McMaster University | Integrated Biomedical Engineering & Health Sciences Program

IBEHS - 4QZ3
Modelling of Biological Systems

Lecture 4

TAYLOR DEVET MASC.

PHD. CANDIDATE BIOLOGICAL AND BIOMEDICAL ENGINEERING
MCGILL UNIVERSITY

SHRINERS HOSPITAL FOR CHILDREN

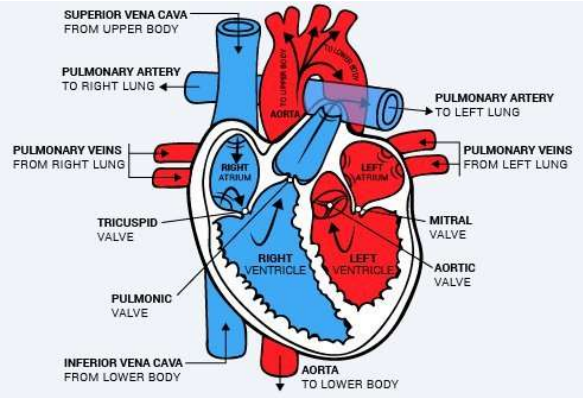
Todays Aims…

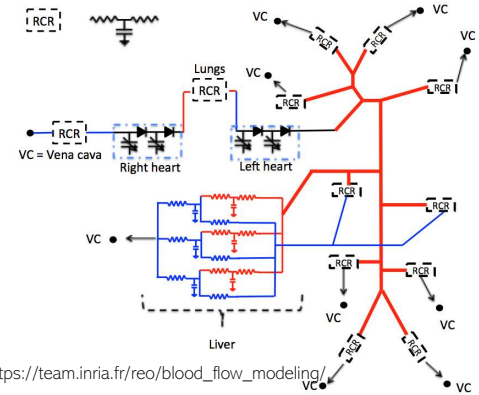
Cardiac Modelling

Macro Vasculature →Micro Vasculature modeling

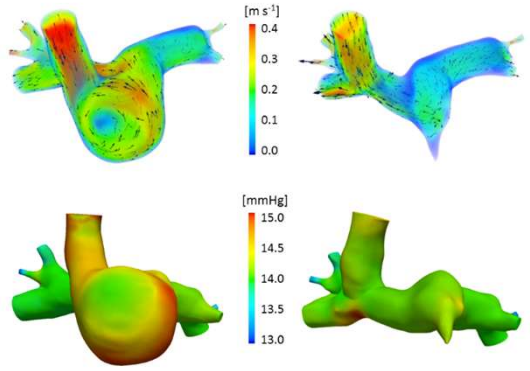
Intro to Pharmacokinetics

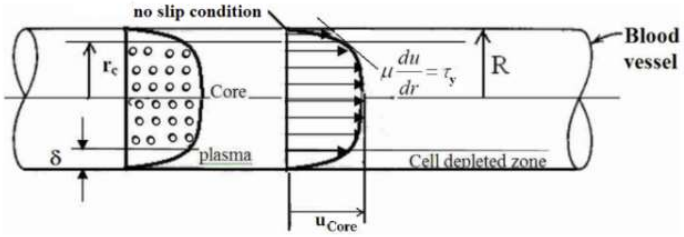
Modelling Blood Flow

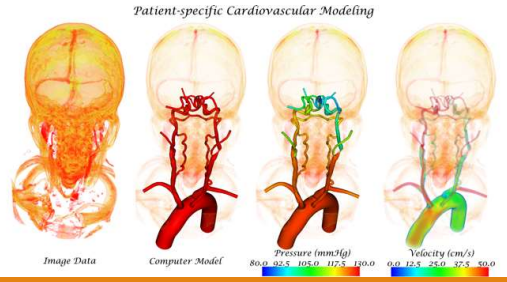




https://team.inria.fr/reo/blood_flow_modeling/







https://royalsocietypublishing.org/doi/10.1098/rsif.2018.0486

https://bloodflow.engin.umich.edu/gallery/patient-specific-blood-flow-simulation/

Macro vasculature

Modelling Blood Flow

Stroke Volume

- SV = L/beat = 70cm^3/beat = 0.070L/beat

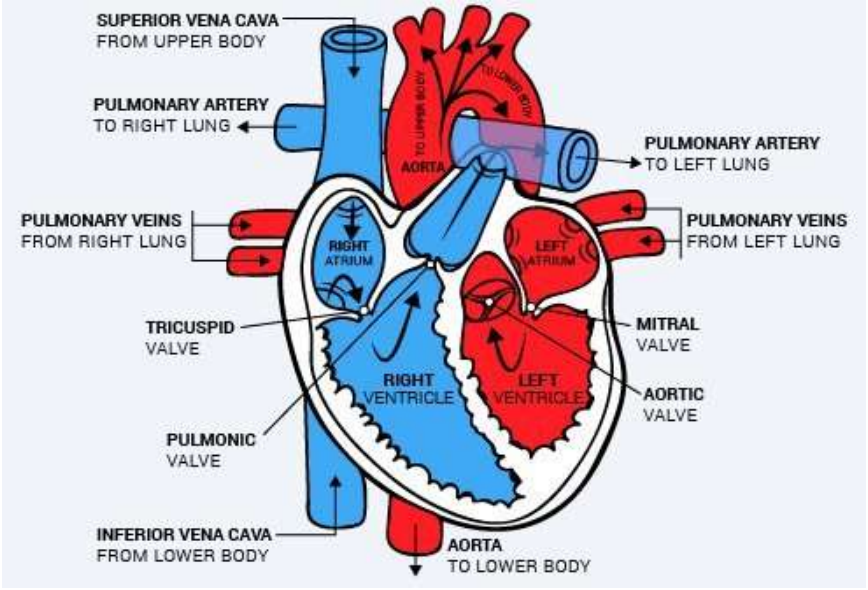
Heart Rate

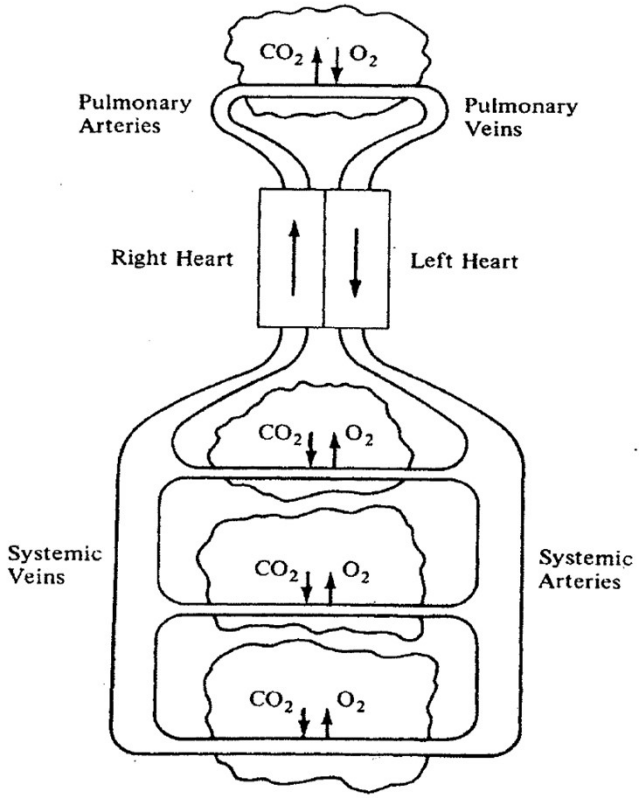
- HR = beats/min = 80 beats/min

Cardiac Output

- CO = Cardiac Output (L/min) = 5.6L/min

CO = SV x HR



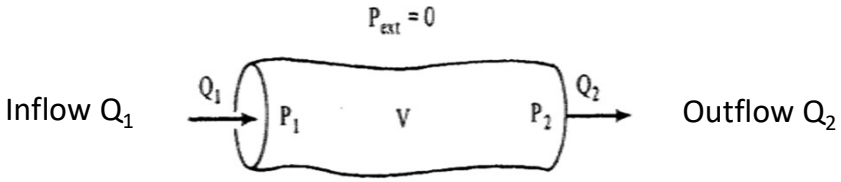


Normal resting blood pressures and volumes

	P(mmHg)	V(liters)
sa	100	1.0
sv	2	3.5
pa	15	0.1
pv	5	0.4

(s=systemic, p=pulmonary, a=artery, v=vein)

Resistance and Compliance Vessels



Blood vessels are characterized by 2 main characteristics

- 1) Resistance – How they resist the blood flowing though them
- 2) Compliance – how they deform due to changes in pressure

P_{ext} = external reference pressure,

At steady state Q1=Q2. Is this true? Why?

How are Q, P1, P2, and V related?

Resistance Vessel

Smaller vessels in the microvasculature

Resists the flow of blood

Assumptions:

- V has to be constant
- only pressure differences matter

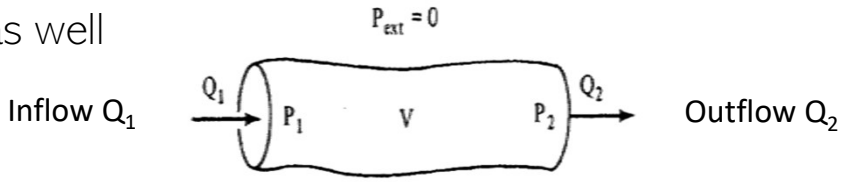
$$Q = \frac{P_1 - P_2}{R} \qquad I = \frac{V}{R}$$

I = Current in Amperes (A)
V = Voltage in Volts (V)
R = Resistance in Ohms (Ω)

NOTE resistive only vessel are idealizations!

- real vessels need to exhibit compliance as well

- here everything is assumed as linear

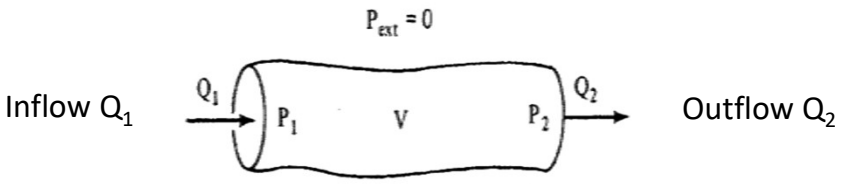


Compliance Vessel

- Larger vessels
- Have resistance to pressure and store it

Assumptions

- assume zero resistance to blood flow
- pressures on both ends of vessel are equal for all Q
- Vd is the "dead volume" at P=0



$$V = V_d + CP$$

NOTE compliance vessels are idealizations!

- real vessels need to exhibit both

- here everything is assumed as linear

However…

- large arteries and veins are "primarily" compliance vessels and changes in V are highly significant
- resistance is in the tissues
  - Primarily at the arteriole level.
  - Here volume changes are less important and large pressure drops are observed.
- Assumptions:
  - Linearity?
  - Steady state?

Vascular Networks

Arterioles

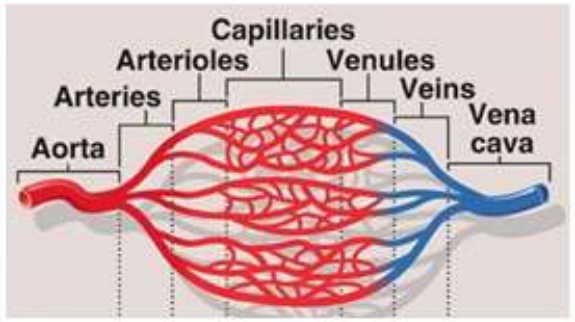
- Flow
  - 95% - 100%
- 25µm diameter.
- <15% total vessel blood volume

Capillaries

- Flow
  - 80% - 90%
- 8 µm diameter
- 40% total vessel blood volume
- primary O2 blood-tissue exchange site

Venules

- flow
  - 60% - 90%
- 25-50 µm diameter.
- 40% total vessel blood volume

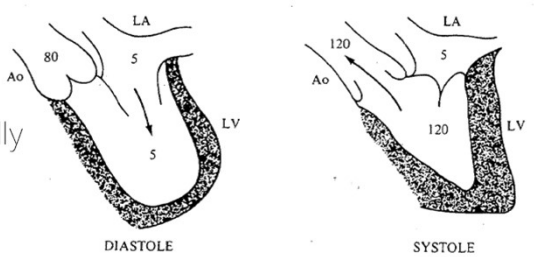


Transit Time = 2-3 s

Source: Chris Thomas' Slides

The Heart as a Pair of Pumps

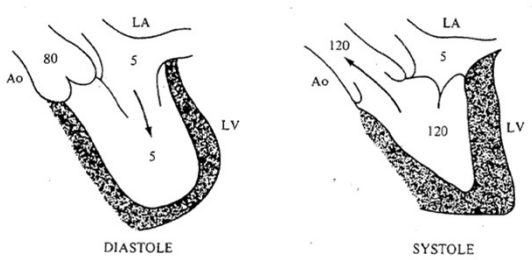
- equipped with an inflow (mitral) valve and an outflow (aortic) valve.
- Diastole
  - ventricle is relaxed
  - the inflow valve is open and the outflow valve is closed
  - left ventricle receives blood from the left atrium at a pressure that is essentially that of the pulmonary veins
- Systole
  - ventricle contracts the inflow valve closes and outflow valve opens.
  - left ventricle actively pumps blood into the systemic arterial tree.
  - left ventricle pressure systemic arterial pressure



$$V(t) = V_d + C(t)P(t)$$

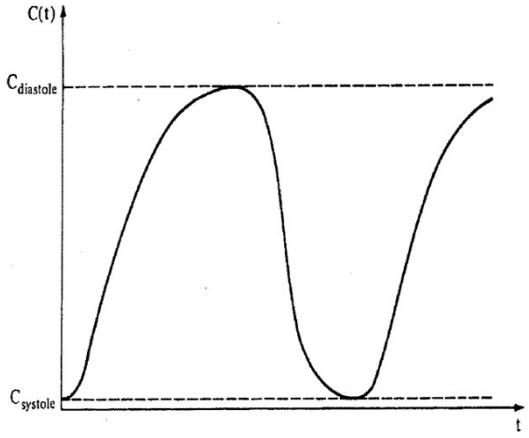
The Heart as a Pair of Pumps

- What determines left ventricle output?
  - consider ventricle is a compliance vessel
  - C(t) is compliance at time=t
  - Systole ? C(t) ↑ ↓
  - Diastole? C(t) ↑ ↓



$$V(t) = V_d + C(t)P(t)$$

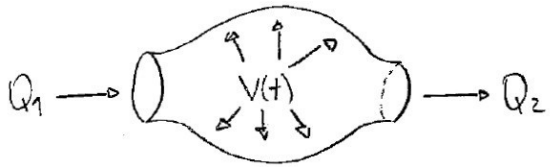
Compliance vs time



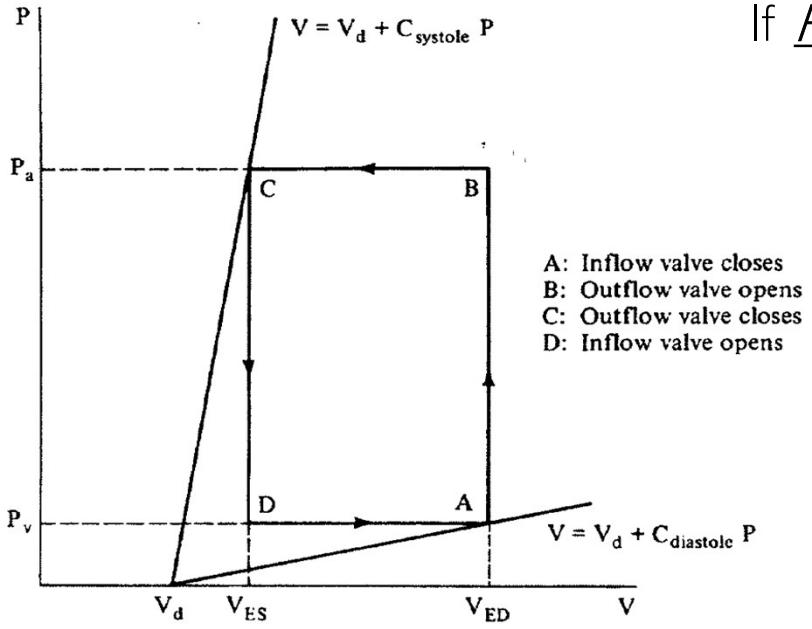
Therefore Stroke Volume (SV) is:

Maximal volumes at end diastole (ED) and end systole (ES):

P_a is pressure in the arteries supplied by the ventricle, P_v is pressure in the veins that fill it.



