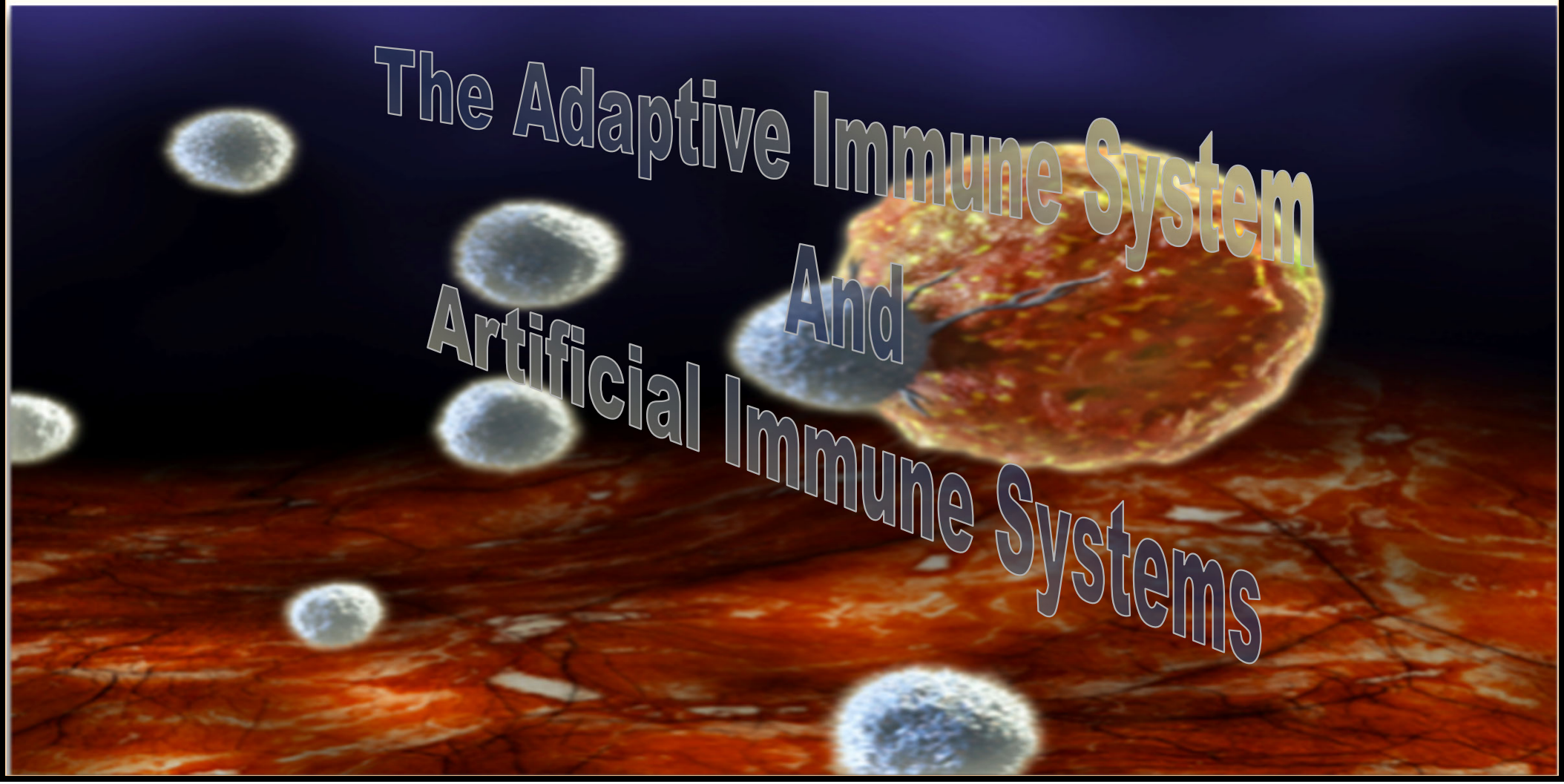
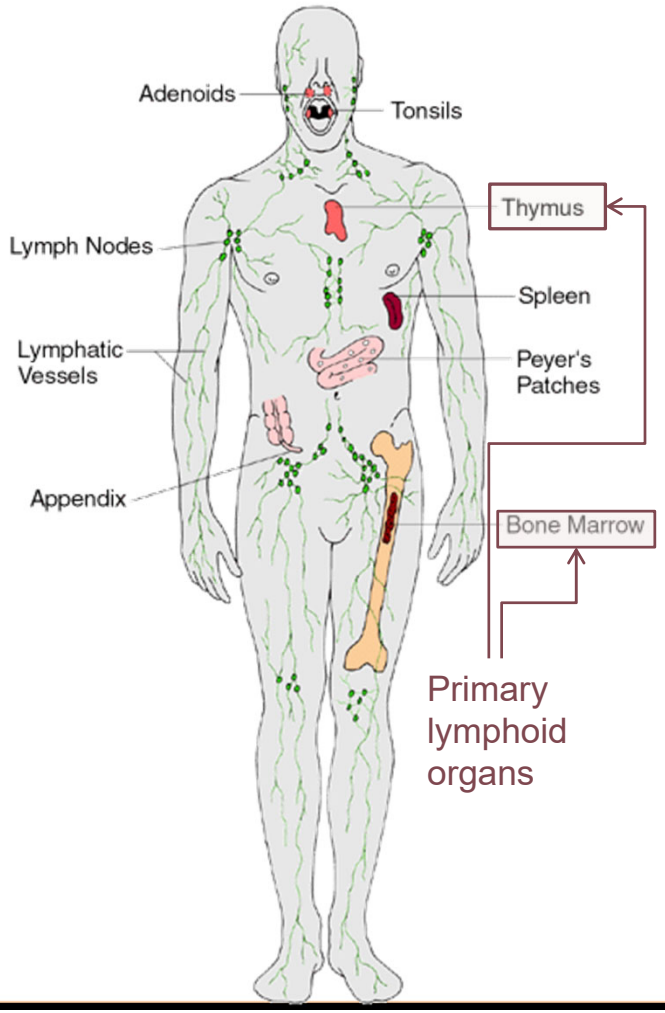
lecture 20



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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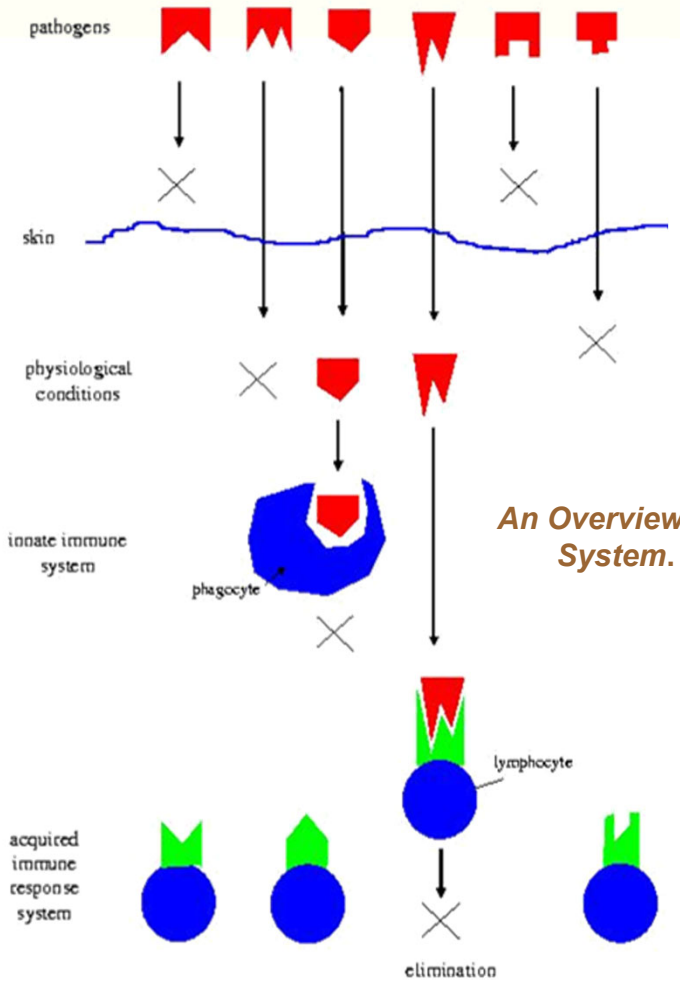
multilayers

- 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***



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

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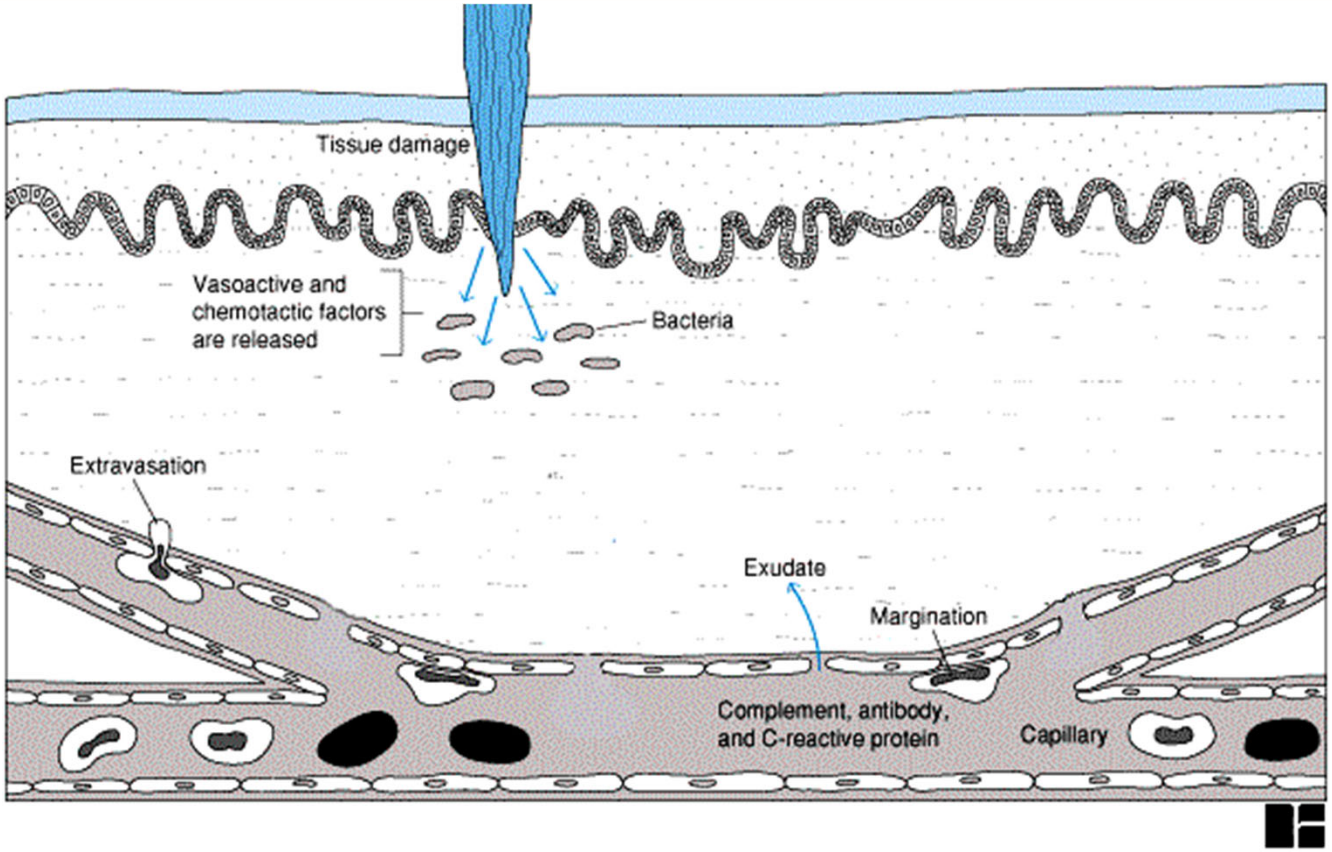
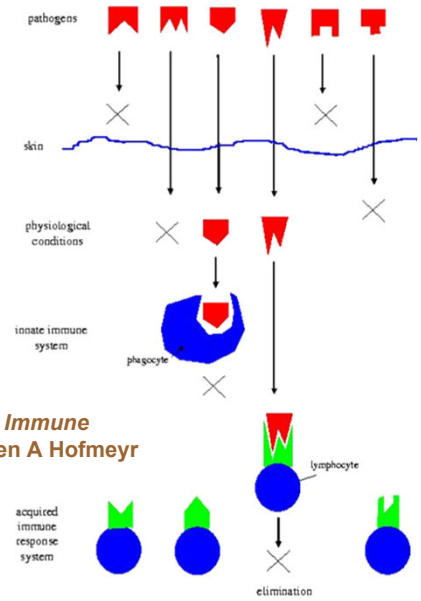
basic mechanisms



