Artificial Immune Systems: Theory and Applications

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Presentation Topics (I)

- Motivation
  - Research Background
  - Immune Engineering
- Introduction to the Biological Immune System
  - A Brief History of Immunology
  - Basic Principles
  - A General Overview of the Defense Mechanisms
  - Anatomy and Properties
  - Innate Immune System
  - Adaptive Immune System
  - The Antibody Molecule and Immune Diversity

Presentation Topics (II)

- Information Processing Within the IS
  - Clonal Selection and Affinity Maturation
  - Repertoire Diversity
  - Reinforcement Learning
  - Pattern Recognition in the Adaptive Immune System
  - Self/Non-Self Discrimination
  - Immune Network Theory
- The Immune and Natural Selection
  - Microevolution
- The Immune and Central Nervous Systems
  - Cognitive Aspects of the Immune System
  - Similarities and Differences

Presentation Topics (III)

- Artificial Immune Systems
- Immune Engineering
  - Theory and Applications
- Immune Engineering Tools
  - SAND: A Simulated Annealing Model to Generate Population Diversity
  - ABNET: A Growing Boolean Artificial Neural Network Based Upon Immunological Principles
  - CLONALG: Computational Implementations of the Clonal Selection Principle
  - aiNet: An Artificial Immune Network Model
- Discussion

PART I

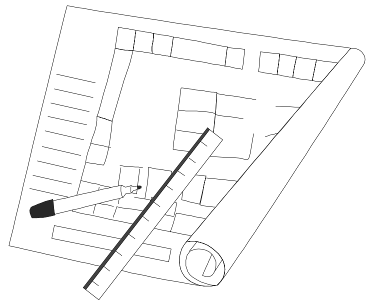
Motivation

&

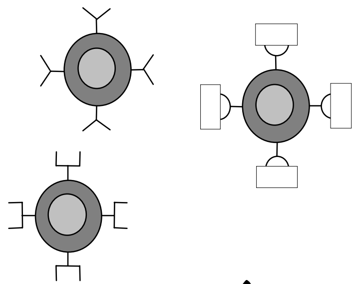
Introduction to the Biological Immune System

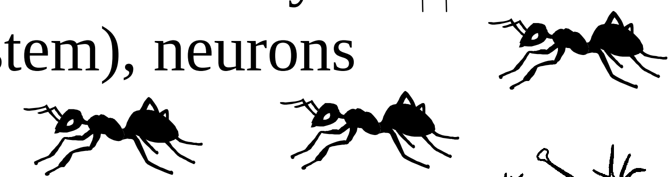
Motivation

- Comprehension and application of general principles that govern the behavior of natural systems.
- Ideas inspired by natural systems can and are being used to *engineer* (or *develop*) dedicate solutions to specific problems. Examples: artificial neural networks, evolutionary computation, DNA computation, etc.

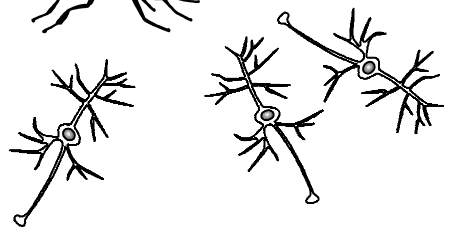


- The cooperation and competition among several simple individuals (agents) results in complex behaviors. Examples: insects colony (ants), lymphocytes (immune system), neurons (brain), etc.





- High degree of robustness of the natural systems (distributed).



Brief History of Immunology

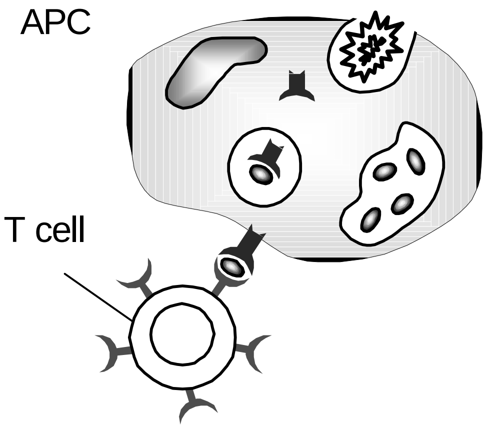
Goals	Period	Pioneers	Notions
Application	1796-1870	Jenner Koch	Immunization (vaccination) Pathology
	1870-1890	Pasteur Metchinikoff	Immunization Phagocytosis
Description	1890-1910	Von Behring & Kitasato Ehrlich	Antibodies Cell receptors
	1910-1930	Bordet Landsteiner	Immune specificity Haptens
Mechanisms (System)	1930-1950	Breinl & Haurowitz Linus Pauling	Antibody synthesis Instructionism
	1950-1980	Burnet Niels Jerne	Clonal Selection Immune network theory
Molecular	1980-1990	Susumu Tonegawa	Structure and Diversity of Cell Receptors

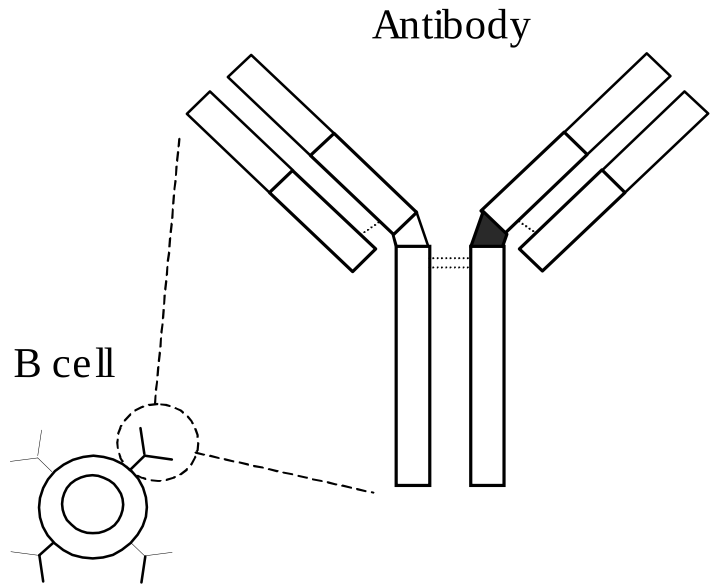
Adapted from Jerne, 1974

Basic Principles

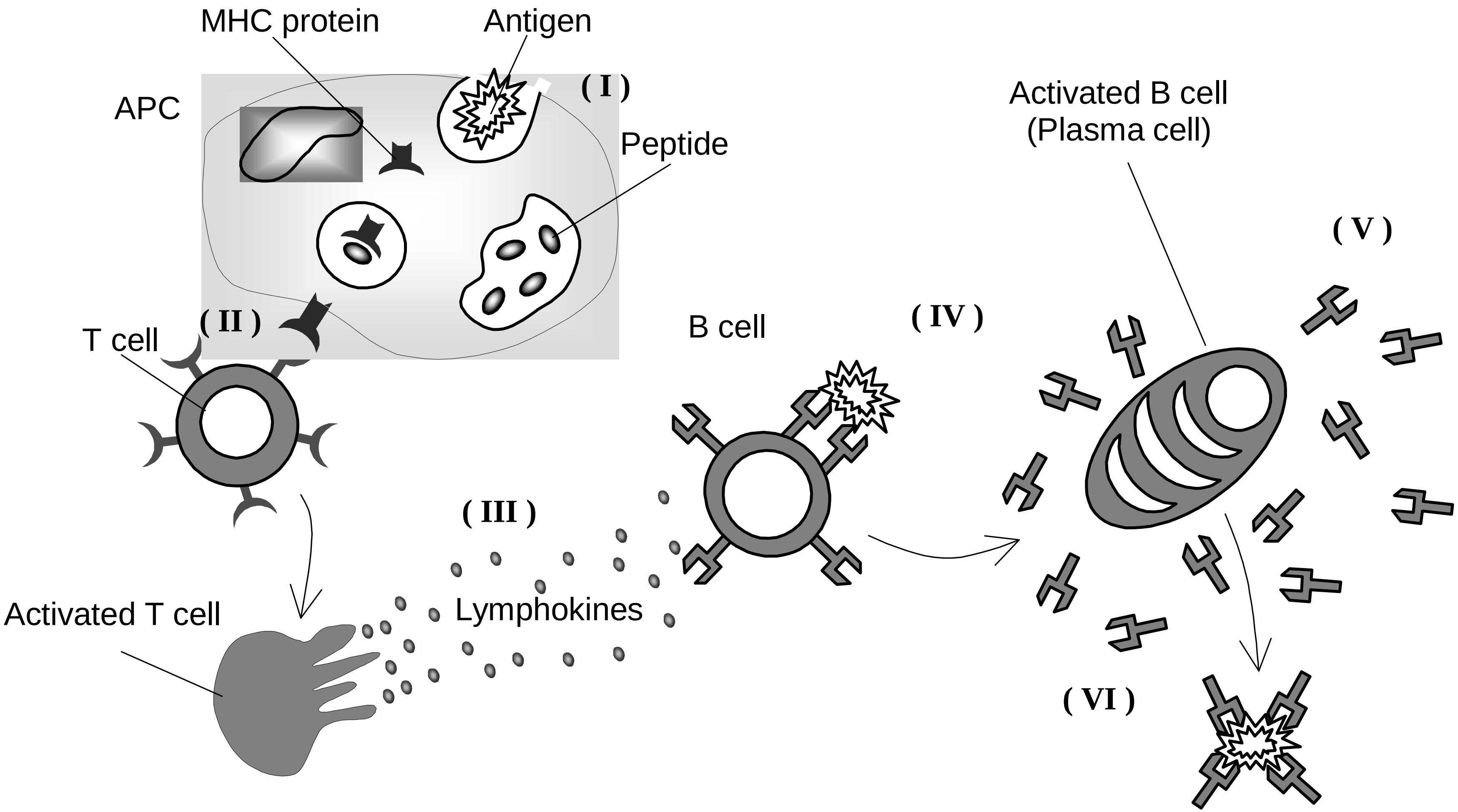
- Adaptive (specific) immunity
- Innate (non-specific) immunity
- Leukocytes:
  - Phagocytes, Antigen Presenting Cells (APCs)
  - Lymphocytes

