Forays into theoretical immunology

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Surveyed here are the author's contributions to theoretical immunology. Topics include the use of quasi-steady state assumptions, the shape space formulation of immune networks, an approach via 'reverse engineering' to T cell vaccination against autoimmune disease, models for allergy and for rashes. The concluding section deals with work in progress on how the immune system can integrate information from various sensors in order to choose from among its variegated effector arms the most appropriate for combating a particular pathogen. It is pointed out that the immune system can serve as a paradigmatic example of distributed autonomous systems.

BIOLOGY has become a leading area of interest for applied mathematicians (like myself). In more traditional areas such as fluid and solid mechanics, most of the research consists of grappling with difficult mathematical problems. The relevant equations in biological applications are often no less difficult to solve, but frequently the investigator must also formulate the required equations in order to attempt a description of an essence of a biological phenomenon. The challenge of formulation was a special attraction for me when I switched almost 30 years ago from fluid mechanics into biology.

Immunology has fascinated me increasingly over the past decade. Here is a field of enormous scientific and medical interest. Its complexity seems to demand mathematical modelling (although the molecular biologists require much convincing). This paper reviews some aspects of theoretical immunology. Both immunological and applied mathematical issues will be mentioned, hopefully in a way that experts in only one field can glide over discussions of the other. The number of theoreticians in immunology is not large, but contributions range over so many aspects of the field that it seems legitimate to concentrate on a personal view in attempting to give some idea of what these theoreticians are up to. See the section on Immunology and Virology in ref. 1 to supplement this presentation by a survey of current issues and achievements in theoretical immunology.

Quasi-steady state assumptions in immunology

My initial immunological paper[2] was a technical one. The paper concerns the classical Jerne plaque assay for antibody, still a feature of textbooks after a quarter of a century[3]. As several others had shown earlier, considerable quantitative information could be obtained about the assay by analysing a pair of nonlinear equations, one partial differential equation describing the diffusion and reaction of the antibody (a chemical secreted by cells of the immune system) together with an ordinary differential equation for the concentration of fixed sites to which the antibody molecule binds. Our principle contribution was a formal demonstration that binding can be regarded as in a 'quasi-steady state' since the concentration of sites is typically small compared to the dissociation constant of the binding reaction. If a variable is in quasi-steady state (physicists often term such variables 'adiabatic'), the differential equation for the time variation of that variable can be approximated by ignoring the time-derivative term, thereby greatly simplifying the analysis. Such a simplification yields, for example, the classical Michaelis–Menten approximation in enzyme kinetics[4,5]. Our contributions to the study of quasi-steady state approximations typically invoke the art of scaling[6] to determine conditions on the parameters that permit such approximations.

As my collaborators and I later showed in other examples, quasi-steady state assumptions are very prevalent in immunology. The underlying reason in most instances is the fact that the various chemical reactions that form the heart of immune response occur on a much shorter time scale than other actions of the immune system[7]. It is remarkable that sometimes a trivial change of variables significantly widens the parameter domain in which a quasi-steady state assumption can be made[8].

Shape space

Nobel laureate N. Jerne made a marked impact on the immunological community with his comparison of the manifold interactions among elements of the immune system with what seem to be comparable interactions among neurons[9]. The strength of immune interactions depends upon the strength of chemical binding between molecules such as the antibody molecules that attack invading antigens (e.g. bacteria and viruses) or between hormone-like signalling molecules (cytokines) and their receptors. Edelstein and Rosen[10] abstractly, and Perelson and Oster[11] far more concretely, had represented the interacting molecules as points in a 'shape space'. I and Perelson were the first to formulate interactions in shape space as a dynamical system. The initial very highly simplified model was centered on a single integro-differential equation for a one-dimensional shape space. Nonetheless, certain general issues could be

illustrated such as the necessity for the immune system to tread a narrow line between stability and controllability[12], in particular for 'memory cells'[13]. Shape space is ideal for examining effects of 'cross-reactivity', the fact that a given molecule can bind to a range of other molecules, with a corresponding range of binding affinities[14]. Just as they do in ordinary space, interactions in shape space tend to form patterns of intensity[15]. In contrast with ordinary patterns, which typically rely on short range activating influences and long range inhibitors, shape space patterns can occur even when inhibition is relatively short range[16]. It is of interest that somewhat related 'shape spaces' have found application in morphometrics[17] and the theory of vision[18].