From Paul Bugl



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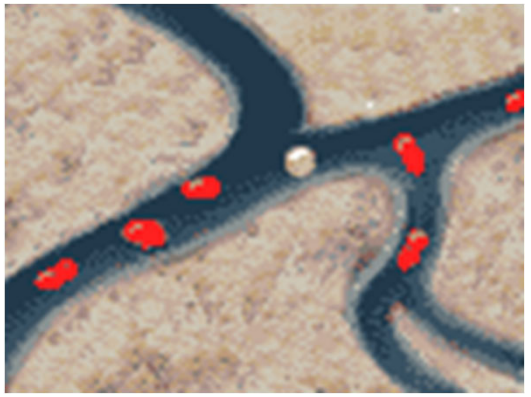

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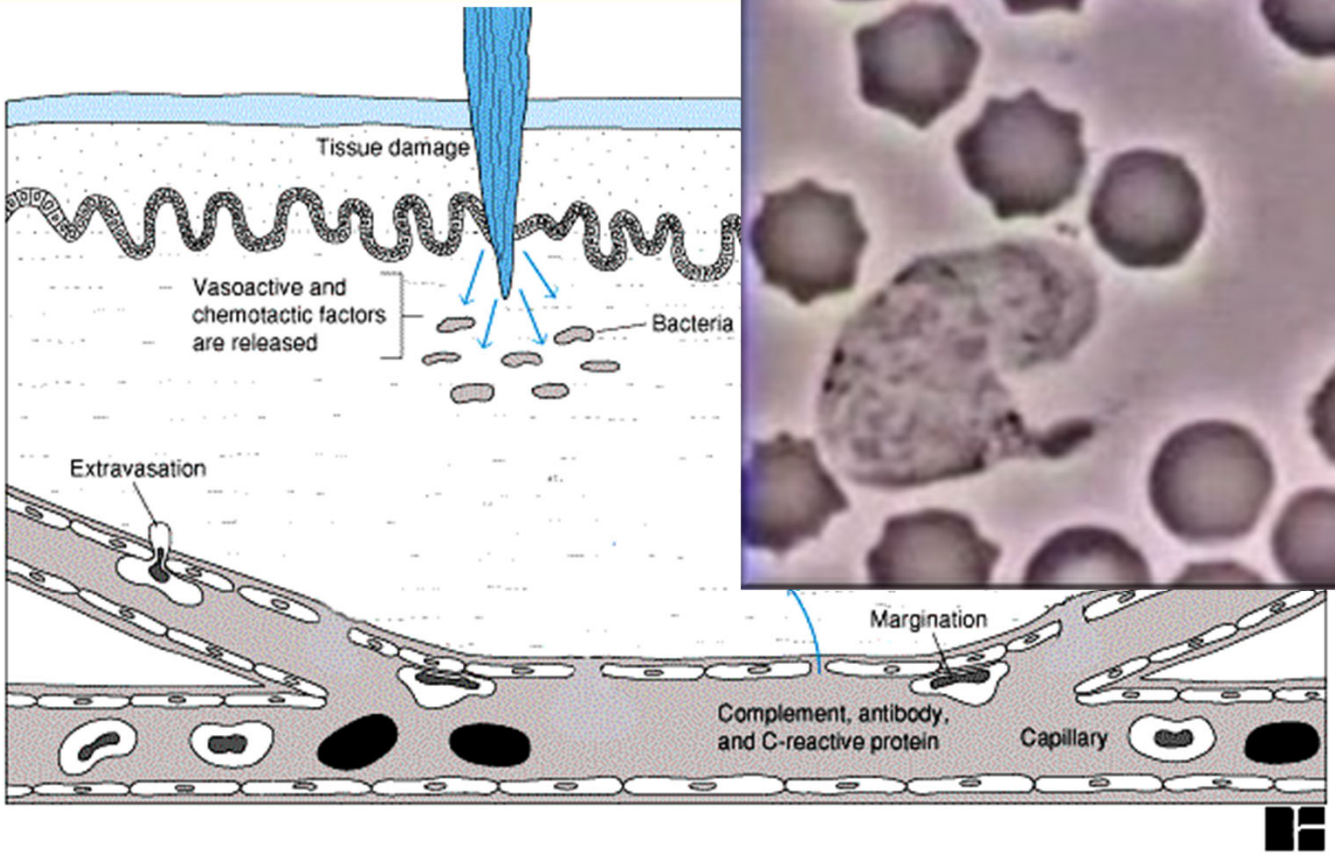
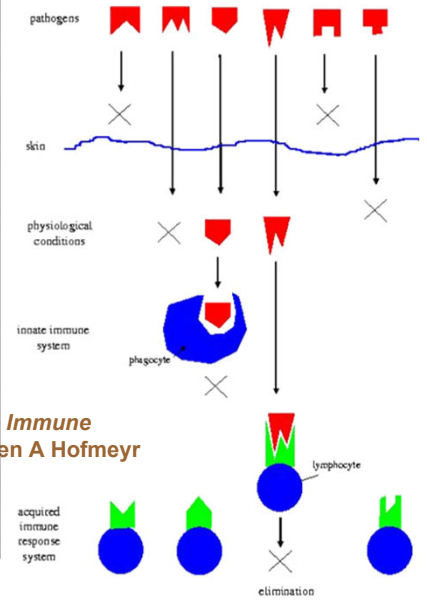
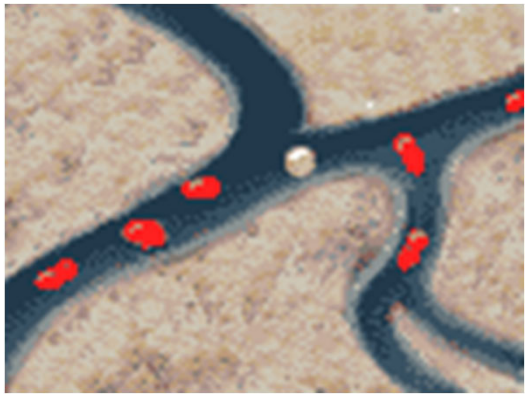
basic mechanisms





Immune
en A Hofmeyr

From Paul Bugl



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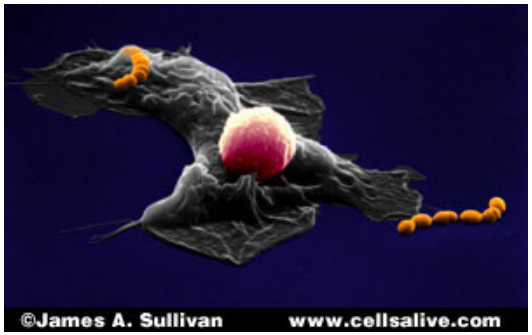
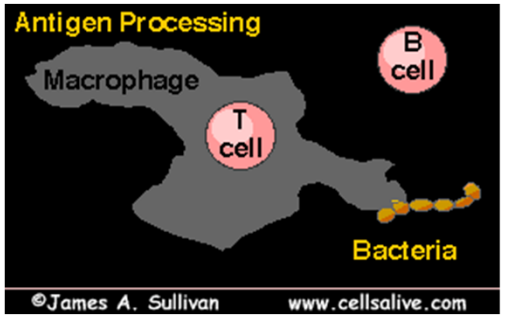
molecular memory defense (in vertebrates)

- **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





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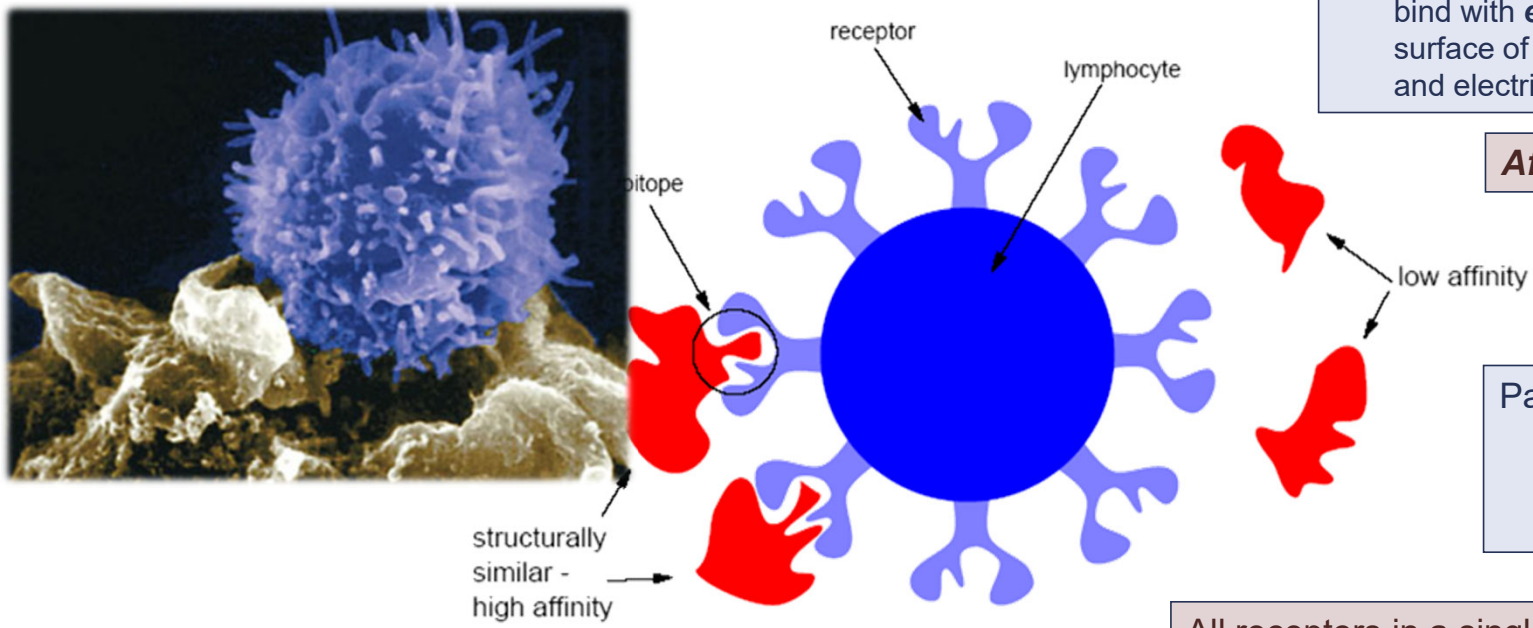
chemical bonds as generalized detectors



