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An Agent-Based Approach to Immune Modelling: Priming Individual Response

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***Abstract*—**This study focuses on examining why the range of experience with respect to HIV infection is so diverse, especially in regard to the latency period. An agent-based approach in modelling the infection is used to extract high-level behaviour which cannot be obtained analytically from the set of interaction rules at the cellular level. A prototype model encompasses local variation in baseline properties, contributing to the individual disease experience, and is included in a network which mimics the chain of lymph nodes. The model also accounts for stochastic events such as viral mutations. The size and complexity of the model require major computational effort and parallelisation methods are used.

***Keywords*—**HIV, Immune modelling, Agent-based system, individual response.

I. Introduction

THE HIV infection can be presented as a viral attack characterised by a targeting of immune cells, a very high mutation rate and considerable variation in disease development between individuals. The macroscopic evolution of the infection is divided into three phases. The first one corresponds to the typical immune response to a viral attack. Lymphocytes specific to the viral strains are produced, and within a few weeks, all the original strains are eradicated. The HIV mutation rate here is critical. It permits the appearance of new strains, which have not been detected by the organism previously, and which can therefore develop freely. As soon as a strain becomes too dominant, its detection probability increases and it is eradicated. While undetected, mutations continue to produce new strains, which develop themselves. During this second phase, there are no symptoms. This is known as the latency period, which can be as short as a few months or last up to ten years. The destruction of a strain also implies destruction of an infected cell, and the heavily loaded immune system cannot cope with the ever increasing number of strains and remain viable, given a rapid decrease in the number of resistant Th cells. During this last phase, known as AIDS, (acquired immunodeficiency syndrome), the immune system breaks down and opportunistic diseases occur, and are ultimately fatal. The objective in this study is to address questions relating to variation in length in individual latency period.

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The immune response is a complex system involving growth, replenishment and mobility of cells, as well as in-built adaptability, through mutation of its defenses to meet new threats. The indications are that the observed variation in length lies in the priming and initial level of fitness of the individual immune response, together with the various factors influencing this [1]. In the long term the recognition, or even prediction, of such "priming patterns" may provide a way of "typing" an individual and targeting intervention appropriately.

However, the experience of antigenic invasion and diversity is non-trivial [1]. The challenge is to determine what assumptions can be made about the nature of the experience, can be modelled, tested against clinical data and hence argued plausibly. The aim is to understand how the cell interactions lead to the observed endpoints.

High-level behaviour of the immune system cannot be extracted analytically from a set of cell-level rules [1], but emerges as a result of stochastic events, which play an important part in the immune response [2]. An "agent-based" approach is used as a means to infer the macroscopic evolution from the microscopic rules.

II. Immune System and HIV Infection

A. Immune Defenses

A brief overview of the immune system is given here. More details can be found in specialised journals and immunology courses, such as [3].

Immunity can be defined as deriving from all mechanisms which allow the body to distinguish between self and non-self recognition. The former entities are tolerated; the latter are eradicated where possible. A non-specific response is based upon the fact that the foreign element does not show, at its surface, the antigens characterising the cells belonging to the body. In contrast, the specific response is based on the accurate recognition of foreign antigens: this involves some memory of previous recognition.

The complex set of cells and organs of the immune system involves the central lymphoid organs, namely the thymus and bone marrow. Bone marrow produces stem cells, which are lymphocyte precursors. These cells then mature, either in the bone marrow itself or in the thymus, to become (i) B lymphocytes or, (ii) T lymphocytes. A key aspect of the

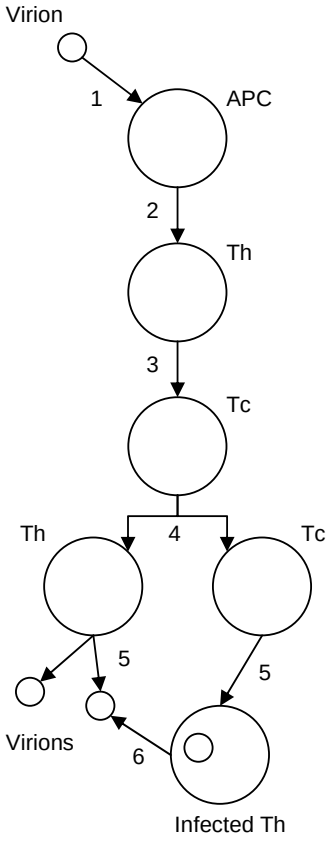

Fig. 1 Virions are detected by APCs (1) which activate Th cells (2). Th cells then activate Tc cells (3), which multiply themselves (4) and destroy (5) both the infected Th and the virions they produced (6)

