PLAN

- Background
- Immune system scenario
- How it works
BACKGROUND
What are faults?
- stress conditions
- invaders
- misbehaving parts

What is tolerance?
- persist/survive
- conquer/evade
- repair/replace/destroy
Bio Tolerance Examples

- Persistent state of microbes
  - Some fraction non-deterministically `go to sleep' (and wake up on schedule), thus providing a fraction of the community that will survive many attacks (by not reacting).
- Disintegrating invaders
- Error detection/Proof reading,
- Correction/DNA repair
- Apoptosis -- destroy the faulty (or unneeded) component and make a new one.
BIOLOGICAL SYSTEMS

- Systems of systems of ... systems
- Including information and physical systems
  - (the ultimate CPS :-)
- Multiple levels of organization / abstraction
- Cross layer / system communication is crucial
Biological Org-Chart

- Organism (microbe, celegans, ... rat ... human)
  - internal processes
  - community -- cooperation/competition
- Organ (brain, heart, liver ...)
  - intra organ (neuron patterns, pump, digest)
  - Organ-organ communication/coordination
- Cell
  - intra-cellular (transcriptional, signaling, metabolic .... processes)
  - cell system / cell-communication
- Protein ....
COORDINATION OF CIRCADIAN TIMING

S. M. Reppert & D. R. Weaver
Nature Vol 18 2002
CASE STUDY
THE IMMUNE SYSTEM
Immune System Overview

Job is protecting the organism from foreign entities

- Distributed
- Adaptive
- Risk/benefit trades
- Security mechanisms

Caveat smattering of observations -- not definitive
Where do immune system elements come from?
Roles

- Phagocyte (P) -- eater
- Antigen Presenting Cells (APC)
  - sample of inside / surroundings
- Killer (K) -- by signal or poison
- Coordination (C) -- activate, signal
- Tagging
PLAYERS : CELLS

- **General purpose**
  - Macrophage (P, APC)
    - garbage collection / eating invaders / signal
  - Dendritic Cell (APC)
    - carries sample with pathogen to show T cells
  - Neutrophils (P aggressive)
    - circulating in blood looking for infection sites
  - Natural Killer Cells (K) -- drill holes in target

- **Pathogen specific**
  - B cells -- antibody factory (APC) -- mature in bone marrow
  - T cells: -- mature in thymus,
    - (C) T helper (Th)
    - (K) CytoToxic Lymphocytes (CTL)
Players: Proteins

- Complement system -- rapid response
  - opsonize or kill pathogens
- Antibodies -- each antibody binds specific target
- Major histocompatibility complexes (MHC)
  - present bug bits (and other peptides)
- Cytokines/Chemokines
  - signals, attractants
SCENARIO
IMMUNE SYSTEM DYNAMICS

Local infection, penetration of epithelium
- macrophage
- tissue
- dendritic cell

Local infection of tissues
- Dendritic cells migrate to lymph nodes
- Phagocyte action
- NK cells activated
- Cytokines and chemokines produced

Lymphatic spread
- Pathogens trapped and phagocytosed in lymphoid tissue
- Adaptive immunity initiated by migrating dendritic cells

Adaptive immunity
- Infection cleared by specific antibody, T-cell dependent macrophage activation and cytotoxic T cells

Protection against infection

Figure 10-2 Immunobiology, 7ed. (© Garland Science 2008)
HOW DOES THE IMMUNE SYSTEM WORK?
TWO LEVEL ARCHITECTURE

- Innate Immune System (IIS)
  - border guards, troops on patrol
  - early defense, non specific
  - alert and control adaptive IS
- Adaptive Immune System (AIS)
  - highly specific
  - aggressive
  - needs control / safety mechanisms
  - Basic interaction mechanism is pattern matching (binding)
  - many patterns, combinations
- Location is important
MHCs are used by cells to display peptides (protein fragments) on their surface.

MHCI samples/presents internal protein fragments

CTls scan MHCI -- looking for cells that have virus inside.

MHCII samples/presents environment protein fragments

Helper T Cells use MHCII as signal to activate troops.
HOW DO MHC'S DISTINGUISH?

