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A Constructive Systems Approach to Understanding the Immune System as a Biological Problem Solver

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***Abstract*- This paper explores a constructive systems approach to understand the immune system, starting from antibodies which are major units bearing specific recognition of the adaptive immune system. The exploration proceeds in stages: Arrayed Recognitions; Networked Recognition/Actions; and Diversified Recognition/Actions. System theoretic aspects of the immune system will be discussed with respect to possible application of immunity-based problem solving.**

I. INTRODUCTION

DNA based computing [1] has revealed that a biological component, i.e. DNA, can solve combinatorial problems such as obtaining a Hamiltonian circuit of a given network. A character of DNA, i.e. complementary matching (another but related character is self-replication), is used. Instead of using biological systems such as ants for obtaining shortest paths [2], an amoeboid organism for solving maze problems [3] has been used in a problem-solving context.

These works revealed that not only biological systems but also a specific character of a mere component (or lower level systems in a hierarchy of biological systems) can solve a problem. Inspired by these works, we studied how a simple elementary component of the immune system, i.e. antibodies, can solve problems such as the stable marriage problem [4] when properly arranged and arrayed (as in a microarray or microchip) [5]. This paper aims to extend the array to a more systematic problem solver by progressively developing a system of agents mounting a receptor and an effector. Throughout the paper, the *stable marriage problem* is used for explaining the different phases of the problem solver. After applying this construct to the immunological problem solver, we briefly discuss next-generation immunity-based systems.

The origin of problem solving dates as far back as the period when artificial tools were invented. Regarding scientific problem solving, Polya [6] examined mathematical problem solving and stressed the importance of using similar problems to solve a problem. In this study, we examine problem solving more rigorously by artificial information systems (i.e. computers).

Problem solving by means-ends analysis (MEA) [7] organizes a search in a dynamically constructed search space of goal-subgoal decomposition. It embodies and simulates human problem solving by a recognition-action cycle as shown in Fig. 1, where solid arcs are recognitions and white arcs are actions. Recognition action cycles are iterated till there is no difference between goal state and current state. Recognitions of the current state, the goal state and the difference are used to select an appropriate operator to apply to the current state, which is supposed to be changed toward the goal state.

The figure has remarkable similarity to a block diagram of feedback control in system theory. An important feature of MEA is that the application of operators is not very rigid: if an operator selected in the heuristics part is not directly applicable to the current problem, the problem will be divided into sub-problems. This flexibility allows a certain degree of freedom in identifying the heuristics, and further contributes to the generality of problems that MEA can handle. In fact, MEA was implemented as a General Problem Solver (GPS) [8] that can deal with many well-known puzzles.

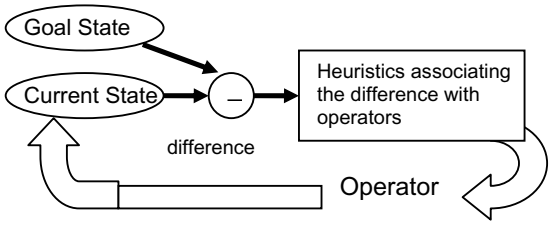

Fig. 1. Problem solving by Means-Ends Analysis (MEA) where solid arcs are recognitions and white arcs are actions.

As an intermediate stepping-stone from the general problem solving by MEA to an immunity-based problem solving, let us briefly consider more general biological problem solving. One difficulty is that units of biological systems such as DNA, cells, individuals, and species do not constitute a usual hierarchical system as is understood in system-component relations found in most artificial systems. A second difficulty that makes biological problem solving remarkable, is that biological systems use concepts distinct from those used in artificial systems to realize robustness. (Robustness is a solution implemented and embedded in the system by a biological problem solving in response to challenges to the survival of the system.) One such example is degeneracy, which is defined as 'the ability of elements that are structurally different to

perform the same function or yield the same output' [9]. This is markedly different from "redundancy" or "stand-by" which use an exact copy (hence structurally identical). We used the concept of "diversity" to implement robustness in an immunity-based design [10], but there may be subtle differences between degeneracy and diversity, since in diversity, even functions may be varied to attain robustness (as mentioned briefly in section V). What is more important in discussing biological problem solving is: Biological problem solving utilizes variations for implementing robustness, whereas artificial problem solving considers variations as disturbances and tries to prevent them from occurring and to minimize their effect. Thus, the "difference" in biological problem solving can be quite different from that in Fig. 1.