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***

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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

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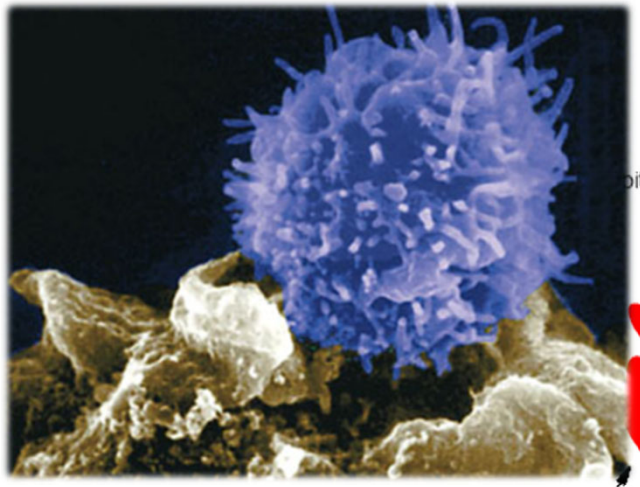
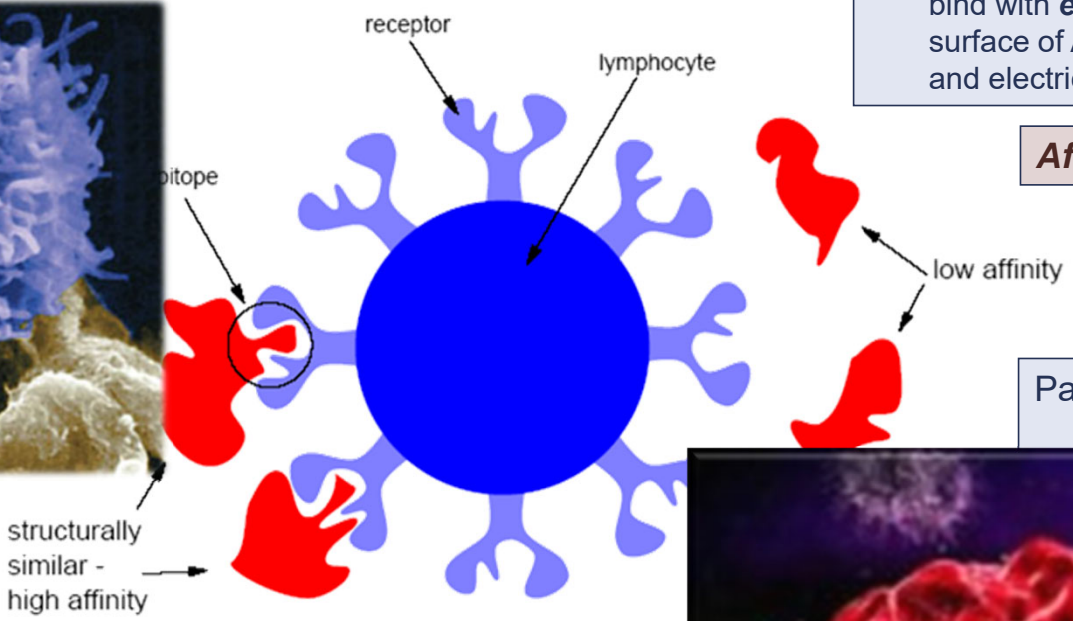
chemical bonds as generalized detectors



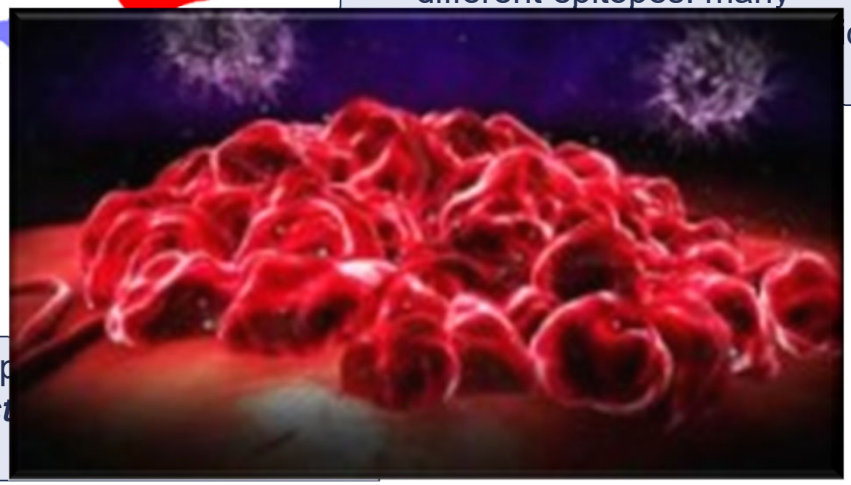


Lymphocyte recognition occurs when its ***receptors*** bind with ***epitopes*** from pathogens on the surface of APCs (by complementary structure and electrical charge)

Affinity: strength of bond

Pathogens may have many different epitopes: many

c



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Aprox 10^5 receptors per lymphocyte: ***estimates*** affinity and quantity of p
number of binding receptors increases with affinity and quantity. ***Act***
event) occurs after a threshold of binding receptors

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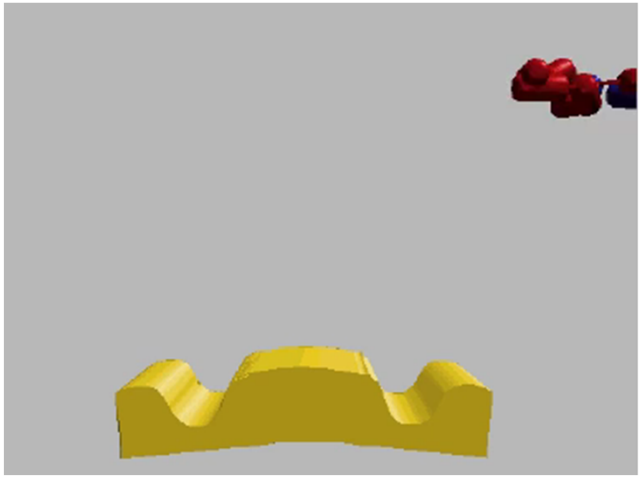
renderings

Antigenic Activation: T-cell binds to antigen presenting cell



Phagocytic Embrace

From Gary Carlson

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molecular pattern matching

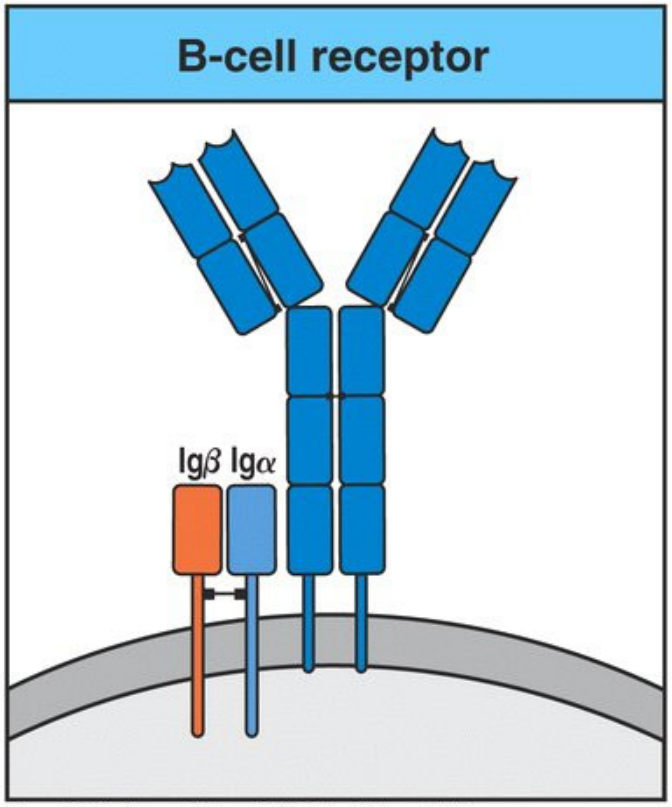
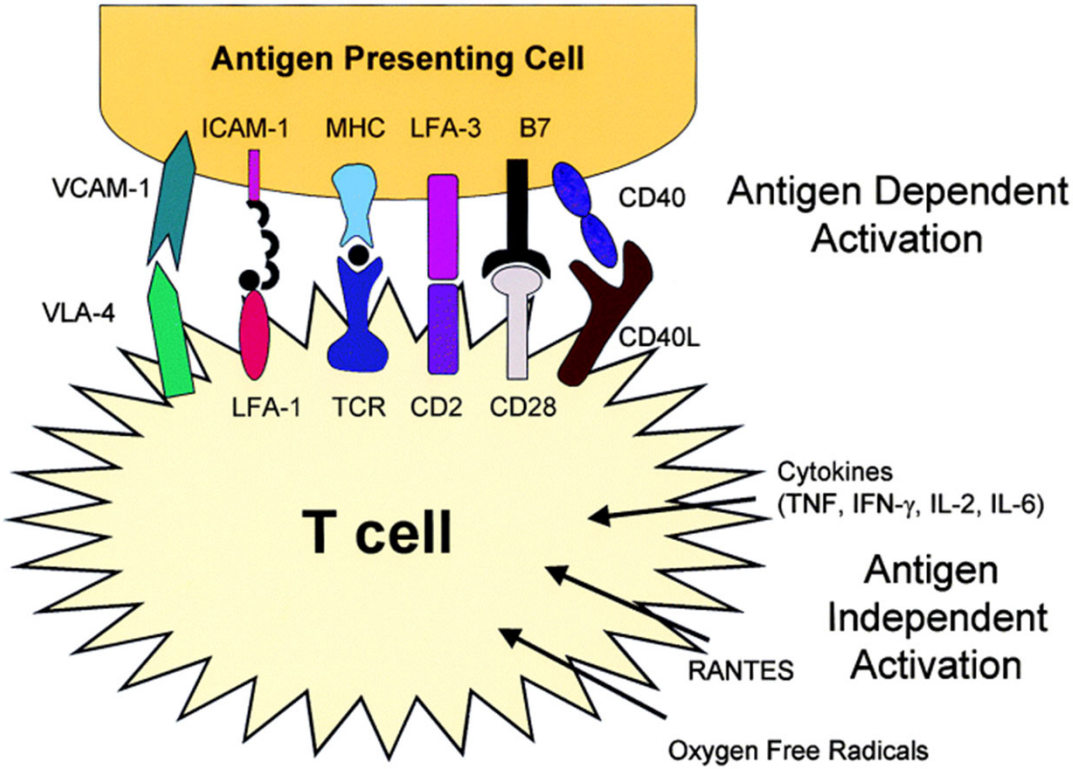


