The Adaptive Immune System and Artificial Immune Systems
Lab Assignments: 35% (ISE-483), 25% (SSIE-583)
- Complete 4/5 assignments based on algorithms presented in class
  - Lab 5: May 1\textsuperscript{st}
    - Ant Clustering Algorithm, (Lab 5 in Brightspace Assignments)
    - Due May 8\textsuperscript{th}

SSIE – 583 - Presentation and Discussion: 35%
- Present and lead the discussion of an article related to the class materials
  - Enginet students post/send video or join by Zoom
- All presentations completed?
Readings until now

resources

- **Class Book**
    - Chapters 1, 2, 4, 7
    - Chapter 5, (6)

- **Lecture notes**
  - Chapter 1: “What is Life?”
  - Chapter 2: “The Logical Mechanisms of Life”
  - Chapter 3: “Formalizing and Modeling the World”
  - Chapter 4: “Self-Organization and Emergent Complex Behavior”
  - Chapter 5: “Reality is Stranger than Fiction”
  - Chapter 6: “Von Neumann and Natural Selection”
  - Chapter 7: “Modeling Evolution: Evolutionary Computation”
    - posted online @ [http://informatics.indiana.edu/rocha/i-bic](http://informatics.indiana.edu/rocha/i-bic)

- **Other materials**
    - Chapters 1, 2, 3, 5, 7, 8
    - Chapter 6
final project schedule

- Projects
  - Due by **May 8th 12th** in Brightspace, “Final Project Paper” assignment
    - ALIFE 2023
      - Not to submit to actual conference due date (March 13th)
      - [https://2023.alife.org/](https://2023.alife.org/)
      - 8 pages, author guidelines:
        - [calls/call-for-papers-extended-abstracts](https://2023.alife.org/calls/call-for-papers-extended-abstracts)
        - MS Word and Latex/Overleaf templates
    - Preliminary ideas by **March 27**
      - Submit to “Project Idea” assignment in Brightspace.
  - Individual or group
    - With very definite tasks assigned per member of group

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**ALIFE 2023**

Tackle a real problem using bio-inspired algorithms, such as those used in the labs.

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**ALIFE 2023**

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Date: 24-28th July, 2023
Venue: Clark Memorial Student Center
Location: Hokkaido University, Sapporo, Hokkaido, Japan
The immune system

- maintain homeostasis
  - in concert with other bodily systems
- **identification** (detection) and **elimination** of non-self (≈external) elements and malfunctioning self elements
  - protect body from threats
    - toxic substances and pathogens
    - self from non-self detection
  - minimize harm to body
    - detect **harmful** non-self from everything else
  - choose appropriate elimination process
    - the right effectors for particular pathogen
Vertebrate immune defense

- Skin
  - Blocks most pathogens
- Physiological conditions
  - Temperature, PH
- Innate immune system
  - Scavenger cells (e.g. phagocytes)
    - Engulf pathogens and other substances
- Adaptive immune system
  - Lymphocytes
    - Adapt to previous pathogens to eliminate them
- Chemical bonding
  - Mechanism for identification/detection and elimination for both innate and adaptive immune system
    - Receptors in cell surfaces bind to pathogens or to other immune system cells or molecules for *signaling*

An Overview of the Immune System. Steven A Hofmeyr
basic mechanisms

From Paul Bugl

An Overview of the Immune System. Steven A Hofmeyr
An Overview of the Immune System

From Paul Bugl
molecular memory defense (in vertebrates)

- **Learns** to recognize *specific* types of pathogens
  - Primary response
    - To new pathogens
      - Slow
    - Retains memory of pathogens
  - Secondary response
    - Quicker, based on *memory* of primary response

- **Lymphocytes:** T, B, or NK Cells (in innate system)
  - Detection and elimination of pathogens via **collective behavior**
    - Trillions of detectors with no centralized control
      - Interacting through simple, localized rules