The third factor that makes biological problem solving complex is that the given problem is the challenge to the survival of the problem solver (the biological system) itself. This self-referential aspect must be considered when capturing the immunity-based problem solving shown in Fig. 2.

Throughout Fig. 1 (MEA), and this Fig. 2 (immunity-based problem solving), the framework for problem solving is: recognize the difference and deploy actions based on the difference. However, actions are oriented toward the system itself for biological problem solving and this immunity-based problem solving, hence the process, is intrinsically adaptation. Figure 2 and the following discussions focus only on the immune system involving antibodies, hence that of adaptive immunity.

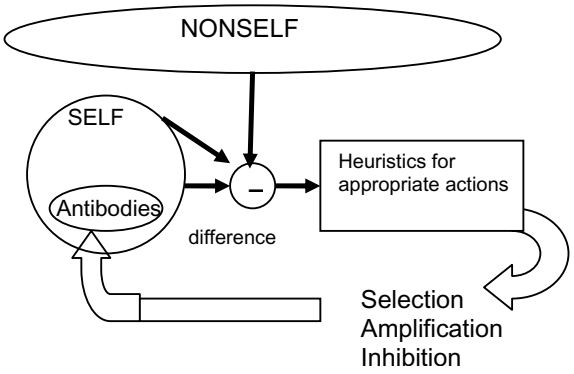

Fig. 2. The immune system as a problem solver. Only antibodies are focused.

In the following sections, an immunity-based problem solver will be explored as below:

1) A recognition part is designed based on antibodies that have specific recognition capabilities (Section II). Even only a collection of antibodies can exhibit computational capability.
2) An effector part is also involved, and the solver is placed within the system, which amounts to implementing agents with not only recognition capability but also be recognized. This self-referential character will pose some system theoretic problems (Section III).
3) Diversity is also involved, which will make the problem solver an adaptive system (Section IV). Fig. 2 will be elaborated by agents with diversity.

II. Arrayed Recognition Can Compute

After DNA-based computing was pioneered, many researches established that not only DNA but also other macro molecules could have computational capability comparable to DNA. For example, protein based computing was proposed [11] and extended [12].

Similarly to DNA-based computing, antibody-based computing utilizes complementary matching between macro molecules, namely antibodies. Since the computational capabilities of DNA-based computing could be inherited to antibody-based computing, we focused on the difference between them.

Affinity between antigens and antibodies can be measured and their intensities can be ordered (as formatted in an affinity matrix). That is, in contrast to **Matching**(DNA_i, DNA_j)=1 (matched) 0 (not matched), **Affinity**($Antigen_i$, $Antibody_j$) could vary from 0 (no agglutination) to 1 (highest agglutination). This difference would suggest that antibody-based computing could potentially implement error tolerance that could not be implemented by DNA-based computing.

A. Stable Marriage Problem

In a naive form, the problem assumes n men and n women with each member having preference lists to the members of the opposite sex. A pair of a man M_i and a woman W_j is called a blocking pair if they are not a pair in the current solution, but M_i prefers W_j to the current partner and W_j prefers M_i to the current partner as well. A matching between men and women with no such blocking pair is called *stable*.

Let us consider the stable marriage problem by antibody-based computing. The stable marriage problem (SMP) can be mapped to the antigen-antibody reaction so that the preference order of each person in SMP will be reflected in the level of affinity between an antibody and an antigen. It should be noted that the agglutination process could be any agglutination (not necessarily between antibodies and antigens) if their affinity levels are measurable and ordered. After agglutinogen and agglutinin are so arranged, the solution of SMP will emerge by observing the concentration of agglutination.

B. Mapping a stable marriage problem to antibody-based computing with an array format

As stated above, mapping a combinatorial problem to antibody-based computing can be done by composing antigen-antibody compounds corresponding to a problem entity. As for the stable marriage problem, the entity is an individual

corresponding to a man or a woman. Antibodies and antigens for a compound corresponding to a particular individual will be determined by considering her (his) preference list over men (women).