Figure 2-23 The Immune System, 2/e (© Garland Science 2005)



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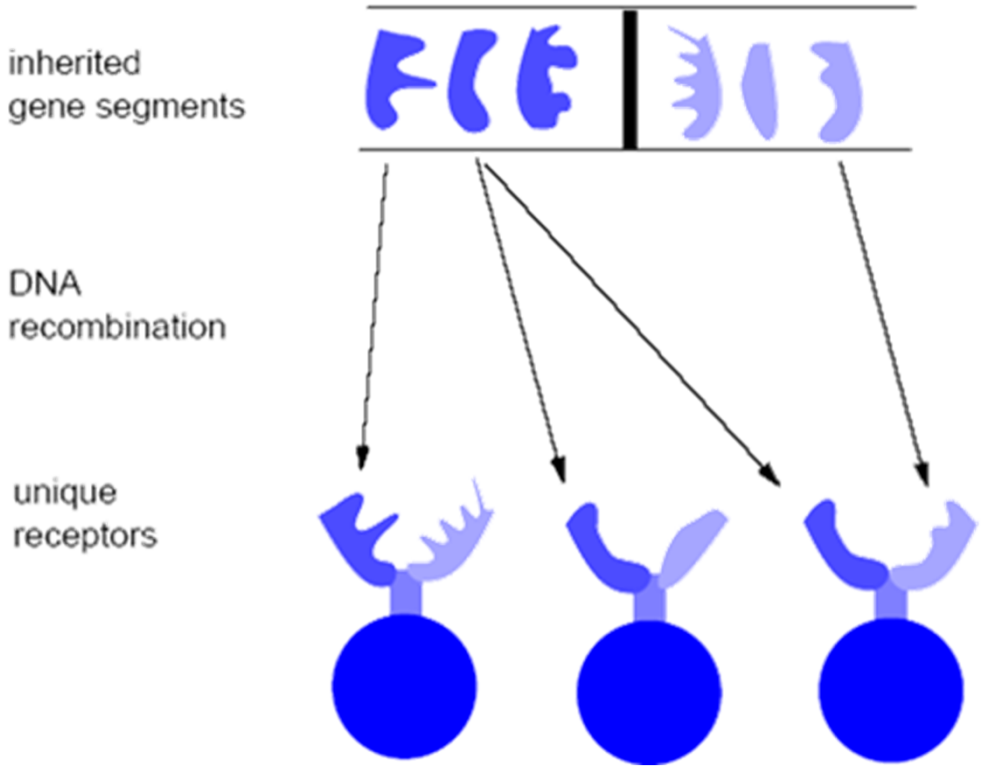
Building up the response repertoire

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

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generating receptor diversity (in B Cells)

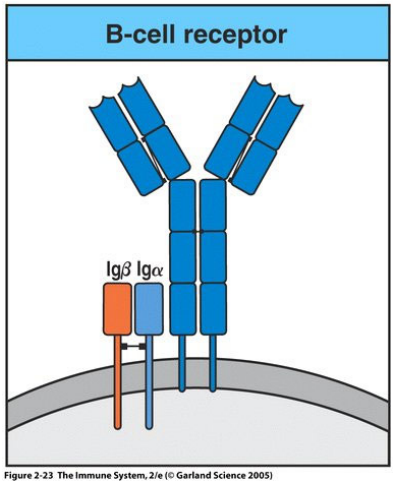
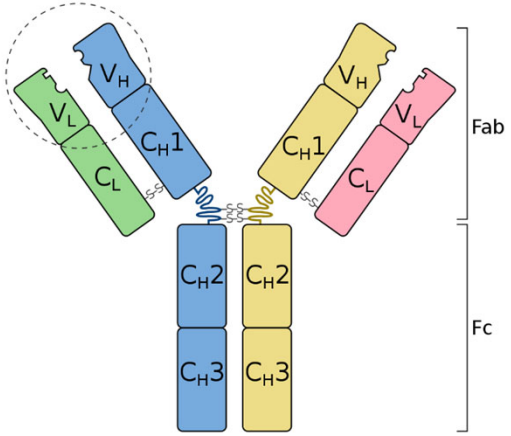
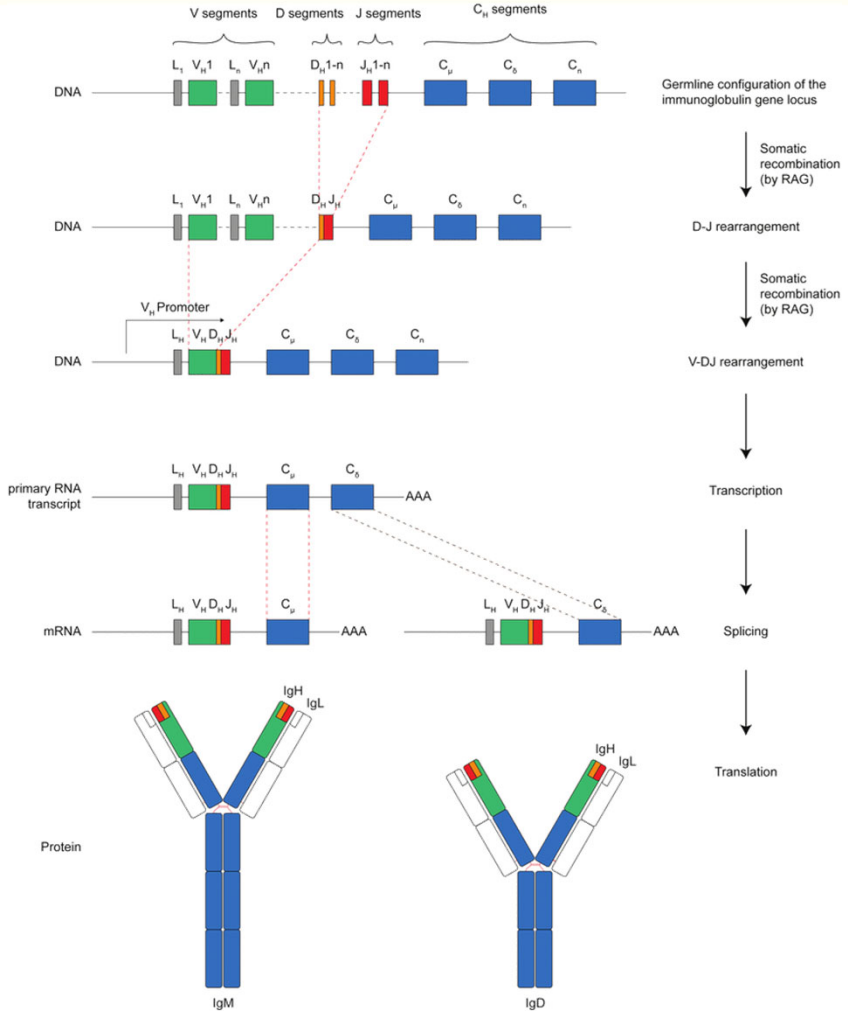


Figure 2-23 The Immune System, 2/e (© Garland Science 2005)





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)

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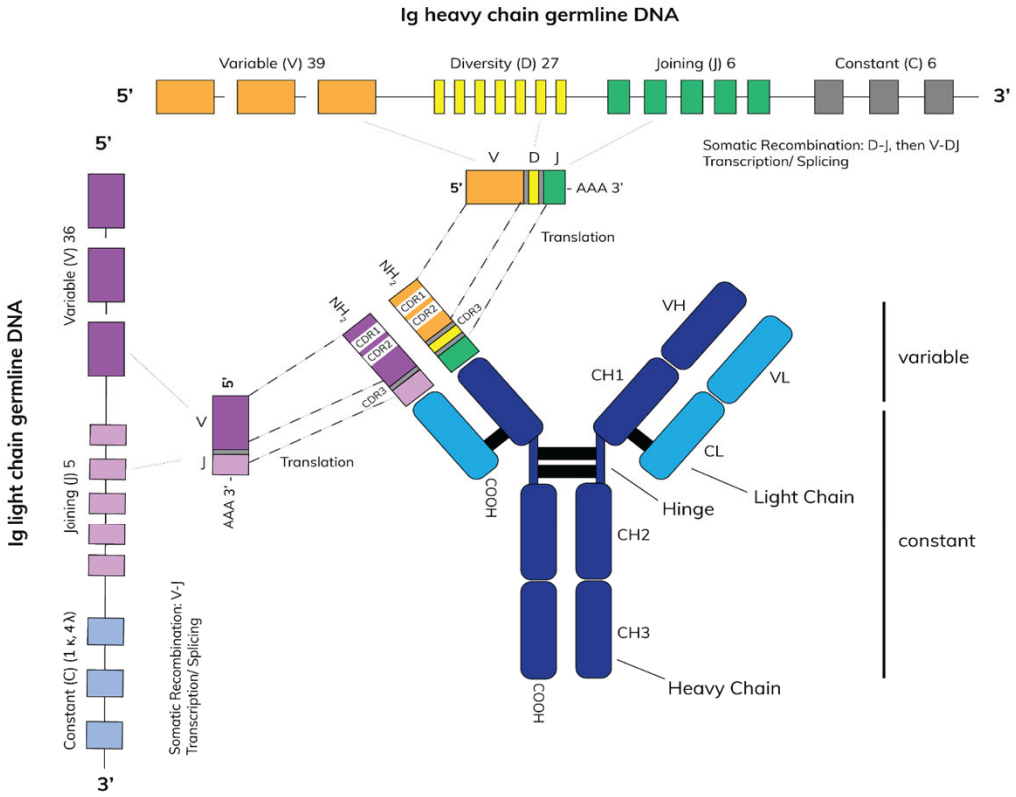
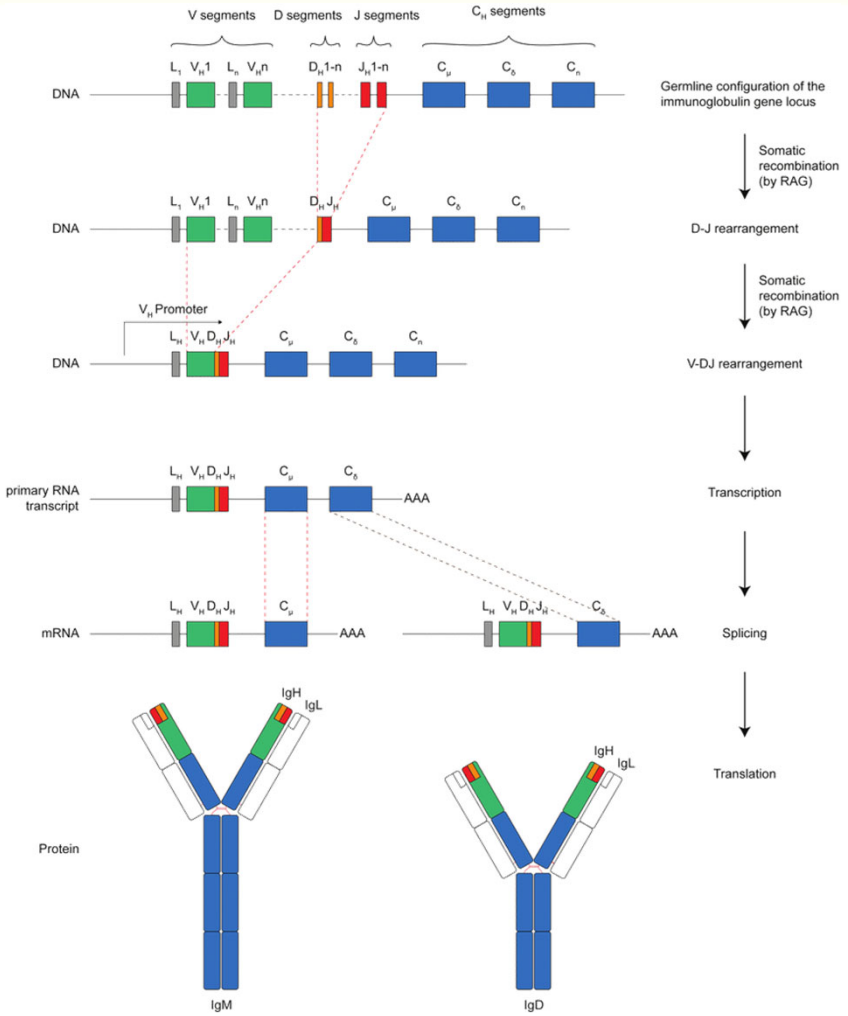
generating receptor diversity (in B Cells)