- Cell Receptors



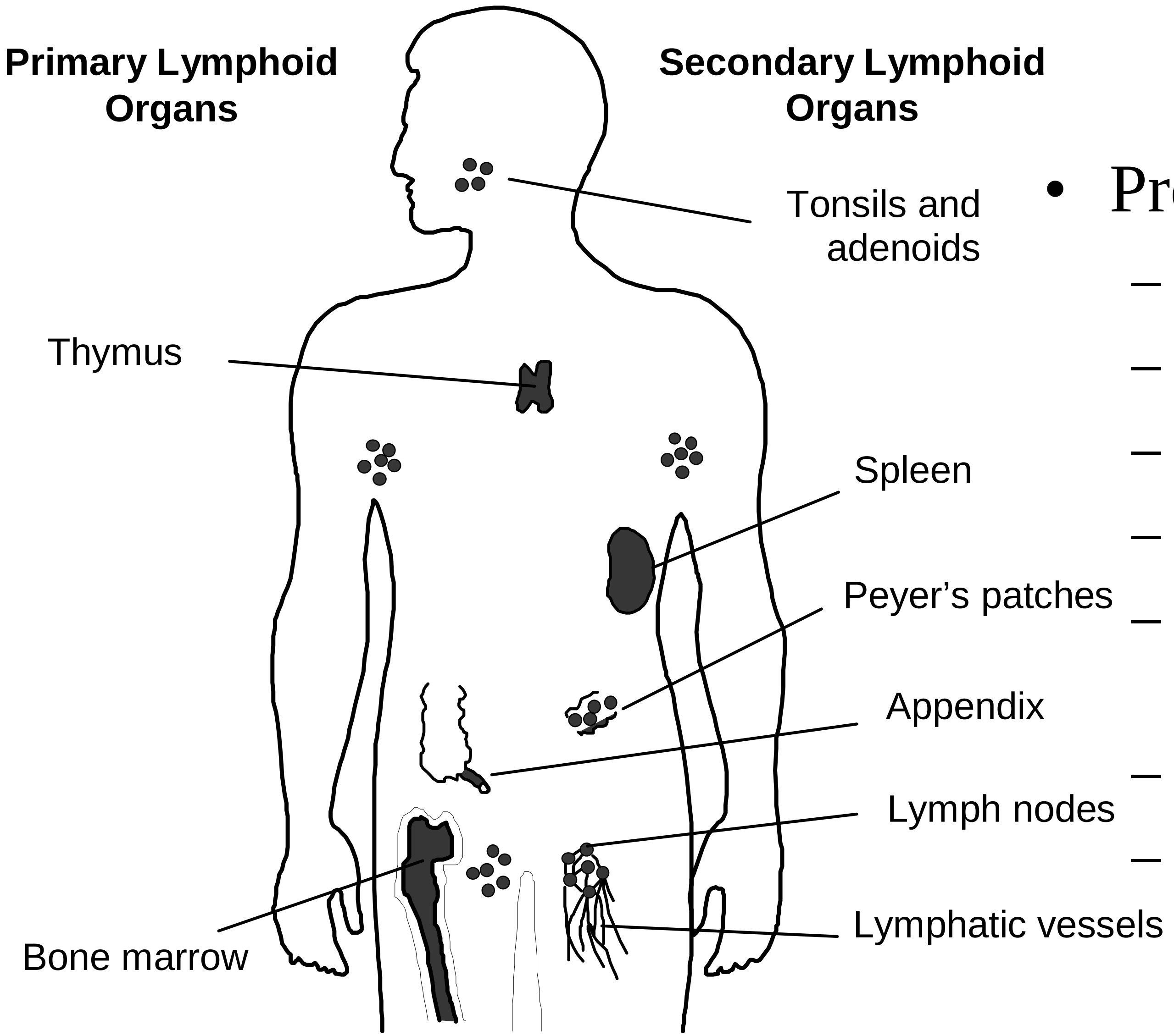


General Overview of the Defenses



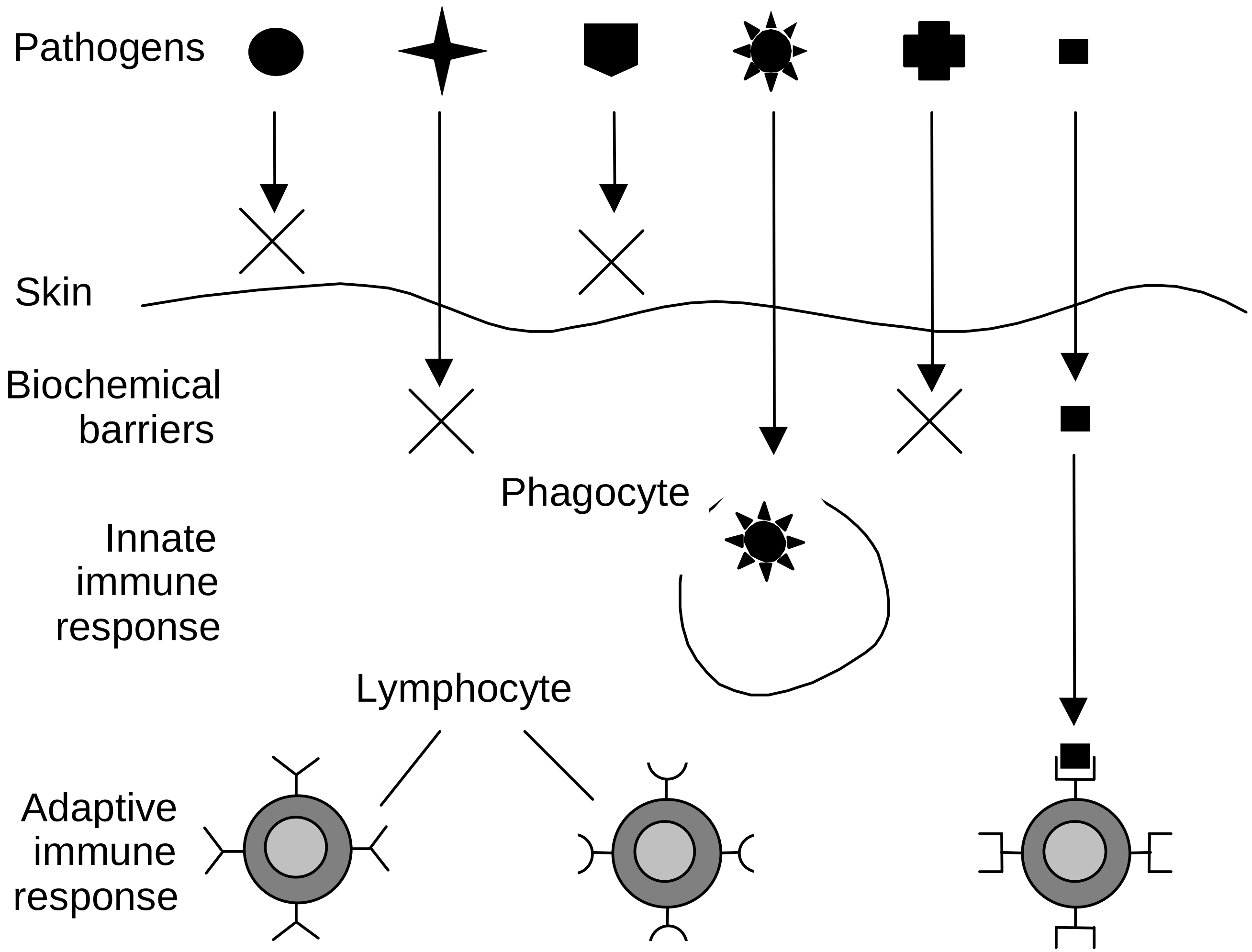
Nossal, 1993

Anatomy & Properties



- Properties
  - uniqueness
  - pattern recognition
  - distributed detection
  - noise tolerance
  - reinforcement learning
  - robustness
  - memory

Multi-Layer Protection

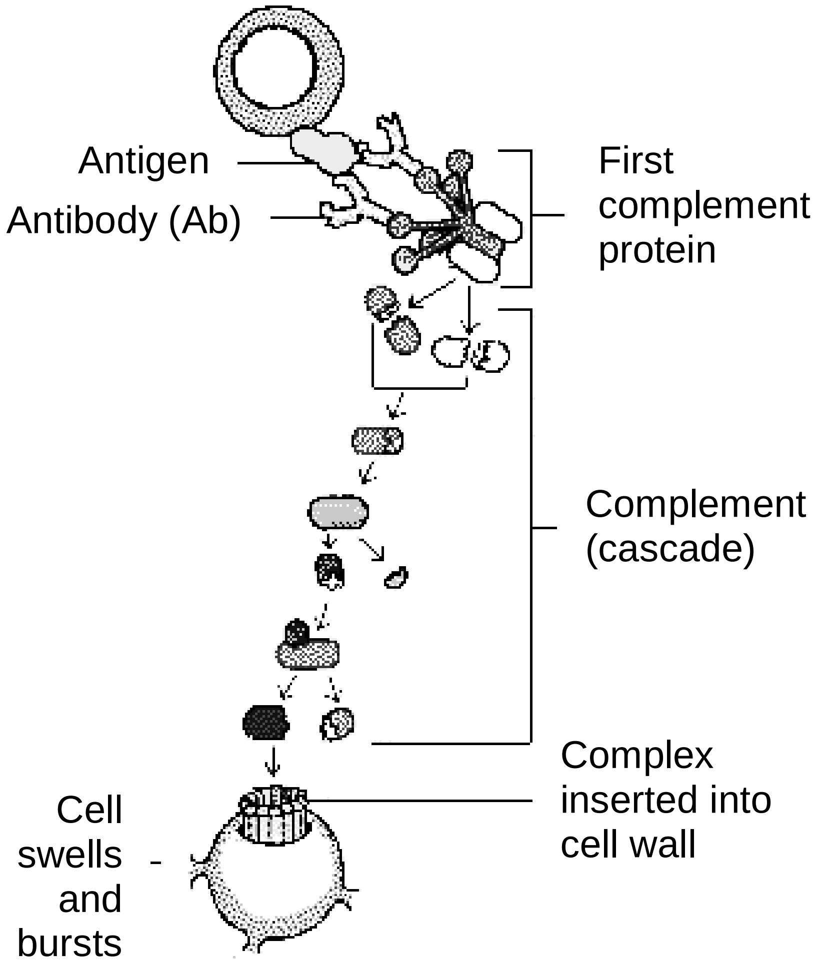


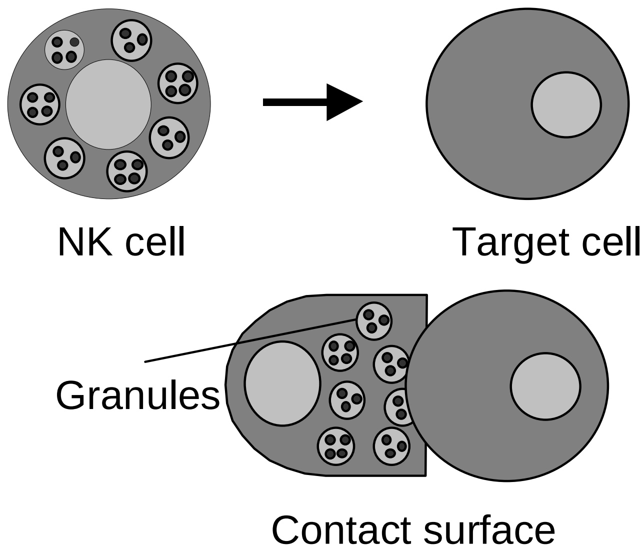
Adapted from Hofmeyr, 2000

Innate Immune System (I)

- Main Characteristics:
  - Non-specific Recognition;
  - Recognition of common constituents of many microorganisms;
  - Activation immediately on contact;
  - Antigenic Presentation; and
  - Distinction between infectious and non-infectious.
- Three arms:
  - Phagocytes, soluble proteins that trigger the complement cascade and natural killer cells (NK).

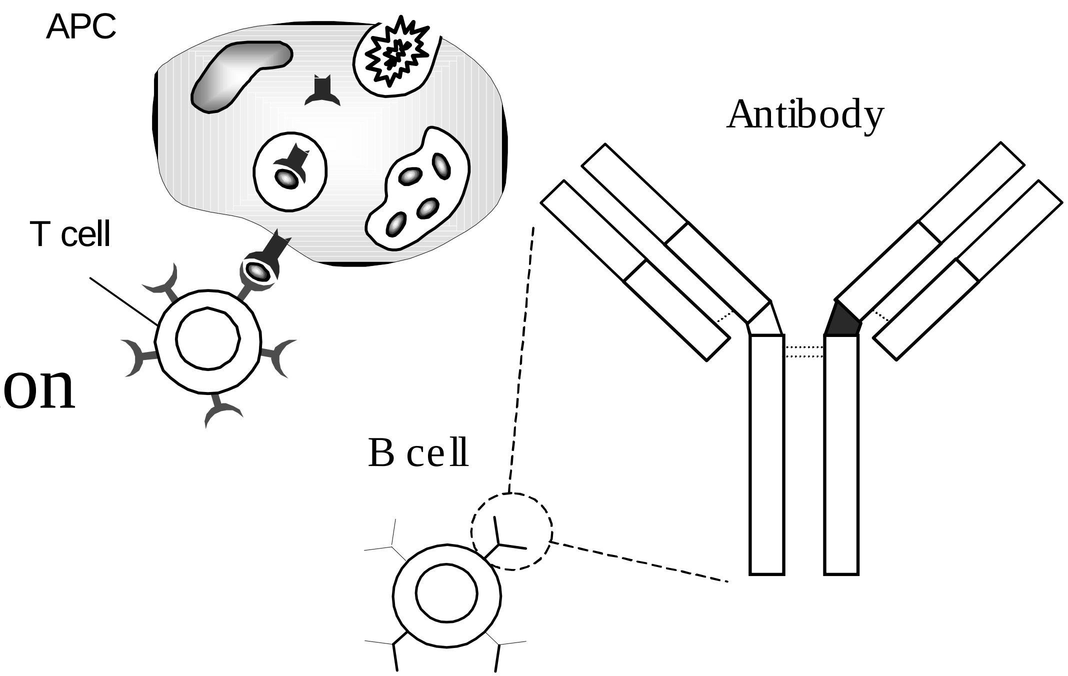
Innate Immune System (II)





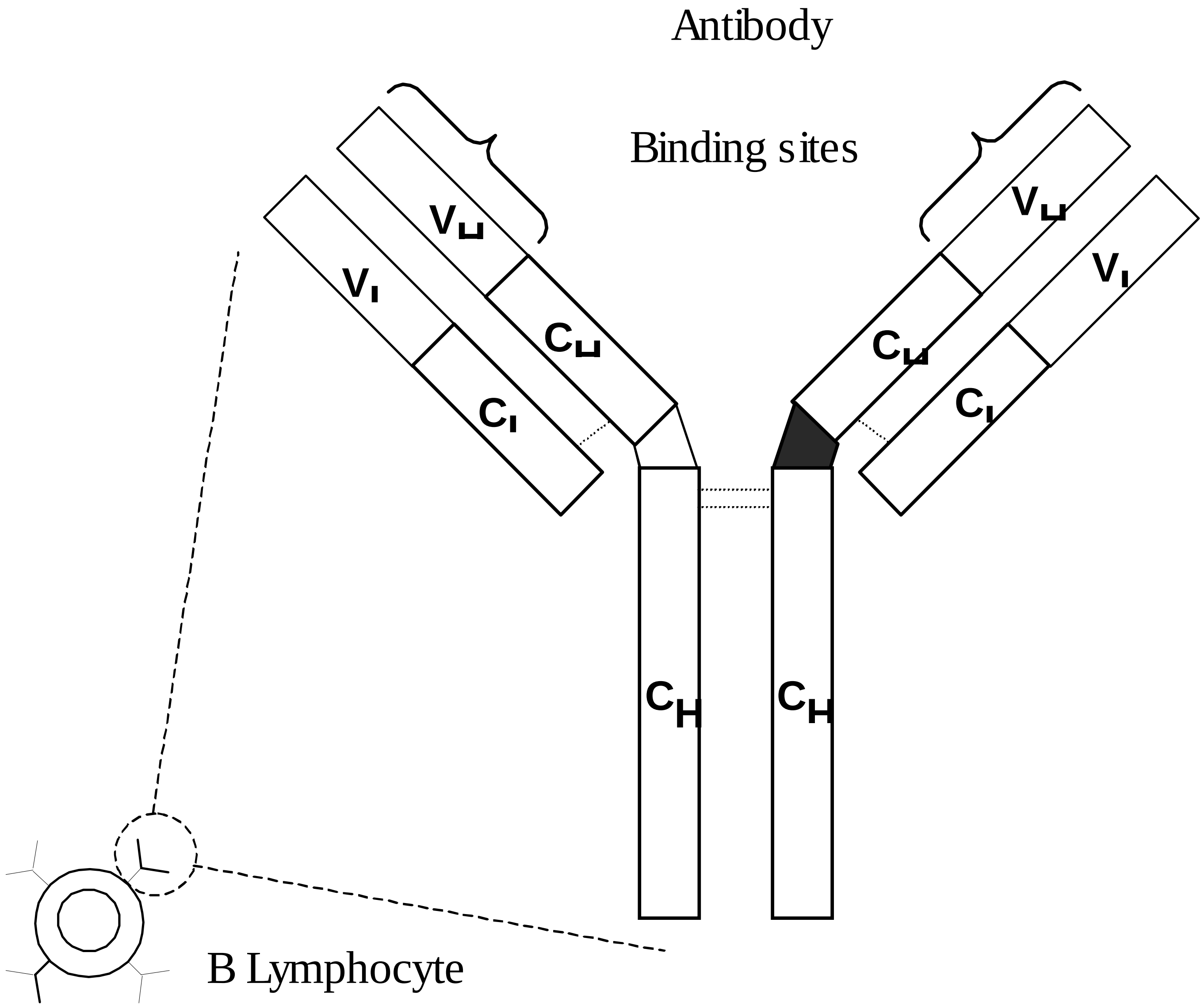
Adaptive Immune System

- Mediated by lymphocytes responsible for recognizing and eliminating pathogens, proportioning long-lasting immunity that might occur through disease exposition or vaccination.
- Lymphocytes:
  - B cell with a BCR
  - T cell with a TCR