Ventricle Pressure-volume diagram



If *F = heart rate* (frequency, in beats/min):

$$Q = FV_{stroke} = FC_{diastole}P_v$$

Ventricular Efficiency (K)

$$K = FC_{diastole}$$

F(HR) is the same for the two sides of the heart

Constant $C_{diastole}$ is greater for right ventricle than in the left ventricle

- hence K is on the right than on the left.

- Also, the two sides of the heart are connected to different venous systems.

Therefore Right and Left Cardiac Outputs are:

sv = systemic venous

pv = pulmonary venous

Mathematical Model of the Uncontrolled Circulation

1. to study the self-regulating properties of the circulation, independent of external control mechanisms

2. to explain the need for external control mechanisms;

3. to serve as a foundation on which we can construct a simple model of circulation control

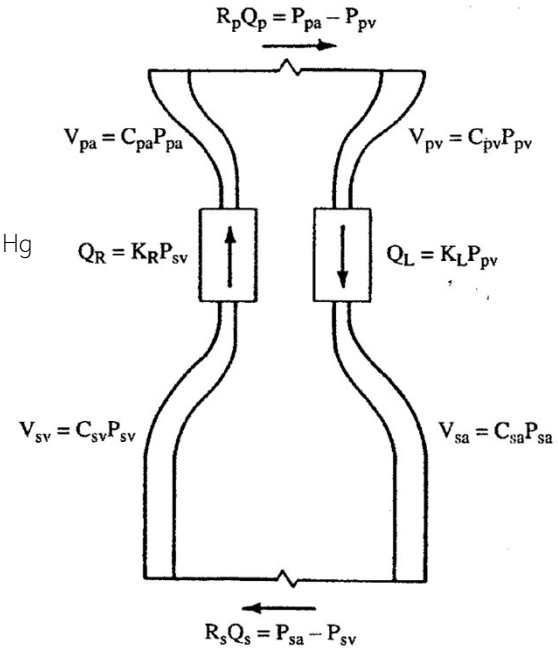
Recall

Q = flow (mL/min)
P = Pressure (mm Hg)
V = Volume (L)
C = Compliance (L/mm)

F = heart rate (beats/min)
P = Pressure (mm Hg)
K = efficiency in (L/min)/mm Hg

Put it all together…

Recall
Q = flow (mL/min)
P = Pressure (mm Hg)
V = Volume (L)
C = Compliance (L/mm)
F = heart rate (beats/min)
P = Pressure (mm Hg)
K = efficiency in (L/min)/mm Hg



$$V_{sa} = C_{sa}P_{sa}$$
$$V_{sv} = C_{sv}P_{sv}$$
$$V_{pa} = C_{pa}P_{pa}$$
$$V_{pv} = C_{pv}P_{pv}$$

$$Q_R = K_RP_{sv}$$
$$Q_L = K_LP_{pv}$$

Recall $V = V_d + CP$ (ignore V_d)

assume that the systemic and pulmonary tissues act like resistance vessels, so that:

$$Q_s = \frac{1}{R_s}(P_{sa} - P_{sv}),$$
$$Q_p = \frac{1}{R_p}(P_{pa} - P_{pv}).$$

Solving the Variables

Now we have an equation for each element of the circulation, with 12 unknowns:

$$Q_{\mathrm{R}}, Q_{\mathrm{L}}, Q_{\mathrm{s}}, Q_{\mathrm{p}}; P_{\mathrm{sa}}, P_{\mathrm{sv}}, P_{\mathrm{pa}}, P_{\mathrm{pv}}; V_{\mathrm{sa}}, V_{\mathrm{sv}}, V_{\mathrm{pa}}, V_{\mathrm{pv}}.$$

Can calculate total blood volume:

assume that the circulation is in a steady state, so that the flow into each of the compliance vessels must equal the flow out.

→ Thus:

Therefore now we have 9 equations and 9 unknowns:

$$Q, P_{\mathrm{sa}}, P_{\mathrm{sv}}, P_{\mathrm{pa}}, P_{\mathrm{pv}}, V_{\mathrm{sa}}, V_{\mathrm{sv}}, V_{\mathrm{pa}}, V_{\mathrm{pv}}$$

Solving the Equations

1. From the pump equations, we get the venous pressures in terms of Q:

Substituting this result in the resistance equations, we get the arterial pressures in terms of Q:

Combining equations…

Substituting all four pressures into the compliance equations, we obtain:

$$V_{sa} = C_{sa} P_{sa}$$
$$V_{sv} = C_{sv} P_{sv}$$
$$V_{pa} = C_{pa} P_{pa}$$
$$V_{pv} = C_{pv} P_{pv}$$

$$V_{\mathrm{sv}} = \frac{C_{\mathrm{sv}}}{K_{\mathrm{R}}} Q,$$
$$V_{\mathrm{pv}} = \frac{C_{\mathrm{pv}}}{K_{\mathrm{L}}} Q,$$
$$V_{\mathrm{sa}} = \left[\frac{C_{\mathrm{sa}}}{K_{\mathrm{R}}} + C_{\mathrm{sa}} R_{\mathrm{s}}\right] Q,$$
$$V_{\mathrm{pa}} = \left[\frac{C_{\mathrm{pa}}}{K_{\mathrm{L}}} + C_{\mathrm{pa}} R_{\mathrm{p}}\right] Q$$

$$V_i = T_i Q,$$
$$i = sv, pv, sa, pa$$

To save writing, we introduce the following combinations of parameters

$$T_{\mathrm{sv}} = C_{\mathrm{sv}}/K_{\mathrm{R}},$$
$$T_{\mathrm{pv}} = C_{\mathrm{pv}}/K_{\mathrm{L}},$$
$$T_{\mathrm{sa}} = (C_{\mathrm{sa}}/K_{\mathrm{R}}) + C_{\mathrm{sa}} R_{\mathrm{s}},$$
$$T_{\mathrm{pa}} = (C_{\mathrm{pa}}/K_{\mathrm{L}}) + C_{\mathrm{pa}} R_{\mathrm{p}}$$

Combining equations…

$$(T_{sa} + T_{sv} + T_{pa} + T_{pv})Q = V_0,$$

substitute previous in to equations for the total blood volume and solve for Q:

$$Q = \frac{V_0}{(T_{sa} + T_{sv} + T_{pa} + T_{pv})}.$$

$$V_i = \frac{T_i V_0}{(T_{sa} + T_{sv} + T_{pa} + T_{pv})},$$

$$P_i = \frac{T_i V_0}{C_i(T_{sa} + T_{sv} + T_{pa} + T_{pv})}$$

Therefore, now have a formula for each unknown. Just need some normal starting values!

Normal Resting Values:

	Systemic	Pulmonary
R:	$R_s = 17.5$	$R_p = 1.79$ mmHg/(liter/min)
C:	$C_{sa} = 0.01$	$C_{pa} = 0.00667$ liters/mmHg
	$C_{sv} = 1.75$	$C_{pv} = 0.08$ liters/mmHg
	Right	**Left**
K:	$K_R = 2.8$	$K_L = 1.12$ (liters/min)/mmHg
V:	$V_0 = 5.0$ liters	

Balancing the Two Sides of the Heart

- Essentially have 2 separate systems that are joined together at the heart
- How are the two sides of the heart and the two circulations coordinated?
- What keeps the outputs of the right and left hearts equal?
- What mechanisms control the partition of blood volume between the systemic and pulmonary circulations?

Example

Assume : K_R Decreases

- Temporarily, QR < QL
- This will increase Psv and lower the Ppv.
- The overall effect of pressure changes will be to drive the cardiac outputs back toward equality.
- A net rate of transfer of volume will persist until equality of output [of both sides] is restored.
- This results in a new equilibrium with a different partition of the blood volume

In the steady-state model, we only need to compute the end result of this process.

Recall:

$$T_{sv} = C_{sv}/K_R$$
$$T_{pv} = C_{pv}/K_L$$
$$T_{sa} = \left(C_{sa}/K_R\right) + C_{sa}R_s$$
$$T_{pa} = \left(C_{pa}/K_L\right) + C_{pa}R_p$$

Recall
Q = flow (mL/min)
P = Pressure (mm Hg)
V = Volume (L)
C = Compliance (L/mm)
F = heart rate (beats/min)
P = Pressure (mm Hg)
K = efficiency in (L/min)/mm Hg

$$\frac{V_p}{V_s} = \frac{V_{pa} + V_{pv}}{V_{sa} + V_{sv}} = \frac{T_{pa} + T_{pv}}{T_{sa} + T_{sv}}$$
$$= \frac{\left(\frac{C_{pa} + C_{pv}}{K_L} + C_{pa}R_p\right)}{\left(\frac{C_{sa} + C_{sv}}{K_R} + C_{sa}R_S\right)}$$

The key to the success of this intrinsic control mechanism is the dependence of cardiac output on venous pressure

External Control Mechanisms

1) Arterioles dilate.
- Result: decreased systemic resistance Rs.
- Concurrently cardiac output rises
- Systemic arterial pressure (Psa) is maintained.

2) The ↑ in cardiac output comes primarily from an ↑ in heart rate while stroke volume remains fairly constant.

Uncontrolled circulation flaws

- uncontrolled model response to change in Rs different response from the observed response

- In the uncontrolled circulation a decrease in Rs results in only a modest increase in cardiac output.

- The most noticeable effect is a substantial decrease in systemic arterial pressure (Psa).

- This shows the need for the external circulatory control mechanisms

Model response to control mechanisms

What happens when we change in R_s ?
Only appears in one equation… but affects the rest
- *This is a system of equations*

What happens to Q and P_{sa} when R_s is reduced to 50% of its normal value (while leaving the other parameters unchanged)?

$$Q = \frac{V_0}{T_{sa} + T_{sv} + T_{pa} + T_{pv}} \qquad P_{sa} = \frac{V_0}{C_{sa}} \cdot \frac{T_{sa}}{T_{sa} + T_{sv} + T_{pa} + T_{pv}}$$

In the model reduce: Rs 50%:

	Normal	$R_s = 50\% R_s^{normal}$
Q	5.6	6.2
P_{sa}	100.0	57

Effect of changing systemic resistance (Rs) on cardiac output (Q) and systemic arterial pressure (P_{sa}) in an uncontrolled circulation model.

Assess changes via sensitivity analysis:

If Y depends on X, and X changes, then the sensitivity of Y to X is defined to be:

$$\sigma_{YX} = \frac{\Delta \log Y}{\Delta \log X} = \frac{\log Y' - \log Y}{\log X' - \log X}$$

$$= \frac{\log\left(Y'/Y\right)}{\log\left(X'/X\right)}$$

where X'=X+ΔX and Y' is the value that Y takes on when X is changed to X'.

From previous table we find:

Conclusions about Rs

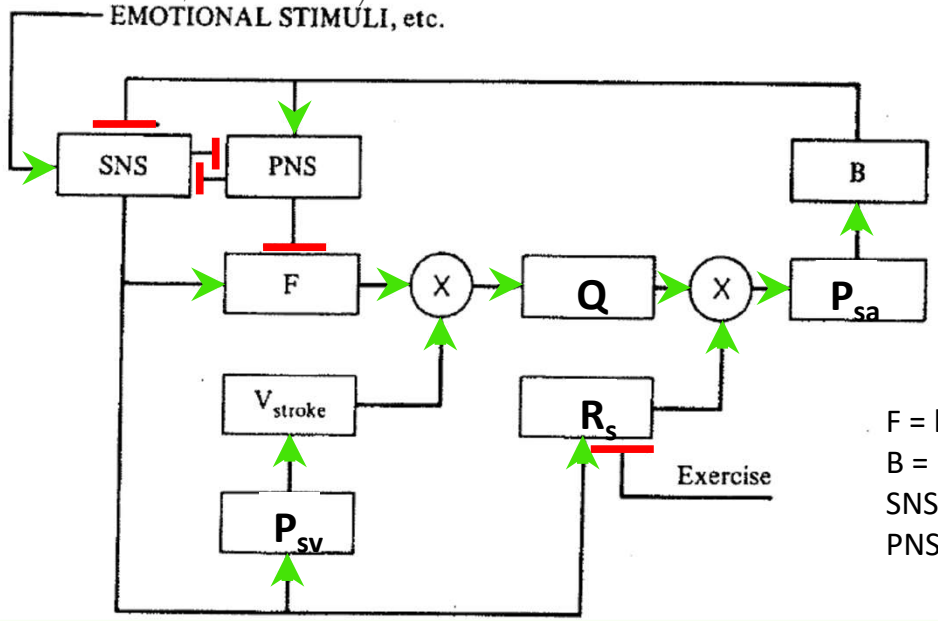
Therefore the sensitivity of Q to Rs and P to Rs are directly linked

→ Any mechanism that accomplishes one will automatically accomplish the other.

→ There has to be other factors at work

Physiological Control

- Baroreceptors (carotid arteries, aortic arch)



F = heart rate
B = baroreceptors
SNS = sympathetic NS
PNS = parasympathetic NS

Baroreceptor Notes

1) The PNS is excited by activity of the baroreceptors →slows heart rate (F).

