The Adaptive Immune System And Artificial Immune Systems
Assignments: 35%
- Students will complete 4/5 assignments based on algorithms presented in class

Lab meets in I1 (West) 109 on Lab Wednesdays
- Lab 0: January 14th (completed)
  - Introduction to Python (No Assignment)
- Lab 1: January 28th
  - Measuring Information (Assignment 1)
  - Graded
- Lab 2: February 11th
  - L-Systems (Assignment 2)
  - Graded
- Lab 3: March 25th
  - Cellular Automata & Boolean Networks (Assignment 3)
  - Graded
- Lab 4: April 8th
  - Genetic Algorithms (Assignment 4)
    - Being graded
- Lab 5: April 22nd
  - Ant Clustering Algorithm (Assignment 5)
    - Due May 4th
Readings until now

- **Class Book**
    - Chapters 1, 2, 3, 5, 7, 8
    - Chapter 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
Projects

- Due by **May 6th** in Oncourse
  - ALIFE 15 (14)
    - Actual conference due date: 2016
    - [http://blogs.cornell.edu/alife14nyc/](http://blogs.cornell.edu/alife14nyc/)
      - 8 pages (LNCS proceedings format)
    - [http://www.springer.com/computer/lncs?SGWID=0-164-6-793341-0](http://www.springer.com/computer/lncs?SGWID=0-164-6-793341-0)
  - Preliminary ideas *overdue!*
- Individual or group
  - With very definite tasks assigned per member of group
importance of the “external tape” in biology

- The “information turn”
  - Unlike Schrödinger, Turing and Von Neumann had no direct effect on molecular biology
  - But the “external tape” separated from the constructor (semiotic closure) has become an unavoidable principle of organization of biocomplexity
  - A new synthesis?
    - In 1971 Brenner: “in the next twenty-five years we are going to have to teach biologists another language still, [...] where a science like physics works in terms of laws, or a science like molecular biology, to now, is stated in terms of mechanisms, maybe now what one has to begin to think of is algorithms. Recipes. Procedures.”

“The concept of the gene as a symbolic representation of the organism — a code script — is a fundamental feature of the living world and must form the kernel of biological theory. [...] at the core of everything are the tapes containing the descriptions to build these special Turing machines.” (Sydney Brenner)

In mind and culture

“The spoken symbol perishes instantly without material trace, and if it lives at all, does so only in the minds of those who heard it” (Samuel Butler)

- **Written language as external symbols**
  - Invention resulted in profound cognitive discontinuity
    - Eric A. Havelock: “The written word—the persistent word—was a prerequisite for conscious thought as we understand it. An irreversible change in human psyche”
    - Walter Ong: “[seeing oral literature as a variant of writing is] “rather like thinking of horses as automobiles without wheels.”
      - “an oxymoron laced with anacronism; (James Gleick)
      - Aleksander Luria studied illiterate people in Uzbekistan: oral people cannot think in oral syllogisms
  - **Vocabulary size**
    - oral language: a few thousand words
    - written language: well over a million words, grows by thousands of words a year

“Spoken words also transport information, but not with the self-consciousness that writing brings. Literate people take for granted their own awareness of words, along with the array of word-related machinery: classification, reference, definition.” (James Gleick)
Extended (embodied) information

“Let the whole outside world consist of a long paper tape”. —John von Neumann, 1948

Network Semiotic Control (cybernetics)

- The power of Turing’s tape in generating complexity is coupling with Von Neumann’s constructor
  - With a universal code, semiotic control can be “plug-and-play”
  - separate but coupled

- Chalmer’s and Clark’s extended mind
  - Cognitive science requires both neuroscience and understanding of semiotic coupling with external tape

**two roles** of information

- data/program
- description/construction
- genotype/phenotype
- language/brain
- symbol/society-mind-body

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decoupling and externalization enable collective behavior

The human mental machinery led our species to have self-awareness but, at the same time, a sense of justice, willing to punish unfair actions even if the consequences of such outrages harm our own interests. Also, we appreciate searching for novelties, listening to music, viewing beautiful pictures, or living in well-designed houses. However, why is this so? What is the meaning of our tendency, among other particularities, to defend and share values, to evaluate the rectitude of our actions and the beauty of our surroundings?

The human mental machinery obviously refers to the brain, so the answer to the preceding questions must come from neural considerations. What brain mechanisms correlate with the human capacity to maintain inner speech, or to carry out judgments of value? To what extent are they different from other primates' comparable behaviors?


Semiotic closure in culture is a general principle (system) of evolution of open-ended complexity

- Are there societies without writing systems capable of constructing complex structures and technology?
  - Brains with symbols are very powerful, but writing systems do not construct.

Brains with tapes

- Same brains (same genes and biochemistry), different collective behavior via external tape.
- Does it make sense to study cognition exclusively by looking at the brain’s molecular level?