Let us consider a scheme for synthesizing antigen-antibody compounds that realize mapping from given preference lists to the compounds. If the woman W_i prefers the man M_j to other men, the compound corresponding to W_i contains antibody AbW_i and the compound corresponding to M_j contains antigen AgM_j that satisfies **Aff**(AbW_i, AgM_j) being highest among other AgM_j (j=1...n).

If M_j is the second in the preference list of W_i, then **Aff**(AbW_i, AgM_j) must be the second highest and so on. AgM_j must realize the preference orders from women W_k other than W_i, hence the affinity **Aff**(AbW_k, AgM_j) must realize the order accordingly. (If AgM_j alone cannot realize the order, then a new antigen realizing the order must be added to the corresponding compound.) Constraints for selecting antibodies and antigens for a compound corresponding to a person can be summed up as follows:

- **Aff**(AbW_i, AgM_j) > **Aff**(AbW_i, AgM_k) if the woman W_i prefers M_j to M_k in her preference list for all $W_i \in W$, and for all distinct pairs M_j, $M_k \in M$; and
- **Aff**(AbM_i, AgW_j) > **Aff**(AbM_i, AgW_k) if the man M_i prefers W_j to W_k in his preference list for all $M_i \in M$, and for all distinct pairs W_j, $W_k \in W$.

Let us next consider an algorithm to solve SMP with an array format. In the array shown in Table 1, row i and column j correspond to the compound for man i (i.e. AbM_i and AgM_i) and that for woman j (i.e. AbW_j and AgW_j). In other words, at the cross-point ij, two antigen-antibody reactions between AbM_i and AgW_j (reflecting man i's preference) and between AbW_j and AgM_i (reflecting woman j's preference) will take place.

Table 1. Arrayed compounds to solve the stable marriage problem. M_i (W_i) stands for the compound for a man i (woman j). The symbol * at the ij cross-point indicates that M_i and W_i are selected as a stable pair due to a high affinity. Each row and each column has only one pair.

Compounds	M_1	M_2	... M_i...	M_n
W_1				
W_2				
⋮			⋮	
W_j			*	
⋮			⋮	
W_n				

Under the assumption that the concentration observed at each cross-point is proportional to both **Aff**(AbM_i, AgW_j) and **Aff**(AbW_j, AgM_i), the array can find a stable matching by selecting one cross-point with highest concentration from each row and column. This matching is certainly a stable one, for suppose otherwise there must be a blocking pair M_k and W_l such that Aff(AbM_k, AgW_l) > Aff(AbM_k, $AgWp(M_k)$) and Aff(AbW_l, AgM_k) > Aff(AbW_l, $AgMp(W_l)$) where $p(M_k)$ denotes a partner of M_k in the current matching. Then the concentration at the cross-point kl is higher than those of $kp(M_k)$ and those of $p(W_l)l$ reflecting the affinity level.

Although obtaining a stable matching shows some computational power, it can be solved in $O(N^2)$ time where N is the number of men (and women). A well-known algorithm exists for giving stable matching for man-oriented matching or woman-oriented matching [13]. By further assuming that the concentration observed at a cross-point can reflect the amount of antibodies and antigens, the array may be capable of obtaining any stable matching in the array from the man-oriented (man optimal and woman pessimal) matching to the woman-oriented (woman optimal and man pessimal) matching.

C. Landsteiner's ABO blood group system as an example

Landsteiner's ABO blood group system [14] is a popular and yet simple example. His blood type system is based on antigens (as agglutinogen) on red blood cells and antibodies (as agglutinin) in the blood serum. Table 2 shows agglutinogen and agglutinin of each blood type. The antibody α (anti-*A*) and antigen *A* have a high level of affinity, so does the antibody β (anti-*B*) and antigen *B*. Thus the blood type A and B will cause agglutination when they are mixed. So does the blood type AB (which has both antigens *A* and *B*) with the other three types when transfused, but blood type O without any antigen will not cause agglutination. It should be noted that Landsteiner's ABO blood group system is used for explanation purposes, and that a similar discussion could be made even for other blood type systems. It should also be noted that the following example maps the relation of higher preference to higher affinity. Hence, the blood type of a matched couple would be more likely to agglutinate.