maturation is the selection of the cell repertoire that the immune system uses to combat infections : each lymphocyte has a receptor allowing the recognition of a specific antigen. B lymphocytes carry out the antibody-mediated specific response, (also known as humoral response and mainly targets bacterial attacks). T lymphocytes become Th (helper) or Tc (cytotoxic) cells. Tc lymphocytes are the effector cells in the cell-mediated specific response, targeting viral attacks. Initially Antigen Presenting Cells (APC) recognise foreign biological entities and start presenting these antigens at their surface. These then encounter Th lymphocytes. If a Th cell encounters an APC presenting an antigen, which it has been specifically designed to recognise, it activates itself. The Th cells' main function is then to coordinate the immune response by activating specific Tc cells. These interactions, leading to the cell-mediated response, are summarized in Fig. 1.

Lymph nodes are secondary lymphoid organs and are colonised by newly created lymphocytes as soon as these cells finish their maturation process. Most of the immune response to viral attacks takes place in these nodes. There are about a thousand of these small defense units located throughout the body, along the lymph network.

B. HIV and AIDS

HIV virions use Th cells as hosts to multiply themselves, as detailed in [4] (and in Fig. 1). The gp120 glycoprotein of the virion envelope first attaches itself to the CD4 receptor, characteristic of these immune cells. Then the virion fuses with the lymphocyte using gp41 and the viral RNA is freed into the cell. The viral reverse transcriptase copies the RNA into DNA and integrates it into the cellular DNA. To be successful, this integration has to take place in activated cells. (For more details, see [5].

One of the most distinctive features of HIV spread is the high rate of mutation observed during the transcription: there is, on average, one error every 10,000 nucleotides. Since the HIV genome contains about 10,000 nucleotides, this means there is on average a single difference between two "brother virions". Most mutations result e.g. in the suppression of an enzyme, and will be unsuccessful. A successful mutation, however, can modify the envelope glycoprotein, thus allowing the new virion to temporarily escape from the immune system defenses.

When a virion achieves such an escape, the associated strain develops freely. As soon as a strain becomes established, risk of detection is higher and most are detected and eradicated. During this interim period however, further mutations will have occurred, adding to the viral load challenging the immune system response. Macroscopic evolution is, therefore, characterised by an ever increasing number of strains, which in turn leads to an increase in the number of virions. When the load becomes too heavy, breakdown of the system occurs, along with opportunistic AIDS-related infections, ultimately leading to the death of the patient.

III. The Modelling Approach

A. Modelling choices

Current computing resources cannot readily model a system as complex as the immune system, so that model focus is typically selective. However, Th cells are central both to the immune system coordination and to the HIV infection, and appear as a common feature in models previously developed (see e.g. [6]-[8]).

Another shared property and limitation of most early models is failure to account for mobility of either host or viral cells. Recognition of a threat is the first step toward activation of an immune cell. This involves specific receptors, but also physical encounters between the cells involved. Some models have dealt with this by specifying a constant probability of movement or encounter (see e.g. [9]) but for the real system it is unlikely that this obtains and a more flexible approach was provided, Mannion et al. [10]. Localised agents can take these ideas further. As most of the immune response to HIV takes place in lymph nodes, a realistic model can limit itself to a set of such nodes. An agent-based approach developed on this "world" can account for mobility both within each node and in the overall system.

Of the two types of specific immune response, cell-mediated dominates in the context of HIV infection. Consequently, our initial model focuses on this aspect.

B. Agent-Based Models

An agent-based model is a model in which the key abstraction elements are agents. The generally-accepted properties for an agent, there being no unique definition, are given by Wooldridge and Jennings [11]:

• Autonomy: it can act without any intervention and has some control over its actions and its internal state.

• Social behaviour: it can interact with other agents through a specific language.

• Reactivity: the agent can scan part of its environment and change its behaviour to take advantage of it.

• Proactivity: it not only reacts to its environment but also acts and takes initiatives, to satisfy identified goals.