Theorists love the intricacies of immune network theory, whether the approach is via shape, space or alternative formulations[19]. Yet, for a variety of reasons, most experimentalists are disenchanted. A colourful expression of this attitude appears in an article entitled 'The complete idiotype network is an absurd immune system'[20]. Although the claim of absurdity can be formally refuted[12], suspicion remains. Nonetheless, experimental evidence is accumulating that a network of self-reacting antibody secreting cells is found in normal individuals[21,22]. From a theoretical point of view, especially relevant here is the approach to networks of Coutinho, Stewart and Varela – see for example ref. 23.

Autoimmunity and reverse engineering

Modellers are confronted with awesome complexity when they attempt to abstract essential features of a phenomenon in immunology. The same problem is faced by modellers of other complex systems. In an attempt to find a way to help deal with this problem, we attacked phenomenology of autoimmune diseases via a method that we termed 'reverse engineering'[24].

Of particular interest to us was the use of 'T cell vaccination' to combat autoimmune diseases, wherein the immune system goes awry and attacks the body's own cells. The relevant experiments concern mice and rats which sometimes can be induced to exhibit diseases that are close in symptoms and cause to human diseases, for example to multiple sclerosis (MS). By inoculation of suitable doses of 'bad guy' T cells (a type of immune cell) the mouse model here can be driven into an MS-like disease called EAE. Smaller doses do not induce disease. In fact the animals are vaccinated, in the sense that if a smaller dose is later followed by the standard disease-giving dose nonetheless no disease develops.

Systems of differential equations often exhibit multiple stable steady states, each with its own 'domain of attraction'. A system that starts in a steady state will remain in that state forever. If the initial conditions are within the domain of attraction of a stable steady state then as time goes on the system approaches closer and closer to the steady state in question.

Deliberately ignoring almost all biological details, Jaeger and I attempted to construct the simplest possible mathematical model that would exhibit the observed phenomenology. This we did by exhibiting a variety of differential equation pairs, all of which had three stable steady states that we could identify with the 'normal', 'vaccinated' and 'diseased' states of the mouse. One of the differential equations described the population dynamics of the 'bad guy' cells, and one described a 'good guy' cell population that regulates the proliferation of the 'bad guys'. Moreover, the 'bad guys' influence the proliferation of the 'good guys'.

Modellers derive satisfaction from constructing equations whose solutions reproduce some complex phenomenology, but biologists do not regard this as a meaningful achievement. What gives our work biological significance is the fact that the models have a life of their own, and thus predict more phenomena than they are set up to reproduce. In particular, a number of versions of the present model predicted that although a high dose of 'bad guys' give disease, an even higher dose might lead to vaccination. Our biological colleagues found this prediction simultaneously counterintuitive and attractive (since such a general model produced the prediction). They performed the relevant experiments – and verified the predictions[25]. See Figure 1.

From the point of view of general scientific methodology, what is significant here is its illustration of an important role of theory in biology – not predicting a measurement to many decimal places, as often happens in physics, but spurring experiments by novel conceptualization.

In another application of 'reverse engineering' to T cell vaccination[26], models reproducing the phenomenology were constructed wherein 'disease' was a transient, not a steady state (as is in fact the case in EAE but not in autoimmune diabetes for example). In spite of a certain success with the reverse engineering approach, however, it must not be thought that this is the preferred approach to modelling complex systems. Reverse engineering is just one weapon in the theoretician's armory. There is no substitute for close examination of the experimental findings and subsequent construction of models that are firmly based on these findings. (Even here, use of reverse engineering reminds the modeller that reproduction of considerable phenomenology is no guarantee that a detailed model is correct – different details may lead to the same set of predictions.) In particular, Borghans and de Boer[27] and Jaeger and Segel[28] have constructed rather different fairly detailed models that both yield similar mathematical structures (i.e. similar phase planes) and hence the same overall predictions as the reverse engineering models for T cell vaccination.

