Populations of Interacting Immune Systems: Evolution and Immunization

JASON BROWNLEE
Technical Report 070410A
Complex Intelligent Systems Laboratory, Centre for Information Technology Research,
Faculty of Information and Communication Technologies, Swinburne University of Technology
Melbourne, Australia
jbrownlee@ict.swin.edu.au

***Abstract*-The acquired immune system of mammals (such as humans, mice, rats, and cattle) is the most studied immune system. Taking a quick look at the 'tree of life' reveals that this intensely studied system belongs to a very small minority of taxa, the jawed vertebrates, raising the question: why did this system evolve when all other plants and animals survive without it? This work reviews some of the ways in which immune systems may interact with each other in the context of evolution, and in terms of host immunization to pathogens.**

Keywords- Immune Systems, Evolutionary Biology, Arms Race, Immunization, Vaccination, Artificial Immune System

I. INTRODUCTION

Immune systems do not exist in isolation either in the context of the various organs and interrelated subsystems of the host organism, or in terms of the populations to which the host organism belongs. In raising the level of abstraction to that of populations of immune systems, one may be interested in the manners in which immune systems interact. This transition may be considered as moving from thinking of the Darwinian struggle of lymphocytes within one host holistically providing a defence to the organism, to populations of these systems holistically providing a defence to a population (or a species). This work considers populations of immune systems, specifically with regard to evolutionary concerns and natural and artificial immunization, and ways in which these systems may interact.

This general review is multi-disciplinary crossing such fields of study as population and evolutionary ecology, microbiology, epidemiology, and immunology. The intent of this broad-brush review is to highlight some systems and processes that may ultimately provide the basis for the inspiration of adaptive computational artificial immune system models.

The review is neatly separated into two sub topics: evolution and immunization. Section II discusses the evolution of the immune system for defence including the evolution of innate and acquired immunity, the economic cost (ecology) involved, and the 'arms race' of the coevolution of host and parasite. Section III discusses immunization in terms of passive and active immunity. Particularly of interest is 'maternal immunity' a natural-passive type immunity, and 'vaccination', an artificial-active type immunity. Finally, section IV discusses the implications of the various evolutionary and immunization concerns as they may relate to the design and investigation of multiple immune system adaptive computational models.

II. EVOLUTION

Evolution has designed a complex, specialised, and multi-layered defence in the immune system [17], although the system is not perfect "*... vertebrates are exquisitely adapted (but not perfectly; autoimmunity and cancers present the costs and failures of immunity)*" [3], page 33. The very fact that we are vulnerable to disease highlights that the immune system is a sub-optimal adaptation [24]. Some suggest the acquired immune system may be an evolutionary misstep [26] given all the positive and negative feedback signals (checks and balances) needed to regulate an immune response.

The study of evolutionary immunology is the investigation into questions ([30]) such as:

(1) What factors defined the emergence and development of the immune system?

(2) What ancestral structures and functions formed the basis of immune responsiveness of the organism?

(3) By what ways and in what sequence the formation of definite immunological functions occurred and how their integration was performed?

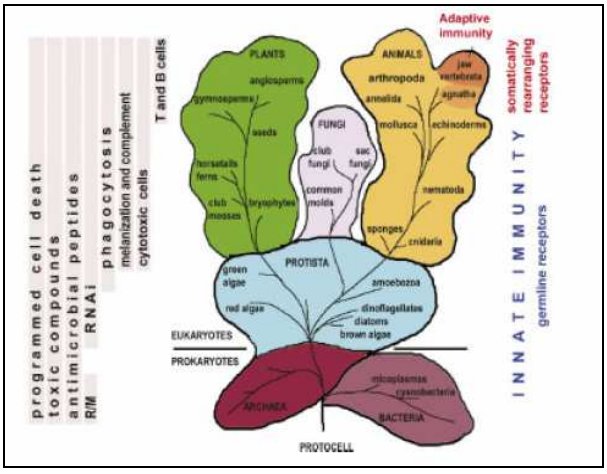

Figure 1 - Overview of the tree of life taken from [17] (page 497)

One may consider the distribution of various immune functions across the tree of life. The image in Figure 1 clearly highlights the ubiquity of innate immunity and the highly specialised acquired immune system in jawed vertebrates.

A. *The Innate and Acquired Immune Systems*

The innate immune system is a collection of defence mechanisms, tissues, and specialised processes that defend the host from its pathogenic environment. The innate defence is inherited, defined in the genome, thus the specificity for the pathogens it may detect is 'hard-wired' throughout the hosts lifetime. The defence provided is fast, practically instantaneous.