"Let the whole outside world consist of a long paper tape". —John von Neumann, 1948

### Natural design principles

**exploring similarities across nature**

<table>
<thead>
<tr>
<th>Natural Design Principles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-similar structures</strong></td>
</tr>
<tr>
<td>Trees, plants, clouds, mountains</td>
</tr>
<tr>
<td>- Morphogenesis</td>
</tr>
<tr>
<td>Mechanism</td>
</tr>
<tr>
<td>- Iteration, recursion, feedback</td>
</tr>
<tr>
<td><strong>Unpredictability</strong></td>
</tr>
<tr>
<td>- From limited knowledge or inherent in nature?</td>
</tr>
<tr>
<td>Mechanism</td>
</tr>
<tr>
<td>- Chaos, measurement</td>
</tr>
<tr>
<td><strong>Emergence, and self-organization</strong></td>
</tr>
<tr>
<td>- Complex behavior from collectives of many simple units or agents</td>
</tr>
<tr>
<td>- Cellular Automata, development, morphogenesis, brains</td>
</tr>
<tr>
<td>Mechanism</td>
</tr>
<tr>
<td>- Parallelism, multiplicity, multi-solutions, redundancy</td>
</tr>
<tr>
<td><strong>(open-ended) Evolution</strong></td>
</tr>
<tr>
<td>- Adaptation, novelty, creativity, learning</td>
</tr>
<tr>
<td>Mechanism</td>
</tr>
<tr>
<td>- Reproduction, transmission, variation, selection</td>
</tr>
<tr>
<td><strong>Collective behavior, network causality</strong></td>
</tr>
<tr>
<td>- Behavior derived from many inseparable sources</td>
</tr>
<tr>
<td>- Environment, ant colonies, embodiment, epigenetics, culture, immune systems, economic markets</td>
</tr>
<tr>
<td>Mechanism</td>
</tr>
<tr>
<td>- Interactivity, stigmergy, non-holonomic constraints</td>
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</tbody>
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The immune system

- **Function**
  - 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

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Primary lymphoid organs
An Overview of the Immune System. Steven A Hofmeyr

**multilayers**

- **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**
basic mechanisms

From Paul Bugl
adaptive immune system

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 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.

All receptors in a single lymphocyte are identical and can only recognize similar epitopes: monospecificity

An interpretative introduction to the Immune System. Steven A Hofmeyr

Aprox $10^5$ receptors per lymphocyte: estimates affinity and quantity of pathogens as the number of binding receptors increases with affinity and quantity. **Activation** (detection event) occurs after a threshold of binding receptors.
Antigenic Activation: T-cell binds to antigen presenting cell

From Gary Carlson

Phagocytic Embrace
molecular pattern matching

Figure 2-23 The Immune System, 2/e (© Garland Science 2003)

Nature.com
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

An interpretative introduction to the Immune System. Steven A Hofmeyr

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

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V(D)J or Somatic Recombination: randomish generation of gene segments (variable, diverse, and joining)

Goldman & Prabhakar. Immunology Overview.
mechanism of receptor diversity

1. **Germ line DNA**
   - Heavy chain variable region genes
   - Diversity genes
   - Joining genes
   - Heavy chain constant region genes

2. **B cell DNA**
   - Recombination and deletion

3. **B cell mRNA**
   - Transcription

4. **Heavy chain peptide**
   - Translation

5. **Light chain peptide**
   - Assembly of heavy and light chains

6. **Antibody**

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

**Controlled, private Natural Selection**

**“randomizer” of DNA (Turing) tape**

Goldman & Prabhakar. Immunology Overview.
An interpretative introduction to the Immune System. Steven A Hofmeyr

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.

antigen: anything that causes antibody generation:

antibodies: soluble form of receptors that bind to pathogen epitopes (opsonize and neutralize)

Humoral response (fluid)

Learning and remembering implemented by lymphocytes: B Cells

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

If activated, migrate to lymph nodes: gland where adaptive response develops
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)

An interpretative introduction to the Immune System. Steven A Hofmeyr
Clonal selection

Of B-Cells

From: Doc Kaiser's Microbiology Home Page
adaptive response

remembering specific learned pathogens

Theory 1: memory cells are long-lived

Theory 2: adapted B cells are constantly restimulated by traces of nonself proteins retained in the body for years

Memory implemented by lymphocytes: B Cells ???

An interpretative introduction to the Immune System. Steven A Hofmeyr
Adaptive response

Associative memory

Similar pathogens trigger response

Principle of vaccination

An interpretative introduction to the Immune System. Steven A Hofmeyr

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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

An interpretative introduction to the Immune System. Steven A Hofmeyr

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

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

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

An interpretative introduction to the Immune System. Steven A Hofmeyr

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
The immune system

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

much more complicated than this!!!
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.

modeling the immune system
from an artificial life perspective
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


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- **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
- 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)

1. $E \xrightarrow{d_E} \{\} \text{ and } R \xrightarrow{d_R} \{\}$
2. $A + R \rightarrow A + R$
3. $A + E \rightarrow A + 2E$
4. $A + E + R \rightarrow A + E + 2R$
Crossregulation Model

1.  

2.  

3.  

4.  

cell death

inhibition

induction

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Dynamical behavior

- 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 with 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 $R_f$

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

- **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 \( R_f \)

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A. Abi-Haidar and L.M. Rocha [2011].
Evolutionary Intelligence. 4(2):69-80.
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

Enjoy the break

Bio-inspired Computing out of the Box

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