\mathbf{G}^*}(\gamma,\tau))}(\mathbf{G}^*, s) \geqslant \beta^{(S^{ext},N^{int})}_{(\tau,\lambda_{\mathbf{G}}(\gamma,\tau))}(\mathbf{G}, s)$$

with $\lambda_{\mathbf{G}}(\gamma,\tau)$ and $\lambda_{\mathbf{G}^*}(\gamma,\tau)$ given by Definition 3.3 (i).

The eagle-eyed reader will have noticed that the above definition does not specify the GENSA readout function. The study of relevant readout functions for the GENSA requires further investigations as enhanced in the conclusion of this paper.

4 Two fundamental GENSAs

In this section, we present two fundamental GENSAs, namely, the Neyman-Pearson GENSA (NP-GENSA) and the Random Distortion Testing GENSA (RDT-GENSA). These two models are fundamental in our research because they model the de-generacy of the GENSA: although these two GENSAs are structurally different in that each is UMS within a specific class of GENSAs and a specific randomization, the RDT-GENSA can be used to palliate failure of the NP-GENSA.

Let us begin by pinpointing key features shared by both the NP-GENSA and the RDT-GENSA. First, these two automata have same external space $\mathcal{S}^{\text{ext}}$, same noise space $\mathcal{N}^{\text{int}}$ and same observation space $\mathcal{X}^{\text{obs}}$, all equal to $\mathbb{R}^d$. They have also same observation function, namely the sum + in $\mathbb{R}^d$:

$$\begin{array}{rccc} \text{obs}: & \mathbb{R}^d \times \mathbb{R}^d & \to & \mathbb{R}^d \\ & (s^{\text{ext}}, n^{\text{int}}) & \mapsto & x^{\text{obs}} = s^{\text{ext}} + n^{\text{int}} . \end{array} \tag{11}$$

Both the NP-GENSA and the RDT-GENSA are characterized by a specific parameter $\theta_0 \in \mathbb{R}^d$, thus a vector belonging to their common external space $\mathcal{S}^{\text{ext}}$. We thus denote these GENSAs by NP-GENSA(θ_0) and RDT-GENSA(θ_0). This θ_0 can be the same for the NP-GENSA and the RDT-GENSA, with however two different roles: NP-GENSA(θ_0) is aimed at detecting the presence of θ_0 in the observation, whereas RDT-GENSA(θ_0) is aimed at emitting θ_0, with an amplitude depending on some change the RDT-GENSA may have detected in its environment. In this respect, NP-GENSA(θ_0) and RDT-GENSA(θ_0) will also have same output space $\mathcal{X}^{\text{out}} = \mathbb{R}^d$, and same readout function, because each of these GENSAs transmits, with a specific amplitude directly issued from its own update function, the model θ_0 to which it is attuned.

Because of the role played by θ_0 in the functioning of NP-GENSA(θ_0) and RDT-GENSA(θ_0), we do not regard θ_0 as a mere parameter but, actually, as a component of the memory of both NP-GENSA(θ_0) and RDT-GENSA(θ_0). In this respect, NP-GENSA(θ_0) and RDT-GENSA(θ_0) have same state space

$$\mathcal{S} = \mathcal{S}_{\theta_0} = \{\theta_0\} \times [0,1] . \tag{12}$$

We find it appropriate to encapsulate θ_0 as a state component to allow for addressing in future work the case where this component of the memory could be altered or even erased. The second element of a state $s = (\theta_0, p) \in \mathcal{S}_{\theta_0}$ is the amplitude with which θ_0 will be re-emitted by NP-GENSA(θ_0) or RDT-GENSA(θ_0). However, in accordance with our brief description above of the readout functions of these automata, this amplitude has a different meaning depending on whether s is a state of NP-GENSA(θ_0) or a state of RDT-GENSA(θ_0): if s is a state of NP-GENSA(θ_0), p quantifies the plausibility that the observation derives from the presence of θ_0 in the external state S^{ext} whereas, in the case of RDT-GENSA(θ_0), p indicates the amplitude of a change in the environment of RDT-GENSA(θ_0).

Recalling that a GENSA is a 10-uple

$$\mathbf{G} = (\mathcal{S}^{\text{ext}}, \mathcal{N}^{\text{int}}, \mathcal{X}^{\text{obs}}, \mathcal{S}, \mathcal{X}^{\text{out}}, \text{obs}, \delta^{\text{obs}}, \text{act}, \varphi^{\text{updt}}, f^{\text{rdout}})$$

and announcing, as of now, that NP-GENSA(θ_0) and RDT-GENSA(θ_0) have same elementary update function φ^{updt}, denoted by $\varphi^{\text{updt}}_{\theta_0}$ below, it follows from the foregoing that NP-GENSA(θ_0) and RDT-GENSA(θ_0) differ by 1) their dissimilarity function, and 2) their activation function to update their state. We exhibit these different dissimilarity and activation functions by considering two different randomizations: with the terminology of Definitions 3.3 and 3.4, the randomization considered in the next section will lead to NP-GENSA(θ_0), as a UMS GENSA in a set of 0-specific GENSAs, whereas the randomization of Section 4.2 yields RDT-GENSA(θ_0) as a UMS GENSA in a set of τ-specific GENSAs, where $\tau > 0$. This structural difference between NP-GENSA(θ_0) and RDT-GENSA(θ_0) underpins the de-generacy of these automata pinpointed in Section 4.3.

Therefore, the construction below of NP-GENSA(θ_0) and that of RDT-GENSA(θ_0) follow the same plan. For each automaton, we start by recalling the role of θ_0. We then introduce the appropriate randomization rand, into which NP-GENSA(θ_0) (resp. RDT-GENSA(θ_0)) are plunged and asked to change state according to the role played by θ_0. We will then derive from this randomization the dissimilarity function of NP-GENSA(θ_0) (resp. RDT-GENSA(θ_0)). This dissimilarity function will yield straightforwardly the tolerance τ and the family $\mathcal{G}$ of GENSAs with respect to which NP-GENSA(θ_0) (resp. RDT-GENSA(θ_0)) is UMS among the τ-specific GENSAs of $\mathcal{G}$. The activation function of NP-GENSA(θ_0) (resp. RDT-GENSA(θ_0)) will be a consequence of theoretical results of the literature.

4.1 Construction of NP-GENSA(θ_0)

As stipulated above, we are given $\theta_0 \in \mathbb{R}^d$ and the state space of NP-GENSA(θ_0) is given by (12). We also assume that $\mathcal{S}^{\text{ext}} = \mathcal{N}^{\text{int}} = \mathcal{X}^{\text{obs}} = \mathbb{R}^d$ and that obs is the sum + equipping the vector space $\mathbb{R}^d$. We must formalize that NP-GENSA(θ_0) is asked to detect the presence of θ_0 in the randomized observation X^{obs} of S^{ext}. The following randomization makes the sensitivity and specificity of NP-GENSA(θ_0) adapted to detect θ_0 on the basis of X^{obs}.

