A Population-Based Clonal Selection Algorithm and Extensions

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***Abstract*-Immune systems do not exist in isolation, rather the cellular and molecular interactions occur within the tissues of a host, and populations of hosts exist together in an environment. This work investigates the relationship between the acquired immune system and a pathogenic environment at the 'host-population' scale. A minimal population-based clonal selection algorithm is proposed and extend to include the host-population immunological principles of inter-population pathogen dynamics, vaccination/inoculation, and transplanted acquired immune cells.**

Keywords-Artificial Immune System, Host, Population, Acquired Immune System, Clonal Selection

I. INTRODUCTION

An acquired immune system does not exist in isolation, rather it is a collection of organs and tissues that collectively represent an integrated part of a host organism, which in turn belongs to a population of organisms. One may consider the hosts of a population interacting with each other, more specifically, interacting with regard to their immune systems. The class of model in which a population of clonal selection-based acquired immune systems interact with each other is referred to as '*multiple system models*' [1,3], at the '*host of a species*' level of abstraction (cell-tissue, tissue-host, host-species) [5]. This class of model may be divided into two principle types (for example see [2]), the first is the proposal of a population of interacting systems, and the second is the extension of the proposal in the evolution of a population of interacting systems. This work considers the former case, and proposes a minimal population-based clonal selection algorithm.

Section II discusses some design principles in realising a population-based clonal selection algorithm. Section III proposes a minimal population-based clonal selection algorithm as a set of independent host systems, each with their own acquired immune system responding to a common pathogenic environment. Section IV extends the minimal algorithm by introducing two classes of interaction between hosts in the population. The first class of interaction is the sampling and transmission of pathogen between systems inspired by inter-host dynamics and inoculation/vaccination. The second class of interaction is the sampling and transmission of hosts cellular repertoire between systems, inspired by the transplantation of immune cells. Finally, section V discusses some future extensions to the minimal population-based clonal selection algorithm.

II. SOME DESIGN PRINCIPLES

This section provides a collection of design principles for devising a population based clonal selection algorithm.

The clonal selection algorithm (for example [4]) is concerned with managing a population of cells in response to antigenic stimuli. This algorithm may be subsumed by a broader algorithm in which each clonal selection algorithm represents a principle component (or unit of adaptation) in the broader algorithm. In this raised level of abstraction, a clonal selection algorithm may be phrased as a 'clonal selection system' in a population of similar clonal selection-based systems.

***Principle**: A single immune system (instance of a the clonal selection algorithm) represents a principle component (in a population) of a larger system*

As in the clonal selection algorithm where each cell is distinct, and may respond to antigenic stimuli differently, in a population of systems, each system itself is distinct. The uniqueness of each system has two principle causes: (1) the stochastic basis of cell generation within each host, and (2) the stochastic properties that result in difference in pathogenic exposures between systems in the population

***Principle**: Immune systems in the population have a distinct information composition given the differentiated initial repertoire construction and subsequent responses to a (a potentially asymmetric) pathogenic environment*

The systems are created differently (different initial coverage of the pathogenic space), thus, each system responds differently to the same pathogenic exposure regimes. In addition, the systems may exist within a pathogenic environment that is not consistent for all systems (asymmetrical pathogenic exposures). The diversity of individual systems provides robustness to the population (species) in the face of an unknown and potentially changing pathogenic environment, thus system diversity promotes species survivability.

***Principle**: The innate diversity of the population of immune systems promotes robustness of the population in the face of an unknown pathogenic environment*

Although not all the properties of the pathogenic

environment may be available to the population, known pathogen may be collected and selectively exposed to systems. This collection and selective exposure may take two forms: (1) the inoculation of systems to known pathogen (controlled exposure to pathogen), and (2) the vaccination of systems to known pathogen (controlled exposure to information for addressing a known pathogen).

***Principle**: Immune systems in the population may be selectively exposed to known pathogen or information concerning known pathogen*

In addition to interacting with pathogens, the immune systems may interact with each other. The basis for the interaction may be varied, such as spatial proximity, similarity, or arbitrary (such as identification markers or tags). The most important interaction between clonal selection systems in the population is that of sharing acquired immune information.

***Principle**: Clonal selection systems in the population may interact with each other by sharing acquired immune information*

Sharing between systems involves the removal or copying of clonal selection acquired information from one system and infusing it into another system (such as memory and effector cellular components).