Communication between agents (linguistic action) is an important aspect of this approach, because each agent has only a limited knowledge of the world in which it evolves. This is in contrast to non-linguistic actions, which deal with modifications of the environment, (which itself is shared by agents). Coordination of the agent actions is essential. Cooperation is not necessary and an agent may oppose another in the sense that competitors take advantage of complementary actions according to an opponent's decision. Reciprocity is also not implied as a decision affecting e.g. movement to a proximate location need not be influenced by an agent already in that location or any decision which it makes. Size of the agent population is clearly vital when effecting a coordination strategy, and, if every agent can mutually interact, the number of interaction pairs increases quadratically with the population size. If interaction can occur between several agents, the coordination overhead increases exponentially and soon challenges available computing facilities [12]. Developing a coordination strategy is therefore both essential and difficult. Managing to avoid conflicts and blocks is often as much as can be managed. The main drawback of this approach is the fact that it is is resource-consuming; for this reason, parallelism is also desirable (Section VI-A).

Traffic planning [13], vehicle monitoring [14], management [15] and social dynamics [16] all provide examples of agentbased modelling. As it provides an intuitive way to model systems of multiple biological entities with varied interactions, through linguistic and non-linguistic actions, it has also been extensively used in Natural Sciences (e.g. [17], [18]). In our particular study, the immune system is a discrete complex system, in which the individual behaviour of every cell aggregates to create high-level behaviour, reflecting the whole system.

Several generic agent-based development environments are available, (e.g. Swarm [19], JADE [20], or Cougaar [21]), but, in large-scale simulations, a fully dedicated approach can be more efficient. In the particular environment of the immune system, detailed knowledge of cell interactions is required to distinguish "priming" tendencies, so we use a bottom-up approach. The first step is the detailed specification of the individual parts of the system (the agents), which are then linked together to form layer components (the lymph node), which are in turn linked until a complete system is formed (the lymph network.

IV. Implementation

A. Lymph Nodes

The immune system is organised so that every lymph node is a small defense unit, in which most of the immune response to HIV is taking place. The world we model need only be a network of such nodes (with emphasis on the local interactions inside the node). There is no need for the response to take place in every node, so we build our nodes as independent matrices. Each matrix element corresponds to a physical neighbourhood. All interactions, therefore, happen inside this local element and there is no need to consider surrounding matrix elements as when using Moore or Von Neumann neighbourhoods [22].

The allocation of the agents is a decisive aspect of the implementation. Memory allocations are among the slowest operations on a computer and, here, we have a model in which thousands of agents are created and destroyed every iteration. Dynamic allocations would make the program too slow. The approach we have chosen is to have, in each matrix element, a set of integers, one for each potential agent located there. Each integer represents an offset used to find the agent in a statically allocated array containing the maximum number of agents we want to implement. Then, an agent moving from one element to another is coded as the alteration of only two integers, one in each element, where the creation/destruction of an agent alters only one local attribute.

The recirculation and the mobility of cells from one node to another is the only physical exchange between lymph nodes. Each node in the model, therefore, needs an entry point and an exit point. An agent reaching the exit point is removed from the node and put into a transfer list. The list is dealt with at the end of the iteration. In the meantime, other agents move and interactions take place over time. This reflects the time taken for the cell in real-life to commute between two nodes. The way in which agents are transferred between the nodes, focus on attributes rather than on the agent itself. Thus, an entry in the transfer list contains the type of the agent, its attributes, and its destination. At the end of the iteration, all lists are put together and the moving agents are transferred to the entry point of their destination node.

B. Cell Interactions

In focusing on the cell-mediated response, we need several types of cells, corresponding in the code to different types of agents, and another type of agent to model the virions. Each type is implemented using a specific C++ class.

The cell mobility is a common property of all four types of cells, even though they have totally different roles. This is

implemented by another class, which is then inherited by the four types described above. It incorporates basic properties such as the age of the agents and permits the four agent classes to contain only type-specific features (e.g. the strain for a virion agent); an advantage of object-oriented programming.

Each agent has a short-term and partial knowledge of its environment; partial in the sense that it is knows only whether there are cells it can interact with in its physical neighbourhood, i.e. the "accessible" matrix element, (e.g. an APC agent will not have any knowledge of Tc cells), and short-term in the sense that it has no memory of the evolution of the neighbourhood.

An APC agent only has one specific attribute, its "presenting state", coded as an integer. As long as the agent is not presenting any antigen at its surface, the integer stays at zero, and the agent's behaviour is focused on moving and looking for "foreign" entities in its physical neighbourhood, in order to find antigens. Then, the "presenting state" records the strain corresponding to the antigens, and the agents starts looking for Th agents in order to activate them, if they are primed to recognise this particular antigen.

A Tc agent has four specific attributes, also coded as integers:

- surface antigens, (as for Th agents);
- "activation state", to deal with the observed change in behaviour of an activated cell;
- "expansion state", to manage the phase during which the agent multiplies;
- "memory state", to manage memory cells.

