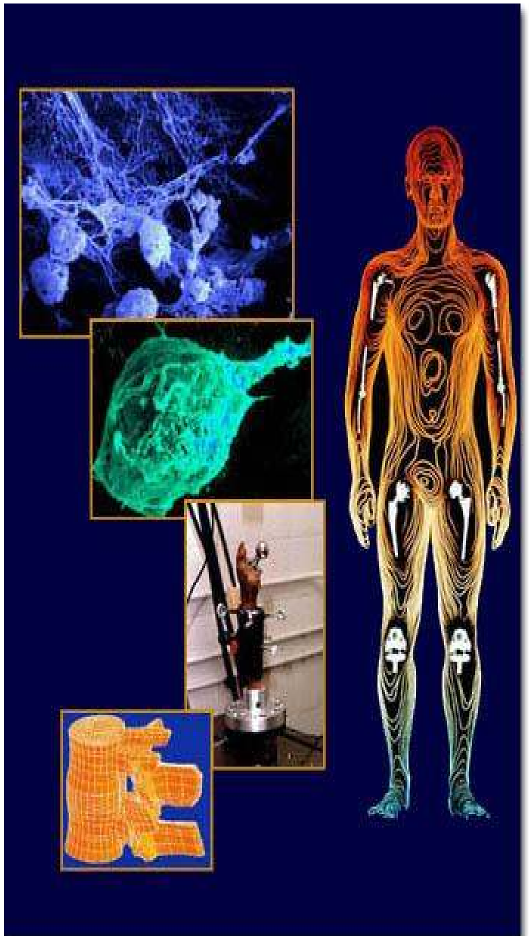
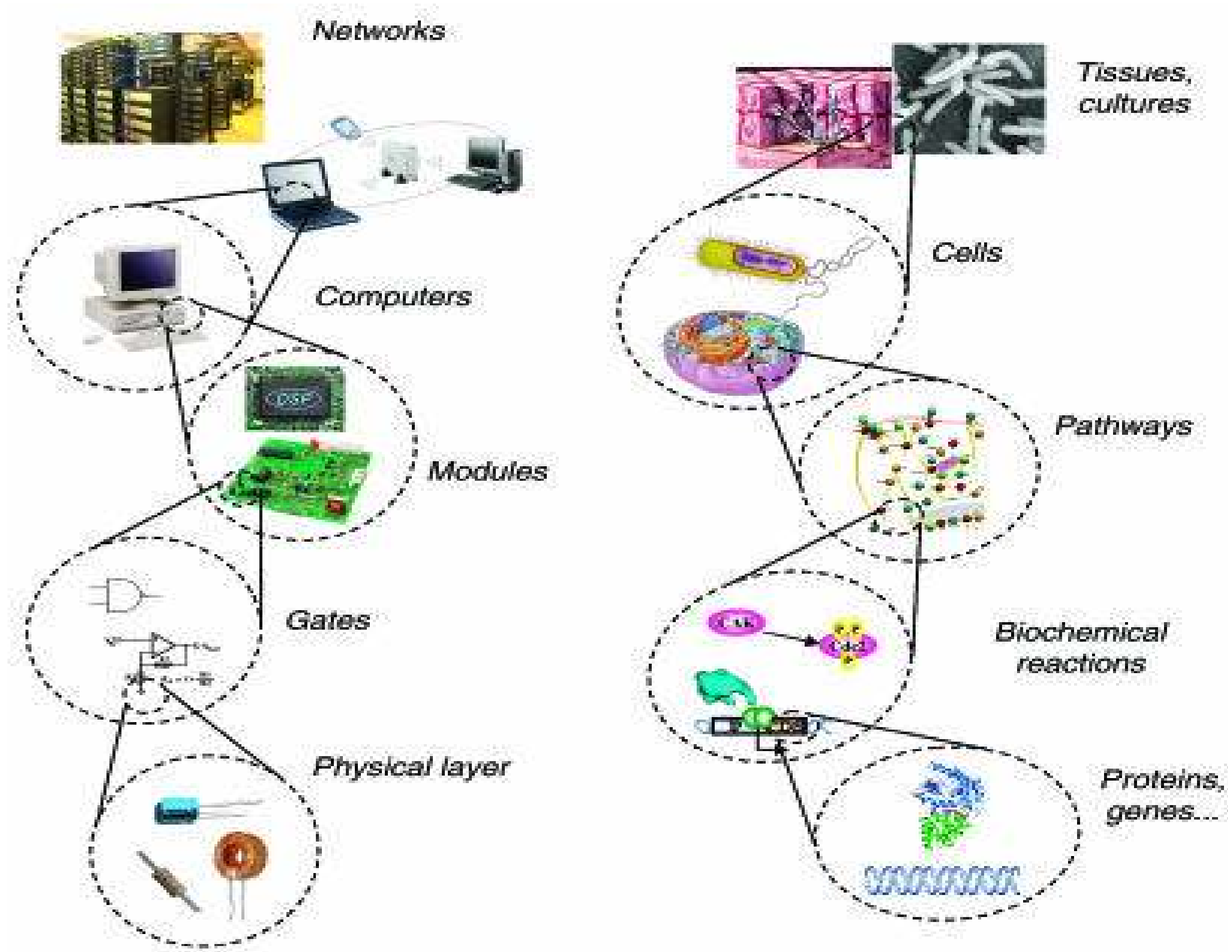
Engineering Analysis of Living Systems





Source: http://openwetware.org/wiki/Reviews/Synthetic_biology

Living systems - Analogy with engineering

Control systems are known from engineering.