- The Clonal Selection Principle

B Cell & Antibodies



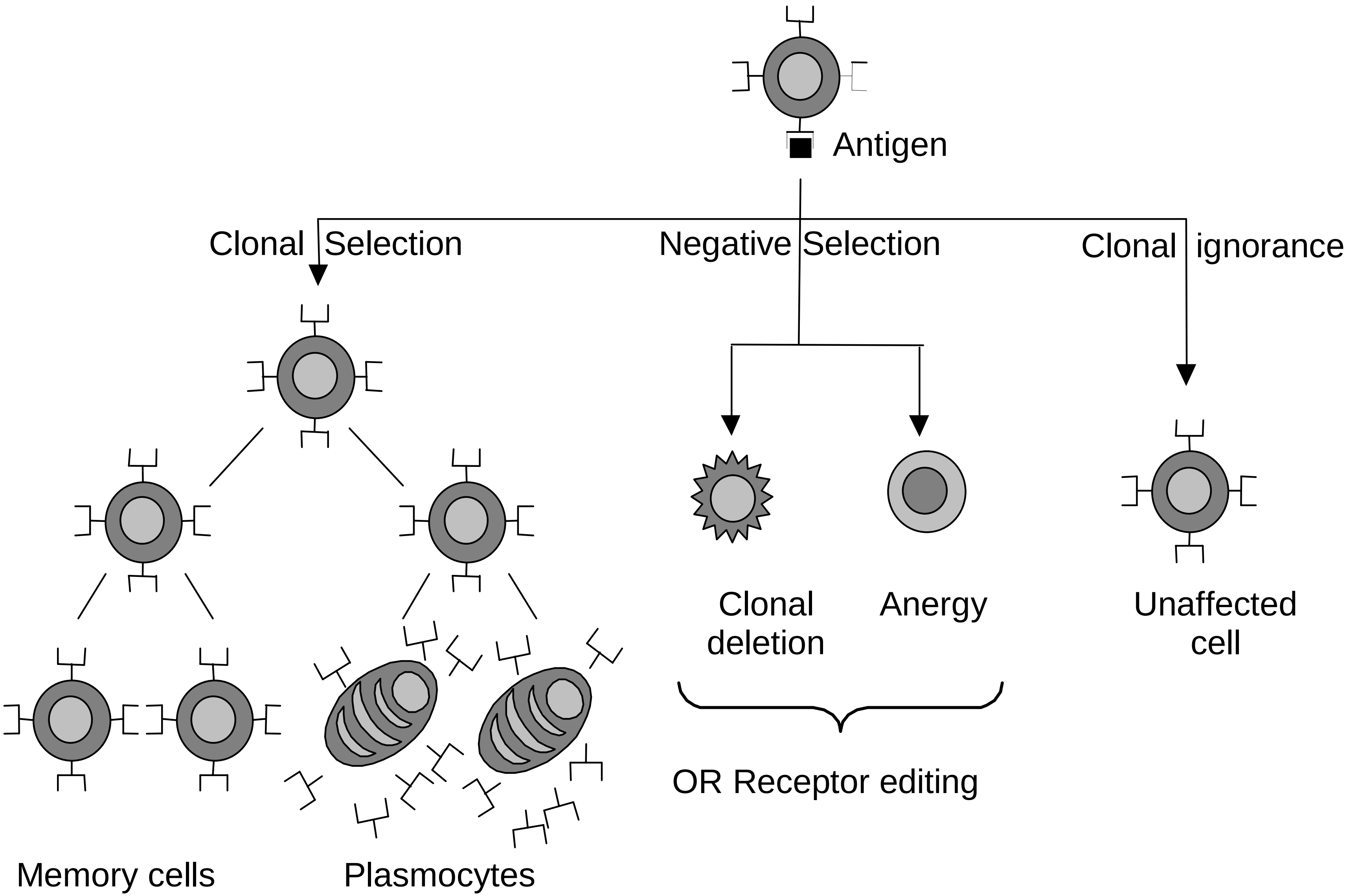
PART II

Information Processing Within the Immune System

Information Processing

- Clonal Selection
- Affinity Maturation
  - Hypermutation
  - Receptor Editing
  - Diversity
- Reinforcement Learning
- Pattern Recognition
- Self/Non-Self Discrimination
- Immune Network Theory

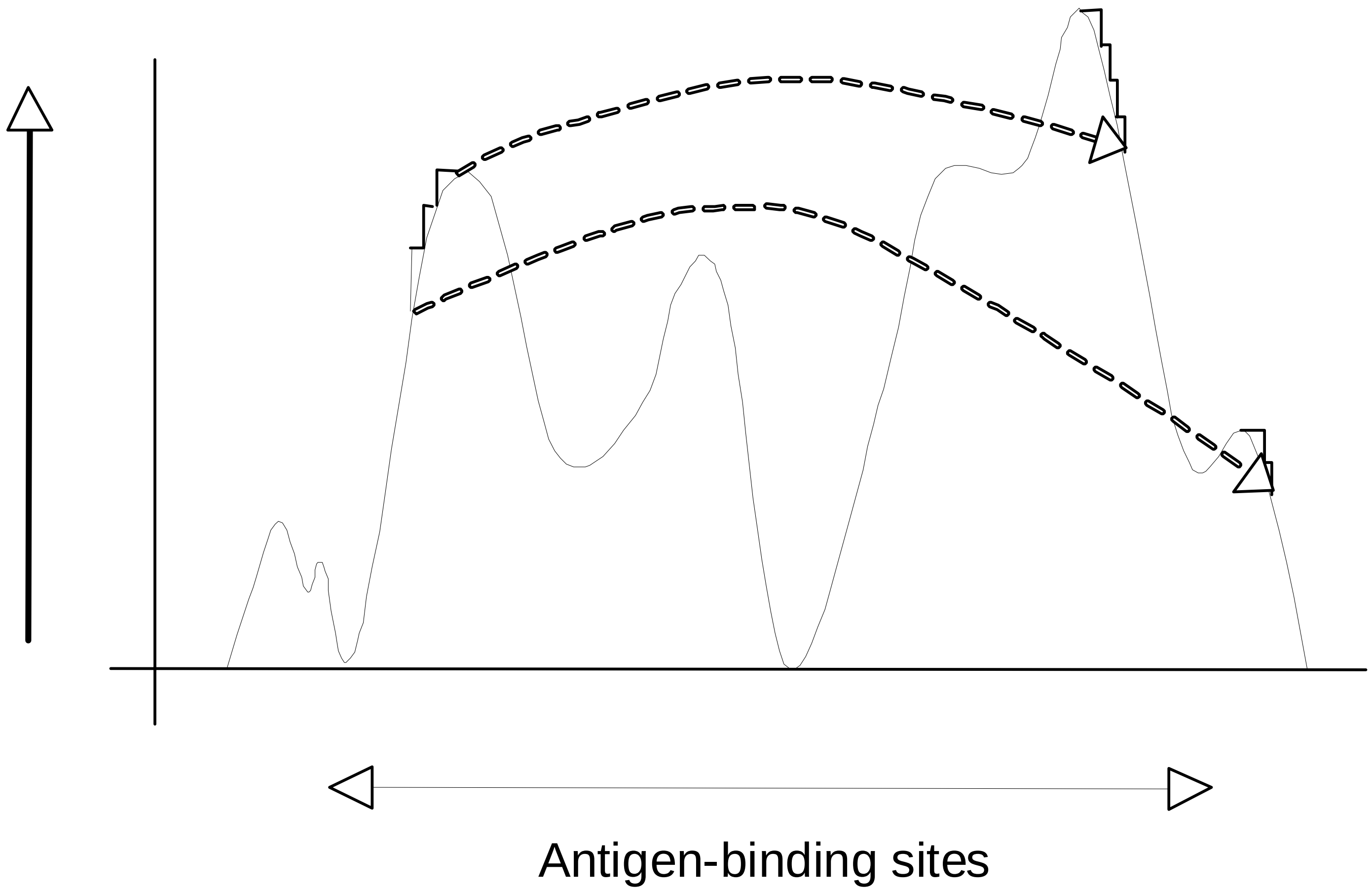
The Clonal Selection Principle



Affinity Maturation

- The most stimulated cells suffer an accelerated mutation process (*hypermutation*)
  - single point mutation;
  - short deletions; and
  - sequence exchange
- Higher affinity cells have higher probabilities of being selected as memory cells, extending their life span
- The mutation rate is proportional to the cell affinity
- An *editing* process allows a broader exploration of the different types of antigenic receptors

Receptor Edition × Mutation



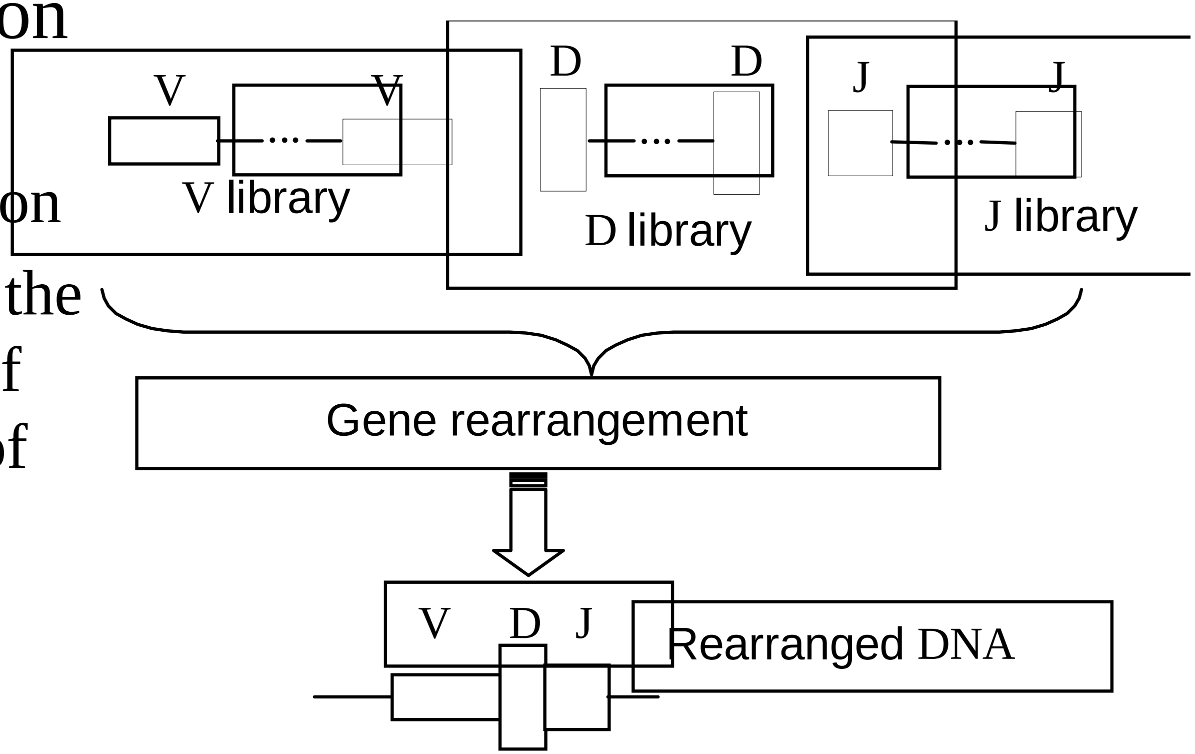
George & Gray, 1999

Repertoire Diversity (I)

- Problem:
  - The amount of different pathogens is much larger than the number of cells and molecules available for combat
- Solution:
  - Capability of producing an enormous amount of different cell receptors
- Question:
  - How is it possible to generate millions of antibody types in an organism with a finite ($\approx 10^5$) number of genes?

Repertoire Diversity (II)

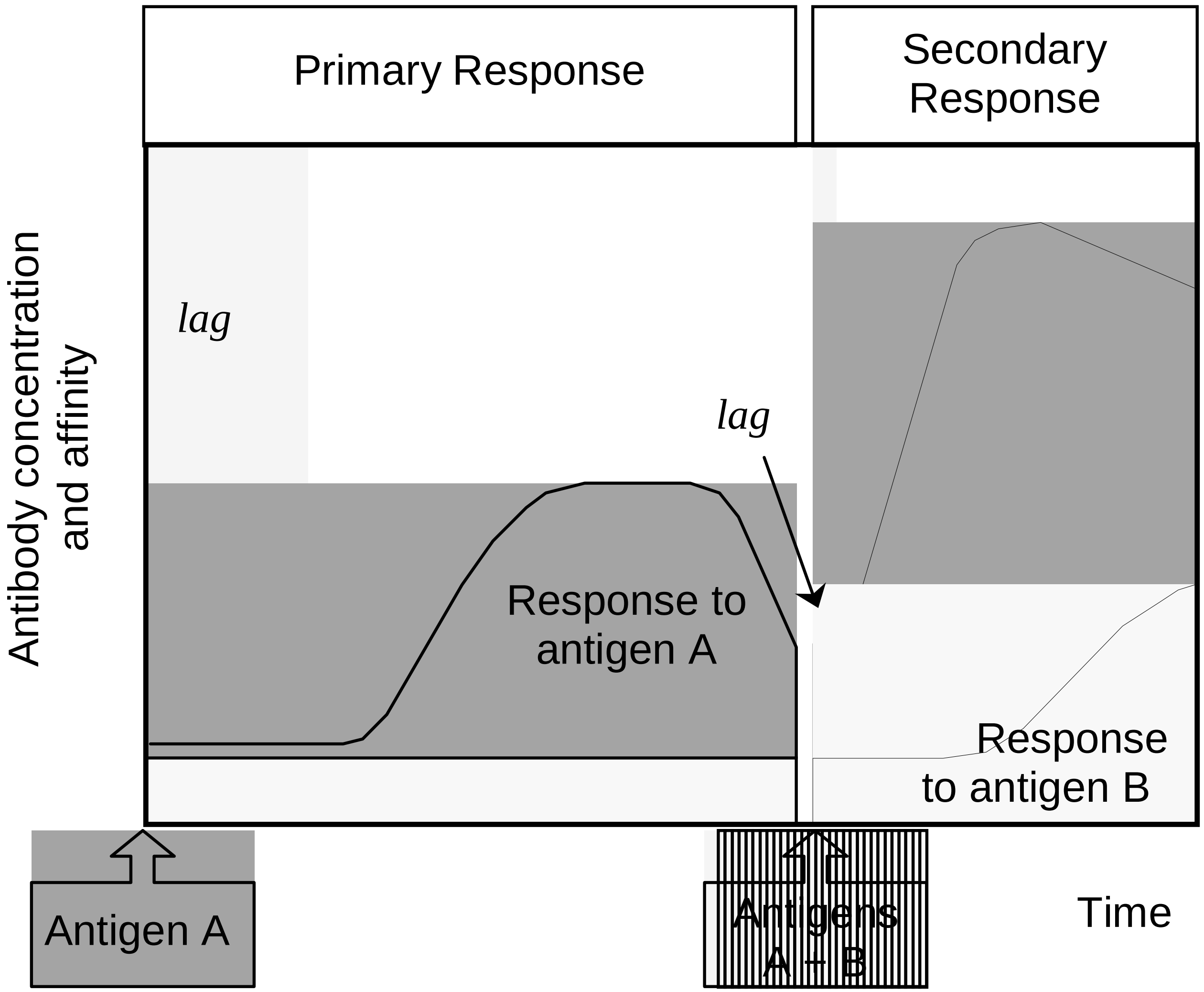
- Diversity generation mechanisms:
  - Gene recombination
  - Extra variation in the connection sites of each component of the library
  - Somatic mutation
  - Receptor editing