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

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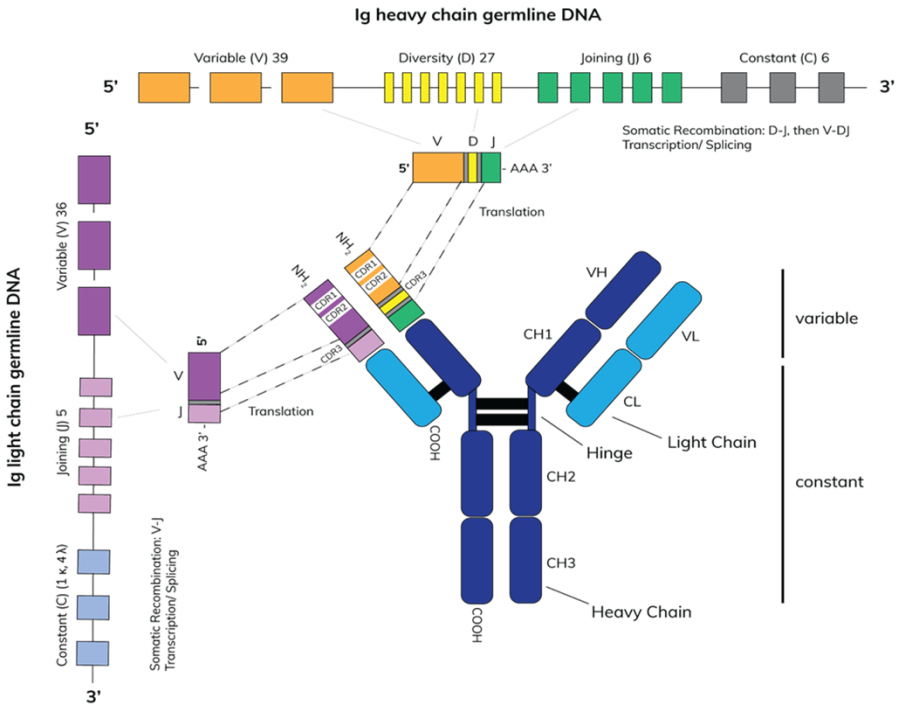
mechanism of receptor diversity



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

Controlled, private Natural Selection

"randomizer" of DNA (Turing) tape

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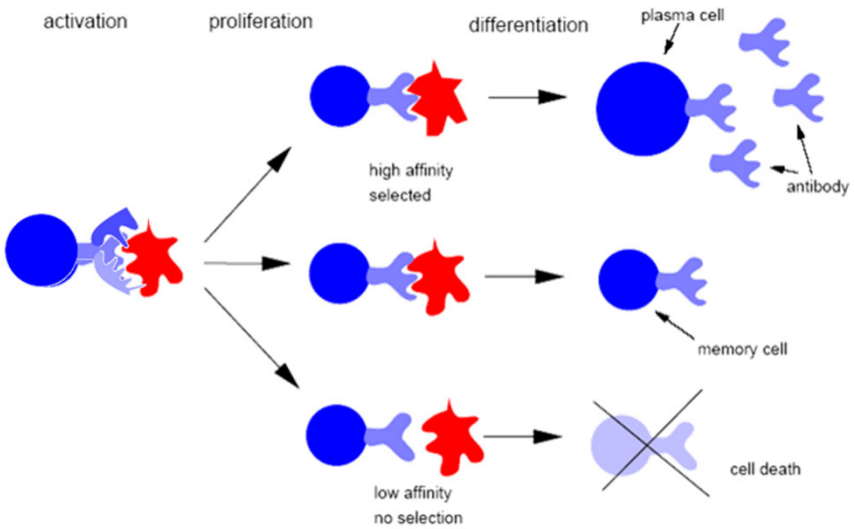
learning specific pathogens



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Learning and remembering implemented by lymphocytes: ***B Cells***

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

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

Humoral response (fluid)

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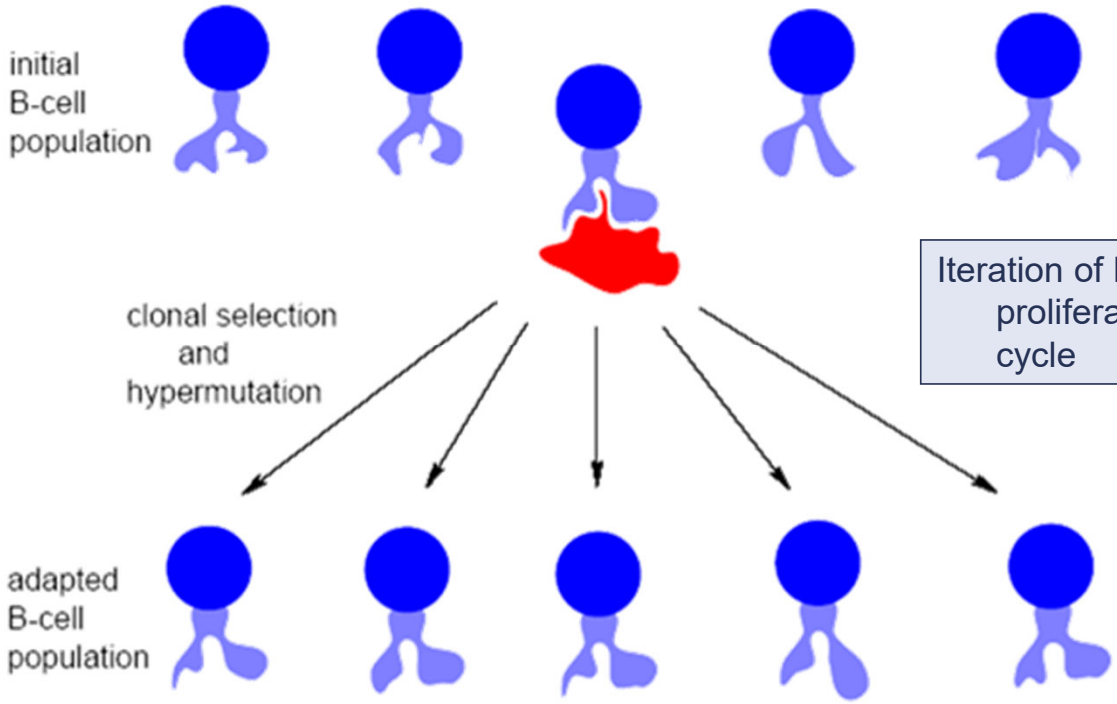
Via Darwinian variation and selection



Iteration of B-cell activation-proliferation-differentiation cycle

Clonal selection and hypermutation:
"private" Darwinian selection

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

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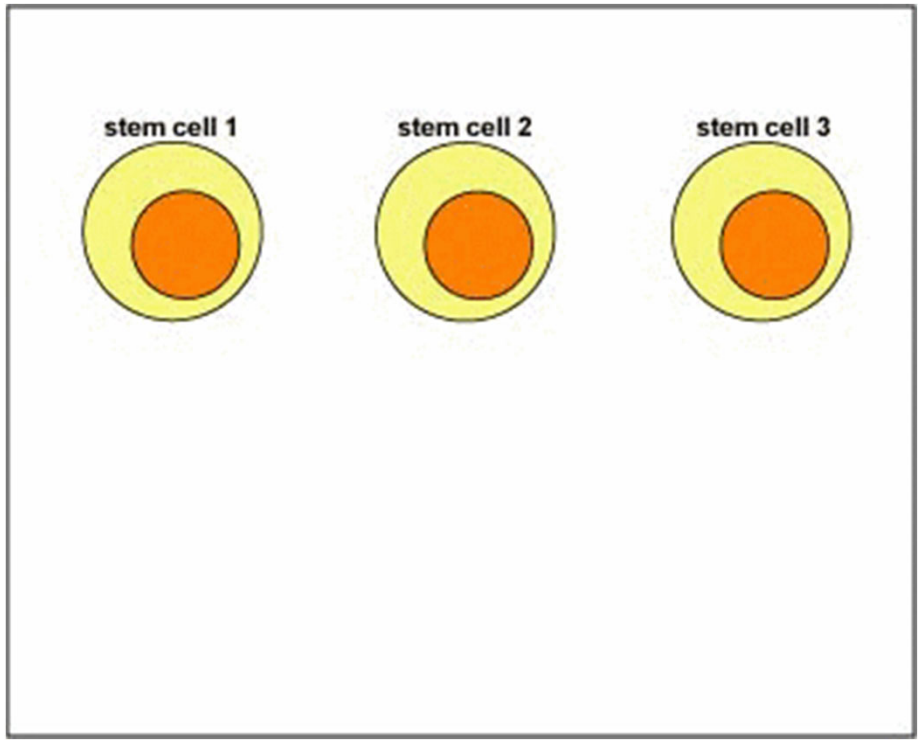
Of B-Cells



