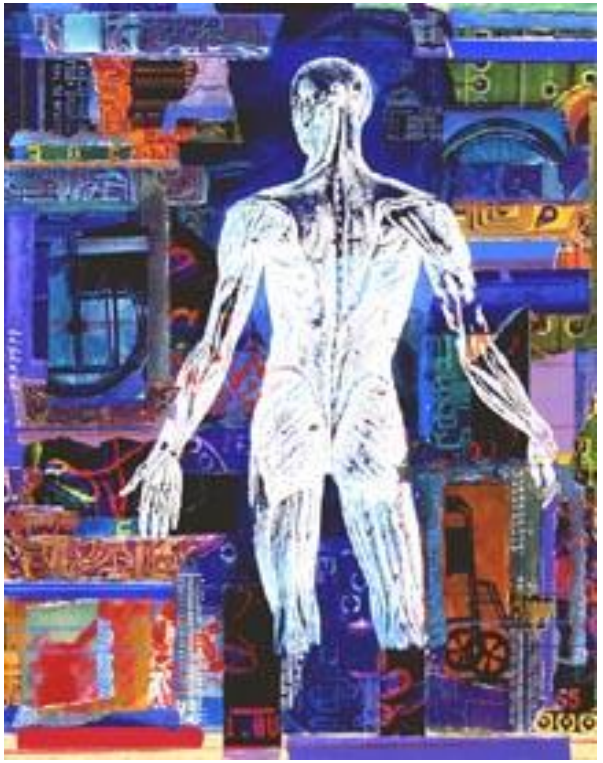
ECE 370
Introduction to Biomedical Engineering

A Systems Approach to Physiology

What is Physiology?

- **Physiology (physi = nature; logos = study):**
  - Study of how the body works to maintain life
  - Cell → tissue → organ → organ system → organism
- **Human physiology:**
  - Dealing with normal life phenomena of the human body.
- **Goal of physiology:**
  - Explain the physical and chemical factors that are responsible for the origin, development, and progression of life.
- **Why do we study physiology?**
  - Understand normal function in order to cure the disease



The Integration Between Systems

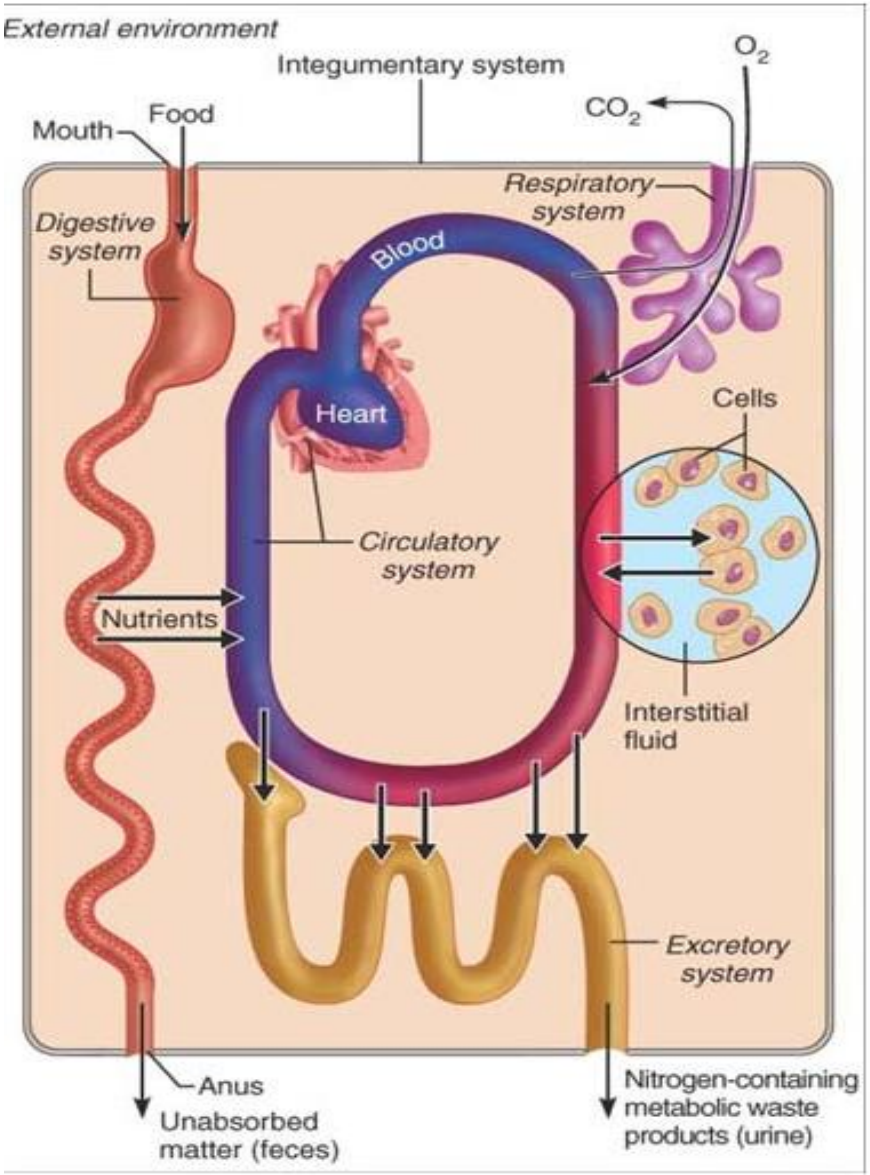
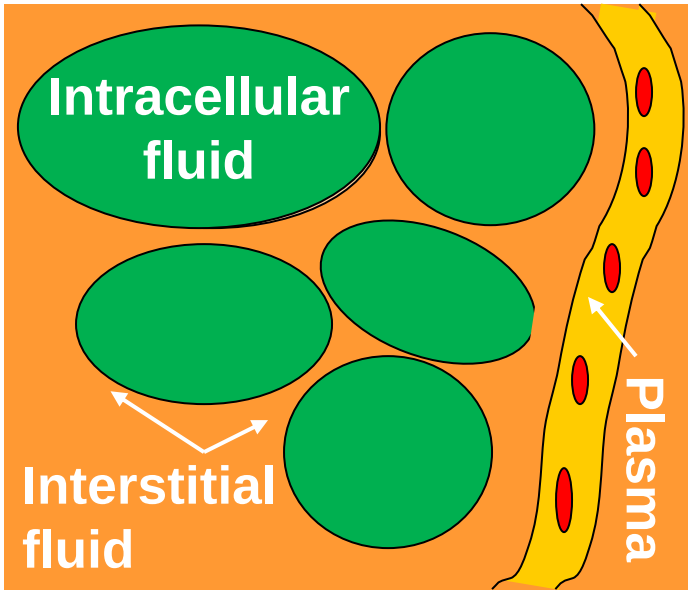
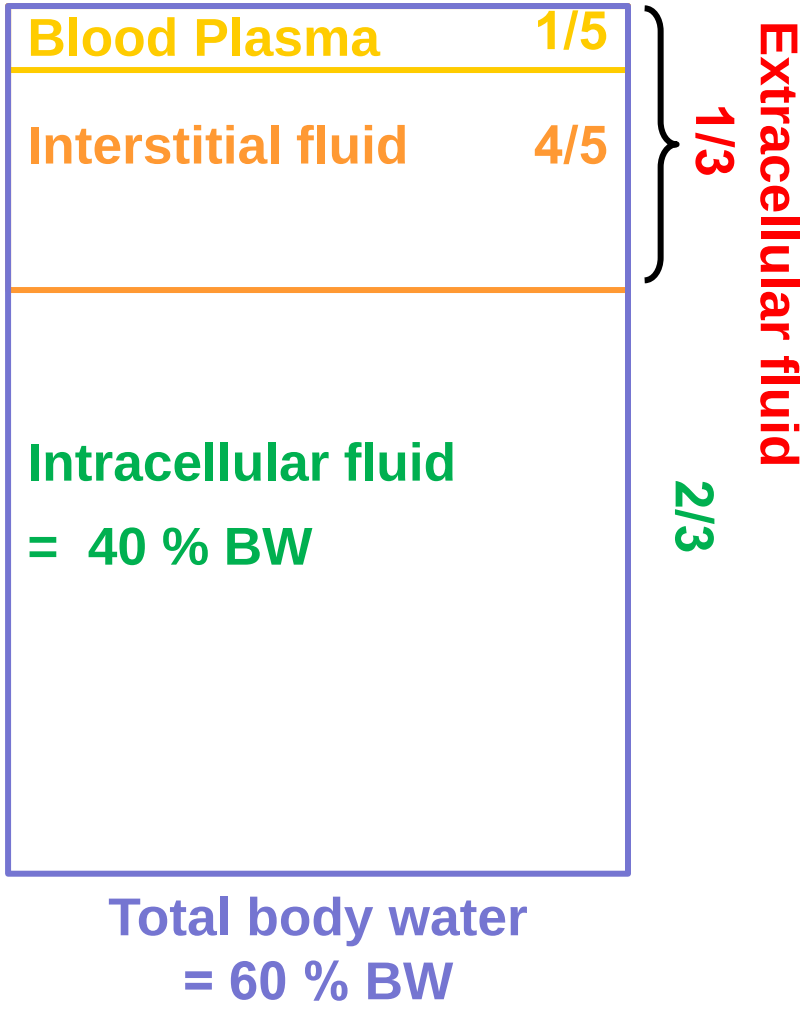


FIGURE 1.2 **Examples of interrelationships among body organ systems.** The integumentary system protects the body as a whole from the external environment. The digestive and respiratory systems, in contact with the external environment, take in nutrients and oxygen, respectively, which are then distributed by the blood to all body cells. Elimination of metabolic wastes is accomplished by the urinary and respiratory systems.

Internal Environment

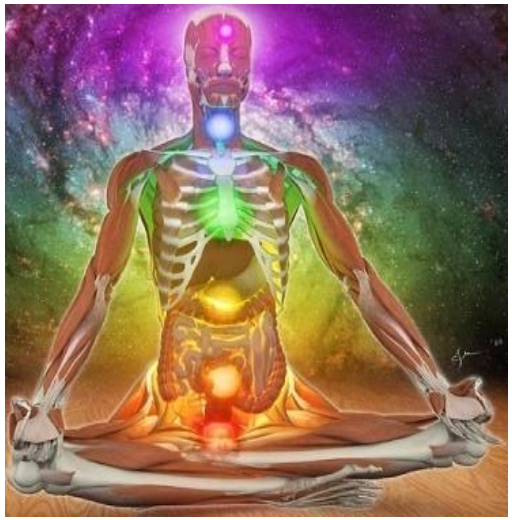
- **Watery internal environment**
  - Appropriately maintained to support life and functioning
  - Intracellular fluid (ICF)
    - The fluid in all the cells
  - Extracellular fluid (ECF)
    - The fluid outside the cells
    - Interstitial fluid (in between cells)
    - Plasma (in blood vessels)