Oprea & Forrest, 1999

- The lymphocytes are the only cells of the human body that do not have the same DNA sequence

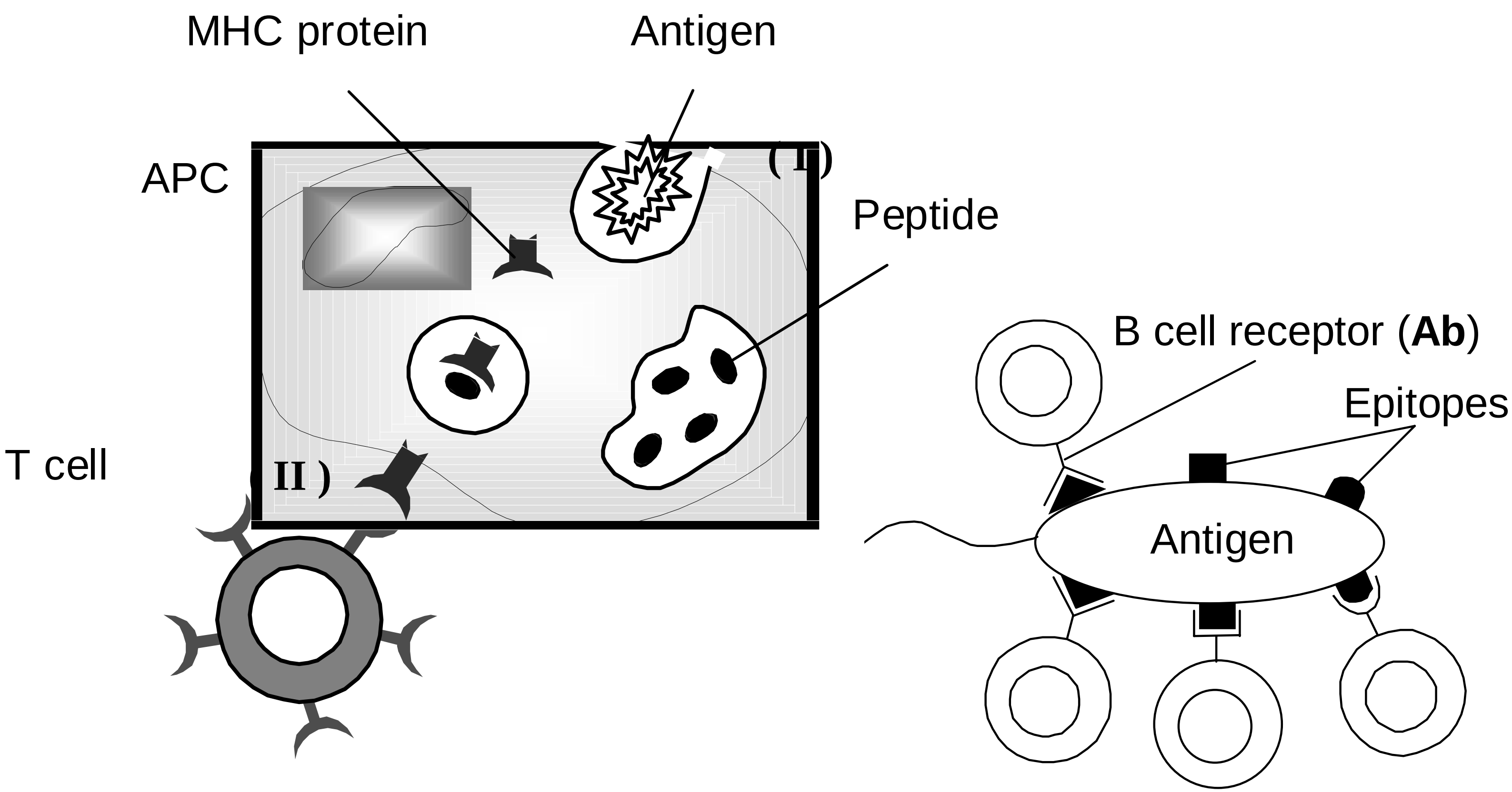
Reinforcement Learning



Janeway et al., 2000

Pattern Recognition

- Intra- × Extra-cellular



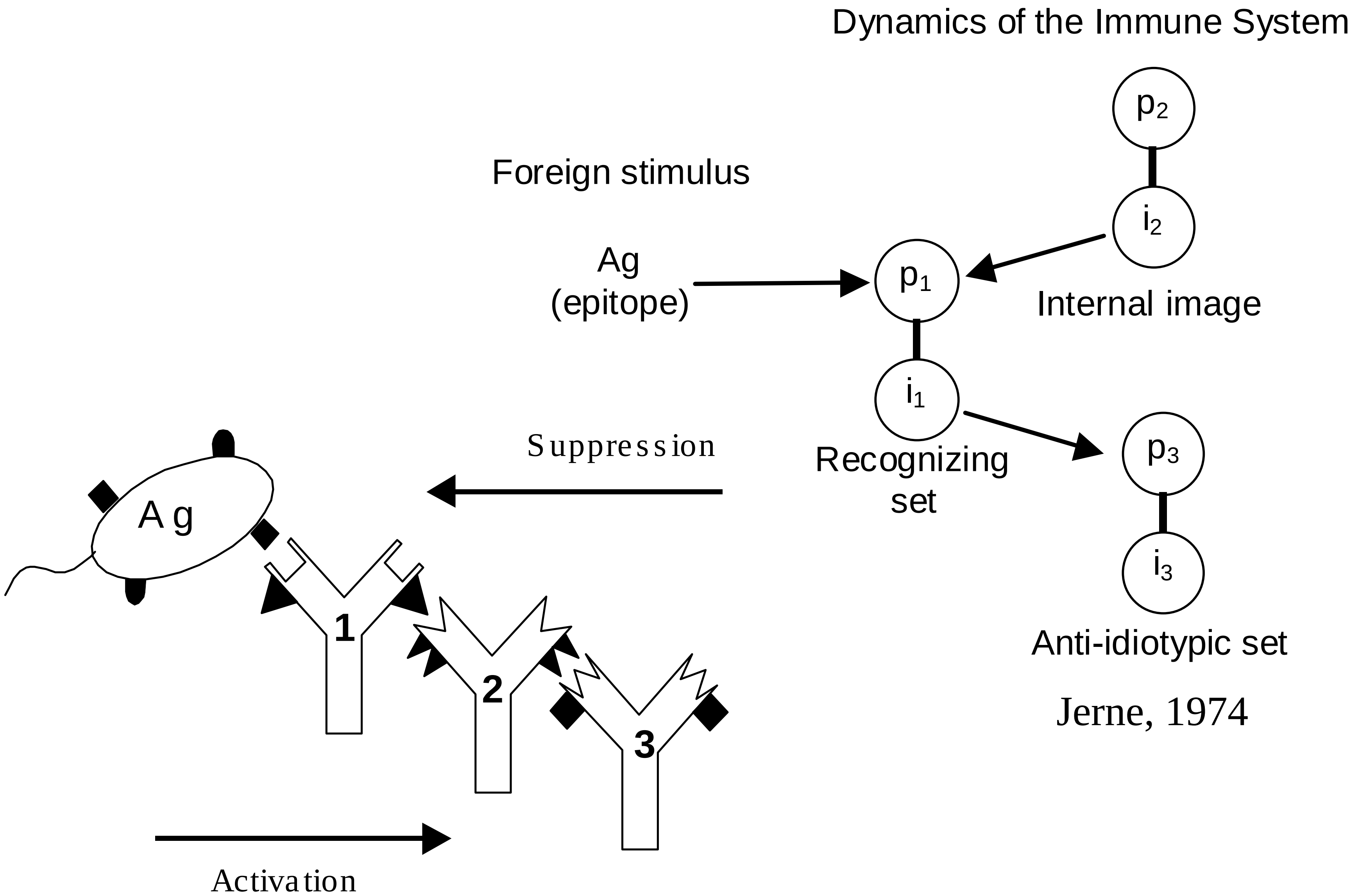
Self/Non-Self Discrimination

- Capability of distinguishing between non-infectious (our own cells and molecules*) from infectious (malefic elements)
- Tolerance: absence of self response
- Selection:
  - Positive; and
  - Negative.
- Co-stimulation

Immune Network Theory (I)

- Introduced in 1974 by Niels K. Jerne
- Novel viewpoint about:
  - lymphocyte activities;
  - antibodies production;
  - pre-immune repertoire selection;
  - tolerance and self/non-self discrimination; and
  - memory and the evolution of the immune system.
- Proposal: *the IS is composed of a set of cells and molecules that recognize each other even in the absence of antigens.*
- Internal Image

Immune Network Theory (II)



Jerne, 1974

Immune Network Theory (III)

- General features
  - structure;
  - dynamics; and
  - metadynamics.
- Existing models
  - Dynamic equations representation.

$$\begin{array}{ccccccc} \text{rate of} & & \text{influx} & & \text{death of} & & \text{reproduction of} \\ \text{population} & = & \text{of new} & - & \text{unstimulated} & + & \text{stimulated} \\ \text{variation} & & \text{cells} & & \text{cells} & & \text{cells} \end{array}$$

PART III

Immune System,
Natural Selection &
The Central Nervous System

Natural Selection (C. Darwin)

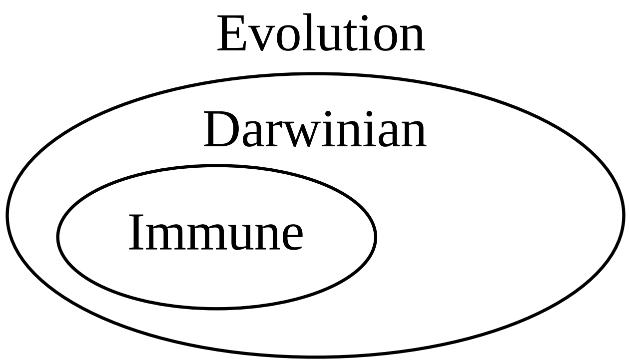
- Hypothesis to the origin of species:
  - the offspring tend to be in larger amount than the parents;
  - the size of the population is approximately constant;
  - competition for survival;
  - small differences within the same species;
  - continuous variation of the genetic information; and
  - there is no limit to the genetic variation and natural selection.
- Natural selection
  - mechanism of preservation of the variation responsible for the creation of novel individuals most fit to the environment.
- Cell:
  - germinal: transmits genetic information to the offspring; and
  - somatic: not associated with reproduction.

Evolutionary Algorithms

- Population based processes based upon the performance, or level of adaptability (fitness) of each individual (Theory of Evolution)
- Initial motivation:
  - Solve optimization problems
- Mechanisms:
  - Selection and Reproduction
- Features:
  - Diversity, cooperation and competition
- Goals:
  - Adaptive tools to solve problems; and
  - Computational models of natural processes.

Microevolution

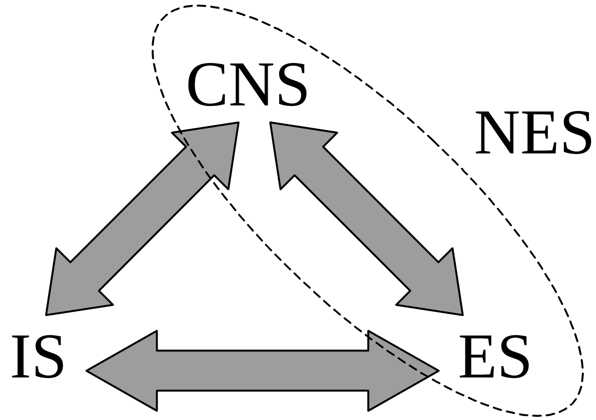
- Characteristics of the clonal selection theory:
  - repertoire diversity;
  - genetic variation; and
  - natural selection.

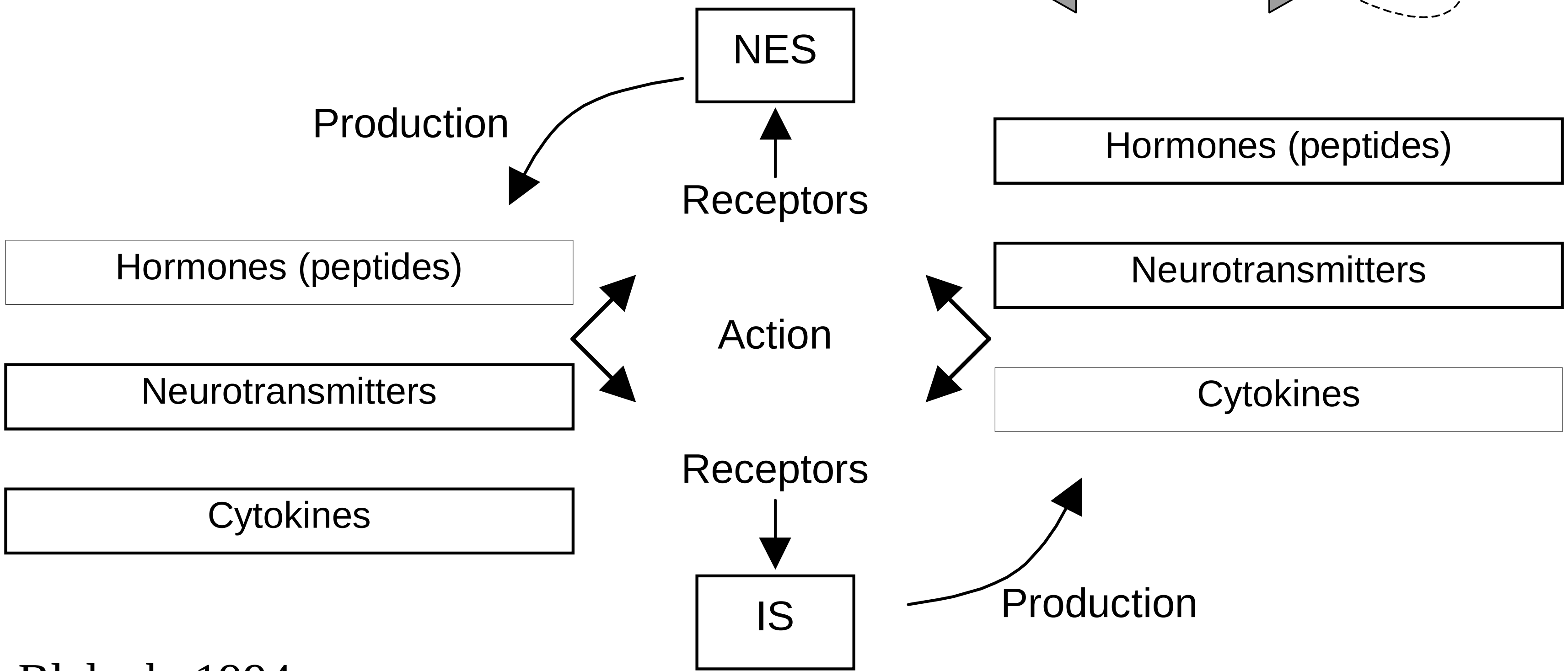


- The ontogenetic blind variation together with natural selection (responsible for the mammals evolution), is still crucial to our day by day ceaseless battle for survival.
- **Biological evolution**: natural selection among organisms.
- **Ontogenetic evolution**: natural selection within an organism.