2) The SNS is inhibited by baroreceptor activity. This has several effects on circulation, including:

(a) increased heart rate

(b) increased venous pressure, and so increased stroke volume

(c) increased systemic resistance

The loop is closed through the mechanics of the circulation:

$Q = F * V_{stroke}$ and $P_{sa} = Q * R_s$

Baroreceptors adjust heart rate until systemic arterial pressure hits a target value

Introducing Heart Rate (F)

Recall:

$$Q_R = K_R P_{sv} \qquad Q_L = K_L P_{pv}$$

$$Q_R = FC_R P_{sv} \qquad Q_L = FC_L P_{pv}$$

Now this is a model of the controlled circulation where the above 2 equations can be included with the steady state relationship:
$Q_R=Q_P=Q_S=Q_L$ and:

$$V_{sa} = C_{sa} P_{sa}$$
$$V_{sv} = C_{sv} P_{sv}$$
$$V_{pa} = C_{pa} P_{pa}$$
$$V_{pv} = C_{pv} P_{pv}$$

$$Q_s = \frac{1}{R_s}(P_{sa} - P_{sv}),$$
$$Q_p = \frac{1}{R_p}(P_{pa} - P_{pv}).$$

How to Solve: make some approximations!

1) Neglect P_{sv} compared to P_{sa} in the equation of the systemic resistance to simplify

$$QR_S = P^*$$

2) neglect pulmonary volumes in comparison with the systemic volumes in the equation of the total blood volume.

$$V_{sa} + V_{sv} = V_0 \quad \text{or:} \quad C_{sa}P^* + C_{sv}P_{sv} = V_0$$

Use above to determine Q and P_{sv}:

Simplified Model

$$Q = \frac{P^*}{R_s}$$

$$P_{sv} = \frac{V_0 - C_{sa}P^*}{C_{sv}}$$

Substitute into →

$$Q_R = FC_RP_{sv}$$

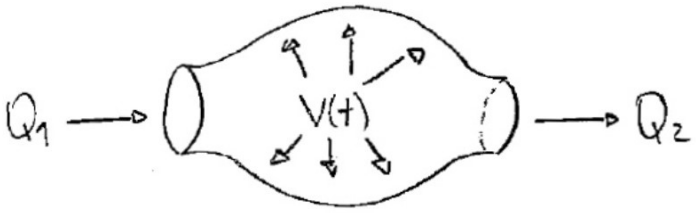
Resultant is solution for heart rate:

$$F = \frac{P^* C_{sv}}{R_s C_R \left(V_0 - C_{sa}P^*\right)}$$

Changes in R_{sv} ?

Increase in Q_R?

Let's Consider this as a dynamic system



$$V(t) = V_d + CP(t)$$

Compliant Vessel expanding due to blood flow

$$\frac{dV}{dt} = C\frac{dP}{dt} \qquad \frac{dV}{dt} = Q_1 - Q_2$$

$$C\frac{dP}{dt} = Q_1 - Q_2 \quad \textbf{(Eqn.1)}$$

1st dynamic cardiovascular model

- monitor changes in blood pressure over time in a systemic artery.
- assume artery is a compliant vessel with inflow of blood Q1
- blood outflow (Q2) flows out to the microcirculation
- assume arterioles and capillaries are lumped together as 'resistance vessels'

$$C_{SA}\frac{dP_{SA}}{dt} = Q_{Ao} - Q_S \quad \textbf{(Eqn.2)}$$

$$Q_s = \frac{P_{SA} - P_{SV}}{R_s} \quad \textbf{(Eqn.3)}$$

Dynamic model cont

$$Q_s = \frac{P_{SA} - P_{SV}}{R_s} \quad \text{(Eqn.3)} \longrightarrow Q_s = \frac{P_{SA}}{R_S} \quad \text{(Eqn.4)}$$

Putting Eqn.4 and 2 together:

$$C_{SA}\frac{dP_{SA}}{dt} = Q_{Ao} - \frac{P_{SA}}{R_S}$$

$$\frac{dP_{SA}}{dt} = \frac{1}{C_{SA}}\left(Q_{Ao} - \frac{P_{SA}}{R_S}\right) \quad \text{(Eqn.5)}$$

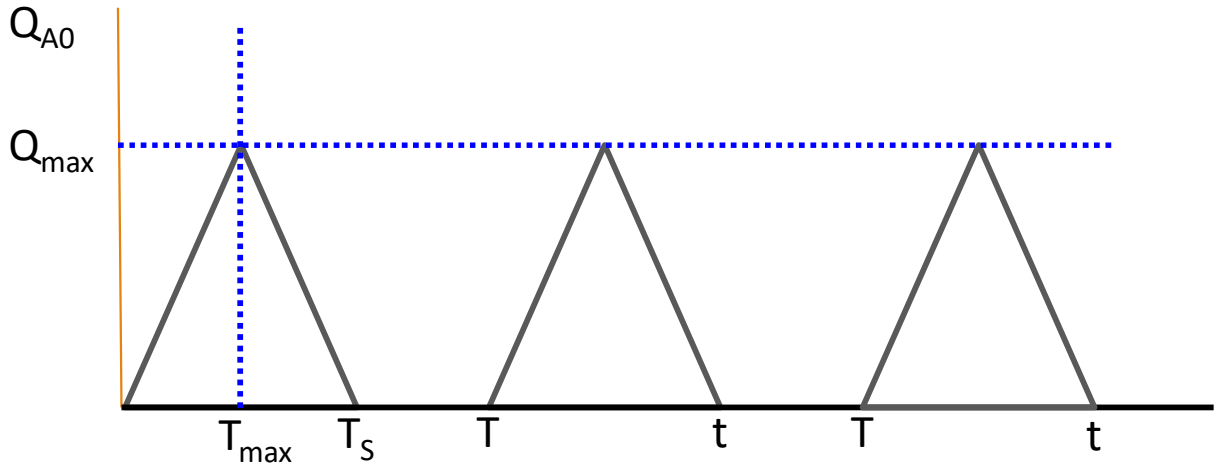
Dynamic model cont

- Now, the outflow from the heart into the systemic artery = $Q_{AO}(t)$
- BUT.... outflow is pulsatile!!
- Simplify as a triangle

Q_{max} = maximum blood flow)
T_{max} = time of max. blood flow (i.e. corresponds with Q_{max} , the waveform peak)
T_S = duration of systole (corresponds to length of base of triangle)
T = duration of one heart beat (period of signal)

(Eqn.6)

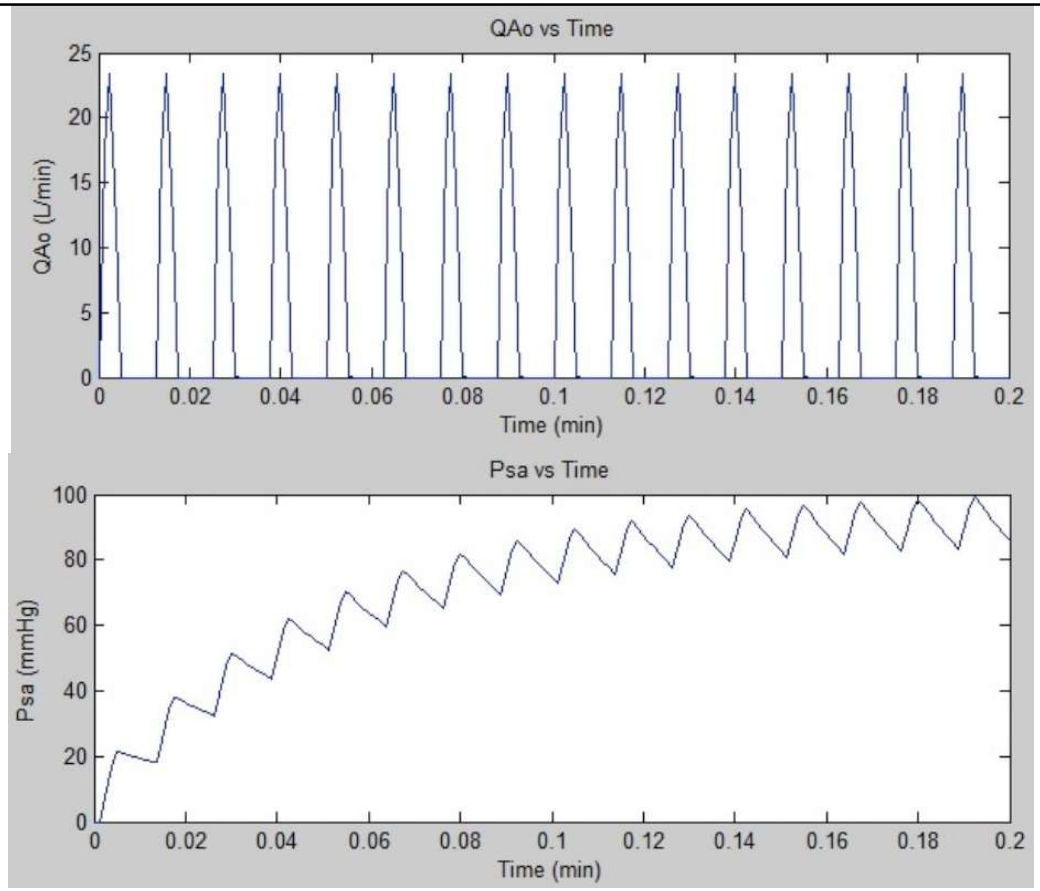
$$Q_{AO}(t) = \begin{cases} {Q_{max}t}/{T_{max}} & 0 \le t \le T_{max} \\ {Q_{max}(T_S - t)}/{(T_S - T_{Max})} & T_{max} \le t \le T_S \\ 0 & T_S \le t \le T \end{cases}$$



In starting any model we need to give the model initial conditions:

```
T = 0.0125;                          % Duration of heartbeat: min
Ts = 0.0050;                         % Duration of systole: min
Stroke_volume = 70e-3;               % Volume ejected by 1 heart beat: L
Tmax = 0.0020;                       % Time at which flow is max: min
Qmax= Stroke_volume/(0.5*Ts);        % Max flow through aortic valve: L/min
dt = .01*T;                          % i.e. 100 time pts per cardiac cycle
% Compliance and resistance values for arteries
Csa = .00175;                        % Systemic arterial compliance: L/mmHg
Rs = 17.86;                          % Systemic resistance: mmHg/(L/min)

% To begin with, QA0 and Psa are zero
% will model 16 heart beats, with a step size of 75ms
```



Done with a fixed step ode1 (Euler) solver using Matlab.

NOTES:

1) Initial condition of the blood pressure was set to 0 mmHg.

2) after several simulated heart beats the model settles to a stable solution where Psa (systolic pressure) achieves ~100 mmHg with a diastolic pressure of 80 mmHg.

3) Increasing pressure would correspond to increase in ejection volume

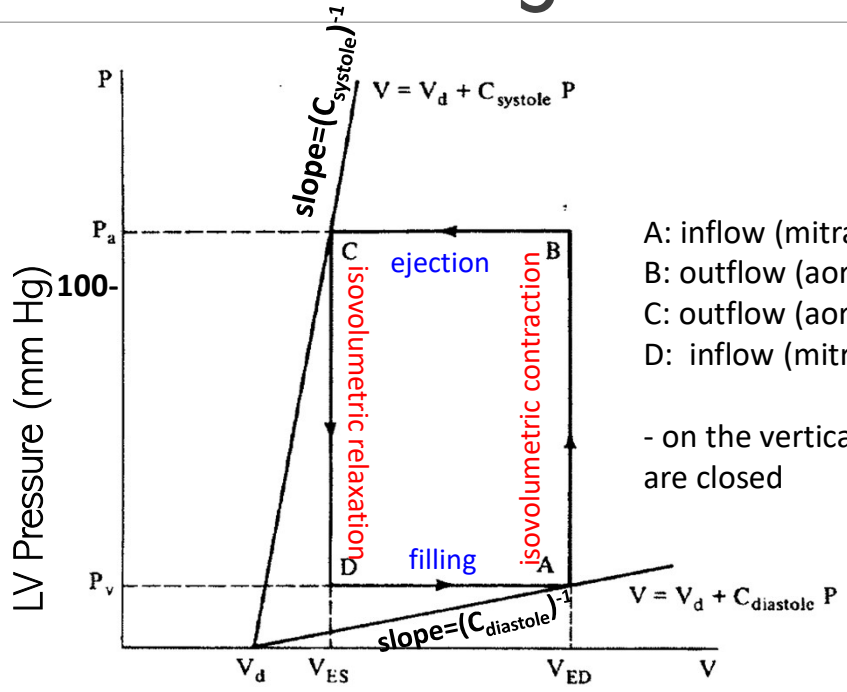
4) It does not reach typical 120/80 mmHg due to initial conditions for arterial compliance and systemic resistance

- These adjust pulse pressure and mean arterial pulse

What about the Left Ventricle?