1. Virus infects cell
2. Viral proteins synthesized in cytosol
3. Peptide fragments of viral proteins bound by MHC class I in ER
4. Bound peptides transported by MHC class I to the cell surface

Bacterium infects macrophage and enters vesicle, producing peptide fragments

Bacterial fragments bound by MHC class II in vesicles

Bound peptides transported by MHC class II to the cell surface

Figure 1-30 Immunobiology, 7th ed. (© Garland Science 2008)
Some cells recognize invaders `raw' -- Mph, NK,
Some just attack when active
Some need more information/restraint
Presentation provides

- Provenance
  - MHCI guarantees peptide from inside cell,
  - MHCII guarantees from environment
- Presenter and receiver must authenticate
- MHCI focus CTL (expensive) on infected cells (groups of viruses). Antibodies (plentiful, cheap) take care of single free viruses
THE COMPLEMENT SYSTEM
A FIRST LINE OF DEFENSE

- A collection of proteins that, when activated form complexes on cell surfaces
  - attract phagocytes
  - drill holes and kill
- Why don't they kill self cells? 3 level protection mechanism
  - DAF on surface accelerates breakdown of CS complex
  - Surface proteins can clip complex elements inactivate
  - CD59 (aka protectin) kicks complex off surface before hole drilled
- Bio caveat DAF/CD59 name protein classes.
  - May differ in detail across organisms
  - DAF of foreign cells may not be effective against host CS (transplant problems).
DIVERSITY

- There is a unique antibody type for each organic compound.
- Each B Cell (and its progeny) produces exactly one type.
- Similarly for T Cells and T Cell receptors.
- How can this be? It would take all of the genes and more.
DIVERSITY

- Solution: Edit the DNA!
- Immature B and T cells have genes with multiple instances of several modules.
- These genes are edited in a series of clip/rejoin operations to mix 'n match
DIVERSITY -- BUT

- Not all combinations are desired.
  - Competence tests -- does the resulting gene produce functioning proteins? Many cells die because mix n match fails at this level
- Tolerance tests
  - TCRs must recognize presentation mechanism and not recognize self
  - ow it commits suicide
Secure Activation

- Innate system components, non specific, always alert
  - Macrophage, DC activated by generic pathogen recognition
- Adaptive components are specific and aggressive, should not be activated if not needed
- TCell 2key match
  - peptide and presenter, and co-stimulation
- B Cell has 2 phase activation:
  - recognize and present its pathogen
  - connect with Tc that has seen the same pathogen
T-cell activation requires both antigen and co-stimulatory signals.

- **No antigen**
  - APC
  - T-cell receptor
  - CD80
  - CD28
  - CD4
  - Naive T cell
  - No antigenic peptide
  - No response

- **No co-stimulation**
  - APC
  - MHC class II
  - T-cell receptor
  - CD4
  - CD28
  - Naive T cell
  - No activation
  - T cell becomes unresponsive

- **Both antigen and co-stimulation**
  - APC
  - Pathogen
  - CD80 or CD86
  - CD28
  - Naive T cell
  - T-cell activation

Figure 2-23 Immunobiology, 7ed. (© Garland Science 2008)
B Cell activation

Antigen bound by B-cell surface receptor
Antigen internalized and degraded to peptide fragments
Fragments bind to MHC class II and are transported to cell surface

Antigen–receptor binding and activation of B cell by T cell

T lymphocyte B lymphocyte

Proliferation and differentiation of B cell to acquire effector function
Cells circulate / patrol / move from birth place to job site
Need to exit vessels at the right spot and right time.
Content/Interest driven addressing (aka zipcode)
cell expresses Selector Ligand
exit point expresses selector when interested (infection present)
if cell is attracted it expresses a hook (receptor) that grabs an intercellular adhesion molecule at the exit
attractants could be cytokines, bug bits (C5a, f-met)
Immune System Logic?

- Key attributes
  - hierarchical organization: proteins, cells, locations
  - component state,
  - space
  - time/delay

- Key mechanism: pattern matching

- Diversity:
  - Multiple roles
  - Specialists ready for (almost) any need
    - counter attack, signal
Activities:
- eating, circulating, forming modules/complexes,
- listening/expressing interest,
- advertising
- replicating
- differentiating/refining specialty
- continuous renewal of supply
- supply reduction: cells dying, proteins degrading
  - junk elimination: wrong, not needed, worn out,
  - dangerous: self attack, virus nursery (tumors...)
**Immune System Logic? III**

- Control/safety mechanisms
  - battle alert system
    - initiate/continue response
  - 3 key activation of T cells
  - 2 phase activation of B cells
  - competence/tolerance tests
  - protection -- degrade, dislodge attacker
What is the mathematics of immune system control?

- There are many trade-offs, effects to balance
- Need rapid response and adaptation
- A very open system!