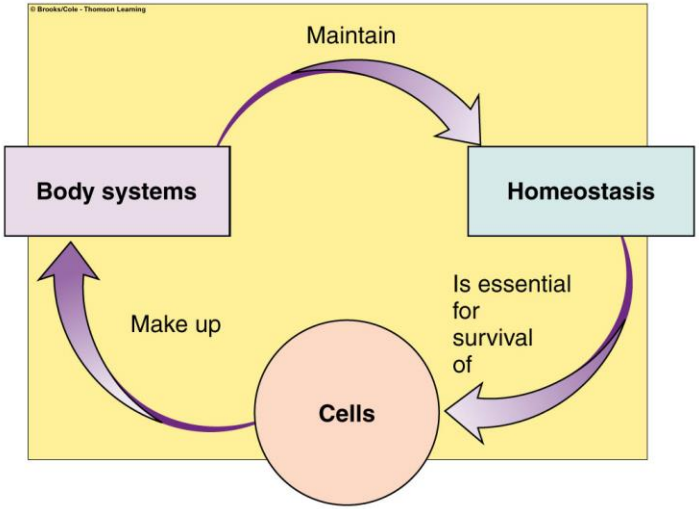




Homeostasis

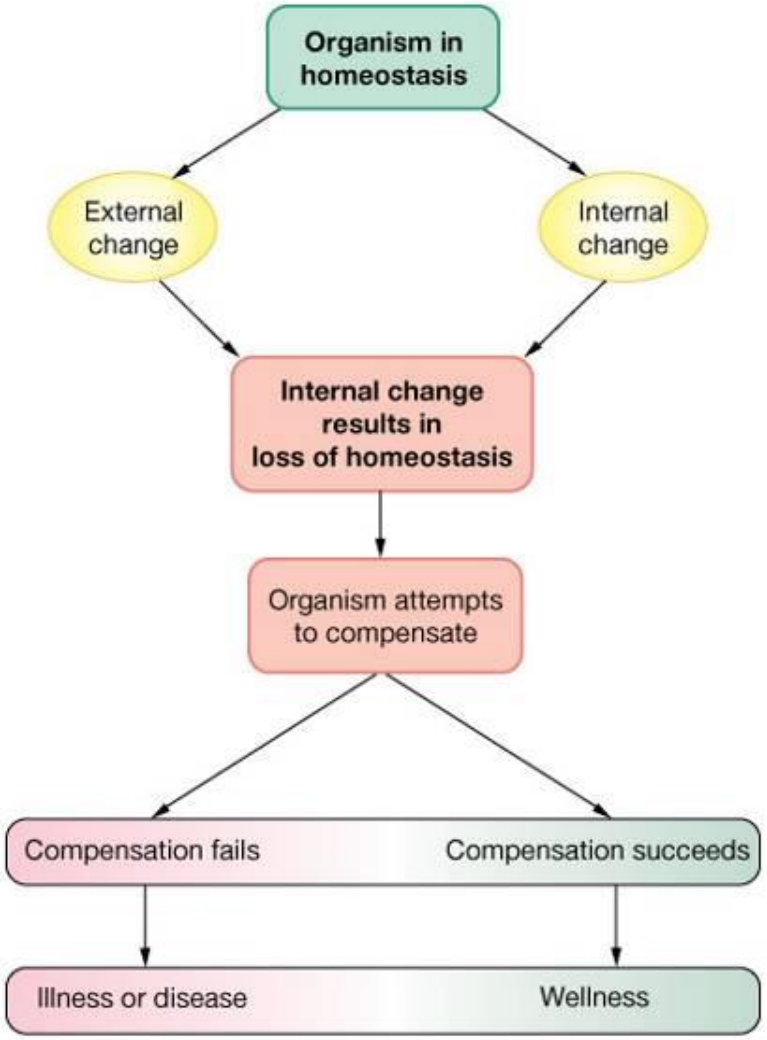
- **Maintenance of relatively constant chemical/physical conditions of the internal environment.**
  - Claude Bernard (The father of modern Physiology)
    - ...The internal environment remains relatively constant though there are changes in the external environment
- **stable ≠ rigidity**
  - Can vary within narrow limit (normal physiological range)
  - Dynamic state
    - External perturbations
    - Short term transient responses or long term adaptation
    - Return to steady state
- **The golden goal of every organ:**
  - Maintain homeostasis → REGULATION





Homeostasis

- **Factors regulated**
  - Concentration of nutrient molecules
  - Concentration of O2 and CO2
  - Concentration of waste products
  - pH
  - Concentration of water, salt and other electrolytes
  - Volume and pressure
  - Temperature
- **In fasting blood**
  - Arterial pH 7.35-7.45
  - Bicarbonate 24-28 mEq/L
  - O2 content 17.2-22.0 ml/100 ml
  - Total lipid 400-800 mg/100 ml
  - Glucose 75-110 mg/100 ml
- **Successful compensation**
  - Homeostasis reestablished
- **Failure to compensate**
  - Pathophysiology → Illness or Death

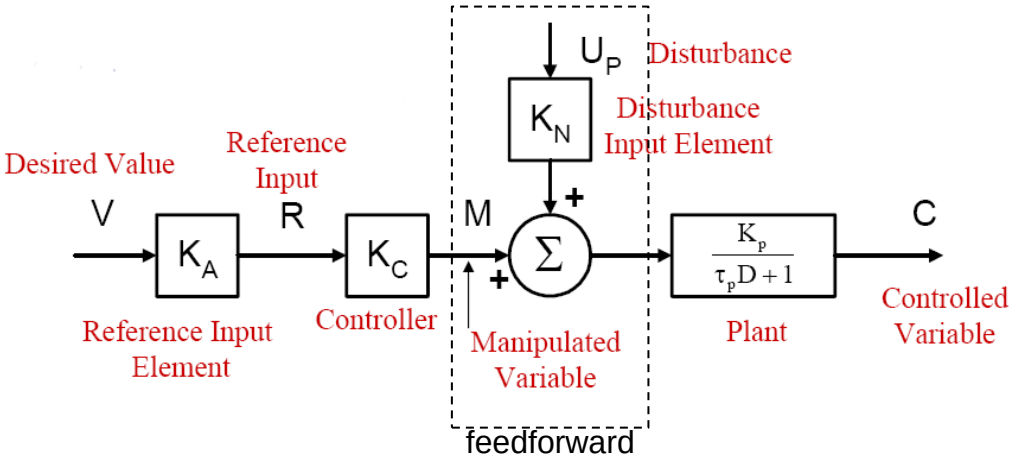


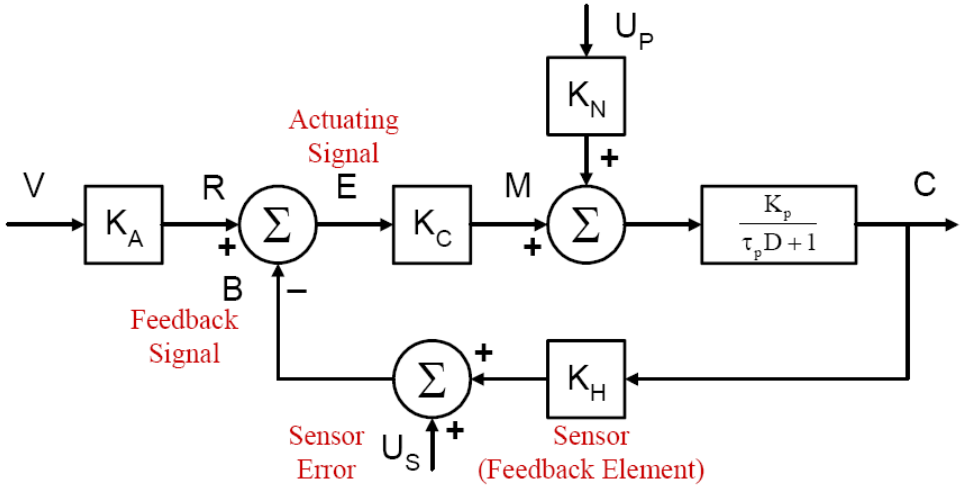
Regulation of Body Functions

- **Regulation**
  - The ability of an organism to maintain stable internal conditions in a constantly changing environment
- **Types of Regulation:**
  - Chemical (hormonal) Regulation
    - A regulatory process performed by hormone or active chemical substance in blood or tissue.
    - Slow response, acts extensively and lasts for a long time.
  - Nervous Regulation
    - A regulatory process in which body functions are controlled by the nervous system
    - Pathway: nerve reflex
      - Types: unconditioned reflex and conditioned reflex
      - Example: baroreceptor reflex of arterial blood pressure
    - Fast response, acts precisely or locally, lasts for a short time
  - Autoregulation
    - A tissue or an organ can directly responding to environmental changes that are independent of nervous and/or hormonal control
    - Characteristics：
      - Amplitude of the regulation is smaller than other two types.
      - Extent of the effect is smaller than other two types.
- **In the human body these three regulations are coordinated and act as one system**
  - “feedback control system”

Control Systems

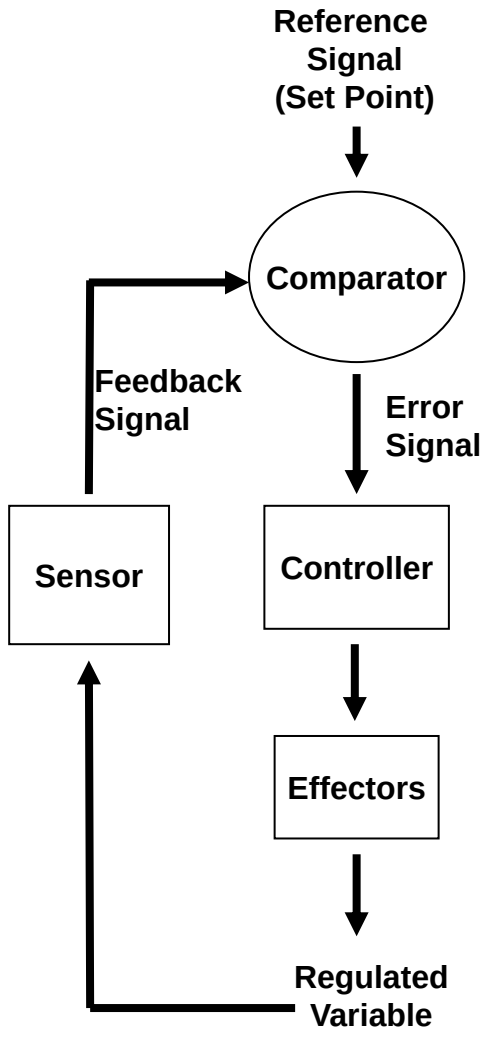
- **Passive Control**
  - Open-loop system
  - Open-loop system with feed-forward
- **Active or Closed Loop Control**
  - Feedback Control
    - “Feedback”
      - a process in which a part of output (feedback signal) from the controlled organ returns to affect or modify the action of the control system.
  - Feedback control mechanism consists of two forms
    - Negative feedback control
    - Positive feedback control





Control Systems

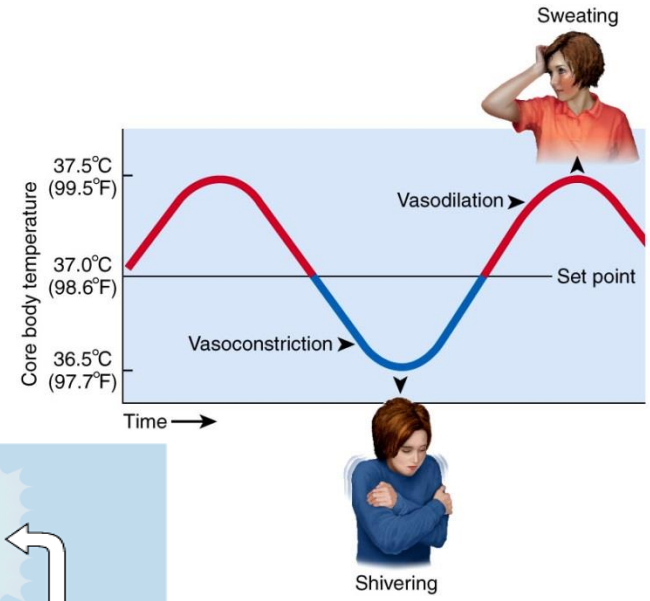
- **Feedback in biological systems**
  - All physiological parameters have a set point
  - Sensor: Detects deviation from set point
  - Integrating center: Determines response
  - Effector: Produces the response
  - Significance:
    - Maintenance of the homeostasis
- **Negative feedback**
  - Change in a variable initiates response to the opposite direction
  - Tends to correct the change and return the system to its steady state
  - The effect is mainly “inhibitory action”
  - Significance:
    - Prevents small changes from becoming too large