Medicine uses terms borrowed from engineering

Set point

Gain

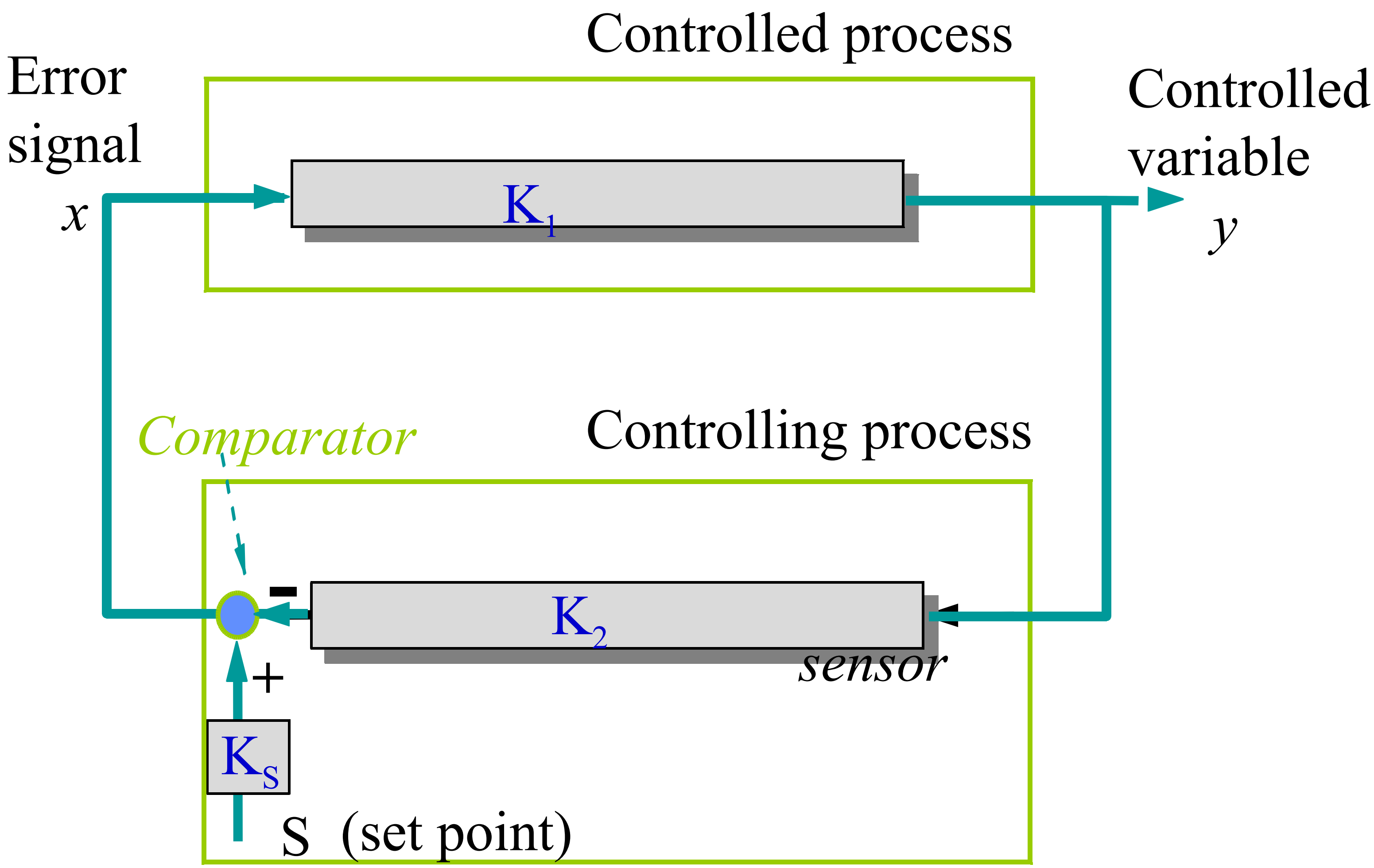
Feedback

- Negative
- Positive

Control systems

- Components of an automatic control system
- Variable is the characteristic of the internal environment that is controlled by this mechanism (internal temp in this example)
- Sensor (receptor) detects changes in variable and feeds that information back to the integrator (control center) (thermometer in this example)
- Integrator (control center) integrates (puts together) data from sensor and stored "setpoint" data (thermostat in this example)
- Setpoint is the "ideal" or "normal" value of the variable that is previously "set" or "stored" in memory
- Effector is the mechanism (furnace in this example) that has an "effect" on the variable (internal temperature in this example)