Let $(\Omega, \Sigma_\Omega, \mathbb{P})$ be a probability space. We equip $\mathbb{R}^d$ with $\Sigma_{\mathbb{R}^d}$ as the usual Borel σ-algebra of $\mathbb{R}^d$. We thus have $(\overline{\mathcal{S}^{\text{ext}}}, \overline{\mathcal{N}^{\text{int}}})_{(\Omega,\Sigma_\Omega,\mathbb{P})} = (\overline{\mathbb{R}^d}, \overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$, where $\overline{\mathbb{R}^d} = (\mathbb{R}^d, \Sigma_{\mathbb{R}^d})$.

We consider the subset $\text{rand}_{\text{det}(\theta_0)} \subset (\overline{\mathbb{R}^d}, \overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$ of all randomizations $(S^{\text{ext}}, N^{\text{int}}) \in (\overline{\mathbb{R}^d}, \overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$ such that $N^{\text{int}} \sim \mathcal{N}(0, I_d)$ and

$$\begin{array}{rccc} S^{\text{ext}}: & \overline{\Omega} & \to & \overline{\mathcal{S}^{\text{ext}}} \\ & \omega & \mapsto & \varepsilon(\omega)\,\theta_0, \end{array} \tag{13}$$

with ε is non-degenerated Bernoulli distributed in $\{0, 1\}$ and independent of N^{int}. The functions $\mathcal{S}^{\text{ext}}$ and N^{int} are thus independent measurable functions of $(\overline{\mathbb{R}^d}, \overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$. Therefore, in summary,

$$\text{rand}_{\text{det}(\theta_0)} = \left\{ \left(S^{\text{ext}} : \overline{\Omega} \to \overline{\mathcal{S}^{\text{ext}}}, N^{\text{int}} : \overline{\Omega} \to \overline{\mathcal{N}^{\text{int}}} \right) \in (\overline{\mathcal{S}^{\text{ext}}}, \overline{\mathcal{N}^{\text{int}}})_{(\Omega,\Sigma_\Omega,\mathbb{P})} \;\middle|\; \left\{ \begin{array}{l} S^{\text{ext}} = \varepsilon\,\theta_0, \varepsilon : \overline{\Omega} \to \overline{\{0,1\}}, \text{non-degenerated}, \\ N^{\text{int}} \text{ and } \varepsilon \text{ independent}, N^{\text{int}} \sim \mathcal{N}(0, I_d) \end{array} \right\} \right.$$

The randomized observation function is thus

$$X^{\text{obs}} = \varepsilon\,\theta_0 + N^{\text{int}} \tag{14}$$

and the decision problem embedded in NP-GENSA(θ_0) consists of deciding on the value of ε on the basis of X^{obs}. In other words, we want to detect the presence ($\varepsilon = 1$) or absence ($\varepsilon = 0$) of θ_0, given the observation X^{obs}. We want to achieve this detection with an optimal sensitivity and a guaranteed specificity.

To achieve this twofold purpose, let us consider the following dissimilarity function:

$$\begin{array}{rccc} \delta^{\text{obs}}_{\text{det}(\theta_0)}: & \mathcal{S}_{\theta_0} \times \mathbb{R}^d & \to & \mathbb{R} \\ & ((\theta_0, p), x^{\text{obs}}) & \mapsto & \langle\, \theta_0\,, x^{\text{obs}} \,\rangle \,/\, \|\theta_0\|\,. \end{array} \tag{15}$$

The relevance of this function for detecting θ_0 when we observe X^{obs} can be emphasized as follows. Take $s = (\theta_0, p) \in \mathcal{S}_{\theta_0}$. Since $\widehat{S^{\text{ext}}} = S^{\text{ext}} = \varepsilon\,\theta_0$ by Eqs. (10), (11), (13), we have

$$\delta^{\text{obs}}_{\text{det}(\theta_0)}(s, \widehat{S^{\text{ext}}}) = \langle\, \theta_0\,, \varepsilon\,\theta_0 \,\rangle \,/\, \|\theta_0\| = \varepsilon\,\|\theta_0\|\,.$$

Therefore, deciding whether $\varepsilon = 0$ or $\varepsilon = 1$ is equivalent to deciding whether $\delta^{\text{obs}}_{\text{det}(\theta_0)}(s, S^{\text{ext}}) = 0$ or not. In particular,

$$\delta^{\text{obs}}_{\text{det}(\theta_0)}(s, S^{\text{ext}}) > 0 \Leftrightarrow \varepsilon = 1 \tag{16}$$

It follows that we will have to choose a null tolerance and thus consider 0-specific GENSAs in what follows.

Since we have chosen $\mathcal{S}^{\text{ext}} = \mathcal{N}^{\text{int}} = \mathcal{X}^{\text{obs}} = \mathcal{X}^{\text{out}} = \mathbb{R}^d$, specified $\mathcal{S}_{\theta_0}$ by (12), obs = + in $\mathbb{R}^d$ by (11), and the dissimilarity function $\delta^{\text{obs}}_{\text{det}(\theta_0)}$ in (15), we set

$$\mathcal{G}_{\text{det}(\theta_0)} = \left\{ \mathbf{G} = (+, \delta^{\text{obs}}_{\text{det}(\theta_0)}, \text{act}_{\mathbf{G}}, \varphi^{\text{updt}}_{\mathbf{G}}, f^{\text{rdout}}_{\mathbf{G}}) \;\middle|\; \left\{ \begin{array}{l} \text{act}_{\mathbf{G}} : \delta^{\text{obs}}(\mathcal{S}_{\theta_0} \times \mathcal{X}^{\text{obs}}) \to [0,1] \\ \varphi^{\text{updt}}_{\mathbf{G}} : \mathcal{S}_{\theta_0} \times [0,1] \to \mathcal{S}_{\theta_0}, f^{\text{rdout}}_{\mathbf{G}} : \mathcal{S}_{\theta_0} \to \mathcal{X}^{\text{out}} \end{array} \right\} \right.$$

We have now $\text{rand}_{\text{det}(\theta_0)} \subset (\overline{\mathbb{R}^d}, \overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$ and $\mathcal{G}_{\text{det}(\theta_0)}$. In addition, we have noticed that we must consider 0-specific GENSAs. Thence the question of whether we can find UMS GENSAs within $\mathcal{K}_0^{\text{rand}_{\text{det}(\theta_0)}}(\mathcal{G}_{\text{det}(\theta_0)})$. The answer to this question is provided by the next result. In what follows, $\|\bullet\|$ designates the Euclidean norm on $\mathbb{R}^d$.