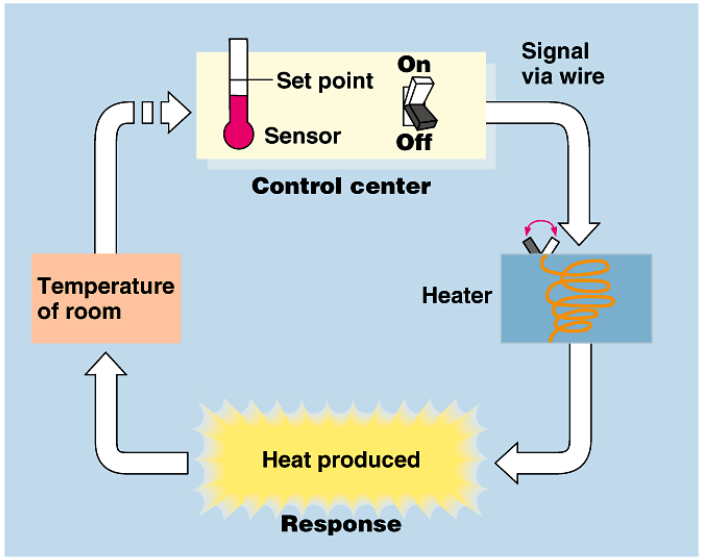


Control Systems

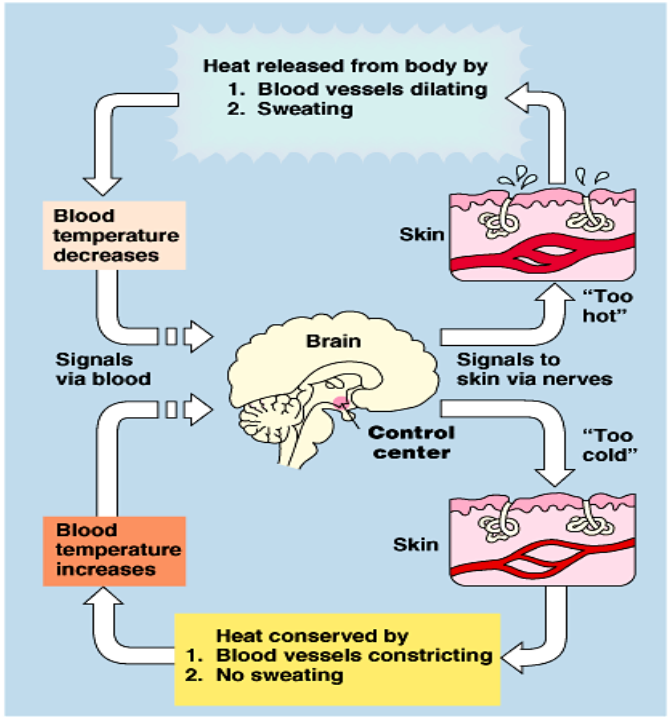
- **Example of negative feedback**
  - Temperature control

	Home	Body
• Set point:	22 °C	37 °C
• Sensor:	Thermistor	Temp receptors (Hypothalamus)
• Integration:	Thermostat	Brain (Hypothalamus)
• Effector:	Burner	Cardiovascular, Muscular, Sweat glands





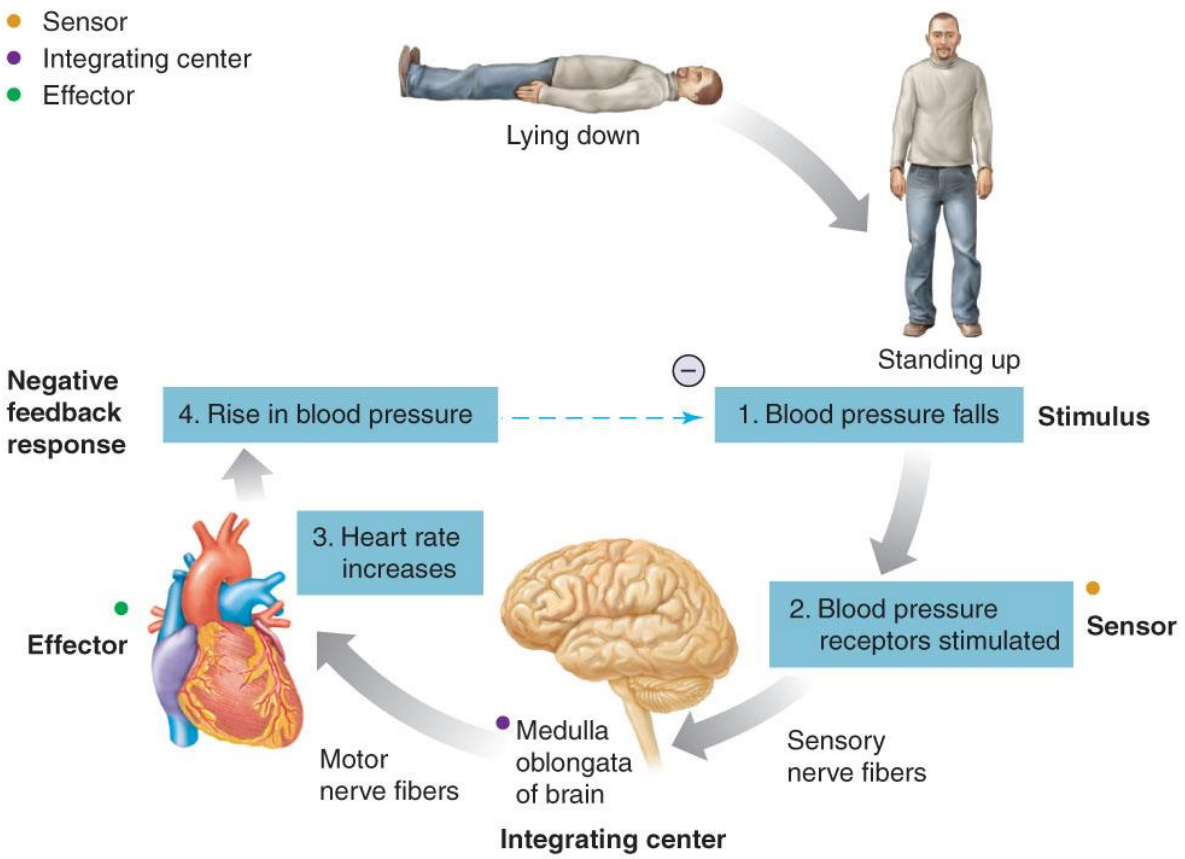
(a) Control of room temperature



(b) Control of body temperature

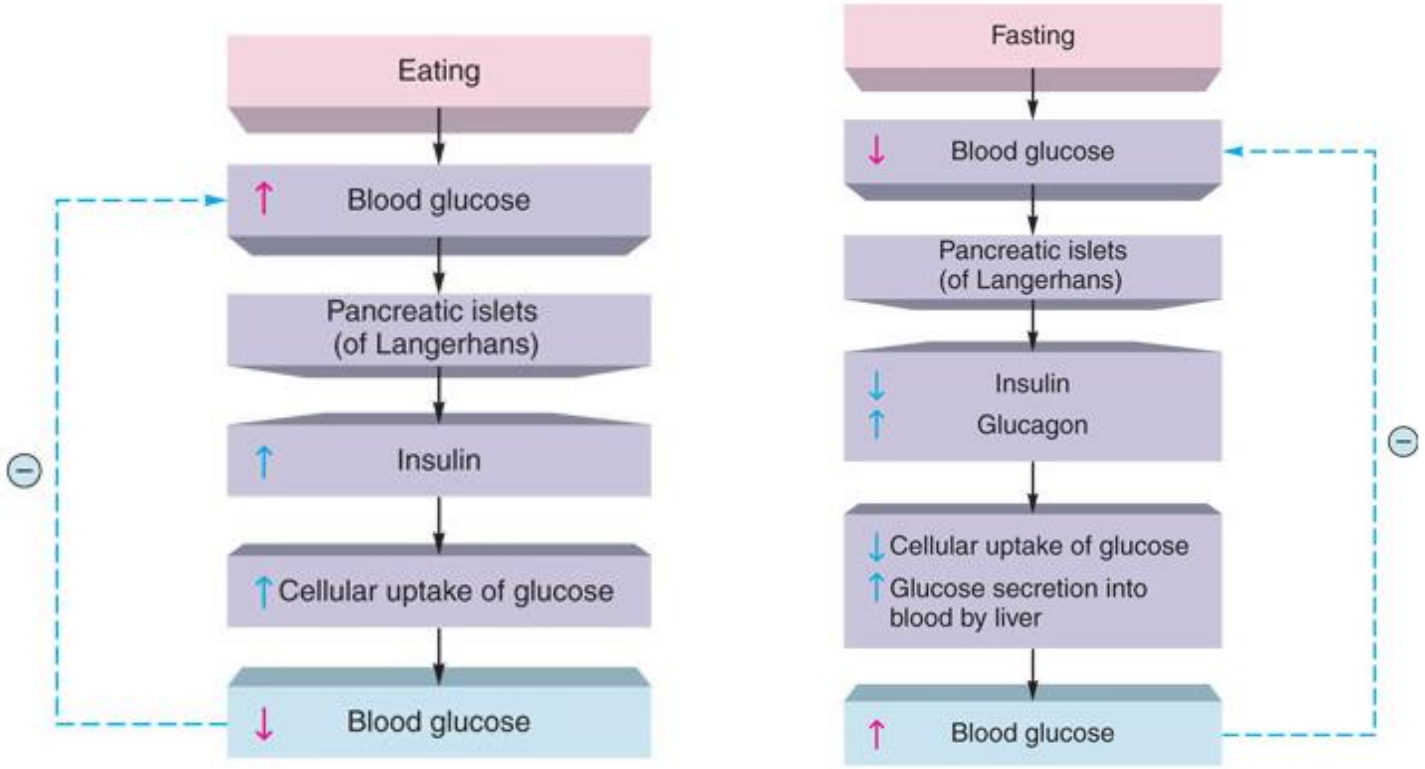
Control Systems

- **Example of negative feedback:**
  - Control of blood pressure
    - Set point: normal blood pressure
    - Sensor: barorecptors
    - Integration Center: brain (hypothalamus/brain stem)
    - Effector: heart / arteries



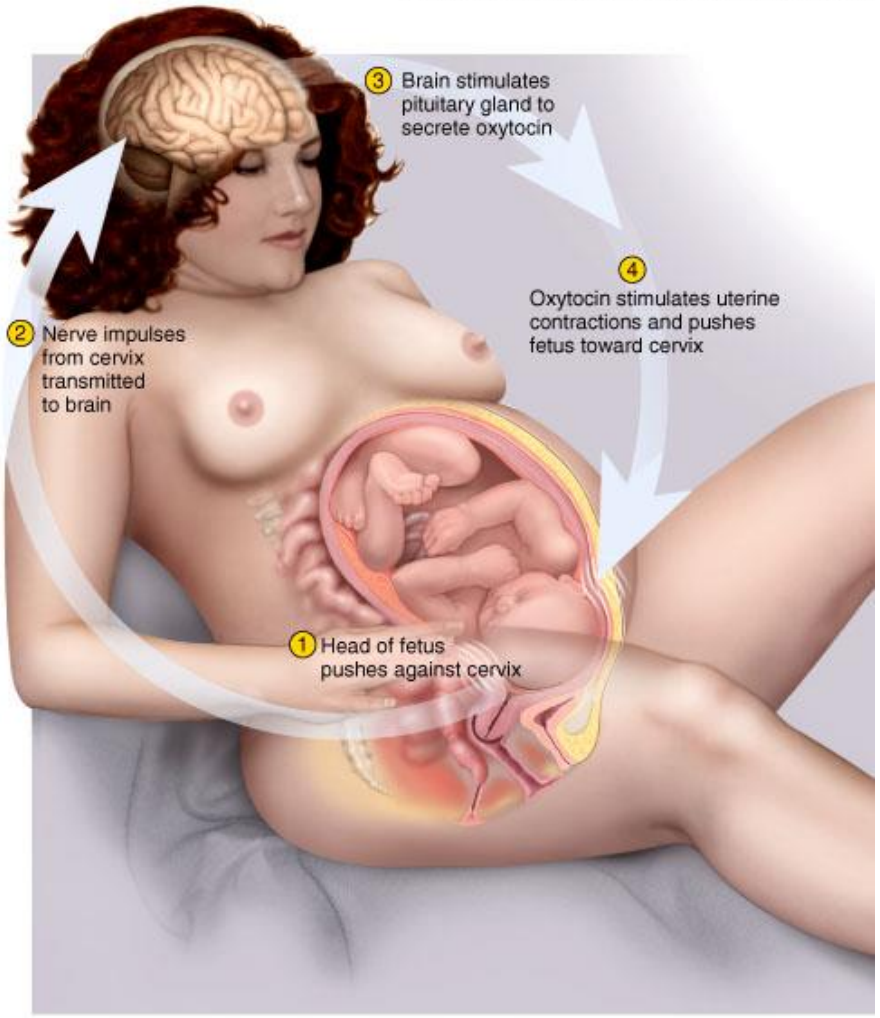
Control Systems

- **Example of negative feedback**
  - Control of blood sugar
    - Set point: 5 mmol/L
    - Sensor: pancreatic cells
    - Integration: Endocrine system
    - Effector: insulin and glucagon