Immune and Central Nervous Systems

- Homeostasis
- Psychoneuroimmunology





Blalock, 1994

Cognition!? (I)

- *Cognition*: symbolic manipulation of the mental representations that compose knowledge, defining the behavior of an individual (Edelman, 1992).
- *Cognitive system*: capable of extracting information and experience from input data through the manipulation of information already contained in the system; it is *intentional* (Cohen, 1992a,b).
- Immune Cognition: N. K. Jerne, I. Cohen, A. Coutinho, F. Varela, A. Tauber, etc.
  – Self/Non-Self recognition, learning and memory;
  – Internal images (network theory).

Cognition!? (II)

- Cognition (*psychology*): the superior functions of the brain, like pattern recognition, self recognition and “intention”:
  - related to stimuli like physical, chemical, emotional, etc.
- *Sensorial* activity of the IS (Blalock, 1994)
- The sensorial aspects of the IS complement the cognitive capabilities of the brain through the recognition (perception) of stimuli that can not be smelt, tasted, seen, etc., to cause physiological responses

Adaptive Biological Cognition

- Search for a context:
  - When to act?
- Signal extraction from noise:
  - How to focus recognition?
- The response problem:
  - Which decision to make?

- **Intentionality ≠ Personality**

The Immune System and the Brain

Immune System

- $\approx 10^{12}$ lymphocytes
- molecular recognition (sixth sense)
- recognition and effector
- learning through increase in size and affinity of specific clones
- interconnected “network of communication”
- chemical communication signals
- decentralized

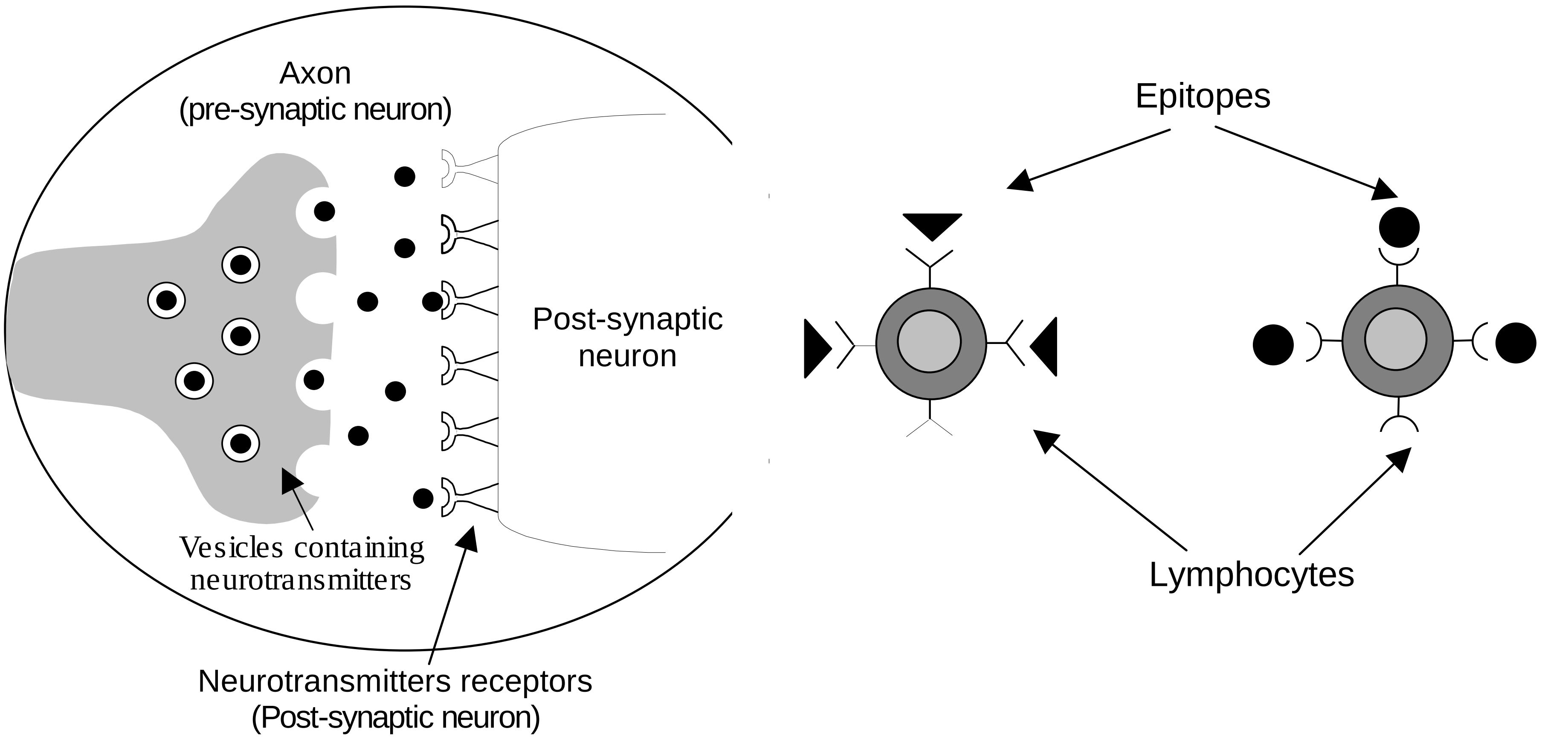
Central Nervous System

- $\approx 10^{10}$ neurons
- vision, audition, taste, touch, smell
- sensorial and motor
- learning by altering connection strengths, not the neurons themselves
- functionally interconnected cells
- electrochemical communication signals
- hierarchical

The Immune System and the Brain

- Parallel processing
- Long-lasting memory
- Knowledge is not transmitted through generations
- Self-knowledge
- Existence of cell receptors
- Contextual recognition
- Noise tolerance
- Generalization

Neuronal and Lymphocyte Receptors



PART IV

Artificial Immune Systems:

Definitions, Scope & Applications

AIS: Definitions

- The AIS are data manipulation, classification, representation and reasoning strategies that follow a plausible biological paradigm: the human immune system (Starlab);
- The AIS are composed by intelligent methodologies, inspired by the biological immune system, toward real-world problem solving (Dasgupta, 1999)
- An AIS is a computational system based on natural immune system metaphors (Timmis, 2000)

AIS: Scope

- Computational methods based on immunological principles;
- Immunity-based cognitive models;
- Immunity-based systems for: anomaly and fault detection, self-organization, collective intelligence, search and optimization, artificial life, computational security, image and signal processing, machine-learning, data analysis, pattern recognition; and
- Immunity-based multi-agent and autonomous decentralized systems.

AIS: Applications (I)

- Robotics:
  - Behavior arbitration mechanisms
  - Emergence of collective behavior
- Control:
  - Identification, synthesis and adaptive control
  - Sequential control
- Optimization:
  - Restrict, **multimodal and combinatorial**
- Neural Network Approaches:
  - Similarities and differences
  - Associative memory
  - **Growing Boolean competitive network**

AIS: Applications (II)

- Anomaly Detection:
  - **Computational security**
  - **Negative selection**
  - DNA-based negative selection
  - Image inspection
  - Image segmentation
  - Time series novelty detection
- Agent-Based Approaches:
  - **Computational security**
  - Intelligent buildings
  - Adaptive noise neutralization

AIS: Applications (III)

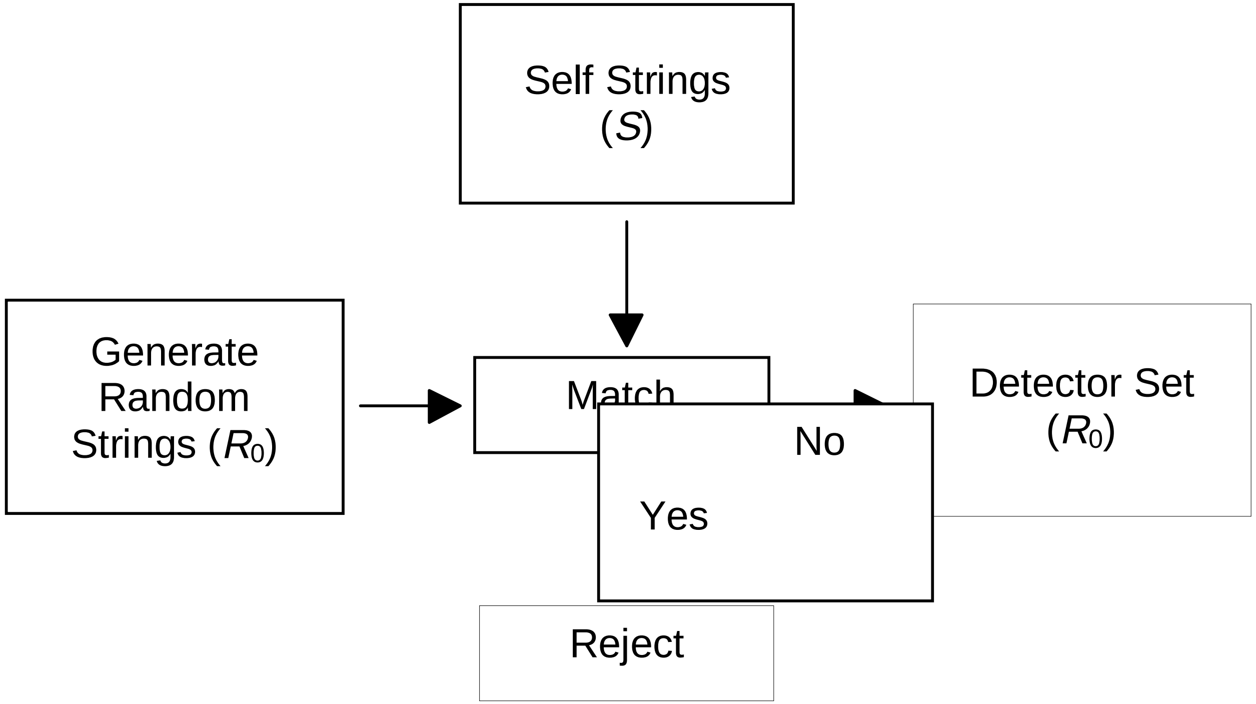
- Learning:
  - Pattern recognition
  - Concept learning
  - The Baldwin effect
  - Generation of emergent properties
- Inductive Problem Solving:
  - Finite-State Automaton
  - Genetic Programming
- Pattern Recognition:
  - **Generic approaches**
  - Spectra recognition

AIS: Applications (IV)

- Computer Models:
  - Cellular Automaton, Multi-Agent and Disease Processes
- Other Applications:
  - Open WebServer coordination
  - Scheduling
  - Data Mining
  - Classifier systems
  - Sensor-based diagnosis
  - Evolution of gene libraries
  - Self identification processes
  - **A Simulated Annealing model of diversity**
  - The reflection pattern in the immune system

Negative Selection Algorithm (I)