- Requires modeling of cardiac contraction and valves opening/closing of the valves.
- Thus, expand model to include left ventricle (LV)
  - a basic pump
  - accepting fluids at low pressure (P1)
  - Transfers to a region where pressure is higher (P2>P1).
- muscular contractions will change LV wall compliance

Pressure-volume diagram for Left Ventricle



A: inflow (mitral) valve closes
B: outflow (aortic) valve opens
C: outflow (aortic) valve closes
D: inflow (mitral) valve opens

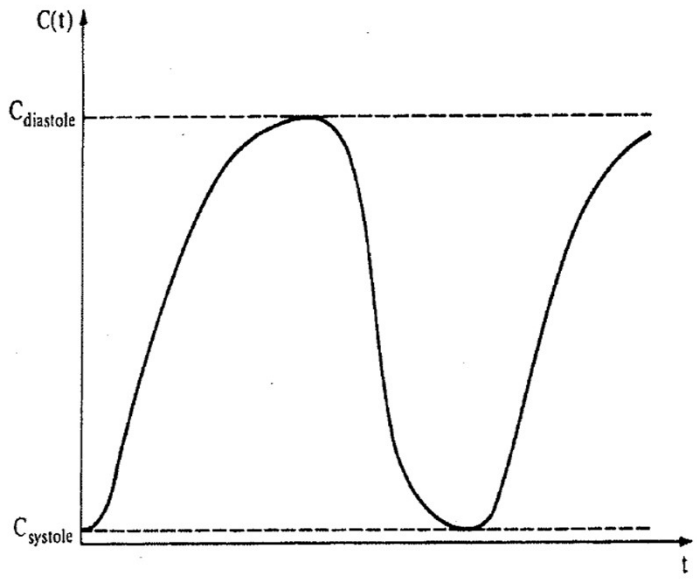
- on the vertical lines, both valves are closed

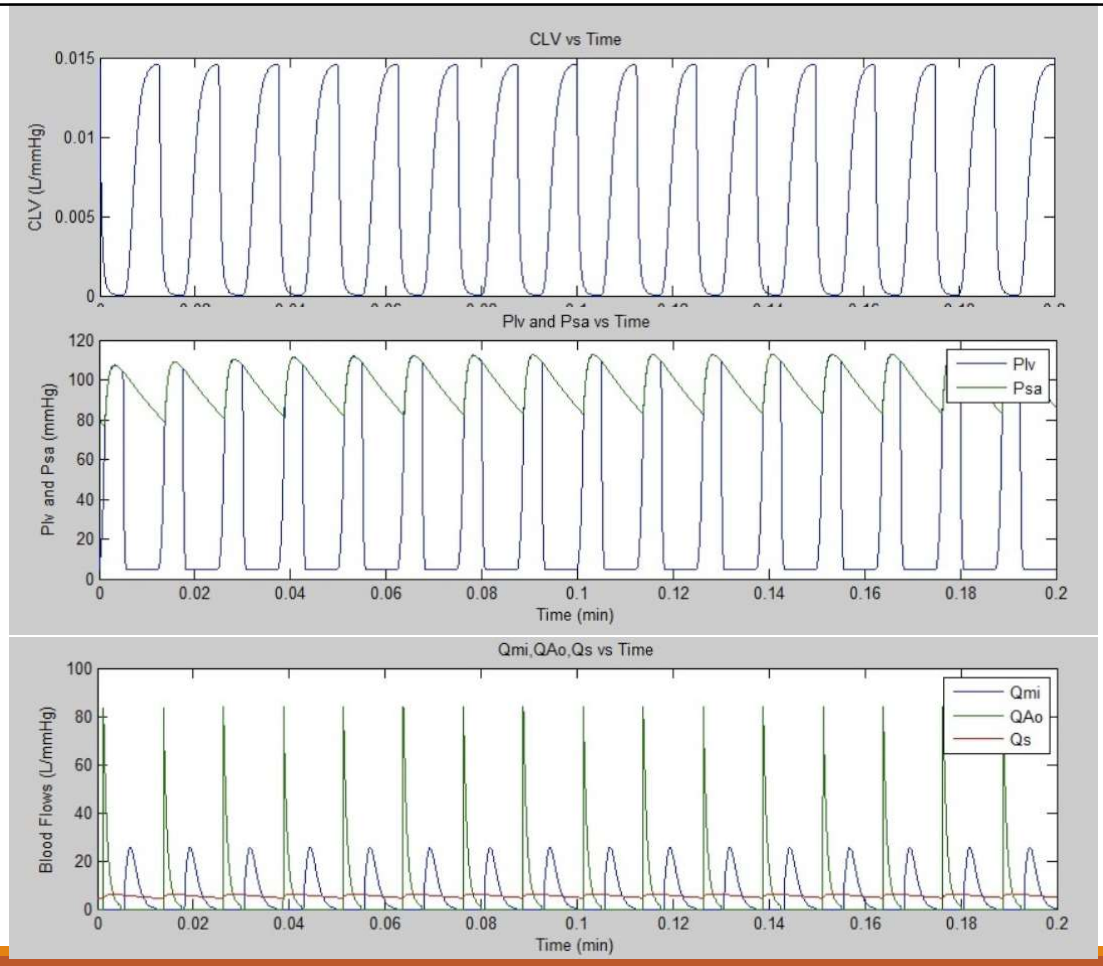
Compliance over time

LV can now be treated similarly to the compliant vessels (model above). However, compliance is no longer static.

- During diastole, ↑ compliance, accommodating ↑ blood volumes.

- During systole, ↓ compliance to be able to contract ejecting blood with higher pressure.



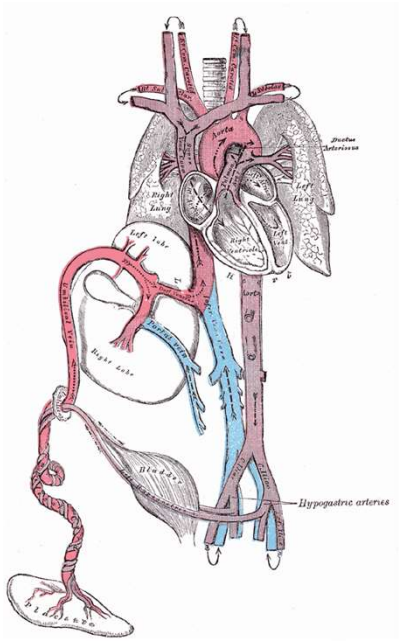

CLV vs Time
CLV (L/mmHg)
0.015
0.01
0.005
0
Plv and Psa vs Time
Plv and Psa (mmHg)
120
100
80
60
40
20
0
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
0.18
0.2
Time (min)
Plv
Psa
Qmi,QAo,Qs vs Time
Blood Flows (L/mmHg)
100
80
60
40
20
0
Time (min)
Qmi
QAo
Qs

Fetal Circulation

1) Ductus Venosus- shunt placental blood to vena cava

2) Foramen Ovale- hole between atria to short circuit blood that would go to lungs

3) Ductus Arteriosus – portal between aorta and pulmonary artery.



Fetal Circulation

At birth, when the infant breathes for the first time the following happens:

1) There is a decrease in the resistance in the pulmonary vasculature

2) This causes the pressure in the left atrium to increase relative to the pressure in the right atrium.

3) This leads to closure of the foramen ovale

4) The newly increased rise in blood oxygen leads to a decrease in prostaglandins, causing closure of the ductus arteriosus.

These closures prevent blood from bypassing pulmonary circulation, and therefore allow the neonate's blood to become oxygenated in the newly operational lungs.

Fetal Circulation

For the fetal circulation there are 6 flows to consider:

QL (left heart output)

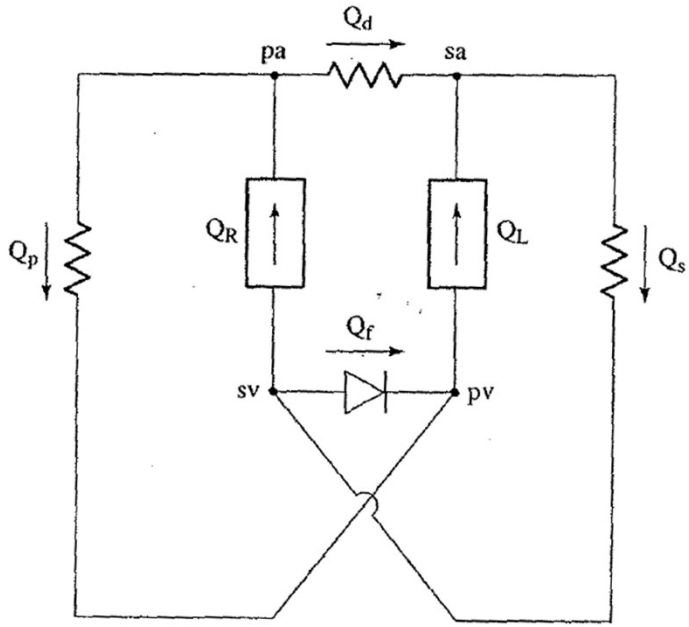
QR (right heart output)

Qp (pulmonary flow=small)

Qs (systemic flow=large since includes placenta)

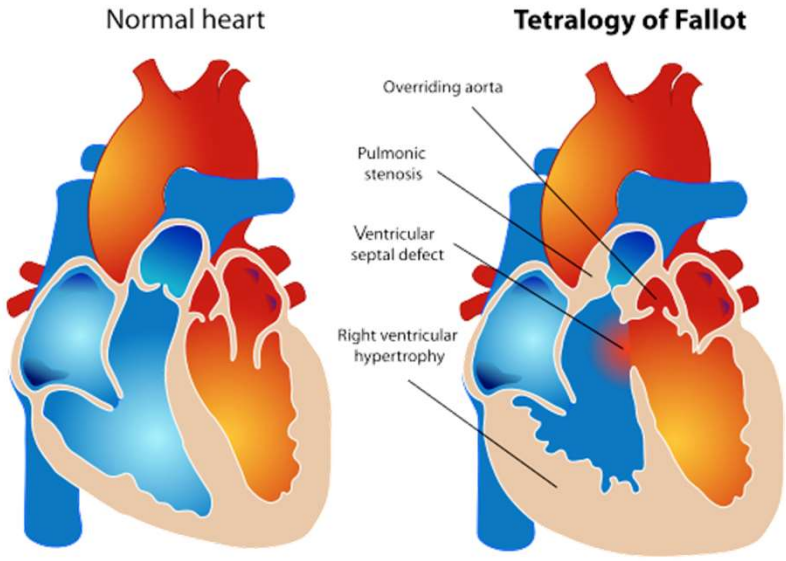
Qd (flow through ductus arteriosus)

Qf (flow through foramen ovale)



Tetralogy of Fallot

How is this modelled?



https://en.wikipedia.org/wiki/Tetralogy_of_Fallot

Engineering vs Physiological Control Systems

1) An Engineering control system is designed to accomplish a defined task, and frequently, the governing parameters have been fine-tuned extensively so that the system will perform its task in an "optimal" manner

- physiological control systems are built for versatility and may be capable of serving several different functions (e.g. respiratory system provides gas exchange, and secondarily helps facilitate heat dissipation)

2) As engineering control systems are synthesized by a designer, the characteristics of the various components are generally known.

- a physiological control system usually consists of components that are unknown and difficult to analyze.

- constant need to apply system identification techniques to determine how these various subsystems behave before we are able to proceed to analyzing the overall control system

Engineering vs Physiological Control Systems

3) Occasionally physiological control systems are non-optimal, or poorly designed!! However, both engineering and physiological control systems break down. Both can have simple failures and catastrophic failures.

4) There is an extensive degree of cross-coupling or interaction among different physiological control systems.

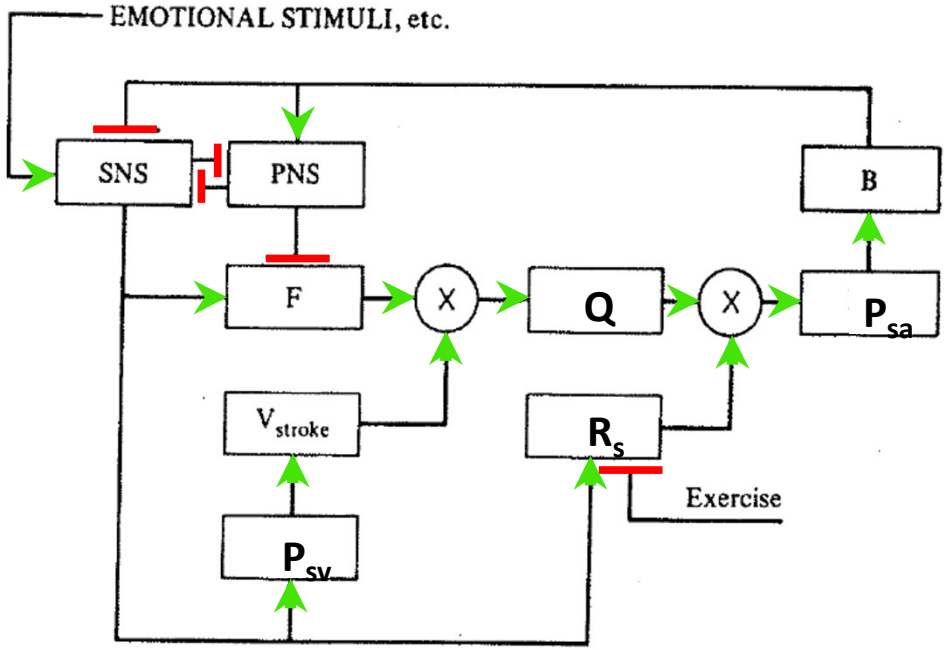
e.g. the healthy cardiovascular system is largely dependent on interactions with respiratory, renal, endocrine, and other organ systems.

5) Physiological control systems, in general, are adaptive. This means that the system may be able to offset any change in output not only through feedback but also by allowing system characteristics to change.

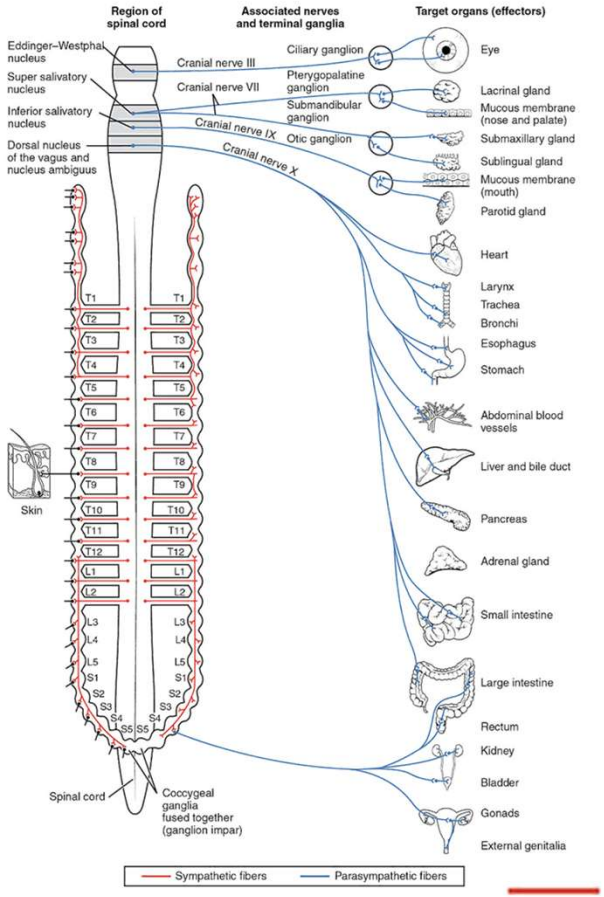
6) physiological systems are generally nonlinear, while engineering control systems can be linear or nonlinear.