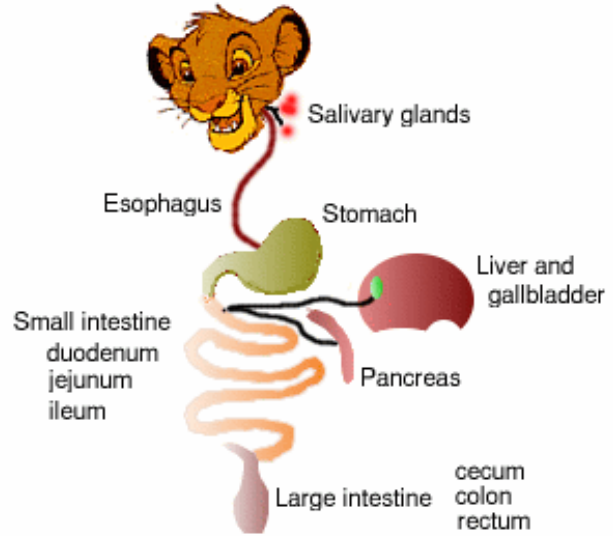
Control Systems

- **Positive feedback**
  - The feedback signal or output from the controlled system increases the action of the control system
  - Significance:
    - Enhance the action of original stimulus or amplify or reinforce change, promote an activity to finish
  - It is known as a vicious circle because it can lead to instability or even death
    - Not as common as negative feedback
    - Always a stop mechanism required
    - Appears when abnormal circumstances disable negative feedback
  - Examples:
    - Blood clotting,
    - Micturition, defecation
    - Na+ inflow in genesis of nerve signals
    - Contraction of the uterus during childbirth (parturition).



Control Systems

- **Feed-forward control**
  - Initiate responses in anticipation of change
  - Direct effect of stimulus on the control system before the action of feedback signal occurs.
    - Disruption or interference signal
  - Significance of Feed-forward
    - adaptive feedback control.
    - makes the human body to foresee and adapt the environment promptly and exactly (prepare the body for the change).
  - Example:
    - Shivering before diving into the cold water
    - Sight of food → enzyme secretion
    - Food in the gastrointestinal tract → insulin secretion in anticipation of glucose arrival



Perturbation:
Sight and smell of food → expect food intake
Feed-forward:
Secretion of enzymes in the mouth and the stomach

Perturbation:
Food in the stomach → expected glucose in the blood stream
Feed-forward:
Secretion of insuline by the pancreas

Constructing Block Diagrams

- **In order to construct a block diagram from a narrative**
  1. Determine the controlled variable(s)
  2. What sort of disturbances or inputs would make the variables deviate from homeostasis? Where would they come from?
  3. Determine the sensor(s) that sense the current value of the variable(s). There may be more than one variable and sensor.
  4. If more than one variable and/or sensor, is there **more than one feedback loop** involved? If so, are any of the loops **positive feedback** loops?
     a. If there are positive feedback loops, how are they terminated within an **overall negative feedback** process?
     b. Are there **short-** and **long-** term controls? Identify them.
  5. Where do these **sensors reside** (e.g. in the medulla, kidney, or vasculature)?
  6. Is there a **set point** or is this a reflex process? If there is a set point, is it constant or can it be reset?
  7. Where is the **controller located**? How do the sensors communicate with the controller (s)?
  8. What are the **effector(s)** and how does the controller communicate with the effectors?
  9. How do the effectors **change** the controlled variables when they **exceed** and when they are **less than** the set point? Is there **more than one organ** involved? If so, how do they **interact**?
  10. What about inputs from **higher centers** of the brain and from **hormones** released from glands?

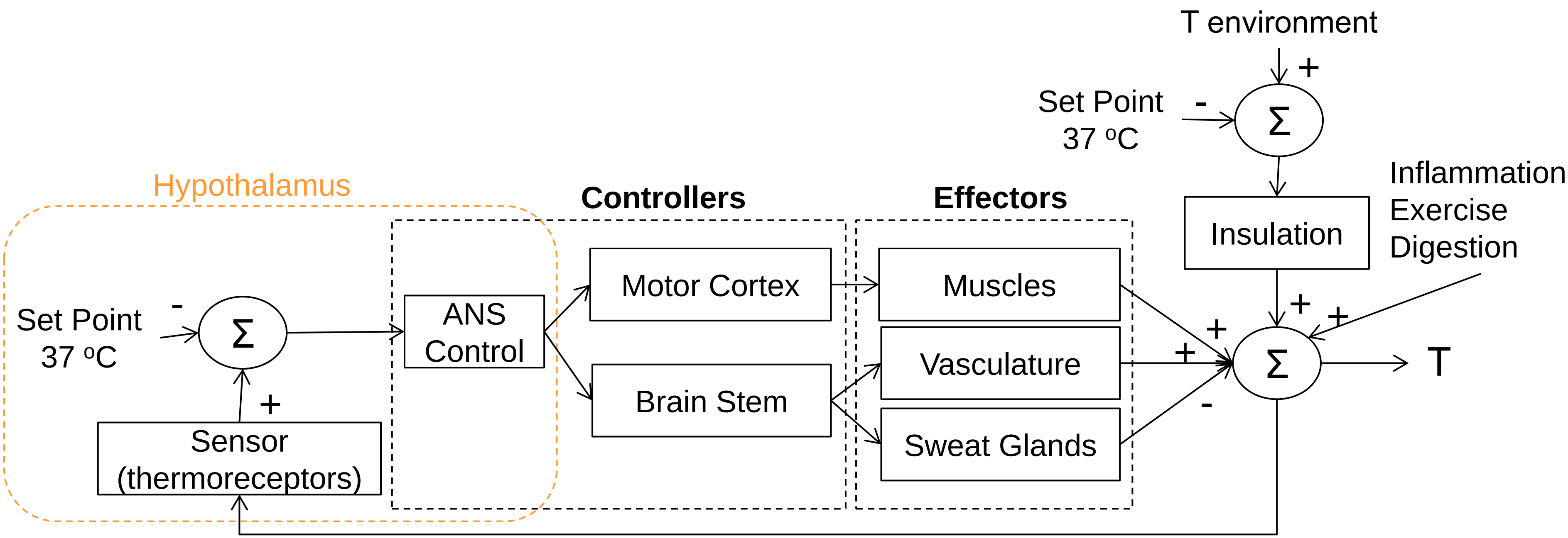
Constructing Block Diagrams

How do the effectors **change** the controlled variables when they **exceed** … set point? Is there **more than one organ** involved? If so, how do they **interact**?

… **positive feedback** loops?

Several organs coordinated by the hypothalamus

High T: Muscles inactive, vessels dilate, sweat glands secrete



Constructing Block Diagrams

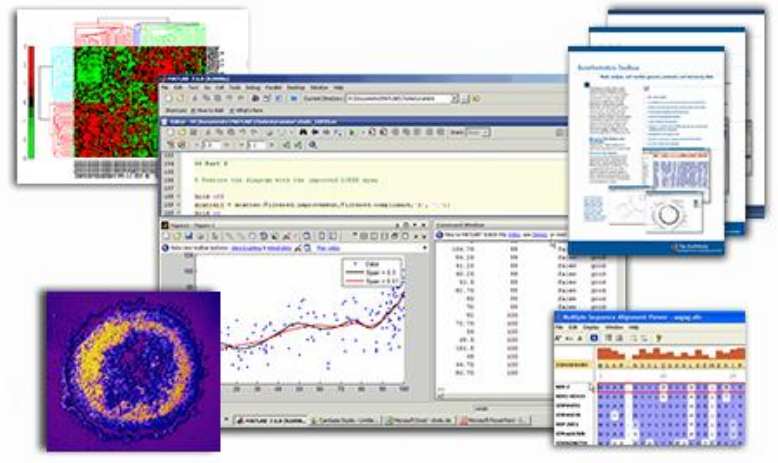
Determine the controlled variable(s)	T of blood
What sort of disturbances or inputs would make the variables deviate from homeostasis? Where would they come from?	T of the environment Inflammation, Exercise, Digestion
Determine the sensor(s) that sense the current value of the variable(s). There may be more than one variable and sensor.	Thermoreceptors
If more than one variable and/or sensor, is there **more than one feedback loop** involved? If so, are any of the loops **positive feedback** loops?	N/A
Where do these **sensors reside** ?	Hypothalamus
Is there a **set point** or is this a reflex process? If there is a set point, is it constant or can it be reset?	Fixed at 37 oC
Where is the **controller located**? How do the sensors communicate with the controller (s)?	Motor Cortex and Brain Stem Through ANS control areas of the hypothalamus
What are the **effector(s)** and how does the controller communicate with the effectors?	Muscles, Vasculature, Sweat Glands Nerves
How do the effectors **change** the controlled variables when they **exceed** and when they are **less than** the set point? Is there **more than one organ** involved? If so, how do they **interact**?	Several organs coordinated by the hypothalamus Low T: Muscles shiver, vessels constrict, sweat glands inactive High T: Muscles inactive, vessels dilate, sweat glands secrete
What about inputs from **higher centers** of the brain and from **hormones** released from glands?	Heat seeking behavior tends to lead us to higher T environment

Mathematical Models

- **What is Mathematical Modeling?**
  - A mathematical model is the formulation in mathematical terms of the **assumptions** believed to underlie a particular real-world problem
  - Mathematical modeling is the **process** of deriving such a formulation
- **Why is it Worthwhile to Model Biological Systems?**
  - To help reveal possible underlying mechanisms involved in a biological process
  - To help interpret and reveal contradictions/incompleteness of data
  - To help confirm/reject hypotheses
  - To predict system performance under untested conditions
  - To supply information about the values of experimentally inaccessible parameters
  - To suggest new hypotheses and stimulate new experiments