In the acquired immune system, evolution has designed a somatic learning system that may recognise any biochemical molecule, although this tool of defence may also destroy the host which it is designed to protect. Acquired immunity is a personalised defence, learned within the context of the hosts' specific pathogenic environment. It is slow acting, requiring an aggregation of antigen encounters generally over about a week before it is ready to fight the pathogen (fast compared to the innate system which specialised over generational time) As a strategy, the system is anticipatory, assuming that future pathogenic encounters will be the same or similar to past pathogenic encounters.

Why evolve an acquired immunity when all other taxa (plants and animals) except jawed vertebrates survive just fine with innate immunity alone?

Receptors' features	Immunity systems	
	innate	adaptive
Distribution in cell populations	uniform	clonal
Specificity	low	high
Affinity	10^3–10^4	10^6–10^{11}
Diversity (the number of variants estimation)	10^2–10^3	10^9–10^{11}
Variability	absent	high
Ligand origination	foreign (non-self)	foreign and self

Figure 2 - Summary of the differences between the innate and acquired immune systems, taken from [30] (page 565)

The acquired immune system is exceedingly complex, such that approximately 5% of the genome of humans is proposed to be for molecules used in the system. This antibody immunity is proposed to have evolved gradually over a long period of time from cells and tissues that previously performed other functions [11]. The following lists some of the problems related to the evolution of acquired immunity [30]:

1. The system was formed in the presence not only of pathogens but also coexisting foreign organisms (in symbiosis)
2. Many kinds of activity in the system are not protective in nature instead serving alternate functions
3. The system performs the learning function *before* the applying the protective mechanism.

Perhaps long-lived complex jawed vertebrates need an acquired immune system [26]. Perhaps it is an attempted solution to the problem of parasitism, providing a small advantage in reproductive success that invertebrates could not afford the cost of resources to evolve, maintain, and use.

B. *Parasitism*

The acquired immune system provides an evolutionary process for learning a host defence in somatic time rather than evolutionary time, subsuming and complementing the generalized response of generational learning via natural selection with a personalised response.

"*...pathogens provide selection pressure that drives differential replication of host immune cell lines, resulting in changes in genetic frequencies within an individual's population of lymphocytes.*" [28]

The co-evolutionary struggle between a host species and parasite species may be conceptualised as an 'arms race', a fight to the death, where partial success means survival [15,21]. Thus, there may be no optimal solution to the problem of parasitism, in fact parasitism requires that the immune system can be penetrated [26].

	Pathogen	**Host**	**Lymphocyte**
Intergenerational interval	Short	Long	Short
Number	High	Low	High
Mutations	Frequent	Infrequent	High diversity/Somatic Hypermutation

Table 1 - Comparison of the evolutionary potential of hosts, pathogens and lymphocytes, taken from [28] (page 707)

Parasite replication rate is much higher than that of their hosts, for example, a bacterium may have 100,000 generations for one human generation. Thus, the offensive strategies of the parasite may evolve faster than the defensive strategies the host. From virulence theory [26], if a parasite is too virulent, it may immobilise or kill the host before its progeny may be transmitted. If too benign, it may be out-competed by a more virulent variant. The strategies of parasites are varied, although most are somewhere in between these two extremes. From the perspective of the parasite, survival is a trade-off between persistence (host survival) and fecundity (replication and transmission), it may increase transmission rate at the cost of survival. From the perspective of the host, there is a trade-off between resistance to disease and the cost of infection. Some evolutionary ecology and epidemiology concerns that effect disease are ([1]) the spatial structuring of the population and the heterogeneity (diversity) of the host population. The likelihood of encountering parasites increases with population density, thus high-density environments result in hosts investing more in immunity [10].

We may consider the acquired lymphocyte and antibody based immune system as subsuming the battle with parasites to *within the host* from the generational-genetic timescale to the lifetime-ontogenetic timescale. Although, at what cost?

C. *Costs of an Immune System*

Ecology is the study of the economics of life in the environment, the identification of strategies, and the assignment of fitness. Identifying and measuring the cost of an immune system (evolutionary ecology of immunity) in isolation is a difficult if not dubious exercise [2]. Nevertheless, one may consider the costs of defence in terms of three aspects [10]:

1. The cost associated with evolving immunity
2. The physiological cost of maintaining the system
3. The physiological cost of utilizing the system for a response

Immunity plays a large role in host survival where host fitness defines reproductive success, which is intertwined with host longevity. Genes essential to survival of the host are stable, they evolve slowly, although genes related to immune system evolve relatively rapidly. The evolution of defensive traits come at the expense of evolving other traits [19].