Table 2. Landsteiner's ABO Blood Group System

Blood Type	A	B	AB	O
Antigen (agglutinogen)	*A*	*B*	*A, B*	None
Antibody (agglutinin)	β	α	None	α, β

In this example, we map the relation that "the woman W_i (the man M_i) prefers the man M_j (the woman W_j) to others" to the relation that "if the blood of W_i (M_i) would agglutinate when the blood of M_j (W_j) were transfused." That is, if the woman W_i prefers the man M_j, then the blood type should be so assigned that the type for W_i comprises antibody AbW_i and antigen AgW_i; and they type for M_j comprises antibody AbM_j and antigen AgM_j and the affinity Aff(AbW_i, AgM_j) is highest.

In the nontrivial preference list shown in Table 3, one assignment would be type O to M_1 and W_1, type A to M_2, and type B to W_2 (Fig. 3). Then the stable matching will be (M_1, W_1) and (M_2, W_2), and other couplings will be unstable. For the other two preference lists (with the graph topologically different from Fig. 3), it is not possible to map the blood type with the above correspondence, and other compounds should be synthesized for realizing the preference lists.

Table 3. An example of a preference list for the two by two stable marriage problem.

	M1	M2
W1	2	1
W2	2	1

	W1	W2
M1	2	1
M2	2	1

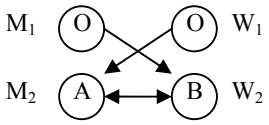

Fig. 3 A blood type assignment reflecting the preference

III. Networked Recognition Can Regulate

A. *Self-referential aspect when the solver is put within the system*

In the previous Arrayed Recognition, one must control the concentration of antibodies or antigens outside from the solver (array). It would be interesting to leave this regulation task to be performed by the solver itself. A significant difference from the previous Arrayed Recognition is to embed the problem solver (a collection of agents) into the system. Thus, the agents can not only recognize but also be recognized, which implies that each agent has not only a receptor counterpart but also an effector counterpart. This would further mean that the system will solve problems in the system itself. Put another way, the system must deal with the self-related version of the problem: e.g., rather than classifying the self and nonself, it must reinforce the self and eliminating nonself.

Self-reference may be an intrinsic nature of biological systems, and could complicate the logic when applied to biological problem solving. Von Neumann already noticed that biological problem solving could entail a self-referential paradox in his seminal work on self-reproducing automata [15]. Autopoiesis also focused on the self-referential aspect of biological systems [16].

B. *Dynamical Model of Networked Recognition*

In network theory [17], the immune system is not merely a "firewall" but also a network of antigen-antibody reactions. That is, when antigen is administered, it stimulates the related cells and causes them to generate antibodies. However, the generated antibodies themselves are antigens to other cells and consequently result in the generation of another antibody. The antigen-antibody reaction percolates like a chain reaction and hence requires a regulatory mechanism.

There is huge diversity among immune system models, even if we restrict ourselves to those that use differential equations. If they were to be described by a single equation with x_i: number of recognizing (or recognized) sets (T-cells, B-cells, antibodies, and antigens) and a_{ij}: interactions from type i to type j (positive for stimulation and negative for suppression), the equation would be:

$$dx_i(t)/dt = F(\{x_i(t)\}, \{a_{ij}(s_i(t), s_j(t), aff_{ij}(t))\}),$$

where s_i denotes state of type i entity (e.g., activated/inactivated, virgin/immune, and so on); and aff_{ij} affinity between these two types. The dimension of x_i (number of types) can vary, for a new type can be born, mutated from other types, or just injected in case of antigens.

What makes this equation peculiar to the immune system is that interactions a_{ij} vary depending on the states of type i and type j entities and the affinity between them. It is this affinity that is incorporated in models of the immune system devised by several techniques such as the "shape-space" model [18], where antigens and antibodies are expressed as points in space, which allows the affinity between them to be measured as a distance between the points. Several spaces such as continuous and discrete ones are considered, hence several distances too (e.g., Euclidean shape space and Hamming shape space).