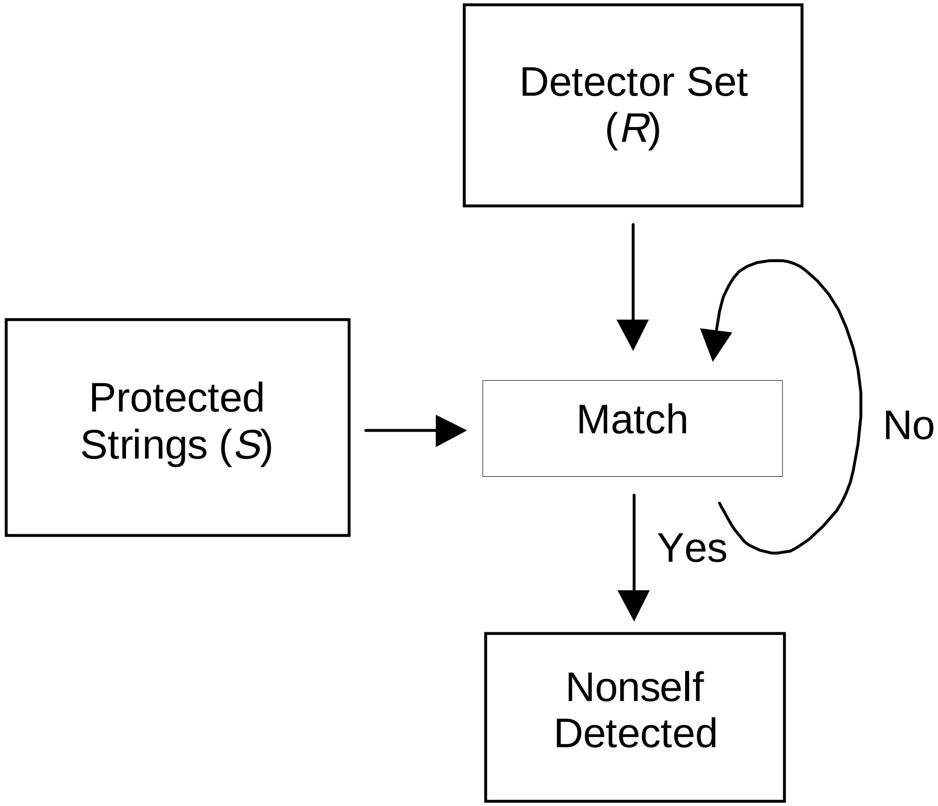
- Censoring



Forrest et al., 1994

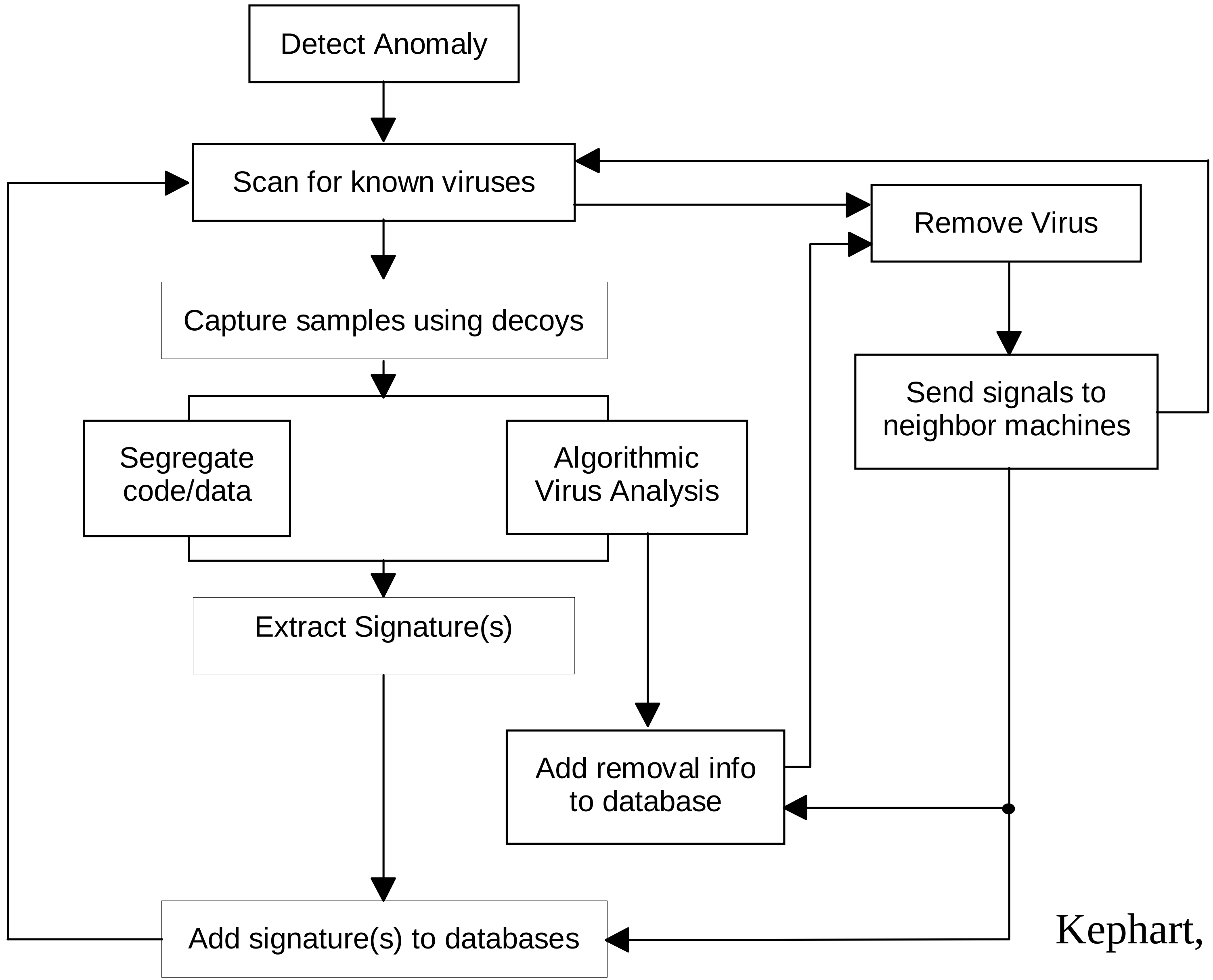
Negative Selection Algorithm (II)

- Monitoring



Forrest et al., 1994

Virus Detection and Elimination



Kephart, 1994

Network Security (I)

IDS: Intrusion detection system

Characteristic of an IDS	**Immune System**
Distribution	Immune network
	Unique antibody sets
Self-Organization	Gene library evolution
	Negative selection
	Clonal selection
Lightweight	Approximate binding
	Memory cells
	Gene expression

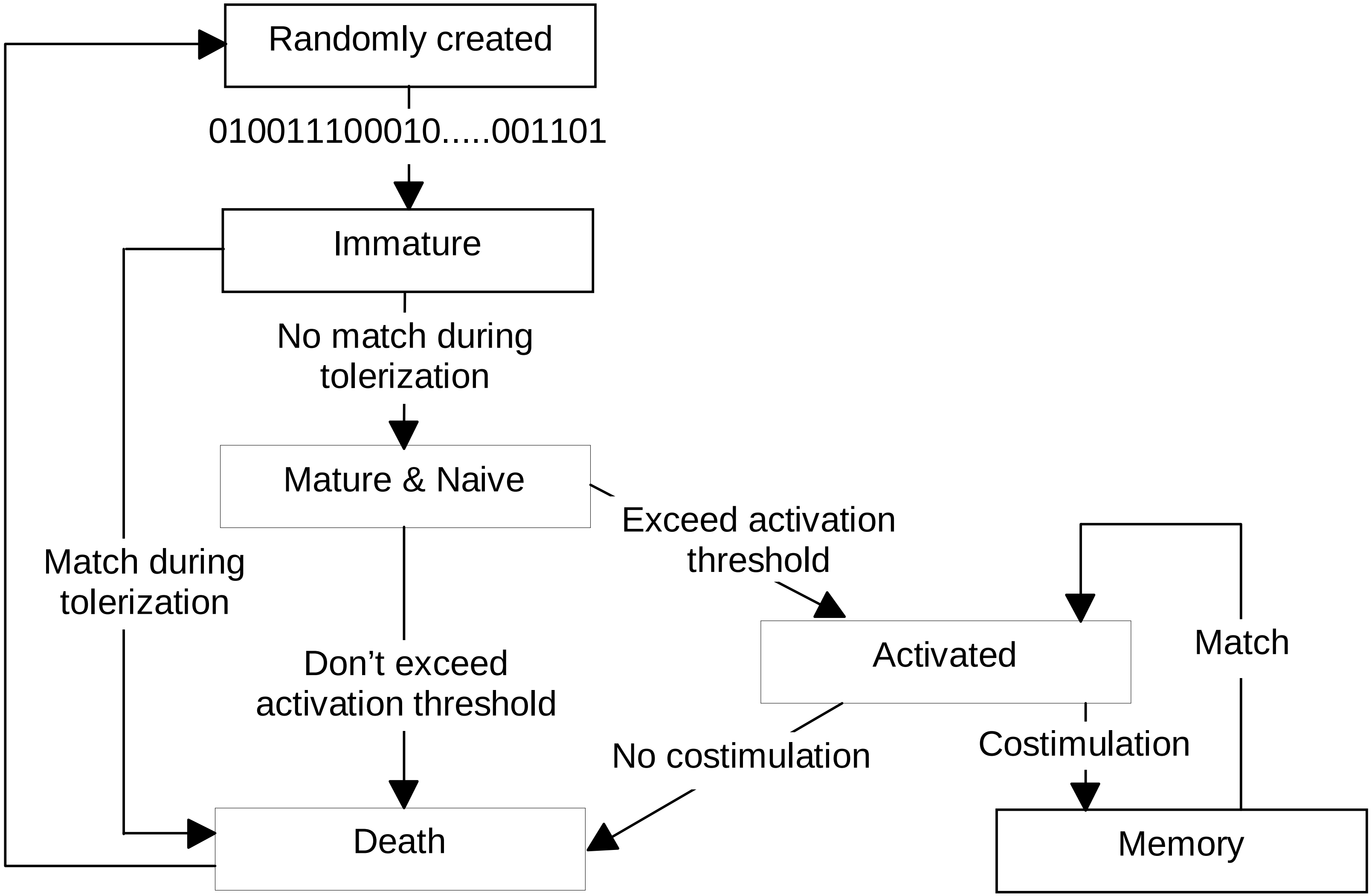
Kim & Bentley, 1999

Network Security (II)

Network Environment	Immune System
Primary IDS	Bone marrow and thymus
Local hosts	Secondary lymph nodes
Detectors	Antibodies
Network intrusions	Antigens
Normal activities	Self
Abnormal activities	Non-Self

Kim & Bentley, 1999

Network Security (III)

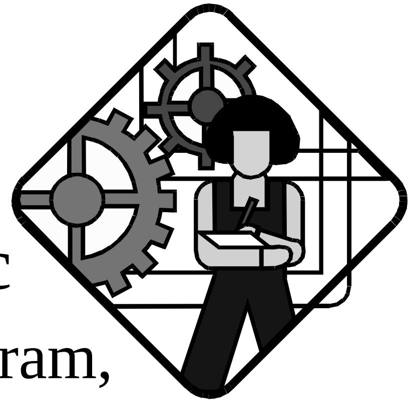


Hofmeyr & Forrest, 1999, 2000

PART V

Immune Engineering: Basic Theory

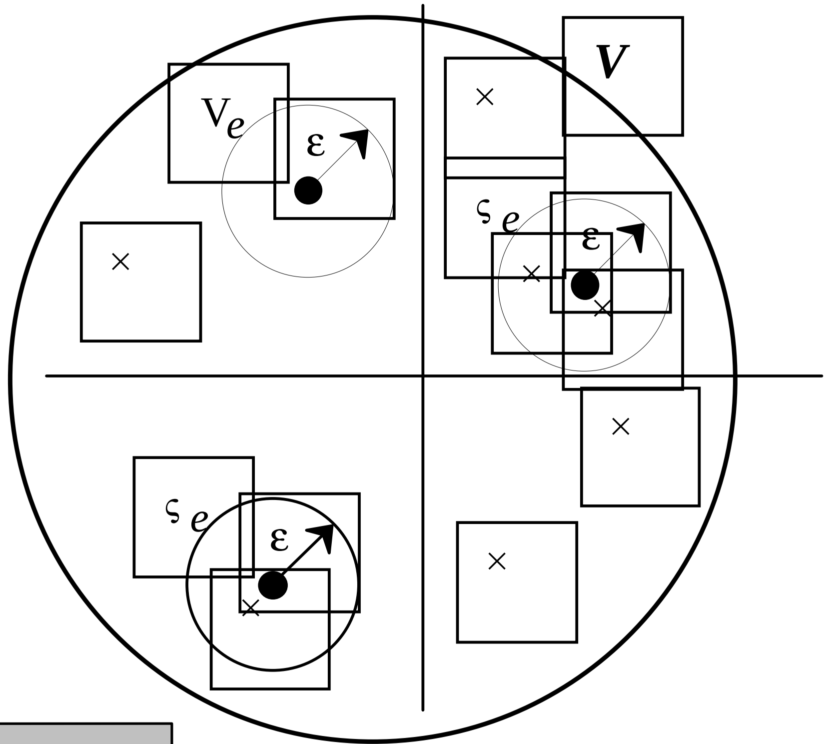
Immune Engineering



- *Engineering* consists of designing basic systems for solving specific tasks (Wolfram, 1986)
- *Traditional Engineering*
  - detailed specification of the behavior of each component of the system (step-by-step procedure)
- *Immune Engineering* (IE)
  - general, or approximate, specification of some aspects of the global behavior of the system, like a performance or adaptability (fitness) measure
  - extraction of information from the problems themselves

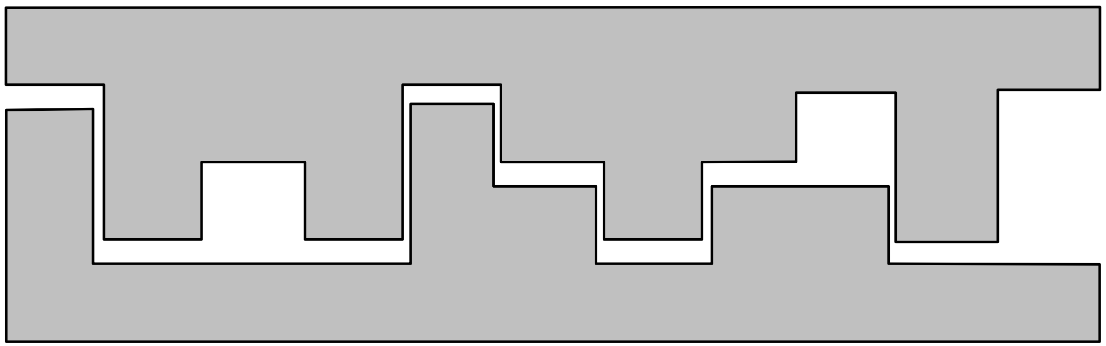
Pattern Recognition

- Shape-Space *S*
  - Complementarity
  - Representations
  - Distance measures
  - $m=<m_1, m_2,..., m_L>$,
  - $m \in S^L \subseteq \Re^L$



Perelson & Oster, 1979

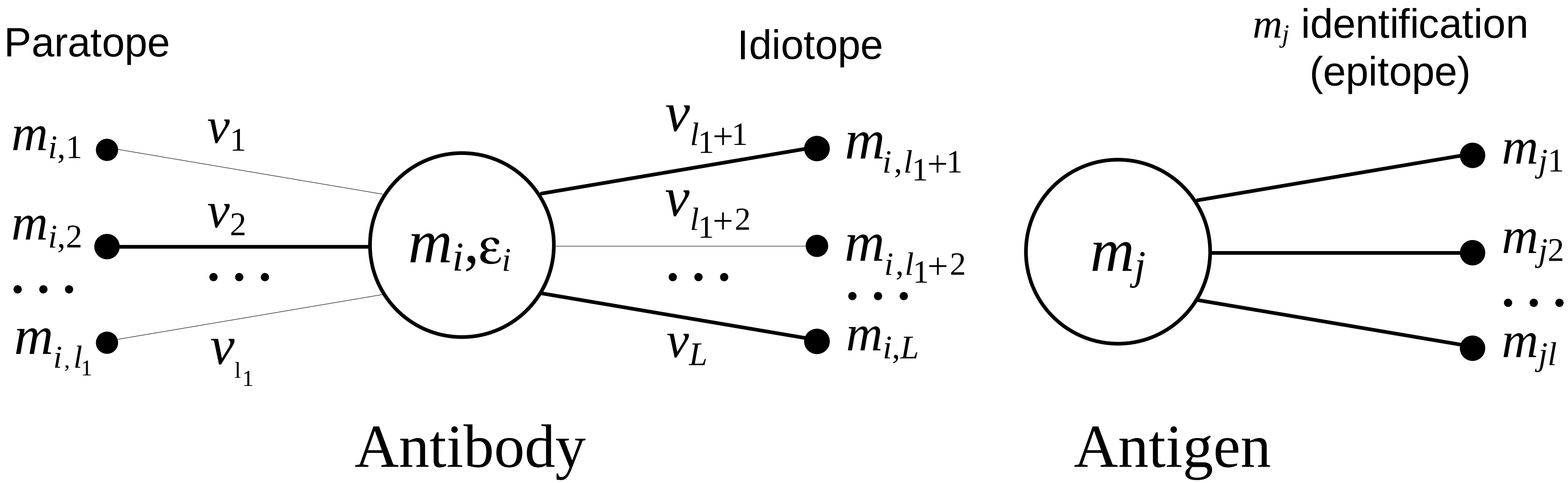
MHC/peptide complex or epitope
(Ligand)



Ab or TCR
(Biding site of a B or T cell)

Immune Engineering

- Definition: *meta-synthesis process that will define the solution tool to a given problem, based upon its own characteristics and immunological principles* (de Castro, 2001).
- Focus on a single cell type: B cell
- Pictorial representation:



AIS & IE

- AIS taxonomy:
  - Structures and hybrid algorithms based on immunological mechanisms and/or metaphors;
  - Computational algorithms inspired by immunological principles;
  - Immunological computation; and
  - Immune engineering.
- Potential applications of the immune engineering:
  - pattern recognition, optimization, function approximation and data analysis (clustering).