Black box schematic for proportional control loop

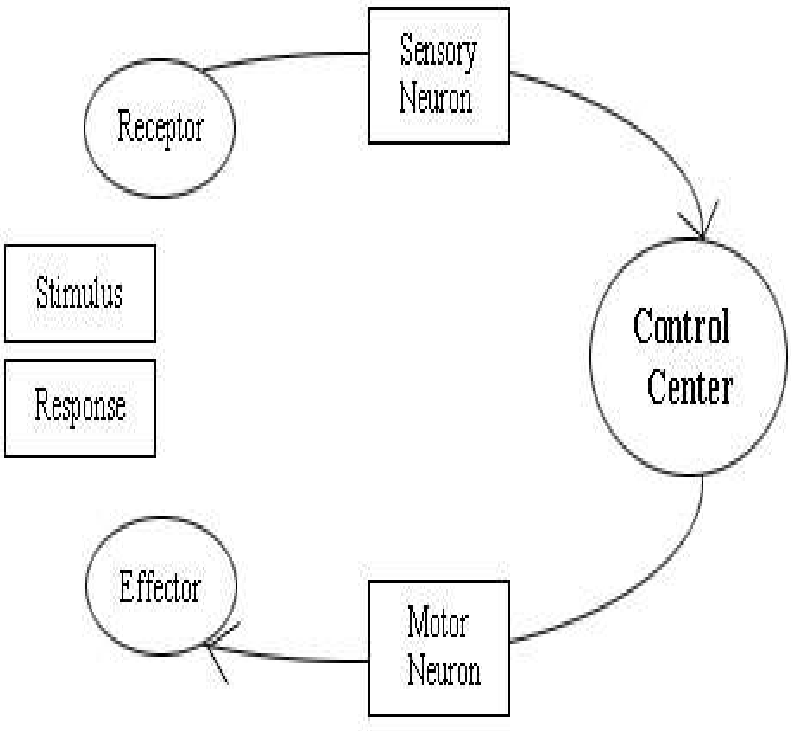


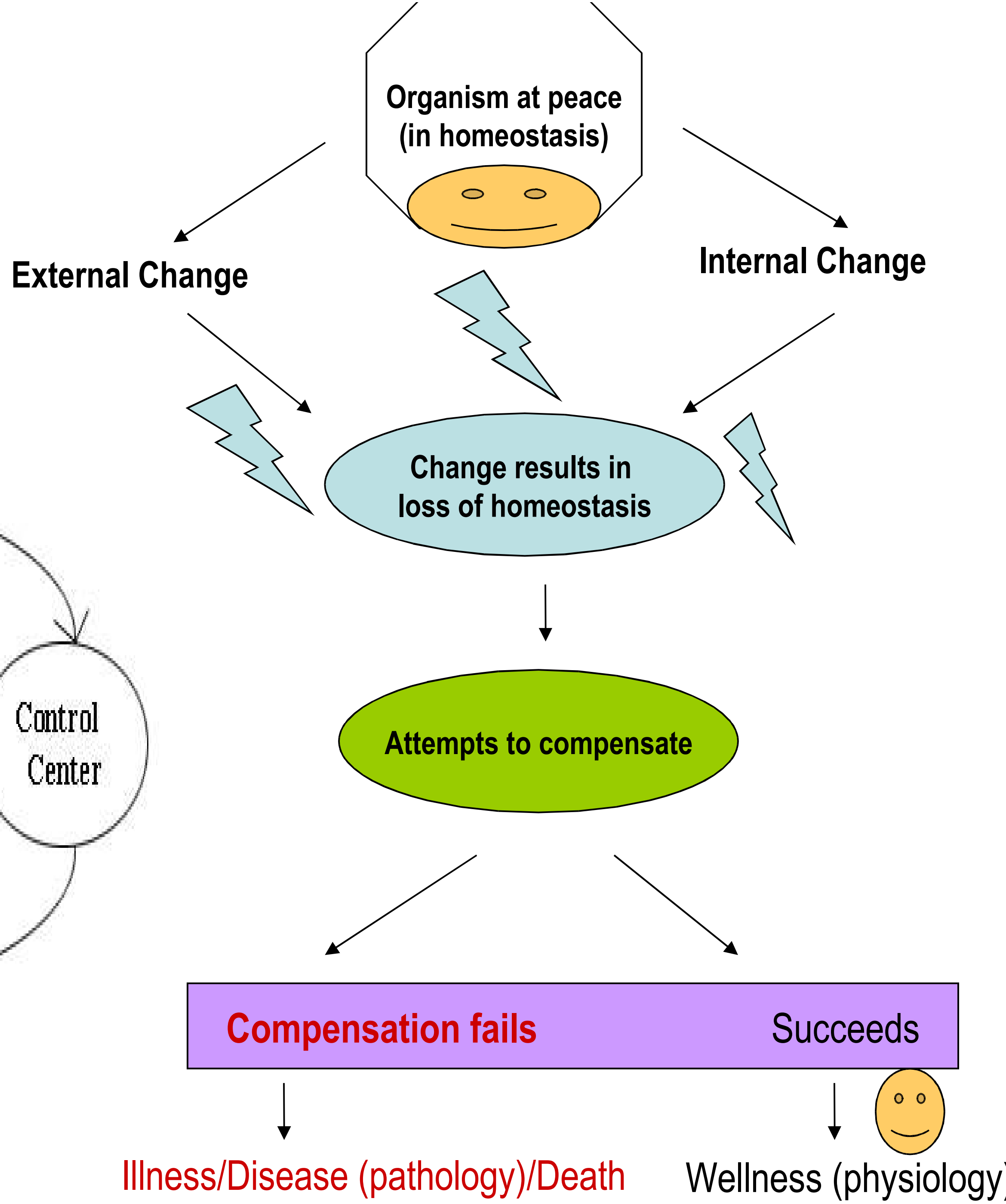
Black box Concept

* y = controlled variable
* x = output signal of the comparator and input of the controlled process
* S = set point value with which the output signal is compared
* x = error signal, indicating the difference between set point and output value.
* Sensor and comparator form the controlling process

- *y = K1 ·x eq. 1*
- *x = (Ks ·S -K2 ·y) eq. 2*
- *Ks = K2 (equal in number and dimension but different in realization)*
- $$y = \frac{K_1 * K_2}{1 + K_1 * K_{2\,1}} * S$$ *eq. 3*

Homeostasis





Feedback types

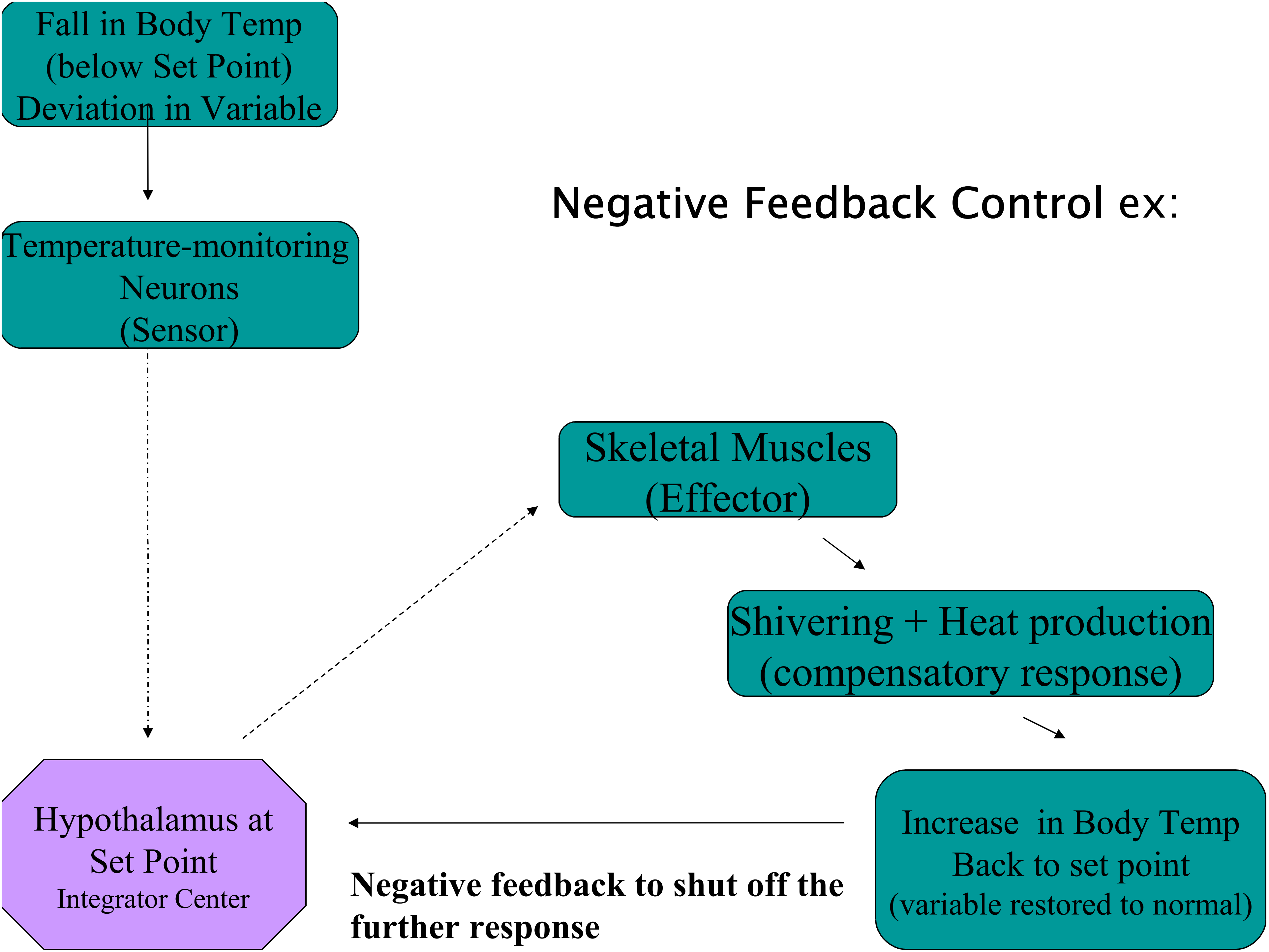
- **Negative feedback** – opposes the change.
  compares the 'change' it to the 'set point' and responds '*opposite to the change*' (most physiological values are maintained 'normal' by this process)

- **Positive feedback** – the '*change is amplified'* further
  e.g. blood clot cascade, childbirth (parturition)
  (happens when a process has to be accomplished)

- both feedbacks require continuous 'sensing'/sampling of the variable (such as pH, temperature, osmolarity, O2, strectch levels etc)

Negative feedback

- Occurs when feedback (from sensor to integrator) results in a reversal of the direction of change
- In example, thermostat's response causes temperature decrease to reverse and become a temperature increase
- Negative feedback tends to stabilize a system, correcting deviations from the setpoint
- Human example: shivering in response to cooling of body during cold weather


Negative Feedback Control ex:
Fall in Body Temp (below Set Point) Deviation in Variable
Temperature-monitoring Neurons (Sensor)
Hypothalamus at Set Point
Integrator Center
Skeletal Muscles (Effector)
Shivering + Heat production (compensatory response)
Increase in Body Temp Back to set point (variable restored to normal)
Negative feedback to shut off the further response

Positive feedback

- Occurs when feedback (from sensor to integrator) results in an amplification of the change (same direction as deviation from setpoint)
- In example, positive feedback would occur if the thermostat's response to a dropping temperature was to switch off the furnace or to switch on the air conditioner (chiller)
- Another example: audio "feedback" occurs when amplified sound is picked up by microphone and then amplified again then picked up and amplified again, and again, and again --each time getting louder
- Can be stopped only if "feedback loop" is broken

Homeostasis - a key concept in living systems

- **Maintenance of dynamic constancy in the internal environment despite changes in external environment.**

- Body has specific mechanisms that regulate various physiological processes, within certain narrow ranges.

- What will happen if there were no homeostasis/ why is homeostasis important?