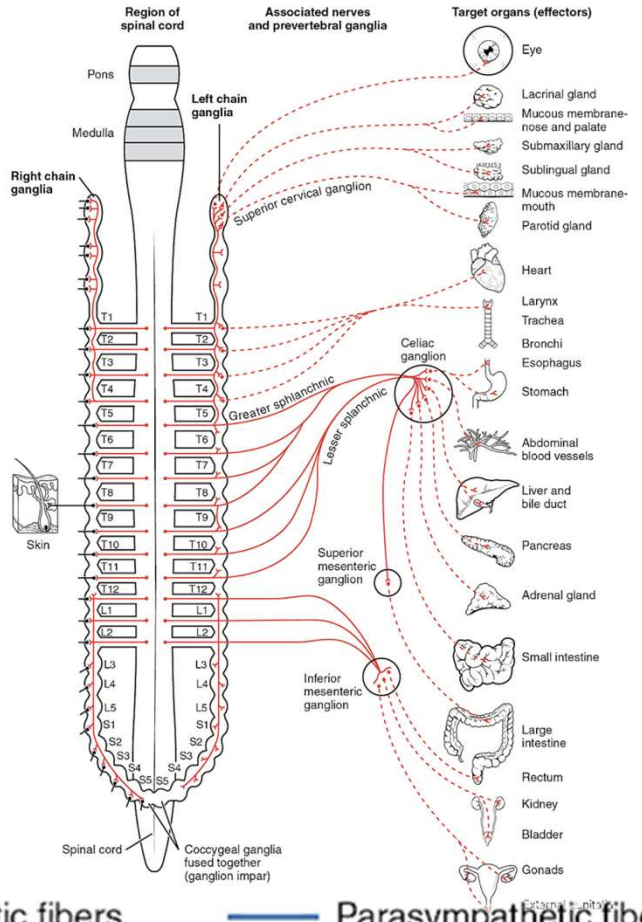
- The engineering designer prefers the use of linear system components since they have properties that are well-behaved and easy to predict.

Consider Balance of PNS and SNS regulation



F = heart rate
B = baroreceptors
SNS = sympathetic NS
PNS = parasympathetic NS


Region of spinal cord
Associated nerves and terminal ganglia
Target organs (effectors)
Eddinger–Westphal nucleus
Super salivatory nucleus
Inferior salivatory nucleus
Dorsal nucleus of the vagus and nucleus ambiguus
Cranial nerve III
Cranial nerve VII
Cranial nerve IX
Cranial nerve X
Ciliary ganglion
Pterygopalatine ganglion
Submandibular ganglion
Otic ganglion
Eye
Lacrinal gland
Mucous membrane (nose and palate)
Submaxillary gland
Sublingual gland
Mucous membrane (mouth)
Parotid gland
Heart
Larynx
Trachea
Bronchi
Esophagus
Stomach
Abdominal blood vessels
Liver and bile duct
Pancreas
Adrenal gland
Small intestine
Large intestine
Rectum
Kidney
Bladder
Gonads
External genitalia
Skin
Spinal cord
Coccygeal ganglia fused together (ganglion impar)
Sympathetic fibers
Parasympathetic fibers


Region of spinal cord
Associated nerves and prevertebral ganglia
Target organs (effectors)
Pons
Medulla
Left chain ganglia
Right chain ganglia
Superior cervical ganglion
Celiac ganglion
Greater splanchnic
Lesser splanchnic
Superior mesenteric ganglion
Inferior mesenteric ganglion
Eye
Lacrinal gland
Mucous membrane-nose and palate
Submaxillary gland
Sublingual gland
Mucous membrane-mouth
Parotid gland
Heart
Larynx
Trachea
Bronchi
Esophagus
Stomach
Abdominal blood vessels
Liver and bile duct
Pancreas
Adrenal gland
Small intestine
Large intestine
Rectum
Kidney
Bladder
Gonads
Skin
Spinal cord
Coccygeal ganglia fused together (ganglion impar)
Sympathetic fibers
Parasympathetic fibers

System Complexity

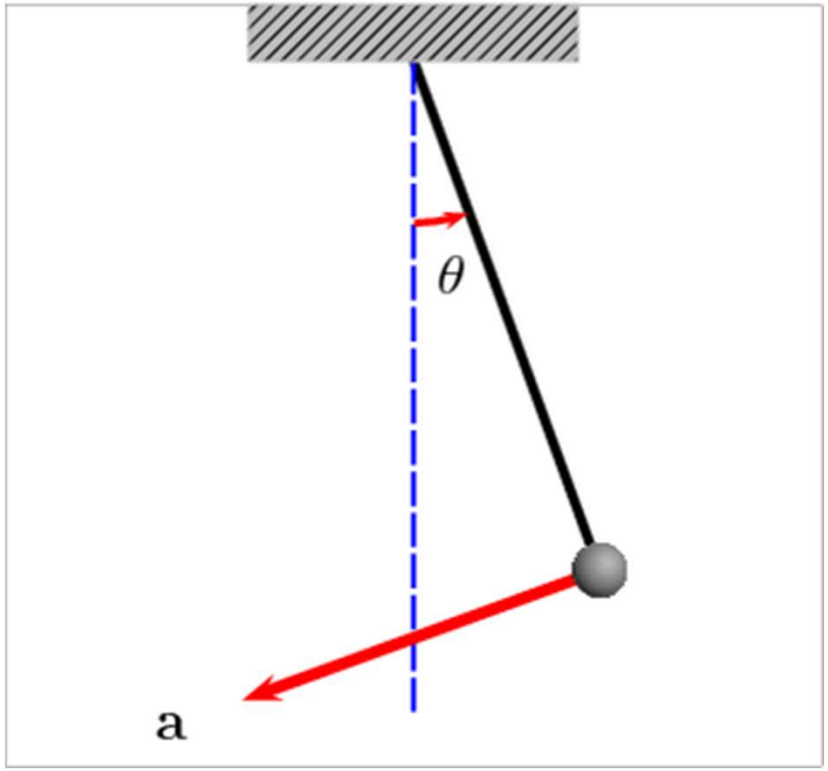
Consider each regulatory system is like a pendulum that influences cardiac contractility

The "simple pendulum" is an isolated system having the following assumptions:

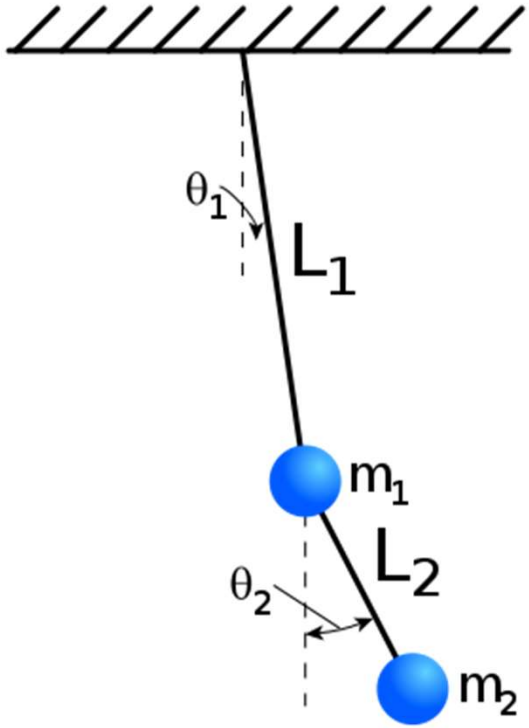
1) The cord is massless, inextensible and always taut
2) The hanging bob is a point mass
3) Motion occurs only in two dimensions (i.e. along an arc).
4) The motion does not lose energy to friction or air resistance.

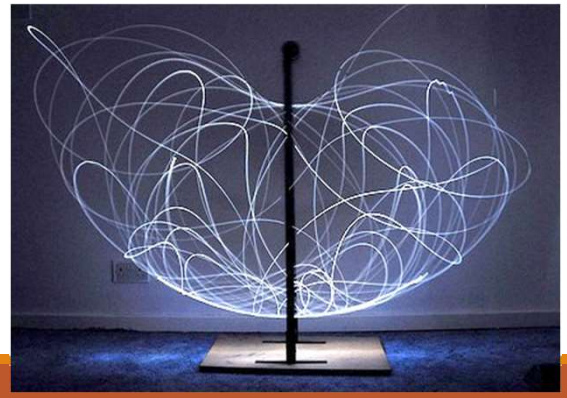
The differential equation which represents the motion of a simple pendulum is

$$\frac{d^2\theta}{dt^2} + \frac{g}{\ell}\sin\theta = 0$$



$$\frac{d^2\theta}{dt^2} + \frac{g}{\ell}\sin\theta = 0$$

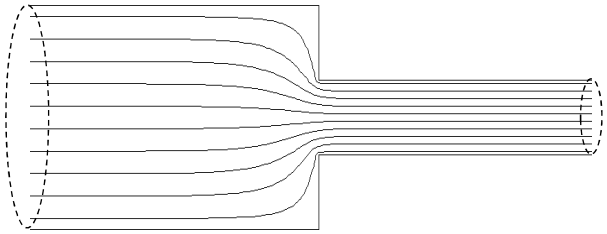

θ1
L1
m1
L2
θ2
m2



Micro Vasculature

Laminar Fluid Flow

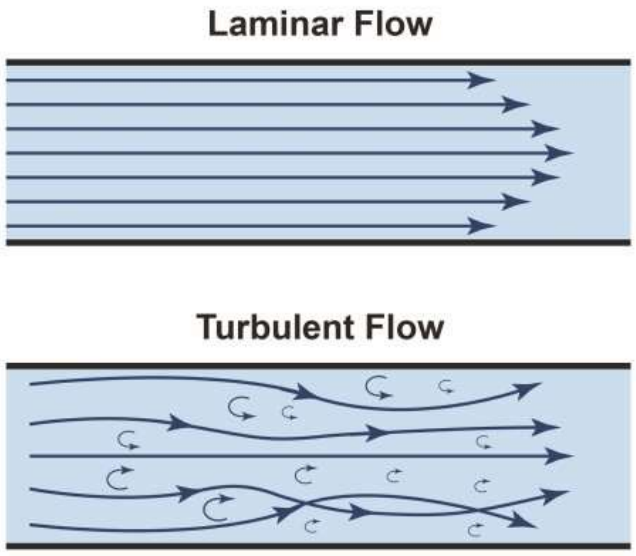
- the smooth motion of adjacent fluid layers sliding continuously past each other without breaking into whirlpools or vortices.
- Also known as streamline flow
- Visualized by lines of constant fluid speed (streamlines).
- Laminar streamlines never cross
- Steady state fluid flow is a special case of laminar flow where fluid velocity is everywhere time independent.



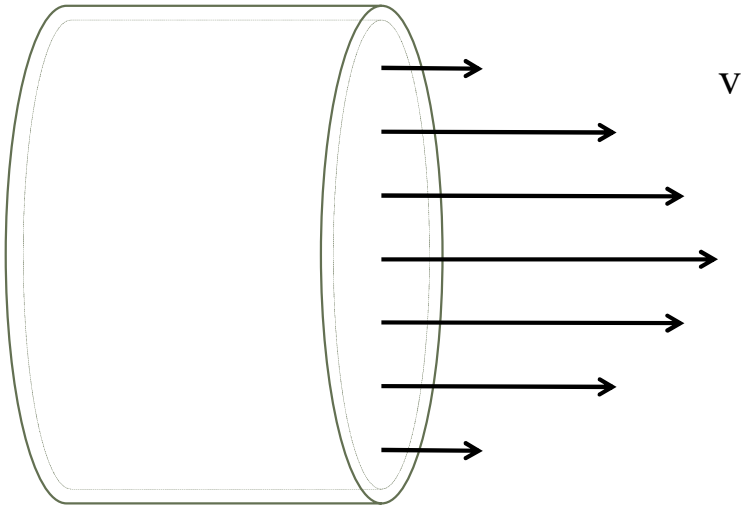
Turbulent Fluid Flow

Fluid experiences mixing or fluctuations in fluid flow

Changes in speed or direction of flow



https://www.automation.com/en-us/articles/2018/demystifying-fluid-turbulence-velocity-and-flow-me



Fluid velocity profile in a blood vessel. Blood flows faster at the center of the vessel than near the walls of the vessel.

Reynolds Number

Reynolds number is a useful measure of the fluid flow proportional to the ratio of inertial to viscous forces.

$$\mathrm{Re} = \frac{inertial\ \ forces}{viscous\ \ forces} = \frac{\rho v a}{\eta}$$

ρ = density of the fluid (kg/m³)

v = velocity (m/s)

a = length

η = fluid viscosity (Pa·s or N·s/m² or kg/(m·s))

Reynolds Number

- if Re<2000, flow is laminar
- Re>3000 flow is turbulent.
- in-between is a transition zone
- "transition" flow depends on other factors, such as pipe roughness and flow uniformity.

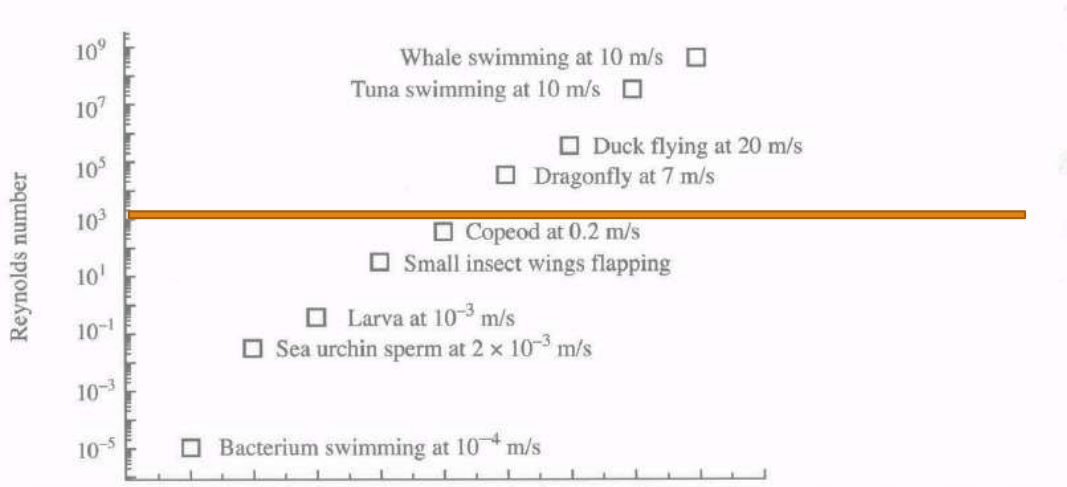


FIGURE 6.10 Reynolds numbers of moving organisms ranging over 14 orders of magnitude. (Data from Vogel. 1994. *Life in Moving Fluids*. Princeton University Press, Princeton, New Jersey.)

Poiseuille's Law

- Here flow (Q) is directly proportional to the pressure gradient

- In turbulent flow:

- Based on Reynolds number: ↑ pipe diameter and/or ↑ flow, with high density blood, tends towards turbulence

- Rapid changes in vessel diameter may lead to turbulent flow (e.g. narrower vessel widening to a larger one)

Q = volumetric flow rate
ΔP = pressure drop across the capillary
L = capillary length
μe = effective viscosity
R = vessel radius

Assumptions

1) Fluid is incompressible and Newtonian
   - i.e. viscous stresses arising from flow, at every point, are linearly proportional to the local strain rate,

2) laminar flow through a pipe of constant circular cross-section that is substantially longer than its diameter

3) Acceleration of fluid within the pipe doesn't happen.