How to Measure Affinities?

- Real-valued Shape-Spaces:

$$D = \sqrt{\sum_{i=1}^{L} (Ab_i - Ag_i)^2} \qquad D = \sum_{i=1}^{L} \left| Ab_i - Ag_i \right|$$

Euclidean distance — Manhattan distance

- Hamming Shape-Spaces:

$$D = \sum_{i=1}^{L} \delta, \text{where} \quad \delta = \begin{cases} 1 & \text{if } \mathbf{Ab}_i \neq \mathbf{Ag}_i \\ 0 & \text{otherwise} \end{cases}$$

Hamming distance

0	0	1	1	0	0	1	1

1	1	1	0	1	1	0	1

XOR : 1 1 0 1 1 1 1 0

D = Affinity: 4

Forrest et al., 1994

0	0	1	1	0	0	1	1

1	1	1	0	1	1	0	1

XOR : 1 1 0 1 1 1 1 0

D = Affinity: $6+2^4=22$

Hunt et al., 1995

PART VI

Immune Engineering: Tools & Applications

General Aspects (I)

- Algorithms:
  - SAND: A Simulated Annealing Model of Diversity
  - CLONALG: The Clonal Selection Algorithm
  - ABNET: An Antibody Network
  - aiNet: An Artificial Immune Network
- The Clonal Selection Principle (CSP):
  - Used by the IS to describe the adaptive immune response to an antigenic stimulus;
  - Most stimulated cells will reproduce under a hypermutation scheme (B cell);
  - Low affinity clones are eliminated; and
  - Self-reactive clones will be purged from the repertoire.

General Aspects (II)

- SAND
  - Generation of a well-distributed initial repertoire.
- CLONALG
  - Pattern recognition and optimization via CSP
- ABNET
  - The CSP is used to control network size, and affinity maturation is responsible for learning (adaptation)
- aiNet
  - CLONALG is used to control network learning, and the immune network theory specifies cell-cell affinities

SAND: Introduction

- Rationale:
  - To generate a set of candidate solutions that best covers the search space.
- Applications:
  - Population (including ANN) initialization.
- Properties:
  - No knowledge about the problem is assumed;
  - Diversity induction through the maximization of an energy (distance) measure among the individuals;
  - Evolution based on competition and cooperation;
  - Multimodal search; and
  - Employs the standard Simulated Annealing algorithm.

SAND: Hamming Shape-Space

- Proposed cost (energy) function:

$$s(i) = \begin{cases} 1, & x_i \neq x_j, \forall j \\ 0, & \text{otherwise} \end{cases}$$

– Search for similar antibodies

$$F(\%) = 100.\frac{4}{L.N^2} \times \sum_{i=1}^{N} \sum_{j=i+1}^{N} HD(i, j)$$

– Percentage HD (affinity)

$$D(\%) = 100.\frac{1}{N} \times \sum_{i=1}^{N} s(i)$$

– Percentage of different antibodies

$$E(\%) = \frac{F(\%) + D(\%)}{2}$$

– Percentage energy

SAND: Euclidean Shape-Space

- Affinity measure: $ED = \sqrt{\sum_{i=1}^{L} (x_i - y_i)^2}$

- Proposed cost (energy) function:

$$\bar{\mathbf{I}} = \frac{1}{N}\sum_{i=1}^{N} \mathbf{I}_i$$

– Average unit vector

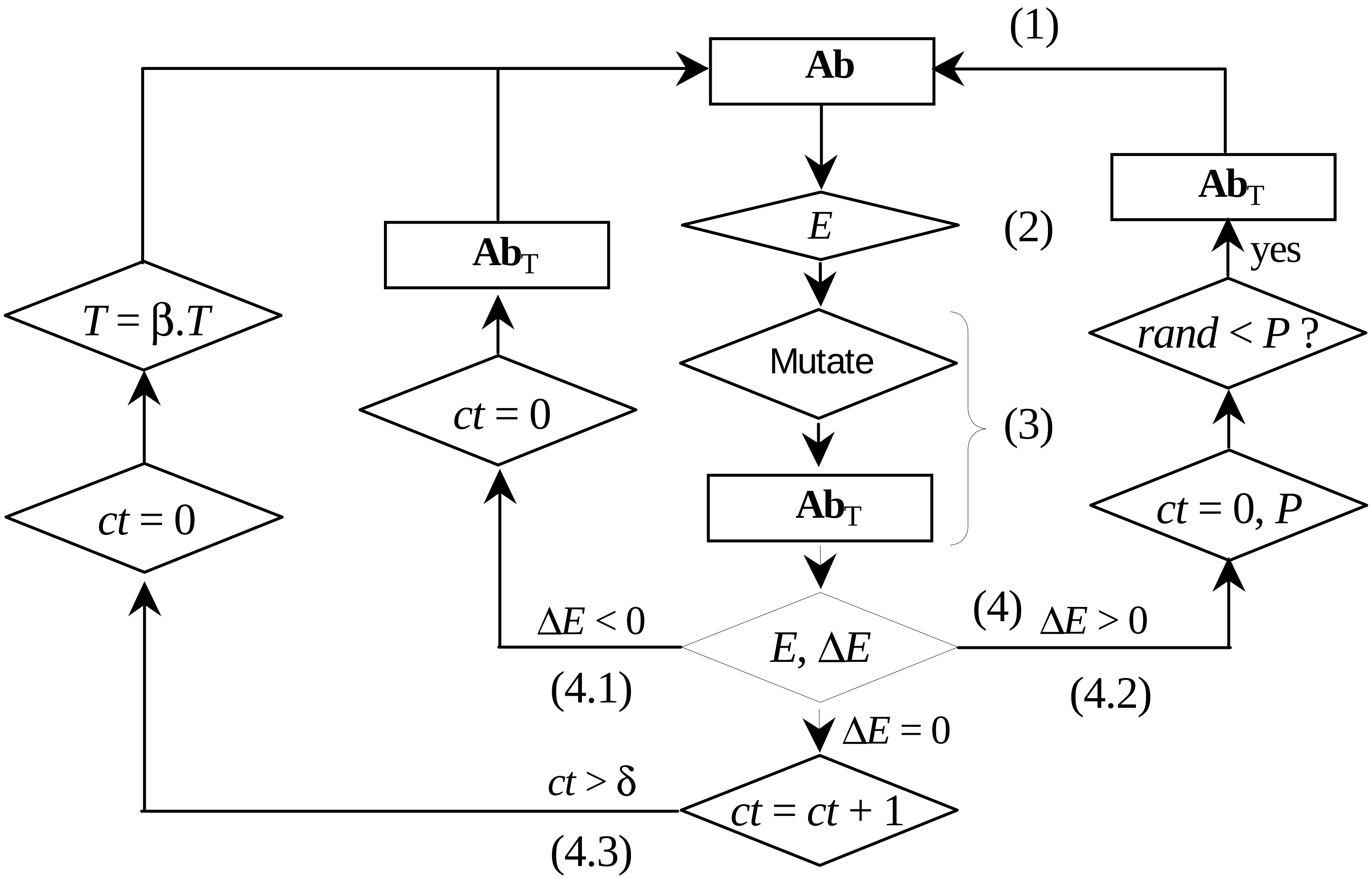
$$\bar{R} = \left(\bar{\mathbf{I}}^T \bar{\mathbf{I}}\right)^{1/2}$$

– Resultant vector (distance from the origin of the coordinate system)

$$E(\%) = 100 \times (1 - \bar{R})$$

– Percentage energy

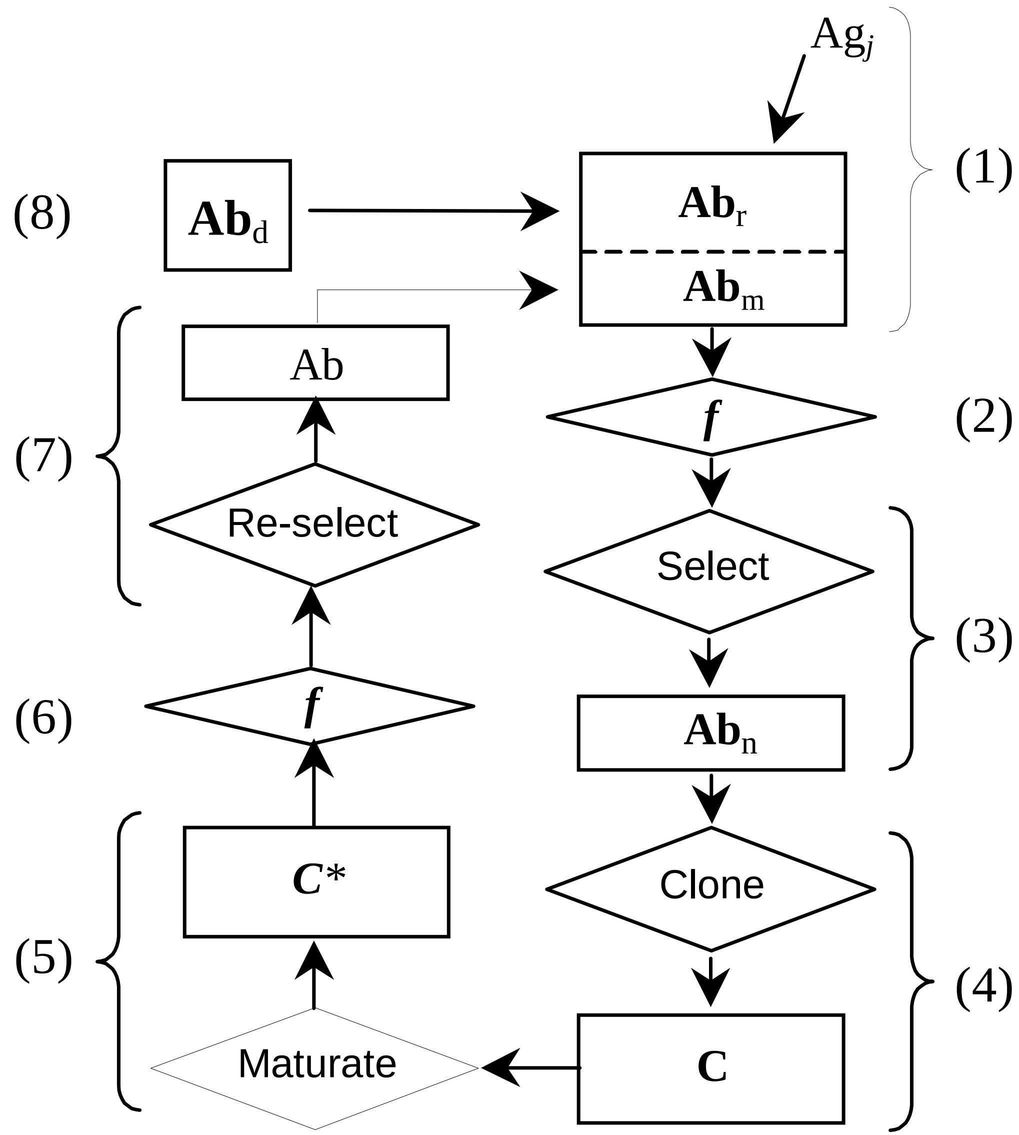
SAND: Pseudocode



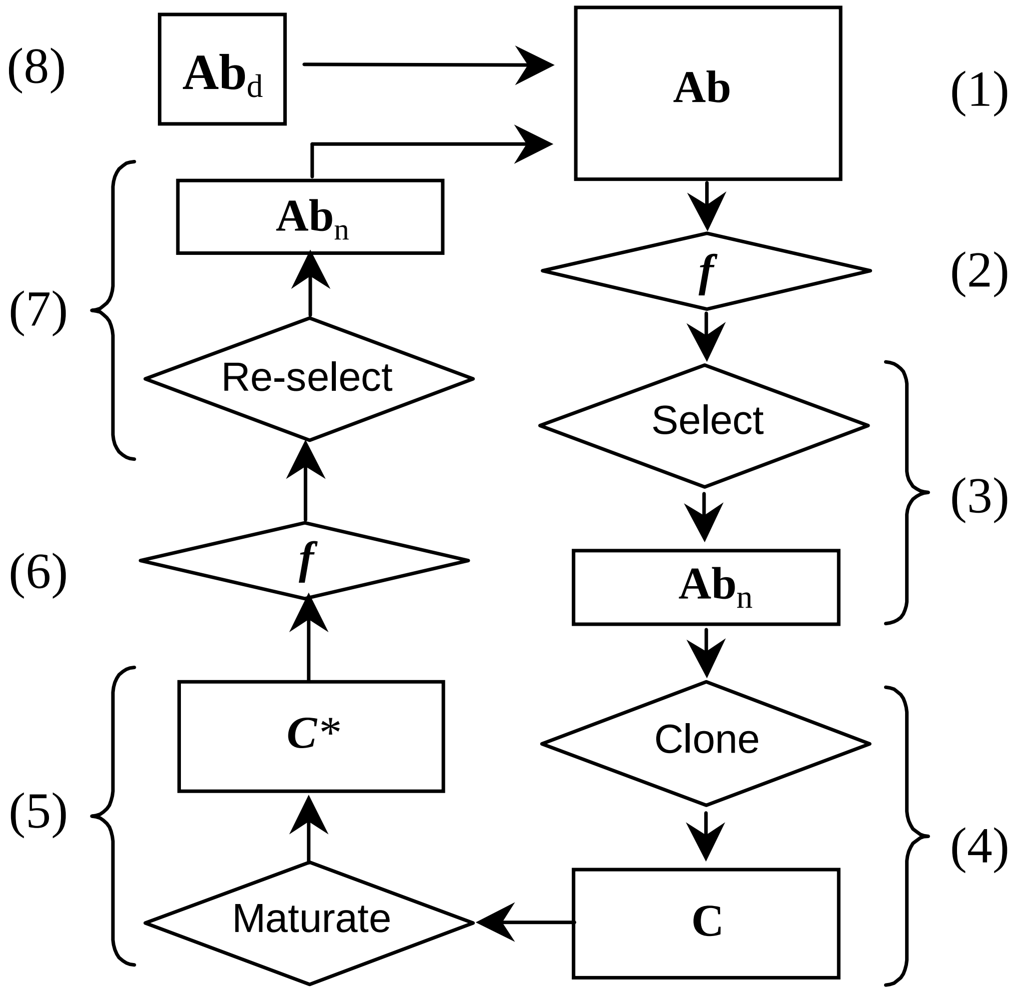
CLONALG: Introduction

- Rationale:
  - Computational implementations of the clonal selection and affinity maturation principles.
- Applications
  - Machine-learning, pattern recognition, multimodal optimization, function approximation.
- Properties:
  - Generation of genetic variation exclusively through a hypermutation mechanism; and
  - Proliferation and differentiation due to antigenic recognition.