Each Tc agent seeks and destroy only agents corresponding to the strain which activated them. When activated, an agent multiplies itself during an expansion phase, corresponding to a non-zero "expansion state". After an immune response, a small number of Tc agents will become memory cells: their "memory state" will keep track of the strain they fought, so that reactivation is easier, and if reactivated, the expansion phase is more productive.

A Th agent has three specific attributes incorporated in the model through integers which respectively code:

- surface antigens; used to recognise viral strains;
- "activation state"; changes the behaviour of the agent when activated;
- "infection state"; reflects the change in behaviour when the agent is infected.

If the Th agent is neither activated nor infected, both integers coding the states are set to zero, and the agent's only objective is to be ready to answer an attack. There is therefore no particular action, apart from moving. The objective of an activated agent is to activate Tc cells. Its "activation state" is coded to the value coding the viral strain, so that it can communicate on the threat. If the agent is infected, it produces new virions belonging to the strain coded in its "infected state", or to a new one if there is a mutation.

An agent coding a virion only has one specific attribute in the model, its viral strain. In order to prevent the code from allocating too much memory for each agent, the viral strain is coded as an integer used as an offset in an array containing all the useful properties of that strain. For instance we need to know, for each strain, which lymphocytes will recognise it for sure and which lymphocytes might recognise it. One characteristic, critical for the realism of the model, is that when a lymphocyte recognises a strain, its category is upgraded.This allows us to introduce some adaptability and emergent behaviour. The high mutation rate implies a large number of strains, increasing as the simulation continues. If we consider only memory use, a list seems useful as a structure to store the strains, since it uses only necessary information, as opposed to a statically allocated structure. However, the bigger the list, the longer it takes to obtain the properties for a particular strain and, since this list has to be accessed thousands of times in every iteration, the whole program is slowed down. We therefore use an array of strains, for which the access time is independent of the number of strains. This array is large (i.e. tens of thousands of potential strains). Considering that an entry in the array can account for various strains in real life, (if they differ on properties such as capside structure we do not code explicitly), we are confident this should give us enough diversity. The virion's unique objective is to infect a Th cell. Therefore, the typical behaviour of a virion in the model can be given as the following triptych, repeated until a lymphocyte is infected: the agent moves, scans its environment looking for a Th cell, and if possible infects the immune cell.

V. Random Number Generation

Many aspects of the real-life system involve stochastic events, and, consequently, most methods and functions in our model have to include random number generation. More details about the stochastic aspect of the immune system can be found in [2], but examples include the process by which new lymphocytes are created: a lymphocyte can only recognize a specific set of antigens so that, to protect itself against any attack, the body has to generate thousands of "variations" between lymphocytes. This has to be implemented using random numbers. Likewise, we noted earlier that one of the most distinctive features of the virions is their high mutation rate, and this implies another use of random numbers. Finally, there is no sensible way to deal with mobility unless we include stochasticity.

A reliable and efficient random number generator is essential. A full-scale model will involve millions of agents in very long simulations. As parallel aspects are involved, it is desirable also for the generator to include such features. There are many generators available, and good ones can also be designed explicitly (see e.g. [23]). Needed here is a top-quality parallel generator, and we chose to use the Scalable Parallel Random Number Generators library (SPRNG) [24]. This library incorporates recent, state-of-the-art developments in the mathematics and computer science of parallel pseudorandom number generation. It is an efficient library

with an existing, active, user base, ensuring high standards. In particular, it allows the streams to be also absolutely reproduced, for computational verification, independent of the number of processors used in the computation and of the loading produced by sharing of the parallel computer. High confidence in the statistical results, at a very low computing cost, is a feature of this library usage.

VI. Limitations and Early Results

A. Parallelisation

To achieve realism, each node must contain hundreds of thousands of agents. In real life, a human body contains about a thousand lymph nodes and mobility occurs between the nodes. Even with fifty nodes, we would have to deal with millions of agents, for about six million iterations. Hence, a parallel approach is strongly indicated.

The parallel nature of the units of the system defenses is reflected by permitting each lymph node experience to be computed by a different computer (called a computing node) on a cluster. This type of spatial parallelisation has previously been studied for Monte-Carlo simulations [25], with the main disadvantage being the communication overload. Here, communication on the cluster deals only with the transfer of agents from one node to another, using the list process described earlier. This parallel approach is implemented using the Message-Passing Interface (MPI) [26]-[27]. It was validated on a cluster composed of a Dell PowerEdge 1750 acting as the master node and sixteen of these machines acting as slaves. More powerful clusters will also be used for full-scale runs.