For velocities and pipe diameters above a threshold, flow is driven to turbulent flow leading to incorrectly larger pressure drops than calculated by the Poiseuille equation

Basic version of Bernoulli's equation:

$$P_1 + \frac{1}{2}\rho v_1^2 + \rho g y_1 = P_2 + \frac{1}{2}\rho v_2^2 + \rho g y_2$$

so that the quantity

$$P + \frac{1}{2}\rho v^2 + \rho g y = \text{const}$$

- between any two points (y_1 and y_2) along the streamline flow.
- an increase in fluid velocity occurs simultaneously with a decrease in pressure or a decrease in the fluid's potential energy.
- Bernoulli's equation can be regarded as a statement of conservation of energy density where each term has dimensions of energy/volume.

Venturi Effect

- describes the change in pressure when fluid flows through a pipe with changing cross-sectional area.

- For simplicity consider the constant height Bernoulli equation Y1 = Y2 with with no change in gravitational potential:

$$P + \frac{1}{2}\rho v^2 = \text{const}$$

Comparing two points along the streamline flow, we can calculate the change in pressure:

$$P_1 - P_2 = \frac{1}{2}\rho\left(v_2^2 - v_1^2\right)$$

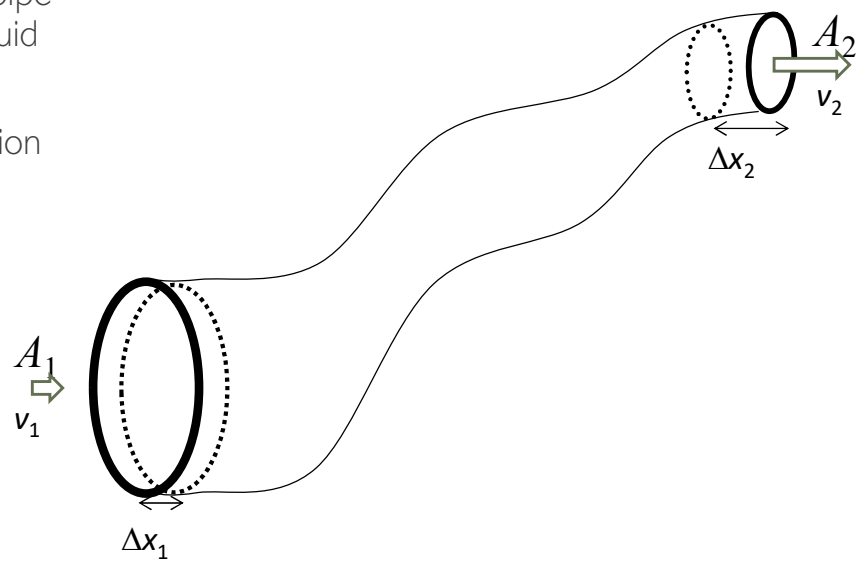
so that a constriction in in a blood vessel results in a drop in pressure.

$$P_1 - P_2 = \frac{1}{2}\rho v_1^2\left[\left(\frac{A_1}{A_2}\right)^2 - 1\right]$$ From the continuity equation

Fluid flow inside a pipe with varying cross section

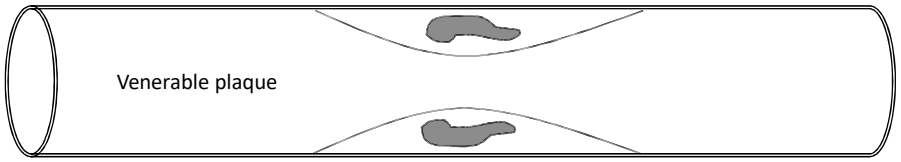
- Fluid will flow faster through a constriction in a pipe or a blood vessel since the product of area and fluid speed is a constant.

- The increase in fluid speed may lead to a transition from laminar to turbulent flow.



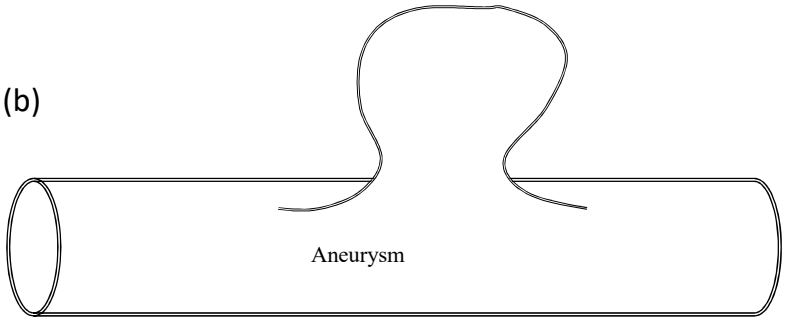
Vessel Volume Changes

(a)



(a) constricted by vulnerable plaque

(b)



(b) expanded by aneurysm

Very Small Vessels

Fåhræus–Lindqvist effect:

- viscosity of a fluid (blood) changes with tube diameter (only if the vessel diameter is between 10 and 300 micrometers).

- erythrocytes move over the center of the vessel, leaving plasma at the wall of the vessel.

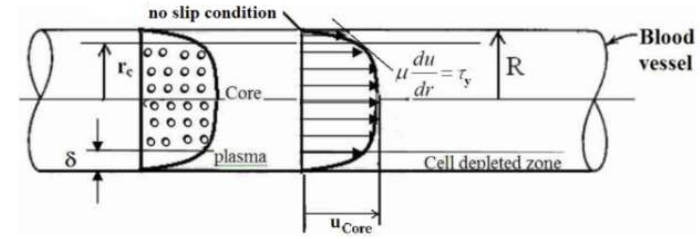
Plasma cell-free layer

- also known as skimming layer

- thin layer adjacent to the capillary wall depleted of red blood cells.

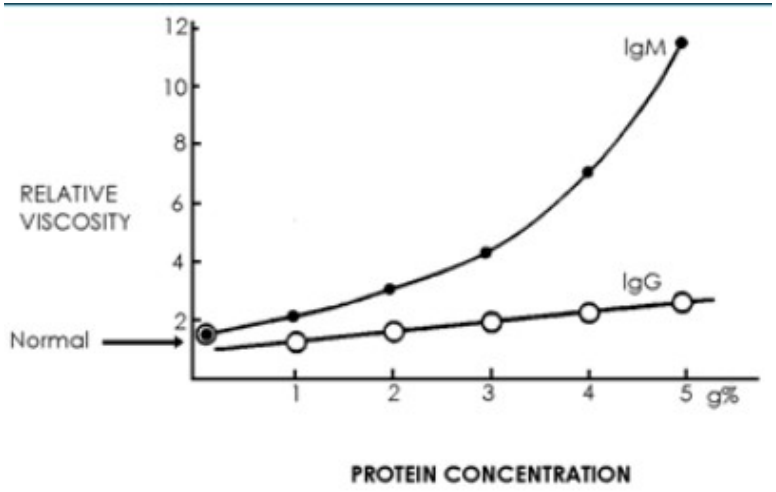
- effective viscosity is lower than that of whole blood

- Because the cell-free layer is very thin (approximately 3 μm) this effect is insignificant in larger capillaries



Very Small Vessels

- in truth, blood is non-Newtonian (in smaller vessels!)
- viscosity depends on cell counts and plasma viscosity
- viscosity also depends on shear rate:
  - when low results in Rouleaux formations and sedimentation




Rouleaux formation

Cardiac Modelling Conclusions

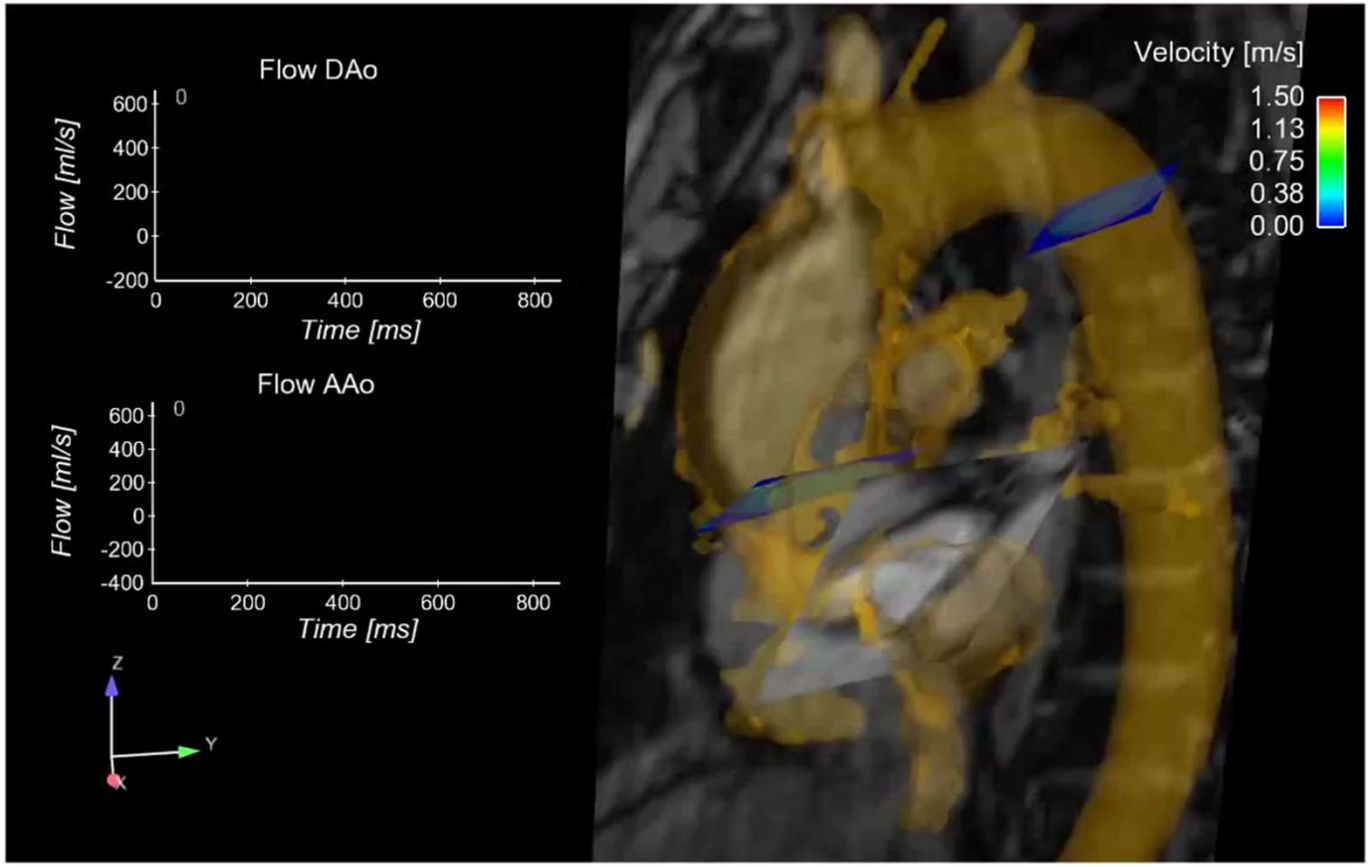
Blood behaves very differently based on the scale we analyze it by

Macro level
- Model as a Newtonian fluid
- Look at pressure, volume, HR etc

Micro level
- Turbulent vs Laminar flow
- Skimming layer

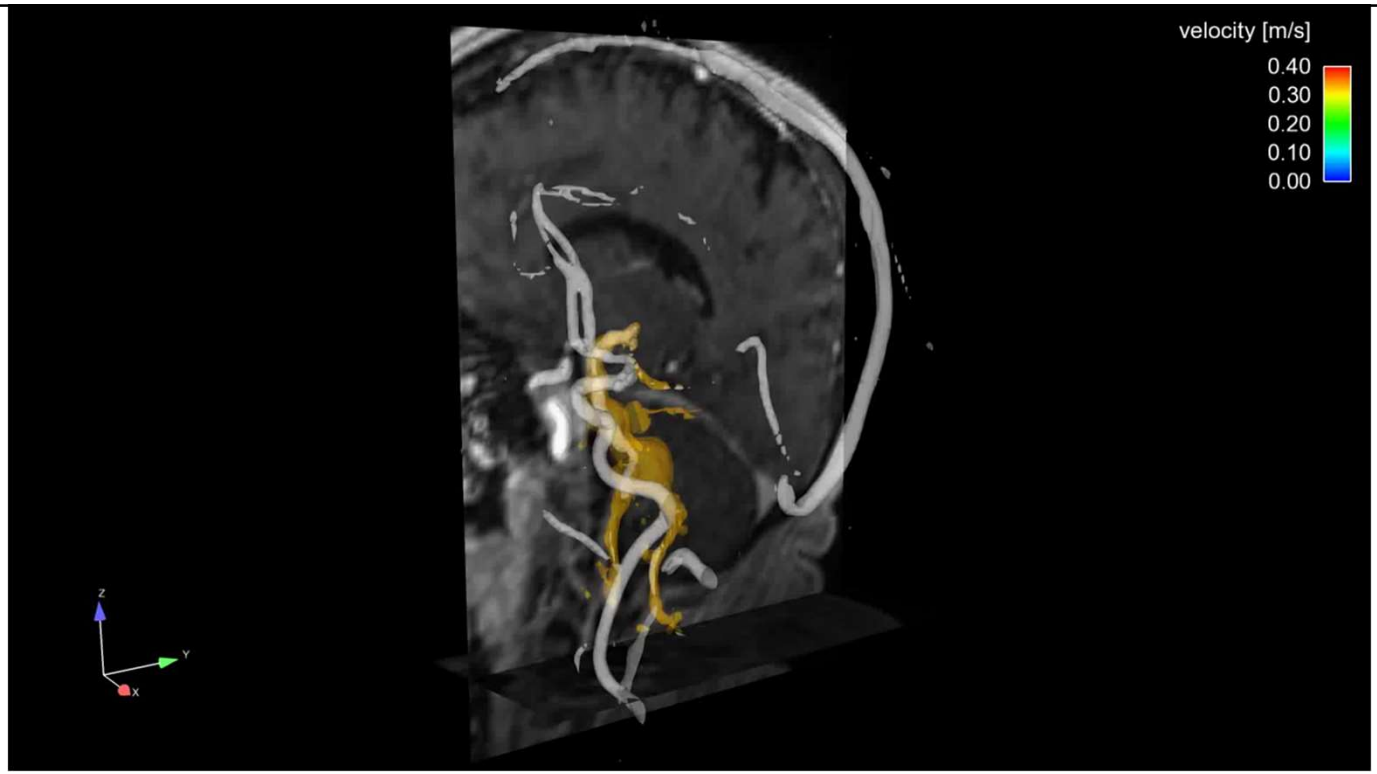
Capillary Level
- Collection of solid shapes

Different considerations based on different scales



MRI 4D flow: Patient with a bicuspid aortic valve

(courtesy Dr. Zhaoyang Fan, UCLA)



MRI 4D flow: Patient with a intracranial aneurism

(courtesy Dr. Zhaoyang Fan, UCLA)

Pharmacokinetics

INTRODUCTION

Pharmacokinetics vs Pharmacodynamics

Pharmacokinetics

- the action of drugs in the body over a period of time
- including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.