CLONALG: Pattern Recognition



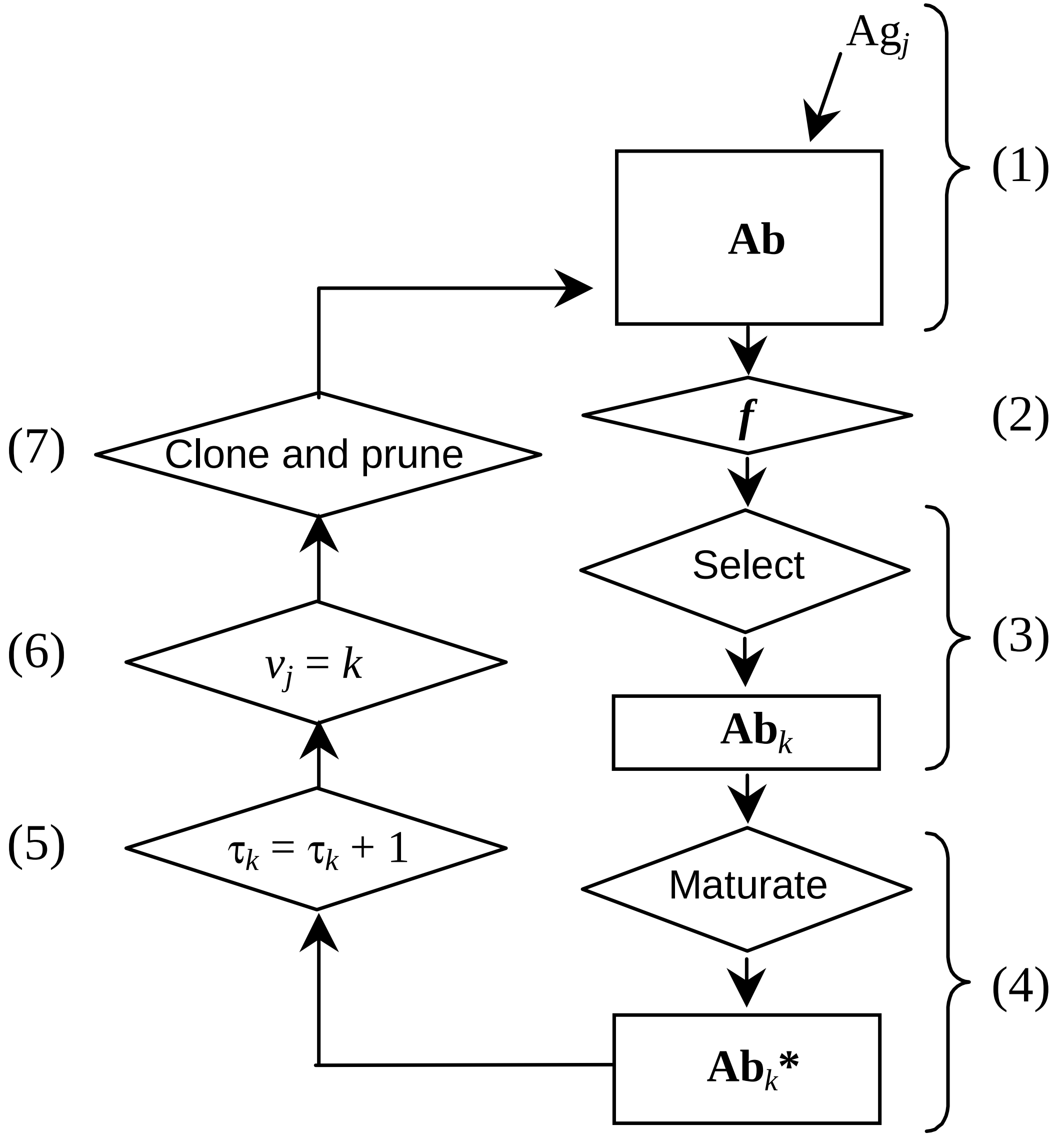
CLONALG: Optimization



ABNET: Introduction

- Rationale:
  - To show that the immune system might provide us with several interesting ideas to develop artificial neural network learning algorithms.
- Applications:
  - Pattern recognition and classification.
- Properties:
  - Unsupervised (self-organized), growing learning with pruning phases;
  - The weight vectors are the antibodies and correspond to internal images of the antigens (input patterns);
  - Boolean connection strengths;
  - Learning through a directed hypermutation mechanism

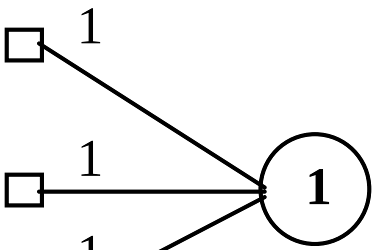
ABNET: General Operation



ABNET: Growing

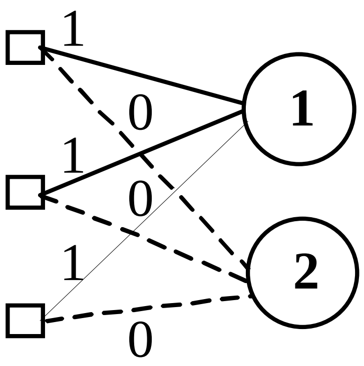
$$s = \arg\max_{j \in O} \mathbf{Ab}_j, \text{ where } O = \{\mathbf{Ab}_j \mid \tau_j > 1\}$$

$\mathbf{Ag}_1$	$\mathbf{Ag}_2$	$\mathbf{Ag}_3$
0	1	1
0	1	0
0	1	0
v_1=1	v_2=1	v_3=1



τ_j =3

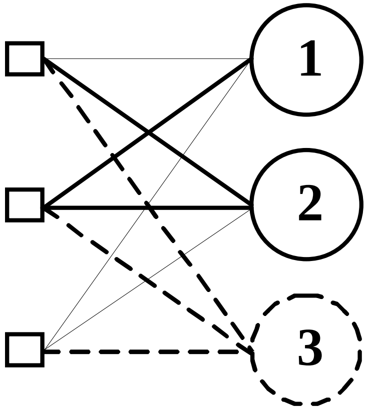
$\mathbf{Ag}_1$	$\mathbf{Ag}_2$	$\mathbf{Ag}_3$
0	1	1
0	1	0
0	1	0



ABNET: Pruning

Ag_1	Ag_2	Ag_3
0	1	1
0	1	0
0	1	0

$v_1=1$ $v_2=2$ $v_3=1$

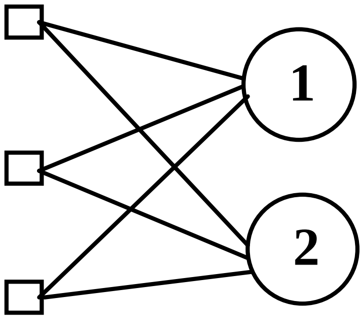


$\mathbf{w}_1=[1,1,1]$, $\tau_1=2$

$\mathbf{w}_2=[0,0,0]$, $\tau_2=1$

$\mathbf{w}_3=[1,0,0]$, $\tau_3=0$

Ag_1	Ag_2	Ag_3
0	1	1
0	1	0
0	1	0



$\mathbf{w}_1=[1,1,1]$

$\mathbf{w}_2=[0,0,0]$

ABNET: Weight Update

1	0	0	0	1	0	1	1	**Ag**
0	0	1	1	1	1	1	0	**Ab**$_k$ (Affinity: 5)

Updating (α = 1)

1	0	0	0	1	0	1	1	**Ag**
0	1	1	1	1	1	1	0	**Ab**$_k$ (Affinity: 6)

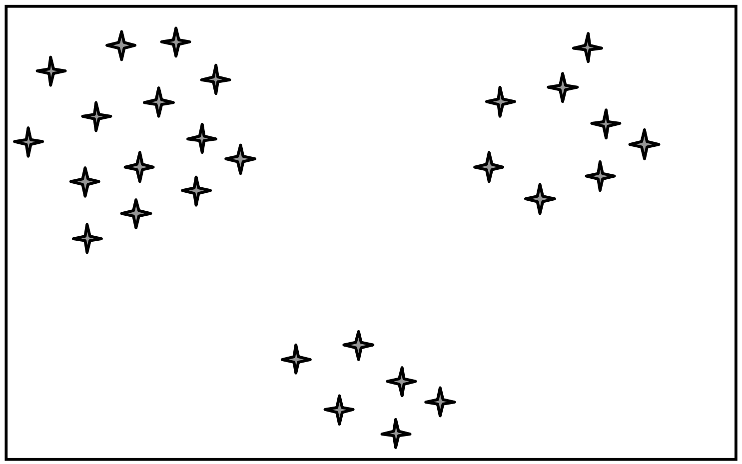
1	0	0	0	1	0	1	1	Ag
0	0	1	1	1	1	1	0	Ab$_k$(Affinity: 5)

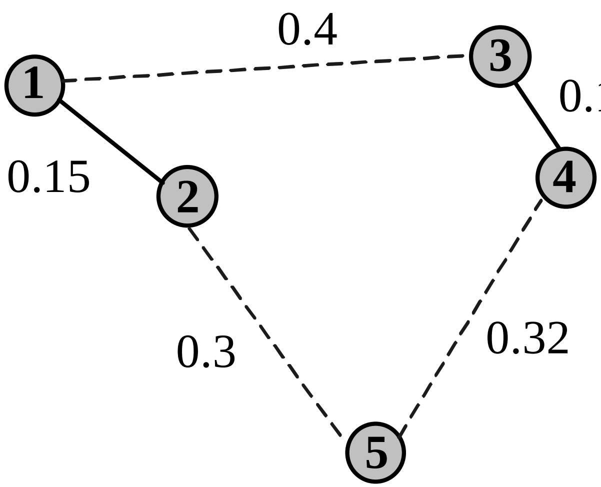
Updating (α = 2)

1	0	0	0	1	0	1	1	Ag
0	1	1	1	0	1	1	0	Ab$_k$(Affinity: 7)

aiNet: Basic Principles (I)

- Definition:
  - The evolutionary artificial immune network, named aiNet, is an *edge-weighted graph*, not necessarily fully connected, composed of a set of nodes, called *cells*, and sets of node pairs called *edges* with a number assigned called *weight*, or *connection strength*, specified to each connected edge.





aiNet: Basic Principles (II)

- Rationale:
  - To use the clonal selection principle together with the immune network theory to develop an artificial network model using a different paradigm from the ANN.
- Applications:
  - Data compression and analysis.
- Properties:
  - Knowledge distributed among the cells
  - Competitive learning (unsupervised)
  - Constructive model with pruning phases
  - Generation and maintenance of diversity

aiNet: Pseudocode

```
function [Abm,S] = aiNet(Ag,L,gen,n,ζ,σd,σs,d);
Ab := generate(N0,L);
for t = 1 to gen,
   for j = 1 to M,
      f          := affinity(Ab,Ag(j,:));
      Abn        := select(Ab,f,n);
      C          := clone(Abn,1,f);
      C*         := dmut(C,Ag(j,:),f);
      f          := affinity(C*,Ag(j,:));
      Abm        := select(C*,f,ζ);
      [Abm,f]    := suppress(Abm,f,σd);
      S          := affinity (Abm,Abm);
      [Abm,S]    := suppress(Abm,S,σs);
   end;
   S       := affinity (Abm,Abm);
   [Abm,S] := suppress(Abm,S,σs);
   Abd     := generate(d,L);
   Ab      := insert(Abm,Abd);
end;
```

LET’S MAKE A TOUR . . .

PART VII

Discussion

Discussion (I)

- Growing interest for the AIS
- Biological Inspiration
  - utility and extension
  - improved comprehension of natural phenomena
- Example-based learning, where different pattern categories are represented by adaptive memories of the system
- Strongly related to other intelligent approaches, like ANN, EC, FS, DNA Computation, etc.

Discussion (II)

- SAND:
  - Generation of highly diversified populations
  - Applications to ANN initialization (de Castro & Von Zuben, 2001)
- CLONALG:
  - High degree of parallelism;
  - By controlling the hypermutation rate, an initial search for most general characteristics can be performed, followed by the search for smaller details;
  - Trade-off between the clone size and the convergence speed; and
  - Possibility of using heuristics to improve convergence and scope of applications.

Discussion (III)

- ABNET:
  - Clustering, or grouping of similar patterns; and
  - Potential to solve binary tasks.
- aiNet:
  - Iterative model ≠ dynamic models (DE);
  - Robustness with low redundancy;
  - Clustering without a direct measure of distance*;
  - ANN: knowledge distributed among the connections;
  - aiNet: knowledge distributed in the cells;
  - Drawback: large amount of user defined parameters;
  - Specific cells: less parsimonious solutions; and
  - General cells: more parsimonious solutions.

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