The human immune response is extremely efficient in terms of communicating threat and sharing information to achieve a unified defense. Trying to mimic the complexity of the communication is non-trivial and can easily become grossly inefficient as no auxiliary networks exist, (as are found in real immune systems). Moreover, as the system size increases, a bad communication strategy can have devastating effects on the computation time. Stochastic aspects of our model, such as mutations, require several simulations for each set of parameters, and cannot afford inefficiency. Consequently communication aspects must be considered and are discussed in detail in a companion paper [28]. For convenience, we summarize the main findings here (see Fig. 2).

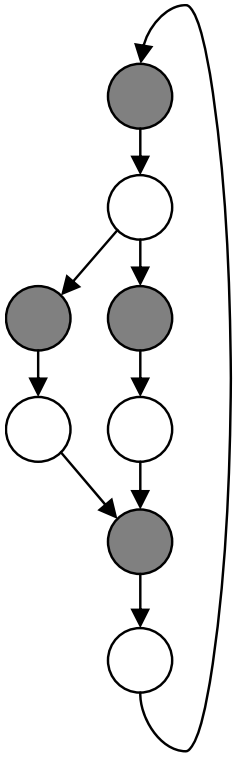

Fig. 2 Data transfer strategy - A network of nodes with two-colouring

1) On each node, a single list for all agents is more efficient than having one list for each type of agent, due to the latency of the cluster.

2) The most efficient data transfer is achieved by creating a network between the lymph nodes, similar to that found in the human body, and by colouring this network so as to balance the data transfer between the nodes: on odd iterations, white nodes send data and coloured nodes receive it; on even iterations the roles are inverted.

B. Validation

The overall behaviour of the model is an aggregation of individual actions, which is an advantage in the sense that it provides a powerful tool to account for mobility and precise interaction rules. However, the disadvantage is that since this macroscopic behaviour cannot be analytically extracted from the set of local rules, validation is a long and difficult process.

The first step is the local validation of the interactions. This step is crucial, as these control the whole system, but is also the most intuitive part. For our model, we just need to run the program on a single node and verify every move, interaction and change of behaviour.

The second step is the validation of the data transfer between the lymph nodes, which ensures that data is neither lost nor created. This forms part of our parallelisation strategy. The last step is the validation of overall behaviour. The difficulty is that there is no simple criterion, such as a convergence rule; the system is continuously evolving. The

only solution here is to run a significant number of simulations, acquire sufficient clinical data (e.g. [29]-[31]), and isolate similar patterns in both sets.

C. Individual Response

Even though the validation process is still under way, we are already seeing early signs of what will correspond to individual responses. First, this is a result of our lymphocyte generation: we mimic the real system, in the sense that immune cell creation involves stochasticity. Each simulation will generate a different set of lymphocytes, recognising a different set of viral strains, in the same way as two patients have different immune systems. These individual variations are also obtained through viral mutations. Even though the overall behaviour stays the same, the actual strains involved will change from a simulation to another, thus introducing variations, e.g. in the production rate and the recognition. Cell mobility also introduces variations, in the sense that even with similar immune systems and viral load, the disease spread will depend on whether there is a physical encounter between the virions and the lymphocytes primed to recognise them.

VII. Conclusion

A. Modelling Choices

The objective of this study is to examine factors contributing to individual experience in HIV infection, addressing in particular questions relating to variation in length in latency period. To investigate these questions, an "agent-based" approach is chosen, as a means of inferring high-level behaviour from a small set of interaction rules at the cellular level as well as including stochastic events.

The model, developed, mimics the immune system, through organisation as a network of matrices, each of them corresponding to a lymph node. Matrix elements can host several agents, of four different types, accounting for virions, Th and Tc lymphocytes, and Antigen Presenting Cells. Thus, it is possible to model the HIV spreading strategy and the cell-mediated immune response. The individual response is modelled through mobility, mutations and adaptability.

As the system we study is so complex, millions of agents are needed, and it is not possible to run the model on a single computer. Therefore, parallel methods have been implemented. Using MPI, every lymph node has been allocated to a different computer on a cluster, and various communication strategies have been tested in complementary experiments.

The local interactions have been validated and the most efficient communication strategy, which mimics the real lymph network, has been optimized. Full-length simulations are currently being computed, and early validation results indicate individual responses.

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