Body temperature (heat denature protein, cold destroys membranes)
Water balance (water would collect in our cells, or we would shrink up)
Ion balance (Na+, K+ pumps wouldn't work, nervous system won't work, heart will stop)
Blood glucose (too low faint, brain ceases to work, too high long term leads to vessel damage)
O_2/CO_2 levels (no O_2 -cells dies, too much CO_2 toxic, leads to acidosis, change in pH - death)

- Effects of temperature, pH/ion concn and toxic substances on enzyme activity and cell function.

(denature protein, cells become leaky, enzymes cannot work properly, leads to eventual cell death)

Important Homeostatic Factors – the Big 6

- **Concentration of nutrients and oxygen -** a certain level of oxygen, glucose, proteins, etc.
- **Concentration of salts and electrolytes -** a certain level of ions such as: K+ or Na+
- **Concentration of wastes -** monitored to ensure levels do not exceed a certain levels. Particularly CO2, Urea, Bile
- **Acid/Base Balance -** A very delicate equilibrium between the levels of acids and bases
- **Temperature -** The 'Core'internal temperature must remain at a fairly constant level. ~98.6 F
- **Pressure and Volume -** Pressure of fluids/gases within the body need to be at equilibrium.
  Ex: balancing pressure between the inside and outside of a cell
  outside/inside of the lungs
  within the circulatory system

Osmoregulation

Osmoregulation

- Osmoregulation is the process of keeping a constant amount of water and salts in the blood.

When the hypothalamus senses too little water in the blood - for example if you have been sweating a lot during exercise - it sends messages to the pituitary gland to release ADH. ADH stops the removal of water from the blood in the kidneys, so the blood water level returns to normal.

When the hypothalamus detects too much water in the blood it stops signalling the pituitary gland to make ADH, so more water is removed from the blood in the kidneys and excreted, and once again the blood water level returns to normal.

Thermoregulation

- The process of keeping the body at a constant temperature.

- Human enzymes work best at 37°C (body temperature). The temperature of the body is monitored by a part of the brain called the hypothalamus. If you are too hot or too cold the hypothalamus sends nerve impulses to the skin, which has three ways to either increase or decrease heat loss from the body's surface.

- Hairs on the skin trap more warmth if they are standing up, and less if they are lying flat. Tiny muscles in the skin can quickly pull the hairs upright to reduce heat loss, or lay them down flat to increase heat loss.

- Glands under the skin secrete sweat onto the surface of the skin in order to increase heat loss by evaporation if the body is too hot. Sweat secretion stops when body temperature returns to normal.

- Blood vessels supplying blood to the skin can swell or dilate (called vasodilation) - so that more heat is carried by the blood to the skin where it can be lost to the air; or shrink down again (called vasoconstriction) - to reduce heat loss through the skin once the body temperature has returned to normal.

Glucoregulation

- **Glucoregulation is the means by which a constant blood sugar level** is maintained. A vital part is played by the hormone insulin, which reduces the level of glucose in the blood.

- When you have eaten carbohydrates (potatoes, bread, rice or pasta) your digestive system releases large quantities of glucose from the food. This glucose is absorbed into the blood. High levels of glucose in the blood causes problems, so the sugar level must be absorbed into the body's cells, where it is needed for respiration, as soon as possible. This will result in blood sugar levels quickly returning to normal.

- When the blood sugar level rises, the **islets of Langerhans** in the pancreas release insulin into the blood. Insulin triggers uptake of sugar into the tissues and muscles, and triggers the liver to turn **glucose** into **glycogen**, which is stored. This brings the blood sugar level down. When blood sugar levels are too low, the pancreas stops producing insulin - so less glucose is taken up by tissues and liver, and blood sugar levels rise again.

Diffusion Dynamics

↑ Concentration gradient of substance dC

↑ Permeability of membrane to substance (P)

↑ Surface area of membrane (A)

↑ Mol wt of substance MW

↑ Distance (thickness) (dX) ↓

$Q = dC\ A\ D\ /\ dX$

Net rate of diffusion Q

Examples

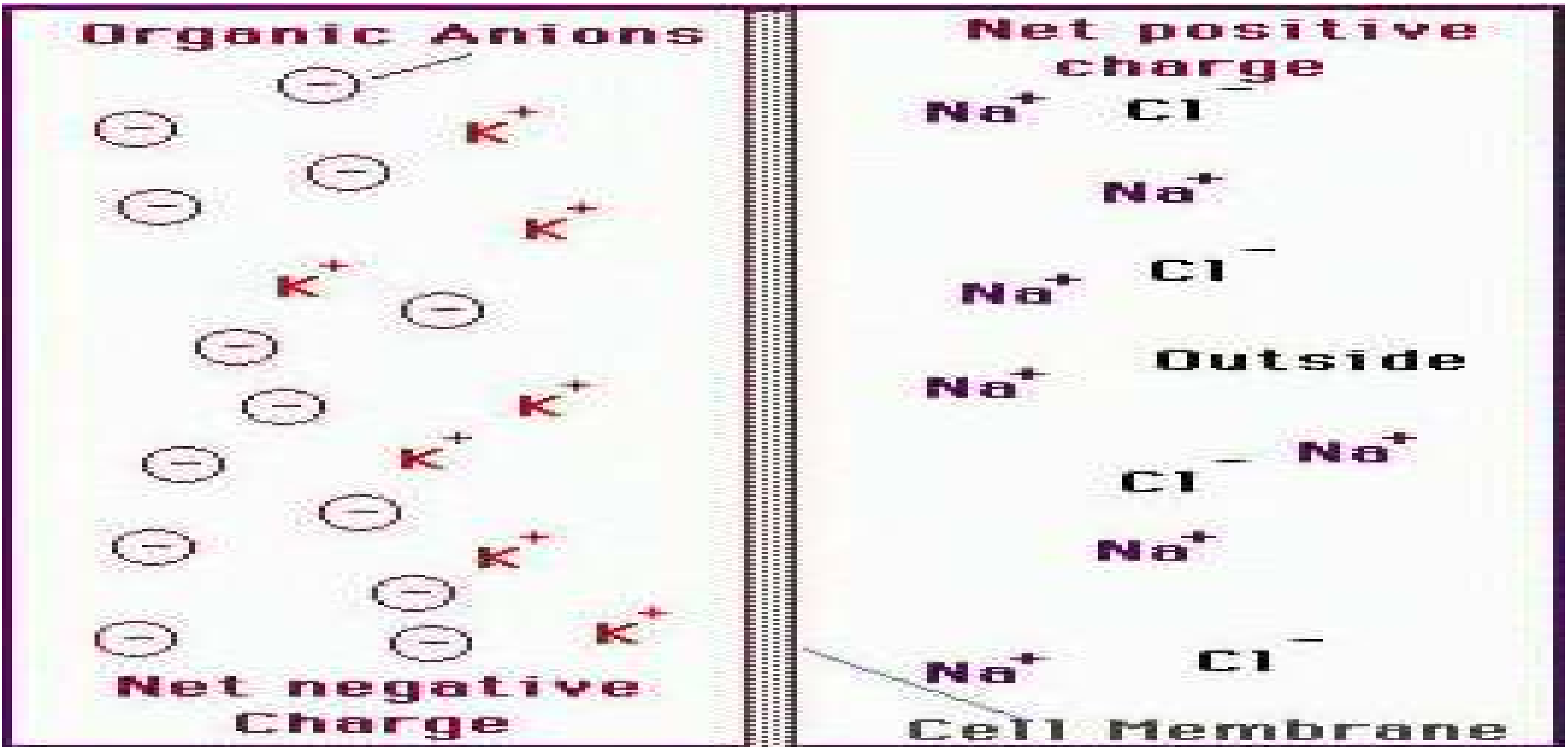
↑ The exchange of oxygen and carbon dioxide between the blood and the air in the lungs.