From: Doc Kaiser's Microbiology Home Page

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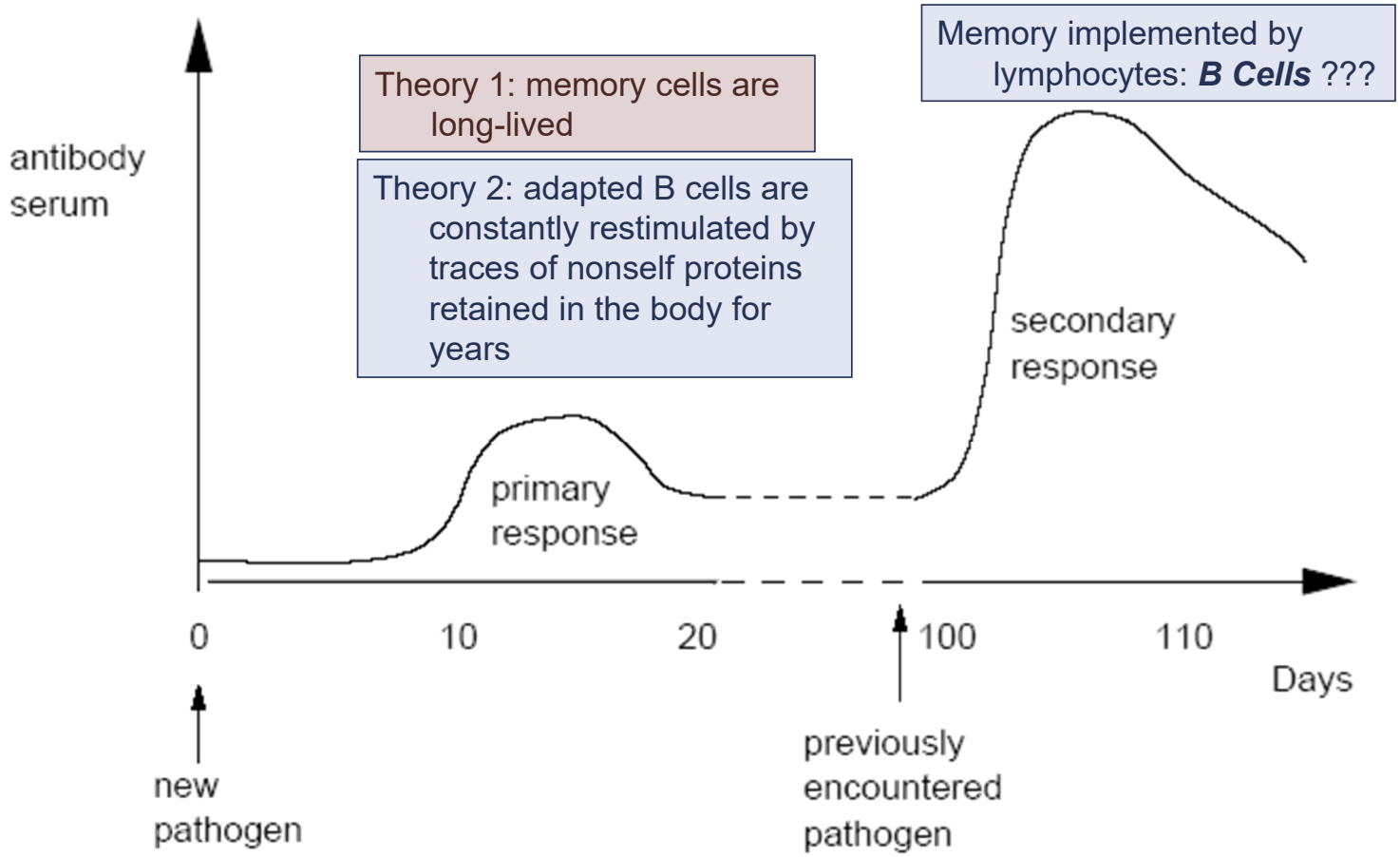
remembering specific learned pathogens



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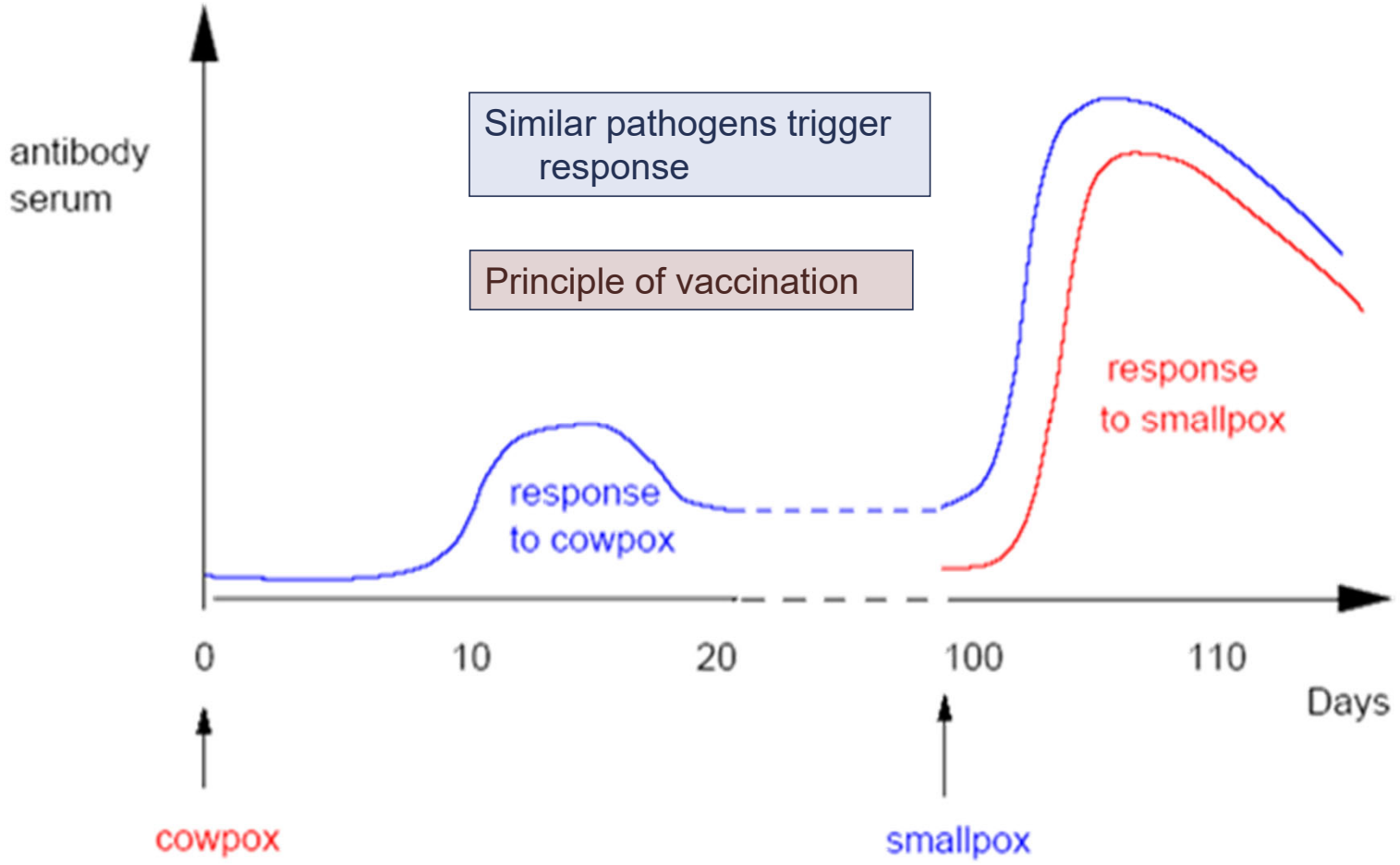
Associative memory



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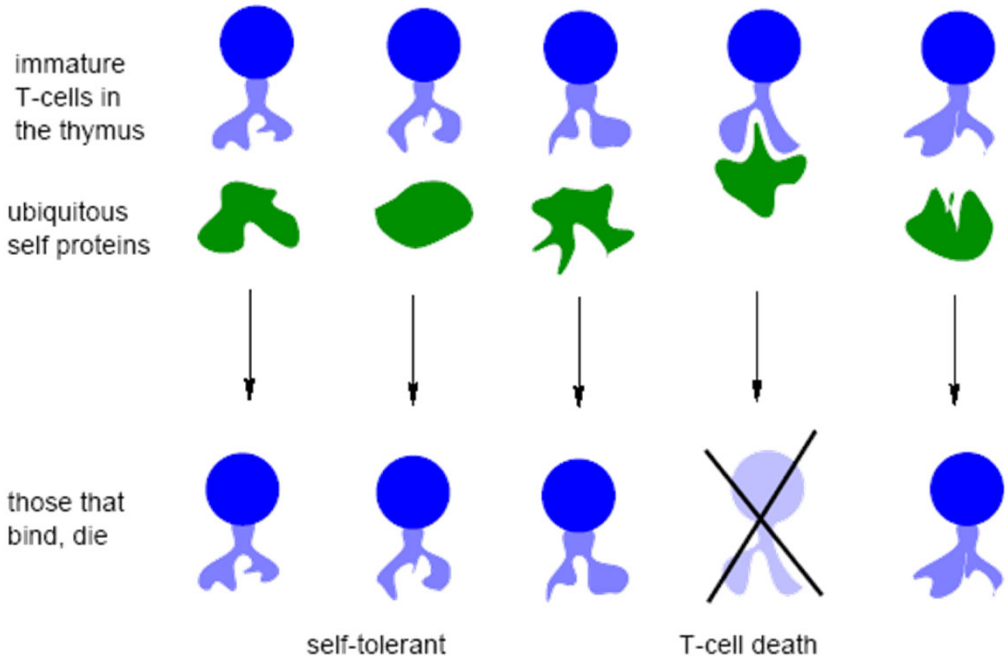
Tolerance to self (negative selection)



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

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)

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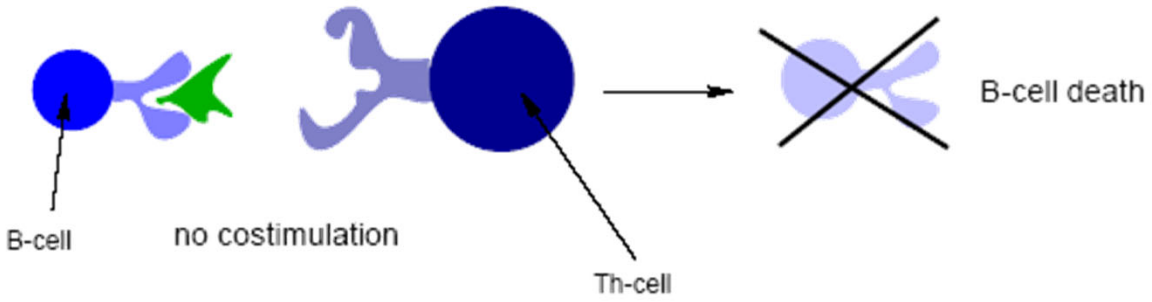
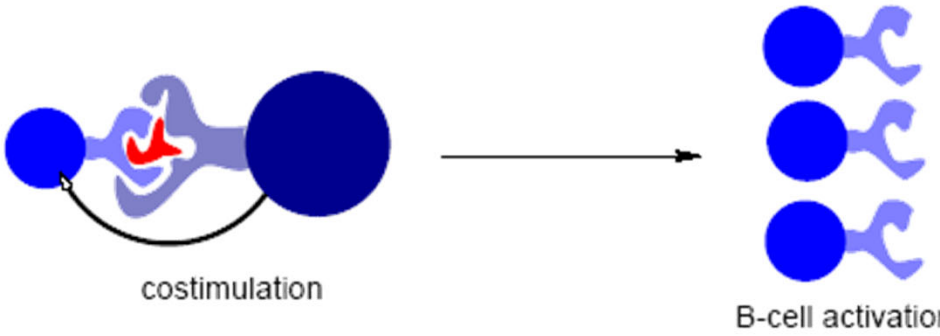
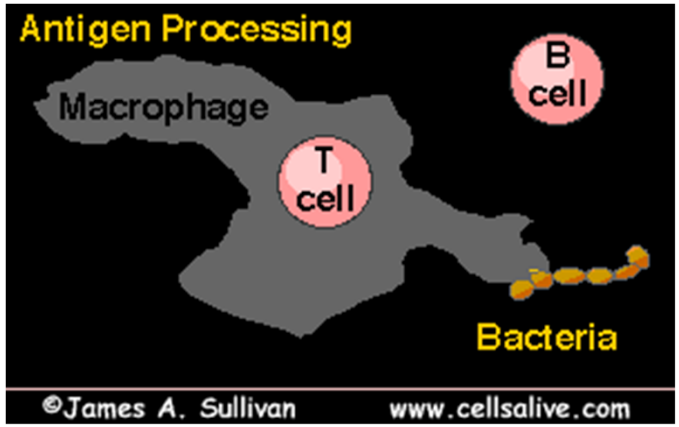
Tolerance to self: costimulation