III. Minimal Population-Based Algorithm

Given the design principles of the previous section, one may propose a minimal population-based clonal selection algorithm. The algorithm is considered from a holistic perspective, where each immune system responds to pathogen according to its internal clonal selection principles, defined by a clonal selection algorithm or extensions (single or multiple internal repertoires).

Step1: *Initialise* all immune systems in the population
Step2: *Stimulate* the systems according to the pathogenic environment
Step3: *Respond* to any exposures according to each systems principles
Step4: *Interaction* between systems in the population
Step5: *Repeat* Step2-Step4, until stop condition is triggered

Figure 1 - Minimal population-based clonal selection algorithm

The principle components of algorithm include a pathogenic environment, a population of immune systems each with their internal clonal selection principles, and interactions between systems in the population.

Pathogenic Environment: The pathogenic environment in which the population of systems is phrased, which define both the population-level exposure regimes (ensemble of pathogen), and each system in the populations individual exposure regime
Population: Interacting with the pathogenic environment is a population structure, composed of individual immune systems. The structure of the population may be organised (lattice) or unorganised (collection) with respect to interactions with pathogen, and each other
System Selection Scheme: The pathogenic environment defines the exposure regime for the population and for systems, although explicit system-selection schemes may be used, for example spatial proximity to pathogenic origin, infected (exposed) systems or susceptibility to pathogen
System Principles: The specific details of how each system responds to pathogen is not required for the population based algorithm. A simple clonal selection algorithm is assumed, although any single or multiple repertoire clonal selection-based algorithm may be employed
System Interactions: The immune systems in the population may (or may not) interact with each other, which may be facilitated in a number of ways (population dynamics, spatial proximity), and which may have a number of consequences. These consequences may include the sharing of acquired immunity and the transmission of pathogen.

Figure 2 - Discussion of the principle components of the population-based algorithm

The procedure outlined in Figure 1 is remarkably similar to the minimal recirculation clonal selection algorithm, outlined in a previous work [7]. A concern is that there is little conceptual difference between a population of clonal selection-based immune systems, and a population of clonal selection-based tissues.

***Ambiguity Concern**: A tissue-based clonal selection algorithm may be considered a population-based clonal selection algorithm*

A tissue-based clonal selection algorithm, such as the recirculation algorithm and extensions (homing algorithm and inflammation algorithm) are algorithms devised on the premise of populations of immune cells. A population of immune systems may also be reduced to a population of immune cells. Thus, the two classes of algorithm share this 'conceptual description' in common. The differences between the two classes of algorithm are many, the focal point of which is the scale at which the acquired immune system is considered. For tissue algorithms, the scale (at a limit) is a single host organism with a single immune system. For population algorithms, the scale (at a minimum) is a population of very simple immune systems that may resemble the complexity of a single acquired immune system. Although, the definition of algorithms at this scale (at a maximum) subsumes the complexity of the tissue algorithms at their limit such that each system at the population level may be an instance of a multiple-tissue based acquired immune system algorithm.

***Difference of Scale**: The focal point of the differences between tissue and host based algorithms is the scale of abstraction of the acquired immune system, multiple hosts subsumes the complexity of multiple tissues*

The scale at which the acquired immune system is considered constrains the abstractions of the system that may be realised. This is an important function of the scale-based approach (for example see the hierarchical framework [5]). A series of tissues are interconnected within a host organism, defined by the (chosen) physiology of the host organism (for example, a cyclic graph structure to facilitate recirculation). In this case, the scale constraints the organisation and interactions between the population of immune cells (tissues), which is a constraint that has no meaning when the scale is raised to that of populations of organisms. In a population, the interactions between the systems may not be explicitly organised, or may be organised by the population dynamics of the organism.

***Constrained Abstractions**: The differences in scale define the differences in the abstractions that may be realised from each scale, as the chosen scale imposes constraints on the function, behaviour, and structure of derived abstractions (an important premise of using a hierarchal scale-based approach to deriving*

abstractions)

The minimal population-based clonal selection algorithm is primarily concerned with the interaction of a collection of independent immune systems with a pathogenic environment, and how the differences in initial composition and subsequent differences in response and acquired immunity may be exploited (Step4 implemented with no interactions). This base algorithm provides the foundation for more elaborate effects facilitated by inter-system (intra-population) interactions. Like a population of immune cells responding to pathogen exposures, a population of immune systems provides multiple adaptive perspectives on the problem manifest in the environment. This point highlights the niche for such an algorithm, and the lack of explicit connectivity highlights the difference of this minimal model and the minimal tissue model (which must be connected).