Proposition 4.1. *Let Φ be the cumulative distribution function of the Gaussian $\mathcal{N}(0, 1)$. Consider any elementary update function $\varphi^{updt}_{\mathbf{G}^*} : \mathcal{S}_{\theta_0} \times [0, 1] \to \mathcal{S}_{\theta_0}$ and any readout function $f^{rdout}_{\mathbf{G}^*} : \mathcal{S}_{\theta_0} \to \mathbb{R}^d$. With the same notation as above, any GENSA*

$$\mathbf{G}^* = (\mathbb{R}^d, \mathbb{R}^d, \mathbb{R}^d, \{\theta_0\}\times[0,1], \mathbb{R}^d, +, \delta^{obs}_{det(\theta_0)}, \Phi, \varphi^{updt}_{\mathbf{G}^*}, f^{rdout}_{\mathbf{G}^*})$$

is UMS in $\mathcal{K}_0^{rand_{det(\theta_0)}}(\mathcal{G}_{det(\theta_0)})$.

Proof. After some routine algebra, it follows from the Neyman-Pearson Lemma [40] that, given any $(S^{\text{ext}}, N^{\text{int}}) \in \text{rand}_{\text{det}(\theta_0)}$,

$$\forall \gamma \in]0,1[, \mathbb{P}\left[\Phi(\langle\, \theta_0\,, X^{\text{obs}} \,\rangle \,/\, \|\theta_0\|) \leqslant \gamma \,|\, \varepsilon = 0\right] = \gamma \tag{17}$$

and, for all $\mathbf{G} \in \mathcal{K}_0^{\text{rand}_{\text{det}(\theta_0)}}(\mathcal{G}_{\text{det}(\theta_0)})$ such that

$$\begin{array}{l} \forall \gamma \in]0,1[, \\ \quad \mathbb{P}\left[\text{act}_{\mathbf{G}}(\langle\, \theta_0\,, X^{\text{obs}} \,\rangle \,/\, \|\theta_0\|) \leqslant \lambda_{\mathbf{G}}(\gamma, 0) \,|\, \varepsilon = 0\right] \geqslant \gamma\,, \end{array} \tag{18}$$

we have also

$$\begin{array}{l} \forall\, \gamma \in]0,1[, \\ \quad \mathbb{P}\left[\Phi(\langle\, \theta_0\,, X^{\text{obs}} \,\rangle \,/\, \|\theta_0\|) > \gamma \,|\, \varepsilon = 1\right] \geqslant \\ \qquad \mathbb{P}\left[\text{act}_{\mathbf{G}}(\langle\, \theta_0\,, X^{\text{obs}} \,\rangle \,/\, \|\theta_0\|) > \lambda_{\mathbf{G}}(\gamma, 0) \,|\, \varepsilon = 1\right]\,. \end{array} \tag{19}$$

We have $\lambda_{\mathbf{G}^*}(\gamma, 0) = \gamma$ and the result then derives from (16), (17), (18), injected into the definitions of specificity and sensitivity given by (11) and (11), respectively. □

According to this proposition and our introductory paragraph, we define NP-GENSA(θ_0) as the 10-uple:

$$\begin{array}{l} \mathbf{G}_{\text{NP}(\theta_0)} = \\ (\mathbb{R}^d, \mathbb{R}^d, \mathbb{R}^d, \{\theta_0\} \times [0,1], \mathbb{R}^d +, \delta^{\text{obs}}_{\text{det}(\theta_0)}, \Phi, \varphi^{\text{updt}}_{\theta_0}, f^{\text{rdout}}_{\theta_0}) \end{array} \tag{20}$$

where

$$\begin{array}{rccc} \varphi^{\text{updt}}_{\theta_0}: & \mathcal{S}_{\theta_0} \times [0,1] & \to & \mathcal{S}_{\theta_0} \\ & ((\theta_0, p), q) & \mapsto & (\theta_0, q) \end{array} \tag{21}$$

and

$$\begin{array}{rccc} f^{\text{rdout}}_{\theta_0}: & \mathcal{S}_{\theta_0} & \to & \mathbb{R}^d \\ & (\theta_0, p) & \mapsto & p\,\theta_0\,. \end{array} \tag{22}$$

Given $s = (\theta_0, p) \in \mathcal{S}_{\theta_0}$ and $X^{\text{in}} = (S^{\text{ext}}, N^{\text{int}})$, we derive from (5) and (21) that the update function of $\mathbf{G}_{\text{NP}(\theta_0)}$ returns

$$\begin{array}{rcl} f^{\text{updt}}_{\text{NP}}(X^{\text{in}}, s) & = & \varphi^{\text{updt}}_{\theta_0}\left(s, \Phi(\,\delta^{\text{obs}}_{\text{det}(\theta_0)}(s, X^{\text{obs}}))\right) \\ & = & \left(\theta_0, \Phi\left(\langle\, \theta_0\,, X^{\text{obs}} \,\rangle \,/\, \|\theta_0\|\,\right)\right). \end{array}$$

and thus, from (22), that the readout function will output

$$f^{\mathrm{rdout}}_{\theta_0}\Big(\theta_0, \Phi\left(\langle\, \theta_0\,, X^{\mathrm{obs}}\,\rangle / \|\theta_0\|\right)\Big) = \Phi\left(\langle\, \theta_0\,, X^{\mathrm{obs}}\,\rangle / \|\theta_0\|\right)\theta_0.$$

As mentioned above, NP-GENSA(θ_0) keeps in memory θ_0, which it attempts to detect on the basis of the randomized observation, and the behaviour of NP-GENSA(θ_0), when the memorization of θ_0 is altered and even lost, could be addressed in future work. Regarding our choice for $f^{\mathrm{rdout}}_{\theta_0}$, the reader may refer to Remark 4.1 below, which concerns both NP-GENSA(θ_0) and RDT-GENSA(θ_0).

4.2 Construction of RDT-GENSA(θ_0)

As for NP-GENSA(θ_0), we are given $\theta_0 \in \mathbb{R}^d$, we set $\mathcal{S}^{\mathrm{ext}} = \mathcal{N}^{\mathrm{int}} = \mathcal{X}^{\mathrm{obs}} = \mathbb{R}^d$ and obs is the sum + in the vector space $\mathbb{R}^d$. The state space is $\mathcal{S}_{\theta_0} = \{\theta_0\} \times [0,1]$ again. In contrast to NP-GENSA(θ_0) aiming at detecting θ_0 in its environment, θ_0 is hereafter used as a signal that RDT-GENSA(θ_0) emits, with an amplitude depending on the amplitude of the change it detects in its environment. More precisely, the rationale is the following one.