In such dynamical models, immunological concepts such as immune memory and tolerance are mapped to attractors of the dynamical systems. Within the context of problem solving, attractors of the system are mapped to solutions, thus the perturbed state (nonself) will be attracted to the solution (self) and hence nonself will be eliminated and self will be preserved.

As discussed above, positive and negative regulation will be interpreted as reinforcement and elimination when the solver is put within the system. In the context of the stable marriage problem, concentration corresponding to the stable pair will be increased, while concentration corresponding to the unstable pair will be depressed or eliminated (Fig. 4). In this analogy, the unstable pair corresponds to the nonself.

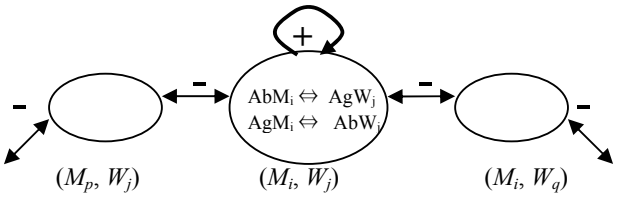

Fig. 4. The pair (M_i, W_j) is a stable pair while other pairs are unstable. Arcs with a positive sign indicate stimulation and those with a negative sign indicate inhibition of the concentration of corresponding compounds.

IV. Selected Recognition Can Adapt

In the means-ends analysis on the one hand, the problem solving process constitutes an intrinsic part of the solution. That is, the order in which operators are applied is a critical part of the solution of a given puzzle. The problem must be fixed throughout the problem solving. Hence, the solver deals with a static problem.

On the other hand, in immunity-based problem solving, the problem itself undergoes changes, because the environment including the nonself is changing and the solver involving the self must change accordingly. Therefore, there is no complete solution and there will always be a gap between the current solution and the current problem. However, the current solution can be used for the next problem when the next problem (the change) also evolved from the current problem. Problem solving does not have a beginning and an end. As in Fig. 5, the current solution is not good for the current environment because the environment is ever-changing, therefore the gap between these two must be managed for the next solution. However, the next solution is built not from scratch but from the current solution. The solution must always chase the environment, which is an online and dynamical adaptation to the dynamical environment. In immunity-based problem solving, the typical environmental change is a challenge from outside (e.g., bacteria and viruses) and a challenge from inside (e.g., cancer). To deal with these challenges, the solver (a collection of agents) must prepare a diverse set for being selected by these problems (challenges) and the selected agents must be further increased.

Again, when the stable marriage problem is used for explanation as shown in Fig. 6, a challenge from outside may correspond to administering compounds corresponding to unstable pairs, which must be eliminated from the inhibition interaction from the set of agents corresponding to stable pairs. Thus, a strong signal pathway that causes inhibition of the agents corresponding to the stable pairs may raise a problem of autoimmune disease. Cancer would correspond to a corruption of the preference table defining the self or some malfunction of mapping from the table to the set of agents constituting the table.

Since there is always a difference between the current solution and the current environment, there must be a diversification of agents.

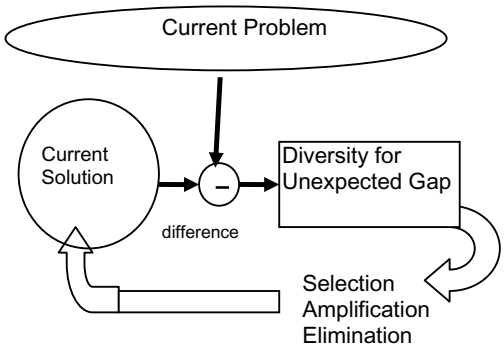

Fig. 5. Adaptation as a biological problem solver.

In the action process shown by white arrows in Fig. 5 which basically mimics the affinity maturation, affinity will increase by exploring diverse agents with slightly varied receptors. This positive way of using diversity can explain the difference from degeneracy. In using diversity for exploring the possibility of increasing affinity further, slight variations of not only structure but function (affinity) can contribute.

This action process has been formalized as an immune algorithm which was presented elsewhere in detail [10]. The most naive immune algorithm has the following three steps carried out in parallel by agents distributed over the system. In the algorithm, agents (corresponding to the immune cells) have not only recognizing and communicating capabilities but also reproduction capability with possible mutation.