Mathematical Models

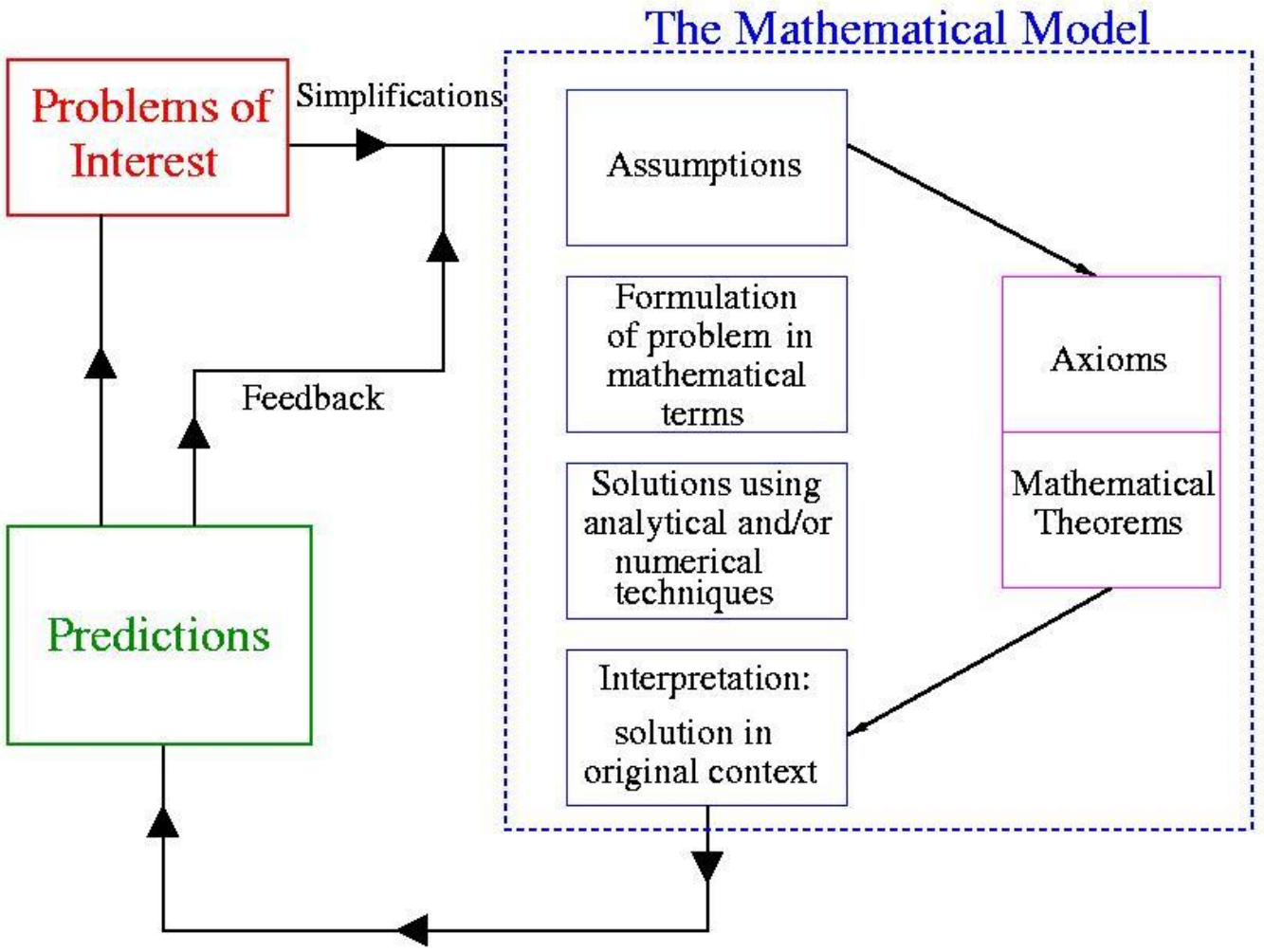
- **What are Some Limitations of Mathematical Models**
  - Not necessarily a ‘correct’ model
  - Unrealistic models may fit data very well leading to erroneous conclusions
  - Simple models are easy to manage, but complexity is often required
  - Realistic simulations require a large number of hard to obtain parameters
- **Disclaimer: Models are not explanations and can never alone provide a complete solution to a biological problem.**



Mathematical Models

- **How Are Models Derived?**
  - Start with at problem of interest
  - Make reasonable simplifying assumptions
  - Translate the problem from words to mathematically/physically realistic statements of balance or conservation laws
- **What do you do with the model?**
  - Solutions—Analytical/Numerical
  - Interpretation—What does the solution mean in terms of the original problem?
  - Predictions—What does the model suggest will happen as parameters change?
  - Validation—Are results consistent with experimental observations?

The Modeling Process



Analysis of Block Diagrams

- **Use Laplace transforms**
- **In a block diagram assume that**
  - G(s)=output/input
  - The output of Σ blocks is the summation of the inputs
  - Start with y and go counterclowise

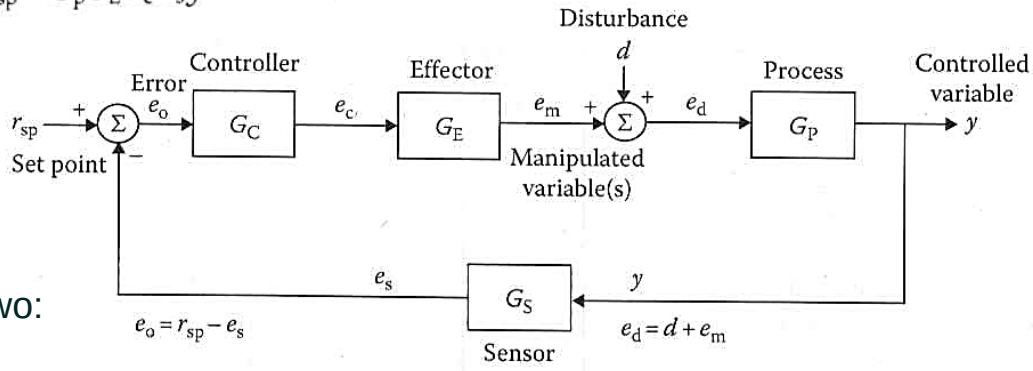
$$y = G_p e_d = G_p[d + e_m] = G_p d + G_p e_m = G_p d + G_p G_E e_c$$

$$y = G_p d + G_p G_E G_c e_o = G_p d + G_p G_E G_c [r_{sp} - e_s]$$

$$y = G_p d + G_p G_E G_c r_{sp} - G_p G_E G_c e_s = G_p d + G_p G_E G_c r_{sp} - G_p G_E G_c G_s y$$

  - Solve for y

$$y = \frac{G_p d}{1 + G_p G_E G_c G_s} + \frac{G_p G_E G_c r_{sp}}{1 + G_p G_E G_c G_s}$$



  - Find the transfer functions (in this case two: one fro r_{sp} and one for d)

$$H_{sp} = \frac{\text{output}}{\text{input}} = \frac{y}{r_{sp}} = \frac{G_p G_E G_c}{1 + G_p G_E G_C G_s}$$

$$H_d = \frac{\text{output}}{\text{input}} = \frac{y}{d} = \frac{G_p}{1 + G_p G_E G_c G_s}$$

Laplace Transforms

- **Why use Laplace Transforms?**
  - Find solution to differential equation using algebra
  - Relationship to Fourier Transform allows easy way to characterize systems
  - No need for convolution of input and differential equation solution
  - Useful with multiple processes in system
- **How to use Laplace**
  - Find differential equations that describe system
  - Obtain Laplace transform
  - Perform algebra to solve for output or variable of interest
  - Apply inverse transform to find solution

What are Laplace Transforms?

- **Note "transform":**
  - f(t) $\rightarrow$ F(s), where t is integrated and s is variable
  - Conversely F(s) $\rightarrow$ f(t), t is variable and s is integrated
- **Properties**
  - t is real, s is complex
  - Inverse requires complex analysis to solve
  - Assumes f(t) = 0 for all t < 0
- **Evaluating F(s) = L{f(t)}**
  - Hard way
    - Solve the integral
  - Easy way
    - Recognize a few different transforms
    - See tables
    - Learn a few different properties
    - Do a little math

$$F(s) = L\{f(t)\} = \int_0^{\infty} f(t)e^{-st}dt$$

$$f(t) = L^{-1}\{F(s)\} = \frac{1}{2\pi j}\int_{\sigma - j\infty}^{\sigma + j\infty} F(s)e^{st}ds$$

TABLE 2–1 Laplace Transform Pairs

$f(t)$	$F(s)$
Unit impulse $\delta(t)$	1
Unit step $1(t)$	$\frac{1}{s}$
t	$\frac{1}{s^2}$
$\frac{t^{n-1}}{(n-1)!} \quad (n = 1, 2, 3, \ldots)$	$\frac{1}{s^n}$
$t^n \quad (n = 1, 2, 3, \ldots)$	$\frac{n!}{s^{n+1}}$
e^{-at}	$\frac{1}{s+a}$
te^{-at}	$\frac{1}{(s+a)^2}$
$\frac{1}{(n-1)!}t^{n-1}e^{-at} \quad (n = 1, 2, 3, \ldots)$	$\frac{1}{(s+a)^n}$
$t^n e^{-at} \quad (n = 1, 2, 3, \ldots)$	$\frac{n!}{(s+a)^{n+1}}$
$\sin \omega t$	$\frac{\omega}{s^2+\omega^2}$
$\cos \omega t$	$\frac{s}{s^2+\omega^2}$
$\sinh \omega t$	$\frac{\omega}{s^2-\omega^2}$
$\cosh \omega t$	$\frac{s}{s^2-\omega^2}$
$\frac{1}{a}(1-e^{-at})$	$\frac{1}{s(s+a)}$
$\frac{1}{b-a}(e^{-at}-e^{-bt})$	$\frac{1}{(s+a)(s+b)}$
$\frac{1}{b-a}(be^{-bt}-ae^{-at})$	$\frac{s}{(s+a)(s+b)}$
$\frac{1}{ab}\left[1+\frac{1}{a-b}(be^{-at}-ae^{-bt})\right]$	$\frac{1}{s(s+a)(s+b)}$
$\frac{1}{a^2}(1-e^{-at}-ate^{-at})$	$\frac{1}{s(s+a)^2}$
$\frac{1}{a^2}(at-1+e^{-at})$	$\frac{1}{s^2(s+a)}$
$e^{-at}\sin \omega t$	$\frac{\omega}{(s+a)^2+\omega^2}$
$e^{-at}\cos \omega t$	$\frac{s+a}{(s+a)^2+\omega^2}$
$\frac{\omega_n}{\sqrt{1-\zeta^2}}e^{-\zeta\omega_n t}\sin \omega_n\sqrt{1-\zeta^2}\,t$	$\frac{\omega_n^2}{s^2+2\zeta\omega_n s+\omega_n^2}$
$-\frac{1}{\sqrt{1-\zeta^2}}e^{-\zeta\omega_n t}\sin(\omega_n\sqrt{1-\zeta^2}\,t-\phi)$ $\phi = \tan^{-1}\frac{\sqrt{1-\zeta^2}}{\zeta}$	$\frac{s}{s^2+2\zeta\omega_n s+\omega_n^2}$
$1-\frac{1}{\sqrt{1-\zeta^2}}e^{-\zeta\omega_n t}\sin(\omega_n\sqrt{1-\zeta^2}\,t+\phi)$ $\phi = \tan^{-1}\frac{\sqrt{1-\zeta^2}}{\zeta}$	$\frac{\omega_n^2}{s(s^2+2\zeta\omega_n s+\omega_n^2)}$
$1-\cos \omega t$	$\frac{\omega^2}{s(s^2+\omega^2)}$
$\omega t-\sin \omega t$	$\frac{\omega^3}{s^2(s^2+\omega^2)}$
$\sin \omega t-\omega t\cos \omega t$	$\frac{2\omega^3}{(s^2+\omega^2)^2}$
$\frac{1}{2\omega}t\sin \omega t$	$\frac{s}{(s^2+\omega^2)^2}$
$t\cos \omega t$	$\frac{s^2-\omega^2}{(s^2+\omega^2)^2}$
$\frac{1}{\omega_2^2-\omega_1^2}(\cos \omega_1 t-\cos \omega_2 t) \quad (\omega_1^2 \neq \omega_2^2)$	$\frac{s}{(s^2+\omega_1^2)(s^2+\omega_2^2)}$
$\frac{1}{2\omega}(\sin \omega t+\omega t\cos \omega t)$	$\frac{s^2}{(s^2+\omega^2)^2}$

