

Immune System Computation and the Immunological Homunculus

Irun R. Cohen

Department of Immunology, Weizmann Institute of Science, Rehovot 76100, Israel
irun.cohen@weizmann.ac.il

Two Questions

Students for the Master of Science degree at the Weizmann Institute of Science are obliged to spend the first year of the two-year program doing three-month rotations through three different laboratories in any of the various faculties at the Institute. In 1998, Na'aman Kam rotated through my laboratory in the Department of Immunology where he did molecular modeling of an antibody (1). His next rotation, he told me, would be with David Harel in the Department of Computer Science and Applied Mathematics. When you get there, said I, tell David Harel about the immune system and ask him two questions:

1. Is the immune system a computer?
2. If a computer scientist would set out to build a computer capable of doing what the immune system does, what kind of computer would it have to be?

Connecting Computer and Biological Sciences

The questions (or to be more accurate, the student who transmitted them) led to a continuing collaboration with David Harel catalyzed by joint Master's, Doctoral and Post-doctoral students who have worked to combine computer science and biological systems: After Na'aman Kam came Sol Efroni (2-4), Naamah Swerdlin (5), Yaki Setty, Hila Amir-Kroll, and Avital Sadot. Students can be a boon to inter-disciplinary research because, being unencumbered by expertise, they fearlessly lead (or carry) their supervisors into unfamiliar territories.

Let us return to the first of the two questions that led me to collaborate with a computer scientist: Is the immune system a computer? Obviously, the immune system differs from the devices made by humans called computers in its construction, operation and use. The more interesting question is whether the immune system is a biologic computing machine, and the most interesting questions are what it computes and how it computes.

A Defense System

Many immunologists, probably most, would not think of the immune system in computational terms. There are two reasons for this: the defense role assigned to the immune system and the clonal selection theory of adaptive immunity.

It has been taught for about a century, and is still taught, that the defining role of the immune system is to defend the body against foreign invaders (6). To attack an invader, your immune system has to detect and identify the invader as distinctly not belonging to your body. Thus, the immune system exists, it is claimed, to discriminate between one's own self-molecules (ignore them) and molecules foreign to the body (attack them). From this classical point of view, the immune system has evolved to discriminate between self and non-self molecules in the most general sense and concretely between one foreign molecule (antigen) and another (7, 8). (An *antigen* is any molecule that can bind to the antigen receptor of a lymphocyte.) The discriminating agent is proposed to be the individual cell, not the system of cells.

Clonal Selection

The emphasis on clones (single cells and their progeny) is anchored in the clonal selection theory of adaptive immunity, the most widely accepted paradigm of immunology. This theory proposes that each lymphocyte, and its clonal progeny, either responds or does not respond to a given antigen molecule (9). Depending on the specific structure of each lymphocyte's unique antigen receptor, that lymphocyte will either attack the antigen molecule, or ignore it. The classical discourse of immunologists about such discriminations has emphasized the antigen receptors on individual immune cells, paying little attention to computation at the level of the system as a whole.

Maintenance

Experimental facts, however, can depart from classical teachings. It is now clear that the immune is responsible for more than body defense; immune system cells promote, even control, processes such as healing wounds and repairing broken bones, growing new blood vessels, building and pruning scar tissue, disposing of dead cells, killing and removing injured or abnormal cells, clearing effete molecules, advancing regeneration of various body tissues, and the like. The dynamic processes initiated in response to injury are termed inflammation; the aim of inflammation is healing (8). The immune system is the system that commences, orchestrates and resolves inflammation. Immune activities, including restorative inflammation and defense against pathogens, can be generalized under the concept of body maintenance. Indeed, the activity of the immune system is responsible for maintaining a peaceful, ongoing host-parasite relationship with the billions of bacteria, the so-called normal flora, that occupy niches throughout our body in the gut, skin and respiratory tract; even our cells – nervous system cells, immune cells, and others – harbor latent viruses quietly held in check by continuous, unimposing and covert immune maintenance. Normal flora and latent viruses become pathogens only when the immune system has been damaged or weakened, for example, by AIDS, cancer or immunosuppressive medications. We may say that the immune system, by managing inflammation, functions to maintain the body in working order in response to the daily grind of