Minimal Algorithm*: The minimal algorithm is defined as a population of non-explicitly interacting clonal-selection based immune systems in a pathogenic environment*

The functional perspective of the minimal algorithm may be exploited in proposed extensions to the algorithm, and in applying the algorithm. In effect, one may consider the population of immune systems, themselves subjected to a clonal-selection (asexual Darwinian) like process. Although, unlike the theory, the systems do not create more instances of themselves after selection, rather, they acquire information by applying a clonal-selection process at a lower level. In this way, the population of systems may be consider one large population of cells which are segregated into non-interacting spatial compartments. The similarity between the two scales is the defence for having a population, when a (perfectly) matching set is sufficient.

Exposure Symmetry*: One may consider the symmetry or asymmetry of the pathogenic exposure environment to the systems in the population. Symmetry implies all systems are exposed (perhaps with some generality) to the same pathogens at the same frequencies, asymmetry implies varied exposure regimes to the systems, which in turn may change overtime.*

The symmetrical pathogenic environment case highlights the properties of the minimal population based clonal selection algorithm in the same manner it highlights the properties of a minimal clonal selection algorithm (and deficiencies). Unlike the minimal clonal selection algorithm, in which a winner takes all (or most), all systems in the population are exposed uniformly. A system may learn an environment, whereas a repertoire may learn an antigenic determinant. In this symmetrical environment case, the unique systems acquire information about the environment differently, thus each system is likely to posses a varied perspective of the environment (there may be a lot of common convergence). The independence of the systems means that the acquired different perspectives remain forever isolated. Integration of the varied perspectives requires an augmentation of the system at a higher scope, introspecting all systems and explicitly forming a cohesive understanding of the environment (presuming such an information-processing outcome is desired)

System Isolation*: The minimal population algorithm (without interaction between systems) facilitates the development of multiple varied perspectives of an environment that remain isolated. Integration would be explicit and require augmentation from a higher level of abstraction*

The 'isolated perspectives' concern of the population algorithm is made more apparent in an asymmetrical pathogenic environment. In such an environment, not only does the heterogenous population acquire information in different ways and rates, but the information content of the environment to which they are exposed also varies. Thus, although the population may collectively represent a map of the environment, there is no way for individual systems to share acquired information. This concern is further highlighted if we consider that the asymmetrical pathogenic exposure regimes for the systems in the population vary over time. In this case, the information acquired by one system is directly useful to other systems, although cannot be exploited.

Information Sharing*: The inability of the minimal population algorithm to share acquired information is exemplified in an asymmetrical environment that changes overtime in which information acquired by one system is directly useful but unable to be shared with other systems*

IV. EXTENSIONS

The minimal population-based clonal selection algorithm provides a foundation on which to incorporate more intelligent intra-population (inter-system) interactions. Perhaps the most important concern is that of the systems inability to transmit acquired information. This section extends the minimal population-based clonal selection algorithm to address this concern in two different ways. The first method is the selective exposure of systems in the population with known pathogen, following the population-immune inspired interactions of inoculation and vaccination. The second method is the transmission of acquired information in the form of acquired immune system substrate (antibodies and mature cells), inspired by the population-immune system interactions of transplantation and passive immunity.

A. *Pathogen Transmission Algorithm*

A given immune system in the population is exposed to a number of different pathogen, at varied frequencies. As noted in the previous section, the exposure regime that a given system is subjected to may vary across the population. A system in the population may record a sample of the pathogen it is exposed to and transmit that sample to other systems in the population in a controlled or uncontrolled manner. This sampling and transmission provides a mechanism by which a given immune system may share information acquired information about the pathogenic environment with other immune systems in the population.