1. Generation of diversity: Diverse agents with distinct specificity of the receptor and the effector are generated.

2. Establishment of self-tolerance: Agents are adjusted to be insensitive to "known patterns" (self) during the developmental phase.

3. Memory of nonself: Agents are adjusted to be more sensitive to "unknown patterns" (nonself) during the working phase.

This action part formalized as an immune algorithm has been used for noise cancellation where noise corresponds to the nonself and the control signal to the self [10]. Since the signal is not labeled beforehand, agents must discriminate the self signal from the nonself signal by the specific features of these signals. Further, the cancellation signal from agents must be discriminated for other agents. Although noise cancellation can be applied even to unknown noise, it must deal with self-reactive agents (which try to cancel the control signal) as if auto-immune disease could happen to the immune system.

In the stable marriage problem, if the challenge to the system is only nonself corresponding to the unstable pairs, then the Networked Recognition (in section III) can inhibit and eliminate the challenge. However, there can be many challenges from the environment such as a change of the preference lists, so stable pairs must undergo change which requires diverse compounds to reflect the change.

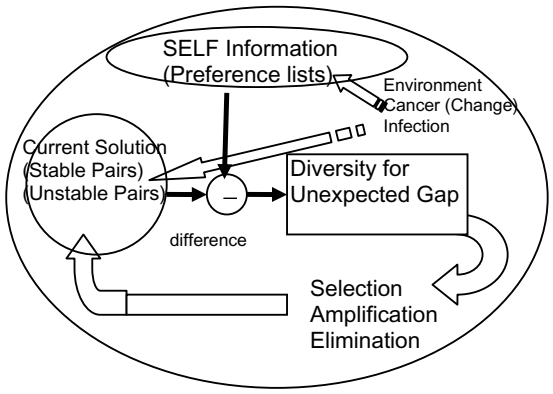

Fig. 6. Immunity-based problem solving applied to stable marriage problem.

V. Next-generation Immunity-based Systems

It is often the case that "fact is stranger than fiction" where biological systems are concerned. Biological systems can be neither simple nor optimal. One reason for the apparent complexity and intangibility is that biological systems have large-scale interactions in a spatio-temporal sense. In space, they are interacting with the environment that includes not only nonself but also self. In time, they undergo an adaptation in an individual time scale as well as an evolution in a species time scale.

Thus, it is suggested that a superficial analogy could be misleading in mimicking biological systems. Biological mimicking should not be done at a phenomenological level, but at a principle level instead.

Another reason for the complexity and intangibility of biological systems is that they took an implementation where "degeneracy" and "diversity" can be used. This implementation seems largely due to the features of the materials they are made of, i.e. proteins.

This would suggest that a constructive systems approach to biological mimicking systems can be not only an alternative to modeling and simulations but also a complementary tool supporting and guiding the modeling and simulation. The huge amount of information now available in the post-genome era permits a systems approach to biology, and this trend is accelerating for immunology as well.

Genetic circuits [19, 20] and even synthetic multicellular systems [21] may not be an unattainable dream. Possible drug production by engineering yeast [22] has had a great impact on the area. These new bio-engineering technologies have provided bioinformatics with not only new tools but also systemic views. The post-genome age is also propelling studies of the immune system focusing on components such as antibodies and MHC (as in [23]), which would lead to studies of its systemic organization.

The next-generation immunity-based systems may depend not only on a modeling/simulation approach but also a constructive approach that might form a bridge between the material and experiment based immunology and model/simulation based informatics on bio-systems, since biology itself can be viewed as engineering [24].

VI. Conclusion

Inspired by DNA-based computing for the Hamiltonian circuit problem, amoeboid organism solving for the maze problem, and ant colony solving for the shortest path, we considered antibody-based computing on the stable marriage problem. This paper explored the possibility of extending antibody-based computing to immunity-based problem solving by comparing and modifying means-ends analysis. In immunity-based problem solving, problems (challenges to the system) are corresponded to nonself. Not only a dynamical regulation framework based on Jerne's idiotypic network theory but also a selection and adaptation framework based on Burnett's clonal selection theory are involved in the extension.

Acknowledgment

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