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





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

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Biological complexity afforded by the Turing tape for self-other recognition

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

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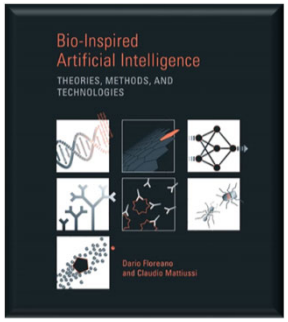
modeling the immune system

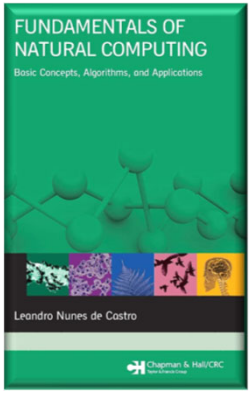
from a bio-inspired computing perspective

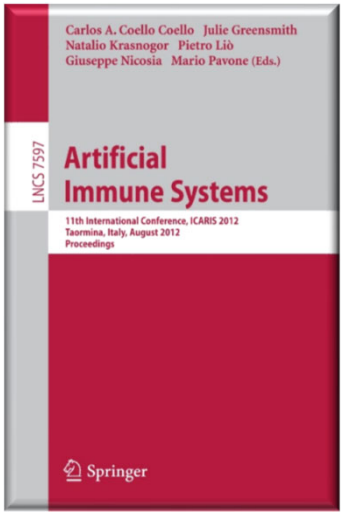
- Objective
  - explore collective dynamics of t-cell cross-regulation
    - *computational intelligence* : build a novel bio-inspired machine learning solution for document classification
    - *computational biology* : understand how well collections of t-cells engaged in crossregulation perform as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

Hart, Emma, and Jon Timmis. "Application areas of AIS: The past, the present and the future." *Applied soft computing* 8.1 (2008): 191-201.

Nunes de Castro, Leandro [2006]. *Fundamentals of Natural Computing: Basic Concepts, Algorithms, and Applications*. Chapman & Hall.







Bersini, Hugues, and Francisco J. Varela. "Hints for adaptive problem solving gleaned from immune networks." *Parallel Problem Solving from Nature: 1st Workshop, PPSN I Dortmund, FRG, October 1–3, 1990 Proceedings 1*. Springer Berlin Heidelberg, 1991.

Forrest, Stephanie, et al. "Self-nonself discrimination in a computer." Proceedings of 1994 IEEE computer society symposium on research in security and privacy.

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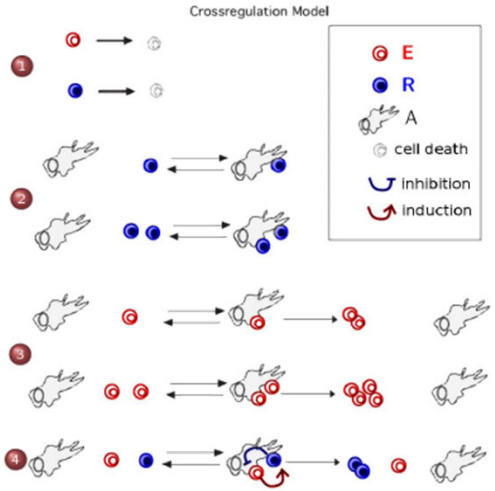
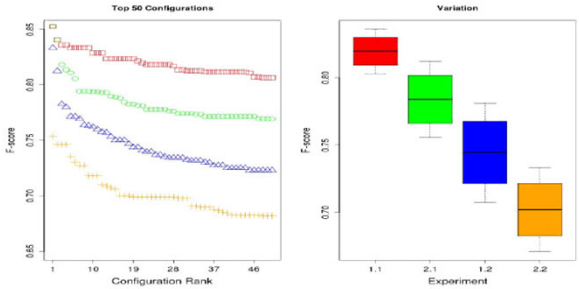
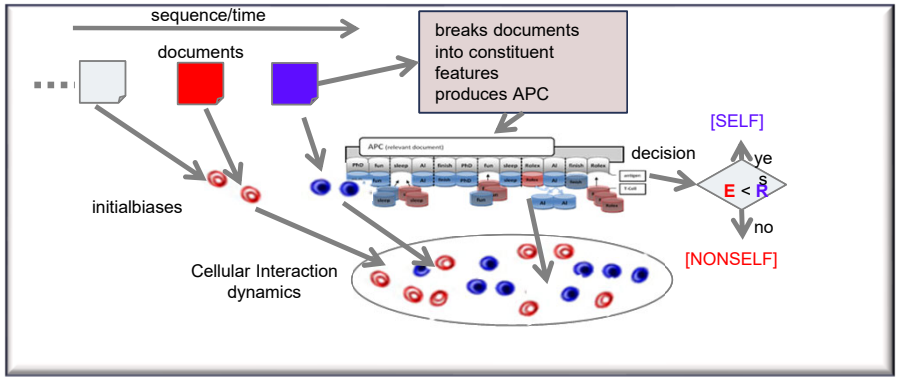
agent-based model of immune cross-regulation dynamics

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





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

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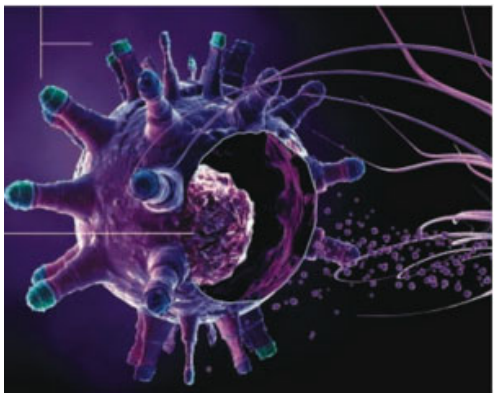
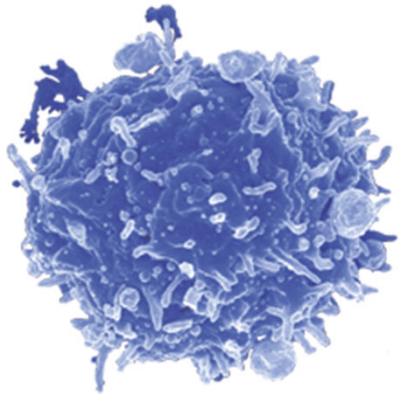
regulating self-organizing dynamics for self/nonself discrimination

- 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)**



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regulating self-organizing dynamics for self/nonself discrimination

- Analytical model of Carneiro et al (2007)
  - 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. $E \xrightarrow[d_E]{} \{\}$ and $R \xrightarrow[d_R]{} \{\}$
2. $A + R \rightarrow A + R$
3. $A + E \rightarrow A + 2E$
4. $A + E + R \rightarrow A + E + 2R$

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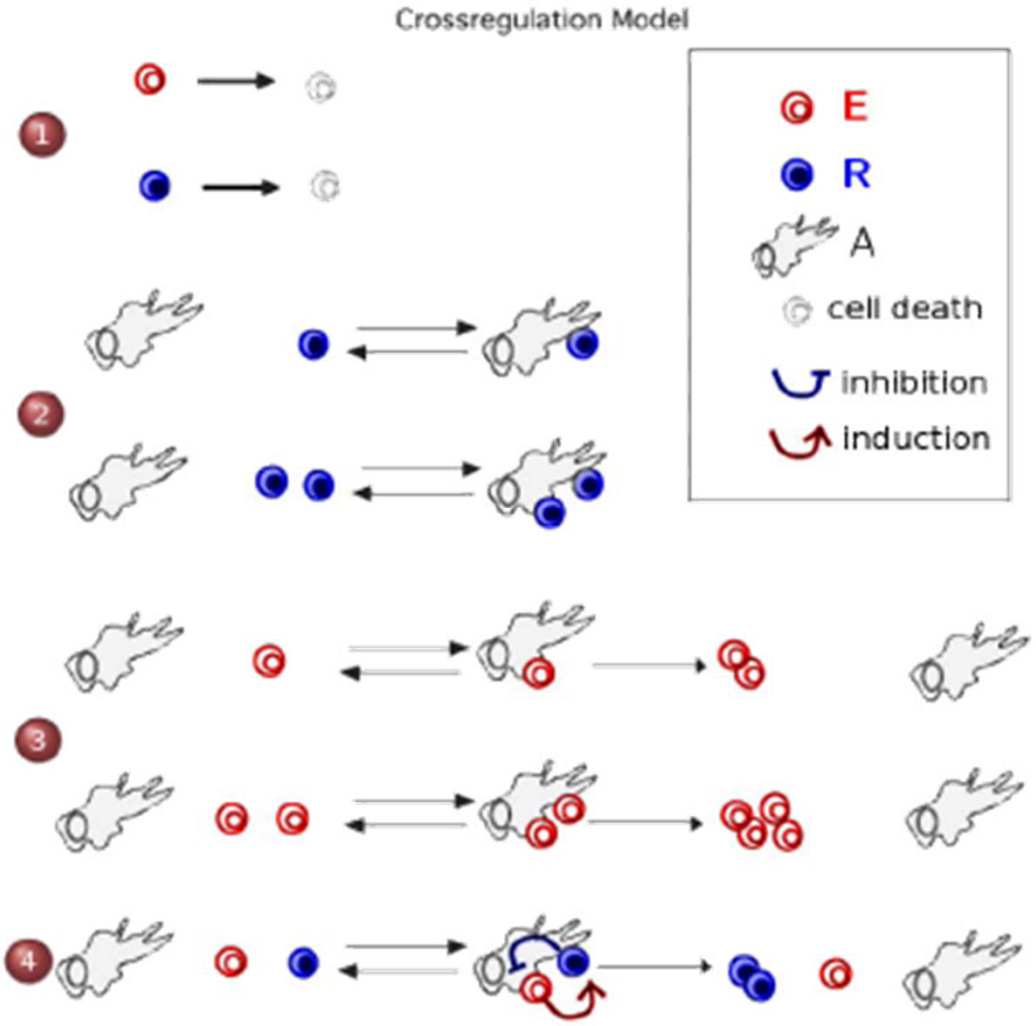

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dynamical behavior

- 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 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**)

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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: $\mathbf{E_f}$ and $\mathbf{R_f}$