***Transmission Principle**: The sampling of pathogen from exposures by a system, and the selective (system controlled or uncontrolled) sharing of the collected samples with other systems in the population*

Individual immune systems must collect and store samples of pathogen (to which they are exposed) for transmission to other systems in the population. This mechanism is referred to as the pathogen-sampling scheme. The sampled pathogen must then be passed on to other immune systems with which a given immune system interacts. This passing on is referred to as the pathogen-transmission scheme. The minimal population-based clonal selection algorithm may be modified to facilitate the sampling and transmission schemes, as follows:

Step1: *Initialise* all immune systems in the population
Step2a: *Stimulate* the systems according to the pathogenic environment
Step2b: *Sample* exposed pathogen according to each systems scheme
Step3: *Respond* to any exposures according to each systems principles
Step4a: *Interaction* between systems in the population
Step4b: *Transmit* sampled pathogen between systems according to a scheme
Step5: *Repeat* Step2-Step4, until stop condition is triggered

Figure 3 - Modification to the minimal population algorithm to facilitate pathogen transmission

The pathogen sampling mechanism is dependent on the pathogenic environment, more explicitly the pathogenic exposure regime the system is subjected to by the environment. The pathogen transmission mechanism is dependent on the intra-population (inter-system) interactions facilitated by the population structure, pathogenic environment, and any interaction-intensions of the individual systems themselves.

Pathogen-Sampling Scheme: The mechanism by which a given immune systems collects samples of pathogen to which it is exposed to, and stores those samples with the intent that such samples will be transmitted to other immune systems with which the system interacts. An example of a simple sampling scheme is the storage (memory of) the last pathogen exposure, which is replaced (updated) by each successive pathogen exposure.
Pathogen-Transmission Scheme: The mechanism by which a given immune system passes on the collected sample of pathogen to other immune systems with which it interacts. An example of a simple pathogen transmission scheme is to transmit a sampled pathogen to the first encountered system, after which time the sample is removed from the transmitting systems sample-storage mechanism.

Figure 4 - Summary of the principle components of the pathogen transmission algorithm

The algorithm is reasonably general, such that it may be specialised in a number of different ways, inspired by population-immune system interactions. The remainder of this section discusses the specialisation of the algorithm to two different general immune-inspired pathogen-transmission scenarios.

Uncontrolled: Pathogen Dynamics

A first simple specialisation of the algorithm is to that of an infectious pathogen that may be transmitted from host-to-host. Transmission is achieved via host contact, the number of hosts, and the time of infectiousness (storage time for transmission), all of which are a function of the pathogen.

***Pathogen Dynamics Principle**: The transmission algorithm may be specialised to facilitate the mechanisms of the intra-population dynamics of a pathogen, including infectiousness, and host susceptibility*

The implementation facilitates pathogen behaviour (host-mediated exposure regime) not considered at either the cellular or tissue scales. So called 'host-mediated' pathogenic exposure regimes facilitate emergent information process such as epidemics (rapidly spreading), and pandemics (compete or close to complete population exposure).

Scheme	Configuration Summary
Sampling Scheme	Samples are collected when a host is exposed to pathogen from the environment or another host. The longevity of the sample in storage is a property of the infectiousness of the pathogen. A host may be a carrier for more than one pathogen at a given time.
Transmission Scheme	A host may transmit a carried pathogen to any systems to which it comes into contact with (for as long as the host is a carrier). Interactions with other immune systems may be random, or mediated by proximity (such as in a spatial)

Table 1 - Summary of the transmission algorithm configuration for pathogen dynamics

This specialisation highlights an important property of the transmission principle, that is that in addition to the environment defining pathogenic exposures, the hosts interactions with other systems may also define pathogenic exposures. Further, the causal influences to inter-population interactions may also be considered indirect influences of host-transmitted pathogenic exposures (for example, such as a hosts proximity to other hosts, or more specifically other hosts from 'high pathogenic exposure' areas of the environment).

***Transmission Exposures**: The transmission algorithm adjusts the system-pathogen (exposure) relationship such that both (1) the environment, and (2) other immune systems are sources of exposures.*

A feature of host-based exposures is that a given host may be a carrier for one or more pathogens, to which an interacting system may be exposed. In effect, a given host may represent a microenvironment of pathogenic exposures.

Controlled: Inoculation and Vaccination

The pathogenic dynamics example provides a specialisation of the transmission algorithm, in which the sampling scheme is defined by the pathogen, and is thus outside the control of the host system. In this example, the host is provided with control over the sampling mechanism. Thus, a host may select both the pathogen, which it may collect and store, and a small sample of host systems from the population in which to transmit the pathogen. This specialisation of the algorithm is inspired by pathogen-inoculation principle from immunology in which a small sample of pathogen is given to a healthy system to illicit immunity to the pathogen.