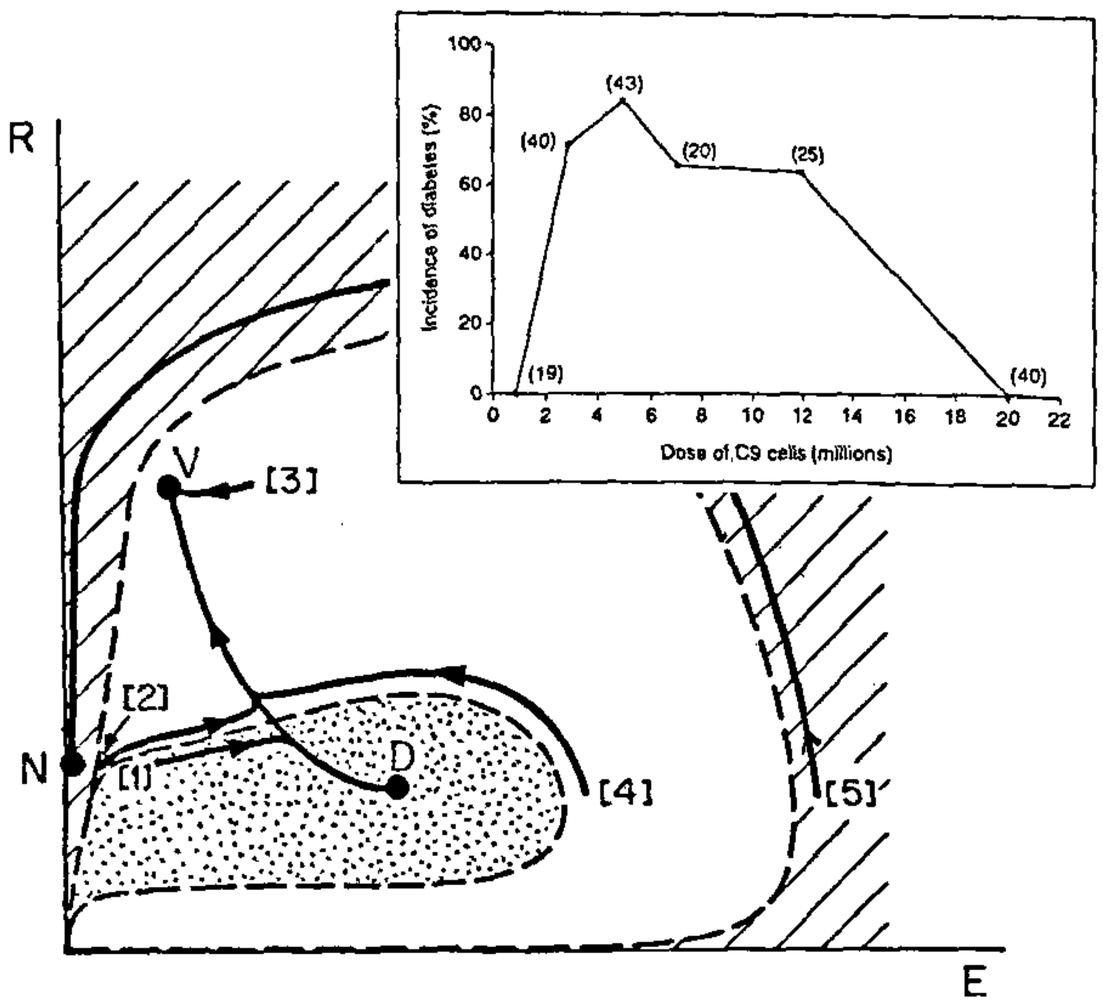

Figure 1. Phase portrait for a 'reverse engineering' model of T-cell vaccination. E and R represent populations of effector and regulator cells. The points labelled N, V and D represent 'normal', 'vaccinated' and 'diseased' stable steady states of the system, with respective domains of attraction hatched, clear, and dotted. Heavy lines delineate trajectories, the paths over which the system develops with time from a variety of initial points. (i) A sufficiently large addition of effectors E to the normal state leads to disease. (ii) A smaller effector dose leads to the vaccinated state. (iii) When the standard disease-giving dose is given to a vaccinated animal, no disease results and the system returns to the vaccinated state. (iv) Surprisingly, a very large dose of effectors, leads to the vaccinated state. (v) An even larger dose leads to the normal state. A very small dose of effectors gives a state of the system that is within the domain of attraction of the normal state and thus leads to a return to that state (not shown). *Inset*: Experimental results for autoimmune diabetes in female nonobese diabetic mice. Disease (hyperglycemia) is monitored one week after injection of the diabetogenic C9 clone (number in parenthesis indicates the number of mice used to obtain an experimental point). The major predictions of the model are verified, notably[4].

Equations used for the model:

$$\frac{dE}{dt} = 0.01 + E\left(3.5 - 0.5R + \frac{100E^2}{25 + E^4}\right),$$

$$\frac{dR}{dt} = 0.01 + R\left(-0.1R + 0.02E^3 - 0.33E^2 + 1.3E + 1\right).$$

[Figure 1, reproduced by permission, is a composite of two figures from ref. 25 – which should be consulted for fuller explanations of the theory and the experiments.]