An effective way of measuring cost is in the reallocation of resources [22], such as the reallocation of energy and nutrients away from body maintenance towards defence. This results in changes to the metabolism, that if maintained could kill the host. Two examples include: (1) a study with bumblebees that starve to death when prevented from increase their food intake during an immune response [33], and (2) the effects of the quality of the nestling-feeding rate in blue tits (birds) when vaccinated with a pathogen [14].

The specificity of an immune response has an associated cost [19]. In generating a specific or general response impacts the future response the host may produce, resulting in an interplay between pathogens and specificity that affect host immunity. A response can be defined in terms of three axes: strength, timing, and specificity [4], and ultimately immune strategies employed by different species may be considered different combinations of these aspects with differing cost-benefit trade-offs.

III. IMMUNIZATION

Generally, immunization implies that a host has been exposed to an antigen (immunogen) inducing an immune response that has educated the system with respect to more effectively and efficiently detecting and neutralising the antigen in the future. When a pathogen enters the host and elicits a response (and the host survives), the host gains a level of immunity to that pathogen. This process can be induced artificially through inoculation (controlled exposure to the pathogen), and is the basis of vaccination. Interestingly, immunity is not limited to this reactive method, and evolution has designed a temporary and passive form of immunity that is employed by mothers to protect children before and after birth.

This section discusses the various natural and artificial forms of immunity of the acquired immune system in terms of active and passive: that is those mechanisms that result in immunity by eliciting an immune response and those that do not. See Table 2 for a summary of examples.

	Natural	***Artificial***
Active	Infection	Vaccination, Inoculation
Passive	Maternal Immunity	Injection of antibodies

Table 2 - Summary of types of immunity

A developmental oddity of the acquired immune system is that the mass of the system is at its peak in early childhood, and decreases with time until early adulthood [28]. Why decrease the resources of the defence system with age, surely size increases with acquired knowledge, and immunity is needed throughout the life of the host.

An answer to this question provides insight into acquired immunity as a strategy. Children are more vulnerable to infection than adults (children under the age of 5 suffer 8 to 24 times more infection than other age groups). Each pathogen encountered by an infant is novel and must be responded to anew. As a strategy, acquired immunity learns the hosts' pathogenic environment early and quickly. It provides an attempt to increase the hosts' early and prolonged survival within its environment. During the early stages of life the system maximises diversity, maximise cell proliferation potential and maximise the rate of memory cell creation. Cell numbers peak in the first six months of life then steadily decline. Further, the developing infant immune system is buffered to the antigenic environment by the temporally inherited maternal immunity (natural passive) gained by the mother over her lifetime. This form of immunity is discussed in the following section.

A. *Passive Immunity*

Passive immunity is the transfer of active humoral immunity in the form of ready-made antibodies to a host organism. Antibodies are relatively short-lived molecules that have no reproductive capability, thus the immunity provided is fast, effective, and temporally.

A common form of natural passive immunity is maternal immunity [8,9,12,18]. Antibodies are provided by the mother to the foetus across the placenta and in breast-fed milk after birth (mucosal immunity). Vaccination of the mother during pregnancy may directly benefit the child as the antibodies produced by the mother will be passed to the foetus [32]. During breastfeeding, lymphocytes in the mother move to lymph nodes near the breast and release large amounts of antibodies into the breast milk. The antibodies enter the gut of the infant and provide protection against bacteria [7], and assists in oral tolerance (avoiding allergic reactions to food).

The antibodies provide an initial and powerful boost in defence to the infant, which endures for a prolonged period after breastfeeding ceases. Breastfeeding stimulates the developing immune system, improving later response to vaccination, although initially suppresses the effector response of the infant immune system causing the failure of effective (artificial) vaccination during this period. It decreases infant mortality rate and provides benefits for the metabolism and disease resistance later in life [31].

Passive immunity may be provided artificially through the transfer of blood or serum, and is applied when there is insufficient time for the host to develop an immune response. Some examples include viral and bacterial infections and poisons such as snake bites [16]. Cell-mediated immunity may also be transferred in this manner (effector systems for detecting and neutralising infected cells rather than foreign molecules) and is called 'adoptive immunization'. This is the transfer of recirculating lymphocytes rather than antibodies, although is difficult as such cells may be attacked as foreign by the host immune system, thus the process is rarely used in humans.