- **Antigen-presenting cells (APC)**
  - Phagocytes ("eating cells") from the innate immune system which are also used to present antigen epitopes on their surface (on MHC and other receptors) to T-Cells
    - Macrophages, dendritic cells, etc
specific recognition in the immune system

chemical bonds as generalized detectors

Lymphocyte recognition occurs when its receptors bind with epitopes from pathogens on the surface of APCs (by complementary structure and electrical charge)

Affinity: strength of bond

Pathogens may have many different epitopes: many lymphocytes may be specific to a single pathogen

An interpretative introduction to the Immune System. Steven A Hofmeyr

Aprox $10^5$ receptors per lymphocyte: estimates affinity and quantity of pathogen; number of binding receptors increases with affinity and quantity. Activation (detection event) occurs after a threshold of binding receptors

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Antigenic Activation: T-cell binds to antigen presenting cell

Phagocytic Embrace

From Gary Carlson
molecular pattern matching

Figure 2-23 The Immune System, 2/e © Garland Science 2005

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Building up the response repertoire

generating receptor diversity (from DNA memory banks)

Receptors are generated via DNA recombination

At any given time there are an estimated $10^8$ varieties of receptors, but there are potentially $10^{16}$ epitope varieties

**Dynamic protection**: turnover of lymphocytes. $10^7$ new lymphocytes generated each day!

10 days to generate a new repertoire

With dynamic protection and immune memory, protection is increased against enormous size of potential pathogens

*An interpretative introduction to the Immune System. Steven A Hofmeyr*
receptors: **antibody (Ab)**, also known as an **immunoglobulin (Ig)**, is a Y shaped protein

**V(D)J or Somatic Recombination:** (nearly) random generation of gene segments (variable, diverse, and Joining)
generating receptor diversity (in B Cells)

V(D)J or Somatic Recombination: (nearly) random generation of gene segments (variable, diverse, and Joining)
mechanism of receptor diversity

somatic recombination

TdT: Terminal deoxynucleotidyl transferase or terminal transferase, adds nucleotides (without a template) to VDJ exons

“randomizer” of DNA (Turing) tape
An interpretative introduction to the Immune System. Steven A Hofmeyr

**adaptive response (clonal selection)**

**learning specific pathogens**

- **B Cells**
  - Learning and remembering implemented by lymphocytes
  - If activated, migrate to *lymph nodes*: gland where adaptive response develops
  - *proliferation*: B cell produces many short-lived clones (cell division) under *somatic hypermutation* (9 orders of magnitude higher than normal mutation)
  - Generate different receptor structures/epitope affinities

- **Antibodies** (immunoglobulin): soluble form of receptors that bind to pathogen epitopes (opsonize and neutralize)
  - Humoral response (fluid)

**Antigen**: anything that causes antibody generation:

- If clones do not bind to pathogenic epitopes in lymph nodes, they die. If binding occurs, they leave the lymph node and differentiate into *plasma* or *memory* B cells. Due to limited resources, Darwinian selection occurs

*An interpretative introduction to the Immune System.*

Steven A Hofmeyr
Via Darwinian variation and selection

**Clonal selection and hypermutation:**
“private” Darwinian selection

Clones “compete” for pathogen epitopes. Higher affinity implies greater rate of reproduction (fitness)

Iteration of B-cell activation-proliferation-differentiation cycle
Of B-Cells

Clonal selection

From: Doc Kaiser's Microbiology Home Page
An interpretative introduction to the Immune System. Steven A Hofmeyr
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An interpretative introduction to the Immune System. Steven A Hofmeyr

Tolerance to self (negative selection)

Somatic hypermutation could lead to autoimmunity

**Tolerance** is implemented by another type of lymphocyte: **T-helper Cells** (matured in the Thymus)

Most self epitopes are expressed in the thymus where Th cells mature

**Clonal selection** or negative selection kills T-cells that bind to self

B-Cells are also tolerized in the bone marrow, but via clonal selection could still become **autoreactive**