Pharmacodynamics

- the study of the biochemical and physiological effects of drugs and the mechanisms of their actions
- including the correlation of their actions and effects with their chemical structure.

http://medical-dictionary.thefreedictionary.com/

Why is This Important?

1) We use drugs in hospitals!
2) Chemical Engineering, implanted devices, drug delivery systems, etc.
3) Anaesthetics
4) Imaging with contrast agents
5) Imaging drug delivery systems
6) Toxicity, bio-elimination

Etc.

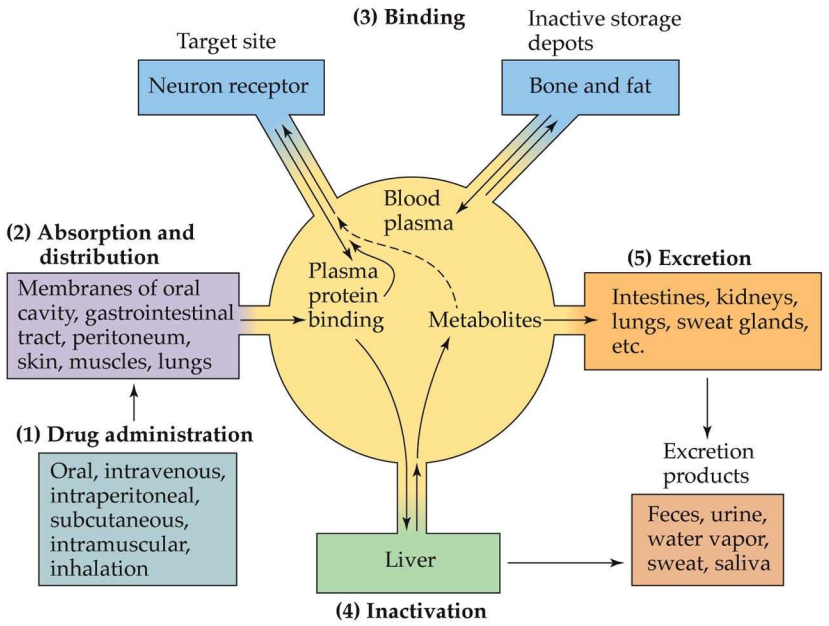
Pharmacokinetics

Drug molecules interact with target sites to affect the nervous system

Pharmacokinetics is the study of drug absorption, distribution within body, and drug elimination over time.

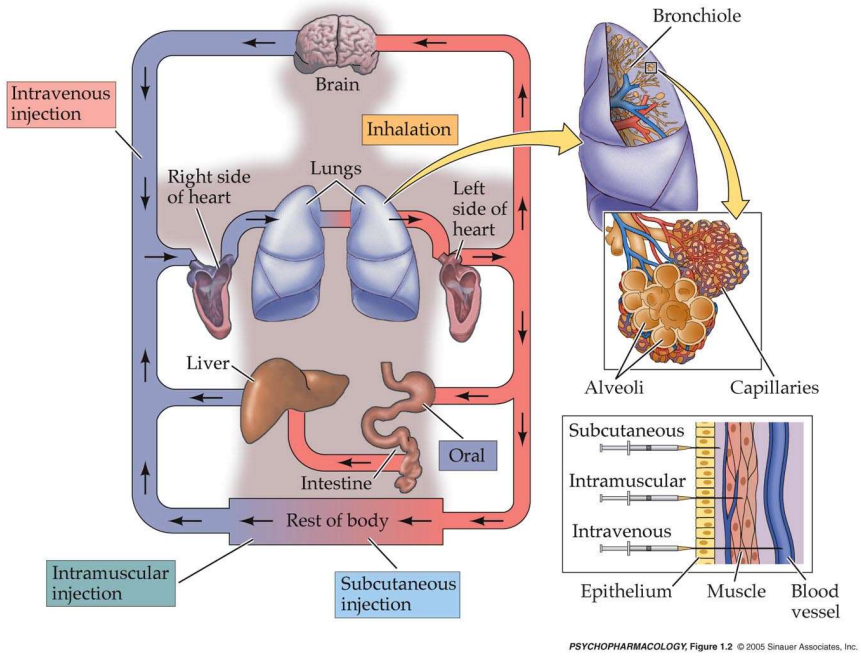
- Absorption depends on the route of administration
- Drug distribution depends on how soluble the drug molecule is in fat (to pass through membranes) and on the extent to which the drug binds to blood proteins (albumin)
- Drug elimination is accomplished by excretion into urine and/or by inactivation by enzymes in the liver

Pharmacokinetics



PSYCHOPHARMACOLOGY, Figure 1.1

Routes of Administration



PSYCHOPHARMACOLOGY, Figure 1.2 © 2005 Sinauer Associates, Inc.

Drug Delivery Systems

- Tablets
- Injections (Syringe)
- Cigarettes
- Beverages
- Patches
- Suppositories
- Candy
- Gum
- Implants
- Gas
- Creams
- Others?
  - Stamps
  - Bandana

Important Terms

Exposure
- A measure for the amount of drug that an organism has really "seen"

Bioavailability
- A measure for the proportion of the dose that reaches the systemic circulation (not the same as exposure)

Clearance
- A measure of the elimination of a compound from the blood given as volume cleared/time
- Usually if <1% left, it is considered cleared

Volume of Distribution
- A measure of the theoretical volume that a compound distributes to.

Unbound Fraction
- The fraction of drug not bound to proteins: $C_{unbound} = fu \times C_{total}$

Half-Life
- A measure of the time it takes for the organism to decrease the concentration of the drug by 50%

Drug Absorption

The rate at which a drug reaches it site of action depends on:

- Absorption
  - involves the passage of the drug from its site of administration into the blood
- Distribution
  - involves the delivery of the drug to the tissues

Drug Absorption

Absorption is the process by which a drug enters the bloodstream without being chemically altered

Factors which influence the rate of absorption

- types of transport
- the physicochemical properties of the drug
- protein binding
- routes of administration
- dosage forms
- circulation at the site of absorption
- concentration of the drug

Drug Absorption

Mechanisms of solute transport across membranes

- passive diffusion
- filtration and bulk flow
- endocytosis
- ion-pairing
- active transport

Membranes

Cell Membranes:

- Permeable to many drug molecules but not to others, depending on their lipid solubility
- Small pores, 8 angstroms, permit small molecules such as alcohol and water to pass through.

Walls of Capillaries

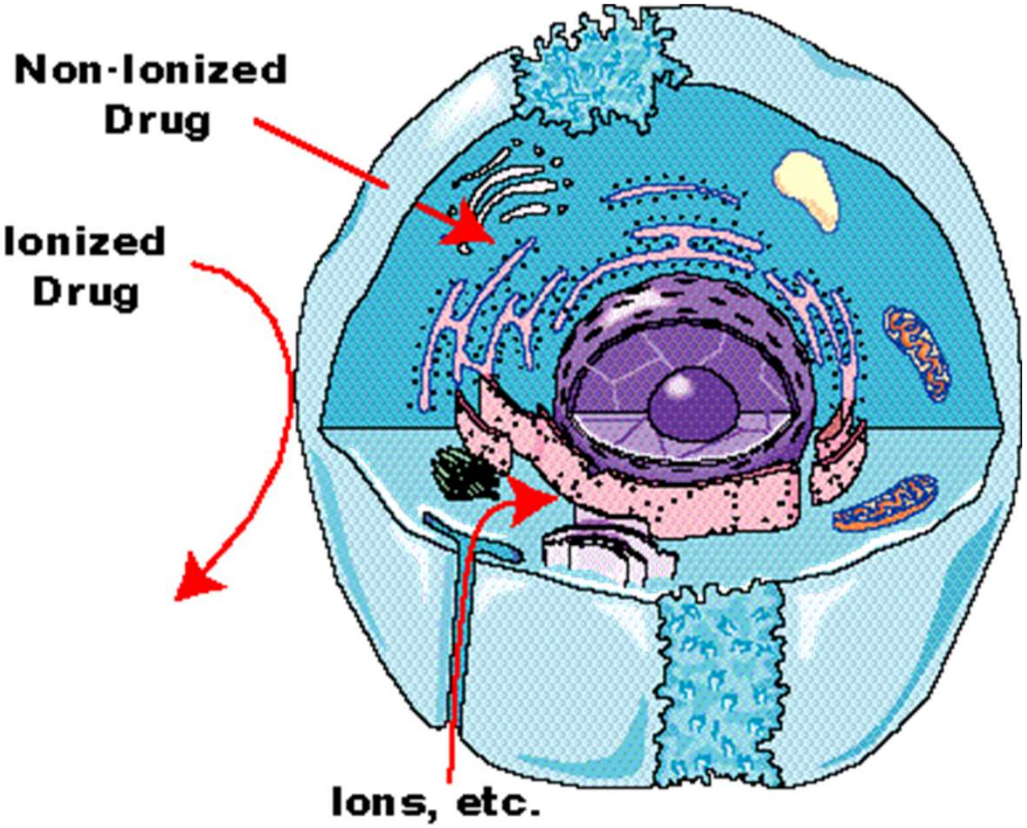
- Pores between the cells are larger than most drug molecules, allowing them to pass freely, without lipid solubility being a factor.

Blood/Brain Barrier

- This barrier provides a protective environment for the brain.
- Speed of transport across this barrier is limited by the lipid solubility of the psychoactive molecule.

Placental Barrier

- This barrier separates two distinct human beings but is very permeable to lipid soluble drugs.


Non-Ionized
Drug
Ionized
Drug
Ions, etc.

Ion Trapping cont:

Higher concentration of a chemical built up because of a pH difference and the pKa value

Alters urine pH to inhibit toxins from being reabsorbed in the tubules in the kidney

Trap a toxin in an ionized form where it can be excreted

Body fluids where a pH difference from blood pH will favor trapping or reabsorption:

- stomach contents
- small intestine
- breast milk
- aqueous humor (eye)
- vaginal secretions
- prostatic secretions

Ion Trapping:

Kidney:

- Nearly all drugs filtered at the glomerulus:
- Most drugs in a lipid-soluble form will be absorbed by passive diffusion.

To increase excretion: change the urinary pH to favor the charged form of the drug:

- Weak acids: excreted faster in alkaline pH (anion form favored)
- Weak bases: excreted faster in acidic pH (cation form favored)

Lipid-Water Partition Coefficient

- The ratio of the concentration of a drug in two immiscible phases:
  - a nonpolar liquid or organic solvent (representing the membrane)
  - an aqueous buffer, pH 7.4 (representing the plasma)

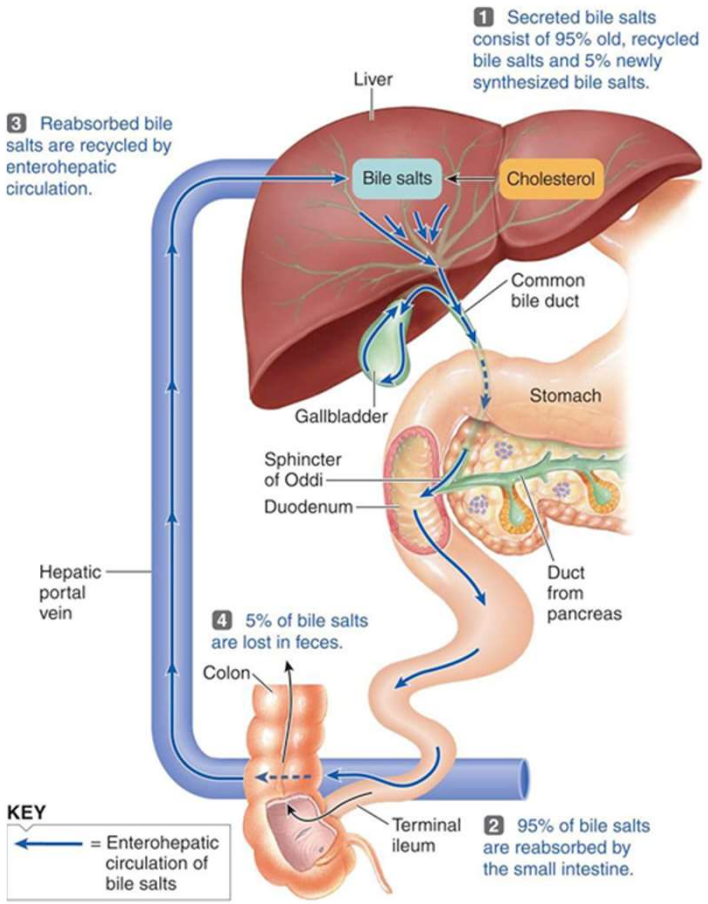
The higher the lipid/water p.c. the greater the rate of transfer across the membrane

-  polarity of a drug, by increasing ionization will  the lipid/ water p.c.
-  polarity of a drug, by suppressing ionization will  the lipid/ water p.c.

Dr. R. Copeland, Howard University, Washington, D.C

First-pass Effect

- Term used for the hepatic (liver) metabolism of a pharmacological agent when it is absorbed from the gut and delivered to the liver via the portal circulation.
- The greater the first-pass effect
  - the less the agent will reach the systemic circulation when the agent is administered orally.
  - the lower the bioavailability of the drug (the rate and extent of drug reaching systemic circulation).


1 Secreted bile salts consist of 95% old, recycled bile salts and 5% newly synthesized bile salts.
Liver
3 Reabsorbed bile salts are recycled by enterohepatic circulation.
Bile salts
Cholesterol
Common bile duct
Gallbladder
Stomach
Sphincter of Oddi
Duodenum
Hepatic portal vein
Duct from pancreas
4 5% of bile salts are lost in feces.
Colon
Terminal ileum
2 95% of bile salts are reabsorbed by the small intestine.
KEY
= Enterohepatic circulation of bile salts

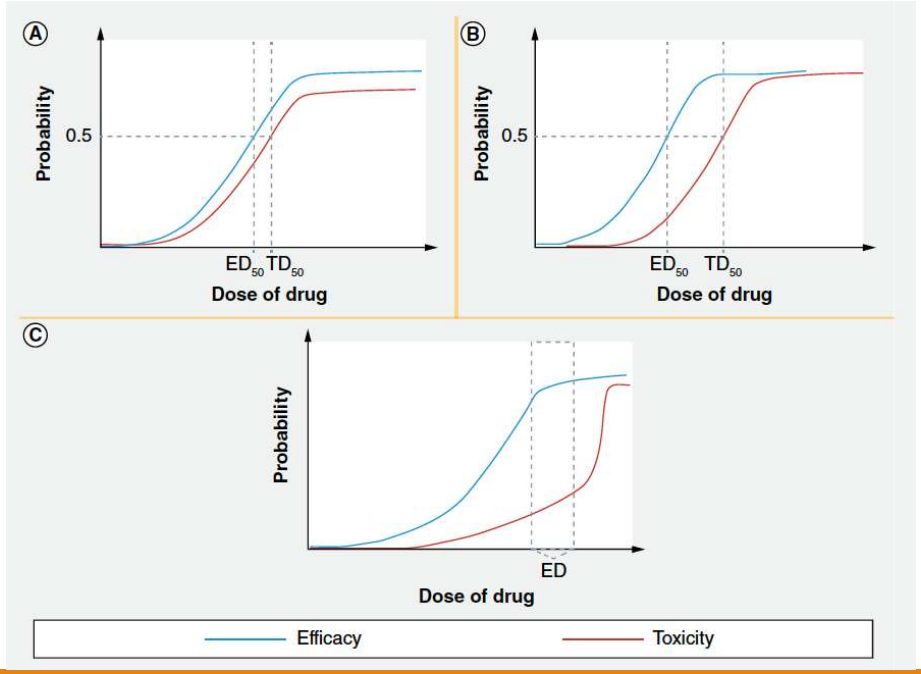
Magnitude of first pass hepatic effect:

Extraction ratio (ER):

Q = hepatic blood flow (~ 90 L per hour).