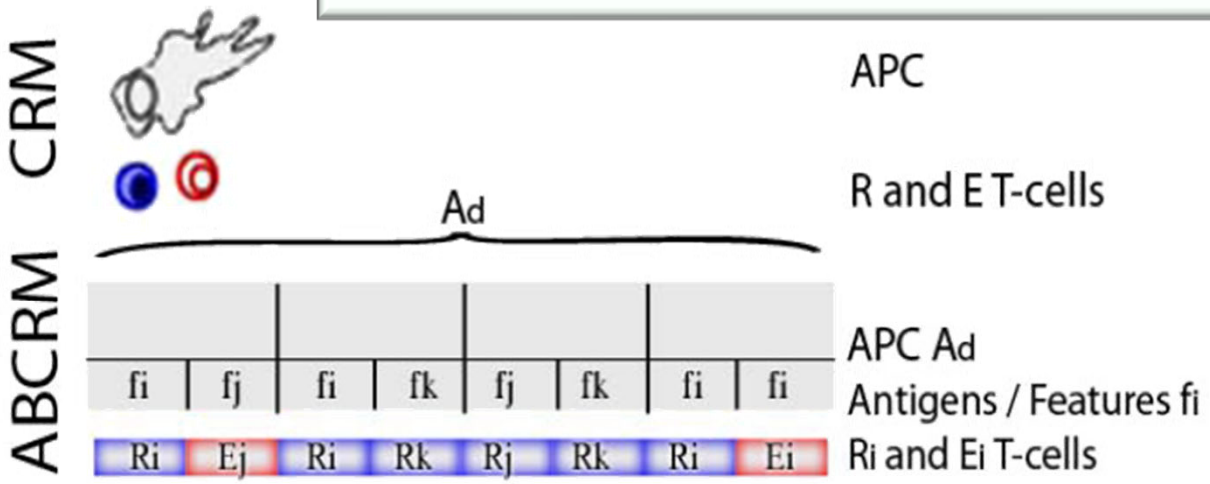

Figure: e.g. $R_i + E_j \rightarrow 2R_i + E_j$ (Rule 4)

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

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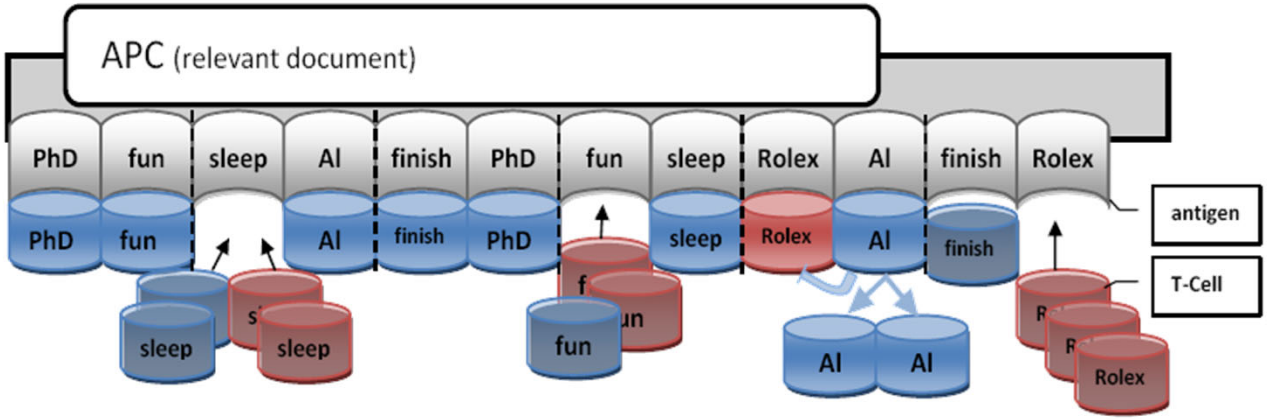
for textual documents

- 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



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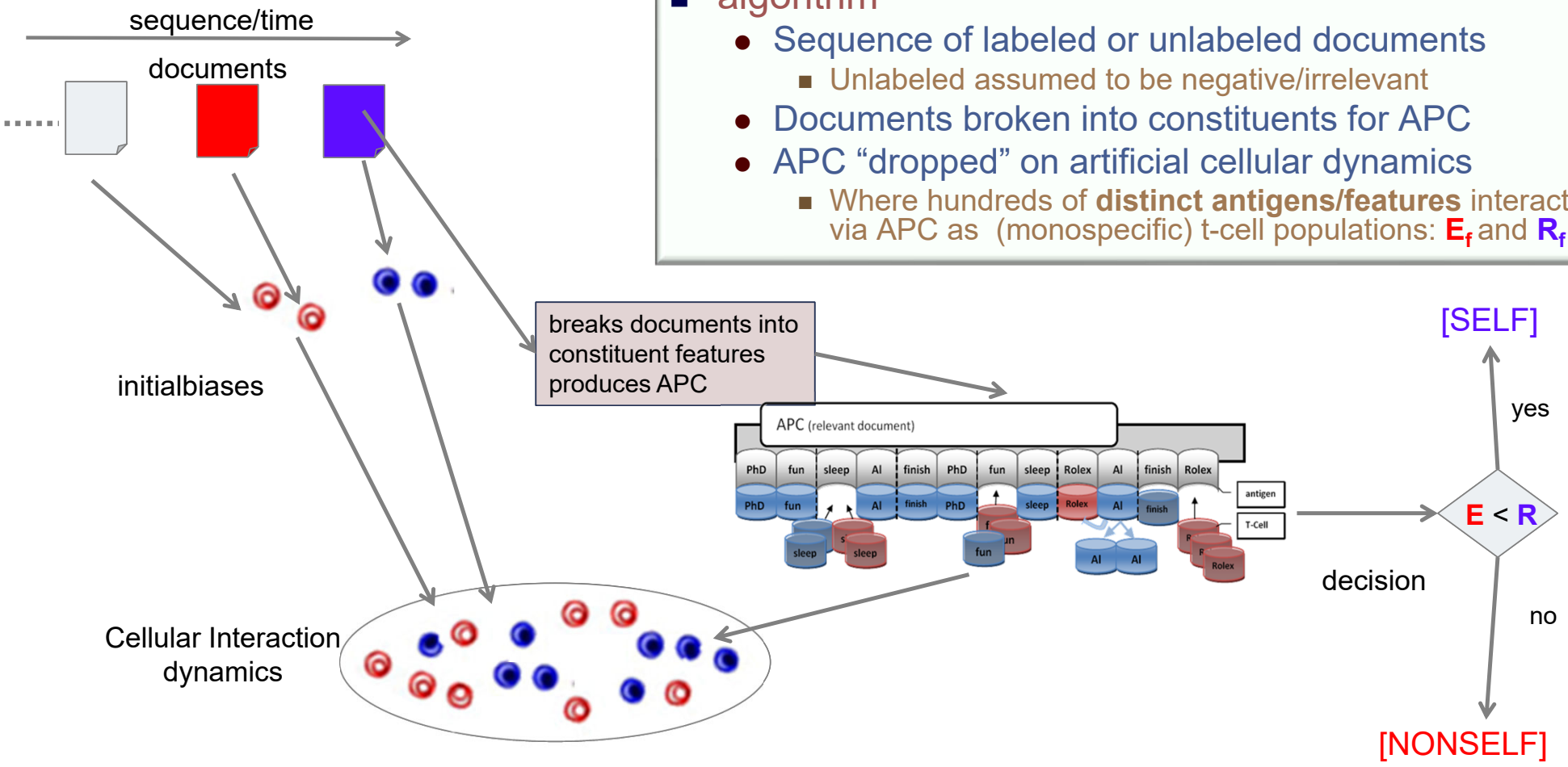
agent-based t-cell crossregulation model

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: $\mathbf{E_f}$ and $\mathbf{R_f}$



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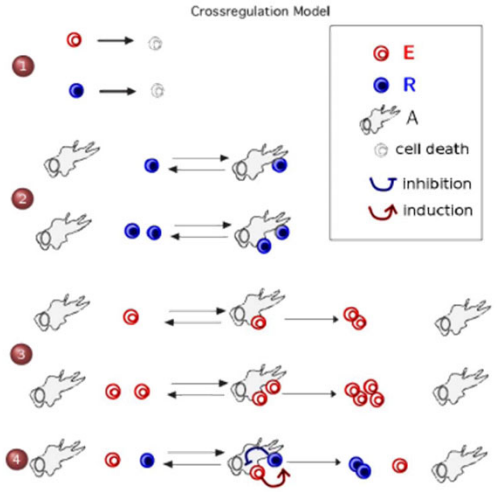
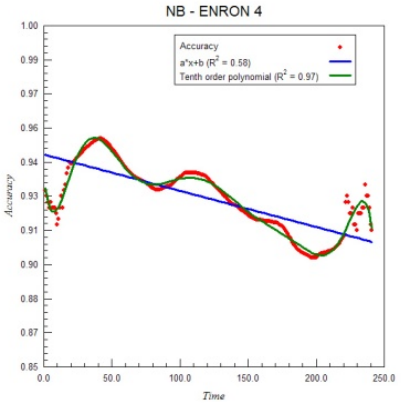
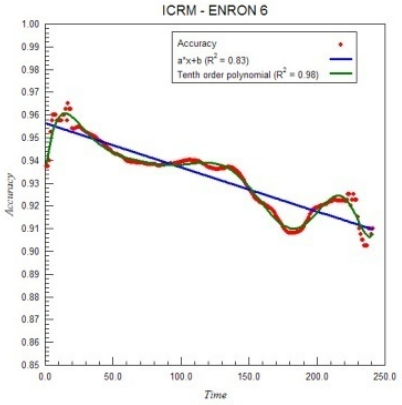
agent-based model of immune cross-regulation dynamics

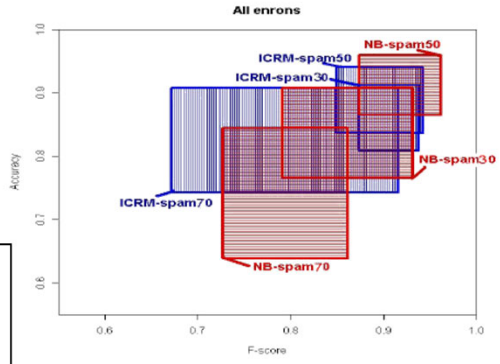
for adaptive (e-mail) spam detection

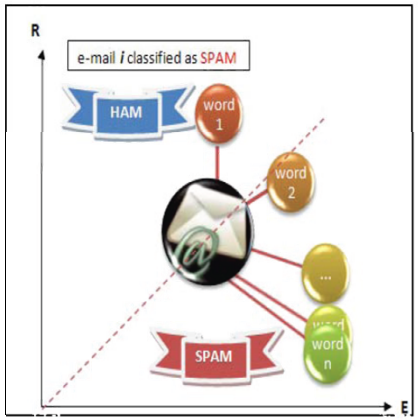






- inspired by the cross-regulation model.
  - Carneiro et al. (2007).
  - Purely dynamical model of t-cell regulation leading to bistable states
    - Harmful non-self detection
  - Studying concept drift





Abi-Haidar & Rocha [2008]. *Alife11.*

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