Properties of Laplace Transforms

Name	Time Function	Laplace Transform
Transform pair	$f(t)$	$F(s)$
Superposition	$\alpha f_1(t) + \beta f_2(t)$	$\alpha F_1(s) + \beta F_2(s)$
Time delay $(\tau \geq 0)$	$f(t-\tau)$	$F(s)e^{-s\tau}$
Time scaling	$f(at)$	$\frac{1}{\lvert a\rvert}F\left(\frac{s}{a}\right)$
Frequency shift	$e^{-at}f(t)$	$F(s+a)$
Differentiation	$\frac{d^m}{dt^m}f(t)$	$s^mF(s) - s^{m-1}f(0) - \cdots - \frac{d^{m-1}}{dt^{m-1}}f(0)$
Integration	$\int f(\xi)d\xi$	$\frac{1}{s}F(s)$
Convolution	$f_1(t) * f_2(t)$	$F_1(s)F_2(s)$
Initial Value Theorem	$f(0^+)$	$\lim_{s\to\infty} sF(s)$
Final Value Theorem	$\lim_{t\to\infty} f(t)$	$\lim_{s\to 0} sF(s)$
Time product	$f_1(t)f_2(t)$	$\frac{1}{2\pi j}\int_{c-j\infty}^{c+j\infty} F_1(\xi)F_2(s-\xi)d\xi$
Multiplication by time	$tf(t)$	$-\frac{d}{ds}F(s)$

$$F(z)=\sum \alpha_r z^r \to \int_{-\infty}^{\infty} g(p)e^{i\chi p}dp \quad \text{where } z=e^{i\omega\chi},\ p=\frac{r}{N},\ \alpha_r \mapsto g(p)$$

The functions $f(\chi)$ and $g(p)$ are called *Fourier transforms* of one another.

$$f(\chi) = (2\pi)^{-1/2}\int_{-\infty}^{\infty} g(p)e^{i\chi p}dp, \quad g(p) = (2\pi)^{-1/2}\int_{-\infty}^{\infty} f(\chi)e^{-i\chi p}d\chi$$

TABLE 2-2 Properties of Laplace Transforms

1	$\mathcal{L}[Af(t)] = AF(s)$
2	$\mathcal{L}[f_1(t) \pm f_2(t)] = F_1(s) \pm F_2(s)$
3	$\mathcal{L}_\pm\left[\frac{d}{dt}f(t)\right] = sF(s) - f(0\pm)$
4	$\mathcal{L}_\pm\left[\frac{d^2}{dt^2}f(t)\right] = s^2F(s) - sf(0\pm) - \dot{f}(0\pm)$
5	$\mathcal{L}_\pm\left[\frac{d^n}{dt^n}f(t)\right] = s^nF(s) - \sum_{k=1}^{n} s^{n-k}f^{(k-1)}(0\pm)$ where $f^{(k-1)}(t) = \frac{d^{k-1}}{dt^{k-1}}f(t)$
6	$\mathcal{L}_\pm\left[\int f(t)\,dt\right] = \frac{F(s)}{s} + \frac{[\int f(t)\,dt]_{t=0\pm}}{s}$
7	$\mathcal{L}_\pm\left[\iint f(t)\,dt\,dt\right] = \frac{F(s)}{s^2} + \frac{[\int f(t)\,dt]_{t=0\pm}}{s^2} + \frac{[\iint f(t)\,dt\,dt]_{t=0\pm}}{s}$
8	$\mathcal{L}_\pm\left[\int\cdots\int f(t)(dt)^n\right] = \frac{F(s)}{s^n} + \sum_{k=1}^{n}\frac{1}{s^{n-k+1}}\left[\int\cdots\int f(t)(dt)^k\right]_{t=0\pm}$
9	$\mathcal{L}\left[\int_0^t f(t)\,dt\right] = \frac{F(s)}{s}$
10	$\int_0^\infty f(t)\,dt = \lim_{s\to 0} F(s)$ if $\int_0^\infty f(t)\,dt$ exists
11	$\mathcal{L}[e^{-at}f(t)] = F(s+a)$
12	$\mathcal{L}[f(t-\alpha)1(t-\alpha)] = e^{-\alpha s}F(s) \quad \alpha \geq 0$
13	$\mathcal{L}[tf(t)] = -\frac{dF(s)}{ds}$
14	$\mathcal{L}[t^2f(t)] = \frac{d^2}{ds^2}F(s)$
15	$\mathcal{L}[t^nf(t)] = (-1)^n\frac{d^n}{ds^n}F(s) \quad n = 1, 2, 3, \ldots$
16	$\mathcal{L}\left[\frac{1}{t}f(t)\right] = \int_s^\infty F(s)\,ds$ if $\lim_{t\to 0}\frac{1}{t}f(t)$ exists
17	$\mathcal{L}\left[f\left(\frac{t}{a}\right)\right] = aF(as)$

Notes on the Laplace Transform

- **Note on step functions in Laplace**
  - Unit step function definition: $u(t) = 1, t \geq 0$

    $u(t) = 0, t < 0$
  - Used in conjunction with f(t) $\rightarrow$ f(t)u(t) because of Laplace integral limits:

    $$L\{f(t)\} = \int_0^\infty f(t)e^{-st}dt$$

- **Notes on** $f(0^+),\ f(0^-)\ \&\ f(0)$
  - The values are only different if f(t) is not continuous @ t=0
  - Example of discontinuous function: u(t)

$$f(0^-) = \lim_{t \to 0^-} u(t) = 0$$

$$f(0^+) = \lim_{t \to 0^+} u(t) = 1$$

$$f(0) = u(0) = 1$$

Using Matlab with Laplace transform

Use Matlab to find the transform of $f(t) = te^{-4t}$

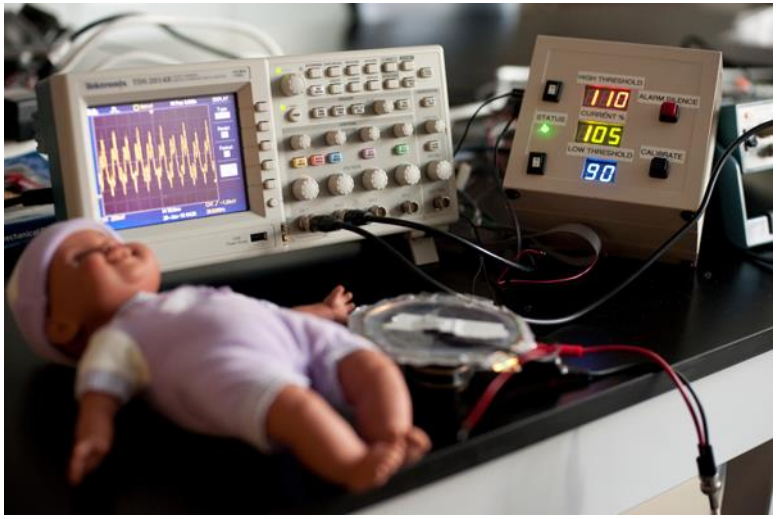
```
syms t,s
laplace(t*exp(-4*t),t,s)
ans =
        1/(s+4)^2
```

Use Matlab to find the inverse transform of $F(s) = \dfrac{s(s+6)}{(s+3)(s^2+6s+18)}$

```
syms s t
ilaplace(s*(s+6)/((s+3)*(s^2+6*s+18)))
ans =
        -exp(-3*t)+2*exp(-3*t)*cos(3*t)
```

Biomedical Engineering Design

- **Why Biomedical Engineering is unique?**
  - Biological basis – unlike engineering, it is not always exact
  - The devices interact with biological systems which exhibit large variations even within similar populations
  - The clinical environment is chaotic
  - The system is living
    - Can not be turned off!
    - Must not be damaged!



- **Before anything is used clinically it must be rigorously tested in clinical trials**

Types of Clinical Research

- **Case Reports**
  - Anecdotal

  ⇒ Problem
- **Observational**
  - Case Control/Retrospective
  - Cross Sectional
  - Prospective (Framington)

  ⇒ Risk Factor Associations
- **Drug Development**
  - (Phase 0, Phase I, & Phase II)

  ⇒ Dose and activity
- **Experimental (Clinical Trial) Phase III**

  ⇒ “Effect”

Types of Clinical Research

- The choice of design depends on the goal of the trial
- Choice also depends on the population, knowledge of the intervention
- Proper design is critical, analysis cannot rescue improper design

Purpose of Control Group

- **To allow discrimination of patient outcomes caused by experimental intervention from those caused by other factors**
  - Natural progression of disease
  - Observer/patient expectations
  - Other treatment
- **Fair comparisons**
  - Necessary to be informative
- **Significance of Control Group**
  - Inference drawn from the trial
  - Ethical acceptability of the trial
  - Degree to which bias is minimized
  - Type of subjects
  - Kind of endpoints that can be studied
  - Credibility of the results
  - Acceptability of the results by regulatory authorities
  - Other features of the trial, its conduct, and interpretation

Type of Controls

- **External**
  - Historical
  - Concurrent, not randomized
- **Internal and concurrent**
  - No treatment
  - Placebo
  - Dose-response
  - Active (Positive) control
- **Multiple**
  - Both an Active and Placebo
  - Multiple doses of test drug and of an active control

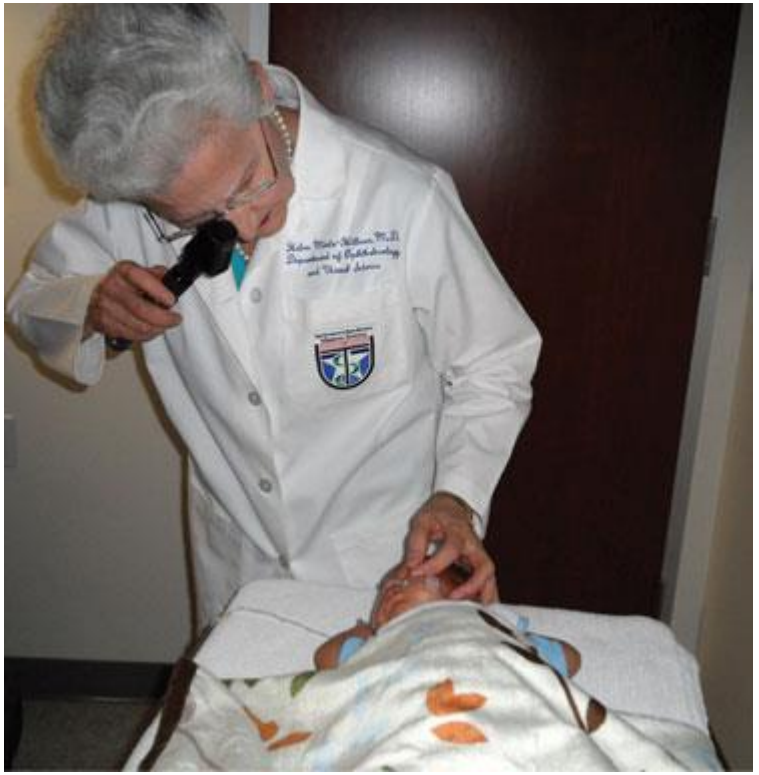
Use of Placebo Control

- **The "placebo effect" is well documented**
- **Could be**
  - No treatment + placebo
  - Standard care + placebo
- **Matched placebos are necessary so patients and investigators cannot decode the treatment**
- **E.g. Vitamin C trial for common cold**
  - Placebo was used, but was distinguishable
  - Many on placebo dropped out of study
  - Those who knew they were on vitamin C reported fewer cold symptoms and duration than those on vitamin who didn't know