The movement of substances across kidney tubules.

The diffusion of sodium and potassium ions through open channels in the plasma membrane.

Table 3-1, p. 52

Membrane Resting Potential



- The membrane potential results from a separation of positive and negative charges across the cell membrane.

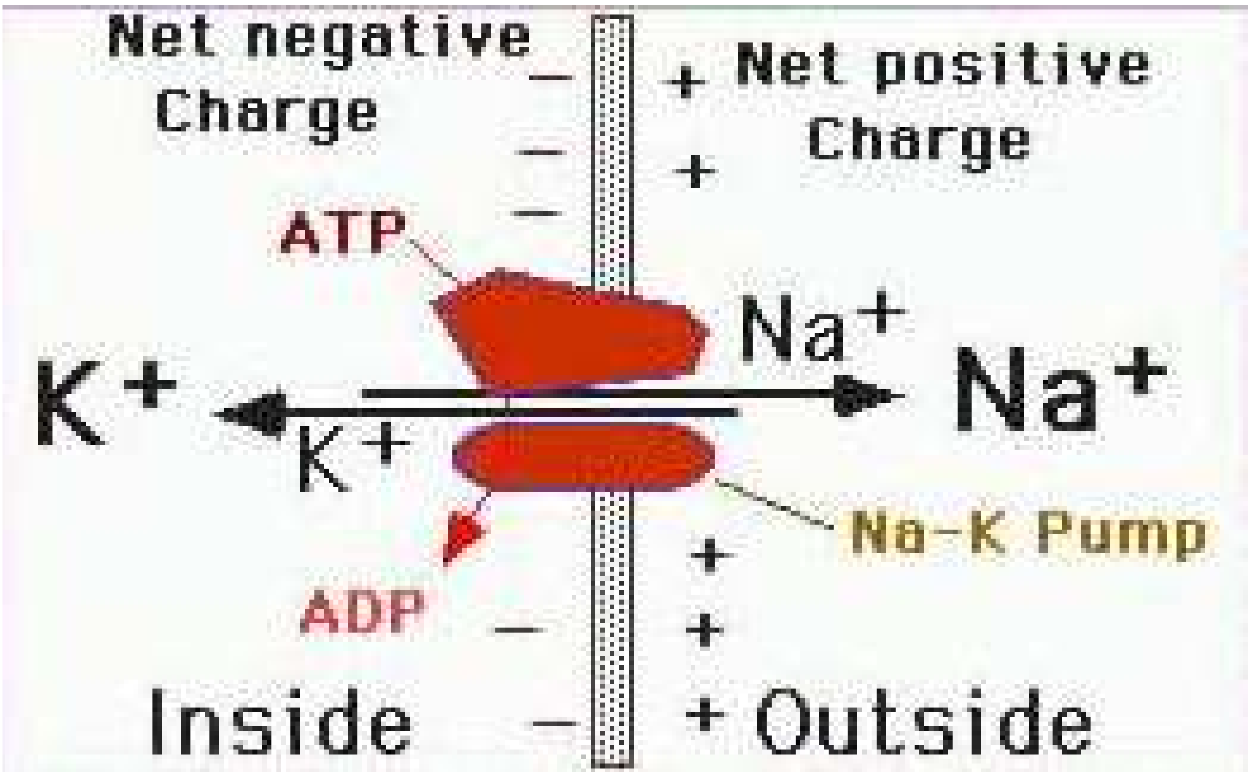
Membrane Potential

- Membrane Potential (MP)- -70 mV is due to separation of opposite charges across cell membrane (called so because it has the "potential" to do work)

- MP is due to differences in concentration and permeability of key ions (Na, K & intracellular anionic proteins) – At rest, there is slight excess of +ve charges outside and a slight excess of –ve charges on the inside

- Sodium is in greater concentration in the ECF and potassium is higher concentration in the ICF and are maintained so by the Sodium-Potassium pump at an expense of energy.