Given a probability space $(\Omega, \Sigma_\Omega, \mathbb{P})$, we consider again the set $(\overline{\mathbb{R}^d}, \overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$ of $(\Omega, \Sigma_\Omega, \mathbb{P})$-randomizations of GENSAs with external state space $\mathbb{R}^d$ and internal noise set $\mathbb{R}^d$, both equipped with the Borel σ-algebra of $\mathbb{R}^d$. We assume that, for some $\tau > 0$, the variations of $\|S^{\mathrm{ext}}\|$ below τ are due to fluctuations of poor interest for the GENSA to detect. The real value τ is called tolerance, as in Definition 3.1. When $\|S^{\mathrm{ext}}\| > \tau$, we then consider that a change has occurred in the environment and has induced an amplitude beyond τ for S^{ext}. The purpose of RDT-GENSA(θ_0) is then to detect the increase of $\|S^{\mathrm{ext}}\|$ beyond the tolerance, given $X^{\mathrm{obs}} = S^{\mathrm{ext}} + N^{\mathrm{int}}$. When such a change occurs, the GENSA is asked to emit an alarm signal collinear to θ_0 to which it is adjusted, the amplitude of the emitted signal being a function of the amplitude of the change detected by RDT-GENSA(θ_0) given X^{obs}. The role of θ_0 in RDT-GENSA(θ_0) is thus fundamentally different from that of θ_0 in NP-GENSA(θ_0). This crucial difference prefigures de-generacy, as addressed in Section 4.3.

To formalize the foregoing, with the same notation as above, consider the subset

$$\mathrm{rand}_{\mathrm{Gauss}} \subset (\overline{\mathbb{R}^d}, \overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$$

of all randomizations $(S^{\mathrm{ext}}, N^{\mathrm{int}}) \in (\overline{\mathbb{R}^d}, \overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$ such that $N^{\mathrm{int}} \sim \mathcal{N}(0, I_d)$. We thus have

$$\mathrm{rand}_{\mathrm{Gauss}} = \left\{ \left(S^{\mathrm{ext}} : \overline{\Omega} \to \overline{\mathcal{S}^{\mathrm{ext}}}, N^{\mathrm{int}} : \overline{\Omega} \to \overline{\mathcal{N}^{\mathrm{int}}}\right) \in (\overline{\mathbb{R}^d}, \overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})} \;\middle|\; \begin{cases} N^{\mathrm{int}} \sim \mathcal{N}(0, I_d), \\ S^{\mathrm{ext}} \text{ and } N^{\mathrm{int}} \text{ independent} \end{cases} \right\}.$$

With respect to the rationale above, the dissimilarity function we choose is now

$$\begin{array}{rccc} \delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0} : & \mathcal{S}_{\theta_0} \times \mathbb{R}^d & \to & \mathbb{R} \\ & ((\theta_0, p), x^{\mathrm{obs}}) & \mapsto & \|x^{\mathrm{obs}}\|\,. \end{array}$$

Although we stick to Definition 2.3 to define $\delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0}$, the outcome of $\delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0}$ does not depend on $(\theta_0, p) \in \mathcal{S}_{\theta_0}$ and thus, on θ_0. This is a key feature for RDT-GENSA(θ_0) to palliate limitations of NP-GENSA(θ_0) in Section 4.3.

Having fixed $\mathcal{S}^{\mathrm{ext}} = \mathcal{N}^{\mathrm{int}} = \mathcal{X}^{\mathrm{obs}} = \mathcal{X}^{\mathrm{out}} = \mathbb{R}^d$, specified $\mathcal{S}_{\theta_0}$, chosen obs = + in $\mathbb{R}^d$, and defined the dissimilarity function $\delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0}$, we proceed similarly to the construction of NP-GENSA(θ_0) by considering the following family of GENSAs

$$\mathcal{G}_{\mathrm{chng},\theta_0} = \left\{ \mathbf{G} = (+, \delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0}, \mathrm{act}_{\mathbf{G}}, \varphi^{\mathrm{updt}}_{\mathbf{G}}, f^{\mathrm{rdout}}_{\mathbf{G}}) \;\middle|\; \begin{cases} \mathrm{act}_{\mathbf{G}} : \delta^{\mathrm{obs}}(\mathcal{S} \times \mathcal{X}^{\mathrm{obs}}) \to [0,1] \\ \varphi^{\mathrm{updt}}_{\mathbf{G}} : \mathcal{S} \times [0,1] \to \mathcal{S} \\ f^{\mathrm{rdout}}_{\mathbf{G}} : \mathcal{S} \to \mathcal{X}^{\mathrm{out}} \end{cases} \right\}$$

We have $\mathrm{rand}_{\mathrm{Gauss}}$, $\mathcal{G}_{\mathrm{chng},\theta_0}$, and the problem of testing whether $\delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0}(s, \widehat{S^{\mathrm{ext}}}) \leqslant \tau$ or not. The question is therefore whether we can find UMS GENSAs within $\mathcal{K}^{\mathrm{rand}_{\mathrm{Gauss}}}_{\tau}(\mathcal{G}_{\mathrm{chng},\theta_0})$. The answer to this problem is provided by the next proposition, in which $\mathcal{R}_{d/2}(\tau, \bullet) = 1 - Q_{d/2}(\tau, \bullet)$, $Q_{d/2}$ being the generalized Marcum function [41] .

Proposition 4.2. *Consider any elementary update function $\varphi^{updt}_{\mathbf{G}^*} : \mathcal{S}_{\theta_0} \times [0,1] \to \mathcal{S}_{\theta_0}$ and any readout function $f^{rdout}_{\mathbf{G}^*} : \mathcal{S}_{\theta_0} \to \mathbb{R}^d$. With the same notation as above, any GENSA*

$$\mathbf{G}^* = (\mathbb{R}^d, \mathbb{R}^d, \mathbb{R}^d, \{\theta_0\} \times [0,1], \mathbb{R}^d, +, \delta^{obs}_{chng,\theta_0}, \mathcal{R}_{d/2}(\tau, \bullet), \varphi^{updt}_{\mathbf{G}^*}, f^{rdout}_{\mathbf{G}^*})$$

is UMS in $\mathcal{K}^{rand_{Gauss}}_{\tau}(\mathcal{G}_{chng,\theta_0})$.

Proof. As for NP-GENSA(θ_0), we have $\widehat{S^{\mathrm{ext}}} = S^{\mathrm{ext}}$. Therefore,

$$\forall s \in \mathcal{S}_{\theta_0}, \delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0}(s, \widehat{S^{\mathrm{ext}}}) = \delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0}(s, S^{\mathrm{ext}}) = \|S^{\mathrm{ext}}\|\,. \quad (23)$$

It then turns out that, given the randomized observation X^{obs}, testing whether $\delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0}(s, \widehat{S^{\mathrm{ext}}}) \leqslant \tau$ or not, is a Random Distortion Testing (RDT) problem with tolerance $\tau > 0$ [42]. After some algebra, we derive two results from [42, Theorem 2]. First,

$$\forall \gamma \in]0,1[, \quad \inf_{\substack{(S^{\mathrm{ext}}, N^{\mathrm{int}}) \in \mathrm{rand}_{\mathrm{Gauss}} \\ s.t.\ \mathbb{P}[\|S^{\mathrm{ext}}\| \leqslant \tau] \neq 0}} \mathbb{P}\left[\mathcal{R}_{d/2}(\tau, \|X^{\mathrm{obs}}\|) \leqslant \gamma \,\middle|\, \|S^{\mathrm{ext}}\| \leqslant \tau)\right] = \gamma\,. \quad (24)$$