Systemic drug bioavailability (F) may be determined from the extent of absorption (f) and the extraction ratio (ER):

Therapeutic Index



Therapeutic index (TI) = TD_{50}/ED_{50}

(B) Better TI when the effect curve is displaced to left (ED_{50} << TD_{50}).

(C) Increased TI by preferentially directing the drug to tumor cells and or reducing toxicity

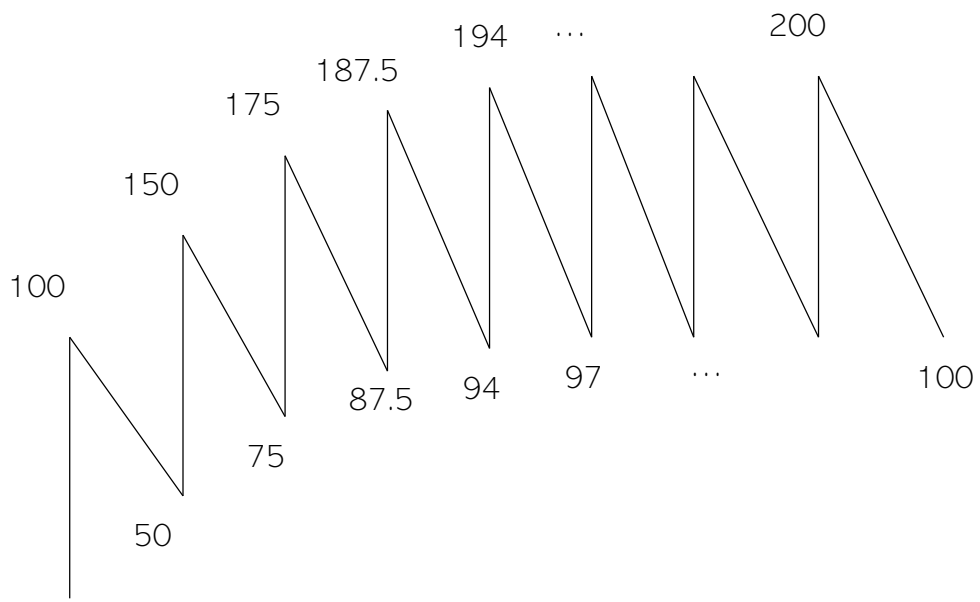
Drug Delivery in Oncology (2014). Alejandro D. Ricart

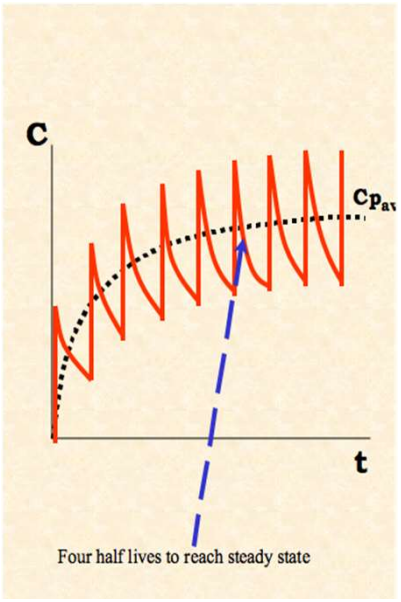
Steady-State

Steady-state occurs after a drug has been given for ~ 5 to 6 elimination half-lives.

- Rate in = Rate Out
- Reached in ~ 5 or 6 half-lives (linear kinetics)
- Important when interpreting drug concentrations in time-dependent manner or assessing clinical response
- Repeated doses are used to maintain a steady state as the body metabolizes/excretes the previous dose

Accumulation to Steady State
100 mg given every half-life



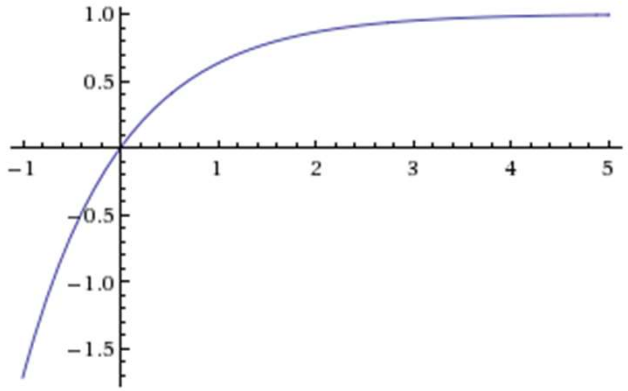


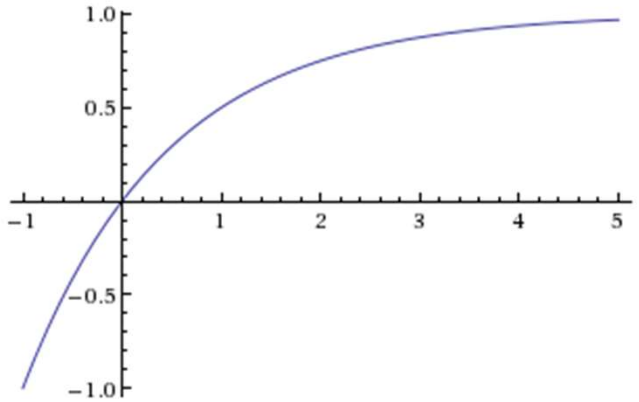
6 doses to reach steady state

Rate of Absorption

exponential VS power model:

k = rate constant (time^{-1})



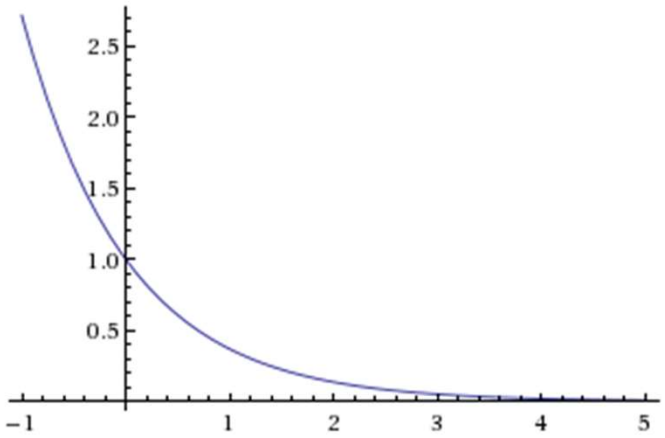


$C(t) = C_i\ (1 - e^{-t/k})$

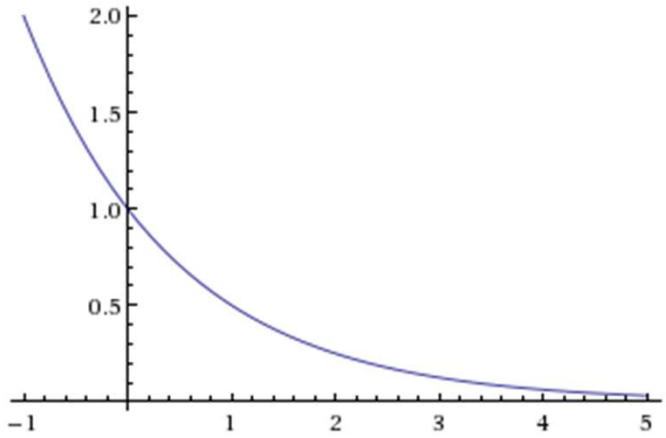
$C(t) = C_i\ (1 - 2^{-t/k})$

Rate of excretion

exponential VS power model:



$C(t) = C_i\ (e^{-t/k})$

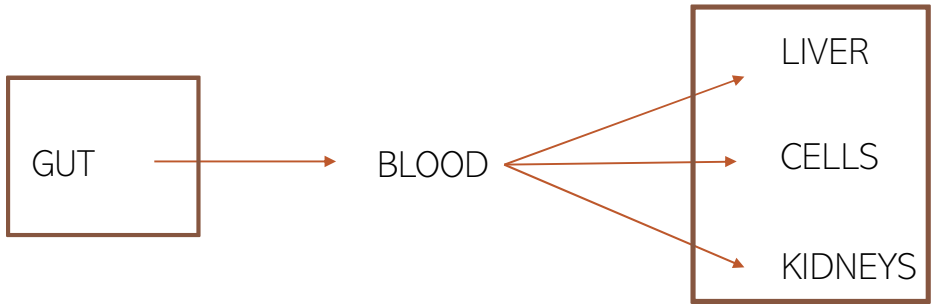


$C(t) = C_i\ (2^{-t/k})$

Pharmacokinetics

Outputs VS inputs – PRODUCT

Multiple inputs/outputs - SUM



Routes of Drug Administration

The route of administration (ROA) that is chosen may have a profound effect upon the speed and efficiency with which the drug acts

Definition

- A route of administration is the path by which a drug, fluid, poison or other substance is brought into contact with the body.

Classification

Routes of administration can broadly be divided into:

- Topical
  - Drugs are applied topically to the skin or mucous membranes, mainly for local action.
- Oral (aka PER OS)
  - used for systemic (non-local) effect, substance is given via the digestive tract.
- Parenteral
  - A drug administered parenterally is one injected via a hollow needle into the body at various sites and to varying depth.
- Rectal
  - Drugs given through the rectum by suppositories or enema.
- Inhalation
  - The lungs provide an excellent surface for absorption when the drug is delivered in gaseous, aerosol or ultrafine solid particle form.

Topical route

I Skin

A-Dermal

- cream, ointment (local action)

B- Transdermal

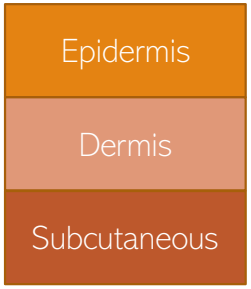
- absorption of drug through skin (i.e. minimal systemic action)
  - I. stable blood levels (controlled drug delivery system)
  - II. No first pass metabolism
  - III. Drug must be potent or patch needs will be [too] large

II Mucosal membranes

- eye drops (onto the conjunctiva)
- ear drops
- intranasal route (into the nose)

Topical route

- Drugs applied locally on the skin are poorly absorbed through the epidermis.
- However, the dermis is permeable to many solutes. Thus systemic absorption of drugs occurs more readily through abraded, burned or denuded skin.
- Inflammation and other conditions that enhance cutaneous blood flow also promote absorption.
- Drugs are applied in the form of ointments, pastes, poultice and cream to the skin for their local action.
- Absorption through skin can be increased by suspending the drug in an oily vehicle and rubbing the preparation into the skin. This method of administration is called inunction.
- To increase absorption drugs are applied onto the various mucous membranes for their local action.



Topical Route

ADVANTAGES

Easy to apply

Low risk of drug interactions

High concentration of antibiotic to affected area

Lack of effects on intestinal flora

Low cost

Avoid first pass metabolism

Easy termination

DISADVANTAGES

Most drugs have too high of a molecular weight and are not lipid soluble

Local skin irritation

Contact dermatitis with some drugs may occur

Skin enzymes can break down drug

Can be used with drugs that require low plasma concentration

Oral route

(aka: Per Os)

- By swallowing.

intended for systemic effects resulting from drug absorption through the various epithelia and mucosa of the gastrointestinal tract.

Oral route (Continued):

-Food and gastrointestinal motility can affect drug absorption.

-- Absorption may be slow, unpredictable and irregular because of the presence of variable amounts of food at various stages of digestion

-- Absorption is slower with food (milk and milk products) for tetracyclines and penicillins, etc. However, for propranolol bioavailability is higher after food, and for griseofulvin absorption is higher after a fatty meal.

Oral route (Continued):

Sometimes may have adverse reactions – e.g. Antibiotics may kill normal gut flora and allow overgrowth of fungal varieties. Thus, antifungal agent may be included with an antibiotic.

Not suitable for unconscious patient - Patient must be able to swallow solid dosage forms. Liquids may be given by tube.

→ May cause irritation to gastric mucosa, nausea and vomiting.

→ Effect too slow for emergencies.

→ Some drugs are destroyed by intestinal enzymes e.g. insulin is destroyed by intestinal enzymes.

→ There is a necessity for cooperation on the part of patient.

Oral route

ADVANTAGES

1) Convenient - portable, no pain, easy to take.

2) Cheap - no need to sterilize, compact, multi-dose bottles, automated machines produce tablets in large quantities.

3) Variety - tablets, capsules, suspensions, mixtures .

DISADVANTAGES:

1) Sometimes inefficient - low solubility drugs may suffer poor availability e.g. Griseofulvin

2) First-pass effect - drugs absorbed orally are transported to the general circulation via the liver. Thus drugs which are extensively metabolized will be metabolized in the liver during absorption. e.g. propranolol

Buccal/Sublingual route:

Some drugs are taken as smaller tablets which are held in the mouth (buccal tablet) or under the tongue (sublingual tablet).

Buccal tablets are often harder tablets [4 hour disintegration time], designed to dissolve slowly.

Buccal/Sublingual route:

- drug is very potent so needs few molecules to be absorbed in order to produce the therapeutic effect.

- major advantage of this route is that venous drainage from mouth (buccal cavity) is poured into the superior vena cava and the drug is saved from first-pass effect.

Buccal/Sublingual route:

ADVANTAGES

1. Avoid hepatic first pass - The liver is by-passed thus there is no loss of drug by first pass effect for buccal administration. Bioavailability is higher.

2. Rapid absorption - Because of the good blood supply to the area, absorption is usually quite rapid.

3. Drug stability - pH in mouth relatively neutral (stomach - acidic). Thus a drug may be more stable.

DISADVANTAGES

1- Holding the dose in the mouth is inconvenient.

2- Small doses only can be accommodated easily.