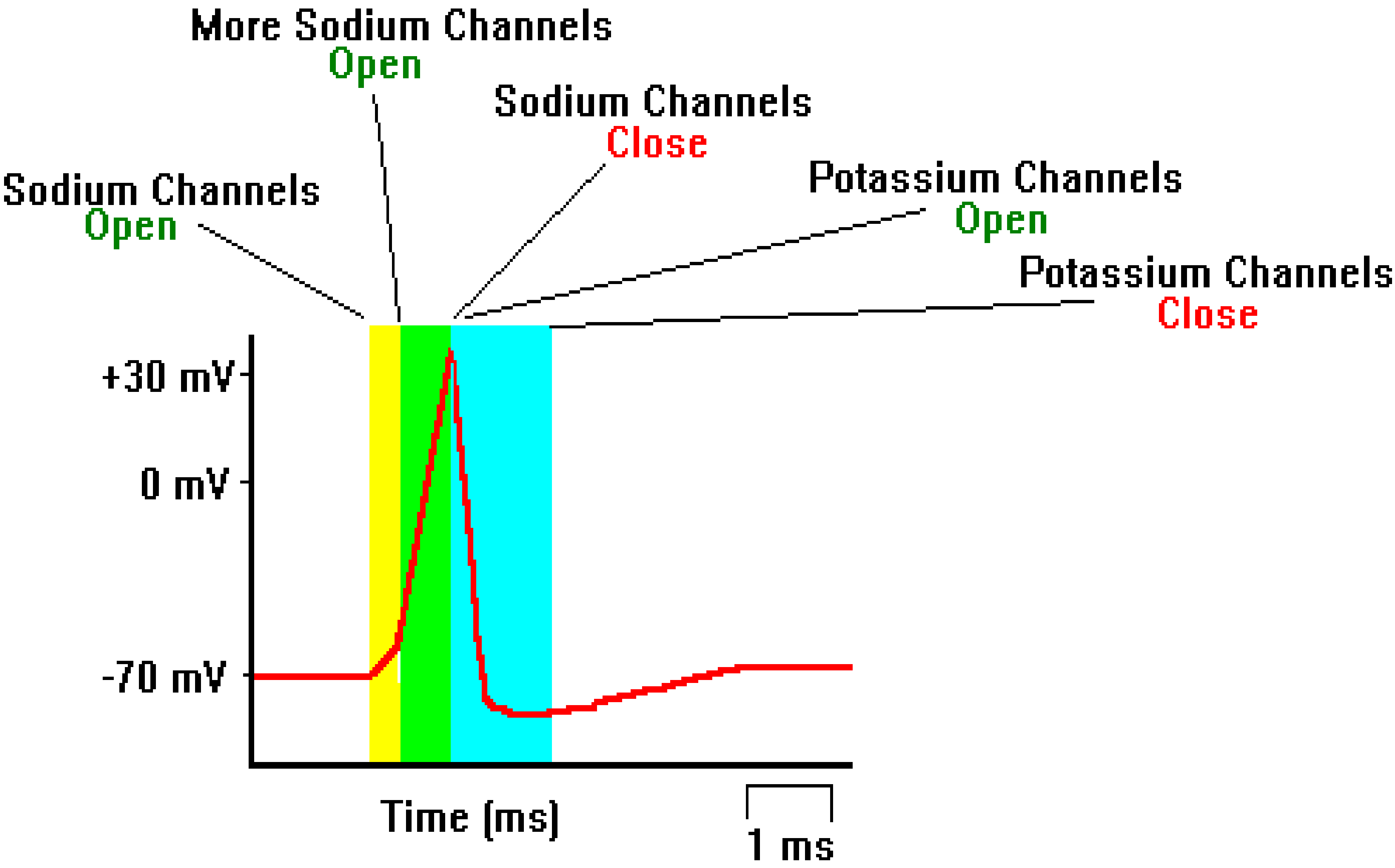
The Sodium–Potassium Pump



extrudes Na out of the cell while taking in K

- Dissipation of ionic gradients is ultimately prevented by Na–K pumps

Events during AP

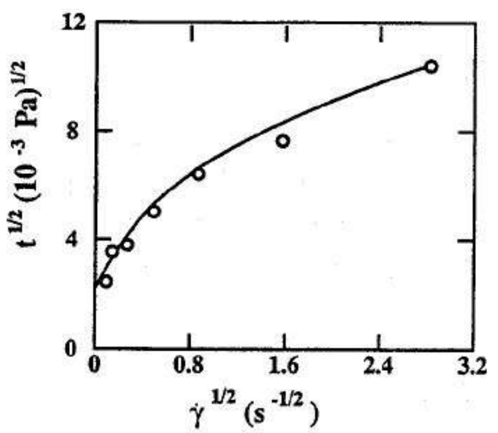


Terms

- **Depolarization** – when membrane is less polarized than resting potential (RP) of -70mV (such as -50mV)
- **Repolarization** is returning back to RP
- **Hyperpolarization** is when it is 'more polarized' -vity increases (such as -90mV)
- **Signal transduction**: the process by which incoming signals are conveyed to the target cells' interior for execution
- **Synapse** is the junction between two neurons & the space between is called the *synaptic cleft*
- The axon terminal of the neuron is called *synaptic knob* which contains vesicles which stores a neurotransmitter

Blood is a non-Newtonian fluid

- The blood has yield stress

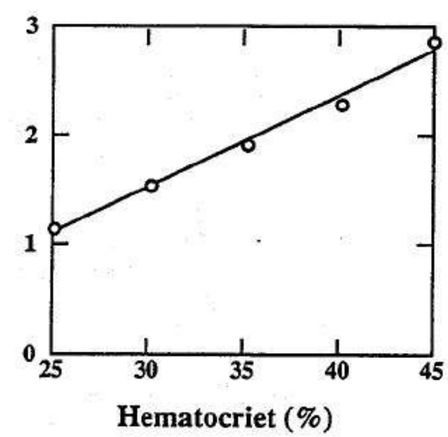


- Low shear rate=> Rouleaux formations and sedimentation=>high apparent viscosity
- High shear rate=> the stacks break down=> newtonian behaviour

- Yield stress depends on H and also on the fibrinogen concentration in plasma

Empirical relation:

$$\sqrt{\tau_0} = \frac{(H-10)*(C_F+0.5)}{100}$$



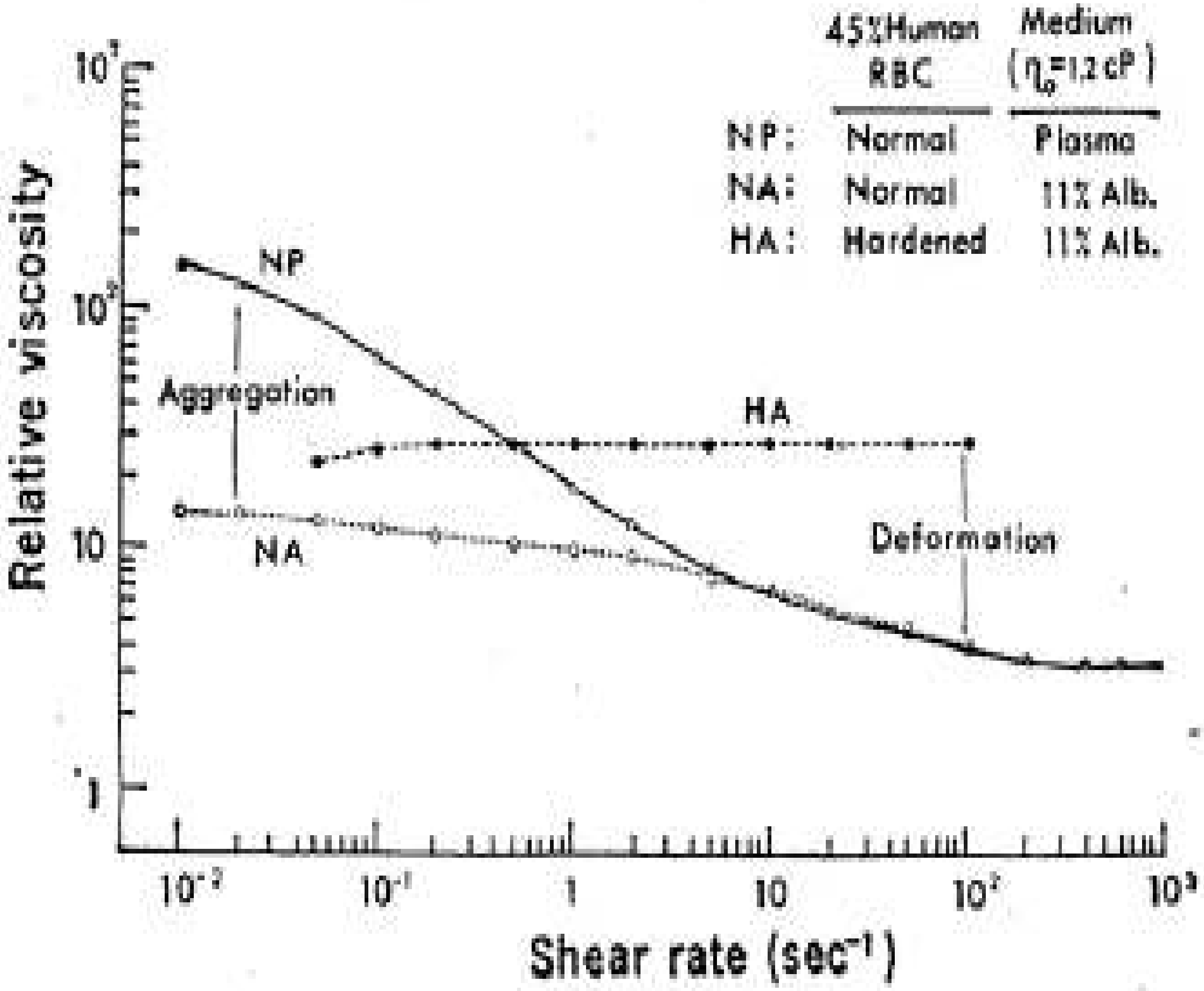
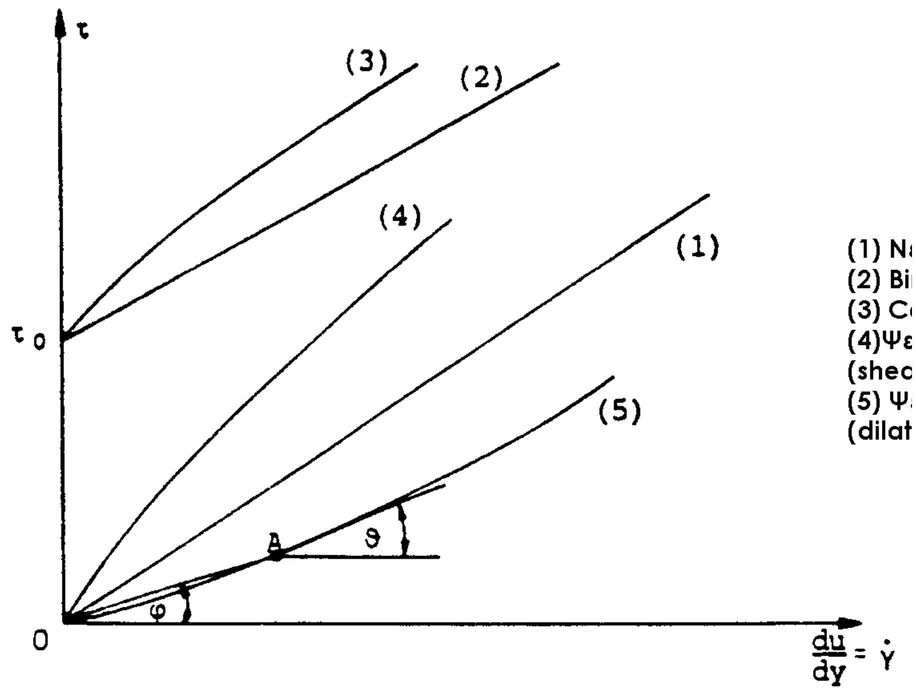