Discovery-Based Trials

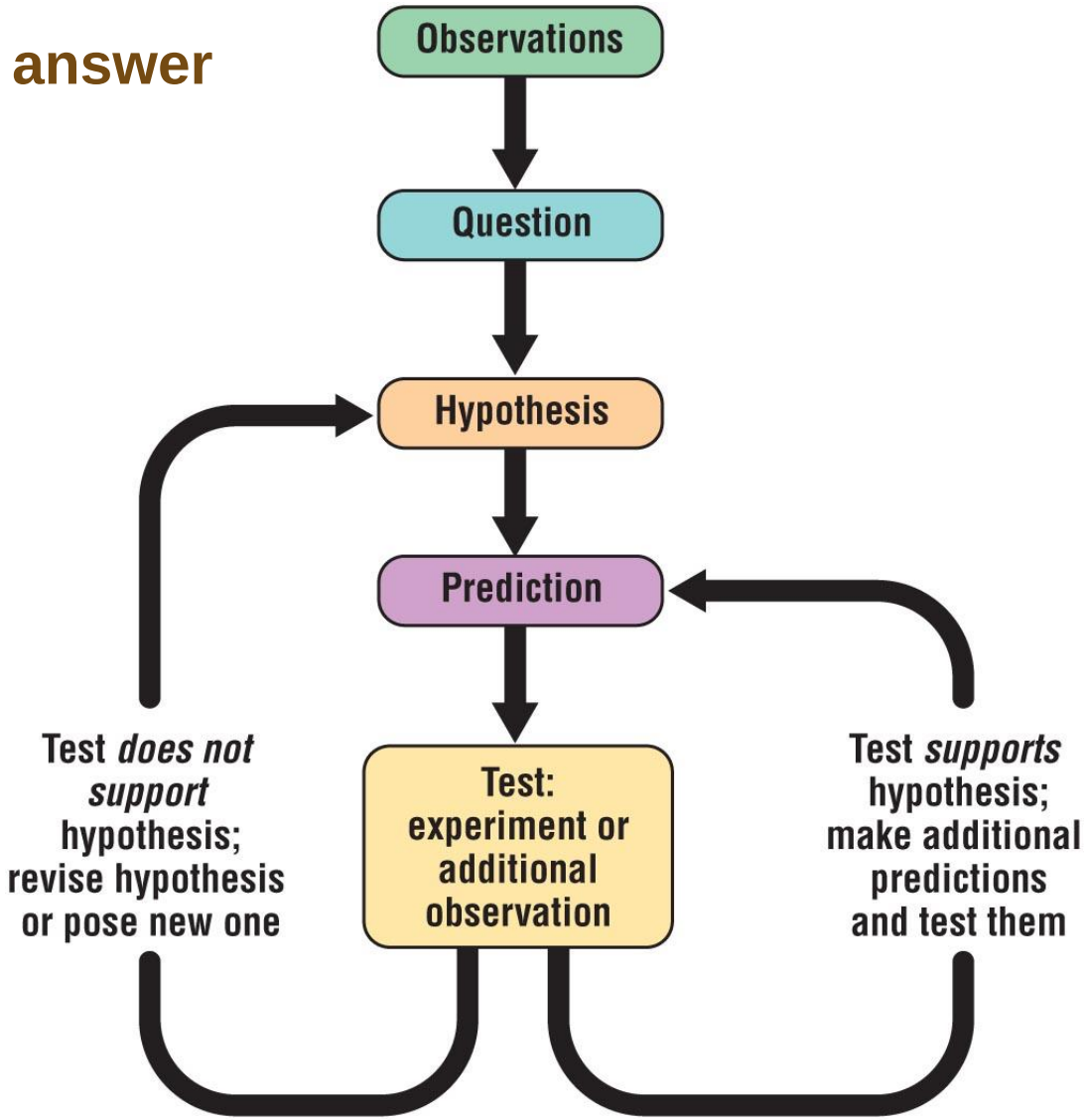
- **Is there a difference in resting heart rate between people who exercise and those who don't?**
  - Measure heart rate in people who exercise
  - Measure heart rate in people who don't exercise
  - Analyze data and from conclusions

- **Study establishes a correlation (relationship) between exercise and heart rate but not causation**



Hypothesis-Based Trials

- **Hypothesis - a tentative answer to a question**
  - an explanation on trial



Scientific Method

- **Hypothesis-based research:**
  - Form hypothesis: question to be answered
    - People who exercise regularly have lower resting heart rate
  - Treatment group: individuals subject to the test condition
    - Randomly choose a group who must exercise (experimental group)
  - Control group: similar individuals not subjected to treatment
    - Randomly choose a group that is not allowed to exercise (control)
  - Dependent variable: outcome you are measuring
    - Heart rate
  - Unbiased: double-blind (placebo) study
  - Random groups
  - Analyze data and form conclusions
- **"Controlled experiment" establishes causation**

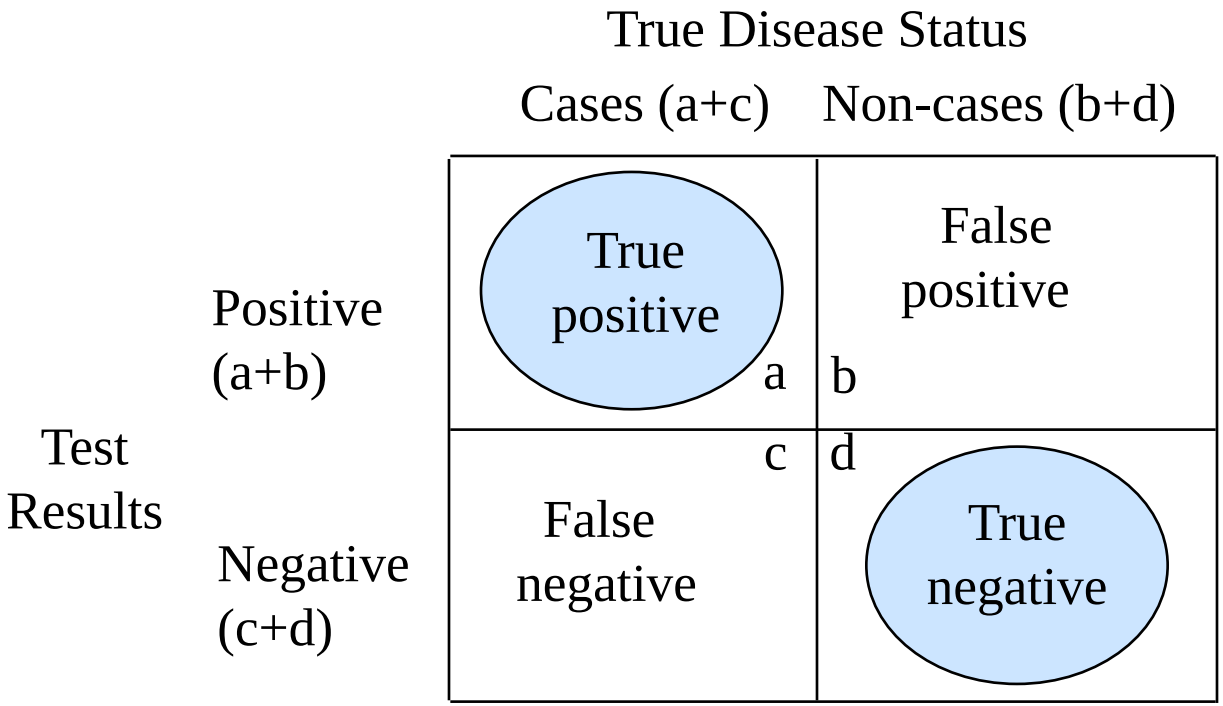
Scientific Method to Develop New Drugs

- **First test effectiveness & toxicity of a new drug**
  - first in vitro (tissue culture) then in vivo (animal models)
- **Then Clinical trials performed:**
  - Phase I Trials: Toxicity and metabolism tested in healthy human volunteers (no toxic effects observed)
  - Phase II Trials: Effectiveness and toxicity tested in target population (effective with minimal toxicity)
  - Phase III Trials: Widespread test of drug in diverse population (gender, ethnicity, other health problems)
  - Phase IV Trials: Drug is tested for other potential uses (sent to FDA for approval)

Quality of Results

- **Reliability – get same result each time**
  - Repeatability– get same result
    - Each time
    - From each instrument
    - From each rater
  - If don't know correct result, then can examine reliability only.
  - Reliability does not ensure validity, but lack of reliability constrains validity
- **Validity – get the correct result**
  - Sensitivity – correctly classify cases
    - Probability (proportion) of correct classification of cases : Cases found / all cases
  - Specificity – correctly classify non-cases
    - Probability (proportion) of correct classification of noncases: Noncases identified / all noncases

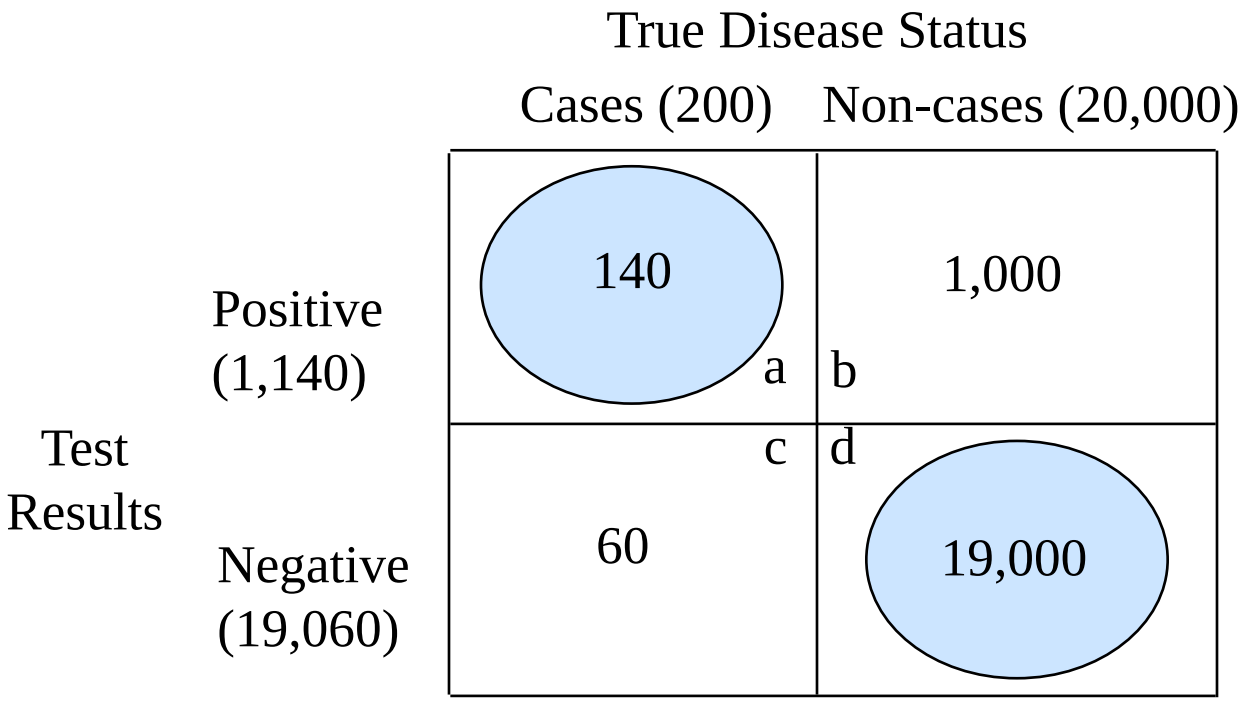
Quality of Results



Sensitivity = $\dfrac{\text{True positives}}{\text{All cases}} = \dfrac{a}{a + c}$

Specificity = $\dfrac{\text{True negatives}}{\text{All non-cases}} = \dfrac{d}{b + d}$