Second, for all

$$\mathbf{G} = (+, \delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0}, \mathrm{act}_{\mathbf{G}}, \varphi^{\mathrm{updt}}_{\mathbf{G}}, f^{\mathrm{rdout}}_{\mathbf{G}}) \in \mathcal{K}^{\mathrm{rand}_{\mathrm{Gauss}}}_{\tau}(\mathcal{G}_{\mathrm{chng},\theta_0})$$

and all $(S^{\mathrm{ext}}, N^{\mathrm{int}}) \in \mathrm{rand}_{\mathrm{Gauss}}$ such that $\mathbb{P}[\|S^{\mathrm{ext}}\| > \tau] \neq 0$,

$$\mathbb{P}\left[\mathcal{R}_{d/2}(\tau, \|X^{\mathrm{obs}}\|) > \gamma \,\middle|\, \|S^{\mathrm{ext}}\| > \rho)\right] \geqslant \mathbb{P}\left[\mathrm{act}_{\mathbf{G}}(\|X^{\mathrm{obs}}\|) > \lambda_{\mathbf{G}}(\gamma, \tau) \,\middle|\, \|S^{\mathrm{ext}}\| > \rho\right]\,. \quad (25)$$

Similarly to the proof of Proposition 4.1, $\lambda_{\mathbf{G}^*}(\gamma,\tau)=\gamma$ and the result follows from (23), (24), and (25), injected into the definitions of specificity and sensitivity given by (11) and (11), respectively. □

We now complete the construction of RDT-GENSA(θ_0), by keeping the same elementary update and readout function as those considered to define NP-GENSA(θ_0) and given by (21) and (22). Therefore, RDT-GENSA(θ_0) is the 10-uple:

$$\begin{aligned}&\mathbf{G}_{\mathrm{RDT}(\theta_0)}\\&\quad=(\mathbb{R}^d,\mathbb{R}^d,\mathbb{R}^d,\{\theta_0\}\times[0,1],\mathbb{R}^d,+,\\&\qquad\delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0},\mathcal{R}_{d/2}(\tau,\bullet),\varphi^{\mathrm{updt}}_{\theta_0},f^{\mathrm{rdout}}_{\theta_0})\,.\end{aligned}\tag{26}$$

According to (5), for $X^{\mathrm{in}}=(S^{\mathrm{ext}},N^{\mathrm{int}})$, the update function of RDT-GENSA(θ_0) is given by

$$\forall(\theta_0,p)\in\mathcal{S}_{\theta_0},f^{\mathrm{updt}}_{\mathrm{RDT}}\Big(X^{\mathrm{in}},(\theta_0,p)\Big)=\Big(\theta_0,\mathcal{R}_{d/2}(\|X^{\mathrm{obs}}\|)\Big)$$

and

$$f^{\mathrm{rdout}}_{\theta_0}\Big(\theta_0,\mathcal{R}_{d/2}(\|X^{\mathrm{obs}}\|)\Big)=\mathcal{R}_{d/2}(\|X^{\mathrm{obs}}\|)\,\theta_0\,.$$

It is thus by using the same elementary update and readout functions as NP-GENSA(θ_0) that θ_0 plays an active role in the functioning of RDT-GENSA(θ_0). In particular, θ_0 is kept in memory and, as for NP-GENSA(θ_0), it can be wondered what effects an alteration of this memorization could have.

Remark 4.1. *Although the general Definition 2.6 does not specify any readout function for the GENSA, we have proposed that the readout functions of the NP-GENSA(θ_0) and the RDT-GENSA(θ_0) output a vector colinear to the model θ_0, with an amplitude in the interval* $[0,1]$. *Some other outputs could probably be proposed. For instance, why not outputting θ_0 or 0, depending on whether the outcome of the activation function is sufficiently large or not? The relevance of $f^{rdout}_{\theta_0}$ is precisely to not output any of the extreme values 0 and θ_0, but the strength of the activation calculated by the GENSA. The quantity $1-act\,(\delta^{obs}(\,s,X^{obs}\,))$, where act is either Φ, for NP-GENSA(θ_0), or $\mathcal{R}_{d/2}(\tau,\bullet)$, for RDT-GENSA($\theta_0$), could model the proportion of input "energy" that the GENSA requires, from its environment, to make evolve its state.*

4.3 NP-GENSA(θ_0) and RDT-GENSA(θ_0) as de-generate GENSAs

We now illustrate that NP-GENSA(θ_0) and RDT-GENSA(θ_0) are de-generate instances of the GENSA, in the sense that they achieve functional redundancy. The rationale is the following. As detailed above, NP-GENSA(θ_0) and RDT-GENSA(θ_0) handle differently the same $\theta_0\in\mathbb{R}^d$: NP-GENSA(θ_0) is asked to detect θ_0 in X^{obs}, whereas RDT-GENSA(θ_0) is aimed at emitting θ_0 with an amplitude depending on the amplitude of some change that RDT-GENSA(θ_0) may have detected in its environment. However, a change in the environment of RDT-GENSA(θ_0) can result from the presence of θ_0 itself in the vicinity of this GENSA. In other words, RDT-GENSA(θ_0) can also be used to detect θ_0 given its observation X^{obs}.

Given a probability space $(\Omega,\Sigma_\Omega,\mathbb{P})$ and $(\overline{\mathbb{R}^d},\overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$ as defined above, let

$$\mathrm{rand}_{\mathrm{dstort}(\theta_0)}\subset(\overline{\mathbb{R}^d},\overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$$

be the set of all randomizations $(S^{\mathrm{ext}},N^{\mathrm{int}})\in(\overline{\mathbb{R}^d},\overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}$ such that $N^{\mathrm{int}}\sim\mathcal{N}(0,I_d)$ and $S^{\mathrm{ext}}=\varepsilon\,\theta_0+\Delta$ where:

- ε is a non-degenerated Bernoulli random variable valued in $\{0,1\}$ where, by non-degenerated, we mean that $\mathbb{P}[\varepsilon=1]\notin\{0,1\}$;
- $\Delta:\overline{\Omega}\to\overline{\mathbb{R}^d}$ regarded as an interference with θ_0, and S^{ext}, as a distorted version of θ_0, in the vein of [42];
- There exists $\tau\in]0,\infty[$ such that $\|\theta_0\|>2\tau$ and $\|\Delta\|\leqslant\tau$,
- ε,Δ and N^{int} are independent.