Monoclonal antibodies (mAb) are an artificial passive immunity where large quantities of identical antibodies are synthesized (from identical cloned lymphocytes) [29]. Unlike polyclonal antibodies that vary in their specificity for an antigen, monoclonal antibodies all have the same specificity, and thus may provide a strong and directed defence. In theory it is possible to synthesize antibodies to recognise any substance. They are primarily used in biomedical research for detection and purification tasks, in the diagnosis of disease, and in the treatment of infections and cancer as delivery mechanisms [27]. The process for producing monoclonal antibodies was first described in 1975 [6], and later refined for human use [13].

B. *Active Immunity*

Active immunity involves the stimulation of the system by an antigen and the development of an immune response. Natural active immunity is the normal function of the acquired immune system for neutralising pathogens.

Artificial active immunity involves intentionally inducing the immune response by introducing an immunogen in a vaccine. A vaccine is typically administered before the patient contracts the disease, although may be administered after assuming the immune response to the immunogen is faster than the response to the infection. There are many different types of vaccines including inactivated (dead) pathogens, live attenuated (low virulence) pathogens, toxoids (inactive toxic compounds from pathogens), and subunit or pieces of pathogens.

Vaccination does not prevent the host from contracting the disease, rather like natural active immunity it provides an improved response to the disease making it harder for it to spread throughout the population. Vaccination is one of the greatest achievements in medicine and public health [5], although the ethics of compulsory vaccination are still debated throughout the world, the benefits of immunity to disease and disease eradication outweigh the costs of a minority of recipients becoming sick.

An aspect of population vaccination is an effect called 'herd immunity' [20,23,25]. This is where the majority of the population (perhaps more than 90%) is vaccinated for a disease, which provides protection for the entire population. An impact of this interesting effect is that vaccination schemes may not be concerned with immunizing the remainder of the unvaccinated population, rather the immunization of enough of the population to reduce the chance (to a desired level) of a member of the population contracting the disease.

IV. Discussion

The evolution of immunity is the interaction of immune systems both with their environment, which may be adversarial in the case of parasites, and with each other in terms of reproduction and natural selection. Sexual recombination of the genetics of immunity provides interactions of immune systems in terms of new arrangements of existent traits. The pressure of natural selection results in the implicit competition between heterogeneous populations of immune systems in a spatio-temporal pathogenic environment.

Immunization provides another example of the interaction of immune systems. Evolution designed the mammalian acquired immune system to be augmented in infancy by the lifetime immunological knowledge of the maternal immune system in a temporary Lamarckian-style inheritance. This natural passive immunity provides a robust replacement defence for the developing system. Additionally this process may be reproduced artificially later in life by the removal of antibodies from one host and then injected into another to provide a short-lasting immediate defence to a pathogen.

Acknowledgments

Tim Hendtlass for his patience and for providing useful feedback on drafts of this paper

References

[1] Alison P. Galvani , Epidemiology meets evolutionary ecology *Trends in ecology & evolution*, vol. 18, pp. 132-139, 2003.

[2] Andrew F. Read and Judith E. Allen, EVOLUTION AND IMMUNOLOGY: The Economics of Immunity *Science* , vol. 290, pp. 1104-1105, Nov 10, 2000.

[3] Baruch Rinkevich, Primitive immune systems: Are your ways my ways? *Immunological Reviews*, vol. 198 , pp. 25–35Apr, 2004.

[4] Bruce R. Levin, Marc Lipsitch, and Sebastian Bonhoeffer, Population biology, evolution, and infectious disease : Convergence and synthesis *Annual Review of Immunology*, vol. 283, pp. 806-809, 1999.

[5] D. Salmon, S. Teret, C. MacIntyre, D. Salisbury, M. Burgess, and N. Halsey, Compulsory vaccination and conscientious or philosophical exemptions: past, present, and future *The Lancet* , vol. 367, pp. 436-442, 2006.

[6] G. Kohler and C. Milstein, Continuous cultures of fused cells secreting antibody of predefined specificity *Nature*, vol. 256, pp. 495-497, 1975.

[7] Herbert B. Slade and Stanley A. Schwartz, Mucosal immunity: The immunology of breast milk *Journal of Allergy and Clinical Immunology* , vol. 80, pp. 348-358, Sep, 1987.

[8] J. Bienenstock and A. D. Befus, Mucosal immunology *Immunology*, vol. 41, pp. 249-270, 1980.

[9] J. Englund, W. P. Glezen, and P. A. Piedra, Maternal immunization against viral disease *Vaccine*, vol. 16, pp. 1456-1463, 1998.