Other models for disease

The attack of the immune system on pathogens sometimes leaves traces that are visible in the skin-rashes. The form of these rashes serves dermatologists as a primary diagnostic tool. Yet, often very little is known why a given disease leads to a characteristic form of rash. In a paper with the double-edged title 'Rash theory'[29] a small start has been made in correlating immune activity with pattern formation.

A paper by Fishman and Segel[30] appears to be the first to model aspects of allergy, over-response of the immune system to foreign substances. In particular, this paper offers explanations for the facts that the standard immunotherapy treatment for allergy often fails, while treatment takes many months when it succeeds[31].

Effector selection

In its fight against invading pathogens, the immune system can call upon a wide variety of weapons. Antibody molecules of tens of millions of different shapes and of several different varieties (isotypes) can lead to the destruction of pathogens by various means, or to the blocking of their invasion into cells. Other 'complement' molecules can kill cells by forming holes in them. Cytotoxic T cells, again of myriad specificities, can kill pathogen-ridden cells. Macrophages and natural killers are among the cells of the innate immune system that also play major direct roles in destroying pathogens.

How does the immune system select the right combination of effector cells and molecules to combat attacks by a wide variety of pathogens to which the body is exposed, each pathogen with its own molecular make-up and its own life style? This question is especially acute in view of the ability of rapidly-reproducing pathogens to mutate even during the course of a single episode of disease.

I have put forth the idea that a key element in effector selection is 'pathogen destruction feedback', wherein evidence of pathogen destruction fosters the proliferation, activation, and suitable migration of immune cells that are effective in ridding the body of the pathogen in question, and to suppression of ineffective cells. Physical scientists generally find this idea almost obviously relevant, but many immunologists are skeptical for they have had so much success in identifying various molecules that guide immune responses. I argue that overall efficiency principles must organize the molecular machinery. Although an entirely preprogrammed response can in principle deal with situations of arbitrarily great complexity, yet such a rigid system is inefficient and prone to error. After all, feedbacks are ubiquitous in biochemistry and physiology. If feedback is needed to coordinate an organism's own metabolism, how much more must it be necessary to coordinate a no less complicated system designed to counter enemies.

In as yet unpublished work general assertions on the importance of feedback have been backed by identification of possible molecular participants in the feedback process. Evidence has been given that a variety of responses are initially attempted, so that the more effective of these responses can be selected after their efficacy has been tested 'in the field'. An important proposal is that spatial dispersion of effector types can permit selection among a number of different possible effectors by means of a single locally-provided signal of successful pathogen killing.

It is not only evidence for pathogen killing that should be monitored. Other variables should enter such as the extent of damage to the host by operation of the immune system; such damage should tend to damp the immune response. Host damage by pathogens, in contrast, should enhance the response to that pathogen – all other things being equal. (The importance of selecting just a few microorganisms for attack stems from the fact[32] that 'although we are prey to a small number of pathogenic microorganisms, we are hosts to countless commensal bacteria, fungi, protozoans, and minute insect species'.) I have proposals on how to combine all the various often-conflicting desiderata to improve immune performance, even though there is no overall performance measure that is to be optimized.

The immune system and artificial intelligence

It has become increasingly evident that ideas for improving the performance of the immune system are relevant to the fields of bottom-up artificial intelligence and of autonomous decentralized systems. Cells of the immune system can profitably be regarded as billions of little robots, each of moderate complexity, which somehow are organized in a totally decentralized fashion to perform a variety of sophisticated tasks. It is fascinating to compare and contrast the operation of the immune system to examples such as the low level 'clean up crew' robots of Mataric[33] or to the scout and effector 'codelet' agents in the high level Copycat model of mental fluidity and analogy-making of Hofstadter and Mitchel[34].

Although the major biological ideas concerning immune feedback are unpublished, a recent article[35] outlines some of these ideas and sketches a few of their implications for distributed autonomous systems.

Conclusion

The time scales in the immune system run from milliseconds (chemical reactions) to decades (immune cell memory) and millennia (evolution). Immunity combats myriad rapidly evolving pathogens. An enormous amount of information is available concerning the operation of the immune system but there lacks sufficient integration of this information into an overall picture. Understanding offers pay offs not only in biology but also in medicine. Thus immunology offers exciting challenges to the theorist who is willing to struggle with learning and organizing the facts, to formulate useful models, and to communicate results to the experimental biologists.

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