In summary, we have:

$$\begin{aligned}&\mathrm{rand}_{\mathrm{dstort}(\theta_0)}=\\&\left\{\Big(S^{\mathrm{ext}}:\overline{\Omega}\to\overline{\mathbb{S}^{\mathrm{ext}}},N^{\mathrm{int}}:\overline{\Omega}\to\overline{\mathcal{N}^{\mathrm{int}}}\Big)\in(\overline{\mathbb{R}^d},\overline{\mathbb{R}^d})_{(\Omega,\Sigma_\Omega,\mathbb{P})}\;\middle|\right.\\&\left.S^{\mathrm{ext}}=\varepsilon\,\theta_0+\Delta\text{ with }\begin{cases}\exists\,\tau>0,\|\theta_0\|/2>\tau\geqslant\|\Delta\|,\\\varepsilon:\overline{\Omega}\to\overline{\{0,1\}}\text{ non-degenerated},\\N^{\mathrm{int}}\sim\mathcal{N}(0,I_d),\\\Delta,N^{\mathrm{int}},\varepsilon\text{ independent.}\end{cases}\right\}.\end{aligned}$$

We can regard $\mathrm{rand}_{\mathrm{dstort}(\theta_0)}$ as a middle ground between $\mathrm{rand}_{\mathrm{det}(\theta_0)}$ and $\mathrm{rand}_{\mathrm{Gauss}}$ since

$$\mathrm{rand}_{\mathrm{det}(\theta_0)}\subset\mathrm{rand}_{\mathrm{dstort}(\theta_0)}\subset\mathrm{rand}_{\mathrm{Gauss}}\,.\tag{27}$$

In $\mathrm{rand}_{\mathrm{dstort}(\theta_0)}$, ε still models the random presence or absence of θ_0 as in $\mathrm{rand}_{\mathrm{det}(\theta_0)}$, but the presence of Δ renders unknown the distribution of S^{ext} when considering $\mathrm{rand}_{\mathrm{Gauss}}$. The randomized observation function is now

$$X^{\mathrm{obs}}=\varepsilon\,\theta_0+\Delta+N^{\mathrm{int}}\,.\tag{28}$$

The detection problem we want to solve now via GENSAs is still that of the presence ($\varepsilon=1$) or the absence ($\varepsilon=0$) of θ_0.

With randomization drawn from $\mathrm{rand}_{\mathrm{dstort}(\theta_0)}$, it turns out that NP-GENSA(θ_0) is not 0-specific in $\mathcal{G}_{\mathrm{det}(\theta_0)}$ anymore: regardless of whatever small Δ can be, there will always be values for Δ for which (17) will be violated [43, Appendix A]. Therefore, NP-GENSA(θ_0) cannot guarantee anymore a given specificity when $\varepsilon=0$.

In contrast, RDT-GENSA(θ_0) can be used instead to make a decision on ε. Actually, it follows from the triangle inequality, and the assumptions on θ_0 and Δ, that

$$(\varepsilon=0\Leftrightarrow\|S^{\mathrm{ext}}\|\leqslant\tau)\text{ and }(\varepsilon=1\Leftrightarrow\|S^{\mathrm{ext}}\|>\tau)\,.\tag{29}$$

Therefore, from Proposition 4.2, (29), (24), (25) and (27), and since ε is non-degenerated,

$$\inf_{(S^{\mathrm{ext}},N^{\mathrm{int}})\,\in\,\mathrm{rand}_{\mathrm{dstort}(\theta_0)}}\mathbb{P}\Big[\mathcal{R}_{d/2}(\tau,\|X^{\mathrm{obs}}\|)\leqslant\gamma\,\Big|\,\varepsilon=0)\Big]=\gamma\tag{30}$$

and

$$\begin{aligned}&\mathbb{P}\Big[\mathcal{R}_{d/2}(\tau,\|X^{\mathrm{obs}}\|)>\gamma\,\Big|\,\varepsilon=1)\Big]\\&\qquad\geqslant\mathbb{P}\Big[\mathrm{act}_{\mathbf{G}}(\|X^{\mathrm{obs}}\|)>\lambda_{\mathbf{G}}(\gamma,\tau)\,\Big|\,\varepsilon=1)\Big]\end{aligned}\tag{31}$$

for any $(S^{\mathrm{ext}},N^{\mathrm{int}})\in\mathrm{rand}_{\mathrm{dstort}(\theta_0)}$ and any $\mathbf{G}\in\mathcal{K}_\tau^{\mathrm{rand}_{\mathrm{dstort}(\theta_0)}}(\mathcal{G}_{\mathrm{chng},\theta_0})$. It follows from the foregoing that $\mathbf{G}_{\mathrm{RDT}(\theta_0)}$ is UMS in $\mathcal{K}_\tau^{\mathrm{rand}_{\mathrm{dstort}(\theta_0)}}(\mathcal{G}_{\mathrm{chng},\theta_0})$ and thus makes it possible to decide on the value of ε with guaranteed specificity and optimal sensitivity.

5 Conclusion and prospects

We have presented the first part of our on-going research dedicated to mathematical models of biological dynamic systems such as the immune system. Central to this research is the GENSA, as defined in the present paper in the form of an automaton. The GENSA can be used as a model of agent, but also as a model of discretized differential equation. As such, the GENSA is expected to apply to various physical systems beyond biological ones. In continuation to [32, 44], we have randomized the GENSA to study statistical properties of this model. By casting the GENSA into a statistical testing framework, we have derived and assessed different similarity and activation functions. In his respect, we have exhibited NP-GENSA(θ_0) and RDT-GENSA(θ_0) to illustrate the functional redundancy that these two types of GENSA verify. With reference to our companion paper [29], NP-GENSA(θ_0) targets known patterns, analogously to how the immune system quickly recognizes conserved signals, whereas RDT-GENSA(θ_0) is aimed at detecting possibly unknown and/or rare patterns through random perturbation tests, mirroring the immune strategy of generating diverse receptors to detect novel antigens.

Note that our results on NP-GENSA(θ_0) (resp. RDT-GENSA(θ_0)) have been stated for a family of GENSAs with same dissimilarity function $\delta^{\mathrm{obs}}_{\mathrm{det}(\theta_0)}$ (resp. $\delta^{\mathrm{obs}}_{\mathrm{chng},\theta_0}$). We made this choice for it suffices to exemplify the de-generacy properties of NP-GENSA(θ_0) and RDT-GENSA(θ_0), without getting the reader bogged down into mathematical details. In fact, we have not fully exploited the Neyman-Pearson Lemma [40] and [42, Theorem 2]. An on-going exploratory work is aimed extending the optimality and de-generacy of NP-GENSA(θ_0) and RDT-GENSA(θ_0) to more general families of GENSAs, with dissimilarity functions larger than those considered in this paper.

It was important to derive de-generate GENSAs to pave the way for further theoretical analysis of functional redundancy, "*[...] generally associated with higher resilience*" [45]. For instance, degeneracy allows the immune system to maintain function despite perturbations and to evolve new solutions through redundancy and fuzziness [46]. More generally, "*Robustness, a system's stability, and resilience, the ability to return to a stable state, are key concepts that span multiple disciplines within and outside the biological sciences*" [47] and "*Determining the processes that generate resilience and robustness to disturbance across levels of biological organization is increasingly important as the pace of global change accelerates [...]*" [48]. Dynamical models such as the GENSA are expected to bring much to our understanding of robustness and resilience of biological systems.