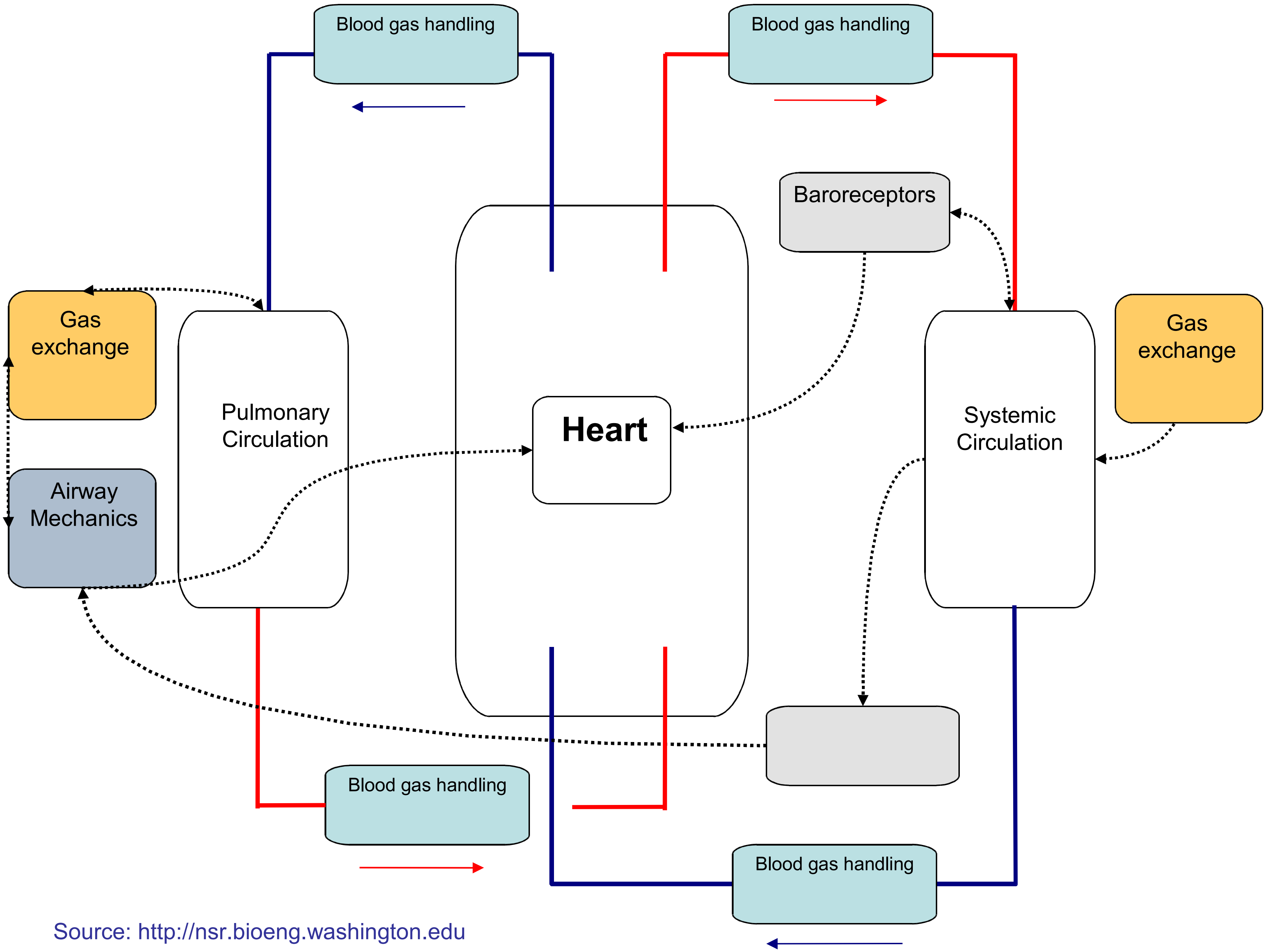
Figure 1. Relative viscosity of RBC suspensions as a function of shear rate in simple shear flow. From S. Chien, *Shear dependence of effective cell volume as a determinant of blood viscosity*, Science, 168, 977 (1970)