**Central tolerance**: T-cells tolerized in one single location (the thymus)
Tolerance to self: costimulation

B-cells need to be **co-stimulated** by receptor binding and T-Cells

Helper T-Cells **verify** the epitopes that bind to B-cells for autoreaction

**An interpretative introduction to the Immune System.** Steven A Hofmeyr
The immune system

- Much is unknown
- Other theories
  - Immune Network Theory
  - Danger theory
- Intracellular pathogens
- Collective symbiosis
- Etc, etc, etc, etc

Biological complexity afforded by the Turing tape for self-other recognition
modeling the immune system from a bio-inspired computing perspective

- **Objective**
  - explore collective dynamics of t-cell cross-regulation
    - *computational intelligence*: build a novel bio-inspired machine learning solution for document classification
    - *computational biology*: understand how well collections of t-cells engaged in crossregulation perform as a classifier.

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Agent-based model of immune cross-regulation dynamics

Applied for binary classification of text (spam and biomedical articles)

- Inspired by the cross-regulation model.
  - Carneiro et al. (2007).
  - Purely dynamical model of t-cell regulation leading to bistable states
    - Harmful non-self detection
    - Studying concept drift

regulating self-organizing dynamics for self/nonself discrimination

- **regulatory t-cells**
  - help prevent autoimmunity by down-regulating other t-cells that might bind to and kill self antigens
- **Analytical model of Carneiro et al (2007)**
  - model self/nonself discrimination
  - Three cell-types or components

1. Antigen Presenting Cells (A)
2. T Effector Cells (E)
3. T Regulatory Cells (R)
- model self/nonself discrimination
- Three cell-types or components
- Four interaction rules

1. Antigen Presenting Cells (A)
2. T Effector Cells (E)
3. T Regulatory Cells (R)

\[
\begin{align*}
E \rightarrow \{\} & \quad \text{and} \quad R \rightarrow \{\} \\
A + R & \rightarrow A + R \\
A + E & \rightarrow A + 2E \\
A + E + R & \rightarrow A + E + 2R
\end{align*}
\]
Dynamical system
- Three cell-types or components
- Four interaction rules

Carneiro et al modeled a single antigen system
- One population of monospecific t-cells
  - Sepulveda (2009) extended analytical model to deal 2 antigens
- Leads to a bistable system
  - Two population attractors

1. [SELF] Co-existence of both E and R (E < R)
2. [NONSELF] Prevalence of E (E >> R)
agent-based t-cell crossregulation model

computational extension to model large numbers of antigens

- Multi-agent dynamical system
  - Three cell-types or components
  - Four interaction rules
  - (very) polyspecific APC
  - hundreds of distinct antigens and respective (monospecific) t-cell populations: $E_f$ and $R_f$

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**Figure:** e.g. $R_i + E_j \rightarrow 2R_i + E_j$ (Rule 4)

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agent-based t-cell crossregulation model for textual documents

- **Bio-inspired classification algorithm**
  - Antigens are textual patterns (features)
  - **Polyspecific**: APC present textual fragments (features) of specific documents (broken into pieces)
  - Hundreds of **distinct antigens/features** represented by (monospecific) t-cell populations: $E_f$ and $R_f$
agent-based t-cell crossregulation model

- algorithm
  - Sequence of labeled or unlabeled documents
    - Unlabeled assumed to be negative/irrelevant
  - Documents broken into constituents for APC
  - APC “dropped” on artificial cellular dynamics
    - Where hundreds of distinct antigens/features interact via APC as (monospecific) t-cell populations: $E_f$ and $R_f$

agent-based model of immune cross-regulation dynamics

for adaptive (e-mail) spam detection

- inspired by the cross-regulation model.
  - Carneiro et al. (2007).
  - Purely dynamical model of t-cell regulation leading to bistable states
    - Harmful non-self detection
    - Studying concept drift