To explore further the model of robustness and resilience that GENSAs can actually propose, invariance should be key because of the abundant symmetrical features encountered in the biological world [10] and its links with robustness. For instance, "*[...] scale-invariance allows a system to detect relative, as opposed to absolute, changes in input signals, and to do so robustly even when intermediates in signaling pathways are varied*" [6]. A key point in our on-going theoretical analysis is the following one. Fundamentally, as a consequence of the RDT theory introduced in [42], RDT-GENSA(θ_0) fundamentally optimizes a criterion based on invariance properties of the problem it addresses. The robustness of RDT-GENSA(θ_0) directly relies to these properties of invariance, in contrast to NP-GENSA(θ_0) whose optimality, specified by the Neyman-Pearson Lemma, is not based on invariance properties.

As already noticed above, Definition 2.6 does not specify any readout function for GENSAs. Nevertheless, we have proposed readout functions for NP-GENSA(θ_0) and RDT-GENSA(θ_0) on the basis of some arguments given in Remark 4.1. It can thus be wondered to what extent the particular choice of readout functions for NP-GENSA(θ_0) and RDT-GENSA(θ_0) can help us exhibit appropriate features that GENSA readout functions should satisfy. Our guide in this respect is to consider that the outcome of the readout function of a given GENSA, say $\mathbf{G}_0$, is a message formalizing the action exerted on $\mathbf{G}_0$ by its exterior. This exterior can itself involve other GENSAs receiving this message emitted by $\mathbf{G}_0$, and emitting themselves messages, thus forming with $\mathbf{G}_0$ a communication network. The issue is then to design suitable readout functions to optimize, in a sense that remains to be specified, this communication network. The study of such a communication network could address, as suggested above, the case of GENSAs with memory affected by a loss or an alteration of the model θ_0, to which NP-GENSA(θ_0) or RDT-GENSA(θ_0) are tweaked. The impact of a network of GENSAs on $\mathbf{S}^{\mathrm{ext}}$ could also be studied and it could also be wondered whether the external environment of a given GENSA could not be modeled, itself, as a network of GENSAs.

As a privileged application of our theoretical framework, one question to address could be how and whether the GENSA and, eventually, networks of GENSAs, can be used by integrating omics dataset to retrieve population dynamics or other time-series. We could begin by integrating omics datasets related to cell proliferation and cycle regulation. For example, modeling basic T cell proliferation dynamics using transcriptomic and phenotypic data would provide a foundational layer. Subsequent integration of findings from [49] on immunological memory collapse, [50] on T cell homeostasis, and on proliferation heterogeneity [26] would require dynamic adaptation of network topologies and degeneracy parameters.

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References

[1] K.J. Schlesinger, S.P. Stromberg, J.M. Carlson, Coevolutionary immune system dynamics driving pathogen speciation, PLOS ONE **9**, 1 (2014). 10.1371/journal.pone.0102821

[2] M. Schatz, A. Phillippy, The rise of a digital immune system, GigaScience **1**, 4 (2012). 10.1186/2047-217X-1-4

[3] T. Pradeu, E. Vivier, The discontinuity theory of immunity, Science Immunology **1** (2016). 10.1126/sciimmunol.aag0479

[4] A. Doncescu, P. Siegel, in *Emerging Trends in Computational Biology, Bioinformatics, and Systems Biology*, edited by Q.N. Tran, H. Arabnia (Morgan Kaufmann, Boston, 2015), Emerging Trends in Computer Science and Applied Computing, pp. 409–427, ISBN 978-0-12-802508-6

[5] J.J. DiStefano, Dynamic Systems Biology Modeling and Simulation, 1st edn. (Amsterdam : Elsevier, Academic Press, 2015)

[6] E. Sontag, A dynamic model of immune responses to antigen presentation predicts different regions of tumor or pathogen elimination, Cell Systems **4** (2017). 10.1016/j.cels.2016.12.003

[7] L. Cuesta-Herrera, L. Pastenes, A. Arencibia, F. Córdova-Lepe, C. Montoya, Dynamics of activation and regulation of the immune response to attack by viral pathogens using mathematical modeling, Mathematics **12**, 2681 (2024). 10.3390/math12172681

[8] V.M. Veliov, A. Widder, Modelling and estimation of infectious diseases in a population with heterogeneous dynamic immunity, Journal of Biological Dynamics **10**, 457 (2016). 10.1080/17513758.2016.1221474

[9] R. Eftimie, J. Gillard, D. Cantrell, Mathematical models for immunology: Current state of the art and future research directions, Bulletin of Mathematical Biology **78** (2016). 10.1007/s11538-016-0214-9

[10] A. Villaverde, Symmetries in dynamic models of biological systems: Mathematical foundations and implications, Symmetry **14**, 467 (2022). 10.3390/sym14030467

[11] J.T. Nardini, R.E. Baker, M.J. Simpson, K.B. Flores, Learning differential equation models from stochastic agent-based model simulations, J. R. Soc. Interface **18**, 20200987 (2021). 10.1098/rsif.2020.0987

[12] M.W. Covert, T.E. Gillies, T. Kudo, E. Agmon, A forecast for large-scale, predictive biology: Lessons from meteorology, Cell Systems **12**, 488 (2021). https://doi.org/10.1016/j.cels.2021.05.014

[13] S. Radosavljevic, T. Banitz, V. Grimm, L.G. Johansson, E. Lindkvist, M. Schlüter, P. Ylikoski, Dynamical systems modeling for structural understanding of social-ecological systems: A primer, Ecological Complexity **56**, 101052 (2023). https://doi.org/10.1016/j.ecocom.2023.101052

[14] H. Ye, R.J. Beamish, S.M. Glaser, S.C.H. Grant, C. hao Hsieh, L.J. Richards, J.T. Schnute, G. Sugihara, Equation-free mechanistic ecosystem forecasting using empirical dynamic modeling, Proceedings of the National Academy of Sciences **112**, E1569 (2015). 10.1073/pnas.1417063112

[15] W. Huang, C. Hauert, A. Traulsen, Stochastic game dynamics under demographic fluctuations, Proceedings of the National Academy of Sciences **112**, 9064 (2015). 10.1073/pnas.1418745112

[16] R. Medzhitov, A. Iwasaki, Exploring new perspectives in immunology, Cell **187**, 2079 (2024). 10.1016/j.cell.2024.03.038

[17] L.B. Nicholson, The immune system, Essays In Biochemistry **60**, 275 (2016). 10.1042/EBC20160017

[18] G.A. Rook, Regulation of the immune system by biodiversity from the natural environment: An ecosystem service essential to health, Proceedings of the National Academy of Sciences **110**, 18360 (2013). 10.1073/pnas.1313731110

[19] T. Pradeu, S. Jaeger, E. Vivier, The speed of change: Towards a discontinuity theory of immunity?, Nature reviews. Immunology **13** (2013). 10.1038/nri3521

[20] A. Iwasaki, R. Medzhitov, Control of adaptive immunity by the innate immune system, Nature Immunology **16**, 343 (2015). 10.1038/ni.3123