Newtonian, Non-Newtonian behaviour

Rheological curves = shear stress-shear rate curves

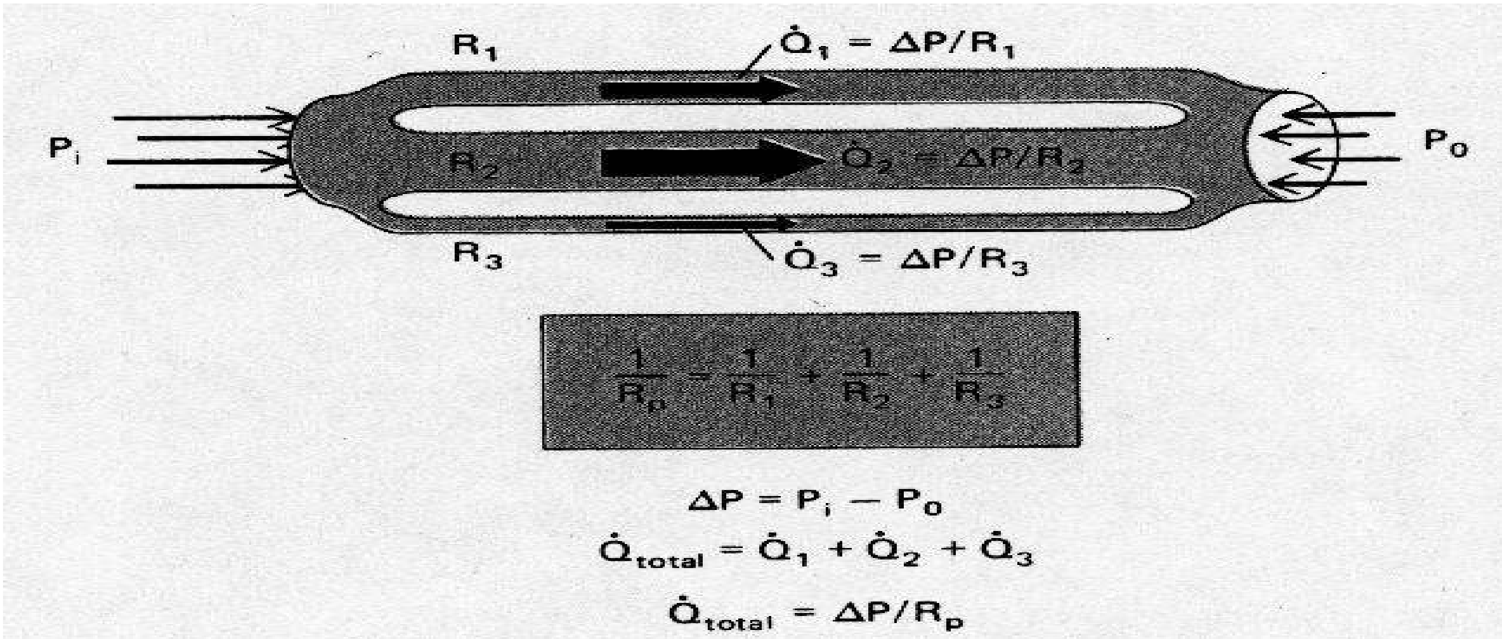


- **Bingham fluids (2)**: $\tau = \tau_0 + k\dot{\gamma}$
- **Casson fluids (3)**: $\sqrt{\tau} = \sqrt{\tau_0} + k\sqrt{\dot{\gamma}}$
- **Pseudoplastics (4, 5)**: $\tau = k\dot{\gamma}^n$

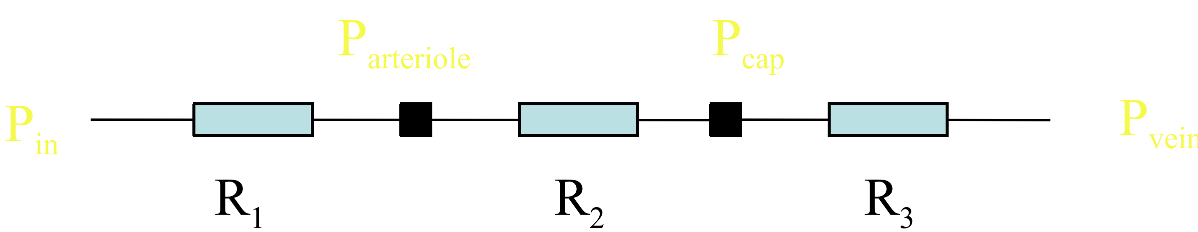


Source: http://nsr.bioeng.washington.edu

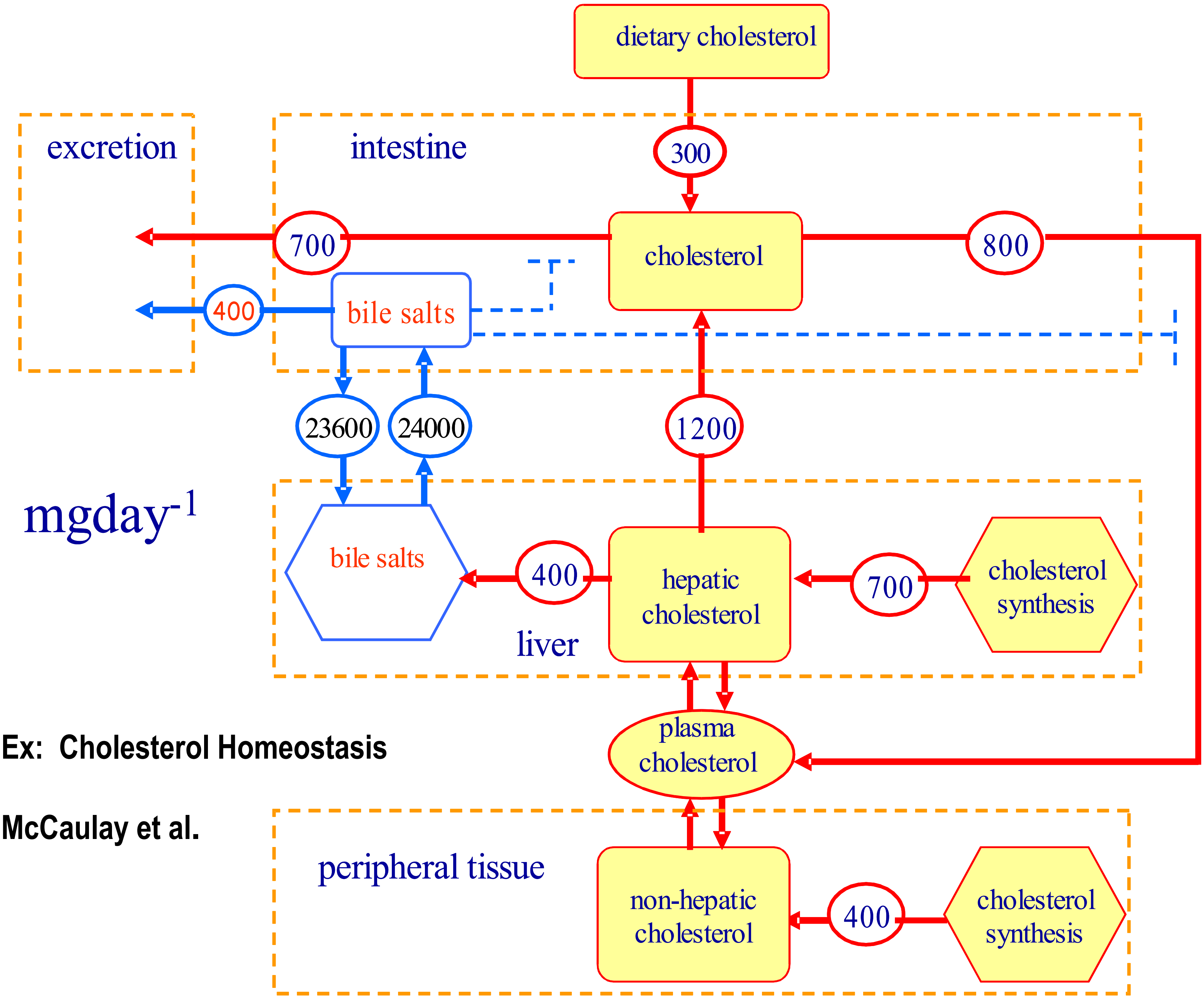
Vascular Resistances in parallel



Vascular Resistances in Series



(From M&H Fig 7-3)



Ex: Cholesterol Homeostasis

McCaulay et al.

Lipid Metabolism and longevity

- A genetic study examined the lipoprotein phenotype in individuals with exceptional longevity.
- CVD is the primary cause of mortality. Elevated plasma cholesterol has consistently stood out as a risk factor for CVD.
- In response, the pharmaceutical industry has produced a wide range of agents for lowering plasma cholesterol.
- Mathematical modelling can help Monitor changes in the state of key variables, such as LDL, Low Density Lipoprotein-Cholesterol (LDL-C) and High Density Lipoprotein-Cholesterol (HDL-C).