[10] J. Rolff and M. T. Siva-Jothy, Invertebrate Ecological Immunology *Science*, vol. 301, pp. 472-475, Jul 25, 2003.

[11] Jan Klein and Nikolas Nikolaidis, The descent of the antibody-based immune system by gradual evolution *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, pp. 169-174, Jan 4, 2005.

[12] L. A. Hanson, M. Korotkova, and E. Telemo, Breast-feeding, infant formulas, and the immune system *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma,*

& *Immunology*, vol. 90, pp. 59-63, 2003.

[13] L. Riechmann, M. Clark, H. Waldmann, and G. Winter, Reshaping human antibodies for therapy *Nature*, vol. 332, pp. 323-327, 1988.

[14] L. RÍberg, J. Ĺ. Nilsson, P. Ilmonen, M. Stjernman, and D. Hasselquist, The cost of an immune response: vaccination reduces parental effort *Ecology Letters*, vol. 3, pp. 382-386, Sep, 2000.

[15] L. Van Valen, A new evolutionary law *Evolutionary Theory*, vol. 1, pp. 1-30, 1973.

[16] Margaret A. Keller and E. Richard Stiehm, Passive Immunity in Prevention and Treatment of Infectious Diseases *Clinical Microbiology Reviews*, vol. 13, pp. 602-614, 2000.

[17] N. Danilova, The evolution of immune mechanisms *Journal of experimental zoology. Part B. Molecular and developmental evolution*, vol. 306, pp. 496-520, 2006.

[18] P. Brandtzaeg, Mucosal immunity: integration between mother and the breast-fed infant *Vaccine*, vol. 21, pp. 3382-3388, 2003.

[19] P. Schmid-Hempel, Variation in immune defence as a question of evolutionary ecology *Proceedings of the Royal Society of London, Series B: Biological Sciences*, vol. 270, pp. 357-366, Feb, 2003.

[20] Paul E. M. Fine, Herd Immunity: History, Theory, Practice *Oxford Journals, Epidemiologic Reviews*, vol. 15, pp. 265-302, 1993.

[21] R. Dawkins and J. R. Krebs, Arms Races between and within Species *Proceedings of the Royal Society of London. Series B, Biological Sciences*, vol. 205, pp. 489-511, 1979.

[22] R. L. Lochmiller and C. Deerenberg, Trade-offs in evolutionary immunology: just what is the cost of immunity? *Oikos: A Journal of Ecology*, vol. 88, pp. 87-98, Jan, 2000.

[23] R. M Anderson and R. M. May, Vaccination and herd immunity to infectious diseases *Nature*, vol. 318, pp. 323-329, Nov 28, 1985.

[24] Randolph M. Nesse, Maladaptation and Natural Selection *The Quarterly Review of Biology*, vol. 80, pp. 62–702005.

[25] Roy M. Anderson, Modern vaccines: immunisation and herd immunity *The Lancet*, vol. 335, pp. 641-646, Mar 17, 1990.

[26] Stephen M. Hedrick, The acquired immune system: a vantage from beneath *Immunity*, vol. 21, pp. 607-615, 2004.

[27] T. A. Waldmann, Immunotherapy: past, present and future *Nature Medicine*, vol. 9, pp. 269-277, 2003.

[28] Thomas W. McDade and Carol M. Worthman, Evolutionary process and the ecology of human immune function *American Journal of Human Biology*, vol. 11, pp. 705-717, 1999.

[29] Tristan J. Vaughan, Jane K. Osbourn, and Philip R. Tempest, Human antibodies by design *Nature Biotechnology*, vol. 16, pp. 535-539, 1998.

[30] V. B. Klimovich, Actual Problems of Evolutionary Immunology *Journal of Evolutionary Biochemistry and Physiology*, vol. 38, pp. 562-574, Sep, 2002.

[31] W. H. Oddy, Breastfeeding protects against illness and infection in infants and children: a review of the evidence *Breastfeeding review : professional publication of the Nursing Mothers' Association of Australia*, vol. 9, pp. 11-18, 2001.

[32] W. P. Glezen and M. Alpers, Maternal immunization *Clinical infectious diseases, International Conference on Acute Respiratory Infections*, vol. 28, pp. 188-239, 1999.

[33] Yannick Moret and Paul Schmid-Hempel, Survival for Immunity: The Price of Immune System Activation for Bumblebee Workers *Science* , vol. 290, pp. 1166-1168, Nov, 2000.