[21] A. Iwasaki, R. Medzhitov, Regulation of adaptive immunity by the innate immune system, Science (New York, N.Y.) **327**, 291 (2010). 10.1126/science.1183021

[22] D.M. MacGillivray, T.R. Kollmann, The role of environmental factors in modulating immune responses in early life, Frontiers in Immunology **Volume 5** (2014). 10.3389/fimmu.2014.00434

[23] H. Aßmus, R. Herwig, K.H. Cho, O. Wolkenhauer, Dynamics of biological systems: Role of systems biology in medical research, Expert review of molecular diagnostics **6**, 891 (2006). 10.1586/14737159.6.6.891

[24] V. Thomas-Vaslin, H.K. Altes, R.J. de Boer, D. Klatzmann, Comprehensive assessment and mathematical modeling of T cell population dynamics and homeostasis, The Journal of Immunology **180**, 2240 (2008). 10.4049/jimmunol.180.4.2240

[25] V. Thomas-Vaslin, A complex immunological idiotypic network for maintenance of tolerance, Frontiers in Immunology **5** (2014). 10.3389/fimmu.2014.00369

[26] J. Vibert, V. Thomas-Vaslin, Modelling T cell proliferation: Dynamics heterogeneity depending on cell differentiation, age, and genetic background, PLOS Computational Biology **13**, 1 (2017). 10.1371/jour-

nal.pcbi.1005417

[27] M.L. Mair, N. Tchitcheck, T.M. Witten, V. Thomas-Vaslin, Network topology and evolution of the gene co-expression of T cells during immuno-senescence, bioRxiv (2021). 10.1101/2021.09.01.458500

[28] I.R. Cohen, S. Efroni, The immune system computes the state of the body: Crowd wisdom, machine learning, and immune cell reference repertoires help manage inflammation, Frontiers in Immunology **10** (2019). 10.3389/fimmu.2019.00010

[29] V. Thomas-Vaslin, D. Pastor, Sensitive living systems: Balancing disorder and complexity in holobionts for communication across ecosystems, EPJ Web Conf. (2026).

[30] S.B. Shinde, M.P. Kurhekar, Review of the systems biology of the immune system using agent-based models, IET Systems Biology **12**, 83 (2018). 10.1049/iet-syb.2017.0073

[31] Y. Jamali, Modeling the immune system through agent-based modeling: A mini-review, Immunoregulation **6**, 3 (2024). 10.32598/Immunoregulation.6.1.7

[32] Pastor, D., Beurier, E., Thomas-Vaslin, V., A multiplicity of statistical models for modeling the degeneracy of living communicating holons, EPJ Web Conf. **263**, 01006 (2022). 10.1051/epjconf/202226301006

[33] M. Uhlén, Affinity as a tool in life science, BioTechniques **44**, 649 (2008), pMID: 18474040. 10.2144/000112803

[34] R. Noble, D. Noble, Harnessing stochasticity: How do organisms make choices?, Chaos: An Interdisciplinary Journal of Nonlinear Science **28**, 106309 (2018). 10.1063/1.5039668

[35] D. Noble, The role of stochasticity in biological communication processes, Progress in Biophysics and Molecular Biology **162**, 122 (2021), on the Physics of Excitable Media. Waves in Soft and Living Matter, their Transmission at the Synapse and their Cooperation in the Brain. https://doi.org/10.1016/j.pbiomolbio.2020.09.008

[36] S. Tonegawa, Somatic generation of antibody diversity, Nature **302**, 575 (1983). 10.1038/302575a0

[37] A. Casrouge, E. Beaudoing, S. Dalle, C. Pannetier, J. Kanellopoulos, P. Kourilsky, Size estimate of the alpha-beta TCR repertoire of naive mouse splenocytes, Journal of immunology (Baltimore, Md. : 1950) **164**, 5782 (2000). 10.4049/jimmunol.164.11.5782

[38] C. Metcalf, A. Tate, A. Graham, Demographically framing trade-offs between sensitivity and specificity illuminates selection on immunity, Nature Ecology & Evolution **1**, 1766 (2017). 10.1038/s41559-017-0315-3

[39] M.K. Kajita, K. Aihara, T.J. Kobayashi, Balancing specificity, sensitivity, and speed of ligand discrimination by zero-order ultraspecificity, Physical Review E **96**, 012405 (2017). 10.1103/PhysRevE.96.012405

[40] E.L. Lehmann, J.P. Romano, Testing Statistical Hypotheses, Springer Texts in Statistics, 3rd edn. (Springer, 2005), ISBN 978-0-387-98864-1

[41] Y. Sun, A. Baricz, S. Zhou, On the monotonicity, log-concavity, and tight bounds of the generalized marcum and nuttall q-functions, IEEE Transactions on Information Theory **56**, 1166 (2010). 10.1109/TIT.2009.2039048

[42] D. Pastor, Q.T. Nguyen, Random Distortion Testing and Optimality of Thresholding Tests, IEEE Transactions on Signal Processing **61**, 4161 (2013). 10.1109/TSP.2013.2265680

[43] Q.T. Nguyen, Contributions to Statistical Signal Processing with Applications in Biomedical Engineering (2012-11-23), https://tel.archives-ouvertes.fr/tel-00818320/document

[44] D. Pastor, E. Beurier, A. Ehresmann, R. Waldeck, Interfacing biology, category theory and mathematical statistics, Electronic Proceedings in Theoretical Computer Science **323**, 136–148 (2020). 10.4204/eptcs.323.9

[45] E. Lange, L. Kranert, J. Krüger, D. Benndorf, R. Heyer, Microbiome modeling: a beginner's guide, Frontiers in Microbiology **Volume 15 - 2024** (2024). 10.3389/fmicb.2024.1368377

[46] Q. Leng, Z. Bentwhich, Beyond self and nonself: Fuzzy recognition of the immune system, Scandinavian Journal of Immunology **56**, 224 (2002). https://doi.org/10.1046/j.1365-3083.2002.01105.x

[47] E. Crespi, R. Burnap, J. Chen, M. Das, N. Gassman, J. Rosa, Epaminondas, R. Simmons, H. Wada, Z.Q. Wang, J. Xiao et al., Resolving the rules of robustness and resilience in biology across scales, Integrative and Comparative Biology **61**, 2163 (2021). 10.1093/icb/icab183

[48] M.N. Vitousek, C.C. Taff, J.L. Williamson, Resilience and robustness: from sub-organismal responses to communities, Trends in Ecology & Evolution **40**, 468 (2025). https://doi.org/10.1016/j.tree.2025.03.001

[49] B. Bellier, V. Thomas-Vaslin, M.F. Saron, D. Klatzmann, Turning immunological memory into amnesia by depletion of dividing T cells, Proceedings of the National Academy of Sciences **100**, 15017 (2003). 10.1073/pnas.1936194100

[50] V. Thomas-Vaslin, H. Altes, R. de Boer, D. Klatzmann, Comprehensive assessment and mathematical modeling of T cell population dynamics and homeostasis, Journal of Immunology **180**, 2240 (2008).