***Inoculation Principle**: The transmission algorithm may be specialised to facilitate the mechanisms of inoculation of a healthy system with a collected sample of pathogen*

The inoculation scheme is simpler than that of the pathogen dynamics scheme in that (1) the host has

control over selecting which pathogen to transmit, and (2) the host has control over selecting a 'healthy' system to transmit a sampled pathogen.

Scheme	Configuration Summary
Sampling Scheme	Samples are collected when a host is exposed to pathogen, although the host has discriminatory control over which pathogen are collected and stored and which are not. Further, the host may decide to discard stored pathogen in the acquisition of additional information from the environment (such as exposure frequency).
Transmission Scheme	A host interacts with systems according to the properties of the environment and the population structure, although the host has control over selection of which encountered system to transmit a sample pathogen to. An example is that a host may select to infrequently inoculate those systems that are a greater distance from where the host was exposed to pathogen.

Table 2 - Summary of the configuration of the inoculation and vaccination specialisation of the transmission algorithm

The host selection mechanism provides a powerful tool for the population of immune systems to artificially manipulate the pathogenic exposure environment. This manipulation will have the intention of improving 'coverage' by the population for the inoculated pathogen. A host may decide to push the limits of the transmission scheme either under special circumstances (adaptive transmission), or all the time. Widespread inoculation may be referred to as vaccination, where the entire population or a large sample of the population of immune systems receive the transmitted pathogen.

***Vaccination Principle**: The transmission of a sampled pathogen by a system to a large sample (if not all) of the immune systems in the population*

Vaccination of a large sample of the population may provide the benefits of vaccinating the entire population given a 'herd immunity' effect. Alternatively, in conjunction with immunity sharing mechanisms (to be discussed next), the immunity acquired via the vaccination may be shared with un-vaccinated systems directly.

B. *Shared Acquired Immunity Algorithm*

The conceptual relationship between the host and the tissue algorithms draws attention to cell perspective in each algorithm. In the tissue based algorithms (the recirculation algorithm in particular), the focus is cells, specifically the trafficking of cells that results from intra-host interactions of tissues. From a tissue perspective, the algorithms consist of structurally organised chains of tissue-units that exchange information acquired regarding a pathogenic environment (for example see the lymphoid tissue architecture [6]). One may exploit the differences in perspective by considering the trafficking behaviour of lymphocytes the population-based algorithm.

***Sharing Principle**: Immune systems in the population may share acquired immunity by explicitly sampling their own cellular repertoire and transmitting sampled cells to selected host systems*

The sharing requires a sampling scheme of a hosts internal cellular repertoire, and the explicit selection of one or more other sibling host systems in the population to transmit sampled cells to. This sampling and transmission facilitates 'horizontal sharing' of acquired immunity within the population. The following describes the changes to the minimal population-based clonal selection algorithm to facilitate horizontal sharing.

Step1: *Initialise* all immune systems in the population
Step2: *Stimulate* the systems according to the pathogenic environment
Step3: *Respond* to any exposures according to each systems principles
Step4a: *Sampling* of cellular repertoire according to each hosts scheme
Step4b: *Interaction* between systems in the population
Step4c: *Transmission* of sampled cells according to each hosts scheme
Step5: *Repeat* Step2-Step4, until stop condition is triggered

Figure 5 - Summary of the sharing population-based clonal selection algorithm

The cell-sampling scheme is responsible for selecting those mature cells most likely to be useful to those host systems to which the sampled cells are transmitted. Thus there is a tight coupling between the selection (sampling) of a hosts cellular repertoire and the selection of the recipient host or hosts. Sampled cells will be mature in that they have been produced as a result of an interaction with the pathogenic environment. More useful, are those cells that are created from a series of exposures, and thus represent more refined and presently useful information about the environment.