Quality of Results



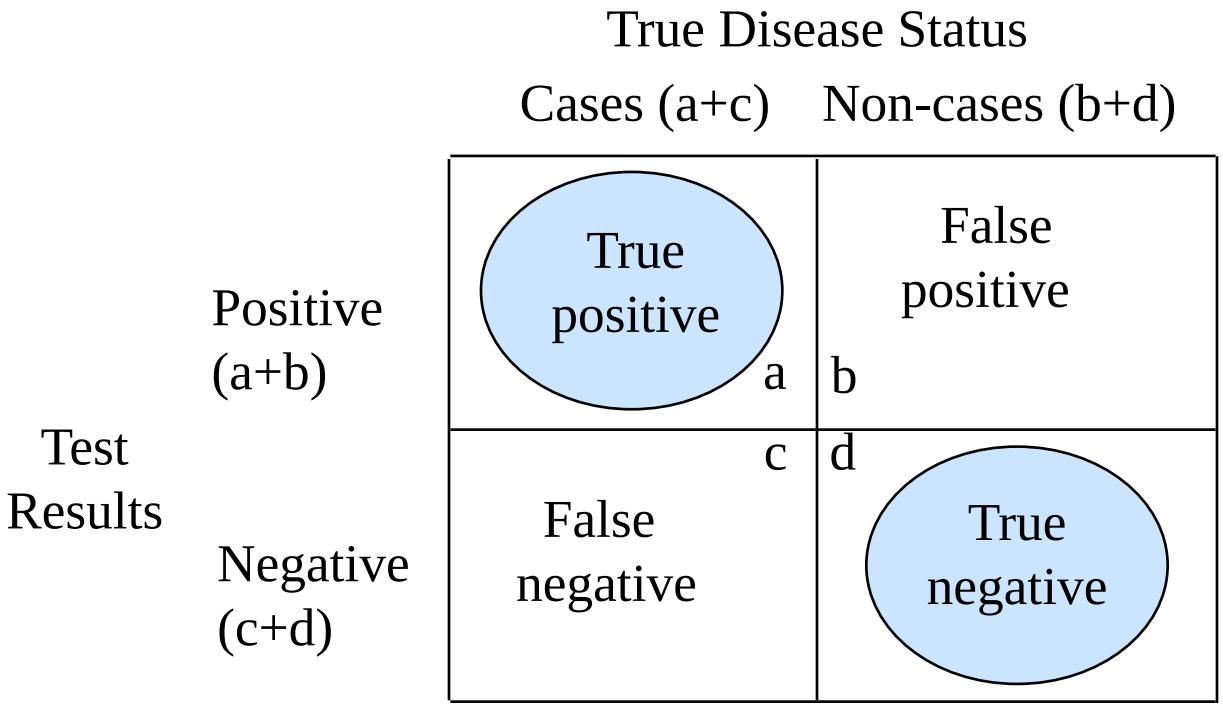
Sensitivity = $\dfrac{\text{True positives}}{\text{All cases}} = \dfrac{140}{200} = 70\%$

Specificity = $\dfrac{\text{True negatives}}{\text{All non-cases}} = \dfrac{19{,}000}{20{,}000} = 95\%$

Interpretation of the Results

- **Probability (proportion) of those tested who are correctly classified**
  - Positive Predictive Value: Cases identified / all positive tests
  - Negative Predictive Value: Non-cases identified / all negative tests

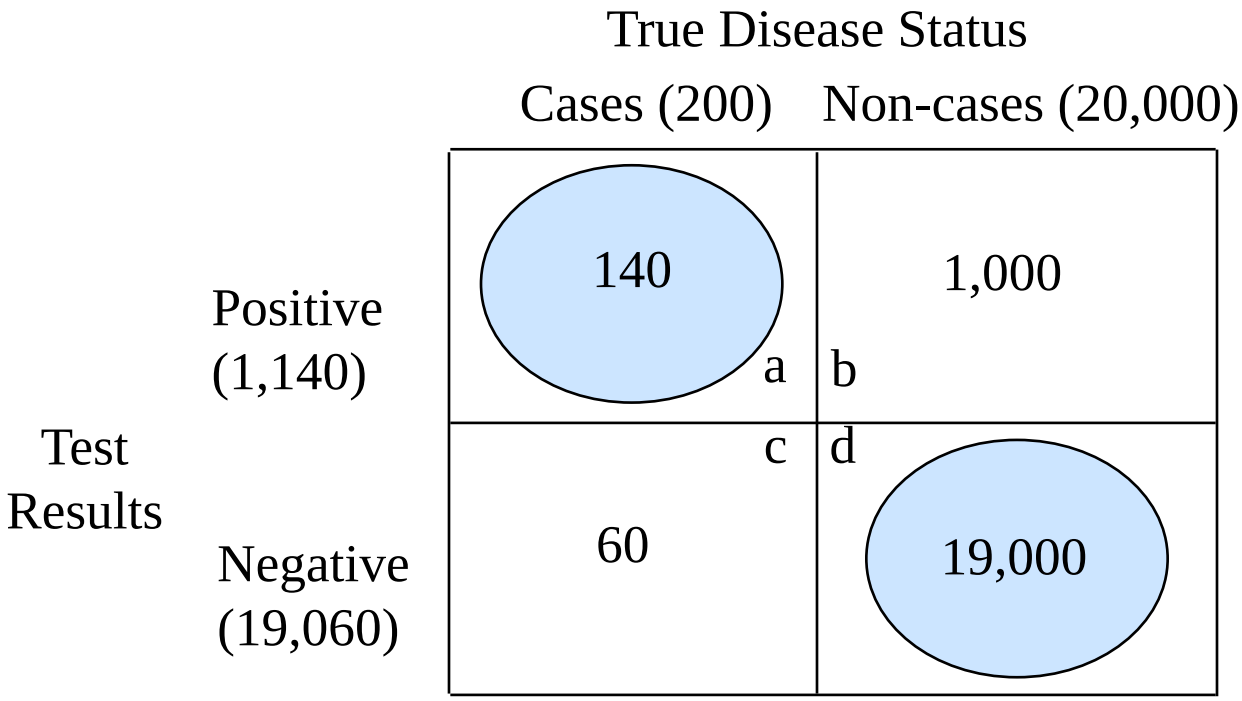
Interpretation of the Results



$$\textbf{PPV} = \frac{\text{True positives}}{\text{All positives}} = \frac{a}{a + b}$$

$$\textbf{NPV} = \frac{\text{True negatives}}{\text{All negatives}} = \frac{d}{c + d}$$

Interpretation of the Results



$$\textbf{PPV} = \frac{\text{True positives}}{\text{All positives}} = \frac{140}{1{,}140} = 12.3\%$$

$$\textbf{NPV} = \frac{\text{True negatives}}{\text{All negatives}} = \frac{19{,}000}{19{,}060} = 99.7\%$$

Interpretation of the Results

- **Example: Mammography screening of unselected women**

	Disease status		
	Cancer	No cancer	Total
Positive	132	985	1,117
Negative	47	62,295	62,342
Total	179	63,280	63,459

Prevalence = 0.3% (179 / 63,459)

- Se = 73.7% Sp = 98.4% PV+ = 11.8% PV– = 99.9%

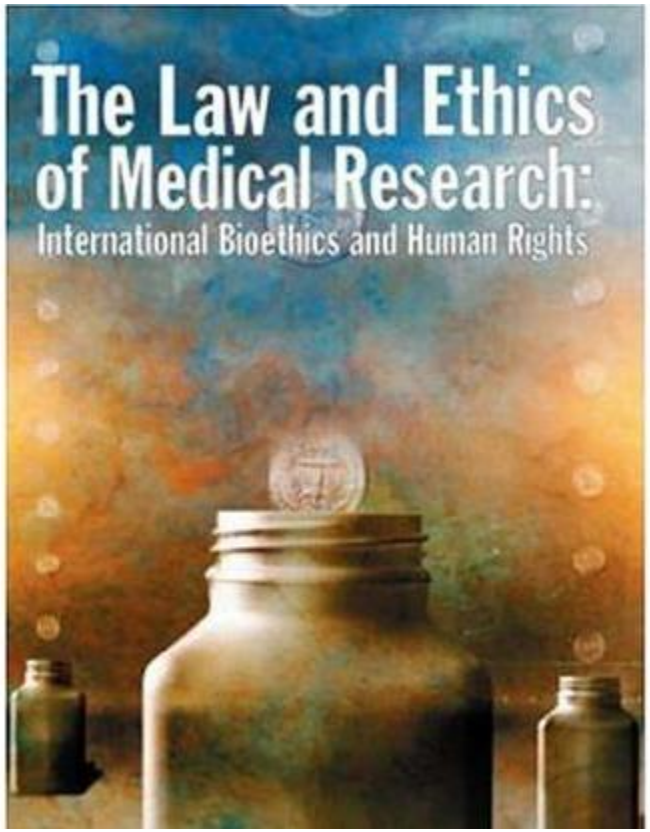
Source: Shapiro S et al., Periodic Screening for Breast Cancer

Moral Issues in Clinical Research

- **The goal of clinical research is generation of useful knowledge about human health and illness**
  - Benefit to participants is not the purpose of research (although it does occur)
  - People are the means to developing useful knowledge; and are thus at risk of exploitation
- **Ethical requirements in clinical research aim to:**
  - minimize the possibility of exploitation;
  - ensure that the rights and welfare of subjects are respected while they contribute to the generation of knowledge.

Ethical Framework: 7 Principles

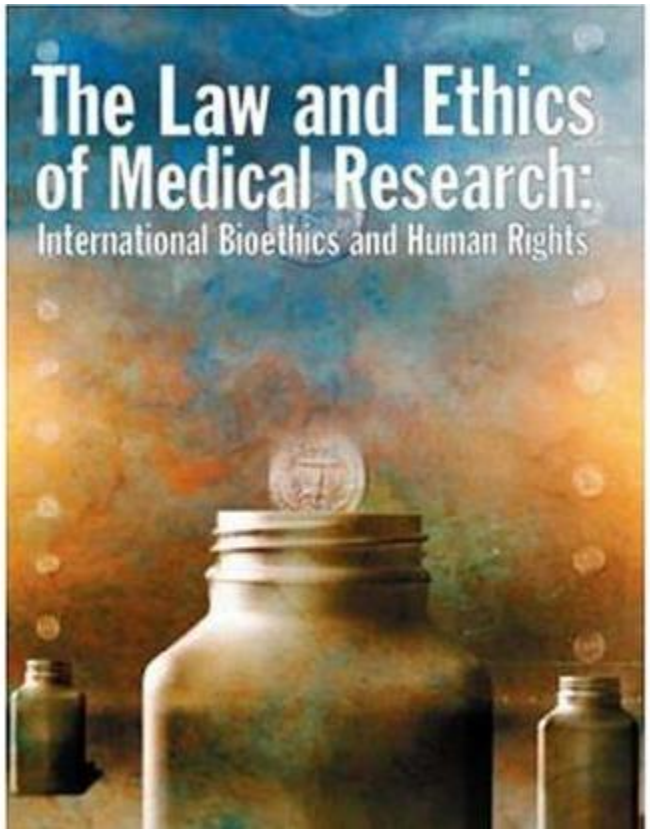
- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit evaluation
- Independent review
- Informed consent
- Respect for enrolled subjects



Emanuel E, Wendler D, Grady C. What makes clinical research ethical? Journal of the American Medical Association 2000; 283(20):2701-11

Ethical Principles

- **Beneficence vs. Non-Maleficence**
  - Beneficence: promotion of well being
    - maximize benefit
  - Non-maleficence - do no harm (commission or omission)
    - minimize harm
- **Respect for persons**
  - Privacy, confidentiality
  - Autonomy - make own decisions
  - Informed consent
- **Justice - fairness**
  - Risks and benefits
  - What is justifiable



Ethical Review

- **Ethics committee (EC)**
  - Community based
  - Membership
    - non-scientist, community participant
  - Safeguard - dignity rights, safety and well being
    - review & approval
      - beneficence, autonomy, justice, non-maleficence
- **Institutional review board (IRB)**
  - Institutional
  - Safeguard - dignity rights, safety and well being
    - review & approval
      - beneficence, autonomy, justice, non-maleficence
      - scientifically sound research?