Cell Sampling Scheme: (selection and removal of cells) The cell sampling scheme is the identification (selection) and collection of acquired immune cells from a given hosts cellular repertoire for transmission to one or more other hosts (as defined by the hosts cell transmission scheme). Those cells sampled for transmission should be mature with regard to the pathogenic environment, and representative of information acquired during the hosts recent exposures. Further, those cells selected will be removed from the hosts repertoire when transmitted, thus the removal of the selected cells should not be too critical to the hosts functioning immunity (redundancy that should be assured by a clonal selection scheme)
Cell Transmission Scheme: (host selection and cell integration) The cell transmission scheme requires the selection of sibling hosts within the systems population of immune systems, and the injection (transmission) of sampled cells to selected hosts. The principle concern in the selection of recipient hosts is that the transmitted cells are likely to be useful. This likelihood may be increased by selecting sibling immune systems in the population that are in turn likely to have been subjected to different pathogen and or at different frequencies (assuming an asymmetric pathogenic environment). Once selected, the transmitted cells must be integrated into the recipient systems cellular repertoire.

Figure 6 - Summary of the principle components of the sharing algorithm

The selection of recipient host systems is the selection of those systems in the population that would most benefit from the sampled acquired immunity. Examples include the transmission of cells from a healthy system (good performance with regard to some system-environment measure), to a system or set of systems that are less healthy (as defined by the same measure). In the absence of such a measure, a good heuristic is the transmission of a representative sample of acquired information to a host that is geographically distant (with regard to the pathogenic environment). This heuristic provides a general sharing scheme in which the hosts of the system seek to provide general coverage to the population by sharing acquired immunity.

***General Sharing Heuristic**: Taking a representative sample of a host's acquired cellular repertoire and transmitting it to one or more geographically distant*

(with regard to pathogenic exposures) hosts

After hosts are selected and the cells are transmitted, the recipient hosts must integrate the received cells into their cellular repertoire. The integration may be reduced to the detail of tissue selection, then cell selection for replacement (the reverse of which may be used to describe the cell selection scheme for transmission). If the host consists of a single tissue, then integration involves cell replacement, likely the hosts effectors, and naïve cells. If the host possesses multiple tissues, integration may require the selection of a tissue that will allow the transmitted cells to recirculate in the host (for example, tertiary tissue that leads to lymph nodes).

V. DISCUSSION

This work has introduced a minimal population-based clonal selection algorithm as a population of independent hosts, each with their own immune systems. To address the limitations of the minimal algorithms lack of intra-population interactions, two extensions were proposed. The first proposed the sampling and transmission of pathogen, in effect making hosts themselves as a secondary source of pathogenic exposures which may be used as a device by pathogen, or as a mechanism for sharing information about the environment between hosts. The second extension proposed the controlled and direct sharing of acquired immunity between immune systems in the population.

The proposed minimal population-based algorithm and extensions highlighted some limitations of the acquired immune system framework ([5]), and provoked some further streams of population-based extensions.

Tissue-Host Disambiguation: The distinction between tissue-based algorithms and host population based algorithms may have been presented in an ambiguous manner. The source of the ambiguity is the abstraction that both systems may be considered to process information with semi-detached populations of cells operating under clonal selection principles. The differences between these two classes of algorithm requires clarification. The principle differences include the following: (1) The systems are inspired by abstraction of the acquired immune system at different scales (host of tissues compared to a population of hosts). (2) The difference in scales result in varied abstractions from which algorithms may be devised, and the varied abstractions impose varied constraints on the information processing that inspired algorithms may perform. (3) The upper-bound in complexity of the tissue-based class of algorithm represents the lower-bound (or close to) in complexity of the host-based class of algorithm.

Generational Algorithm: The next logical step in extension of the minimal population-based clonal selection algorithm is the proposal of a generational population-based algorithm in which systems 'give birth' to progeny systems. The base generational algorithm may be extended first in the sharing of acquired immunity between generations (maternal immunity), and second by introducing the acquisition and processing of information over generational time using the process of neo-Darwinian evolution.

Arms Race: Beyond a generational extension to the minimal population-based clonal selection algorithm, one may consider extensions in which immune systems in a population compete with each other. This represents a complement to the present sharing and transmission extensions of the algorithm, where hosts cooperate with each other. Directly competing immune systems may represent a co-evolutionary arms race where the knowledge gained by one system comes at the detriment of another, which in turn may counter. A simpler arms race may be invoked, by allowing pathogen to directly evolve (using neo-Darwinian evolution) in the presence of the a population of immune systems, to which the systems must counter-adapt.

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